CURRICULUM VITAE OF PROFESSOR (DR.) GOUTAM BRAHMACHARI)

In Brief: Goutam Brahmachari, *M.Sc (1st Class 1st), PhD, D.Sc., FRSC*, is a full professor of organic chemistry at Visva-Bharati University, Santiniketan, India. His group contributed significantly to developing effective and practical synthetic methods for carbon-carbon and carbon-heteroatom bond formation in constructing medicinally important heterocyclic scaffolds using C-H functionalization, cascade and *cross*-coupling approaches. Prof. Brahmachari also made outstanding contributions to natural product chemistry by unearthing the chemical profiles of several traditionally used Indian medicinal plants, studying their chemistry and biology, and thus presenting novel phytochemicals of interest. ***With about 27 years of experience in teaching and research***, he has produced **287** scientific publications, including original research papers, review articles, books, and invited book chapters in synthetic organic chemistry and natural products chemistry. He has already authored/edited **28** books from the leading scientific publishers. He has supervised 20 Ph.D. fellows so far. He is the Series Editor of the Elsevier Book Series '*Natural Product Drug Discovery*'. Prof. Brahmachari is an Elected Fellow of the Royal Society of Chemistry and a recipient of the Acharya P. C. Ray Memorial Lecture Award-2025 from the Indian Science News Association (ISNA), Kolkata, Dr. Satyajit Chakraborti Memorial Award-2025 (global contribution to chemical science) from IEM, Kolkata, CRSI (Chemical Research Society of India) Bronze Medal-2021 (contributions to research in chemistry), Dr. Basudev Banerjee Memorial Award-2021 (Contribution in chemical sciences) from the Indian Chemical Society, INSA (Indian National Science Academy) Teachers Award-2019, Dr. Kalam Best Teaching Faculty Award-2017, and Academic Brilliance Award-2015 (Excellence in Research). Prof. Brahmachari was featured in the World Ranking of the Top 2% Scientists (Organic Chemistry Category) in 2020-24 (both in whole career and single years), in the AD Scientific World Ranking of Scientists -2022-2024, as the ScholarGPS Highly Ranked Scholar-2022-2024 (Lifetime, securing a position in the top 0.05% of all scholars worldwide). Current Citations: 7507; *h*-index: 44; *i*10-index: 143 (as of 26.08.2025)

(ORCID: http://orcid.org/0000-0001-9925-6281)

VIDWAN: https://vidwan.inflibnet.ac.in/profile/152899

Prof. G. Brahmachari

(CRSI Bronze Medal Awadee-2021; Dr. Basudev Banerjee Memorial Awardee 2021; INSA Teachers Awardee-2019)

1. **Name in Full:** **BRAHMACHARI** // **GOUTAM**
   Surname Forename

2. **Designation and Name of the Institution:** **Full Professor of Chemistry, Department of Chemistry, Siksha-Bhavana, VISVA-BHARATI (A Central University), Santiniketan-731235, West Bengal, India** [University Employee ID No. 1998048]

3. **a. Date of Birth:** **14th April 1969 (14.04.1969)**
   b. Citizen: **Indian** **c. Gender:** **Male**

4. **Fellow & Life membership**
   (a) Fellow: Royal Society of Chemistry, London (UK) (**FRSC**)
   (b) Life Member: **CRSI** (LM 1914), **ISCA** (L24650), **ICS (8547)**

5. **Address**
   (a) Official: **Laboratory of Natural Products & Organic Synthesis, Department of Chemistry, Siksha-Bhavana, Visva-Bharati (A Central University), Santiniketan-731235, Birbhum, West Bengal, India**
   (b) Residential: **Dinendrapalli, Simantapalli (North), Santiniketan-731235, Birbhum, WB, India**
   (c) Email: brahmg2001@yahoo.co.in; brahmg2001@gmail.com; goutam.brahmachari@visva-bharati.ac.in
   (d) Mobile No./Contact No: + **91-9434385744 / +91-8617324394**

6. **Subject:** **CHEMICAL SCIENCES (Organic Chemistry)**

7. **Educational Qualifications:** **M.Sc. (1st Class 1st), Ph.D. (Organic Chemistry), D.Sc. (Organic Chemistry)**

8. **Professional Experience**
   Teaching and Research (Independent) at the University Level: About 27 years

9. Field of Research

Synthetic organic chemistry, Green chemistry, Synthetic methodologies, Natural Products Chemistry

10. Administrative experiences: As shown in the following Table.

Sl. No.	Details of such an experience
1	Successfully executed the responsibilities of the Head of the Department, Department of Chemistry, Siksha-Bhavana, Visva-Bharati, as part of administrative responsibility from 04.03.2020 (afternoon) to 22.12.2023 (afternoon). The Head of the Department is responsible for running the Department both academically and administratively, including planning, execution, finance, budget, Department projects, and many others.
2	Coordinator of the University's International Collaborations Wing since 21.09.2022
3	Working as a member of the University's "*Students' Grievance Redressal Committee*" since 04.08.2023
4	Working as a member of the University's "Building Committee" since 02.12.2020
5	Member of the Academic Council (since 24.07.2011), Board of Studies of the parent and other Universities
6	Member of the Research Board (Visva-Bharati) 14.12.2017 to 14.12.2020
7	Member of the University Vision-2035 Committee

11. Master's and Doctoral Dissertations Supervised

Ph. D. students supervised: 20 (*Degrees already awarded*)
Present PhD fellows working with: 05
Master's Dissertations supervised: 60

12. Project Coordinator (Sponsored Research Projects) [Total Grants Amount: INR 210 Lakh]

Successfully completed several research projects sponsored by UGC (New Delhi), CSIR (New Delhi), DST (West Bengal), DBT (New Delhi), and SERB-DST (New Delhi)

I. As PI/Co-PI

- Research Project entitled "Electrochemical synthesis of functionalized heterocycles of biological relevance" sponsored by CSIR, New Delhi, No. No. 02/0464/23/EMR-II dated 07.07.2023 (2023-2026) Amount: INR 30 Lakh. [**Ongoing**]
- Research Project entitled "*Electrosynthesis of functionalized heterocycles via C-H functionalization*" sponsored by Science and Engineering Research Board (SERB), Department of Science and Technology (DST), New Delhi, No. No. CRG/2022/000275 dated 08.12.2022 (2022-2025); Amount: INR 50 Lakh. [**Ongoing**].
- Research Project entitled "Studies on the chemical constituents and biological activities of *Casia sophera* Linn. (Caesalpiniaceae) – an important Indian medicinal plant" sponsored by CSIR, New Delhi, No. 02(0260)/16/EMR-II dt 28.04.16; (1.6.2016 to 31.05.2019) Amount: INR 20 Lakh [**Completed**].
- Research Project entitled "Pharmacokinetics and toxicology of toxins in boiled aqueous extract of *Cleistanthus collinus* leaves" sponsored by Department of Biotechnology, Ministry of

Science & Technology, Govt. of India, No.BT/PR12571/TRM/120/25/2014 dt. 15.07.2016 (period 2016-2019), Amount: INR 39.62 Lakh [as *project Joint-investigator*] [**Completed**].

- Research Project entitled "*Design for Energy-Efficient Synthesis of Biologically Relevant Heterocycles*" sponsored by Science and Engineering Research Board (SERB), Department of Science and Technology (DST), New Delhi, No. EMR/2014/001220 dt 08.09.2015 (2015-2018); Amount: INR 35.26 Lakh [**Completed**].
- Research Project entitled "*A sincere drive to develop eco-friendly methodologies for some useful organic transformations in the absence of organic solvents*" sponsored by CSIR, New Delhi, No. 02(0110)/12/EMR-II dt 01.11.2012 (2012-2015); Amount: INR 12.65 Lakh [**Completed**].
- Research Project entitled "*Acaciaside A from Acacia auriculiformis: a novel compound for the control of Bancroftian filariasis*" sponsored by Department of Biotechnology, Ministry of Science & Technology, Govt. of India, No. BT/PR8779/Med/14/1282/2007 dt. 24.09.2008 (period 24.09.2008-23.09.2011), Amount: INR 45.81 Lakh [as *project Joint-investigator*] [**Completed**].
- Research Project entitled "*Naturally Occurring Flavonoids: Isolation, Chemistry and Assessment of Bio-Activity*" sponsored by UGC, New Delhi, No. F.34-357/2008(SR) dt 02.01.2009 (period 01.02.2009 – 31.01.2012). Amount: INR 6,76,800/- [**Completed**].
- Research Project entitled "*Studies on chemical constituents of Limnophila plants available around Santiniketan (Birbhum, West Bengal)*" sponsored by the Department of Science & Technology (West Bengal) [No. 230(Sanc.)/ST/P/S&T/2G-7/2007 dt. 24.07.2008 (2008-2011)]. Amount: INR 7,01,500/- [**Completed**].
- Research Project entitled "*Studies on naturally occurring flavonoids*" sponsored by UGC, New Delhi, No. F.31-152/2005(SR) dt. 31.03.2006 (period 01.05.2006 – 30.04.2008) Amount: INR 55,000/- [**Completed**].

II. Involved in the Institutional research projects

Departmental UGC-SAP Programme, Departmental FIST (DST)-Level 0, 1, 2 programmes, and the University's DST-PURSE programme

13. Academic career and professional attainments:

(a) Academic career (Bachelor's degree onwards)

Degree	Institution	Year	Remarks
Bachelors [B.Sc. (Hons.) in Chemistry]	VISVA-BHARATI	1990	First Class Second
Masters [M.Sc. in Chemistry (Organic Chemistry Specialization)]	VISVA-BHARATI	1992	First Class First
Ph.D.	VISVA-BHARATI	1997	Organic Chemistry
D.Sc.	VISVA-BHARATI	2023	Organic Chemistry

(b) Professional experience

Positions held	Institution	From (year)	To (year)	Experience
Full Professor of Chemistry	Chemistry Department, Visva-Bharati (a Central University), WB, India	24.07.2011	Continuing	14 years (currently)
Head of the Department	-do-	4.03.2020	22.12.2023	About 4 years
Associate Professor	-do-	24.08.2008	23.07.2011	3 years
Reader (selected and joined afresh in an open post)	-do-	24.07.2005	23.07.2008	3 years
Lecturer (Senior scale)	-do-	08.12.2002	23.07.2005	2 years 8months
Lecturer in Chemistry	-do-	08.12.1998	07.12.2002	4 years

(c) Recognitions such as Fellowships, awards, prizes, certificates, academic/professional distinctions received, and Editorial Board member of National/International Journals

Type of Recognition	Title of Recognition	Name of Awarding agency	Year of award
Highest academic Degree	Awarded Doctor of Science (D.Sc.) Degree in Chemistry	Visva-Bharati University	2023
Award	Acharya P. C. Ray Memorial Lecture	Indian Science News Association (ISNA), Kolkata	2025
Award	Dr. Satyajit Chakraborti Memorial Award-2025 (global contribution to chemical science)	Institute of Engineering & Management (IEM), Kolkata	2025
Award	CRSI Bronze Medal Award (for the contribution to research in Chemistry)	Chemical Research Society of India (CRSI), Bangalore	2021
Award	Dr. Basudev Banerjee Memorial Award-2021 (contributions in chemical sciences) from the	Indian Chemical Society, Kolkata	2021
Fellowship	Elected Fellow, Royal Society of Chemistry (FRSC)	Royal Society of Chemistry, London, UK	2017
Award	INSA Teachers Award -2019	Indian National Science Academy, New Delhi	2019
Award	Dr. Kalam Best Teaching Award	Dr. Kalam Educational Trust, Chennai	2017
Award	Academic Brilliance Award (Award for Excellence in Research)	Prime Time Research Media Private Limited (Education Expo TV (EET) CRS), New Delhi	2015
Recognition	Featured in“the World Ranking of Top 2% Scientists" in the Organic Chemistry category (both whole career and single years)	Stanford University Scientists	2020-2024

Recognition	Featured in the "AD Scientific World Ranking of Scientists"	AD Scientific	2022-2024
Recognition	Featured as the ScholarGPS Highly Ranked Scholar (Lifetime, securing a position in the top 0.05% of all scholars worldwide	ScholarGPS	2022-2023
Reviewer award	Reviewer Excellence Awardee	*Journal of Chemical Sciences*, published by the Indian Academy of Sciences, Bangalore	2019
Reviewer award	Publons 1%Top Reviewer Award-2018 & 2019	Publons (Web of Science)	2018-2019
Recognition	CAS Registry® Innovator-2020	The American Chemical Society	2020
Recognition	Research abstracts in the prestigious *Organic Chemistry Portal*	https://www.organic-chemistry.org/abstracts/lit9/241.shtm; https://www.organic-chemistry.org/abstracts/lit9/738.shtm	2025
Recognition	Highly cited author (2014-15) for the *ACS Sustainable Chemistry & Engineering*	The American Chemical Society	2014-2015
Recognition	Featured in the top 10% of highly cited articles from the Royal Society of Chemistry	The Royal Society of Chemistry, UK	2022
Book series editor	Founder Series Editor of the Elsevier Book series "*Natural Product Drug Discovery*"	Elsevier Science, USA (https://shop.elsevier.com/books/discovery-and-development-of-antidiabetic-agents-from-natural-products/brahmachari/978-0-12-809450-1)	2016 onwards
Journal editorship	Co-Editor-in-Chief for the *Current Green Chemistry*	Bentham Science (https://www.benthamscience.com/journal/141/editorial-board)	2020 onwards
Journal guest-editorship	*Current Organo-catalysis* (one thematic issue), *Current Green Chemistry* (three thematic issues)	Bentham Science (links: https://www.benthamdirect.com/content/journals/cocat/3/2 https://www.benthamscience.com/issue/13064 https://www.benthamscience.com/issue/7662 https://www.benthamscience.com/issue/7695	2016, 2022
Journal Editorial Advisory Board	*Tetrahedron Green Chemistry, University Journal of Green Chemistry, Current Catalysis, Current Organocatalysis, Current Green Chemistry; Rasayan*	Respective journal administrations	2015 onwards

Member	*Journal of Chemistry; Journal of Biochemistry and Molecular Biology Research; Journal of Scientific Research and Advances; Iranian Chemical Communication, and others*		
Session Chairing	Session Chairing in Seminars/Conferences and Invited Talks delivered at several national and international symposia.	-	-
Life-member of Scientific Organisations	Indian Chemical Society (ICS) of India (Life Member, No. 8547), Indian Science Congress Association (ISCA) (ISCA, L24650), and Chemical Research Society of India (CRSI) (CRSI, LM 1914).	-	-

14. Website Pages for Public Viewing

VB Webpage: https://www.visvabharati.ac.in/GautamBrahamachari.html

Departmental website: http://vbchem.ac.in/GoutamBrahamachari/

ORCID ID: http://orcid.org/0000-0001-9925-6281

Google Scholar: https://scholar.google.co.in/citations?hl=en&user=aj7NvGQAAAAJ&view_op=list_works

Research Gate Page: https://www.researchgate.net/profile/Goutam_Brahmachari2/publications

LinkedIn page: https://in.linkedin.com/in/goutam-brahmachari-9308b662

VIDWAN: https://vidwan.inflibnet.ac.in/profile/152899

Scopus Page: https://www.scopus.com/authid/detail.uri?authorId=6603056427

Exaly Project Webpage: https://exaly.com/author/2358812/g-brahmachari/rankings

Web of Science: https://www.webofscience.com/wos/author/record/736637

https://www.webofscience.com/wos/author/record/H-9416-2017

15. Citation Indices

Citations: 7507; h-index: 44; i10-index: 143 (as accessed on 26.08.2025 at the Google Scholar platform)

Graphical representation of the year-wise citations (Google Scholar Personal page)
(https://scholar.google.co.in/citations?user=aj7NvGQAAAAJ&hl=en)

16. Editorship of Book Series

Elsevier Series Editor – Book Series 'Natural Product Drug Discovery'
(https://www.elsevier.com/catalog/all/all/all/natural-product-drug-discovery)

17. A list of ten (10) best research publications published in recent times (Please note: All the works were planned, designed and performed exclusively working in India)

No.	Paper details	Remarks
1.	Debojyoti Mukherjee, Indrajit Karmakar, **Goutam Brahmachari*** (2025). Sono- and mechanochemical dual syntheses of bio-relevant aryldiazenyl-substituted phosphine oxides/phosphonates via P(O)-H functionalisation. *Green Chemistry*, **27**, 2565-2577. [Print ISSN: 1463-9262; Online ISSN: 1463-9270; IF 9.2 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript
2.	Debojyoti Mukherjee, Indrajit Karmakar, **Goutam Brahmachari*** (2024). Electro- and mechanochemical strategy as a dual synthetic approach for biologically relevant 3-nitro-imidazo-[1,2-*a*]pyridines. *The Journal of Organic Chemistry*, **89**, 12071-12084. [Print Edition ISSN: 0022-3263; Web Edition ISSN: 1520-6904; IF 3.6 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript
3.	Indrajit Karmakar, **Goutam Brahmachari*** (2024). Electro-rearranged di-functionalization of 4-hydroxy-α-benzopyrones. *The Journal of Organic Chemistry*, **89**, 10524-10537. [Print Edition ISSN: 0022-3263; Web Edition ISSN: 1520-6904; IF 3.6 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript
4.	Anindita Bhowmick, **Goutam Brahmachari*** (2023). C(sp)–C(sp3) Bond formation through ligand- and additive-free CuO-mediated decarboxylative direct cross-coupling of coumarin-/chromone-3-carboxylic acids and terminal alkynes. *Organic Letters*, **25**, 7095-7099. [ISSN 1523-7060); IF 5.0 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript
5.	Pintu Karmakar, Indrajit Karmakar, Debojyoti Mukherjee, Anindita Bhowmick, **Goutam Brahmachari*** (2023). Mechanochemical solvent-free one-pot synthesis of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles through a copper(I)-catalyzed click reaction. *Chemistry – a European Journal*, **29**, e202302539. [Print ISSN:0947-6539; Online ISSN:1521-3765); IF 5.02 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript

6.	Indrajit Karmakar and **Goutam Brahmachari*** (2022), Electrochemical and mechanochemical synthesis of dihydrofuro[3,2-*c*]chromenones via intramolecular C_{sp3}–H cross-dehydrogenative oxygenation within warfarin frameworks: an efficient and straightforward dual approach. *Green Chemistry*, **24**, 2825-2838. [Print ISSN: 1463-9262; OnlineISSN: 1463-9270; IF 9.2 (2024); **Q1**] (***Selected as a 2022 HOT Green Chemistry Article***)	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript
7.	Mullicka Mandal and **Goutam Brahmachari*** (2022), Visible light-promoted intramolecular C-O bond formation via Csp3-H functionalization: a straightforward synthetic route to biorelevant dihydrofuro[3,2-*c*]chromenone derivatives. *The Journal of Organic Chemistry*, **87**, 4777-4787. [Print Edition ISSN: 0022-3263; Web Edition ISSN: 1520-6904; IF 3.6 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript
8.	Goutam Brahmachari*, Indrajit Karmakar and Pintu Karmakar (2021), Catalyst- and solvent-free C*sp2*−H functionalization of 4-hydroxycoumarins *via* C-3 dehydrogenative aza-coupling under ball-milling. *Green Chemistry*, **23**, 4762-4770. [Print ISSN: 1463-9262; OnlineISSN: 1463-9270; IF 9.2 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript
9.	**Goutam Brahmachari*** (2020). Catalyst- and additive-free decarboxylative C-4 phosphorylation of coumarin-3-carboxylic acids at ambient conditions. *Advanced Synthesis & Catalysis*, **362**, 5411-5421. [Print ISSN:1615-4150; Online ISSN:1615-4169; IF 4.0 (2024); **Q1**]	Single-authored
10.	**Goutam Brahmachari***, Nayana Nayek, Indrajit Karmakar, Khondekar Nurjamal, Swapan K. Chandra, Anindita Bhowmick (2020). Series of functionalized 5-(2-arylimidazo[1,2-*a*]pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-diones: a water-mediated three-component catalyst-free protocol revisited. *The Journal of Organic Chemistry*, **85**, 8405-8414. [Print Edition ISSN: 0022-3263; Web Edition ISSN: 1520-6904; IF 3.6 (2024); **Q1**]	Conceptualization of the problem, design and development of the strategy, monitoring, data analyses, and writing and editing of the manuscript

18. Detailed List of Publications

Publication Summary at a glance

Total publications: 287 (as of 26.08.2025)	***Others***
Original Research Articles: **166** Accounts/Featured articles: **03** Scientific Reviews: **27** Educational/popular articles/reports: **03** Editorials in guest-edited journal issues: **04** Invited Book Chapters in edited volumes: **56** Books: **28**	**Conference Proceedings: 160** **Invited Talks: About 60**

18 a) Invited Accounts/Featured articles [showing latest impact factor (IF(2024)]

3. **Goutam Brahmachari*** (2024). Practice of green chemistry strategies in synthetic organic chemistry: a glimpse of our sincere efforts in green chemistry research. *Chemical Communications*, **60**, 8153-8169. doi: 10.1039/D4CC02249A (***Invited Feature Article***) [IF 4.2 (2024)]

2. **Goutam Brahmachari*** (2024). Photo- and electrochemical organic transformations involving radical pathway: a retrospection of our green chemistry-inspired synthetic endeavors. *Synlett,* **35**, 2273-2288. doi: 10.1055/s-0043-1775382 (***Invited Personal Account***) [IF 1.7 (2024)]

1. **Goutam Brahmachari*** (2016). Designing of organic transformations at ambient conditions: our sincere efforts to the cause of green chemistry practice. *Chemical Record*, **16**, 98-123. doi: 10.1002/tcr.201500229 (***Invited Personal Account***) [IF 7.5 (2024)]

18 b) Original Research Papers Published [showing latest impact factor (IF(2024)]

166. Pintu Karmakar, **Goutam Brahmachari*** (2025). Sono-And Mechanochemistry-Assisted Dual Strategies for Cyanomethylation of Carboxylic Acids: Robust and Practical Synthetic Protocols to a Diverse Series of Cyanomethyl Esters. *Chemistry – a European Journal*, e-first article (Very Important paper), DOI: 10.1002/chem.202501966 [IF 5.02 (2024)]

165. Koushik Pal, Pintu Karmakar, **Goutam Brahmachari*** (2025). Mechanochemistry-driven solvent-free synthesis of biologically relevant diversely substituted 2-amino-1,4-naphthoquinones. *RSC Mechanochemistry*, e-first article, DOI: 10.1039/D5MR00068H

164. Pintu Karmakar, Atanu Diger, **Goutam Brahmachari*** (2025). Mechanochemistry-Driven Synthetic Approach for Halogenated Derivatives of 2-Amino-1,4-Naphthoquinones, Indoles, Indazoles and Coumarins. *Asian Journal of Organic Chemistry*, 14, e202500428. [IF 2.7 (2024)]

163. Debojyoti Mukherjee, Indrajit Karmakar, **Goutam Brahmachari*** (2025). Sono- and mechanochemical dual syntheses of bio-relevant aryldiazenyl-substituted phosphine oxides/phosphonates via P(O)-H functionalisation. *Green Chemistry*, **27**, 2565-2577. [IF 9.2 (2024)]

162. Anindita Bhowmick, **Goutam Brahmachari*** (2025). Iron(III) triflate-assisted skeletal rearrangement of warfarin framework: A direct synthetic route to a diverse series of biorelevant flavone-coumarin molecular hybrids. *Asian Journal of Organic Chemistry*, **14**, e202400676. [IF 2.7 (2024)]

161. **Goutam Brahmachari**,* Sasadhar Majhi, Sohini Chatterjee, Bhagirath Mandal, Narayan Chandra Mandal, and Suchandra Chatterjee (2025). Chemical composition and biological activities of natural essential oil extracted from flowers of *Cassia sophera* Linn. *Current Indian Science*, **3**, e2210299X338639.

160. T. Yadav*, I. Karmakar, A. K. Vishwkarma, E. Shakerzadeh, **Goutam Brahmachari***, Pramod K. Singh, N. Masmali, S. N. F. Yusuf (2025). The impact of bromine substitution on molecular structure and spectroscopic properties of (*E*)-3-(2-phenylhydrazineylidene) chromane-2,4-dione. *Journal of the Indian Chemical Society*, **102**, 101531. [IF 3.4 (2024)]

159. Debojyoti Mukherjee, Indrajit Karmakar, **Goutam Brahmachari*** (2024). Electro- and mechanochemical strategy as a dual synthetic approach for biologically relevant 3-nitro-imidazo-[1,2-*a*]pyridines. *The Journal of Organic Chemistry*, **89**, 12071-12084. [IF 3.6 (2024)]

158. Indrajit Karmakar, **Goutam Brahmachari*** (2024). Electro-rearranged di-functionalization of 4-hydroxy-α-benzopyrones. *The Journal of Organic Chemistry*, **89**, 10524-10537. [IF 3.6 (2024)]

157. **Goutam Brahmachari**,* Indrajit Karmakar, Mullicka Mandal, Bhagirath Mandal (2024). Ultrasound-assisted catalyst-free Knoevenagel condensation of carbonyl compounds with C – H acids in water. *Current Green Chemistry*, **11**, 210-220. [IF 1.7 (2024)]

156. Pintu Karmakar, Indrajit Karmakar, Debojyoti Mukherjee, Anindita Bhowmick, **Goutam Brahmachari*** (2023). Mechanochemical solvent-free one-pot synthesis of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles through a copper(I)-catalyzed click reaction. *Chemistry – a European Journal*, **29**, e202302539. [IF 5.02 (2024)]

155. Anindita Bhowmick, **Goutam Brahmachari*** (2023). C(sp)–C(sp3) Bond formation through ligand- and additive-free CuO-mediated decarboxylative direct cross-coupling of coumarin-/chromone-3-carboxylic acids and terminal alkynes. *Organic Letters*, **25**, 7095-7099. [IF 5.0 (2024)]

154. A. K. Vishwkarma, T. Yadav,* E. Shakerzadeh, I. Karmakar, **Goutam Brahmachari**,* A. Kumar, P. K. Singh, M. Srivastava, A. Pathak (2023). Structural and vibrational spectroscopic signature of a bio-relevant molecule: (*E*)-3-(2-(4-methoxyphenyl)-hydrazineylidene)chromane-2, 4-dione. *Computational and Theoretical Chemistry*, **1229**, 114306. [IF 3.0 (2024)]

153. S. Dutta, S. Mahalanobish, S. Saha, M. Mandal, S. Begam, P. Sadhukhan, S. Ghosh, **Goutam Brahmachari**, P. C. Sil (2023). Biological evaluation of the novel 3,3′-((4-nitrophenyl)methylene)bis(4-hydroxy-2*H*-chromen-2-one) derivative as potential anticancer agents via the selective induction of reactive oxygen species-mediated apoptosis. *Cellular Signalling*, **111**, 110886. [IF 3.7 (2024)]

152. Pintu Karmakar, Indrajit Karmakar, Debopam Pal, Suravi Das, **Goutam Brahmachari*** (2023). Electrochemical regioselective C(*sp*2)–H selenylation and sulfenylation of substituted 2-amino-1,4-naphthoquinones. *The Journal of Organic Chemistry*, **88**, 1049-1060. [IF 3.6 (2024)]

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150. Nayana Nayek, **Goutam Brahmachari*** (2023). Visible-light-mediated self-sensitized oxidative and regioselective C(sp2)−H selenylation and sulfenylation of substituted 2-amino-1,4-naphthoquinones. *European Journal of Organic Chemistry*, **26**, e202201343. [IF 2.7 (2024)]

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4 **Goutam Brahmachari*** and Dilip Gorai (2006). Recent Developments in the Research of Naturally Occurring Flavonoids: An Overview, In: *Chemistry of Natural Products: Recent Trends & Developments*, Goutam Brahmachari (Editor), Research Signpost, Trivandrum, Kerala, India, pp.61-159. (ISBN: 81-308-0140-X)

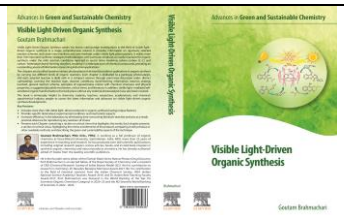
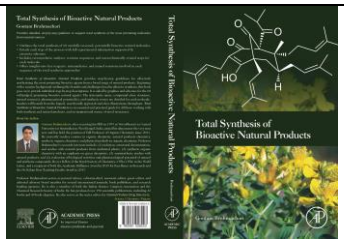
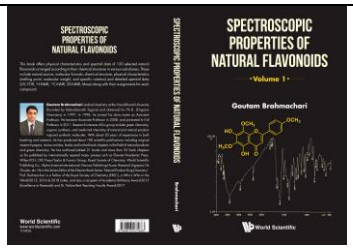
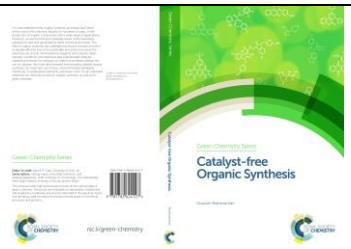
3 **Goutam Brahmachari*** (2006). Prospects of Natural Products Research in the 21st Century: A Sketch, In: *Chemistry of Natural Products: Recent Trends & Developments*, Goutam Brahmachari (Editor), Research Signpost, Trivandrum, Kerala, India, pp.1-22. (ISBN: 81-308-0140-X)

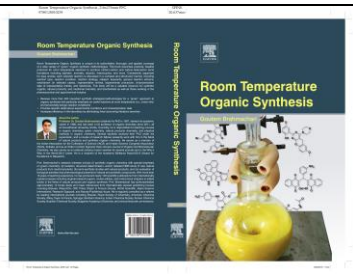
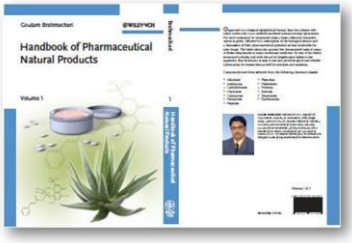
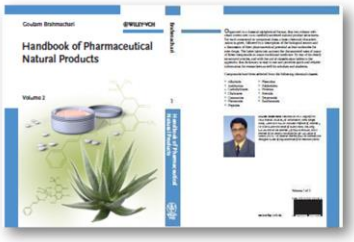
2 **Goutam Brahmachari*** (2006). Antioxidants of Flowering Plants. In: *Floriculture, Ornamental and Plant Biotechnology: Advances and Topical Issues (1st Edition)*, Vol. IV, Teixeira da Silva JA (Editor), Global Science Books, London, UK, PP-373-378. (ISBN: 4-903313-09-3)

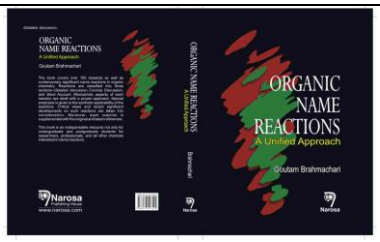
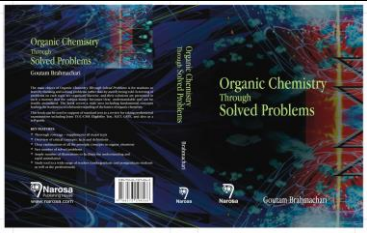
1 **Goutam Brahmachari*** (2005). Progress in the Research of Naturally Occurring Xanthones: Tetraoxygenated Constituents. In: *Recent Progress in Medicinal Plants*, Vol. 14, pp. 99-194, (Editors. J.N. Govil, V.K. Singh & K. Ahmed), Studium Press LLC, Texas, USA. (ISBN: 9780976184966)

18 g) Books (authored and edited)

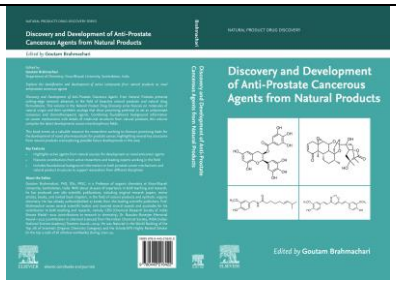
(I) Single-authored books

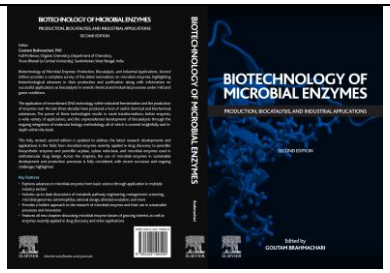
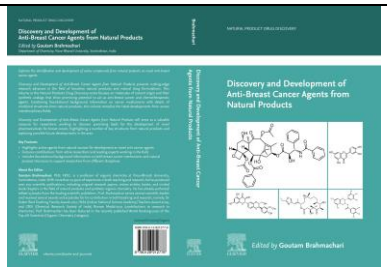
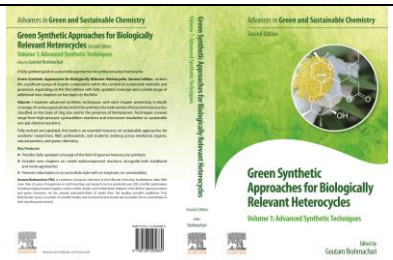
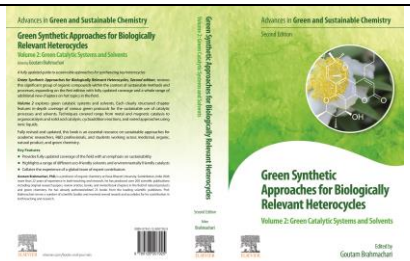
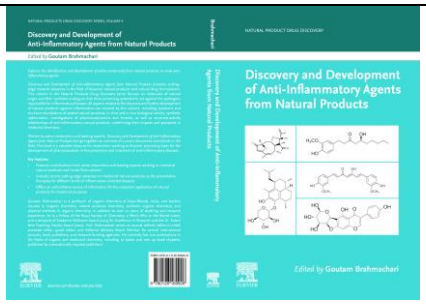
Sl. No.	Book Cover	Book Details
9		**Visible Light-Driven Organic Synthesis** (*with a foreword by Prof. Lutz Ackermann*), 1st Edn., Elsevier, Amsterdam, The Netherlands, August 2024. ISBN: 978-0-323-95893-6 (Print); eBook ISBN: 9780323958943
8		**Total Synthesis of Bioactive Natural Products** (*with a foreword by Prof. Srinivasan Chandrasekaran*), Academic Press (Elsevier), Amsterdam, The Netherlands, May 2019; ISBN: 9780081028223
7		**Spectroscopic Properties of Natural Flavonoids** (*with a foreword by Prof. Amit Basak*), World Scientific Publishing Co., Singapore, October 2018; ISBN: 978-981-3275-68-3
6		**Catalyst-Free Organic Synthesis** (under Green Chemistry Series; Book No. 51), The Royal Society of Chemistry, Cambridge, London, November 2017, ISBN: 978-1-78262-412-7. ***Book review:*** "…….This book Catalyst-free organic synthesis, by Goutam Brahmachari, is very comprehensive, and has exhibited the state-of-the-art technology in green chemistry. This book is a great piece of technical literature and unique in regards to being about "Catalyst-free" as there are many books on "catalyst-based organic synthesis". ……The book provides a broad overview of state-of-the-art catalyst-free reactions in organic synthesis. It is strongly recommended for chemical researchers as well as for interested teachers and students, especially those who are involved in catalysis' (*Green Process and Synthesis*, 2018, 7, 180, https://doi.org/10.1515/gps-2017-0184) reviewed by Prof. Can Jin: Zhejiang University of

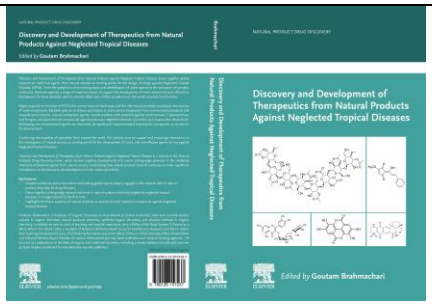
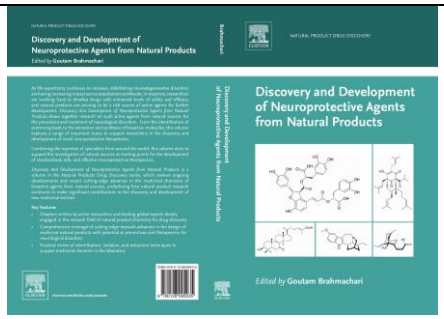
		Technology, Hangzhou 310014, P.R. China; and Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, 5612 AP Eindhoven, The Netherlands.
5		**Room Temperature Organic Synthesis** (*with a foreword by Prof. Paul Anastas*), Elsevier, Amamsterdam, The Netherlands, March 2015; ISBN: 9780128010259.
4		**Handbook of Pharmaceutical Natural Products - Vol. 1** (Hardcover), 1st Edition, 2010. XX, 926 Pages, ISBN-10: 3-527-32148-9; ISBN-13: 978-3-527-32148-3. Publisher: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.
3		**Handbook of Pharmaceutical Natural Products - Vol. 2** (Hardcover), 1st Edition, 2010. XX, 926 Pages, ISBN-10: 3-527-32148-9; ISBN-13: 978-3-527-32148-3. Publisher: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. ***Book Revew-1.*** "…the author has succeeded in compiling an impressive and highly informative reference text on many pharmaceutically relevant natural products. I would recommend this book to everyone involved in research with biologically active natural products as a convenient and practical source of high quality information….." (*ChemMedChem*, 2010, 5, 10, 1788-1789) reviewed by Prof. Dr. Karl-Heinz Altmann, ETH Zrich (Switzerland). ***Book Review-2.*** "… a useful addition to the bookshelf of every natural material specialist…" – *Pharmazie in unserer Zeit*, 2010, 39(5), 415 (review in German) by Prof. Dr. Thomas Winckler, Jena (Germany). ***Book Review-3.*** "…..This book is clearly for specialists, the natural product chemist and the pharmaceutical chemist… I do not know whether

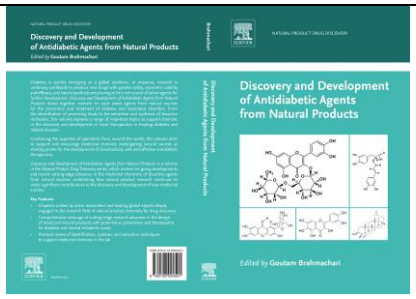
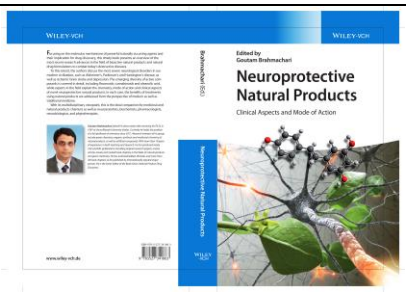
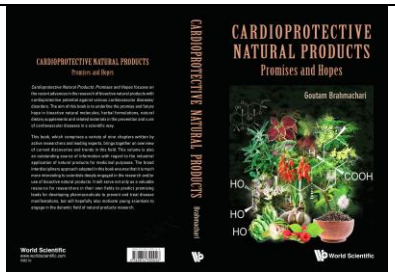
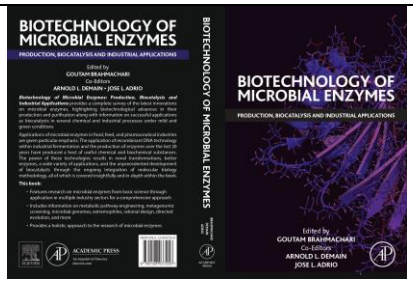
		Goutam Brahmachari intends a revised edition in the future but I am sure there will be an ongoing demand for a book like this" (*Reference Reviews*, 2011, 25, 3, 42-43) by John Goodier, Consultant, Goldhawk Information, London, UK. Visit: http://www.wiley-vch.de/publish/en/books/ISBN3-527-32148-9/
2		**Organic Name Reactions: A Unified Approach**, (*with a foreword by Prof. S. Chandrasekaran*), Alpha Science International Ltd., Oxford, U.K., 2006 (ISBN: 1-84265-304-0); co-published by Narosa Publishing House Private Ltd., New Delhi, India, 2006 (ISBN: 81-7319-719-2), Reprints 2007, 2009, 2011, 2012, 2014, 2016, 2017, 2021.
1		**Organic Chemistry Through Solved Problems** (*with a foreword by Prof. Swapnadip Thakur*), Narosa Publishing House Private Ltd., New Delhi, India, 2007 (ISBN: 81-7319-816-0), Reprints 2009, 2011, 2012, 2014, 2017.

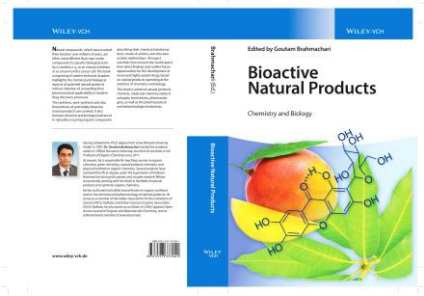
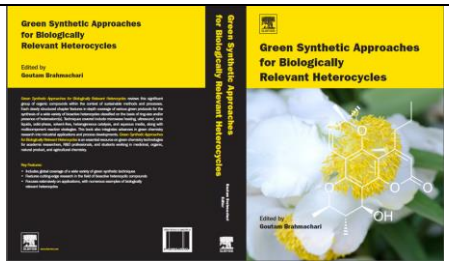
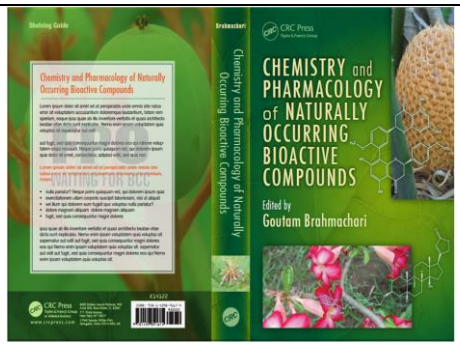
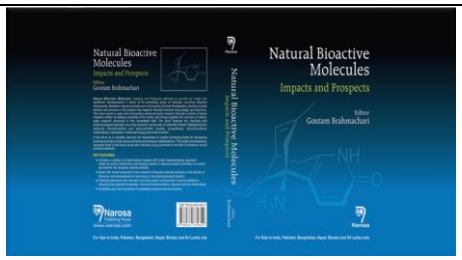
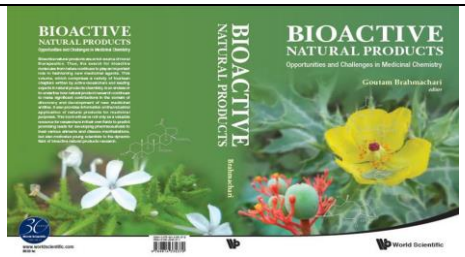
(II) Edited Books

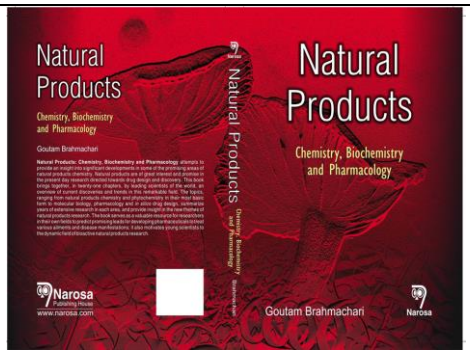
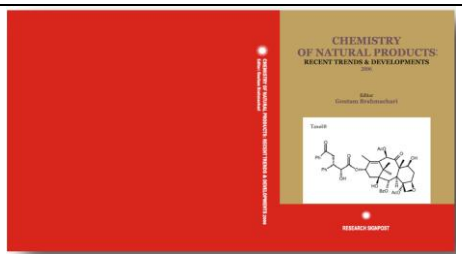
Sl. No.	Book Cover	Book Details
19		**Discovery and Development of Anti-Prostate Cancer Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 6)** (*with foreword by* Prof. Bimal K Banik), Elsevier, February 2025. ISBN: 9780443218422 (Print); eBook ISBN: 9780443218439

18		**Biotechnology of Microbial Enzymes: Production, Biocatalysis and Industrial Applications**, 2nd Edition, Academic Press, London, Elsevier, 2023, ISBN: 9780443190599
17		**Discovery and Development of Anti-Breast Cancer Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 5)** (*with foreword by* Prof. Subrata Ghosh and Prof. Ramapati Tripathi), Elsevier, 2021. ISBN: 9780128212776
16		**Green Synthetic Approaches for Biologically Relevant Heterocycles – Volume 1**, (*with a foreword by Prof. Dr. Peter Licence*), 2nd edition, **Elsevier Inc.**, Waltham, MA, USA, 2021 (ISBN: 978-0-12-820586-0)
15		**Green Synthetic Approaches for Biologically Relevant Heterocycles – Volume 2**, (*with a foreword by Prof. Dr. Vinod K. Singh*), 2nd edition, **Elsevier Inc.**, Waltham, MA, USA, 2021 (ISBN: 978-0-12-820792-5)
14		**Discovery and Development of Anti-Inflammatory Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 4)** (*with a foreword by* Prof. G. Mugesh, IISc, Bangalore), Elsevier, 2019. ISBN: 9780128169926

13		**Discovery and Development of Therapeutics from Natural Products Against Neglected Tropical Diseases (Natural Product Drug Discovery Series – Vol. 3)** (*with a foreword by Prof. Alan Fairlamb, University of Dundee, UK*), Elsevier, April, 2019. ISBN: 978-0-12-815723-7
12		**Discovery and Development of Neuroprotective Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 2)** (*with a foreword by* Dr. Volkan Kisakürek, Zürich, Switzerland), Elsevier, 2017. ISBN: 9780128095935 (June, 2017) **Book Review 1**. (E. A. Abourashed, *Journal of Natural Products*, **2018**, *81*, 1917-1918) "….As health care providers continue to seek new and effective approaches for managing neurodegenerative diseases, Discovery and Development of Neuroprotective Agents from Natural Products attempts to narrow the drug discovery gap through its current and comprehensive coverage of the subject matter. The book provides a well-balanced content that spans major neurodegenerative diseases and potential therapeutic agents that may be obtained from natural sources and/or synthetic routes based on naturally occurring lead compounds…..The book should appeal to a broad audience with diverse backgrounds including chemistry, biology, pharmacy, and medicine. It can also be a valuable resource for researchers, academicians, and graduate students. In addition to enjoying the book's content, its readers will probably be able to identify viable research directions for the discovery and development of new and promising neuroprotective agents." Prof. Ehab A. Abourashed, Medical College of Wisconsin School of Pharmacy, Milwaukee, Wisconsin, United States. **Book Review 2**. (S. Chandrasekhar, *Current Science*, **2018**, *115*, 2164-2165) "This book discusses about recent developments in the area of neuroprotective natural products with respect to their isolation, characterization, and their pharmaceutical applications in the area of neurodegenerative diseases……..Overall the book gives a detailed insight into natural products as neuroprotective agents and is recommended for colleges/institutions and industries working in the

		areas of natural products isolation and/or in the exploration of compounds for their activity on the central nervous system." Prof. Srivari Chandrasekhar, CSIR-Indian Institute of Chemical Technology, Hyderabad, India.
11		**Discovery and Development of Antidiabetic Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 1)** (*with a foreword by Dr. David G. I. Kingston and Dr. Arnold L. Demain*), Elsevier, 2016. ISBN: 9780128094501
10		**Neuroprotective Natural Products: Clinical Aspects and Mode of Action**, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2017 (ISBN: 978-3527341863).
9		**Cardioprotective Natural Products: Promises and Hopes**, (*with a foreword by Dr. Bradley K. McConnell, University of Houston, USA*), World Scientific Publishing Co., Singapore, November 2017 (ISBN: 978-981-3231-15-3)
8		**Biotechnology of Microbial Enzymes: Production, Biocatalysis and Industrial Applications** (ISSBN: 978-0-12-803725-6), **Academic Press**, London, Elsevier, 2016 (co-editors: Dr. Arnold L. Demain and Dr. Jose L. Adrio).

7		**Bioactive Natural Products: Chemistry & Biology** (*with a foreword by Prof. Bimal K Banik*), **Wiley-VCH Verlag GmbH & Co. KGaA**, Weinheim, Germany, 2015 (ISBN: 9783527337941).
6		**Green Synthetic Approaches for Biologically Relevant Heterocycles**, (*with a foreword by Prof. Sciott McN. Sieburth*), **Elsevier Inc**., Waltham, MA, USA, 2014 (ISBN: 978-0-12-800700-0).
5		**Chemistry and Pharmacology of Naturally Occurring Bioactive Compounds**, (*with a foreword by Prof. Raphael Mechoulam and Prof. Takuo Okuda*), **CRC Press/Taylor Francis Group**, LLC, USA, 2013 (ISBN: 978-1-4398-9167-4).
4		**Natural Bioactive Molecules: Impacts & Prospects**, (*with a foreword by Prof. Dr. Arnold Demain*), Alpha Science International Ltd., Oxford, U.K., 2013 (ISBN: 978-1-84265-780-5); co-published by Narosa Publishing House Private Ltd., New Delhi, India, 2013 (ISBN: 978-81-8487-235-4).
3		**Bioactive Natural Products: Opportunities and Challenges in Medicinal Chemistry**, (*with a foreword by Dr. David J. Newman*), World Scientific Publishing Co., Singapore, 2011 (ISBN: 978-981-4335-37-9).

2		**Natural Products: Chemistry, Biochemistry and Pharmacology**, (*with a foreword by Prof. Jorg Heukelbach and Prof. Ricke Speare*), Alpha Science International Ltd., Oxford, U.K., 2009 (ISBN: 978-1-84265-450-7); co-published by Narosa Publishing House Private Ltd., New Delhi, India, 2009 (ISBN: 978-81-7319-886-1).
1		**Chemistry of Natural Products: Recent Trends and Developments**, (*with a foreword by Dr. Manksukh C. Wani*), Research Signpost, Trivandrum, Kerala, India 2006 (ISBN: 81-308-0140-X).

19. Scientific Contributions of Professor Goutam Brahmachari

(a) In Brief (50 words)

Professor Goutam Brahmachari has made a significant contribution to synthetic organic chemistry, particularly in developing effective and practical methodologies for carbon-carbon and carbon-heteroatom bond formation in constructing medicinally important heterocyclic scaffolds using C-H functionalization, cascade and cross-coupling approaches. In addition, Professor Brahmachari also made outstanding contributions to the chemistry of natural products.

(b) Scientific contribution (200 words)

In his longstanding professional and scientific career (27 years), Professor Goutam Brahmachari has demonstrated original and significant research contributions in organic chemistry. His main research activities include the development of new synthetic methodologies, green chemistry, and natural product chemistry. Brahmachari's group contributed significantly to developing effective and practical synthetic methods for carbon-carbon and carbon-heteroatom bond formation in constructing medicinally important heterocyclic scaffolds using C-H functionalization, cascade and cross-coupling approaches. In addition, Prof. Brahmachari also made outstanding contributions to natural product chemistry by unearthing the chemical profiles of several traditionally used Indian medicinal plants, studying their chemistry and biology, and thus presenting novel phytochemicals of interest. He has published 166 original research papers and 37 review/feature articles and supervised 20 Ph.D. students so far. Besides his original research, Prof. Brahmachari has contributed much by authoring and editing many highly acclaimed reference books (28) and book chapters (56) in the relevant areas. He serves the community truly.

In recognition of his academic and scientific contributions (with current citations 7507, *h*-index 44, and *i*-10: 141, as of 26.08.2025), Prof. Brahmachari has been conferred with several awards and accolades, including being elected Fellow of the Royal Society of Chemistry (2017), Dr. Satyajit Chakraborti Memorial Award-2025 (global contribution to chemical science) from IEM, Kolkata, CRSI Bronze Medal-2021, Dr. Basudev Banerjee Memorial Award-2021, INSA Teachers Award-2019, and Founder Series Editorship of Elsevier Book Series, '*Natural Products Drug Discovery*'. Prof. Brahmachari has

also been featured in the World Ranking of the Top 2% Scientists in 2020-24, AD Scientific World Ranking of Scientists-2022-2024, as the ScholarGPS Highly Ranked (in the top 0.05%) Scholar-2022-2024.

(c) Scientific contribution in extended form

During the twenty-seven years of his professional and scientific career in a well-regarded Central University in India, Professor Goutam Brahmachari, *PhD, DSc., FRSC*, has executed commendable scientific endeavours with utmost sincerity in Chemical Sciences. Beyond serving the role of a university teacher in training and motivating thousands of his undergraduate and postgraduate students during this longstanding tenure to helping them to become successful human resources of our great nation in their fields (as teachers, chemists, scientists and molecular inventors), he has also been contributing in the domain of scientific knowledge concerned by dint of undertaking dedicated research programmes supported by the leading funding bodies in India, such as UGC, CSIR, SERB-DST and DBT. His main research contributions address the broad field of organic chemistry, categorized into two distinct sections: Synthetic Organic Chemistry, focusing on Green and Sustainable Chemistry, and *Natural Product Chemistry*. Brahmachari's primary research interests include (i) Synthetic organic chemistry, (ii) the Practice of green and sustainable chemistry, (iii) Bioactive natural products from traditionally used medicinal plants, (iv) Semi-synthetic studies with natural products, and (v) Evaluation of biological activities and pharmacological potential of natural and synthetic compounds.

Brahmachari's group contributed significantly to developing effective and practical synthetic methods for carbon-carbon and carbon-heteroatom bond formation in constructing medicinally important heterocyclic scaffolds using C-H functionalization, cascade and cross-coupling approaches. As part of his ongoing research in this domain, he has developed a legacy in practising green and sustainable chemistry by designing several distinct and innovative green protocols for many new series of bio-relevant heterocyclic scaffolds based on his views '*Benign by Design*'. His dedicated endeavour to the green and sustainable chemistry research programme focuses on energy-efficiency issues besides other usual greener aspects in designing relatively eco-friendly synthetic protocols for functional organic molecules. Using conventional energy sources (fossil fuels) is one of the major causes of environmental pollution, with all kinds of subsequent outcomes, including rapid depletion of traditional energy sources. In resonance with this view, his dedicated research programme aims to attain energy efficiency in performing a chemical reaction by carefully screening reaction conditions capable of carrying out a particular transformation at ambient conditions. Besides, designing catalyst-free synthetic processes is a somewhat challenging concept toward a safe, cost-effective, waste-free, simple, and sustainable environment! His research group has published a significant amount of research in designing room temperature-based and/or catalyst-free synthetic methods for biologically relevant organic scaffolds (satisfying recent trends in molecular hybridizations) without cooling and/or heating to make good use of Nature's spontaneous energy source to find out an effective way-out toward the steps in protecting our environment and its sustainability from the perspective of a chemical inventor. In addition, he and his team explored the practical applications of several green energy tools, such as ball-milling, ultrasound irradiation, visible light (including abundant sunlight) and electrosynthesis in developing new synthetic methodologies and their intriguing chemistry.

As a natural product chemist, he has unearthed chemical profiles of several traditionally used Indian medicinal plants, studied their chemistry and biology, and thus presented novel naturally occurring

leads and their derivatives for their further exploration in the field of ongoing research in drug discovery and development by the organic, medicinal and pharmaceutical chemists working globally in this remarkable area of prime interest. Besides his dedicated research in this remarkable field, he has also been contributing to this goal by serving as the founder series editor of the Elsevier book series, '*Natural Product Drug Discovery'*. In addition, he has also contributed to the theoretical/computational exploration of many of these novel natural and synthetic molecules and their X-ray crystallographic behaviour.

All such credentials are reflected in his **287** scientific publications, including original research papers (**166**), review/feature articles (**37**), books (**28**) and invited book chapters (**56**) in edited volumes in the field of organic synthesis and natural products, published from internationally reputed presses, including ACS, RSC, Elsevier, Wiley, Springer, Taylor & Francis, CSIR, and others. Dr. Brahmachari serves in several international journals as an editorial advisory board member and co-editor-in-chief for *Current Green Chemistry*. He guest-edited a number of of internationally reputed journals' special issues as well. He has been contributing regularly (focusing on green advances in the field since its 45th volume) to the RSC's SPR on Organophosphorus Chemistry – one of the most prestigious book series. In addition, he serves the scientific community professionally in many other ways; he also serves CRSI, IACS and ISCA as a life member and RSC as its Fellow. Dr. Brahmachari delivered invited/plenary/keynote lectures in several national and international seminars/conferences/workshops to motivate the next generation of chemists.

In addition to his original research contributions, Dr. Brahmachari is also deeply involved in authoring and editing major reference books with a motto to boost ongoing global research and contribute to knowledge in the existing domain. Such major reference works would guide and help advanced students and young researchers in the field. As mentioned in the publication list, Dr. Brahmachari has already produced quite a large number of such books (major references; authored and edited; **28** so far), which have been published by internationally reputed publishing houses, such as Academic Press, Elsevier, Wiley-VCH, CRC Press/Taylor & Francis, World Scientific, Alpha Science International, and the Royal Society of Chemistry. These books received forewords from internationally distinguished scientists, and many of these publications were also reviewed in reputed journals by eminent scholars. In the recent past, Dr. Brahmachari authored three land-marking books – *'Visible Light-Driven Organic Synthesis* (ISBN: 9780323958936)' (2024) and '*Room Temperature Organic Synthesis* (ISBN: 9780128010259)' (2015) from Elsevier, and '*Catalyst-free Organic Synthesis* (ISBN: 978-1-78262-412-7) (2018) from RSC under their Green Chemistry Series) for the first time of their kinds in the global scientific platform, and a two-volume set edited book '*Green Synthetic Approaches for Biologically Relevant Heterocycles – Vol. 1 & 2* (ISBN: 978-0-12-820586-0 & ISBN: 978-0-12-820792-5)' (2021) from Elsevier. Dr. Brahmachari has also produced **56** authoritative book chapters in edited volumes.

He has produced **287** independent scientific publications, including original research papers, review articles, books, and invited book chapters in synthetic organic chemistry and natural products chemistry. Twenty students completed their PhDs under Prof. Brahmachari's supervision. ***His current h-index is 44, i-10 is 141, and total citations are 7,507*** [as of 26.08.2025; https://scholar.google.co.in/citations?user=aj7NvGQAAAAJ&hl=en]. In recognition of his academic and scientific contributions, Prof. Brahmachari has been conferred with several awards and accolades, including elected Fellow of the Royal Society of Chemistry, Acharya P. C. Ray Memorial Lecture Award-2025 from the Indian Science News Association (ISNA), Kolkata, Dr. Satyajit Chakraborti Memorial Award-2025 (global contribution to chemical science) from the Institute of Engineering and Management, Kolkata, Kolkata, CRSI Bronze Medal-2021, Dr. Basudev Banerjee Memorial Award-

2021 (Contribution in chemical sciences) from the Indian Chemical Society, INSA Teachers Award-2019, Founder Series Editorship of Elsevier Book Series, '*Natural Product Drug Discovery*'. Prof. Brahmachari has also been featured in the World Ranking of the Top 2% Scientists (Organic Chemistry Category) in 2020-24 (both in whole career and single years), in the AD Scientific World Ranking of Scientists-2022-2024, as the ScholarGPS Highly Ranked Scholar-2022-2024 (Lifetime, securing a position in the top 0.05% ao all scholars worldwide).

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Sono-And Mechanochemistry-Assisted Dual Strategies for Cyanomethylation of Carboxylic Acids: Robust and Practical Synthetic Protocols to a Diverse Series of Cyanomethyl Esters

Pintu Karmakar[a] and Goutam Brahmachari*[a]

This paper is dedicated to Prof. Srinivasan Chandrasekaran on the occasion of his forthcoming 80th birthday on 15th November, 2025

We herein disclose a dual synthetic approach involving sonochemical and mechanochemical strategies for a diverse series of cyanomethyl esters of carboxylic acids. Both synthetic protocols offer a straightforward, efficient, and practical alternative to preparing this important class of biologically and synthetically promising organic compounds. Significant advantages of the newly developed methods include mild reaction conditions, avoidance of any metal catalysts and external oxidants, shorter reaction times (in minutes), good to excellent yields, broad substrate scope and tolerance of other various functional groups, gram-scale applicability, and reusability of the solid surface.

1. Introduction

In synthetic organic chemistry, nitrile or cyano compounds are promising building blocks for constructing a diverse array of important complex molecular structures.[1] In addition, these compounds act as valuable synthetic intermediates, providing easy access to versatile groups of organic compounds, including amines, amides, carbonyls, carboxylic acids, esters, and many others.[2,3] Hence, methodologies for introducing the cyano group into an organic compound have been of significant interest to synthetic chemists.

A literature survey reveals that the cyano functionality plays an important role in demonstrating biological potency in bioactive natural compounds and their synthetic analogues. For example, cyanogenic glycosides, such as amygdalin and linamarin, serve as chemical defense agents in the plant kingdom.[4] Another group of compounds containing cyano-substituted alkaloidal architectures, such as cytisine derivatives and cyanocycline A, exhibit potent biological activities.[5] Furthermore, certain marine-derived natural products, such as axisonitrile-3, possess either nitrile or isonitrile functionalities crucial to their antimicrobial and anticancer properties.[6] A few selected examples of bioactive cyano group-containing molecules are shown in Figure 1.[7]

The direct functionalization of carboxylic acids represents a powerful strategy for constructing structurally diverse and value-added molecules from readily available precursors. Directly incorporating a cyanomethyl group into acid frameworks is especially appealing, as the strategy offers a straightforward way to develop targeted cyanomethyl ester derivatives. Over the last few years, with the discovery of the cyanomethylation process, a variety of cyanomethylating reagents like acetonitrile and its derivatives,[8,9] trimethylsilylacetonitrile (TMSAN)[10] have emerged. However, these cyanomethylating agents have certain limitations, particularly requiring harsh reaction conditions and/or nonapplicability toward a wide range of substrates. Recently, bromoacetonitrile has thus successfully emerged as a cost-effective and efficient cyanomethylating agent for organic substrates.[11]

Our comprehensive literature survey disclosed just one synthetic methodology for cyanomethylation of carboxylic acids; in 2015, Wan and co-workers[12] reported a cyanomethylation strategy for carboxylic acids using cyanoacetic acid as the reagent in the presence of *n*-Bu_4NI (TBAI) as a catalyst, *tert*-BuOOH as an external oxidant, and NaOAc as an additive, under heating at 80 °C for 12 hours (Scheme 1a). With the inherent synthetic elegance, this method is still associated with several limitations, particularly using external oxidants and additives to the catalytic system, heating, and prolonged reaction time (12 hours). Hence, the design and development of facile and eco-friendly practical synthetic strategies to functionalize cyanomethyl esters is highly warranted. As part of our green chemistry-driven organic synthesis,[13] we have been successful in exploring a dual approach, both sonochemical and mechanochemical strategies, to access a huge array of diversely substituted cyanomethyl carboxylates, as outlined in Scheme 1b. These newly developed methods offer several notable advantages, including metal-free synthesis, avoidance of any additives, external oxidants, and solvents (in the case of mechanochemistry), short reaction times (in minutes), broad substrate scopes, good to excellent yields (up to 96%), reusability of the solid surface, and gram-scale synthetic applications. The applications of sonochemical[14]

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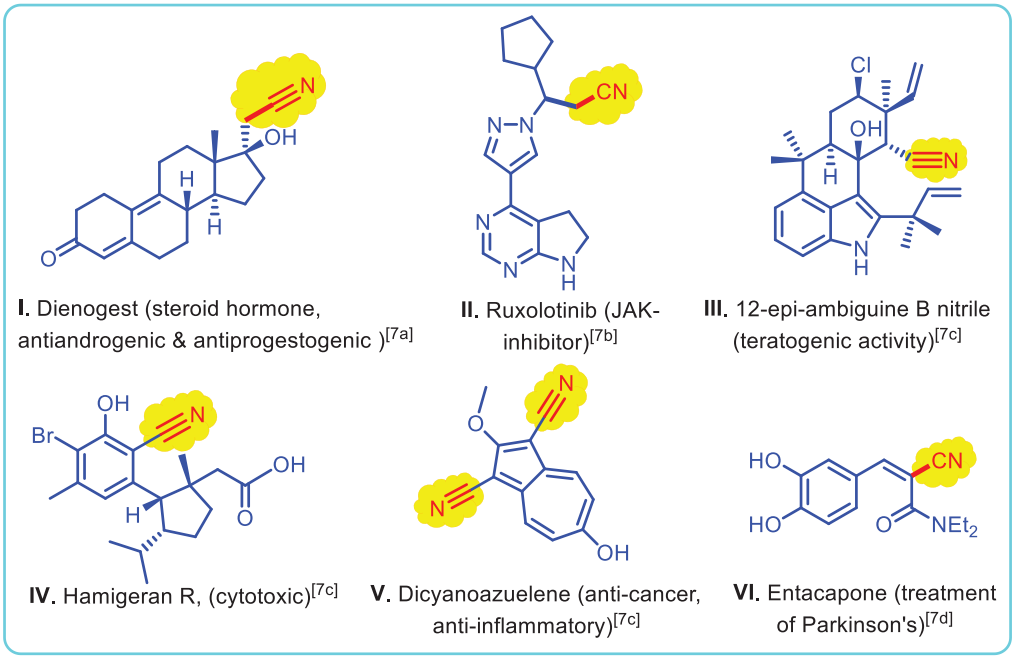
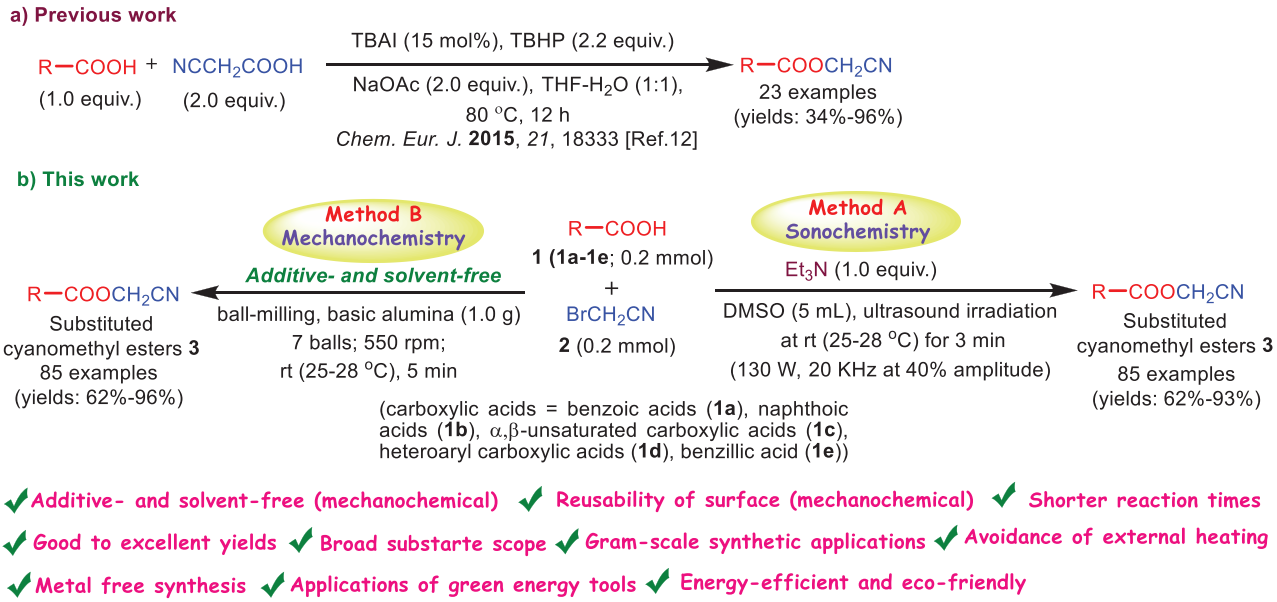


Figure 1. Representative examples of a few bioactive natural and synthetic nitrile drug molecules[7].



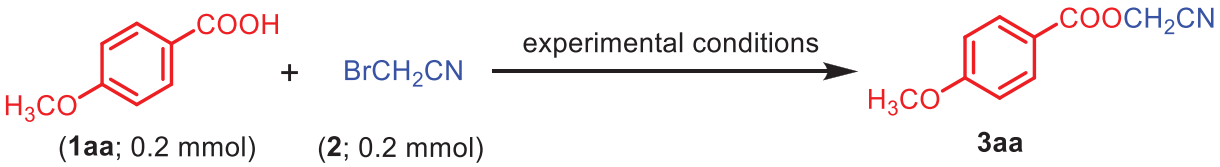
Scheme 1. Dual synthetic approaches (sono- and mechanochemical) for diversely substituted cyanomethyl esters **3**.

and mechanochemical[15] strategies are emerging techniques in synthetic organic chemistry.

2. Results and Discussion

We envisioned that the cyanomethylation reaction between a carboxylic acid and bromoacetonitrile should proceed through a nucleophilic substitution, which might need a base, and accordingly, we performed our model reaction by stirring the mixture of *p*-methoxybenzoic acid (**1aa**; 0.2 mmol), bromoacetonitrile (**2**, 0.2 mmol), and triethylamine (TEA, as a base; 0.2 mmol, 1.0 equiv.) in dimethyl sulfoxide (DMSO; 5 mL) under ambient conditions for 12 hours (720 minutes), when we were successful in isolating the desired product, cyanomethyl 4-methoxybenzoate (**3aa**), in a moderate yield of 42% (Table 1, entry 1). With this somewhat encouraging observation, we then carried out a series of six reactions in six different solvents, such as acetonitrile (CH_3CN), 1,2-dichloromethane (1,2-DCM), *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, ethanol, and water, keeping other reaction parameters unchanged, and found that none of these solvents is superior to dimethyl sulfoxide (DMSO) (Table 1, entries 2–7).

Table 1. Optimization of Reaction Conditions under Ultrasonication[a],[b]



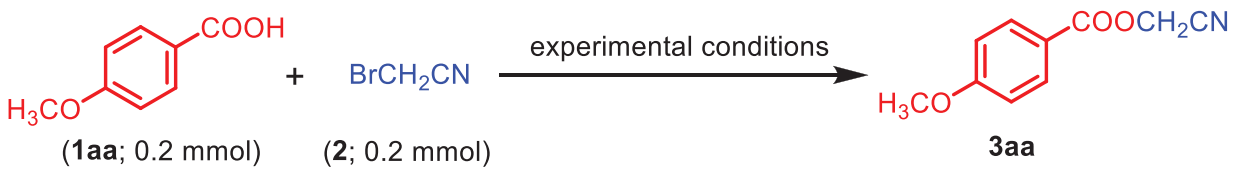
Entry	Cyanomethylating agent [2] [equiv.]	Additive [equiv.]	Solvent [5 mL]	Conditions [amplitude %]	Time [minutes]	Yield [%][a],[b]
1	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMSO	stirring at rt	240	42
2	$BrCH_2CN$ (1.0)	Et_3N (1.0)	CH_3CN	stirring at rt	240	21
3	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DCM	stirring at rt	240	13
4	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMF	stirring at rt	240	trace
5	$BrCH_2CN$ (1.0)	Et_3N (1.0)	1,4-dioxane	stirring at rt	240	–
6	$BrCH_2CN$ (1.0)	Et_3N (1.0)	EtOH	stirring at rt	240	trace
7	$BrCH_2CN$ (1.0)	Et_3N (1.0)	H_2O	stirring at rt	240	27
8	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMSO	ultrasound (30%)	5	73
9	**$BrCH_2CN$ (1.0)**	**Et_3N (1.0)**	**DMSO**	**ultrasound (40%)**	**3**	**89**
10	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMSO	ultrasound (50%)	3	68
11	$BrCH_2CN$ (1.0)	–	DMSO	ultrasound (40%)	5	–
12	$BrCH_2CN$ (1.0)	Et_3N (0.5)	DMSO	ultrasound (40%)	3	63
13	$BrCH_2CN$ (1.0)	Et_3N (1.5)	DMSO	ultrasound (40%)	3	84
14	$BrCH_2CN$ (1.0)	*N*, *N*-DIPEA (1.0)	DMSO	ultrasound (40%)	3	73
15	$BrCH_2CN$ (1.0)	DABCO (1.0)	DMSO	ultrasound (40%)	3	47
16	$BrCH_2CN$ (1.0)	DBU (1.0)	DMSO	ultrasound (40%)	3	42
17	$BrCH_2CN$ (1.0)	^tBuOK (1.0)	DMSO	ultrasound (40%)	3	37
18	$BrCH_2CN$ (1.0)	K_2CO_3 (1.0)	DMSO	ultrasound (40%)	3	68
19	$BrCH_2CN$ (1.0)	Cs_2CO_3 (1.0)	DMSO	ultrasound (40%)	3	63
20	$BrCH_2CN$ (0.5)	Et_3N (1.0)	DMSO	ultrasound (40%)	3	68
21	$BrCH_2CN$ (1.5)	Et_3N (1.0)	DMSO	ultrasound (40%)	3	84
22	$BrCH_2CN$ (1.0)	Et_3N (1.0)	CH_3CN	ultrasound (40%)	5	47
23	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DCM	ultrasound (40%)	5	16
24	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMF	ultrasound (40%)	5	trace
25	$BrCH_2CN$ (1.0)	Et_3N (1.0)	Dioxane	ultrasound (40%)	5	–
26	$BrCH_2CN$ (1.0)	Et_3N (1.0)	EtOH	ultrasound (40%)	5	47
27	$BrCH_2CN$ (1.0)	Et_3N (1.0)	H_2O	ultrasound (40%)	5	52

[a] Reaction conditions: A mixture of *p*-methoxybenzoic acid (**1aa**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was reacted with Et_3N or other bases as additives in 5 mL of varying solvent(s) under either room temperature (rt, 25–28 °C) stirring or ultrasound irradiation (US; 130 W, 20 kHz at 30–50% amplitude).
[b] Isolated yields. *Note*: For the best-suited conditions (entry 9), the isolated yield indicates an average value of three repeated reactions.

Under this purview, we considered applying ultrasound irradiation to expedite the reaction with greater yield. Accordingly, we conducted our model reaction in dimethyl sulfoxide solvent under ultrasonication (130 W, 20 kHz) in three different amplitudes (viz. 30%, 40%, and 50%) and eventually isolated the target compound **3aa** with respective yields of 73%, 89%, and 68% within 3–5 minutes (Table 1, entries 8–10).

With these results at hand, we then performed a set of nine trial reactions with our model entry to elicit the impact of triethylamine by varying its equivalencies (Table 1, entries 11–13) and also replacing it with other bases (*viz*. *N*,*N*-DIPEA, DABCO, DBU, ^tBuOK, K_2CO_3, and Cs_2CO_3) (Table 1, entries 14–19). The experimental outcomes established triethylamine as the most suitable base for this transformation. Afterward, we conducted another set of eight more trial reactions with the model entry by varying the equivalency of bromoacetonitrile (Table 1, entries 20 and 21) and also by varying the solvents (viz. acetonitrile, 1,2-dichloromethane, *N*,*N*-dimethylformamide, 1,4-dioxane, ethanol, and water) (Table 1, entries 22–27), keeping the other reaction parameters intact. The results of these trial reactions suggested the optimum equivalency of bromoacetonitrile as 1.0 and dimethyl sulfoxide (DMSO) as the best-suited solvent for the transformation. Finally, we achieved the optimized reaction conditions for our model reaction in cyanomethylating a carboxylic

Table 2. Optimization of Reaction Conditions under Ball-Milling[a],[b]



Entry	Solvent [1.5 mL]	Additive [equiv.]	Cyano-methylating agent [2] [equiv.]	Surface	Condition	No. of balls /rpm	Time [minutes]	Yield [%][a],[b]
1	-	-	**$BrCH_2CN$ (1.0)**	**Basic alumina**	**ball milling**	**7/550**	**5**	**94**
2	-	-	$BrCH_2CN$ (0.5)	Basic alumina	ball milling	7/550	5	47
3	-	-	$BrCH_2CN$ (1.5)	Basic alumina	ball milling	7/550	5	89
4	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	7/600	5	84
5	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	7/450	10	68
6	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	8/550	5	89
7	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	6/550	10	58
8	-	-	$BrCH_2CN$ (1.0)	Acidic alumina	ball milling	7/550	5	16
9	-	-	$BrCH_2CN$ (1.0)	Neutral alumina	ball milling	7/550	60	-
10	-	Et_3N (1.0)	$BrCH_2CN$ (1.0)	Neutral alumina	ball milling	7/550	5	73
11	-	Et_3N (1.0)	$BrCH_2CN$ (1.0)	Neutral alumina	ball milling	7/550	10	78
12	CH_3CN	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	13
13	DMSO	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	27
14	EtOH	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	Trace
15	H_2O	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	21
16[c]	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	7/550	5	94

[a] Reaction conditions: A mixture of *p*-methoxybenzoic acid (**1a**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was reacted in the presence of basic alumina as a surface (1.0 g) for 5 minutes either under ball milling (using a 25 mL stainless-steel jar and balls of 10 mm in diameter, and rotation in an inverted direction with a break of 5 seconds at 2.5-minutes interval) in the absence of any catalysts and solvents without any further additives or by simple stirring at room temperature (25–28 °C);
[b] Isolated yields;
[c] using tungsten carbide jar and balls; pH was measured (1.0 g of acidic/neutral/basic alumina suspended in 5 mL of distilled water, followed by stirring for 10 minutes and then leaving undisturbed for 1 hour) for acidic alumina as 6.08, neutral alumina as 7.07, and basic alumina as 8.14. *Note*: For the best-suited conditions (entry 1), the isolated yield indicates an average value of three repeated reactions.

acid by irradiating the mixture of *p*-methoxybenzoic acid (**1aa**; 0.2 mmol), bromoacetonitrile (**2**; 0.2 mmol) and triethylamine (1.0 equiv.) in dimethyl sulfoxide (5 mL), with ultrasound at 40% amplitude for 3 minutes to isolate the desired compound 3aa in 89% yield (Table 1, entry 9). Compound **3aa** is a new compound characterized by detailed spectral (^{1}H-, ^{13}C-NMR, and HRMS) studies. Table 1 explicitly summarizes all these experimental outcomes in optimizing the reaction conditions.

With the optimized sonochemical conditions at hand, we then envisioned, based on our research experience and understanding, that the same transformation could be attained upon mechanochemical conditions in a high-speed ball mill. With this view, we attempted our model reaction between *p*-methoxybenzoic acid (**1aa**) and bromoacetonitrile (**2**) by grinding the mixture on a basic alumina (1.0 g) surface with seven stainless steel balls at 550 rpm when we successfully isolated our desired product **3aa** in 94% yield at 5 minutes (Table 2, entry 1); the yield and reaction time, both are almost comparable to the sonochemical procedure (Table 1, entry 9). To conclude on the best-suited mechanochemical conditions, we then performed several other trial reactions with this model entry by varying the equivalency of cyanomethylating agent (Table 2, entries 2 and 3), milling parameters, such as the number of balls, frequency (rpm), and milling time (Table 2, entries 4–7), nature of the solid surface and additives (Table 2, entries 8–11); however, we did not observe any marked improvement. The conventional stirrings using varying solvents at ambient conditions were also ineffective (Table 2, entries 12–15). We also carried out a control experiment using a tungsten carbide jar and balls to rule out any catalytic intervention by stainless steel jar and balls (Table 2, entry 16). Finally, we discovered an alternative and efficient protocol for the same transformation to access the desired product **3aa** in an excellent yield of 94% (Table 2, entry 1) under ball-milling using seven stainless steel balls (10 mm in diameter) milled for 5 minutes (rotation in an inverted direction with a 30-second break at 2.5-minute interval) at 550 rpm in the presence of basic alumina (1.0 g) as the surface. Table 2 offers compiled experimental outcomes.

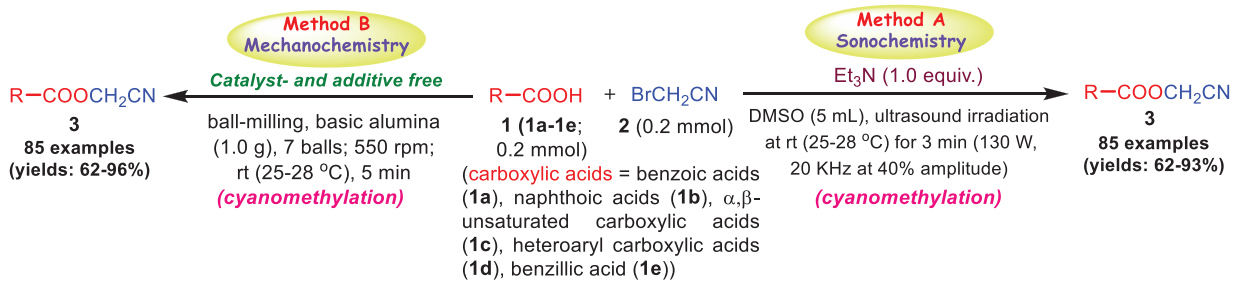
We have thus successfully developed a dual synthetic strategy for the direct cyanomethylation of carboxylic acids, thereby offering eco-friendly and practical synthetic routes to access cyanomethyl ester derivatives by using sonochemical (Method A) and mechanochemical (Method B) approaches (Scheme 1b). At this stage, we turned our attention to exploring the scope of the developed methodologies under the respective optimized reaction conditions, and also comparing the efficacies of both methods, categorically in terms of corresponding yields and reaction times. Accordingly, we screened a set of twenty diversely substituted benzoic acids (**1ab**-**1au**), containing both electron-donating and electron-withdrawing groups (such as methyl, *tert*-butyl, amino, methoxy, ethoxy, chloro, bromo, fluoro, and iodo), and carried out the cyanomethylation reaction by reacting with bromoacetonitrile (**2**) separately under the optimized reaction conditions for sonochemical (Method A) and mechanochemical (Method B) processes. We observed that all the reactions took place very efficiently and smoothly under both processes and isolated the desired cyanomethyl ester derivatives in excellent yields ranging from 75 to 93% in the sonochemical and 82 to 92% in the mechanochemical method, within respective reaction times of 3 and 5 minutes (Table 3, compounds **3ab**-**3au**). We then planned to check the functional group tolerance for both methods, and afterwards performed the cyanomethylation reaction with another set of 10 different benzoic acid derivatives (**1av**-**1az** and **1aa**′-**1ae**′), having other functionalities, such as -$N(CH_3)_2$, -$NHCOCH_3$, -NO_2, -OH, -O-CH_2-O-, CF_3, $COCH_3$, $OCOCH_3$, and CN, under the identical reaction conditions. All the benzoic acid derivatives underwent the reaction very efficiently in both processes, exhibiting excellent functional group tolerance, affording the desired esters **3av**-**3az** and **3aa**′-**3ae**′ with isolated yields ranging from 62 to 88% within 3 minutes under ultrasonication (Method A) and 65 to 94% within 5 minutes under ball milling (Method B) (Table 3, compounds **3av**-**3az** and **3aa**′-**3ae**′).

Encouraged by these results, we then planned to perform the reaction with a series of di-, tri-, or poly-substituted benzoic acids to evaluate the scope and versatility of both strategies, and accordingly, we conducted the cyanomethylation of a diverse range of poly-substituted benzoic acids (**1af"**-**1ap"**) under both the sono- and mechanochemical conditions. To our delight, we isolated the corresponding cyanomethyl esters **3af"**-**3ap"** in all cases (Table 3, compounds **3af"**-**3ap"**) with good to excellent yields ranging from 77–89% under ultrasonication (Method A) within 3 minutes, and 77–90% under ball-milling (Method B) within 5 minutes. In addition, [1,1′-biphenyl]-4-carboxylic acid (**1aq"**), phthalic acid (**1ar"**; required 2.0 equiv. of 2), and its nitro-derivative (**1as'**; required 2.0 equiv. of 2) also took part efficiently under identical conditions, furnishing the corresponding cyanomethyl esters **3aq"**-**3as"** with respective isolated yields of 84%, 74%, and 83% within 3 minutes under sonochemical method and 82%, 70%, and 86% within 5 minutes under mechanochemical method (Table 3, compounds **3aq"**-**3as"**). Furthermore, in another drive, biologically significant carboxylic acid scaffolds, such as chromene-8-carboxylic acid (**1at"**), and 2- and 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acids (**1au"**-**1av"**), were converted to their corresponding cyanomethyl ester derivatives **3at"**-**3av'** with ease using the similar strategy, isolating products in the respective yields of 88%, 66%, and 69% under sono- and 86%, 62%, and 63% under the mechanochemical approach (Table 3, compounds **3at"**-**3av"**).

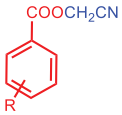
With these successful experimental outcomes, we endeavored to extend the scope of the carboxylic acid substrate once more. Both sonochemical and mechanochemical methods worked efficiently for naphthoic acids, such as 2-(naphthalen-1-yl)acetic acid (**1ba**), 2-(naphthalen-2-yl)acetic acid (**1bb**), and 2-hydroxy-1-naphthoic acid (**1bc**), furnishing the corresponding cyanomethyl ester derivatives **3ba**-**3bc** in excellent yields ranging from 84–89% under ultrasonication (Method A) within 3 minutes, and 80–87% under ball-milling (Method B) within 5 minutes, under the standard reaction conditions (Table 3, compounds **3ba**-**3bc**). Next, we thought about α,β-unsaturated carboxylic acids for this transformation, and carried out a set of five reactions between substituted cinnamic acids (**1ca**-**1ce**) and bromoacetonitrile (**2**) under identical reaction conditions, following both methods separately. All the reactions took place satisfactorily, thereby affording the respective differently substituted cyanomethyl esters **3ca**-**3ce** (Table 3, compounds **3ca**-**3ce**) with good yields ranging from 74–87% under ultrasonication (Method A) within 3 minutes, and 79–85% under ball-milling (Method B) within 5 minutes. Phenyl-3-propiolic acid (**1cf**) also participated in the transformation in both methods to give cyanomethyl 3-phenylpropiolate (**3cf**) with an excellent yield of 86% and 84% under sonication and ball-milling, respectively (Table 3, compound **3cf**).

In a further attempt, we first conducted the transformation with biologically potent nicotinic acid (pyridine-3-carboxylic acid, **1da**) as a heterocyclic carboxylic acid, following both processes under identical reaction conditions. Delightfully, we isolated cyanomethyl nicotinate (**3 da**) in an excellent yield of 86% and 89%, respectively, within the same time frame (Table 3, compound **3 da**). Encouraged by this result, we then carried out a set of thirteen more reactions between a diverse range of bio-relevant heterocyclic acids (**1db**-**1dn**) (viz. nicotinic acid derivatives, 2-amino-isonicotinic acid, pyridine-2,6-dicarboxylic acid, indole-2- and 3-carboxylic acids, furan-2-carboxylic acid, thiophene-2- and 3-carboxylic acids, quinoline-3- and isoquinoline-3-carboxylic acids, and quinoxaline-2-carboxylic acid) and bromoacetonitrile(**2**; used 2.0 equiv. for **1df** as it bears two carboxylic acid groups in its molecule) under the optimized reaction conditions. All these reactions were also found to be implemented smoothly, thereby affording the desired cyanomethyl esters (**3db**-**3dn**) in similar yields ranging from 77–90% for ultrasonication and 73–91% for mechanochemical methodology (Table 3, compounds **3db**-**3dn**). This transformation was also successfully applied to a broad range of another class of bio-relevant heterocyclic carboxylic acids, coumarin-3-carboxylic acids (**1do**-**1dz**, and **1da"**), containing various functional groups containing both electron-donating and withdrawing functionalities (such as methyl, *tert*-butyl, hydroxy, methoxy, fluoro, chloro, bromo, nitro, and naphthyl). All these reactions afforded the desired cyanomethyl coumarin-3-carboxylates (**3do**-**3dz**, and **3da"**) in good yields, ranging from 66–91% for Method

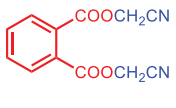
Table 3. Sonochemical and mechanochemical synthesis of diversely functionalized cyanomethyl esters (**3**)[a],[b]



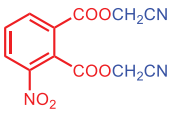
i) Scope of benzoic acids



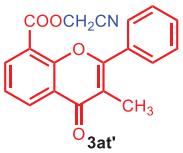
3aa: R = 4-OCH_3,	**Method A:** 89%; **Method B:** 94%	**3aw**: R = 4-$NHCOCH_3$,	**Method A:** 82%; **Method B:** 87%
3ab: R = H,	**Method A:** 93%; **Method B:** 87%	**3ax**: R = 4-NO_2,	**Method A:** 87%; **Method B:** 85%
3ac: R = 2-CH_3,	**Method A:** 86%; **Method B:** 91%	**3ay**: R = 2-OH,	**Method A:** 62%; **Method B:** 65%
3ad: R = 3-CH_3,	**Method A:** 89%; **Method B:** 86%	**3az**: R = 3-OH,	**Method A:** 79%; **Method B:** 85%
3ae: R = 2,4,6-$(CH_3)_3$,	**Method A:** 93%; **Method B:** 89%	**3aa'**: R = 2,3-$(OCH_2O$-),	**Method A:** 83%; **Method B:** 88%
3af: R = 2-$C(CH_3)_3$,	**Method A:** 87%; **Method B:** 92%	**3ab'**: R = 2-CF_3,	**Method A:** 87%; **Method B:** 85%
3ag: R = 3-OCH_3,	**Method A:** 89%; **Method B:** 92%	**3ac'**: R = 4-OCH_3,	**Method A:** 88%; **Method B:** 94%
3ah: R = 3,5-$(OCH_3)_2$,	**Method A:** 90%; **Method B:** 86%	**3ad'**: R = 2-$OCOCH_3$,	**Method A:** 87%; **Method B:** 89%
3ai: R = 4-CH_2CH_3,	**Method A:** 93%; **Method B:** 96%	**3ae'**: R = 4-CN,	**Method A:** 86%; **Method B:** 89%
3aj: R = 2-Cl,	**Method A:** 82%; **Method B:** 87%	**3af'**: R = 2-CH_3-6-NH_2,	**Method A:** 84%; **Method B:** 87%
3ak: R = 3-Cl,	**Method A:** 77%; **Method B:** 82%	**3ag'**: R = 4-NH_2-6-OH,	**Method A:** 83%; **Method B:** 86%
3al: R = 2,4,6-tri-Cl,	**Method A:** 91%; **Method B:** 87%	**3ah'**: R = 2-NH_2-3,4,5-$(OCH_3)_3$,	**Method A:** 79%; **Method B:** 77%
3am: R = 3-Br,	**Method A:** 79%; **Method B:** 83%	**3ai'**: R = 2-NH_2-6-Br,	**Method A:** 82%; **Method B:** 84%
3an: R = 4-Br,	**Method A:** 75%; **Method B:** 79%	**3aj'**: R = 2-NH_2-4-Cl,	**Method A:** 83%; **Method B:** 85%
3ao: R = 3-F,	**Method A:** 81%; **Method B:** 84%	**3ak'**: R = 2-NH_2-6-F,	**Method A:** 88%; **Method B:** 85%
3ap: R = 4-F,	**Method A:** 84%; **Method B:** 78%	**3al'**: R = 2-OCH_3-4-Cl,	**Method A:** 89%; **Method B:** 84%
3aq: R = 2,5-di-F,	**Method A:** 84%; **Method B:** 86%	**3am'**: R = 2-CH_3-5-F,	**Method A:** 85%; **Method B:** 83%
3ar: R = 4-I,	**Method A:** 87%; **Method B:** 91%	**3an'**: R = 2-CH_3-5-I,	**Method A:** 83%; **Method B:** 80%
3as: R = 2-NH_2,	**Method A:** 85%; **Method B:** 88%	**3ao'**: R = 3-OCH_3-4-CH_3,	**Method A:** 88%; **Method B:** 90%
3at: R = 3-NH_2,	**Method A:** 79%; **Method B:** 82%	**3ap'**: R = 3-OCH_3-4-OH,	**Method A:** 77%; **Method B:** 80%
3au: R = 4-NH_2,	**Method A:** 88%; **Method B:** 85%	**3aq'**: R = 4-C_6H_5,	**Method A:** 84%; **Method B:** 82%
3av: R = 4-$N(CH_3)_2$,	**Method A:** 88%; **Method B:** 91%		



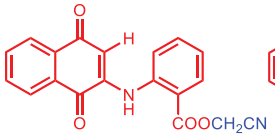
3ar'
Method A: 74%; 3 min
Method B: 70%; 5 min



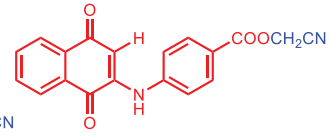
3as'
Method A: 83%; 3 min
Method B: 86%; 5 min



3at'
Method A: 88%; 3 min
Method B: 86%; 5 min

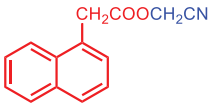


3au'
Method A: 66%; 3 min
Method B: 62%; 5 min

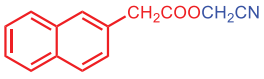


3av'
Method A: 69%; 3 min
Method B: 63%; 5 min

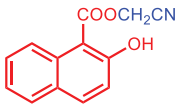
ii) Scope of naphthoic acids



3ba
Method A: 89%; 3 min
Method B: 87%; 5 min

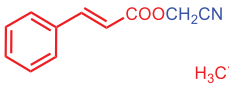


3bb
Method A: 84%; 3 min
Method B: 80%; 5 min

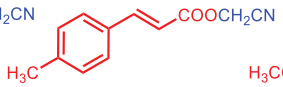


3bc
Method A: 88%; 3 min
Method B: 84%; 5 min

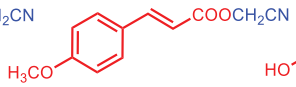
iii) Scope of α,β-Unsaturated carboxylic acids



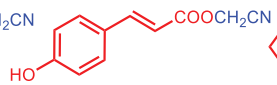
3ca
Method A: 83%; 3 min
Method B: 85%; 5 min



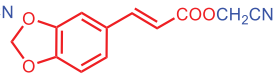
3cb
Method A: 80%; 3 min
Method B: 84%; 5 min



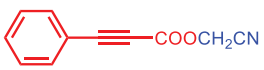
3cc
Method A: 83%; 3 min
Method B: 85%; 5 min



3cd
Method A: 74%; 3 min
Method B: 79%; 5 min



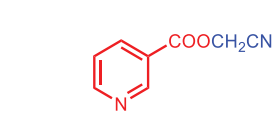
3ce
Method A: 87%; 3 min
Method B: 84%; 5 min



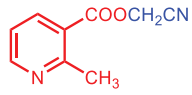
3cf
Method A: 86%; 3 min
Method B: 84%; 5 min

Table 3. (Continued)

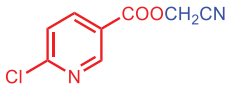
iv) Scope of heterocyclic carboxylic acids



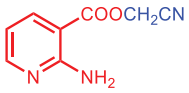
3da
Method A: 86%; 3 min
Method B: 89%; 5 min



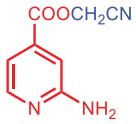
3db
Method A: 88%; 3 min
Method B: 85%; 5 min



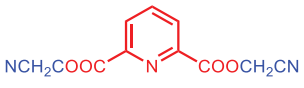
3dc
Method A: 81%; 3 min
Method B: 86%; 5 min



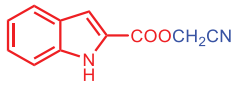
3dd
Method A: 82%; 3 min
Method B: 85%; 5 min



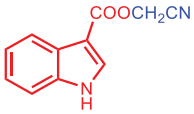
3de
Method A: 79%; 3 min
Method B: 82%; 5 min



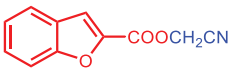
3df
Method A: 77%; 3 min
Method B: 73%; 5 min



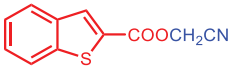
3dg
Method A: 90%; 3 min
Method B: 87%; 5 min



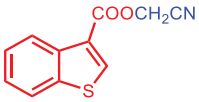
3dh
Method A: 82%; 3 min
Method B: 85%; 5 min



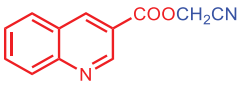
3di
Method A: 87%; 3 min
Method B: 89%; 5 min



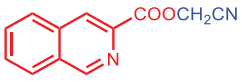
3dj
Method A: 85%; 3 min
Method B: 87%; 5 min



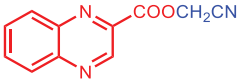
3dk
Method A: 78%; 3 min
Method B: 81%; 5 min



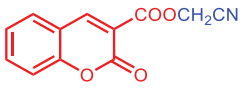
3dl
Method A: 80%; 3 min
Method B: 85%; 5 min



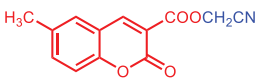
3dm
Method A: 85%; 3 min
Method B: 90%; 5 min



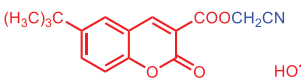
3dn
Method A: 89%; 3 min
Method B: 91%; 5 min



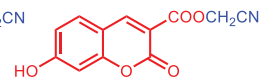
3do
Method A: 83%; 3 min
Method B: 81%; 5 min



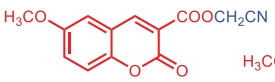
3dp
Method A: 86%; 3 min
Method B: 82%; 5 min



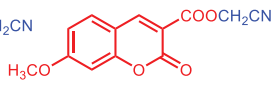
3dq
Method A: 91%; 3 min
Method B: 88%; 5 min



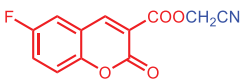
3dr
Method A: 73%; 3 min
Method B: 75%; 5 min



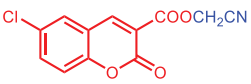
3ds
Method A: 81%; 3 min
Method B: 77%; 5 min



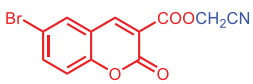
3dt
Method A: 73%; 3 min
Method B: 71%; 5 min



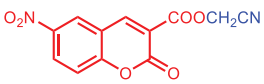
3du
Method A: 73%; 3 min
Method B: 77%; 5 min



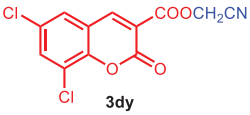
3dv
Method A: 80%; 3 min
Method B: 78%; 5 min



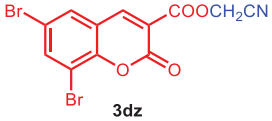
3dw
Method A: 68%; 3 min
Method B: 65%; 5 min



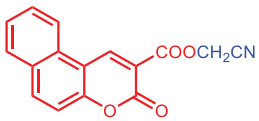
3dx
Method A: 66%; 3 min
Method B: 69%; 5 min



3dy
Method A: 74%; 3 min
Method B: 72%; 5 min

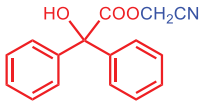


3dz
Method A: 83%; 3 min
Method B: 80%; 5 min

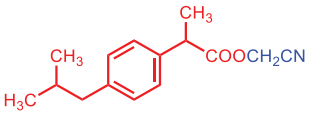


3da'
Method A: 72%; 3 min
Method B: 70%; 5 min

v) Scope of miscellaneous carboxylic acids



3ea
Method A: 86%; 3 min
Method B: 88%; 5 min

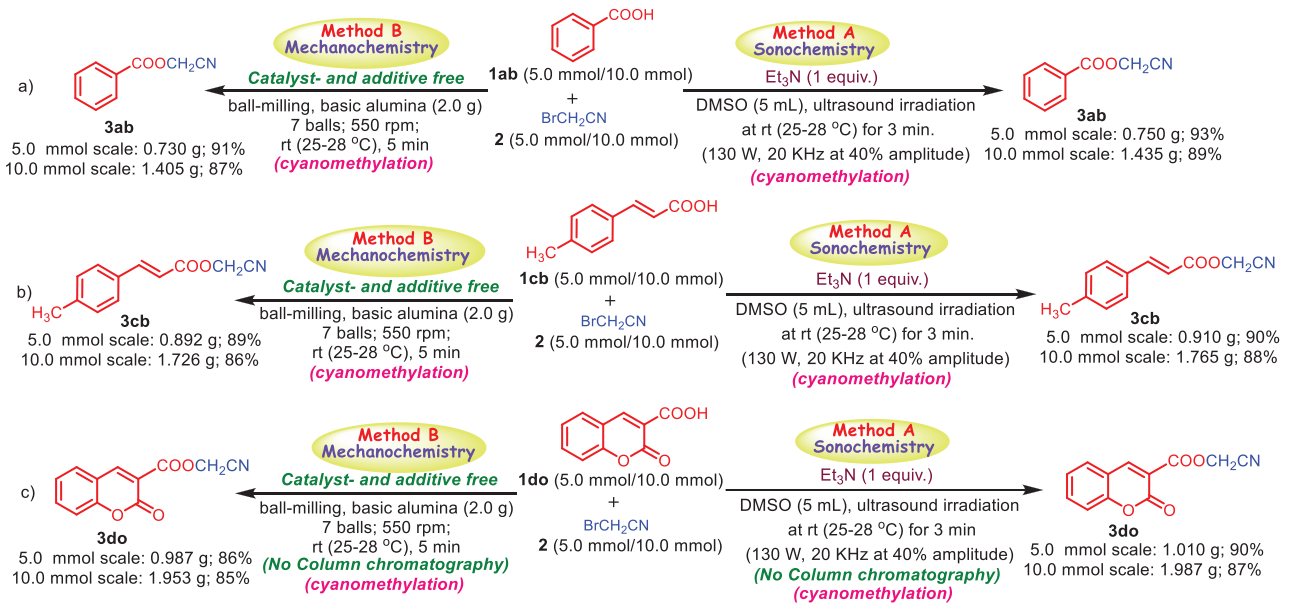


(Ibuprofen cyanomethylester; **3eb**)
Method A: 73%; 3 min
Method B: 78%; 5 min

[a] Reaction conditions: A mixture of carboxylic acids (**1**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was reacted separately under both ultrasonication (Method A) and ball-milling (Method B) reaction conditions.
[b] Isolated yields.

A and 65–88% for Method B within just 3 and 5 minutes of operation, respectively (Table 3, compounds **3do**-**3dz**, and **3da'**). Furthermore, we explored that benzillic acid (**1ea**) and 2-(4-isobutylphenyl)propanoic acid (Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) molecule; **1eb**) also underwent cyanomethylation reaction, affording the corresponding cyanomethyl esters **3ea** and **3eb** in the corresponding good yields of 88% and 73% under ultrasonication and 86% and 78% under the ball-milling approach within just 3 and 5 minutes, respectively. All the experimental results are shown in Table 3.

However, we observed that simple aliphatic carboxylic acids, such as *n*-propionic acid, *n*-butanoic acid, and betulinic acid, a natural triterpenoic acid, do not undergo the reaction in either method. This is perhaps due to the lower stability of their respective conjugate ions (*i.e.*, carboxylate ions) compared to those from aromatic carboxylic acids and benzylic acids. Again, amino acids (such as alanine, phenylalanine, and tryptophan) were also found to remain unreacted, and we anticipate that their strong zwitterionic structure restricts them from participating in the reaction.



Scheme 2. Gram-scale synthetic applications for representative entries: a) with benzoic acid **1ab**; b) with (*E*)-3-(*p*-tolyl)acrylic acid **1cb**; and c) with coumarin-3-carboxylic acid **1do**.

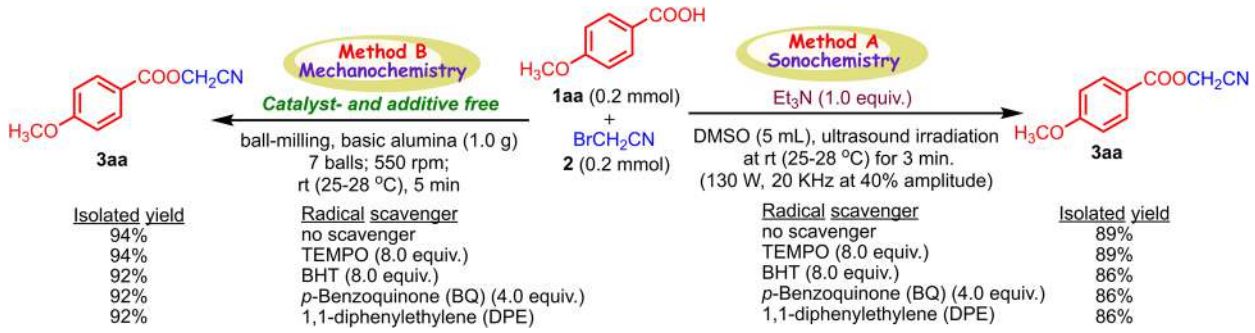
All the isolated products **3** (except **3do**-**3dz**, and **3da′**), synthesized following both Method A (sonochemical) and Method B (mechanochemical), were purified using the column chromatographic technique (*see experimental)*. All are new compounds except **3ab**, **3ac**, **3ad**, **3ak**, **3an**, **3ao**, **3ap**, **3ax**, **3ae′**, **3ba**, and **3ca**. Each synthesized compound was fully characterized based on its detailed spectral studies, including ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR (for **3ao**, **3ap**, **3aq**, **3ab′**, **3ak′**, **3am′** and **3du**), and HRMS (*see experimental*).

To further assess the scalability of both approaches, we carried out gram-scale synthetic applications (5.0 and 10.0 mmol-scales; 25- and 50-fold enhancement; Scheme 2) for three representative entries, *viz*. benzoic acid (**1ab**), (*E*)-3-(*p*-tolyl)acrylic acid (**1cb**), and coumarin-3-carboxylic acid (**1do**). The sonochemical approach (Method A) furnished the products **3ab**, **3cb**, and **3do** with excellent yields of 93%, 90%, and 90% at 5.0 mmol and 89%, 88%, and 87% at 10.0 mmol reactions, respectively, all within just 3 minutes (*see Experimental*). Similarly, the mechanochemical method (Method B) delivered impressive results, affording 91%, 89%, and 86% at 5.0 mmol and 87%, 86%, and 85% at 10.0 mmol reactions within 5 minutes (*see Experimental*). The yields and the reaction times observed in the gram-scale synthesis closely mirrored those obtained for the sub-millimolar-scale reactions.

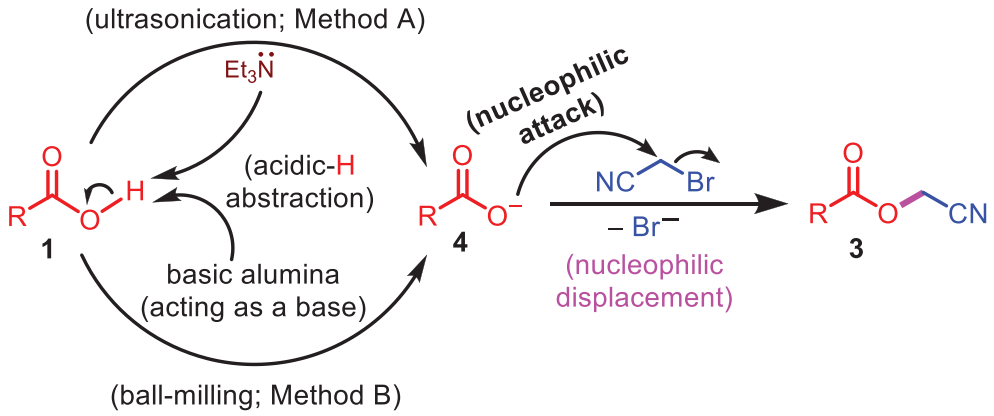
At this point, our efforts were shifted toward uncovering potential mechanistic insights of this sono- and mechanochemically-assisted cyanomethylation strategy applied to a diverse range of carboxylic acids using bromoacetonitrile. With this view, we conducted a set of control experiments with our model reaction in the presence of four different radical scavengers, such as TEMPO, BHT, *p*-benzoquinone (BQ), and 1,1-diphenylethylene (DPE) (Scheme 3). None of the radical scavengers affected the conversion when carried out either sonochemically or mechanochemically, thereby suggesting that the transformation follows an ionic pathway in both cases.

Hence, we propose a plausible reaction mechanism for the sono- and mechanochemical transformation herein proposed, as depicted in Scheme 4. Under ultrasound irradiation, the abstraction of the acidic hydrogen from carboxylic acid **1** by the base, triethylamine (Et_3N), is much facilitated,[16] resulting in the corresponding carboxylate ion intermediate **4**. Once again, we observed (Table 2) that among the three types of alumina (acidic, basic, and neutral) used as the surface,[17] only the basic alumina came out as the most superior surface-cum-catalyst for this chemical conversion. This is because basic alumina (α-alumina), an activated form of aluminum oxide (Al_2O_3), comprising a hexagonal close-packed structure, with aluminum ions surrounded by oxygen anions in a layered arrangement, can act as both an acid and a base, depending upon the circumstances.[18] Hence, when it is subjected to the carboxylic acid **1**, it behaves as a base by abstracting the acidic proton, which is facilitated under high mechanochemical force in a ball mill, to generate the carboxylate ion intermediate **4**. Simultaneously, the amphoteric property of basic alumina is supposed to be responsible for enhancing the electrophilicity of the methylenic carbon of bromoacetonitrile ($BrCH_2CN$; **2**) through electrophilic polarization by coordinating with the unshared electron pairs of the bromine atom by its layered aluminum cations (Al^{3+}).[18] The in situ-generated carboxylate ion **4**, now acting as a nucleophile,[19] undergoes a rapid nucleophilic displacement reaction (preferably via S_N2 pathway) at the methylenic carbon center of the activated bromoacetonitrile electrophile **2**, to afford the desired cyanomethylated product **3** (Scheme 4) through sono-/mechanochemical esterification.[20]

Additionally, the reusability of the solid surface (basic alumina) was examined by conducting the model reaction on a scale of 0.2 mmol to yield cyanomethyl 4-methoxybenzoate (**3aa**), as illustrated in Figure 2. We were pleased to observe that the solid surface demonstrated excellent reusability, maintaining



Scheme 3. Control experiments with radical scavengers.



Scheme 4. Proposed mechanism.

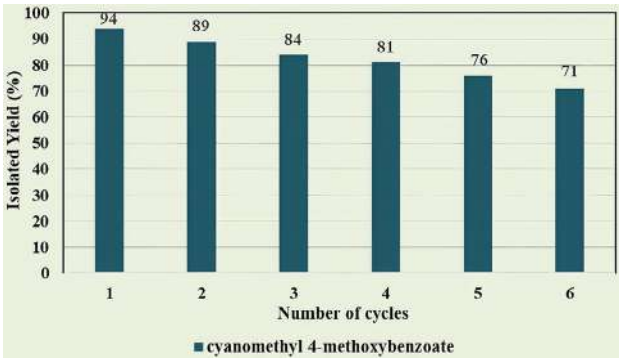


Figure 2. Reusability of the solid surface.

its catalytic efficiency over six consecutive cycles with no significant decrease in activity. Compound **3aa** was isolated in yields of 94%, 89%, 84%, 81%, 76%, and 71% within a uniform reaction time of 5 minutes for each cycle (Figure 2). It is worth noting that after collecting the solid surface during the work-up of each cycle, it was preheated at 70 °C in an oven for subsequent reuse.

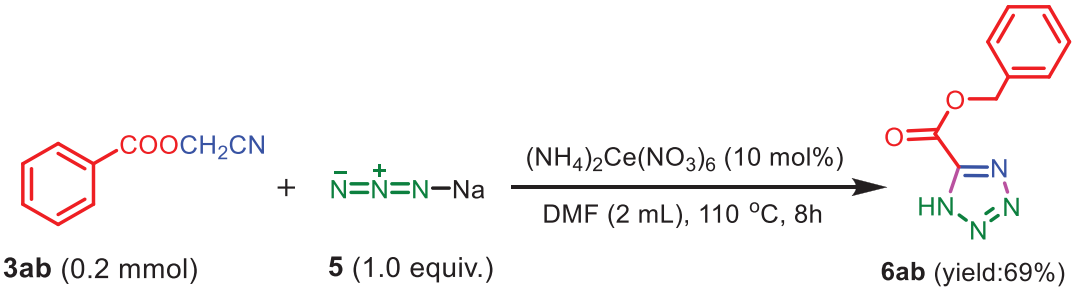
We then planned to extend the synthetic application of the synthesized cyano derivatives by screening a cycloaddition reaction. For this purpose, we tried to synthesize 5-substituted-1*H*-tetrazole (**6ab**) using ceric ammonium nitrate (CAN) via a [3 + 2] cycloaddition of the selected nitrile (**3ab**) with NaN_3 (**5**; 1.0 equiv.) in DMF at 110 °C for 8 hours, following the standard procedure (Scheme 5).[21] We successfully isolated our aimed product **6ab,** in 69% yield.

3. Conclusions

In conclusion, we have unearthed dual synthetic approaches, based on sonochemical and mechanochemical strategies, as efficient and straightforward practical alternative synthetic protocols for diversely functionalized cyanomethyl esters of a vast array of carboxylic acids upon reacting the substrate molecules with bromoacetonitrile as an eco-friendly and cost-effective cyanomethylating agent. Both the ultrasound-assisted sonochemical and the high-speed ball mill-assisted mechanochemical processes are fast (3-5 minutes) and high-yielding (up to 96%). The sonochemical transformation occurs at ambient conditions, while the mechanochemical process avoids using solvents. The key advantages of the newly developed methods are metal-free synthesis, avoidance of any additives and external oxidants, short reaction times (in minutes), broad substrate scope and tolerance of other various functional groups, good to excellent yields, reusability of the solid surface, and gram-scale synthetic applications.

4. Experimental Section

General method: All the chemicals, except 2-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1au"**), 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1av"**), coumarin-3-carboxylic acids (**1do-1dz** and **1da"**), and solvents used in this work were purchased from reputed companies. The substrates 2-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1au"**)[22a]



Scheme 5. [3 + 2] cycloaddition of nitrile **3ab** with sodium azide (**5**) to the corresponding 5-substituted tetrazole **6ab**[a,b].[a]Reaction conditions: A mixture of cyanomethyl ester (**3ab**; 0.2 mmol), NaN_3 (**5**; 1.0 equiv.), and 10 mol% of CAN as a catalyst, dissolved in 2.0 mL of dimethyl formamide (DMF), was stirred for 8 hours at 110 °C, and upon completion of the reaction, the desired product **6ab** was isolated following the standard procedure.[21] [b]Isolated yield.

and 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1av"**)[22b] and coumarin-3-carboxylic acids (**1do-1dz** and **1da"**)[23] were prepared following the reported methods.[22,23] All the synthesized starting compounds are known, and their physical and spectral data are consistent with the previously reported data.[22,23] ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were collected at 400, 100, and 376 MHz, respectively, on a Bruker DRX spectrometer. Waters (G2-XS Q-TOF) high-resolution mass spectrometer was utilized to collect HRMS spectra. The melting points were recorded on a Chemiline CL-725 melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 (Merck) plates. Sonics-make ultrasound probe-sonicator (Model: VCX 130) with a frequency of 20 kHz and energy of 130 W was used for sonication. A PM 100, Retsch GmbH, Germany, ball-milling apparatus was used for mechanochemical reactions.

General procedure for the synthesis of functionalized cyanomethyl esters 3 under the sonochemical method (Method A): Carboxylic acid (**1**; 0.2 mmol), bromoacetonitrile (**2**; 0.2 mmol), and triethylamine were added sequentially to an oven-dried glass vessel (20 mL), followed by the addition of 5 mL of dimethyl sulfoxide (DMSO). The mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 3 minutes (monitored by TLC). Upon completion of the reaction, the entire content was transferred into a 25 mL separating funnel, followed by the addition of 20 mL of a 3:1 (v/v) mixture of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the crude mass, which was then subjected to column chromatographic purification (except for compounds **3do-3dz**, and **3da'**) using EtOAc–hexane mixtures as eluents to isolate the desired products, cyanomethyl esters **3** (**3aa-3az**, **3aa"-3av"**, **3ba-3bc**, **3ca-3cf**, **3da-3dz**, **3da'**, **3ea**, and **3eb**). The synthesized compounds were fully characterized by spectroscopic studies, including ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR (for compounds **3ao**, **3ap**, **3aq**, **3ab'**, **3ak'**, **3am'**, and **3du**), and HRMS. The physical and spectral data for known compounds (viz. **3ab**, **3ac**, **3ad**, **3ak**, **3an**, **3ao**, **3ap**, **3ax**, **3ae'**, **3ba**, and **3ca**) were consistent with previously reported data[12] (see the Supporting Information).

Gram-scale synthesis of three representative compounds 3ab, 3cb, and 3do, under the sonochemical method (Method A): A mixture of benzoic acid (**1ab**; 5.0 mmol/10.0 mmol)/(*E*)-3-(*p*-tolyl)acrylic acid (**1cb**; 5.0 mmol/10.0 mmol)/coumarin-3-carboxylic acid (**1do**; 5.0 mmol/10.0 mmol) as substrates, and bromoacetonitrile (**2**; 5.0 mmol/10.0 mmol) as cyanomethylating agent was added sequentially to an oven-dried glass vessel (20 mL), followed by adding 5 mL/10 mL of dimethyl sulfoxide. Each reaction mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 3 minutes (monitored by TLC). Upon completion of each reaction, the resultant reaction mixture was worked up (using 250 mL separating funnel and adding 60 mL of ethyl acetate-water (3:1 v/v) mixture for solvent-partitioning) and purified following the same procedure (eluents for flash chromatography: hexane/ethyl acetate 92:8 v/v for **3ab** and 87:13 v/v for **3cb**) as mentioned in the general method (Method A) to obtain pure product **3ab, 3cb, and 3do** in 93% (0.750 g), 90% (0.910 g), and 90% (1.010 g) for 5.0 mmol and 89% (1.435 g), 88% (1.765 g), and 87% (1.987 g) for 10.0 mmol experiments, respectively.

General procedure for the synthesis of functionalized cyanomethyl esters (3) under ball-milling (Method B): A mixture of carboxylic acids (**1**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was subjected to ball-milling in the presence of basic alumina (1.0 g) as the surface at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) made of the same material for 5 minutes. The ball-milling operation was conducted with an inverted rotation direction, with intervals of 2.5 minutes and breaks of 30 seconds. After completion of the reaction (monitored by TLC), the entire content was transferred into a 125 mL separating funnel, followed by adding 30 mL of a mixture (3:1 v/v) of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to obtain a crude mass, which was subjected to column chromatographic purification (except for compounds **3do-3dz**, and **3da'**) using EtOAc–hexane mixtures as eluents to yield pure products of substituted cyanomethyl esters **3** (**3aa-3az**, **3aa"-3av"**, **3ba-3bc**, **3ca-3cf**, **3da-3dz**, **3da'**, **3ea,** and **3eb**).

Gram-scale synthesis of three representative compounds 3ab, 3cb, and 3do under ball-milling (Method B): A mixture of benzoic acid (**1ab**; 5.0 mmol/10.0 mmol)/(*E*)-3-(*p*-tolyl)acrylic acid (**1cb**; 5.0 mmol/10.0 mmol)/coumarin-3-carboxylic acid (**1do**; 5.0 mmol/10.0 mmol) as substrates, and bromoacetonitrile (**2**; 5.0 mmol/10.0 mmol) as a cyanomethylating agent was subjected to ball-milling in the presence of basic alumina (3.0 g for both 5.0 and 10.0 mmol-scale) as the surface at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) made of the same material for 5 minutes (monitored by TLC). The ball-milling operation was conducted with an inverted rotation direction, with intervals of 2.5 minutes and breaks of 30 seconds. Upon completion of each reaction, the resultant reaction mixture was worked up (using 250 mL separating funnel and adding 60 mL of ethyl acetate-water (3:1 v/v) mixture for solvent-partitioning) and purified following the same procedure (eluents for flash chromatography: hexane/ethyl acetate 92:8 v/v for **3ab** and 87:13 v/v for **3cb**) as

mentioned in the general method (Method B) to obtain pure product **3ab, 3cb, and 3do** in 91% (0.730 g), 89% (0.892 g), and 86% (0.987 g) for 5.0 mmol and 87% (1.405 g), 86% (1.726 g), and 85% (1.953 g) for 10.0 mmol experiments, respectively.

The physical and spectral data of the synthesized cyanomethyl esters 3 and 5-substituted tetrazole 6ab are given below:

Cyanomethyl 4-methoxybenzoate (**3aa**). White solid; yield: 89% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 94% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, 2H, J = 8.8 Hz, H-2, H-6), 6.94 (d, 2H, J = 8.8 Hz, H-3, H-5), 4.93 (s, 2H, -OCH_2CN), 3.87 (s, 3H, C_4-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.71 (C_1-COOCH_2CN), 164.36 (C-4), 132.28 (C-2, C-6), 120.19 (C-1), 114.82 (-OCH$_2$CN), 114.07 (C-3, C-5), 55.64 (C_4-OCH_3), 48.69 (-OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_3H$; 192.0661; found: 192.0668.

Cyanomethyl benzoate (**3ab**).[12] Pale brown liquid; yield: 93% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (28 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, 2H, J = 7.2 Hz, H-2, H-6), 7.59–7.57 (m, 1H, H-4), 7.45–7.43 (m, 2H, H-3, H-5), 4.93 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.91 (C_1-COOCH_2CN), 134.05 (C-4), 129.88 (C-2, C-6), 128.61 (C-3, C-5), 128.28 (C-1), 114.62 (-OCH$_2$CN), 48.83 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_2H$; 162.0555; found, 162.0571.

Cyanomethyl 2-methylbenzoate (**3ac**).[12] White solid; yield: 86% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 77–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, 2H, J = 8.4 Hz, H-3, H-6), 7.29 (d, 2H, J = 8.4 Hz, H-4, H-5), 4.96 (s, 2H, -OCH_2CN), 2.45 (s, 3H, C_2-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.11 (C_1-COOCH_2CN), 145.24 (C-2), 130.16 (C-3, C-6), 129.52 (C-4, C-5), 125.23 (C-1), 114.70 (-OCH$_2$CN), 48.79 (-OCH$_2$CN), 21.87 (C_2-CH_3) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_2H$; 176.0712; found: 176.0722.

Cyanomethyl 3-methylbenzoate (**3ad**).[12] White semi-solid; yield: 89% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 93:7. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, 2H, J = 9.2 Hz, H-2, H-6), 7.42 (d, 1H, J = 7.6 Hz, H-5), 7.35 (t, 1H, J = 7.6 Hz, H-4), 4.94 (s, 2H, -OCH_2CN), 2.40 (s, 3H, C_3-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.19 (C_1-COOCH_2CN), 138.67 (C-1), 134.98 (C-2), 130.57 (C-6), 128.65 (C-4), 127.87 (C-3), 127.22 (C-5), 114.63 (-OCH$_2$CN), 48.86 (-OCH$_2$CN), 21.28 (C_3-CH_3) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_2H$; 176.0712; found: 176.0701.

Cyanomethyl 2,4,6-trimethylbenzoate (**3ae**). White semi-solid; yield: 93% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 2H, H-3, H-5), 4.93 (s, 2H, -OCH_2CN), 2.32 (s, 6H, C_2-CH_3, C_6-CH_3), 2.30 (s, 3H, C_4-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 168.33 (C_1-COOCH_2CN), 140.74 (C-1), 136.13 (C-2, C-6), 128.84 (C-3, C-5), 128.10 (C-4), 114.46 (-OCH$_2$CN), 48.37 (-OCH$_2$CN), 21.26 (C_2-CH$_3$, C_6-CH$_3$), 20.06 (C_4-CH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_{13}NO_2H$; 204.1025; found: 204.1037.

Cyanomethyl 2-(*tert*-butyl)benzoate (**3af**). White solid; yield: 87% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 92% (40 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, J = 8.8 Hz, H-5, H-6), 7.59 (d, 2H, J = 8.4 Hz, H-3, H-4), 5.21 (s, 2H, -OCH_2CN), 1.30 (s, 9H, 3 × C_2-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.21 (C_1-COOCH_2CN), 158.02 (C-1), 130.05 (C-5, C-6), 126.50 (C-3, C-4), 125.75 (C-2), 116.70 (-OCH$_2$CN), 50.21 (-OCH$_2$CN), 35.57 (C_2-C(CH$_3$)$_3$), 31.32 (3 × C_2-C(CH$_3$)$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_{15}NO_2H$; 218.1181; found: 218.1189.

Cyanomethyl 3-methoxybenzoate (**3ag**). White solid; yield: 89% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 92% (35 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 74–75 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (d, 1H, J = 7.6 Hz, H-2), 8.02–7.98 (m, 2H, H-4, H-6), 7.81–7.79 (m, 1H, H-5), 5.74 (s, 2H, -OCH_2CN), 4.34 (s, 3H, C_3-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.60 (C_1-COOCH$_2$CN), 159.41 (C-3), 130.24 (C-2), 129.23 (C-1), 121.79 (C-6), 120.32 (C-4), 116.03 (-OCH$_2$CN), 114.01 (C-5), 55.41 (C_3-OCH$_3$) 49.86 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_9NO_3H$; 192.0661; found: 192.0650.

Cyanomethyl 3,5-dimethoxybenzoate (**3ah**). White solid; yield: 90% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 87:13, mp = 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, 2H, J = 2.4 Hz, H-2, H-6), 6.96–6.68 (m, 1H, H-4), 4.94 (s, 2H, -OCH_2CN), 3.82 (s, 6H, C_3-OCH_3, C_5-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.88 (C_1-COOCH$_2$CN), 160.89 (C-3, C-5), 129.66 (C-1), 114.54 (-OCH$_2$CN), 107.61 (C-2, C-6), 106.90 (C-4), 55.73 (C_3-OCH$_3$, C_5-OCH$_3$) 49.04 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{11}NO_4H$; 222.0766; found: 222.0760.

Cyanomethyl 4-ethoxybenzoate (**3ai**). White semi-solid; yield: 93% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 96% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 88:12. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (d, 2H, J = 8.8 Hz, H-2, H-6), 7.05 (d, 2H, J = 8.8 Hz, H-3, H-5), 5.17 (s, 2H, -OCH_2CN), 4.13–4.08 (q, 2H, J = 7.2 & 6.8 Hz, C_4-OCH_2CH$_3$), 3.87 (s, 3H, C_4-OCH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.40 (C_1-COOCH$_2$CN), 163.23 (C-4), 131.84 (C-2, C-6), 119.78 (C-1), 116.27 (-OCH$_2$CN), 114.72 (C-3, C-5), 63.75 (C_4-OCH$_2$CH$_3$) 49.50 (-OCH$_2$CN), 14.48 (C_4-OCH$_2$CH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{11}NO_3H$; 206.0817; found: 206.0833.

Cyanomethyl 2-chlorobenzoate (**3aj**). Deep brown liquid; yield: 82% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, 1H, J = 7.6 Hz, H-6), 7.50–7.49 (m, 2H, H-4, H-5), 7.38–7.34 (m, 1H, H-3), 4.97 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.75 (C_1-COOCH$_2$CN), 134.77 (C-2), 133.98 (C-6), 132.09 (C-3), 131.62 (C-4), 127.40 (C-1), 126.94 (C-5), 114.30 (-OCH$_2$CN), 49.10 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6ClNO_2H$; 192.0661; found: 192.0684.

Cyanomethyl 3-chlorobenzoate (**3ak**).[12] Deep brown liquid; yield: 77% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, 1H, J = 8.0 Hz, H-2), 7.51 (d, 2H, J = 8.0 Hz, H-3, H-5), 7.39–7.36 (m, 1H, H-4), 4.98 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.75 (C_1-COOCH$_2$CN), 134.78 (C-3), 133.96 (C-2), 132.08 (C-6), 131.62 (C-4), 126.92 (C-5), 126.71 (C-1), 114.25 (-OCH$_2$CN), 49.08 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6ClNO_2H$; 192.0661; found: 192.0677.

Cyanomethyl 2,4,6-trichlorobenzoate (**3al**). Pale brown solid; yield: 91% (48 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (46 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 93:7, mp = 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 2H, H-3, H-5), 4.99 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.71 (C_1-COOCH$_2$CN), 137.53 (C-4), 133.13 (C-2, C-6), 129.92 (C-1), 128.37 (C-3, C-5), 113.45 (-OCH$_2$CN), 49.63 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_4Cl_3NO_2H$; 263.9386; found: 263.9379.

Cyanomethyl 3-bromobenzoate (**3am**). White semi-solid; yield: 79% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 83% (40 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 85:15. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.08 (m, 1H, H-2), 8.00–7.98 (m, 1H, H-6), 7.96–7.93 (m, 1H, H-4), 7.57–7.53 (m, 1H, H-3), 5.23 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.53 (C_1-COOCH$_2$CN), 137.00 (C-2), 131.90 (C-6), 131.36 (C-4), 130.18 (C-1), 128.61 (C-5), 122.06 (C-3), 115.91 (-OCH$_2$CN), 49.08 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6BrNO_2H$; 239.9660; found: 239.9643.

Cyanomethyl 4-bromobenzoate (**3an**).[12] White solid; yield: 75% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 79% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 86:14, mp = 145 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.96 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 7.73 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 5.21 (s, 2H, -OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6BrNO_2H$; 239.9660; found: 239.9680.

Cyanomethyl 3-fluorobenzoate (**3ao**).[12] White semi-solid; yield: 81% (29 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 1H, *J* = 9.2 Hz, H-2), 7.76–7.73 (m, 1H, H-4), 7.67–7.61 (m, 2H, H-3, H-5), 5.24 (s, 2H, -OCH_2CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 111.71 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6FNO_2H$; 180.0461; found: 180.0471.

Cyanomethyl 4-fluorobenzoate (**3ap**).[12] White semi-solid; yield: 84% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 78% (28 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.05 (m, 2H, H-2, H-6), 7.42–7.38 (m, 2H, H-3, H-5), 5.22 (s, 2H, -OCH_2CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 104.28 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6FNO_2H$; 180.0461; found: 180.0455.

Cyanomethyl 2,5-difluorobenzoate (**3aq**). White solid; yield: 84% (33 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 1H, H-6), 7.34–7.28 (m, 1H, H-3), 7.20–7.14 (m, 1H, H-4), 4.98 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.78 (C_1-COOCH$_2$CN), 159.31 (d, $J^4_{C\text{-}F}$ = 2 Hz, C-2), 157.03 (d, $J^2_{C\text{-}F}$ = 23 Hz, C-5), 123.04 (d, $J^3_{C\text{-}F}$ = 9 Hz, C-6), 122.80 (d, $J^3_{C\text{-}F}$ = 9 Hz, C-3), 118.92 (d, $J^2_{C\text{-}F}$ = 26 & 8 Hz, C-3), 118.53 (d, $J^2_{C\text{-}F}$ = 26 Hz, C-4), 117.39 (d, $J^4_{C\text{-}F}$ = 4 Hz, C-1), 114.10 (-OCH$_2$CN), 49.26 (-OCH$_2$CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 113.28 (d) & − 117.03 (d) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_5F_2NO_2H$; 198.0367; found: 198.0363.

Cyanomethyl 4-iodobenzoate (**3ar**). White solid; yield: 87% (50 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (52 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 95:5, mp = 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 7.75 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 4.95 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.67 (C_1-COOCH$_2$CN), 138.25 (C-2, C-6), 131.38 (C-3, C-5), 127.40 (C-1), 114.36 (-OCH$_2$CN), 102.52 (C-4), 49.10 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6INO_2H$; 287.9521; found: 287.9534.

Cyanomethyl 2-aminobenzoate (**3as**). Brown solid; yield: 85% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (31 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 93:7, mp = 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.81 (m, 1H, H-6), 7.34–7.29 (m, 1H, H-3), 6.69–6.64 (m, 2H, H-4, H-5), 4.89 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 166.26 (C_1-COOCH$_2$CN), 151.22 (C-2), 135.44 (C-6), 131.24 (C-3), 116.94 (C-4), 116.63 (C-5), 114.90 (-OCH$_2$CN), 108.28 (C-1), 49.60 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_8N_2O_2H$; 177.0664; found: 177.0652.

Cyanomethyl 3-aminobenzoate (**3at**). Brown solid; yield: 79% (28 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (29 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 1H, H-2), 7.22–7.05 (m, 2H, H-3, H-4), 6.87–6.66 (m, 1H, H-5), 5.48 (br s, 1H, C_3-N*H*), 5.17 (s, 2H, -OCH_2CN), 4.37 (s, 1H,C_3-N*H*) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.03 (C_1-COOCH$_2$CN), 149.29 (C-4), 147.14 (C-1), 129.47 (C-2), 119.28 (C-6), 116.67 (C-3), 114.17 (C-4), 113.50 (-OCH$_2$CN), 49.60 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_8N_2O_2H$; 177.0664; found: 177.0677.

Cyanomethyl 4-aminobenzoate (**3au**). Brown solid; yield: 88% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 124–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, 2H, *J* = 8.8 Hz, H-2, H-6), 6.63 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 4.88 (s, 2H, -OCH_2CN), 4.17 (br s, 2H, C_4-NH_2) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.98 (C_1-COOCH$_2$CN), 152.13 (C-4), 132.32 (C-2, C-6), 116.83 (C-1), 115.10 (-OCH$_2$CN), 113.90 (C-3, C-5), 48.42 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_8N_2O_2H$; 177.0664; found: 177.0669.

Cyanomethyl 4-(dimethylamino)benzoate (**3av**). White solid; yield: 88% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, 2H, *J* = 8.8 Hz, H-2, H-6), 6.64 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 4.90 (s, 2H, -OCH_2CN), 3.06 (s, 6H, 2 × C_4-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.25 (C_1-COOCH$_2$CN), 154.01 (C-4), 131.97 (C-2, C-6), 115.25 (C-1), 114.10 (-OCH$_2$CN), 110.82 (C-3, C-5), 48.34 (-OCH$_2$CN), 40.14 (2 × C_4-CH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{12}N_2O_2H$; 205.0977; found: 205.0991.

Cyanomethyl 4-acetamidobenzoate (**3aw**). White solid; yield: 82% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 50:50, mp = 153 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.38 (s, 1H, C_4-N*H*COCH$_3$), 7.94 (d, 2H, *J* = 8.4 Hz, H-2, C-6), 7.75 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 5.18 (s, 2H, -OCH_2CN), 2.09 (s, 3H, C_4-NHCOCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 169.70 (C_4-NHCOCH$_3$), 164.83 (C_1-COOCH$_2$CN), 145.10 (C-4), 131.40 (C-2, C-6), 122.31 (C-1), 118.97 (C-3, C-5), 116.75 (-OCH$_2$CN), 50.09 (-OCH$_2$CN), 24.79 (C_4-NHCOCH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{10}N_2O_3H$; 219.0770; found: 219.0785.

Cyanomethyl 4-nitrobenzoate (**3ax**).[12] White solid; yield: 87% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35–8.33 (m, 2H, H-2, H-6), 8.25 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 5.03 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.34 (C_1-COOCH$_2$CN), 151.30 (C-4), 133.26 (C-1), 131.36 (C-2, C-6), 124.00 (C-3, C-5), 113.97 (-OCH$_2$CN), 49.60 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6N_2O_4H$; 207.0406; found: 207.0417.

Cyanomethyl 2-hydroxybenzoate (**3ay**). White solid; yield: 62% (22 mg, 0.2 mmol scale, Sonochemistry), yield: 65% (23 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 1H, C_2-O*H*), 7.86–7.84 (m, 1H, H-6), 7.56–7.52 (m, 1H, H-3), 7.03 (d, 1H, *J* = 8.0 Hz, H-3), 6.96–6.92 (m, 1H, H-4), 4.99 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.52 (C_1-COOCH$_2$CN), 144.98 (C-2), 137.23 (C-6), 130.14 (C-3), 129.55 (C-1), 119.86 (-OCH$_2$CN), 118.14 (C-5), 117.62 (C-4), 49.04 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_7NO_3H$; 178.0504; found: 178.0495.

Cyanomethyl 3-hydroxybenzoate (**3az**). White solid; yield: 79% (28 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 83:17, mp = 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, 1H, *J* = 7.6 Hz, H-2), 7.51 (s, 1H, H-6), 7.33 (t, 1H, *J* = 8.0 Hz, H-

4), 7.13–7.11 (m, 1H, H-5), 6.43 (br s, 1H, C_3-O*H*), 4.95 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.20 (C_1-COOCH_2CN), 156.17 (C-3), 130.19 (C-2), 129.08 (C-1), 122.40 (C-6), 121.73 (C-4), 116.67 (C-5), 114.60 (-OCH$_2$*C*N), 49.11 (-OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7NO_3H$; 178.0504; found: 178.0528.

Cyanomethyl benzo[*d*][1,3]dioxole-4-carboxylate (**3aa′**). White solid; yield: 83% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 91–92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 1H, H-6), 7.43 (d, 1H, *J* = 1.6 Hz, H-4), 6.85 (d, 1H, *J* = 8.0 Hz, H-5), 6.06 (s, 2H, -OCH_2O-), 4.92 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 164.35 (C_1-COOCH_2CN), 152.73 (C-2), 148.06 (C-3), 126.37 (C-6), 121.70 (C-1), 114.69 (-OCH$_2$*C*N), 109.70 (C-4), 108.35 (C-5), 102.21 (-OCH_2O-), 48.86 (-OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_7NO_4H$; 206.0453; found: 206.0470.

Cyanomethyl 2-(trifluoromethyl)benzoate (**3ab′**). White solid; yield: 87% (39 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 94:6, mp = 90 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.93–7.90 (m, 2H, H-3, H-6), 7.86–7.83 (m, 2H, H-4, H-5), 5.28 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 164.86 (C_1-COOCH$_2$CN), 132.93 (d, $J^2_{C\text{-}F}$ = 22 Hz, C-6), 130.54 (C-2), 128.51 (C_2-*C*F$_3$), 127.29 (d, $J^3_{C\text{-}F}$ = 6 Hz, C-3), 127.05 (d, $J^4_{C\text{-}F}$ = 4 Hz, C-4), 126.95 (d, $J^3_{C\text{-}F}$ = 4 Hz, C-5), 121.89 (t, $J^1_{C\text{-}F}$ = 272 Hz, C-1), 115.44 (-OCH$_2$*C*N), 50.43 (-OCH$_2$CN) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 58.28 ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_6F_3NO_2H$; 230.0429; found: 230.0438.

Cyanomethyl 4-acetylbenzoate (**3ac′**). White solid; yield: 89% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 94% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 65:35, mp = 91–92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, 2H, *J* = 8.0 Hz, H-2, H-6), 8.03 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 4.99 (s, 2H, -OCH_2CN), 2.65 (s, 3H, C_4-COCH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.42 (C_4-*C*OCH$_3$), 164.27 (C_1-COOCH$_2$CN), 141.15 (C-4), 131.57 (C-1), 130.42 (C-2), 130.16 (C-6), 128.54 (C-3, C-5), 114.31 (-OCH$_2$*C*N), 49.27 (-OCH$_2$CN), 27.06 (C_4-*C*OCH$_3$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_9NO_3H$; 204.0661; found: 204.0650.

Cyanomethyl 2-acetoxybenzoate (**3ad′**). White solid; yield: 87% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 88:12, mp = 86 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 1H, H-6), 7.65–7.60 (m, 1H, H-3), 7.36–7.32 (m, 1H, H-5), 7.15–7.13 (m, 1H, H-4), 4.89 (s, 2H, -OCH_2CN), 2.36 (s, 3H, C_2-OCOCH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.61 (C_2-OCOCH$_3$), 162.71 (C_1-COOCH$_2$CN), 151.14 (C-2), 135.20 (C-6), 131.98 (C-3), 126.32 (C-5), 124.21 (C-4), 121.16 (C-1), 114.38 (-OCH$_2$*C*N), 48.96 (-OCH$_2$CN), 20.97 (C_2-OCO*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_9NO_4H$; 220.0610; found: 220.0614.

Cyanomethyl 4-cyanobenzoate (**3ae′**).[12] White solid; yield: 86% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 138–139 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.17 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 7.80 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 5.01 (s, 2H, -OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_6N_2O_2H$; 187.0508; found: 187.0523.

Cyanomethyl 2-amino-6-methylbenzoate (**3af′**). White solid; yield: 84% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 93–95 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.11 (m, 1H, H-3), 6.55–6.52 (m, 2H, H-4, H-5), 5.37 (br s, 2H, C_2-NH_2), 4.92 (s, 2H, -OCH_2CN), 2.47 (s, 3H, C_6-CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.60 (C_1-COOCH$_2$CN), 150.84 (C-2), 141.00 (C-3), 133.54 (C-5), 120.70 (C-6), 114.94 (C-4), 114.77 (-OCH$_2$*C*N), 110.29 (C-1), 48.17 (-OCH$_2$CN), 23.86 (C_6-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_{10}N_2O_2H$; 191.0821; found: 191.0816.

Cyanomethyl 4-amino-2-hydroxybenzoate (**3ag′**). White semi-solid; yield: 83% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.31 (s, 1H, C_2-O*H*), 7.60 (d, 1H, *J* = 8.4 Hz, H-6), 7.26 (s, 1H, H-3), 6.16 (s, 1H, H-5), 4.91 (s, 2H, -OCH_2CN), 4.26 (br s, 2H, C_4-NH_2) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.07 (C_1-*C*OOCH$_2$CN), 164.22 (C-2), 154.59 (C-4), 131.94 (C-6), 114.63 (-OCH$_2$*C*N), 107.45 (C-3), 100.98 (C-1), 100.63 (C-5), 48.46 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_8N_2O_3H$; 193.0613; found: 193.0627.

Cyanomethyl 2-amino-3,4,5-trimethoxybenzoate (**3ah′**). White semi-solid; yield: 79% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 77% (41 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.01 (s, 1H, H-6), 6.21 (br s, 2H, C_2-NH_2), 5.11 (s, 2H, -OCH_2CN), 3.85 (s, 3H, C_3-OCH_3), 3.73 (s, 3H, C_4-OCH_3), 3.71 (s, 3H, C_5-OCH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.19 (C_1-COOCH$_2$CN), 147.80 (C-3), 142.41 (C-4), 141.92 (C-5), 139.50 (C-2), 115.86 (-OCH$_2$*C*N), 107.22 (C-6), 100.63 (C-1), 60.16 (C_3-OCH_3), 59.84 (C_4-OCH_3), 55.78 (C_5-OCH_3), 48.53 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_{14}N_2O_5H$; 267.0981; found: 267.0999.

Cyanomethyl 2-amino-6-bromobenzoate (**3ai′**). White solid; yield: 82% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (43 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 148–149 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, 1H, *J* = 8.8 Hz, H-3), 6.86 (d, 1H, *J* = 1.6 Hz, H-5), 6.78–6.75 (m, 1H, H-4), 5.81 (br s, 2H, C_2-NH_2), 4.89 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.84 (C_1-COOCH$_2$CN), 151.87 (C-2), 132.51 (C-3), 130.33 (C-5), 119.91 (C-5), 119.25 (C-4), 114.73 (-OCH$_2$*C*N), 107.66 (C-1), 48.50 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7BrN_2O_2H$; 211.0274; found: 211.0285.

Cyanomethyl 2-amino-4-chlorobenzoate (**3aj′**). White solid; yield: 83% (35 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 158 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, 1H, *J* = 2.8 Hz, H-4), 7.25–7.23 (m, 1H, H-3), 6.62 (d, 1H, *J* = 8.8 Hz, H-5), 4.89 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.39 (C_1-COOCH$_2$CN), 149.82 (C-4), 135.52 (C-2), 130.28 (C-6), 121.00 (C-3), 118.35 (C-5), 114.60 (-OCH$_2$*C*N), 108.88 (C-1), 48.57 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7ClN_2O_2H$; 211.0274; found: 211.0269.

Cyanomethyl 2-amino-6-fluorobenzoate (**3ak′**). White semi-solid; yield: 88% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.17 (m, 1H, H-6), 6.45 (d, 1H, *J* = 8.4 Hz, H-3), 6.37–6.32 (m, 1H, H-5), 4.91 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.61 (C_1-COOCH$_2$CN), 163.51 (d, $J^1_{C\text{-}F}$ = 257 Hz, C-6), 152.67 (d, $J^4_{C\text{-}F}$ = 5 Hz, C-2), 135.23 (d, $J^3_{C\text{-}F}$ = 12 Hz, C-5), 114.69 (-OCH$_2$*C*N), 112.34 (d, $J^4_{C\text{-}F}$ = 3 Hz, C-3), 103.85 (d, $J^2_{C\text{-}F}$ = 24 Hz, C-4), 99.04 (d, $J^3_{C\text{-}F}$ = 14 Hz, C-1), 48.50 (-OCH$_2$CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 104.40 ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7CFN_2O_2H$; 195.0570; found: 195.0582.

Cyanomethyl 4-chloro-2-methoxybenzoate (**3al′**). White solid; yield: 89% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 82:18, mp = 100 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 1H, *J* = 2.8 Hz, H-6), 7.51–7.48 (m, 1H, H-3), 6.95 (d, 1H, *J* = 9.2 Hz, H-5), 4.92 (s, 2H, -OCH_2CN), 3.91 (s, 3H, C_2-OCH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.02 (C_1-*C*OOCH$_2$CN), 158.68 (C-2), 134.83 (C-6), 131.92 (C-3), 125.42 (C-4), 118.33

(C-1), 114.50 (-OCH$_2$CN), 113.73 (C-5), 56.49 (C$_2$-OCH$_3$), 48.86 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_8ClNO_3H$; 226.0271; found: 226.0286.

Cyanomethyl 5-fluoro-2-methylbenzoate (**3am′**). White solid; yield: 85% (33 mg, 0.2 mmol scale, Sonochemistry), yield: 83% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 96:4, mp = 105 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 7.63 (d, 1H, *J* = 9.2 Hz, H-6), 7.44 (d, 2H, *J* = 6.8 Hz, H-4, H-3), 5.19 (s, 2H, -OC*H*$_2$CN), 3.50 (s, 3H, C$_2$-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 164.42 (C$_1$-COOCH$_2$CN), 159.94 (d, $J^1_{C\text{-}F}$ = 241 Hz, C-5), 136.17 (d, $J^4_{C\text{-}F}$ = 2 Hz, C-2), 133.89 (d, $J^3_{C\text{-}F}$ = 8 Hz, C-6), 128.85 (d, $J^3_{C\text{-}F}$ = 7 Hz, C-1), 120.14 (d, $J^2_{C\text{-}F}$ = 21 Hz, C-3), 123.74 (d, $J^2_{C\text{-}F}$ = 23 Hz, C-4), 115.97 (-OCH$_2$*C*N), 49.83 (-O*C*H$_2$CN), 20.24 (C$_2$-*C*H$_3$) ppm. ^{19}F NMR (376 MHz, DMSO-d$_6$): δ = − 116.43 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_8FNO_2H$; 194.0617; found: 194.0628.

Cyanomethyl 5-iodo-2-methylbenzoate (**3an′**). White solid; yield: 83% (50 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (48 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 94:6, mp = 87–88 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.25 (d, 2H, *J* = 2.0 Hz, H-6, H-3), 7.77–7.75 (m, 1H, H-5), 7.04–6.99 (m, 1H, H-4), 4.93 (s, 2H, -OC*H*$_2$CN), 2.55 (s, 3H, C$_2$-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 164.07 (C$_1$-*C*OOCH$_2$CN), 142.08 (C-6), 141.65 (C-2), 140.09 (C-1), 139.60 (C-3), 133.91 (C-4), 132.82 (C-5), 114.47 (-OCH$_2$*C*N), 48.83 (-O*C*H$_2$CN), 21.58 (C$_2$-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_8INO_2H$; 301.9678; found: 301.9665.

Cyanomethyl 4-methyl-3-methoxybenzoate (**3ao′**). White solid; yield: 88% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 90% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 94:6, mp = 89–90 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.58–7.56 (m, 1H, H-2), 7.45 (d, 1H, *J* = 1.2 Hz, H-6), 7.21 (d, 1H, *J* = 7.6 Hz, H-5), 4.95 (s, 2H, -OC*H*$_2$CN), 3.88 (s, 3H, C$_3$-OC*H*$_3$), 2.27 (s, 3H, C$_4$-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 165.18 (C$_1$-*C*OOCH$_2$CN), 157.86 (C-3), 134.26 (C-4), 130.76 (C-2), 126.56 (C-1), 122.53 (C-6), 114.71 (-OCH$_2$*C*N), 110.70 (C-5), 55.59 (C$_3$-OCH$_3$), 48.86 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{11}NO_3H$; 206.0817; found: 206.0801.

Cyanomethyl 4-hydroxy-3-methoxybenzoate (**3ap′**). White semi-solid; yield: 77% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 10.23 (br s, 1H, C$_4$-O*H*), 7.52–7.50 (m, 1H, H-2), 7.45 (s, 1H, H-6), 6.90 (d, 1H, *J* = 8.4 Hz, H-5), 5.15 (s, 2H, -OC*H*$_2$CN), 3.83 (s, 3H, C$_3$-OC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 164.54 (C$_1$-COOCH$_2$CN), 152.51 (C-4), 147.60 (C-3), 124.17 (C-2), 118.48 (C-1), 116.26 (-OCH$_2$*C*N), 115.44 (C-2), 112.67 (C-5), 55.68 (C$_3$-O*C*H$_3$), 49.36 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_4H$; 208.0610; found: 208.0627.

Cyanomethyl [1,1′-biphenyl]-4-carboxylate (**3aq′**). White solid; yield: 84% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 87:13, mp = 132–135 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.13 (d, 2H, *J* = 8.0 Hz, H-2, H-6), 7.70 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 7.63 (d, 2H, *J* = 7.6 Hz, C$_4$-H-2′, H-6′), 7.51–7.47 (m, 2H, C$_4$-H-3′, H-5′), 7.44–7.41 (m, 1H, H-4′), 4.99 (s, 2H, -OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 164.95 (C$_1$-COOCH$_2$CN), 146.96 (C-4), 139.62 (C-4′), 130.67 (C-2, C-6), 129.12 (C-3, C-5), 128.59 (C$_4$-C-1′), 127.43 (C$_4$-C-2′, C-6′), 127.40 (C$_4$-C-3′, C-5′), 126.57 (C-1), 114.65 (-OCH$_2$*C*N), 48.95 (-O*C*H$_2$CN) ppm. HRMS (ESI) *m/z* [M + H]$^+$ calcd. for $C_{15}H_{11}NO_2H$; 238.0868; found, 238.0892.

Bis(cyanomethyl) 3-nitrophthalate (**3ar′**). Pinkish solid; yield: 74% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 70% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30, mp = 271 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 7.88–7.85 (m, 2H, H-3, H-6), 7.82–7.79 (m, 2H, H-4, H-5), 5.21 (s, 4H, C$_1$-OC*H*$_2$CN, C$_2$-OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 165.45 (C$_1$-COOCH$_2$CN, C$_2$-COOCH$_2$CN), 132.82 (C-3, C-6), 129.55 (C-1, C-2), 129.44 (C-4, C-5), 115.55 (C$_1$-OCH$_2$*C*N, C$_2$-OCH$_2$*C*N), 50.31 (C$_1$-OCH$_2$CN, C$_2$-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_8N_2O_4H$; 245.0562; found: 245.0585.

Bis(cyanomethyl) 3-nitrophthalate (**3as′**). White solid; yield: 83% (49 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (50 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 60:40, mp = 134–135 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.62 (d, 1H, *J* = 8.4 Hz, H-4), 8.49–8.47 (m, 1H, H-6), 8.04–7.99 (m, 1H, H-5), 5.33 (s, 2H, C$_2$-OC*H*$_2$CN), 5.28 (s, 2H, C$_1$-OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 163.78 (C$_2$-*C*OOCH$_2$CN), 162.33 (C$_1$-*C*OOCH$_2$CN), 145.83 (C-3), 136.64 (C-6), 132.63 (C-4), 130.17 (C-5), 127.91 (C-2), 127.50 (C-1), 115.44 (C$_2$-OCH$_2$*C*N), 114.99 (C$_1$-OCH$_2$*C*N), 51.02 (C$_2$-O*C*H$_2$CN), 50.65 (C$_1$-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_7N_3O_6H$; 290.0413; found: 290.0402.

3-Methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylic acid (**3at′**). White solid; yield: 88% (56 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (55 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 75:25, mp = 213–215 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.54–8.52 (m, 1H, Ar-H), 8.33–8.31 (m, 1H, Ar-H), 7.81–7.79 (m, 2H, Ar-H), 7.57–7.55 (m, 3H, Ar-H), 7.50–7.46 (m, 1H, Ar-H), 4.99 (s, 2H, -C*H*$_2$-), 2.25 (-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 178.08 (*C*O), 162.67 (Ar*C*OO-), 161.17 (*C*), 154.82 (*C*), 136.83 (*C*H), 132.77 (*C*), 132.51 (*C*H), 130.84 (*C*H), 129.41 (2 × *C*H), 128.75 (2 × *C*H), 124.27 (*C*H), 123.51 (*C*), 118.05 (*C*), 117.99 (*C*), 114.32 (-CH$_2$*C*N), 49.27 (-*C*H$_2$-), 11.97 (-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{17}H_{12}O_4H$; 281.0814; found: 281.0820.

Cyanomethyl 2-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoate (**3au′**). Brownish-red semi-solid; yield: 66% (44 mg, 0.2 mmol scale, Sonochemistry), yield: 62% (41 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 97:3. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 10.13 (s, 1H, -N*H*), 8.10–8.04 (m, 2H, Ar-H), 7.98 (d, 1H, *J* = 11.2 Hz, Ar-H), 7.91–7.87 (m, 1H, Ar-H), 7.85–7.81 (m, 1H, Ar-H), 7.80–7.76 (m, 1H, Ar-H), 7.73 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.34–7.31 (m, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 5.24 (s, 2H, -OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 183.23 (*C*O), 181.32 (*C*O), 165.25 (Ar*C*OO-), 144.12 (*C*), 140.07 (*C*), 135.30 (*C*H), 135.15 (*C*H), 133.13 (*C*H), 132.31 (*C*), 131.89 (*C*H), 130.23 (*C*), 126.42 (*C*H), 125.49 (*C*H), 124.16 (*C*H), 122.24 (*C*H), 118.49 (*C*), 115.91 (-OCH$_2$*C*N), 104.94 (*C*H), 50.08 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{19}H_{12}N_2O_4H$; 333.0875; found: 333.0869.

Cyanomethyl 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoate (**3av′**). Brownish-red semi-solid; yield: 69% (46 mg, 0.2 mmol scale, Sonochemistry), yield: 63% (42 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 96:4. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 9.52 (s, 1H, -N*H*), 8.08 (d, 1H, *J* = 7.2 Hz, Ar-H), 8.03 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.97 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.90–7.86 (m, 1H, Ar-H), 7.84–7.79 (m, 1H, Ar-H), 7.61 (d, 2H, *J* = 8.4 Hz, Ar-H), 6.43 (s, 1H, Ar-H), 5.21 (s, 2H, -OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 183.24 (*C*O), 181.33 (*C*O), 164.21 (Ar*C*OO-), 144.81 (*C*), 144.00 (2*C*), 135.00 (*C*H), 133.05 (*C*H), 132.30 (*C*), 131.04 (2 × *C*H), 130.47 (*C*), 126.33 (*C*H), 125.41 (*C*H), 122.99 (*C*), 122.19 (*C*H), 116.18 (-OCH$_2$*C*N), 104.95 (*C*H), 49.73 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{19}H_{12}N_2O_4H$; 333.0875; found: 333.0889.

Cyanomethyl 2-(naphthalen-1-yl)acetate (**3ba**).[12] White solid; yield: 89% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 88:12, mp = 82 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.85–7.81 (m, 3H, H-1, H-4, H-5), 7.74 (s, 1H, H-6), 7.51–7.48 (m, 2H, H-2, H-3), 7.41–7.38 (m, 1H, H-7), 4.74 (s, 2H, -OC*H*$_2$CN), 3.89 (s, 2H, C$_8$-C*H*$_2$-) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{14}H_{11}NO_2H$; 226.0868; found: 226.0853.

Cyanomethyl 2-(naphthalen-2-yl)acetate (**3bb**). White solid; yield: 84% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 84:16, mp = 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.89 (m, 2H, H-1, H-4), 7.84 (d, 1H, J = 8.0 Hz, H-2), 7.59–7.56 (m, 1H, H-3), 7.55–7.51 (m, 1H, H-5), 7.48–7.44 (m, 1H, H-8), 7.55–7.51 (m, 1H, H-6), 7.43–7.41 (m, 1H, H-7), 4.67 (s, 2H, -OCH_2CN), 4.16 (s, 2H, C_8-CH_2-) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 170.02 (C_8-COOCH$_2$CN), 133.91 (C-9), 131.91 (C-10), 128.98 (C-1), 128.71 (C-4), 128.32 (C-2), 127.77 (C-8), 126.80 (C-3), 126.10 (C-5), 125.56 (C-7), 123.41 (C-6), 114.31 (-OCH$_2$CN), 48.73 (-OCH_2CN), 38.26 (C_8-CH_2-) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{14}H_{11}NO_2H$; 226.0868; found: 226.0847.

Cyanomethyl 2-hydroxy-1-naphthoate (**3bc**). White solid; yield: 88% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.36 (s, 1H, C_7-OH), 8.42 (d, 1H, J = 8.4 Hz, H-6), 7.78 (d, 1H, J = 8.4 Hz, H-5), 7.72 (d, 1H, J = 8.8 Hz, H-4), 7.67–7.63 (m, 1H, H-3), 7.58–7.54 (m, 1H, H-1), 7.31 (d, 1H, J = 8.8 Hz, H-2), 5.03 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 169.32 (C_1-COOCH$_2$CN), 162.00 (C-2), 137.76 (C-9), 130.34 (C-3), 127.71 (C-4), 126.34 (C-8), 124.66 (C-10), 124.20 (C-5), 123.67 (C-6), 119.44 (C-7), 114.24 (-OCH$_2$CN), 103.91 (C-1), 49.03 (-OCH_2CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{13}H_9NO_3H$; 228.0661; found: 228.0674.

Cyanomethyl cinnamate (**3ca**).[12] White solid; yield: 83% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.78 (m, 1H, C_1-CH = CH-), 7.56–7.54 (m, 2H, H-2, H-6), 7.43–7.41 (m, 3H, H-3, H-4, H-5), 6.47–6.44 (m, 1H, C_1-CH = CH-), 4.85 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.25 (C_1-COOCH$_2$CN), 147.89 (C_1-CH = CH-), 133.37 (C-1), 131.23 (C-4), 129.17 (C-2, C-6), 128.52 (C-3, C-5), 115.36 (C_1-CH = CH-), 114.66 (-OCH$_2$CN), 48.53 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{11}H_9NO_2H$; 188.0712; found: 188.0730.

Cyanomethyl (*E*)-3-(*p*-tolyl)acrylate (**3cb**). White solid; yield: 80% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 87:13, mp = 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, 1H, J = 16 Hz, C_1-CH = CH-), 7.44 (d, 2H, J = 8.0 Hz, H-2, H-6), 7.22 (d, 2H, J = 8.0 Hz, H-3, H-5), 6.40 (d, 1H, J = 16 Hz, C_1-CH = CH-), 4.84 (s, 2H, -OCH_2CN), 2.39 (s, 3H, C_1-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.43 (C_1-COOCH$_2$CN), 147.89 (C_1-CH = CH-), 141.87 (C-1), 131.06 (C-3), 129.88 (C-2, C-6), 128.54 (C-3, C-5), 114.73 (-OCH$_2$CN), 114.17 (C_1-CH = CH-), 48.45 (-OCH$_2$CN), 21.66 (C_4-CH_3) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{12}H_{11}NO_2H$; 202.0868; found: 202.0848.

Cyanomethyl (*E*)-3-(4-methoxyphenyl)acrylate (**3cc**). White solid; yield: 83% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 86:14, mp = 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, 1H, J = 16 Hz, C_1-CH = CH-), 7.49 (d, 2H, J = 8.8 Hz, H-2, H-6), 6.91 (d, 2H, J = 8.4 Hz, H-3, H-5), 6.30 (d, 1H, J = 16 Hz, C_1–CH = CH-), 4.83 (s, 2H, -OCH_2CN), 3.84 (s, 3H, C_4-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.55 (C_1-COOCH$_2$CN), 162.11 (C-4), 147.50 (C_1-CH = CH-), 130.30 (C-2, C-6), 126.48 (C-1), 114.82 (-OCH$_2$CN), 114.55 (C-3, C-5), 112.60 (C_1-CH = CH-), 55.53 (C_4-OCH$_3$), 48.38 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{12}H_{11}NO_3H$; 218.0817; found: 218.0795.

Cyanomethyl (*E*)-3-(4-hydroxyphenyl)acrylate (**3 cd**). White solid; yield: 74% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 79% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 89:11, mp = 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 1H, C_1-CH = CH-), 7.43 (d, 2H, J = 8.4 Hz, H-2, H-6), 6.87 (d, 2H, J = 8.4 Hz, H-3, H-5), 6.30–6.26 (m, 1H, C_1-CH = CH-), 4.85 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.69 (C_1-COOCH$_2$CN), 158.65 (C-4), 147.64 (C_1-CH = CH-), 130.56 (C-2, C-6), 126.48 (C-1), 116.14 (C-3, C-5), 115.39 (-OCH$_2$CN), 112.45 (C_1-CH = CH-), 48.41 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{11}H_9NO_3H$; 204.0661; found: 204.0677.

Cyanomethyl (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)acrylate (**3ce**). White solid; yield: 87% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 138–139 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.69 (d, 1H, J = 15.6 Hz, C_1-CH = CH-), 7.46 (d, 1H, J = 1.2 Hz, H-2), 7.26–7.24 (m, 1H, H-5), 6.97 (d, 1H, J = 8.0 Hz, H-6), 6.59 (d, 1H, J = 16 Hz, C_1-CH = CH-), 6.09 (s, 2H, -OCH_2O-), 5.07 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.33 (C_1-COOCH$_2$CN), 149.86 (C-3), 148.11 (C-4), 146.74 (C_1-CH = CH-), 128.11 (C-1), 125.77 (C-2), 116.19 (-OCH$_2$CN), 113.63 (C-4), 108.51 (C-5), 106.85 (C-6), 101.73 (-OCH_2O-), 49.01 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{12}H_9NO_4H$; 232.0610; found: 232.0622.

Cyanomethyl 3-phenylpropiolate (**3cf**). White solid; yield: 86% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 2H, H-2, H-6), 7.53–7.48 (m, 1H, H-4), 7.43–7.39 (m, 2H, H-3, H-5), 4.86 (s, 2H, C_1-C ≡ C-COOCH_2-) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 152.20 (C_1-COOCH$_2$-), 133.42 (C-2, C-6), 131.58 (C-4), 128.89 (C-3, C-5), 118.78 (C-1), 113.77 (-OCH$_2$CN), 90.06 (C_1-C ≡ C-), 78.81 (C_1-C ≡ C-), 49.30 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{11}H_7NO_2H$; 186.0555; found: 186.0569.

Cyanomethyl nicotinate (**3 da**). Blackish brown liquid; yield: 86% (28 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (29 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (s, 1H, H-2), 8.84 (d, 1H, J = 4.0 Hz, H-4), 8.33 (d, 1H, J = 8.0 Hz, H-6), 7.47–7.44 (m, 1H, H-5), 5.01 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.83 (C_3-COOCH$_2$CN), 154.48 (C-2), 151.13 (C-4), 137.70 (C-6), 124.25 (C-3), 123.77 (C-5), 114.13 (-OCH$_2$CN), 49.21 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_8H_6N_2O_2H$; 163.0508; found: 163.0527.

Cyanomethyl 2-methylnicotinate (**3db**). White solid; yield: 88% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 60:40, mp = 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, 1H, J = 3.6 Hz, H-2), 8.25 (d, 1H, J = 8.0 Hz, H-6), 7.29–7.27 (m, 1H, H-4), 4.98 (s, 2H, -OCH_2CN), 2.87 (s, 3H, C_2-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.56 (C_3-COOCH$_2$CN), 161.00 (C-2), 153.07 (C-4), 138.88 (C-6), 122.97 (C-3), 121.21 (C-5), 114.36 (-OCH$_2$CN), 49.00 (-OCH$_2$CN), 25.06 (C_2-CH$_3$) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_8H_8N_2O_2H$; 177.0664; found: 177.0668.

Cyanomethyl 6-chloronicotinate (**3dc**). White semi-solid; yield: 81% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 83:17. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.02 (d, 1H, J = 2.0 Hz, H-2), 8.28–8.25 (m, 1H, H-4), 7.47 (d, 1H, J = 8.4 Hz, H-5), 5.00 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.10 (C_3-COOCH$_2$CN), 157.11 (C-6), 151.57 (C-2), 139.93 (C-4), 124.72 (C-5), 123.10 (C-3), 113.96 (-OCH$_2$CN), 49.34 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_8H_5ClN_2O_2H$; 197.0118; found: 197.0127.

Cyanomethyl 2-aminonicotinate (**3dd**). White solid; yield: 82% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 65:35, mp = 148–150 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (d, 1H, J = 5.2 Hz, H-4), 6.97 (s. 1H, H-6), 6.90–6.88 (m, 1H,

H-5), 6.39 (s, 2H, C_2-NH_2), 5.21 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 164.28 (C_3-COOCH$_2$CN), 160.59 (C-2), 149.30 (C-4), 136.15 (C-6), 115.87 (-OCH$_2$CN), 109.90 (C-3), 107.56 (C-5), 50.12 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_8H_7N_3O_2H$; 178.0617; found: 178.0601.

Cyanomethyl 2-aminoisonicotinate (**3de**). White solid; yield: 79% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (31 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 50:50, mp = 165–166 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.27 (m, 1H, H-3), 8.13–8.10 (m, 1H, H-5), 6.67–6.64 (m, 1H, H-6), 4.92 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.33 (C_4-COOCH$_2$CN), 159.79 (C-2), 155.24 (C-3), 140.36 (C-5), 114.50 (-OCH$_2$CN), 113.07 (C-6), 103.87 (C-4), 48.75 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_8H_7N_3O_2H$; 178.0617; found: 178.0638.

Bis(cyanomethyl) pyridine-2,6-dicarboxylate (**3df**). White solid; yield: 77% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 73% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 55:45, mp = 144 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, 2H, *J* = 8.0 Hz, H-3, H-5), 8.17–8.13 (m, 1H, H-4), 5.07 (s, 4H, C_2-OCH_2CN, C_6-OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.99 (C_2-COOCH$_2$CN, C_6-COOCH$_2$CN), 146.79 (C-2, C-6), 139.21 (C-4), 129.64 (C-3, C-5), 113.91 (2 × -OCH$_2$CN), 49.91 (2 × -OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7N_3O_4H$; 246.0515; found: 246.0529.

Cyanomethyl 1*H*-indole-2-carboxylate (**3dg**). White solid; yield: 90% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (35 mg, 0.2 mmol scale, Mechanochemistry), mp = 163–164 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.13 (s, 1H, C_1-N*H*), 7.69 (d, 1H, *J* = 8.0 Hz, H-3), 7.47 (d, 1H, *J* = 8.4 Hz, H-7), 7.32–7.29 (m, 2H, H-5, H-6), 7.13–7.09 (m, 1H, H-4), 5.26 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 160.00 (C_2-COOCH$_2$CN), 137.90 (C-9), 126.64 (C-8), 125.45 (C-3), 125.12 (C-3), 122.42 (C-4), 120.57 (C-7), 116.15 (-OCH$_2$CN), 112.75 (C-5), 109.50 (C-6), 49.50 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_8N_2O_2H$; 201.0664; found: 201.0645.

Cyanomethyl 1*H*-indole-3-carboxylate (**3dh**). Violet solid; yield: 82% (33 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 83:17, mp = 172–174 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.18 (s, 1H, C_1-N*H*), 8.23 (s, 1H, H-2), 7.99 (d, 1H, *J* = 4.4 Hz, H-4), 7.53–7.52 (m, 1H, H-7), 7.25–7.23 (m, 2H, H-5, H-6), 5.17 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 162.83 (C_3-COOCH$_2$CN), 136.48 (C-9), 133.86 (C-3), 125.53 (C-8), 122.81 (C-4), 121.81 (C-7), 120.24 (C-5), 116.66 (-OCH$_2$CN), 112.65 (C-6), 104.34 (C-3), 48.34 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_8N_2O_2H$; 201.0664; found: 201.0657.

Cyanomethyl benzofuran-2-carboxylate (**3di**). White solid; yield: 87% (35 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 112–113 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, 1H, *J* = 8.0 Hz, H-3), 7.66–7.65 (m, 1H, H-7), 7.60 (d, 1H, *J* = 8.4 Hz, H-4), 7.53–7.49 (m, 1H, H-5), 7.35 (t, 1H, *J* = 7.6 Hz, H-6), 5.02 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.81 (C_2-COOCH$_2$CN), 156.26 (C-9), 143.24 (C-8), 128.75 (C-3), 126.65 (C-2), 124.36 (C-4), 123.32 (C-7), 116.42 (C-5), 114.08 (-OCH$_2$CN), 112.59 (C-6), 49.01 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7NO_3H$; 202.0504; found: 202.0529.

Cyanomethyl benzo[*b*]thiophene-2-carboxylate (**3dj**). White solid; yield: 85% (37 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 104–106 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H, H-3), 7.92–7.88 (m, 2H, H-4, H-7), 7.53–7.49 (m, 1H, H-5), 7.46–7.43 (m, 1H, H-6), 4.99 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.22 (C_2-COOCH$_2$CN), 142.85 (C-9), 138.50 (C-8), 132.69 (C-3), 130.55 (C-2), 127.87 (C-4), 126.06 (C-7), 125.42 (C-5), 122.94 (C-6), 114.26 (-OCH$_2$CN), 49.17 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7NO_2SH$; 218.0276; found: 218.0289.

Cyanomethyl benzo[*b*]thiophene-3-carboxylate (**3dk**). White solid; yield: 78% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 81% (35 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 75:25, mp = 95 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, 1H, *J* = 8.4 Hz, H-2), 8.48 (s, 1H, H-7), 7.89 (d, 1H, *J* = 8.0 Hz, H-4), 7.54–7.50 (m, 1H, H-5), 7.47–7.43 (m, 1H, H-6), 4.99 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 160.62 (C_3-COOCH$_2$CN), 139.90 (C-8), 138.85 (C-2), 136.38 (C-9), 125.97 (C-7), 125.59 (C-4), 124.56 (C-3), 124.47 (C-5), 122.72 (C-6), 114.67 (-OCH$_2$CN), 48.56 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7NO_2SH$; 218.0276; found: 218.0282.

Cyanomethyl quinoline-3-carboxylate (**3dl**). White solid; yield: 80% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 75:25, mp = 137–138 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.42 (d, 1H, *J* = 1.6 Hz, H-2), 8.87 (d, 1H, *J* = 2.0 Hz, H-4), 8.17 (d, 1H, *J* = 8.4 Hz, H-8), 7.95 (d, 1H, *J* = 8.0 Hz, H-5), 7.89–7.86 (m, 1H, H-6), 7.67–7.64 (m, 1H, H-7), 5.07 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.96 (C_3-COOCH$_2$CN), 150.29 (C-10), 149.63 (C-2), 139.82 (C-4), 132.83 (C-8), 129.66 (C-5), 129.38 (C-6), 128.02 (C-7), 126.66 (C-9), 120.90 (C-3), 114.28 (-OCH$_2$CN), 49.24 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_8N_2O_2H$; 213.0664; found: 213.0679.

Cyanomethyl isoquinoline-3-carboxylate (**3dm**). Pale brown solid; yield: 85% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 90% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 55:45, mp = 133–134 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.34 (s, 1H, H-4), 8.64 (s, 1H, H-1), 8.08 (d, 1H, *J* = 7.6 Hz, H-8), 8.00 (d, 1H, *J* = 7.6 Hz, H-5), 7.86–7.78 (m, 2H, H-6, H-7), 5.09 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 164.34 (C_3-COOCH$_2$CN), 153.17 (C-4), 139.55 (C-10), 135.32 (C-9), 131.73 (C-1), 130.52 (C-8), 130.35 (C-3), 128.29 (C-5), 127.94 (C-6), 125.52 (C-7), 114.39 (-OCH$_2$CN), 49.46 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_8N_2O_2H$; 213.0664; found: 213.0681.

Cyanomethyl quinoxaline-2-carboxylate (**3dn**). White solid; yield: 89% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30, mp = 125 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.55 (s, 1H, H-3), 8.29–8.27 (m, 1H, H-5), 8.22–8.19 (m, 1H, H-8), 7.98–7.93 (m, 1H, H-6), 7.93–7.89 (m, 1H, H-7), 5.15 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.94 (C_2-COOCH$_2$CN), 144.99 (C-3), 144.22 (C-9), 141.57 (C-10), 140.60 (C-2), 133.32 (C-5), 131.67 (C-8), 130.73 (C-6), 129.61 (C-7), 113.86 (-OCH$_2$CN), 49.85 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7N_3O_2H$; 214.0617; found: 214.0606.

Cyanomethyl 2-oxo-2*H*-chromene-3-carboxylate (**3do**). Pale brown solid; yield: 83% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 81% (37 mg, 0.2 mmol scale, Mechanochemistry), mp = 81–82 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.68–8.67 (m, 1H, H-4), 7.70–7.65 (m, 2H, H-5, H-8), 7.38–7.36 (m, 2H, H-6, H-7), 4.98 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.62 (C_3-COOCH$_2$CN), 156.17 (C_2-CO), 155.60 (C-10), 151.13 (C-4), 135.64 (C-8), 130.14 (C-5), 125.37 (C-7), 117.62 (C-9), 117.09 (C-6), 115.76 (C-3), 114.13 (-OCH$_2$CN), 49.43 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_8NO_4H$; 230.0453; found: 230.0438.

Cyanomethyl 6-(methyl)-2-oxo-2*H*-chromene-3-carboxylate (**3dp**). Pale brown solid; yield: 86% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (40 mg, 0.2 mmol scale, Mechanochemistry), mp = 171 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.83 (s, 1H, H-4), 7.74 (s, 1H, H-8), 7.61–7.59 (m, 1H, H-5), 7.36 (d, 1H, *J* = 8.4 Hz, H-7), 5.21 (s, 2H, -OCH_2CN), 2.38 (s, 3H, C_6-CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 161.55 (C_3-COOCH$_2$CN), 155.79 (C_2-CO), 153.03 (C-10),

150.58 (C-4), 136.19 (C-8), 134.36 (C-3), 130.07 (C-5), 117.45 (C-3), 116.05 (C-7), 115.85 (C-9), 115.55 (-OCH$_2$*C*N), 49.91 (-O*C*H$_2$CN), 20.19 (C$_6$-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_9NO_4H$, 244.0610; found: 244.0628.

Cyanomethyl 6-(*tert*-butyl)-2-oxo-2*H*-chromene-3-carboxylate (**3dq**). Pale brown solid; yield: 91% (52 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (50 mg, 0.2 mmol scale, Mechanochemistry), mp = 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1H, H-4), 7.77–7.74 (m, 1H, H-8), 7.61 (d, 1H, *J* = 2.4 Hz, H-5), 7.31 (d, 1H, *J* = 8.8 Hz, H-7), 4.99 (s, 2H, -O*C*H$_2$CN), 1.36 (s, 9H, C$_6$-C(*C*H$_3$)$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.70 (C$_3$-*C*OOCH$_2$CN), 156.51 (C$_2$-*C*O), 153.71 (C-10), 151.64 (C-4), 148.64 (C-9), 133.63 (C-8), 126.20 (C-5), 117.11 (C-6), 116.64 (C-7), 115.30 (C-3), 114.18 (-OCH$_2$*C*N), 49.36 (-OCH$_2$CN), 34.75 (C$_6$-*C*(CH$_3$)$_3$), 31.28 (C$_6$-C(*C*H$_3$)$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{16}H_{15}NO_4H$, 286.1079; found: 286.1097.

Cyanomethyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate (**3dr**). Brown solid; yield: 73% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 75% (37 mg, 0.2 mmol scale, Mechanochemistry), mp = 214–215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.81 (s, 1H, H-4), 7.80 (d, 1H, *J* = 8.4 Hz, H-8), 6.87–6.84 (m, 1H, H-5), 6.74–6.73 (m, 1H, H-6), 5.17 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.93 (C$_3$-*C*OOCH$_2$CN), 161.85 (C$_2$-*C*O), 157.57 (C-7), 156.11 (C-10), 151.24 (C-4), 132.67 (C-6), 116.02 (-OCH$_2$*C*N), 114.33 (C-8), 113.50 (C-9), 110.43 (C-3), 101.88 (C-5), 49.62 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_7NO_5H$, 246.0402; found: 246.0422.

Cyanomethyl 6-methoxy-2-oxo-2*H*-chromene-3-carboxylate (**3ds**). Pale yellow solid; yield: 81% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 77% (40 mg, 0.2 mmol scale, Mechanochemistry), mp = 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1H, H-4), 7.30 (s, 2H, H-5, H-7), 7.04 (s, 1H, H-8), 4.98 (s, 2H, -O*C*H$_2$CN), 3.87 (C$_6$-O*C*H$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.76 (C$_3$-*C*OOCH$_2$CN), 156.62 (C$_2$-*C*O), 156.41 (C-6), 150.93 (C-4), 150.27 (C-10), 124.18 (C-5), 118.23 (C-7), 117.89 (C-9), 115.93 (C-3), 114.14 (-OCH$_2$*C*N), 110.86 (C-8), 56.09 (C$_6$-OCH$_3$), 49.43 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_9NO_5H$, 260.0559; found: 260.0549.

Cyanomethyl 7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (**3dt**). Pale brown solid; yield: 73% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 71% (37 mg, 0.2 mmol scale, Mechanochemistry), mp = 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1H, H-4), 7.73–7.65 (m, 2H, H-6, H-8), 7.39–7.36 (m, 1H, H-5), 4.99 (s, 2H, -O*C*H$_2$CN), 2.61 (C$_7$-O*C*H$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.60 (C$_3$-*C*OOCH$_2$CN), 156.17 (C$_2$-*C*O), 155.57 (C-7), 151.10 (C-4), 135.89 (C-10), 135.61 (C-6), 130.13 (C-8), 125.36 (C-5), 117.62 (C-9), 115.75 (C-3), 114.13 (-OCH$_2$*C*N), 49.41 (-OCH$_2$CN), 40.89 (C$_7$-O*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_9NO_5H$, 260.0559; found: 260.0567.

Cyanomethyl 6-fluoro-2-oxo-2*H*-chromene-3-carboxylate (**3du**). Pale brown semi-solid; yield: 73% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 77% (38 mg, 0.2 mmol scale, Mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.86 (s, 1H, H-4), 7.86–7.84 (m, 1H, H-5), 7.69–7.64 (m, 1H, H-7), 7.54–7.51 (m, 1H, H-8), 5.22 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.29 (C$_3$-*C*OOCH$_2$CN), 158.05 (d, $J^1_{C\text{-}F}$ = 239 Hz, C-6), 155.46 (C$_2$-*C*O), 151.33 (C-9), 149.65 (d, $J^4_{C\text{-}F}$ = 3 Hz, C-4), 122.49 (d, $J^2_{C\text{-}F}$ = 25 Hz, C-5), 118.58 (d, $J^3_{C\text{-}F}$ = 10 Hz, C-3), 118.41 (d, $J^3_{C\text{-}F}$ = 8 Hz, C-7), 115.83 (-OCH$_2$*C*N), 115.48 (d, $J^2_{C\text{-}F}$ = 24 Hz, C-8), 50.07 (-OCH$_2$CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −117.38 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NFO_4H$, 248.0359; found: 248.0344.

Cyanomethyl 6-chloro-2-oxo-2*H*-chromene-3-carboxylate (**3dv**). Pale brown solid; yield: 80% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 78% (41 mg, 0.2 mmol scale, Mechanochemistry), mp = 178–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.85 (s, 1H, H-4), 8.09 (s, 1H, H-5), 7.80 (d, 1H, *J* = 8.4 Hz, H-7), 7.49 (d, 1H, *J* = 8.8 Hz, H-8), 5.23 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.27 (C$_3$-*C*OOCH$_2$CN), 155.28 (C$_2$-*C*O), 153.50 (C-10), 149.40 (C-4), 134.57 (C-5), 129.46 (C-7), 128.65 (C-6), 119.10 (C-9), 118.37 (C-8), 116.87 (C-3), 115.84 (-OCH$_2$*C*N), 50.10 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NClO_4H$, 264.0064; found: 264.0077.

Cyanomethyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate (**3dw**). Pale brown solid; yield: 68% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 65% (40 mg, 0.2 mmol scale, Mechanochemistry), mp = 176–178 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.85 (s, 1H, H-4), 8.23 (d, 1H, *J* = 2.4 Hz, H-5), 7.94–7.91 (m, 1H, H-7), 7.44 (d, 1H, *J* = 9.2 Hz, H-8), 5.23 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 160.91 (C$_3$-*C*OOCH$_2$CN), 154.89 (C$_2$-*C*O), 153.56 (C-6), 148.97 (C-4), 136.97 (C-5), 132.12 (C-7), 119.26 (C-10), 118.26 (C-8), 116.48 (C-9), 116.07 (-OCH$_2$*C*N), 115.47 (C-3), 49.72 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NBrO_4H$, 307.9558; found: 307.9552.

Cyanomethyl 6-nitro-2-oxo-2*H*-chromene-3-carboxylate (**3dx**). Yellow liquid; yield: 66% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 69% (38 mg, 0.2 mmol scale, Mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.08 (s, 1H, H-4), 8.98 (d, 1H, *J* = 2.0 Hz, H-5), 8.55–8.53 (m, 1H, H-7), 7.68 (d, 1H, *J* = 9.2 Hz, H-8), 5.26 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.00 (C$_3$-*C*OOCH$_2$CN), 158.32 (C$_2$-*C*O), 154.75 (C-6), 149.53 (C-4), 143.74 (C-9), 129.16 (C-5), 126.44 (C-7), 118.09 (C-10), 117.87 (C-8), 117.65 (C-3), 115.76 (-OCH$_2$*C*N), 50.18 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6N_2O_6H$, 275.0304; found: 275.0321.

Cyanomethyl 6,8-dichloro-2-oxo-2*H*-chromene-3-carboxylate (**3dy**). White solid; yield: 74% (44 mg, 0.2 mmol scale, Sonochemistry), yield: 72% (43 mg, 0.2 mmol scale, Mechanochemistry), mp = 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.86 (s, 1H, H-4), 8.11–8.10 (m, 1H, H-7), 8.08–8.07 (m, 1H, H-5), 5.24 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 160.99 (C$_3$-*C*OOCH$_2$CN), 154.46 (C$_2$-*C*O), 149.32 (C-8), 149.12 (C-7), 133.79 (C-5), 128.59 (C-7), 128.53 (C-6), 120.94 (C-10), 120.19 (C-9), 117.64 (C-3), 115.79 (-OCH$_2$*C*N), 50.21 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_5NCl_2O_4H$; 297.9674; found: 297.9678.

Cyanomethyl 6,8-dibromo-2-oxo-2*H*-chromene-3-carboxylate (**3dz**). Brownish-yellow semi-solid; yield: 83% (64 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (62 mg, 0.2 mmol scale, Mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.84 (s, 1H, H-4), 8.29 (d, 1H, *J* = 2.0 Hz, H-7), 8.23 (d, 1H, *J* = 2.0 Hz, H-5), 5.24 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 160.93 (C$_3$-*C*OOCH$_2$CN), 154.56 (C$_2$-*C*O), 150.75 (C-10), 149.09 (C-4), 139.06 (C-7), 132.09 (C-5), 120.58 (C-6), 117.46 (C-8), 116.43 (C-9), 115.76 (-OCH$_2$*C*N), 110.20 (C-3), 50.17 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NBrO_4H$; 307.9558; found: 307.9572.

Cyanomethyl 3-oxo-3*H*-benzo[*f*]chromene-2-carboxylate (**3da′**). Greenish yellow solid; yield: 72% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 70% (39 mg, 0.2 mmol scale, Mechanochemistry), mp = 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.48 (m, 1H, H-4), 8.60 (d, 1H, *J* = 8.4 Hz, H-8), 8.35 (d, 1H, *J* = 9.2 Hz, H-7), 8.09 (d, 1H, *J* = 8.0 Hz, H-2′), 7.81–7.77 (m, 1H, H-5′), 7.69–7.65 (m, 1H, H-3′), 7.59 (d, 1H, *J* = 8.8 Hz, H-4′), 5.26 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.87 (C$_3$-*C*OOCH$_2$CN), 155.77 (C$_2$-*C*O), 146.04 (C-4), 136.97 (C-8), 129.83 (C-5, C-6), 129.26 (C-7), 129.14 (C-2′), 129.10 (C-5′), 126.65 (C-4′), 122.39 (C-3′), 116.56 (C-4′), 115.92 (C-9), 114.33 (-OCH$_2$*C*N), 111.97 (C-10), 49.92 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{16}H_9NO_4H$; 280.0610; found: 280.0619.

Cyanomethyl 2-hydroxy-2,2-diphenylacetate (**3ea**). White solid; yield: 86% (46 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (47 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30, mp = 125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 4H, H-3, H-4, H-5, H-6), 7.39–7.36 (m, 6H, H-2, H-2′, H-3′, H-4′, H-5′, H-6′), 4.82 (s, 2H, -O*C*H$_2$CN),

3.86 (s, 1H, -O*H*) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 173.13 (C_1-$COOCH_2CN$), 140.83 (C-1, C-1′), 128.74 (C-2, C-2′), 128.54 (C3, C-4, C-3′, C-4′), 127.33 (C-5, C-6, C-5′, C-6′), 113.59 (-OCH_2CN), 81.55 (C_1-*C*(OH)$COOCH_2CN$), 49.84 (-OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{13}NO_3H$; 268.0974; found: 268.0997.

Cyanomethyl 2-(4-isobutylphenyl)propanoate (3eb). White semi-solid; yield: 73% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 78% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 96:4. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.18 (d, 2H, *J* = 7.6 Hz, H-2, H-6), 7.12 (d, 2H, *J* = 8.0 Hz, H-3, H-5), 4.95 (s, 2H, -O*C*H_2CN), 3.90–3.85 (m, 1H, -*CH*$COOCH_2CN$), 2.41 (d, 2H, -*C*H_2CH$(CH_3)_2$), 1.85–1.74 (m, 1H, -CH_2*CH*$(CH_3)_2$), 1.39 (d, 3H, *J* = 6.8 Hz, -*C*H_3CHCOOCH_2CN), 0.84 (d, 6H, *J* = 6.4 Hz, -CH_2CH(*C*$H_3)_2$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 173.10 (C_1-$COOCH_2CN$), 140.24 (C-1, C-1′), 137.05 (C-2, C-2′), 129.32 (C3, C-4, C-3′, C-4′), 127.15 (C-5, C-6, C-5′, C-6′), 115.90 (-OCH_2CN), 49.31 (-O*C*H_2CN), 44.28 (-CH_3*C*HCOOCH_2CN), 43.65 (-*C*H_2CH$(CH_3)_2$), 29.68 (-CH_2*C*H$(CH_3)_2$), 22.21 (-*C*H_3CHCOOCH_2CN), 18.48 (-CH_2CH(*C*$H_3)_2$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{15}H_{19}NO_2H$; 246.1494; found: 246.1481.

Benzyl 1*H*-tetrazole-5-carboxylate (**6ab**). White semi-solid; yield: 69% (28 mg, 0.2 mmol scale), eluent used for the flash column was hexane/EtOAc 97:3. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.29–8.28 (m, 2H, Ar-H), 8.04 (s, 1H, Ar-H), 7.59 (s, 3H, Ar-H & -*C*H_2), 6.82 (s, 1H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 156.18 (Ar*C*OO-), 154.75 (*C*), 131.18 (*C*H), 129.11 (2 × *C*H), 127.46 (2 × *C*H), 103.60 (*C*), 97.46 (-*C*H_2-) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_8N_4O_2H$; 205.0726; found: 205.0743.

Supporting Information

Electronic Supporting Information (ESI) available: scanned copies of ^1H-NMR, ^{13}C-NMR, and ^{19}F-NMR (for compounds **3ao**, **3ap**, **3aq**, **3ab′**, **3ak′**, **3am′**, and **3du**) for all the synthesized compounds **3** (**3aa**-**3az**, **3aa"-3av"**, **3ba**-**3bc**, **3ca**-**3cf**, **3da**-**3dz**, **3da′**, **3ea**, and **3eb**) and **6ab** are supplied (PDF).

FAIR data, including the primary NMR FID files, for all the synthesized compounds **3** and **6ab** (ZIP).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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Sono- and mechanochemical dual syntheses of bio-relevant aryldiazenyl-substituted phosphine oxides/phosphonates *via* P(O)–H functionalisation†‡

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We herein disclose a dual-synthetic approach involving sonochemical and mechanochemical strategies for diversely functionalised (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates. Both methods offer highly efficient, practical and straightforward alternative routes for accessing this important class of biologically promising phosphoramide derivatives containing phosphorus–nitrogen (P–N) bonds. Significant advantages of the newly developed methods include mild reaction conditions, avoidance of any catalysts and additives, shorter reaction times, good to excellent yields, broad substrate scope, gram-scale applicability, operational simplicity, low *E*-factors, and eco-friendliness.

Green foundation

1. The described research outcomes highlight the fruitful application of ultrasonics and ball-milling as useful green energy tools in exploring highly efficient, practical and straightforward alternative routes for accessing an important class of biologically promising phosphoramide derivatives containing phosphorus–nitrogen (P–N) bonds. The notable green chemistry advances in this endeavour include mild reaction conditions, avoidance of any catalysts and additives, shorter reaction times, good to excellent yields with low *E*-factors, and gram-scale synthetic applicability.
2. The green chemistry achievements for this research are quantitative regarding the reduction in reaction times (5–7 minutes compared to 12–24 h in earlier methods), lowering in *E*-factors (0.36–0.89 g/g), and gram-scale synthetic applications. Qualitatively, these alternative methods avoid using any catalysts/additives, reduce the use of solvents, and do not require external heating, making them energy-efficient.
3. Further research in the direction of making the processes more energy-efficient, avoidance of column chromatographic purifications, and kilogram-scale synthetic applications is prescribed.

1. Introduction

Organophosphorus compounds not only play a vital role in life processes,[1] but plenty of such phosphorus-containing derivatives are known to have applications in asymmetric catalysis,[2] flame retardants,[3] materials science,[4] agricultural science,[5] and medicinal chemistry[6] due to their interesting structural, physical and biological properties. Although organophosphorus molecules are ubiquitous in bioactive natural and synthetic compounds, those bearing phosphorus–nitrogen (P–N) bonds are rare.[7] Fig. 1 offers examples of three natural phosphoramides (**I–III**)[8a–c] with antibiotic properties and a set of arylaza phosphonates (**IV** and **V**)[8d,e] as synthetic polymeric analogues with useful materials properties, especially excimer laser ablation. Hence, the design and synthesis of functionalised phosphoramide derivatives have recently become an emerging field of research in organophosphorus chemistry for synthetic organic chemists due to their promising medicinal and materials properties.

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†This paper is dedicated to Professor Hiriyakkanavar Ila on the occasion of her 80th birthday.

‡Electronic supplementary information (ESI) available: Scanned copies of ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{31}P NMR, ^{19}F NMR (for **4ga** and **4gd**), 2D NMR (for one representative compound, **4gd**), and single-crystal X-ray crystallographic information for **4ib** are provided as supplementary materials. Copies of HRMS for trapped adducts **5–8** are also documented. CCDC 2393356. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4gc05501b

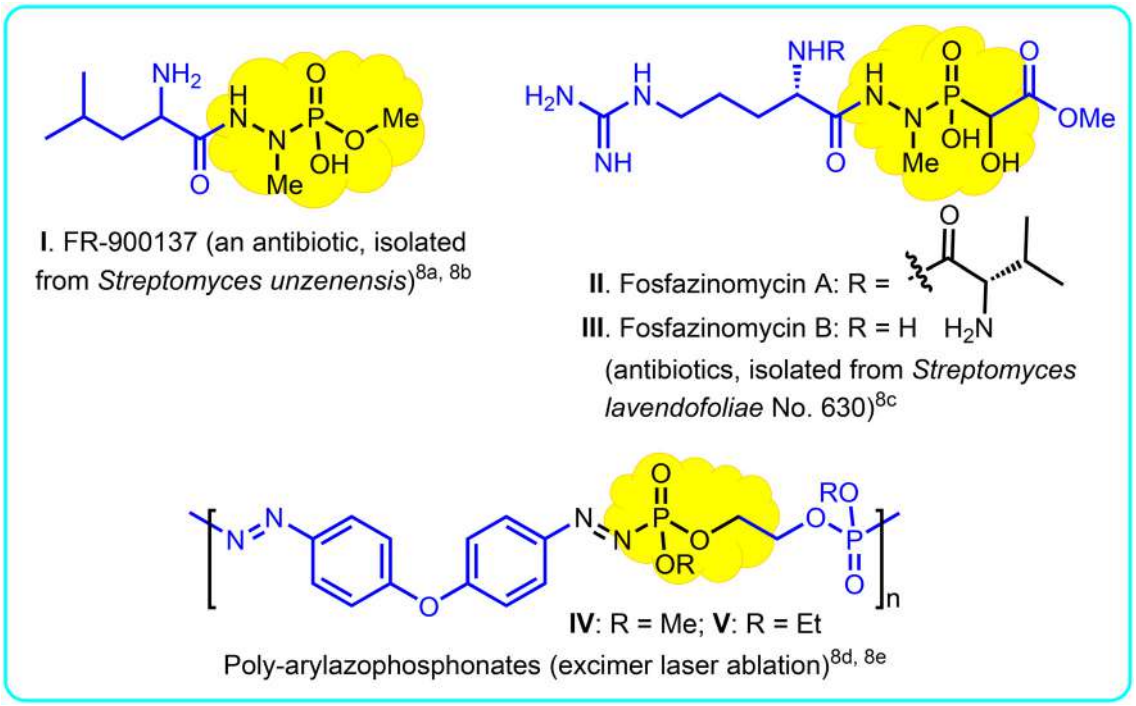
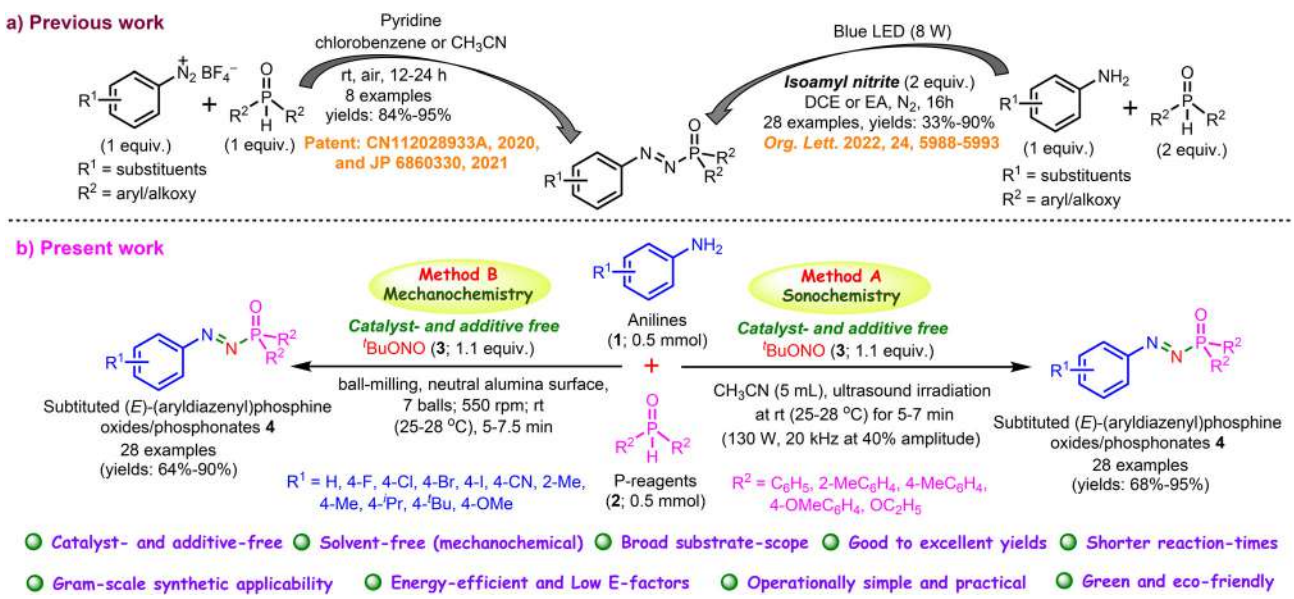


Fig. 1 Examples of a few bioactive natural and synthetic phosphoamidates.[8]

(*E*)-Aryldiazenyl-substituted phosphine oxides and phosphonates belong to a sub-group of phosphoamidates, and a literature survey reveals that there are only two previous synthetic reports for accessing these molecules. In 1998, Nuyken and co-workers[9] first synthesised only eight derivatives of phosphoamidates by stirring a mixture of aryl diazonium salts and phosphine oxides/phosphonates in the presence of pyridine as a base in a dichloromethane/acetonitrile solvent at room temperature for 12–24 h (Scheme 1a). Recently, in 2022, Lee and co-workers[10] reported a visible-light-induced alternative route for the synthesis of a series of such compounds from the one-pot three-component reaction between substituted anilines, phos-



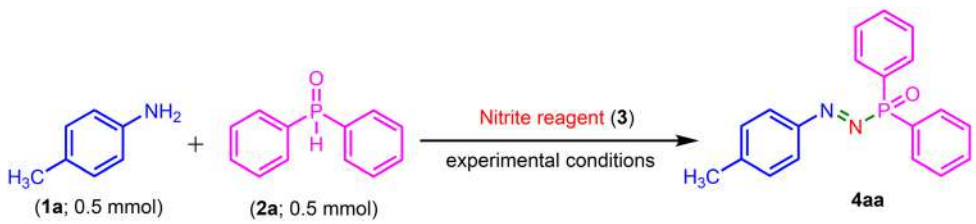
Scheme 1 (a) Earlier reports on the synthesis of (*E*)-aryldiazenyl-substituted phosphine oxides/phosphonates; and (b) sonochemical and mechanochemical syntheses of diversely substituted (*E*)-aryldiazenyl-substituted phosphine oxides/phosphonates.

phine oxides/phosphonates and isoamyl nitrite dissolved in either dichloroethane or ethyl acetate upon irradiation with blue light for 16 h under a nitrogen atmosphere (Scheme 1a). Although this visible-light-assisted protocol seems more advantageous than the previous one, mainly regarding substrate scope, it still suffers from a long reaction time (16 h), low yields of products in most cases, and use of non-aerial systems. Under this purview, designing and developing more efficient, eco-friendly, and practical synthetic routes to functionalised phosphoamidates is highly warranted. As part of our green chemistry-driven organic synthesis,[11] we eventually succeeded in developing a dual approach, both sonochemical and mechanochemical strategies, to access a series of diversely substituted (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates, as outlined in Scheme 1b. The salient features of these newly developed methods are the avoidance of any catalysts and additives, mild reaction conditions, good to excellent yields within shorter reaction times of minutes, low *E*-factors, scalability, practicality and eco-friendliness. The sonochemical method uses acetonitrile as solvent, whereas the mechanochemical process is solvent-free. The applications of sonochemical[12] and mechanochemical[13] strategies are well-documented in synthetic organic chemistry.

2. Results and discussion

We commenced our investigation with our model reaction involving a one-pot, three-component reaction between *p*-toluidine (**1a**), diphenylphosphine oxide (**2a**) and *tert*-butyl nitrite (**3**) targeting the desired product, (*E*)-diphenyl(*p*-tolyldiazenyl) phosphine oxide (**4a**), upon stirring the reactants dissolved in acetonitrile (CH_3CN) under ambient conditions, and we were delighted to isolate the desired product **4a** from this reaction, although in a low yield of 29% after 120 min (Table 1, entry 1). We also observed that this reaction is highly solvent-specific – the model reaction was found not to occur in dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, ethanol, and water when stirred under ambient conditions (Table 1, entries 2–6). Now, we turned our attention to enhancing the reaction yield (Table 1, entry 1), and we envisioned using ultrasound might do the job. Accordingly, we applied ultrasound at 30% amplitude to the model entry for 10 min, which helped in increasing the isolated yield up to 44% (Table 1, entry 7). Hence, we then increased the ultrasonic power to 40% amplitude when we isolated **4a** in 95% yield at 5 min (Table 1, entry 8). At this stage, we performed a set of twelve more reactions by varying ultrasonication power and time, nitrite reagents and their equivalency, and solvents

Table 1 Optimisation of the reaction conditions under ultrasonication[a,b]



Entry	Nitrite reagent (**3**) (equiv.)	Solvent (5 mL)	Conditions (amplitude %)	Time (min)	Yield[a,b] (%)
1	^{t}BuONO (1.1)	CH_3CN	Stirring at rt	120	29
2	^{t}BuONO (1.1)	DMSO	Stirring at rt	120	—
3	^{t}BuONO (1.1)	DMF	Stirring at rt	120	—
4	^{t}BuONO (1.1)	1,4-Dioxane	Stirring at rt	120	—
5	^{t}BuONO (1.1)	EtOH	Stirring at rt	120	Trace
6	^{t}BuONO (1.1)	H_2O	Stirring at rt	120	—
7	^{t}BuONO (1.1)	CH_3CN	Ultrasound (30%)	10	44
8	**^{t}BuONO (1.1)**	**CH_3CN**	**Ultrasound (40%)**	**5**	**95**
9	^{t}BuONO (1.1)	CH_3CN	Ultrasound (40%)	10	88
10	^{t}BuONO (1.1)	CH_3CN	Ultrasound (40%)	3	43
11	^{t}BuONO (1.1)	CH_3CN	Ultrasound (50%)	5	72
12	^{t}BuONO (0.75)	CH_3CN	Ultrasound (40%)	5	74
13	^{t}BuONO (1.5)	CH_3CN	Ultrasound (40%)	5	89
14	^{t}BuONO (1.1)	DMSO	Ultrasound (40%)	10	Trace
15	^{t}BuONO (1.1)	DCM	Ultrasound (40%)	10	42
16	^{t}BuONO (1.1)	Dioxane	Ultrasound (40%)	10	—
17	^{t}BuONO (1.1)	DMF	Ultrasound (40%)	10	—
18	^{t}BuONO (1.1)	EtOH	Ultrasound (40%)	10	64
19	^{t}BuONO (1.1)	H_2O	Ultrasound (40%)	10	69
20	$NaNO_2$ (1.1)	CH_3CN	Ultrasound (40%)	10	53

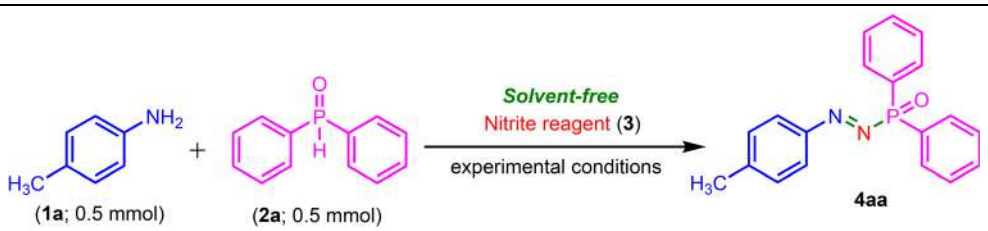
[a] Reaction conditions: a mixture of *p*-toluidine (**1a**; 0.5 mmol) and diphenylphosphine oxide (**2a**; 0.5 mmol) was reacted with *tert*-butyl nitrite or sodium nitrite in the absence of any catalyst in 5 mL of varying solvent(s) under either room temperature (rt, 25–28 °C) stirring or ultrasound irradiation (US; 130 W, 20 kHz at 40–50% amplitude). [b] Isolated yields.

(Table 1, entries 9–20) when the best-suited reaction conditions for our model reaction came out as irradiating the reaction mixture of *p*-toluidine (**1a**, 0.5 mmol), diphenylphosphine oxide (**2a**, 0.5 mmol) and *tert*-butyl nitrite (**3**, 0.55 mmol, 1.1 equiv.) in acetonitrile (5 mL) with ultrasound at 40% amplitude for 5 min, thereby furnishing the target product, (*E*)-diphenyl(*p*-tolyldiazenyl)phosphine oxide (**4aa**), in 95% yield (Table 1, entry 8). Compound **4aa** is a new compound fully characterised by its detailed spectral (^{1}H-, ^{13}C- and ^{31}P-NMR, DEPT-135, and HRMS) studies. The overall results are summarised in Table 1.

Upon establishing the optimised sonochemical conditions for our model reaction, we were motivated to investigate the applicability of a ball-mill as another widely used green tool in organic synthesis. We envisioned that the mechanochemical transformation might be implemented solvent-free, and accordingly, we performed the model reaction with *p*-toluidine (**1a**, 0.5 mmol), diphenylphosphine oxide (**2a**, 0.5 mmol) and *tert*-butyl nitrite (**3**, 0.55 mmol, 1.1 equiv.) by grinding the reaction mixture in a ball-mill using neutral alumina as a surface and seven stainless steel balls at 550 rpm for just 5 min, when we were able to isolate the targeted product **4aa** in an excellent yield of 90% (Table 2, entry 1), almost a similar yield obtained out of the sonochemical method. We carried out 15 more trial reactions (Table 2, entries 2–16) with the model entry under varying conditions (such as variations in surface materials, nitrating agents, number of balls, rotation-speed, *etc*.) to validate the best-suited mechanochemical conditions. We also performed a control experiment using a tungsten carbide jar and balls to rule out any catalytic intervention by a stainless steel jar and balls (Table 2, entry 17). Eventually, we were delighted to unearth another alternative and efficient method for the same transformation under ball-milling using neutral alumina (2.0 g) as the surface and seven stainless steel balls (10 mm in diameter) milled for 5 min (rotation in an inverted direction with a 5 s break at 2.5 min interval) at 550 rpm, from where we isolated **4aa** in 90% yield (Table 2, entry 1). All these results are summarised in Table 2.

Thus, we have now accomplished a dual approach for the direct P–H functionalisation of phosphine oxides/phosphonates as practical and useful alternative green synthetic routes to access biologically promising diverse series of aryldiazenyl-substituted phosphine oxides/phosphonates by using sonochemical (Method A) and mechanochemical (Method B) strategies (Scheme 1b). Having established the optimised reaction conditions for both methods, we planned to explore the scope of the developed protocols and compare their efficacies in terms of respective yields and reaction times of this one-pot, three-component transformation. As part of this endeavour, we first conducted a set of nine reactions by treating the aniline derivatives (**1b–1j**), bearing both electron-donating and electron-withdrawing functionalities (such as methyl, iso-propyl, *tert*-butyl, methoxy, cyano, fluoro, chloro, bromo, and iodo), with diphenylphosphine oxide (**2a**) and *tert*-butyl nitrite (**3**)

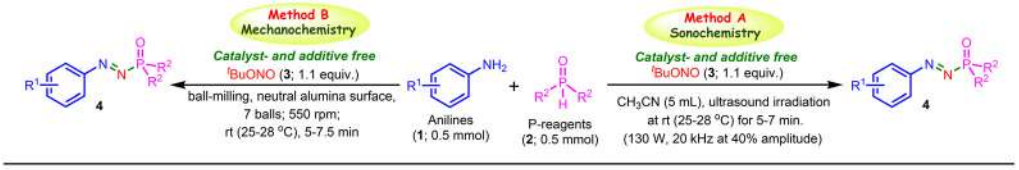
Table 2 Optimisation of the reaction conditions under ball-milling

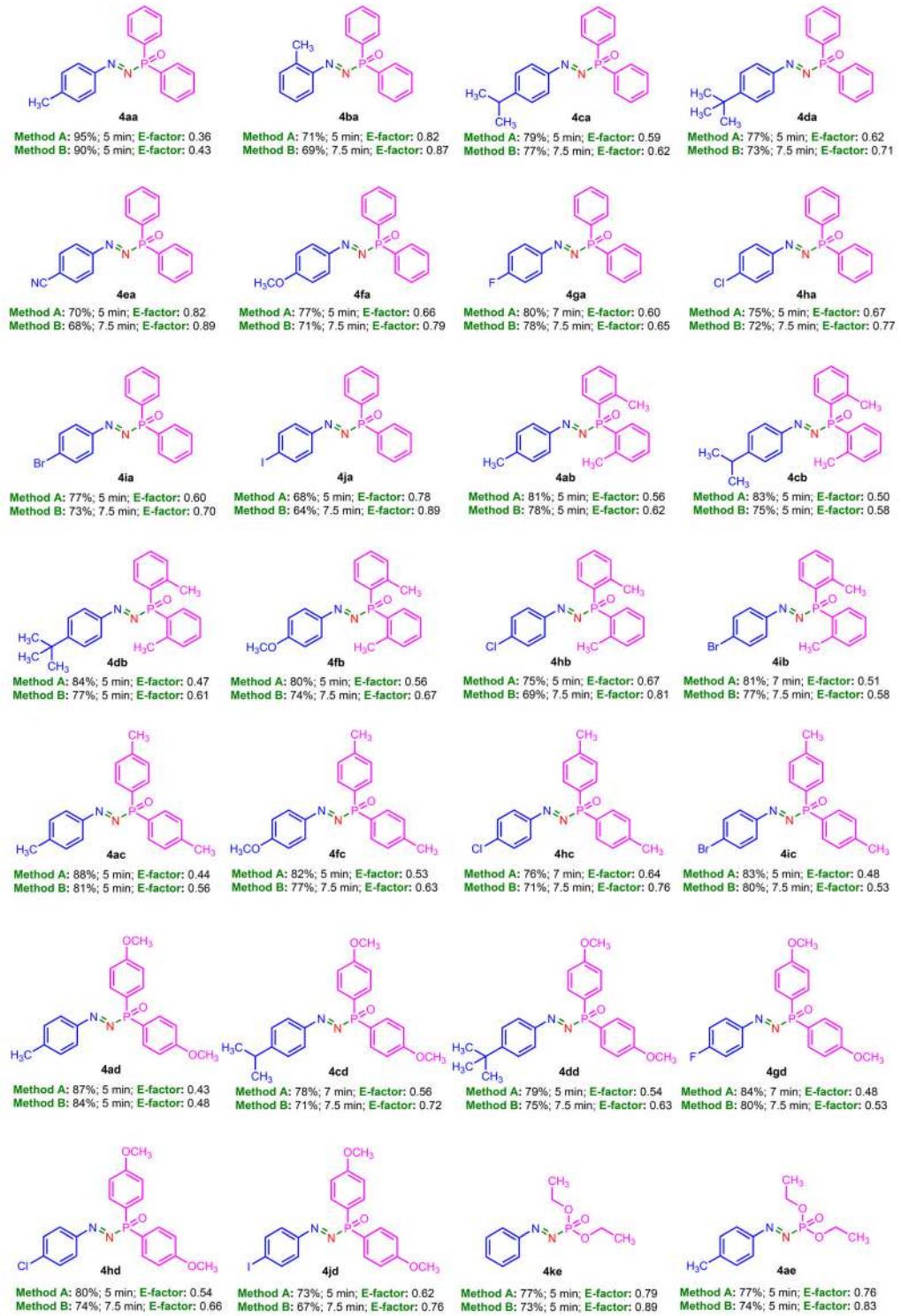


Entry	Surface (2 g)	Nitrite reagent (3) (equiv.)	Conditions	No. of balls/rpm	Time (min)	Yield[a,b] (%)
1	**Neutral alumina**	**^{t}BuONO (1.1)**	**Ball-milling**	**7/550**	**5**	**90**
2	Neutral alumina	^{t}BuONO (0.5)	Ball-milling	7/550	10	39
3	Neutral alumina	^{t}BuONO (0.75)	Ball-milling	7/550	10	64
4	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	7/600	5	90
5	Neutral alumina	^{t}BuONO (1.5)	Ball-milling	7/550	5	89
6	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	8/550	5	88
7	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	6/550	10	86
8	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	7/450	15	72
9	Neutral alumina	$NaNO_2$ (1.1)	Ball-milling	7/550	10	66
10	Basic alumina	^{t}BuONO (1.1)	Ball-milling	7/550	10	80
11	Acidic alumina	^{t}BuONO (1.1)	Ball-milling	7/550	10	81
12	Silica	^{t}BuONO (1.1)	Ball-milling	7/550	10	Trace
13	NaCl	^{t}BuONO (1.1)	Ball-milling	7/550	10	Trace
14	—	^{t}BuONO (1.1)	Stirring at rt	—	120	Trace
15	—	$NaNO_2$ (1.1)	Stirring at rt	—	120	Trace
16	Neutral alumina	—	Ball-milling	7/550	60	—
17[c]	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	7/550	5	90

[a] Reaction conditions: a mixture of *p*-toluidine (**1a**; 0.5 mmol) and diphenylphosphine oxide (**2a**; 0.5 mmol) was reacted with either *tert*-butyl nitrite or sodium nitrite under ball-milling (using a 25 mL stainless-steel jar and balls of 10 mm diameter, and rotation in an inverted direction with a break of 5 s at 2.5 min intervals) in the absence of additives. [b] Isolated yields. [c] Using tungsten carbide jar and balls.

Table 3 Sonochemical and mechanochemical syntheses of diversely functionalised (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates (**4**)[a,b]





[a] Reaction conditions: a mixture of anilines (**1**; 0.5 mmol) and phosphine oxides/phosphonate (**2**; 0.5 mmol) was reacted with *tert*-butyl nitrite (**3**; 0.55 mmol, 1.1 equiv.) under both ultrasonication (Method A) and ball-milling (Method B) reaction conditions, respectively. [b] Isolated yields.

separately under the optimised conditions for sonochemical (Method A) and mechanochemical (Method B) processes. All the reactions took place smoothly in both methods, furnishing the desired (*E*)-diphenyl(aryldiazenyl)phosphine oxides (**4ba–4ja**) in good yields ranging from 68–95% in the sonochemical method and 64–90% in the mechanochemical method, within respective reaction time periods of 5–7 min and 5–7.5 min (Table 3, compounds **4ba–4ja**). Encouraged by these results, we then planned to extend the scope of diarylphosphine oxide **2**; we thus performed a set of sixteen more reactions between substituted diarylphosphine oxides (*viz.* di-*o*-tolylphosphine oxide **2b**, di-*p*-tolylphosphine oxide **2c**, and bis(4-methoxyphenyl)phosphine oxide **2d**), diversely functionalised aromatic primary amines (**1a**, **1c**, **1d**, and **1f–1j**) and *tert*-butyl nitrite (**3**) under identical reaction conditions, following both methods individually. All the reactions occurred satisfactorily both sono- and mechanochemically. We isolated the corresponding differently substituted (*E*)-diaryl(aryldiazenyl)phosphine oxides **4** (Table 3, compounds **4ab**, **4cb**, **4db**, **4fb**, **4hb**, **4ib**, **4ac**, **4fc**, **4hc**, **4ic**, **4ad**, **4cd**, **4dd**, **4gd**, **4hd**, and **4jd**) in good yields ranging from 73–88% under ultrasonication (Method A) within 5–7 min, and 67–84% under ball-milling (Method B) within 5–7.5 min. Delightfully, diethyl phosphonate (**2e**) also participated in the transformation in both methods under similar reaction conditions, thereby affording aryldiazenyl-substituted phosphonate derivatives, such as diethyl (*E*)-(phenyldiazenyl)phosphonate (**4ke**) and diethyl (*E*)-(*p*-tolyldiazenyl)phosphonate (**4ae**), with an identical yield of 77% for **4ke** at 5 min following both methods, and with 73% and 74% yields for **4ae** at 5 min under sonication and ball-milling, respectively (Table 3, compounds **4ke** and **4ae**). However, dialkylphosphine oxide was highly reluctant to undergo this reaction, as evidenced by our experimental observations that we could not detect the formation of the desired product when the model reaction was performed with dimethylphosphine oxide [$Me_2P(O)H$] in both methods (Methods A and B) even after 30 minutes of operation. This is perhaps because the alkyl groups cannot stabilise the proposed *in situ*-generated phosphonyl radical from the P-reagent. All the experimental results are shown in Table 3.

All the isolated products, **4**, synthesised following both Method A (sonochemical) and Method B (mechanochemical), were purified using the column chromatographic technique (see the Experimental section). All are new compounds except **4ea**, **4fa**, **4ke** and **4ae**. Each synthesised compound was fully characterised based on their detailed spectral studies, including ^{1}H-NMR, ^{13}C-NMR, DEPT-135, ^{31}P-NMR, ^{19}F-NMR (for **4ga** and **4gd**), 2D-NMR (for one representative compound, **4gd**), and HRMS (see the Experimental section). Further confirmation of the structural framework, as deduced from the spectral analyses, was established from the single-crystal X-ray diffraction studies for a representative entry, (*E*)-((4-bromophenyl)diazenyl)di-*o*-tolylphosphine oxide (**4ib**; CCDC 2393356‡); space group: $P\bar{1}$; unit cell parameters: a 6.9964(6) Å, b 8.4138 (8) Å, c 17.0464(18) Å; α 86.124(8)°, β 89.703(8)°, γ 73.686(8)° (see the ESI‡). Fig. 2 shows the ORTEP diagram of the molecule **4ib**.

To evaluate the greenness of these two newly developed methods, we herein calculated (see the ESI‡) *E*-factor (g/g)[14] for all the synthesised compounds **4**. The calculated *E*-factors were found to be in the range of 0.82–0.36 for the sonochemical method and 0.89–0.43 for the mechanochemical method. The calculated parameters indicate the considerable greenness of both methods; the respective *E*-factors for each entry are shown in Table 3. Again, to determine the synthetic practicality of both approaches, we carried out gram-scale synthetic applications (5.0 and 10.0 mmol-scales; 10- and 20-fold enhancement; Scheme 2) for our model compound, (*E*)-diphenyl (*p*-tolyldiazenyl)phosphine oxide (**4aa**). The sonochemical method (Method A) furnished the product **4aa** with a satisfactory yield of 91% after 5 min in both experiments (see the Experimental section). The mechanochemical method (Method B) afforded 84% and 81% yields in the 5.0 mmol and 10.0 mmol reactions, respectively, after 7.5 min (see the Experimental section). The yields and the reaction times observed in the gram-scale synthesis were almost identical to those for the millimolar scale reactions.

Finally, we performed a set of control experiments with our model reaction in the presence of three different radical scavengers, such as TEMPO, BHT and *p*-benzoquinone (BQ), to pursue an idea of the possible mechanistic pathway of this one-pot, three-component reaction between anilines (**1**), substituted phosphine oxides/phosphonates (**2**) and *tert*-butyl nitrite (**3**) following either ultrasonication or ball-milling processes, resulting in the formation of (*E*)-diaryl(aryldiazenyl) phosphine oxides/phosphonates (**4**). The results of the control experiments are depicted in Scheme 3. Each of the radical scavengers was found to inhibit the reaction when carried out either sonochemically or mechanochemically, thereby

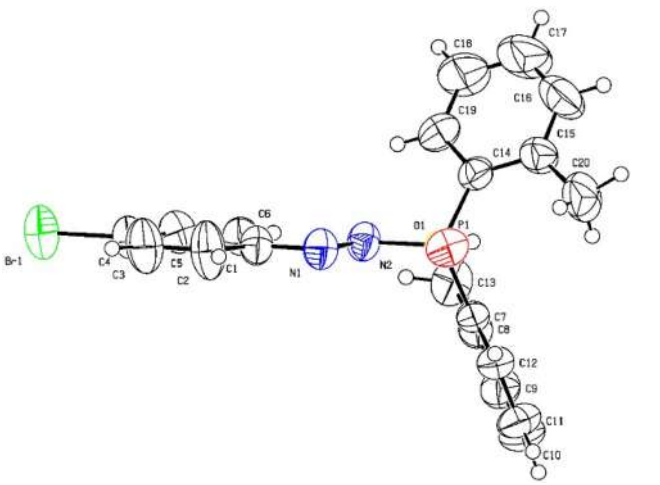
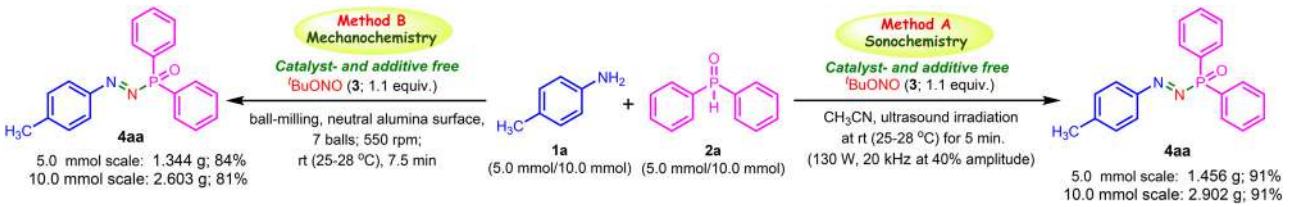
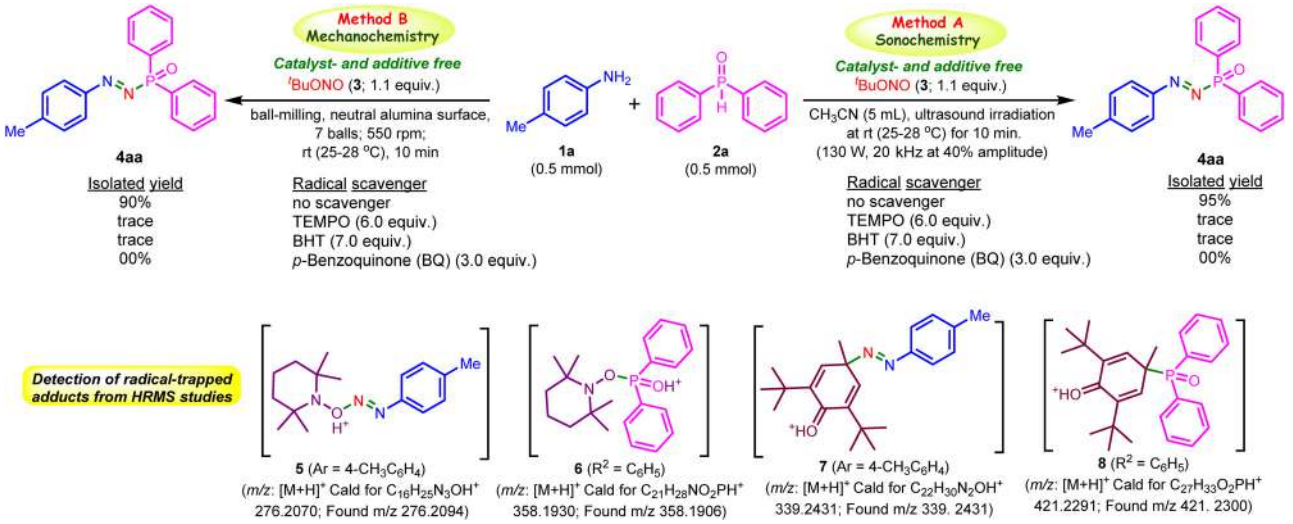


Fig. 2 ORTEP view of molecule **4ib** (CCDC 2393356‡), showing the atom-labeling scheme (displacement ellipsoids are drawn at the 50% probability level).



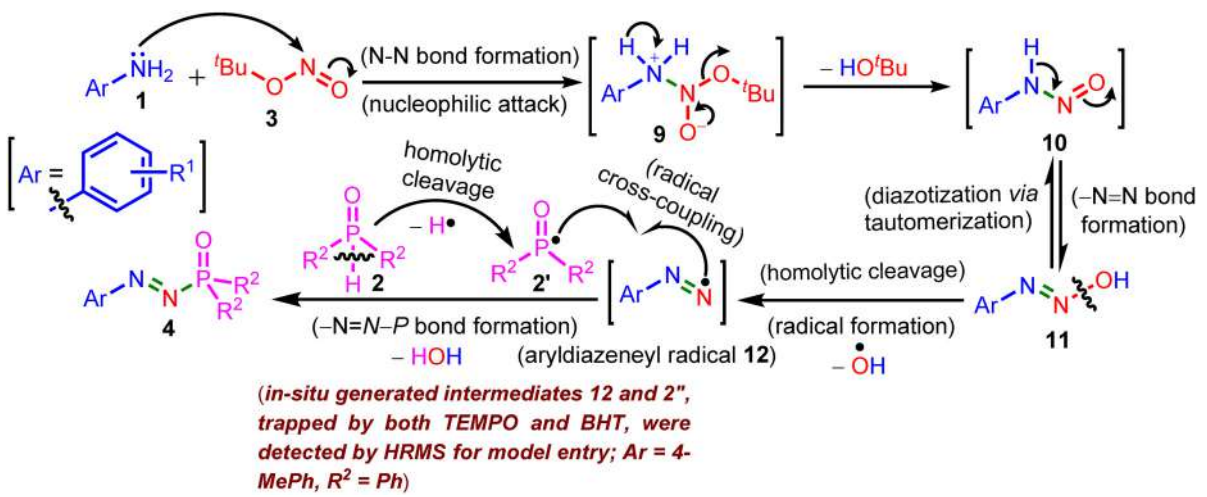
Scheme 2 Gram-scale synthetic applications under both sono- and mechanochemical methods.



Scheme 3 Control experiments with radical scavengers.

suggesting that the transformation follows a radical pathway in both processes. Delightfully, we successfully detected the TEMPO-adducts **5** and **6** and the BHT-adducts **7** and **8** (Scheme 3) from the HRMS analysis, which supported our presumption of the generation of possible radical intermediates, such as aryldiazenyl radical **12** (trapped adducts **5** and **7**) and phosphonyl radical **2′** (trapped adducts **6** and **8**).

Based on the results of the control experiments (Scheme 3), we herein proposed a possible mechanism (Scheme 4) for the sono- and mechanochemical transformations. Aromatic primary amine **1** and *tert*-butyl nitrite (**3**) first react together under the reaction conditions to form (*E*)-1-hydroxy-2-aryldiazene (**11**),[10,15] which then undergoes a homolytic cleavage of its N–OH bond to generate an aryldiazenyl radical inter-



Scheme 4 Proposed reaction mechanism.

mediate (**12**, as trapped by TEMPO and BHT). Simultaneously, phosphine oxide **2** also forms a phosphonyl radical intermediate **2′** (as trapped by TEMPO and BHT). Finally, these *in situ*-generated radical intermediates **12** and **2′** undergo rapid hetero-cross-coupling to afford the desired product **4** (Scheme 4).

3. Conclusions

We have developed practical and straightforward alternative synthetic protocols for diversely functionalised (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates (**4**) based on sonochemical and mechanochemical strategies as a dual approach from the three-component one-pot reaction between substituted anilines (**1**), diarylphosphine oxides/dialkyl phosphonates (**2**) and *tert*-butyl nitrite (**3**). The sonochemical method utilises the advantages of ultrasound irradiation under catalyst- and additive-free conditions under ambient conditions, while the mechanochemical process implements the chemical transformation with the same efficiency under high-speed solvent-free ball-milling conditions. The key advantages of the newly developed methods are mild reaction conditions that use ultrasound and ball-milling as green tools, avoidance of any catalysts and additives, shorter reaction times, good to excellent yields, broad substrate scope and tolerance of various functional groups, scalability, operational simplicity, low *E*-factors, and eco-friendliness.

4. Experimental section

4.1. General method

Chemicals and solvents used in this work were purchased from reputed companies. ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded at 400, 100, and 162 MHz, respectively, using a Bruker DRX spectrometer. $CDCl_3$ and DMSO-d_6 were used as solvents, and TMS was used as an internal standard for recording the NMR spectra. The ^{1}H-NMR signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet), and the chemical shift values for both ^{1}H- and ^{13}C-NMR spectra are presented in δ (ppm). Coupling constants are reported as J values in Hz. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. A Waters (G2-XS Q-TOF) high-resolution mass spectrometer was utilised to record the HRMS spectra. X-ray single-crystal crystallographic data were collected using an X′ Calibur CCD area-detector diffractometer. The melting points were recorded on a Chemiline CL-725 melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was performed using silica gel 60 F254 (Merck) plates. A Sonics-made ultrasound probe-sonicator (model: VCX 130) with a frequency of 20 kHz and energy of 130 W was used for sonication. A PM 100 (Retsch GmbH, Germany) ball-milling apparatus was used for mechanochemical reactions. Safety statement on the procedures: We did not detect/encounter any unexpected, new, and/or significant hazards or risks associated with the reported work.

4.2. General procedure for the synthesis of functionalised (*E*)-(aryldiazenyl)phosphine oxides/phosphonates (4) under the sonochemical method (Method A)

Anilines (**1**; 0.5 mmol), diarylphosphine oxides/dialkyl phosphonates (P-reagents, **2**; 0.5 mmol), and *tert*-butyl nitrite (^{t}BuONO, **3**; 1.1 equivalent) were added sequentially to an oven-dried glass vessel (20 mL). 5 mL of acetonitrile was then added to the vessel. The mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 5–7 minutes (monitored by TLC). Upon completion of the reaction, the whole content was transferred into a 25 mL separating funnel, followed by addition of 20 mL of a mixture (3 : 1 v/v) of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the crude mass, which was then subjected to column chromatographic purification using EtOAc–hexane mixtures as eluents to isolate the desired products (*E*)-(aryldiazenyl)phosphine oxides/phosphonates **4** (**4aa–4ja**, **4ab**, **4cb**, **4db**, **4fb**, **4hb**, **4ib**, **4ac**, **4fc**, **4hc**, **4ic**, **4ad**, **4cd**, **4dd**, **4gd**, **4hd**, **4jd**, **4ae**, and **4ke**). The synthesised compounds were fully characterised by spectroscopic studies, including ^{1}H-NMR, ^{13}C-NMR, DEPT-135, ^{31}P-NMR, ^{19}F-NMR (for compounds **4ga** and **4gd**), 2D-NMR (for compound **4gd**), single-crystal X-ray diffraction (XRD) studies (for compound **4ib**) and HRMS. The physical and spectral data for known compounds (*viz.* **4ea**, **4fa**, **4ae** and **4kl**) were consistent with previously reported data[10] (see the ESI‡).

4.3. Gram-scale synthesis of one representative compound 4aa under the sonochemical method (Method A)

p-Toluidine (**1a**; 5.0 mmol/10.0 mmol), diphenylphosphine oxide (**2a**; 5.0 mmol/10.0 mmol), and *tert*-butyl nitrite (^{t}BuONO, **3**; 1.1 equivalent) were added sequentially to an oven-dried glass vessel (20 mL), followed by adding 5 mL/10 mL of acetonitrile. Each reaction mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 5 minutes (monitored by TLC). Upon completion of each reaction, the resultant reaction mixture was worked up and purified following the same procedure as mentioned in the general method (Method A) to obtain pure product **4aa** in 91% yield for both 5.0 mmol-scale (1.456 g of **4aa**) and 10.0 mmol-scale (2.902 g of **4aa**) experiments.

4.4 General procedure for the synthesis of functionalised (*E*)-(aryldiazenyl)phosphine oxides/phosphonates (4) under ball-milling (Method B)

A mixture of anilines (**1**; 0.5 mmol), P-reagent (**2**; 0.5 mmol), and ^{t}BuONO (**3**; 1.1 equivalent) was subjected to ball-milling in the presence of neutral alumina (1.5 g) as the surface at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) made of the same material for 5–7.5 minutes. The ball-milling operation was conducted with an inverted

rotation direction, with intervals of 2.5 minutes and breaks of 5 seconds. After completion of the reaction (monitored by TLC), the entire content was transferred into a 250 mL separating funnel, followed by adding 30 mL of a mixture (3 : 1 v/v) of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to obtain a crude mass, which was subjected to column chromatographic purification using EtOAc–hexane mixtures as eluents to yield pure products of substituted (*E*)-(aryldiazenyl)phosphine oxides/phosphonates **4** (**4aa–4ja**, **4ab**, **4cb**, **4db**, **4fb**, **4hb**, **4ib**, **4ac**, **4fc**, **4hc**, **4ic**, **4ad**, **4cd**, **4dd**, **4gd**, **4hd**, **4jd**, **4ae**, and **4ke**).

4.5 Gram-scale synthesis of one representative compound 4aa under ball-milling (Method B)

A mixture of *p*-toluidine (**1a**; 5.0 mmol/10.0 mmol), diphenylphosphine oxide (**2a**; 5.0 mmol/10.0 mmol), and *tert*-butyl nitrite (^{t}BuONO, **3**; 1.1 equivalents) were subjected to ball-milling in the presence of neutral alumina (1.5 g for 5.0 mmol-scale/6.0 g for 10.0 mmol-scale) as the surface at 550 rpm using a 25 mL (5.0 mmol-scale)/50 mL (10.0 mmol-scale) stainless steel jar with seven balls (10 mm in diameter) made of the same material for 7.5 minutes (monitored by TLC). The ball-milling operation was conducted with an inverted rotation direction, with intervals of 2.5 minutes and breaks of 5 seconds. Upon completion of each reaction, the resultant reaction mixture was worked up and purified following the same procedure as mentioned in the general method (Method B) to obtain a pure product **4aa** in 84% yield for 5.0 mmol-scale (1.344 g of **4aa**) and 81% yield for 10.0 mmol-scale (2.603 g of **4aa**) experiments.

4.6. The physical and spectral data of the synthesised (*E*)-aryldiazenyl-substituted phosphine oxides/phosphonates 4

(*E*)-Diphenyl(*p*-tolyldiazenyl)phosphine oxide (4aa). Light reddish solid; yield: 95% (152 mg, 0.5 mmol scale, sonochemistry), yield: 90% (144 mg, 0.5 mmol scale, mechanochemistry), mp = 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 4H, Ar–H), 7.88 (d, 2H, J = 8.0 Hz, Ar–H), 7.58–7.54 (m, 2H, Ar–H), 7.52–7.47 (m, 4H, Ar–H), 7.30 (d, 2H, J = 8.0 Hz, Ar–H), 2.42 (s, 3H, Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.15 (d, $J_{C–P}$ = 44 Hz, *C*), 145.19 (*C*), 132.62 (2 × *C*H), 132.50 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 130.08 (d, $J_{C–P}$ = 176 Hz, 2 × *C*), 129.92 (2 × *C*H), 128.74 (d, $J_{C–P}$ = 12 Hz, 4 × CH), 123.41 (2 × *C*H), 21.82 (Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.84 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2OPH^+$, 321.1151; found: *m*/*z* 321.1133.

(*E*)-Diphenyl(*o*-tolyldiazenyl)phosphine oxide (4ba). Red oil; yield: 71% (113 mg, 0.5 mmol scale, sonochemistry), yield: 69% (110 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.89 (m, 4H, Ar–H), 7.59–7.56 (m, 2H, Ar–H), 7.52–7.43 (m, 6H, Ar–H), 7.35 (d, J = 6.8 Hz, 1H, Ar–H), 7.24–7.20 (m, 1H, Ar–H), 2.64 (s, 3H, Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 154.65 (d, $J_{C–P}$ = 43 Hz, *C*), 141.51 (*C*), 134.22 (2 × *C*H), 132.62 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 131.94 (2 × *C*H), 128.79 (2 × *C*), 128.67 (2 × *C*H), 126.40 (2 × *C*H), 113.37 (2 × *C*H), 17.48 (Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.38 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2OPH^+$, 321.1151; found: *m*/*z* 321.1158.

(*E*)-((4-Isopropylphenyl)diazenyl)diphenylphosphine oxide (4ca). Black semi-solid; yield: 79% (138 mg, 0.5 mmol scale, sonochemistry), yield: 77% (135 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.86 (m, 6H, Ar–H), 7.44–7.40 (m, 6H, Ar–H), 7.29–7.26 (m, 2H, Ar–H), 2.90–2.82 (m, 1H, Ar–C*H*$(CH_3)_2$) 1.17–1.14 (m, 6H, Ar–CH$(CH_3)_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.59 (*C*), 153.06 (d, $J_{C–P}$ = 44 Hz, *C*), 132.36 (d, $J_{C–P}$ = 2 Hz, 2 × *C*H) 132.14 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 129.42 (d, $J_{C–P}$ = 116 Hz, 2 × *C*), 128.47 (d, $J_{C–P}$ = 12 Hz, 4 × *C*H), 127.05 (2 × *C*H), 123.23 (2 × *C*H) 34.07 (Ar–*C*H$(CH_3)_2$), 23.45 (Ar–CH(*C*H$_3$)$_2$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.73 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2OPH^+$, 349.1464; found: *m*/*z* 349.1472.

(*E*)-((4-(*tert*-Butyl)phenyl)diazenyl)diphenylphosphine oxide (4da). Dark reddish semi-solid; yield: 77% (140 mg, 0.5 mmol scale, sonochemistry), yield: 73% (133 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.89 (m, 6H, Ar–H), 7.49–7.41 (m, 8H, Ar–H), 1.28 (s, 9H, 3CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.85 (*C*), 152.66 (d, J = 43 Hz, *C*), 132.44 (d, $J_{C–P}$ = 2 Hz, 2 × *C*H), 132.23 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 129.47 (d, $J_{C–P}$ = 116 Hz, 2 × *C*), 128.55 (d, $J_{C–P}$ = 12 Hz, 4 × CH), 126.02 (2 × *C*H), 122.97 (2 × *C*H), 35.14 (Ar–*C*(CH_3)), 30.96 (3 × Ar–C(*C*H$_3$)) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.76 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2OPH^+$, 363.1612; found: *m*/*z* 363.1626.

(*E*)-4-((Diphenylphosphoryl)diazenyl)benzonitrile (4ea).[10] Purple solid; yield: 70% (116 mg, 0.5 mmol scale, sonochemistry), yield: 68% (112 mg, 0.5 mmol scale, mechanochemistry), mp = 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.96 (m, 6H, Ar–H), 7.83 (d, 2H, J = 8.4 Hz, Ar–H), 7.63–7.60 (m, 2H, Ar–H), 7.57–7.52 (m, 4H, Ar–H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.43 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}N_3OPH^+$, 332.0947; found: *m*/*z* 332.0930.

(*E*)-((4-Methoxyphenyl)diazenyl)diphenylphosphine oxide (4fa).[10] Dark reddish solid; yield: 84% (68 mg, 0.5 mmol scale, sonochemistry), yield: 76% (62 mg, 0.5 mmol scale, mechanochemistry), mp = 101–103 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (d, 2H, J = 9.2 Hz, Ar–H), 7.87–7.83 (m, 4H, Ar–H), 7.65–7.61 (m, 2H, Ar–H), 7.59–7.54 (m, 4H, Ar–H), 7.13 (d, 2H, J = 8.8 Hz, Ar–H), 3.85 (Ar–OCH_3), ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 25.22 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_2PH^+$, 337.1100; found: *m*/*z* 337.1103.

(*E*)-((4-Fluorophenyl)diazenyl)diphenylphosphine oxide (4ga). Pinkish red solid; yield: 80% (130 mg, 0.5 mmol scale, sonochemistry), yield: 78% (126 mg, 0.5 mmol scale, mechanochemistry), mp = 147–149 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.05–8.02 (m, 2H, Ar–H), 7.94–7.89 (m, 4H, Ar–H), 7.67–7.61 (m, 6H, Ar–H), 7.46 (t, J = 8.4 Hz, 2H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.66 (d, $J_{C–F}$ = 252 Hz, *C*), 150.96 (d, $J_{C–P}$ = 45 Hz, *C*), 132.96 (2 × *C*H), 131.99 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H) 129.45 (d, $J_{C–P}$ = 116 Hz, 2 × *C*), 129.11

(d, J_{C-F} = 12 Hz, 2 × *C*H), 125.61 (d, J_{C-P} = 9 Hz, 4 × *C*H), 116.88 (d, J_{C-F} = 23 Hz, 2 × *C*H) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 25.73 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −104.39 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_2OPH^+$, 325.0901; found: *m*/*z* 325.0921.

(*E*)-((4-Chlorophenyl)diazenyl)diphenylphosphine oxide (4ha). Reddish semi-solid; yield: 75% (128 mg, 0.5 mmol scale, sonochemistry), yield: 72% (122 mg, 0.3 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.91 (m, 4H, Ar–H), 7.61–7.57 (m, 2H, Ar–H), 7.54–7.47 (m, 6H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 152.81 (d, J_{C-P} = 43 Hz, *C*), 140.29 (2 × *C*), 132.84 (2 × *C*H), 132.50 (d, J_{C-P} = 9 Hz, 4 × *C*H) 129.23 (d, J_{C-P} = 116 Hz, 2 × *C*), 129.65 (2 × *C*H), 128.86 (d, J_{C-P} = 15 Hz, 4 × *C*H), 124.52 (2 × *C*H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.66 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2OPH^+$, 341.0605; found: *m*/*z* 341.0591.

(*E*)-Diphenyl(*p*-tolyldiazenyl)phosphine oxide (4ia). Red solid; yield: 77% (149 mg, 0.5 mmol scale, sonochemistry), yield: 73% (140 mg, 0.5 mmol scale, mechanochemistry), mp = 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 4H, Ar–H), 7.84 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.67–7.65 (m, 2H, Ar–H), 7.61–7.57 (m, 2H, Ar–H), 7.54–7.49 (m, 4H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.16 (d, J_{C-P} = 44 Hz, *C*), 132.89 (d, J_{C-P} = 2 Hz, 4 × *C*H), 132.70 (2 × *C*H) 132.54 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.22 (d, J_{C-P} = 116 Hz, 2 × *C*), 129.09 (*C*), 128.90 (d, J_{C-P} = 12 Hz, 4 × *C*H), 124.66 (2 × *C*H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.75 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}BrN_2OPH^+$, 385.0100; found: *m*/*z* 365.0089.

(*E*)-((4-Iodophenyl)diazenyl)diphenylphosphine oxide (4ja). Red solid; yield: 68% (147 mg, 0.5 mmol scale, sonochemistry), yield: 64% (138 mg, 0.5 mmol scale, mechanochemistry), mp = 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.93 (m, 4H, Ar–H), 7.88 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.67 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.61–7.57 (m, 2H, Ar–H), 7.54–7.49 (m, 4H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.69 (d, J_{C-P} = 44 Hz, *C*), 138.74 (2 × *C*H), 132.89 (2 × *C*H), 132.52 (d, J_{C-P} = 8 Hz, 4 × *C*H) 129.14 (d, J_{C-P} = 117 Hz, 2 × *C*), 128.89 (d, J_{C-P} = 12 Hz, 4 × *C*H), 124.56 (2 × *C*H), 102.01 (C) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.66 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}IN_2OPH^+$, 432.9961; found: *m*/*z* 432.9952.

(*E*)-Di-*o*-tolyl(*p*-tolyldiazenyl)phosphine oxide (4ab). Dark red semi-solid; yield: 81% (141 mg, 0.5 mmol scale, sonochemistry), yield: 78% (136 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.83–7.74 (m, 4H, Ar–H), 7.56 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.45–7.41 (m, 2H, *J* = 7.6 Hz, Ar–H), 7.40–7.35 (m, 4H, Ar–H), 2.41 (s, 3H, Ar–C*H*$_3$), 2.29 (s, 6H, 2Ar–C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 152.61 (d, J_{C-P} = 43 Hz, *C*), 145.46 (*C*), 141.66 (d, J_{C-P} = 9 Hz, 2 × *C*), 133.08 (2 × *C*H), 132.95 (d, J_{C-P} = 6 Hz, 2 × *C*H), 131.76 (d, J_{C-P} = 11 Hz, 2 × *C*H), 130.37 (2 × *C*H), 128.69 (d, J_{C-P} = 110 Hz, 2 × *C*), 126.11 (d, J_{C-P} = 12 Hz, 2 × *C*H), 122.83 (2 × *C*H), 21.31 (Ar–*C*H$_3$), 21.29 (d, *J* = 4 Hz, 2 × Ar–*C*H$_3$)ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 31.33 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2OPH^+$, 349.1464; found: *m*/*z* 349.1459.

(*E*)-((4-Isopropylphenyl)diazenyl)di-*o*-tolylphosphine oxide (4cb). Reddish semi-solid; yield: 83% (165 mg, 0.5 mmol scale, sonochemistry), yield: 75% (141 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.86 (m, 4H, Ar–H), 7.47 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.38 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.32–7.27 (m, 4H, Ar–H), 3.05–2.95 (m, 1H, Ar–C*H*(CH$_3$)$_2$), 2.49 (s, 6H, (2 × Ar–C*H*$_3$)), 1.29 (d, *J* = 7.2 Hz, 6H, Ar–CH(C*H*$_3$)$_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.72 (*C*), 153.47 (d, J_{C-P} = 44 Hz, *C*), 142.66 (d, J_{C-P} = 9 Hz, 2 × *C*) 133.80 (d, J_{C-P} = 10 Hz, 2 × *C*H) 132.69 (d, J_{C-P} = 2 Hz, 2 × *C*H), 131.71 (d, J_{C-P} = 10 Hz, 2 × *C*H), 128.87 (d, J_{C-P} = 112 Hz, 2 × *C*), 127.40 (2 × *C*H), 125.84 (d, J_{C-P} = 13 Hz, 2 × *C*H), 123.58 (2 × *C*H) 34.47 (Ar–*C*H(CH$_3$)$_2$), 23.81 (Ar–CH(*C*H$_3$)$_2$), 22.12 (d, *J* = 2 Hz, 2 Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.00 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{25}N_2OPH^+$, 377.1777; found: *m*/*z* 377.1753.

(*E*)-((4-(*tert*-Butyl)phenyl)diazenyl)di-*o*-tolylphosphine oxide (4db). Reddish semi-solid; yield: 84% (164 mg, 0.5 mmol scale, sonochemistry), yield: 77% (150 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.91–7.86 (m, 2H, Ar–H), 7.55 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.48–7.45 (m, 2H, Ar–H), 7.32–7.27 (m, 4H, Ar–H), 2.44 (s, 6H, 2Ar–C*H*$_3$), 1.36 (s, 9H, Ar–C(C*H*$_3$)$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.88 (*C*), 153 (d, J_{C-P} = 44 Hz, *C*), 142.65 (d, J_{C-P} = 9 Hz, 2 × *C*), 133.77 (d, J_{C-P} = 10 Hz, 2 × *C*H), 132.66 (d, J_{C-P} = 2 Hz, 2 × *C*H), 131.69 (d, J_{C-P} = 9 Hz, 2 × *C*H), 128.87 (d, J_{C-P} = 112 Hz, 2 × *C*), 126.28 (2 × *C*H), 125.82 (d, J_{C-P} = 12 Hz, 2 × *C*H), 123.18 (2 × *C*H), 35.40 (Ar–*C*(CH$_3$)$_3$), 31.22 (Ar–C(*C*H$_3$)$_3$), 22.08 (d, *J* = 3 Hz, 2 ×Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.97 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}N_2OPH^+$, 391.1934; found: *m*/*z* 391.1924.

(*E*)-((4-Methoxyphenyl)diazenyl)di-*o*-tolylphosphine oxide (4fb). Reddish semi-solid; yield: 80% (146 mg, 0.5 mmol scale, sonochemistry), yield: 74% (135 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.77–7.72 (m, 2H, Ar–H), 7.53 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.39–7.32 (m, 4H, Ar–H), 7.13 (d, 2H, *J* = 9.2 Hz, Ar–H), 3.85 (Ar–OC*H*$_3$), 2.25 (s, 6H, 2Ar–C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.95 (*C*), 149.51 (d, J_{C-P} = 44 Hz, *C*), 141.96 (d, J_{C-P} = 9 Hz, 2 × *C*), 133.32 (d, J_{C-P} = 9 Hz, 4 × *C*H), 132.09 (d, J_{C-P} = 11 Hz, 2 × *C*H), 129.06 (d, J_{C-P} = 111 Hz, 2 × *C*), 126.39 (d, J_{C-P} = 11 Hz, 2 × *C*H), 125.81 (2 × *C*H), 115.33 (2 × *C*H), 56.34 (Ar–O*C*H$_3$), 21.63 (2 × Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 29.31 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2PH^+$, 365.1419; found: *m*/*z* 365.1404.

(*E*)-((4-Chlorophenyl)diazenyl)di-*o*-tolylphosphine oxide (4hb). Reddish semi-solid; yield: 75% (138 mg, 0.5 mmol scale, sonochemistry), yield: 69% (127 mg, 0.3 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.81–7.76 (m, 2H, Ar–H), 7.70 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.59–7.55 (m, 2H, Ar–H), 7.42–7.36 (m, 4H, Ar–H), 2.30 (s, 6H, (2 × Ar–C*H*$_3$)) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 152.47 (d, J_{C-P} = 44 Hz, *C*), 141.71 (d, J_{C-P} = 9 Hz, 2 × *C*), 139.20 (*C*), 133.10–133.00 (m, 4 × *C*H), 129.60 (2 × *C*H), 131.80

(d, J_{C-P} = 9 Hz, 2 × *C*H), 130.02 (2 × *C*H), 128.26 (d, J_{C-P} = 109 Hz, 2 × *C*), 126.16 (d, J_{C-P} = 12 Hz, 2 × *C*H), 21.27 (*J* = 3 Hz, Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 30.12 ppm. HRMS (ESI-TOF): *m*/*z* [M + H + 2]$^+$ calcd for $C_{20}H_{18}ClN_2OPH^+$, 371.0889; found: *m*/*z* 371.0897.

(*E*)-((4-Bromophenyl)diazenyl)di-*o*-tolylphosphine oxide (4ib). Brick red solid; yield: 81% (167 mg, 0.3 mmol scale, sonochemistry), yield: 77% (160 mg, 0.3 mmol scale, mechanochemistry), mp = 156–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.829 (s, 4H, Ar–H), 7.77–7.72 (m, 2H, Ar–H), 7.58–7.54 (m, 2H, Ar–H), 7.41–7.35 (m, 4H, Ar–H), 2.25 (s, 6H, 2 Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 153.08 (d, J_{C-P} = 43 Hz, *C*), 142.10 (d, J_{C-P} = 10 Hz, 2 × *C*), 133.61 (2 × *C*H), 133.37 (d, J_{C-P} = 6 Hz, 4 × *C*H), 132.24 (d, J_{C-P} = 12 Hz, 2 × *C*H), 128.88 (d, J_{C-P} = 15 Hz, 2 × *C*), 127.70 (*C*), 125.59 (d, J_{C-P} = 12 Hz, 2 *C*H), 124.89 (2 × *C*H), 21.63 (Ar–*C*H_3), 21.60 (Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 30.72 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}BrN_2OPH^+$, 413.0413; found: *m*/*z* 413.0405.

(*E*)-Di-*p*-tolyl(*p*-tolyldiazenyl)phosphine oxide (4ac). Dark red semi-solid; yield: 88% (153 mg, 0.5 mmol scale, sonochemistry), yield: 81% (141 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.81 (m, 6H, Ar–H), 7.31–7.28 (m, 2H, Ar–H), 2.42 (s, 3H, Ar–CH_3), 2.39 (s, 6H, 2Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.10 (d, J_{C-P} = 43 Hz, *C*), 144.04 (d, J_{C-P} = 173 Hz, 2 × *C*), 132.50 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.87 (2 × *C*H), 129.48 (d, J_{C-P} = 13 Hz, 4 × *C*H), 126.54 (d, J_{C-P} = 118 Hz, 2 × *C*), 123.37 (2 × *C*H), 121.26 (*C*), 21.80 (3 × Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.05 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2OPH^+$, 349.1464; found: *m*/*z* 349.1467.

(*E*)-((4-Methoxyphenyl)diazenyl)di-*p*-tolylphosphine oxide (4fc). Dark reddish semi-solid; yield: 82% (149 mg, 0.5 mmol scale, sonochemistry), yield: 77% (140 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, 2H, *J* = 9.2 Hz, Ar–H), 7.84–7.79 (m, 4H, Ar–H), 7.27 (dd, 4H, *J* = 2.8 Hz, *J* = 8 Hz, Ar–H), 6.95 (d, 2H, *J* = 8.8 Hz, Ar–H), 3.85 (Ar–OCH_3), 2.37 (s, 6H, 2 × Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.35 (*C*), 149.67 (d, J_{C-P} = 445 Hz, *C*), 142.96 (d, J_{C-P} = 2 Hz, 2 × *C*), 132.39 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.37 (d, J_{C-P} = 13 Hz, 4 × *C*H), 126.84 (d, J_{C-P} = 119 Hz, 2 × *C*), 125.69 (2 × *C*H), 114.22 (2 × *C*H), 55.78 (Ar–O*C*H_3), 21.72 (2 × Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.60 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2PH^+$, 365.1413; found: *m*/*z* 365.1424.

(*E*)-((4-Chlorophenyl)diazenyl)di-*m*-tolylphosphine oxide (4hc). Red liquid; yield: 76% (140 mg, 0.5 mmol scale, sonochemistry), yield: 71% (131 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, 2H, *J* = 4.8 Hz, Ar–H), 7.85–7.81 (m, 4H, Ar–H), 7.46 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.31–7.29 (m, 4H, Ar–H), 2.39 (s, 6H, 2 Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 152.73 (d, J_{C-P} = 43 Hz, *C*), 143.40 (d, J_{C-P} = 3 Hz, 2 × *C*), 139.96 (*C*), 132.45 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.60 (2 × *C*H), 129.50 (d, J_{C-P} = 5 Hz, 4 × *C*H), 125.95 (d, J_{C-P} = 120 Hz, 2 × *C*), 124.40 (2 × *C*H), 21.77 (Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.75 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2OPH^+$, 369.0918; found: *m*/*z* 369.0903.

(*E*)-((4-Bromophenyl)diazenyl)di-*p*-tolylphosphine oxide (4ic). Dark reddish liquid; yield: 80% (165 mg, 0.5 mmol scale, sonochemistry), yield: 83% (171 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.81 (m, 6H, Ar–H), 7.79 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.32–7.29 (m, 4H, Ar–H), 2.39 (s, 6H, 2 × Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.10 (d, J_{C-P} = 42 Hz, *C*), 143.45 (d, J_{C-P} = 3 Hz, 2 × *C*), 132.57 (d, J_{C-P} = 4 Hz, 4 × *C*H), 132.46 (2 × *C*H), 129.59 (d, J_{C-P} = 13 Hz, 4 × CH), 128.76 (*C*), 125.98 (d, J_{C-P} = 118 Hz, 2 × *C*), 124.56 (2 × *C*H), 21.82 (2 × Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.80 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}BrN_2OPH^+$, 413.0409; found: *m*/*z* 413.0413.

(*E*)-Bis(4-methoxyphenyl)(*p*-tolyldiazenyl)phosphine oxide (4ad). Black semi-solid; yield: 87% (165 mg, 0.5 mmol scale, sonochemistry), yield: 84% (159 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.78–7.73 (m, 6H, Ar–H), 7.35 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.07 (d, *J* = 6.8 Hz, 4H, Ar–H), 3.77 (s, 6H, (2 × Ar–OCH_3)), 2.35 (s, 1H, Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 162.90 (*C*), 152.64 (d, J_{C-P} = 43 Hz, *C*), 145.37 (2 × *C*), 134.15 (d, J_{C-P} = 10 Hz, 4 × *C*H), 130.38 (2 × *C*H), 122.95 (2 × *C*H), 120.82 (d, J_{C-P} = 122 Hz, 2 × *C*), 114.80 (d, J_{C-P} = 13 Hz, 4 × *C*H), 55.68 (2 Ar–O*C*H_3), 21.50 (Ar–*C*H_3), ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 27.09 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_3PH^+$, 381.1363; found: *m*/*z* 381.1386.

(*E*)-((4-Isopropylphenyl)diazenyl)bis(4-methoxyphenyl)phosphine oxide (4cd). Dark reddish semi-solid; yield: 78% (160 mg, 0.5 mmol scale, sonochemistry), yield: 71% (145 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.84 (m, 6H, Ar–H), 7.34 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.99–6.97 (m, 4H, Ar–H), 3.82 (s, 6H, 2 Ar–OCH_3), 3.01–2.91 (m, 1H, Ar–C*H*(CH_3)$_2$), 1.25 (d, 6H, *J* = 7.2 Hz, Ar–CH(CH_3)$_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.96 (*C*), 155.46 (2 × *C*), 153.22 (d, J_{C-P} = 44 Hz, *C*) 134.26 (d, J_{C-P} = 10 Hz, 2 × *C*H) 127.24 (2 × *C*H), 123.42 (2 × *C*H), 120.97 (d, J_{C-P} = 123 Hz, 2 × *C*), 114.32 (d, J_{C-P} = 13 Hz, 4 × *C*H), 55.43 (2 Ar–O*C*H_3), 34.38 (Ar–*C*H(CH_3)$_2$), 23.76 (Ar–CH(*C*H_3)$_2$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.14 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{25}N_2O_3PH^+$, 409.1676; found: *m*/*z* 409.1667.

(*E*)-((4-(*tert*-Butyl)phenyl)diazenyl)bis(4-methoxyphenyl) phosphine oxide (4dd). Yellowish semi-solid; yield: 79% (167 mg, 0.5 mmol scale, sonochemistry), yield: 75% (158 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.85 (m, 6H, Ar–H), 7.52 (d, 2H, *J* = 8.8 Hz, Ar–H), 6.99 (dd, 4H, *J* = 2.8 Hz, *J* = 8.8 Hz, Ar–H), 3.84 (s, 6H, 2Ar–OCH_3), 1.34 (s, 9H, 3CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.99 (d, J_{C-P} = 3 Hz, 2 × *C*), 157.67 (*C*), 152.82 (*J* = d, 43 Hz, *C*), 134.42 (d, J_{C-P} = 9 Hz, 4 × *C*H), 126.19 (2 × *C*H), 123.11 (2 × *C*H), 121.08 (J_{C-P} = 124 Hz, 2 × *C*), 114.36 (J_{C-P} = 14 Hz, 4 × *C*H), 55.48 (2 × Ar–O*C*H_3), 35.39 (Ar–*C*(CH_3)), 31.25 (3 × Ar–C(*C*H_3)) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.07 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}N_2O_3PH^+$, 423.1832; found: *m*/*z* 423.1852.

(*E*)-((4-Fluorophenyl)diazenyl)(3-methoxyphenyl)(4-methoxyphenyl)phosphine oxide (4gd). Reddish semi-solid; yield: 84% (162 mg, 0.5 mmol scale, sonochemistry), yield: 76% (154 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99–7.96 (m, 2H, Ar–H), 7.80 (t, 4H, J = 9.2 Hz, Ar–H), 7.413 (t, 2H, J = 8 Hz, Ar–H), 7.12 (d, 4H, J = 4.8 Hz, Ar–H), 3.79 (s, 6H, 2Ar–OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.54 (d, $J_{C–F}$ = 252 Hz, *C*), 162.78 (d, $J_{C–P}$ = 2 Hz, *C*), 150.90 (d, $J_{C–P}$ = 45 Hz, *C*), 134.04 (d, $J_{C–F}$ = 90 Hz, 2 × *C*H), 125.44 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 120.57 (d, $J_{C–P}$ = 122 Hz, 2 × *C*) 116.85 (d, $J_{C–F}$ = 23 Hz, 2 × *C*H), 114.73 (d, $J_{C–P}$ = 13 Hz, 4 × *C*H), 55.52 (2 × Ar–O*C*H$_3$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 27.32 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −104.90 ppm. HRMS (ESI-TOF): m/z [M + H + 1]$^+$ calcd for $C_{20}H_{18}FN_2O_3PH^+$, 386.1145; found: m/z 386.1157.

(*E*)-((4-Chlorophenyl)diazenyl)bis(4-methoxyphenyl)phosphine oxide (4hd). Reddish semi-solid; yield: 80% (160 mg, 0.5 mmol scale, sonochemistry), yield: 74% (148 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, 2H, Ar–H), 7.81 (s, 4H, Ar–H), 7.43 (s, 2H, Ar–H), 7.13 (s, 4H, Ar–H), 3.80 (s, 6H, 2Ar–OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 162.67 (d, $J_{C–P}$ = 2 Hz, *C*), 152.27 (d, $J_{C–P}$ = 43 Hz, *C*), 138.43 (2 × *C*), 133.96 (d, $J_{C–P}$ = 10 Hz, 4 × *C*H), 129.83 (2 × CH), 124.23 (2 × *C*H), 120.40 (d, $J_{C–P}$ = 122 Hz, 2 × *C*), 114.64 (d, $J_{C–P}$ = 12 Hz, 4 × *C*H), 54.42 (2 × Ar–O*C*H$_3$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 27.42 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2O_3PH^+$, 401.0836; found: m/z 401.0826.

(*E*)-((4-Iodophenyl)diazenyl)bis(4-methoxyphenyl)phosphine oxide (4jd). Red semi-solid; yield: 73% (180 mg, 0.5 mmol scale, sonochemistry), yield: 67% (166 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.83 (m, 6H, Ar–H), 7.65 (d, 2H, J = 8.8 Hz, Ar–H), 6.99 (dd, 4H, J = 2.4 Hz, J = 8.0 Hz, Ar–H), 3.83 (s, 6H, 2Ar–OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.16 (d, $J_{C–P}$ = 2 Hz, 2 × *C*), 152.61 (d, $J_{C–P}$ = 44 Hz, *C*), 137.62 (2 × *C*H), 133.41 (d, $J_{C–P}$ = 10 Hz, 4 × *C*H), 123.47 (2 × *C*H), 119.36 (d, $J_{C–P}$ = 124 Hz, 2 × *C*), 113.46 (d, $J_{C–P}$ = 13 Hz, 4 × *C*H), 100.50 (*C*), 54.47 (2 × Ar–O*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.14 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{18}IN_2O_3PH^+$, 493.0172; found: m/z 493.0169.

Diethyl (*E*)-(*p*-tolyldiazenyl)phosphonate (4ae).[10] Red oil; yield: 77% (99 mg, 0.5 mmol scale, sonochemistry), yield: 74% (95 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, J = 8.4 Hz, Ar–H), 7.31 (d, 2H, J = 8.0 Hz, Ar–H), 4.39–4.30 (m, 4H, 2 × –OCH_2CH$_3$), 2.43 (s, 3H, Ar–CH_3) 1.42–1.38 (m, 6H, 2 × –OCH$_2$CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.04 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{11}H_{17}N_2O_3PH^+$, 257.1050; found: m/z 257.1029.

Diethyl (*E*)-(phenyldiazenyl)phosphonate (4ke).[10] Red oil; yield: 77% (93 mg, 0.5 mmol scale, sonochemistry), yield: 73% (88 mg, 0.5 mmol scale, mechanochemistry), mp = 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, 2H, J = 7.2 Hz, Ar–H), 7.59–7.56 (m, 1H, Ar–H), 7.53–7.49 (m, 2H, Ar–H), 4.42–4.29 (m, 4H, 2 × –OCH_2CH$_3$), 1.42–1.38 (m, 6H, 2 × –OCH$_2$CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.49 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{10}H_{15}N_2O_3PH^+$, 243.0893; found: m/z 243.0881.

Data availability statement

The data underlying this study are available in the published article and its ESI.‡

Conflicts of interest

There are no conflicts of interest to declare.

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Electro- and Mechanochemical Strategy as a Dual Synthetic Approach for Biologically Relevant 3-Nitro-imidazo-[1,2-*a*]pyridines

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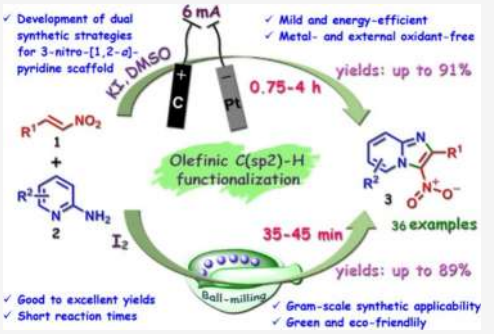
ABSTRACT: We herein disclose a dual synthetic approach involving electrochemical and mechanochemical strategies for diversely functionalized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines. Both methods offer a practical and straightforward alternative route for accessing this important class of biologically promising nitrogen-containing heterocycles. Significant advantages of the newly developed methods include mild and energy-efficient reaction conditions, avoidance of transition metal catalysts, external heating and additional oxidants, shorter reaction times, good to excellent yields, broad substrate scope, gram-scale applicability, operational simplicity, and eco-friendliness. Furthermore, a synthetic application was extended by successfully reducing synthesized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines to their corresponding amino derivatives.



1. INTRODUCTION

Imidazo[1,2-*a*]pyridines represent a group of nitrogen-containing heterocycles with valuable applications in pharmaceutical and medicinal chemistry, agrochemistry, and materials sciences.[1] This functional structural motif is abundantly found in bioactive natural products[2] and their synthetic analogues.[3] Figure 1 shows a few bioactive imidazo[1,2-*a*]pyridine derivatives and marketed drug molecules bearing this scaffold.[4,5]

Due to their promising multifaceted applications, several synthetic endeavors for accessing functionalized imidazo[1,2-*a*]pyridine derivatives are reported in the literature.[6] Still, the design and development of alternative eco-friendly and more practical methodologies for such an important organic scaffold are warranted. As part of our ongoing green chemistry research,[7] we felt it pertinent to design and develop practical and efficient alternative synthetic protocols for polyfunctionalized imidazo-[1,2-*a*]pyridines using *β*-nitrostyrenes and 2-aminopyridines as the readily available starting materials. Upon a literature survey, we encountered just a few such previous reports[8] on the preparation of 2-aryl-3-nitro-imidazo-[1,2-*a*]pyridines with the aid of CuBr/air/DMF,[8a] TBAI/TBHP/DMF,[8b] $NaICl_2$/DMF,[8c] I_2/H_2O_2/DMSO,[8d] I_2/TBHP/pyridine,[8e] and Au/Al_2O_3 (γ-Al_2O_3)[8f] under heating conditions in all cases, and also out of a three-component raection between substituted 2-aminopyrines, benzaldehydes, and nitromethane upon refluxing for 6 h in acetonitrile under *N*-iodo-succinamide (NIS) catalysis[8g] (Scheme 1). To avoid using any metal catalysts, additional oxidants, and high temperature, coupled with enabling the transformation to be more energy-efficient, eco-friendly, and fast-going with a better substrate scope, we thus engaged ourselves to explore alternative protocols for the targeted compounds. As an outcome of our sincere endeavors, we eventually succeeded in developing a dual approach, both electrochemical and mechanochemical strategies, to have a series of diversely functionalized 2-aryl-3-nitro-imidazo-[1,2-*a*]pyridines, as outlined in Scheme 1. Mild and energy-efficient reaction conditions, avoidance of transition metal catalysts, external heating and additional oxidants, good to excellent yields within shorter reaction times, scalability, and eco-friendliness are the notable advantages of these newly developed methods. Both electrochemical[7a,c,9] and mechanochemical[7b,10] strategies in synthetic organic chemistry are now growing rapidly.

2. RESULTS AND DISCUSSION

We started our investigation to optimize the reaction conditions first for the electrochemically promoted cyclization between (*E*)-(2-nitrovinyl)benzene (**1a**) and pyridin-2-amine (**2a**) as our model reaction. Initially, we checked the reaction simply by stirring the reaction mixture of **1a** and **2a** in dimethyl sulfoxide (DMSO) at ambient temperature (25−28 °C) when the reaction was found not to occur even at 4 h (Table 1, entry 1). A similar result was observed when we performed the reaction by adding 0.04 M potassium iodide (KI) (Table 1, entry 2). We then opted for an electrochemical condition for the model reaction by using a pair of undivided C||Pt electrodes and a direct current (DC) of 6 mA, keeping KI (0.04 M) as the electrolyte (Table 1, entry 3); gratifyingly, the reaction took

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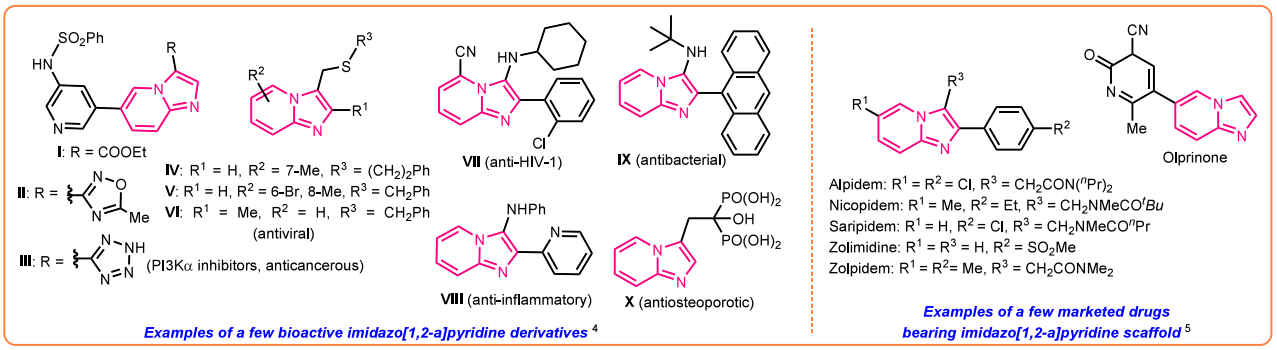
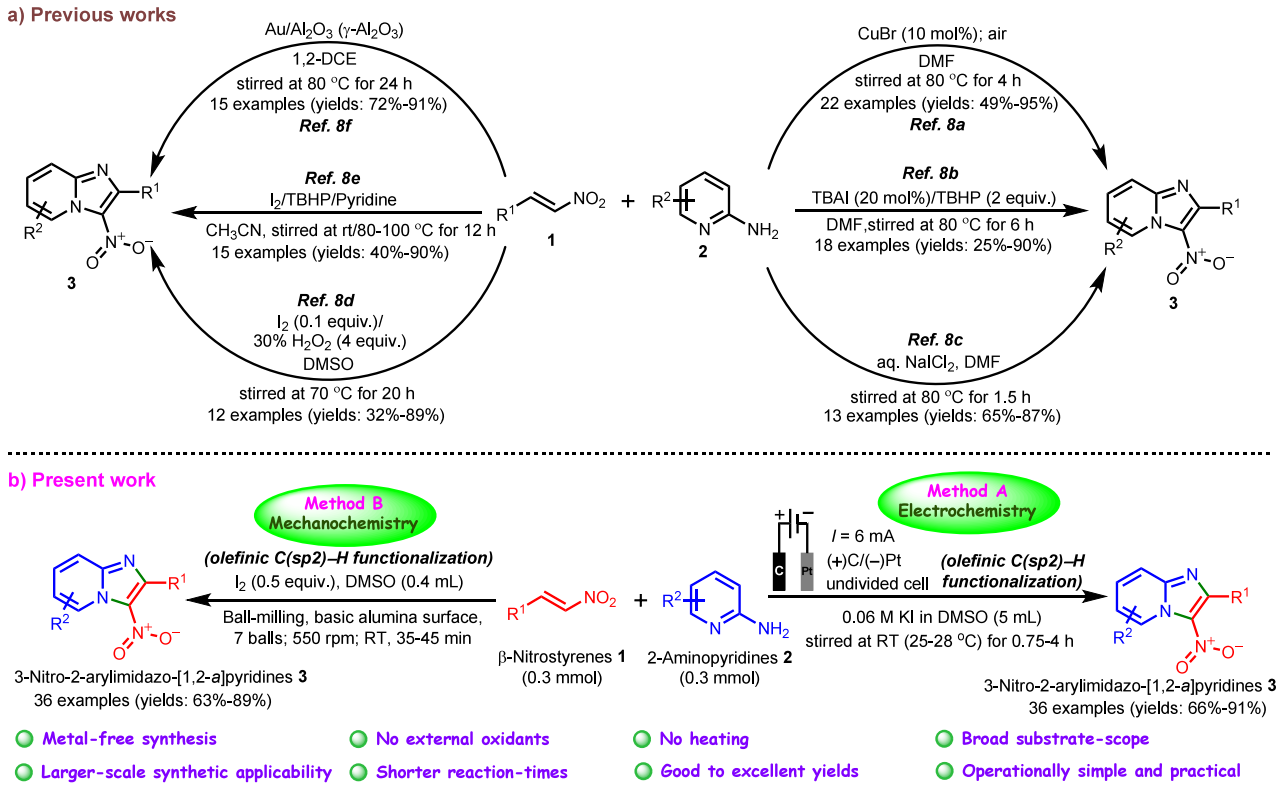


Figure 1. Examples of a few bioactive imidazo[1,2-*a*]pyridine derivatives[4] and marketed drug molecules[5] bearing this scaffold.

Scheme 1. (a) Earlier Reports on the Synthesis of 3-Nitro-imidazo-[1,2-*a*]pyridines; and (b) Electrochemical and Mechanochemical Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines



place under this electrochemical condition, resulting in the formation of the desired cyclized product, 3-nitro-2-phenylimidazo[1,2-*a*]pyridine (**3a**), in good yields of 86% at 2 h at ambient temperature (25−28 °C). Encouraged by this result, we carried out three more reactions electrochemically using the KI electrolyte in its three varying molar concentrations of 0.05, 0.06, and 0.07 M in DMSO, retaining all other parameters the same (Table 1, entries 4−6) when we isolated the product **3a** in 88% yield at 2 h in the first case (Table 1, entry 4) and in an identical yield of 91% at 45 min in the other two reactions (Table 1, entries 5 and 6). Lowering the flow of current (DC) resulted in a decrease in the isolated product (71% yield upon passing a DC of 3 mA; Table 1, entry 7), while no incremental effect on the reaction was observed upon enhancing the flow of current (89% yield upon passing a DC of 12 mA; Table 1, entry 8). The alteration in using the pair of electrodes, such as Pt||Pt (Table 1, entry 9), Pt||C (Table 1, entry 10), and C||C (Table 1, entry 11), was also found not to work well. We then performed a set of 10 more reactions with varying solvents, such as acetonitrile (CH_3CN), *N*,*N*-dimethylformamide (DMF), ethanol (EtOH), methanol (MeOH), water, aqueous ethanol (1:1), 1,2-dichloroethane (1,2-DCE), 1,1-dichloromethane (DCM), 1,4-dioxane, and tetrahydrofuran (THF), retaining other parameters constant (Table 1, entries 12−21). None of these reactions proceeded even at 4 h, except isolating a 71% yield of the product **3a** at 3 h in acetonitrile solvent (Table 1, entry 12).

For further exploration of the best-suited reaction conditions, we then performed a series of trial reactions with the model reaction using different supporting electrolytes (such as KBr, KCl, NaCl, ^{n}Bu$_4$NBF$_4$, ^{n}Bu$_4$NPF$_6$, LiClO$_4$, ^{n}Bu$_4$NI, and ^{n}Bu$_4$NBr$_3$), each at a concentration of 0.12 M DMSO, under the galvanostatic mode (C||Pt as the pair of electrodes; I = 6 mA) at ambient temperature (25−28 °C) (Table 1, entries 22−29). Also, an alternating current (AC) was tested in place of a direct current (DC) (Table 1, entry 30). Again, it was observed that an

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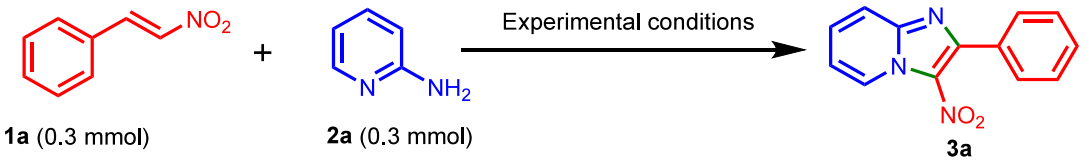
Table 1. Optimization of Reaction Conditions under Electrosynthesis[a]



1a (0.3 mmol) **2a** (0.3 mmol) **3a**

entry	electrolyte (M)	cell (+ ‖ −)	solvent (5 mL)	current (mA)	time (min)	yield (%)[a,b]
1			DMSO		240	
2	KI (0.04)		DMSO		240	
3	KI (0.04)	C ‖ Pt	DMSO	6	120	86
4	KI (0.05)	C ‖ Pt	DMSO	6	120	88
5	**KI (0.06)**	**C ‖ Pt**	**DMSO**	**6**	**45**	**91**
6	KI (0.07)	C ‖ Pt	DMSO	6	45	91
7	KI (0.06)	C ‖ Pt	DMSO	3	240	71
8	KI (0.06)	C ‖ Pt	DMSO	12	40	89
9	KI (0.06)	Pt ‖ Pt	DMSO	6	120	29
10	KI (0.06)	Pt ‖ C	DMSO	6	120	82
11	KI (0.06)	C ‖ C	DMSO	6	120	85
12	KI (0.06)	C ‖ Pt	CH_3CN	6	180	71
13	KI (0.06)	C ‖ Pt	DMF	6	240	trace
14	KI (0.06)	C ‖ Pt	EtOH	6	240	
15	KI (0.06)	C ‖ Pt	MeOH	6	240	
16	KI (0.06)	C ‖ Pt	H_2O	6	240	
17	KI (0.06)	C ‖ Pt	EtOH:H_2O	6	240	
18	KI (0.06)	C ‖ Pt	1,2-DCE	6	240	
19	KI (0.06)	C ‖ Pt	DCM	6	240	
20	KI (0.06)	C ‖ Pt	1,4-dioxane	6	240	
21	KI (0.06)	C ‖ Pt	THF	6	240	
22	KBr (0.12)	C ‖ Pt	DMSO	6	240	
23	KCl (0.12)	C ‖ Pt	DMSO	6	240	
24	NaCl (0.12)	C ‖ Pt	DMSO	6	240	
25	$^nBu_4NBF_4$ (0.12)	C ‖ Pt	DMSO	6	240	
26	$^nBu_4NPF_6$ (0.12)	C ‖ Pt	DMSO	6	240	
27	$LiClO_4$ (0.12)	C ‖ Pt	DMSO	6	240	
28	TBAI (0.12)	C ‖ Pt	DMSO	6	240	trace
29	TBATB (0.12)	C ‖ Pt	DMSO	6	240	
30[c]	KI (0.06)	C ‖ Pt	DMSO	6	240	
31[d]	KI (0.06)	C ‖ Pt	DMSO	6	45	91

[a]Reaction conditions: A mixture of (*E*)-(2-nitrovinyl)benzene (**1a**; 0.3 mmol) and pyridin-2-amine (**2a**; 0.3 mmol) dissolved in a different electrolyte solution(s) at a constant current in an undivided cell at 0.5 cm distance at room temperature (25−28 °C). Electrode size: 0.7 cm × 0.7 cm × 0.2 cm. [b]Isolated yields. [c]Alternating current (AC). [d]Reaction under nitrogen atmosphere. M = molarity.

inert atmosphere (after evacuation of the air, the reaction chamber was refilled with nitrogen gas) did not affect the reaction (Table 1, entry 31). Eventually, we arrived at the optimized reaction conditions for this electrochemical reaction between (*E*)-(2-nitrovinyl)benzene (**1a**) mmol) and pyridin-2-amine (**2a**) as a model entry, in terms of yield and time, when a graphite plate was used as the anode and a platinum plate as the cathode in an undivided cell using 0.06 M KI-electrolyte in DMSO [viz. 1.0 equiv of KI (i.e., 50 mg of KI) dissolved in 5 mL of DMSO] at ambient temperature at a constant current of 6 mA (DC). The target product **3a** was isolated with a yield of 91% in 45 min (Table 1, entry 5). All of the trial reactions for the electrosynthetic process were compiled in Table 1. Compound **3a** was fully characterized by its detailed spectral (^{1}H NMR, ^{13}C NMR, DEPT-135, and HRMS) studies, and its physical and spectral properties are similar to those reported in the literature.[8]

Upon optimizing the reaction conditions for the electrochemically promoted cyclization between *β*-nitrostyrenes and 2-aminopyridines, we then focused on gaining insight into the mechanistic pathway of this transformation. For this purpose, we first conducted cyclic voltammetry (CV) experiments of the reactants used in the model reaction [viz. (*E*)-(2-nitrovinyl)-benzene (**1a**), pyridin-2-amine (**2a**), and potassium iodide (KI); see the Supporting Information], and also performed a series of control experiments (Scheme 3). Figure 2 summarizes the CV results. The cyclic voltammograms of both pyridin-2-amine (**2a**) and KI exhibited oxidation peak(s): **2a** recorded its oxidation peak at +1.53 V (vs Ag/Ag^+), while KI showed its two oxidation peaks at +0.91 V (vs Ag/Ag^+) and +1.09 V (vs Ag/Ag^+), thereby suggesting that both of them become oxidized at the anode surface. Hence, we propose that 2-aminopyridine **2** and KI simultaneously expel an electron each to the anode and produce an amino radical-cation **2′** and an iodine radical, respectively. The in situ generated amino radical-cation **2′** then undergoes deprotonation, followed by a regioselective attack at the *α*-carbon center of the olefinic double bond of *β*-nitrostyrene **1** via the radical pathway to form a secondary carbon-radical adduct **4** that is immediately attacked by the in situ formed iodine radical,

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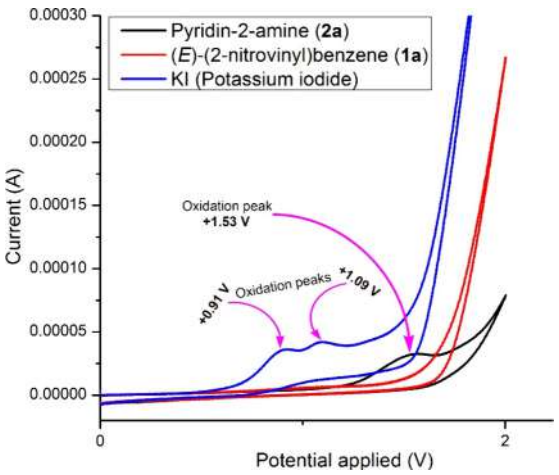


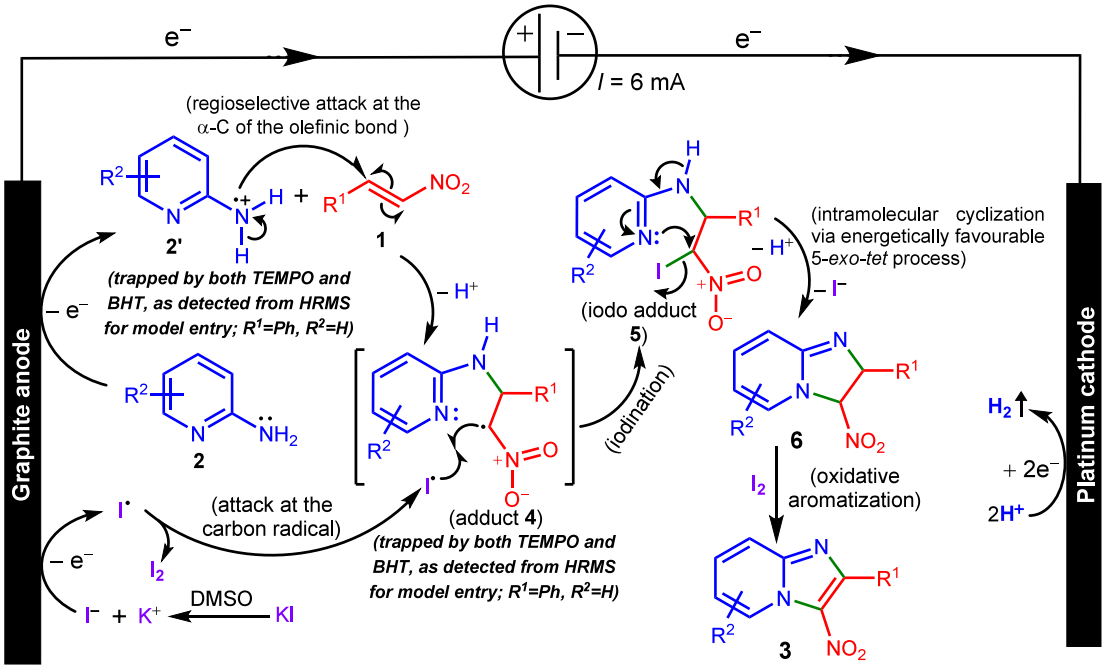
Figure 2. Cyclic voltammetry of (*E*)-(2-nitrovinyl)benzene (**1a**), pyridin-2-amine (**2a**), and potassium iodide (KI) (for detailed experimental details, see the Supporting Information).

thereby resulting in the formation of an iodo-adduct **5**. This iodoadduct **5**, in turn, undergoes an intramolecular cyclization via an energetically 5-*exo-tet* process to form intermediate **6**; the iodide ion, as regenerated in this step, takes part in the next cycle. In the final step, intermediate **6** undergoes oxidative aromatization by molecular iodine (I_2 formed in the reaction mixture out of the radical recombination of the in situ generated iodine radicals) under the reaction conditions, thus affording the desired product, 3-nitro-imidazo-[1,2-*a*]pyridine **3**. At the cathode surface, hydrogen is liberated upon reduction of the free protons (Scheme 2).

The proposed mechanism received good support from the results of our control experiments with the model reaction (Scheme 3). All of the radical scavenging agents, such as TEMPO, butylated hydroxytoluene (BHT), and *p*-benzoquinone (BQ), inhibited the reaction completely (Scheme 3a), thereby supplementing the radical pathway for the electrochemical conversion. To our delight, we detected both the TEMPO- and the BHT-trapped adducts **8**−**11** for the proposed in situ formed amino radical upon deprotonation of **2′** and carbon-radical adduct **4** from the HRMS spectral studies of the respective reaction mixtures (Scheme 3b; see the Supporting Information). Again, the in situ generation of molecular iodine during the current flow is evidenced by the fact that the reaction was deterred by adding sodium thiosulfate solution to the reaction mixture (Scheme 3a). This molecular iodine, in turn, implements oxidative aromatization of intermediate **6**, not by the air, as evidenced by the fact that the reaction took place under an inert (nitrogen gas) atmosphere (Table 1, entry 31). Potassium iodide thus acts as an electrolyte, redox-mediator, and oxidizing agent in implementing the conversion.

Considering the role of in situ generated iodine radical and molecular iodine from potassium iodide used as the electrolyte in the DMSO solvent under electrochemical conditions, we then envisioned that the use of molecular iodine in DMSO might be effective in carrying out the transformation under mechanochemical conditions. Accordingly, we performed the model reaction with (*E*)-(2-nitrovinyl)benzene (**1a**; 0.3 mmol) and pyridin-2-amine (**2a**; 0.3 mmol) by grinding the reaction mixture in a ball-mill in the presence of molecular iodine (0.5 equiv) and DMSO (0.4 mL) using seven stainless steel balls at 550 rpm for 1 h, when we were able to isolate the targeted product **3a** just in 28% yield (Table 2, entry 1). Encouraged by this result, we decided to optimize this mechanochemical transformation, and accordingly, we carried out a total of 25 trial reactions with the model entry under varying conditions. We also performed a control experiment using a tungsten carbide jar and balls to rule out any catalytic intervention by the stainless steel jar and balls (Table 2, entry 26). Subsequently, we were delighted to unearth another alternative and efficient method for the same transformation under ball-milling using basic alumina (2.0 g) as the surface and seven stainless steel balls (10 mm in diameter) milled for 35 min (rotation in an inverted direction

Scheme 2. Proposed Mechanism for the Electrosynthesis of 3-Nitro-imidazo-[1,2-*a*]pyridines 3



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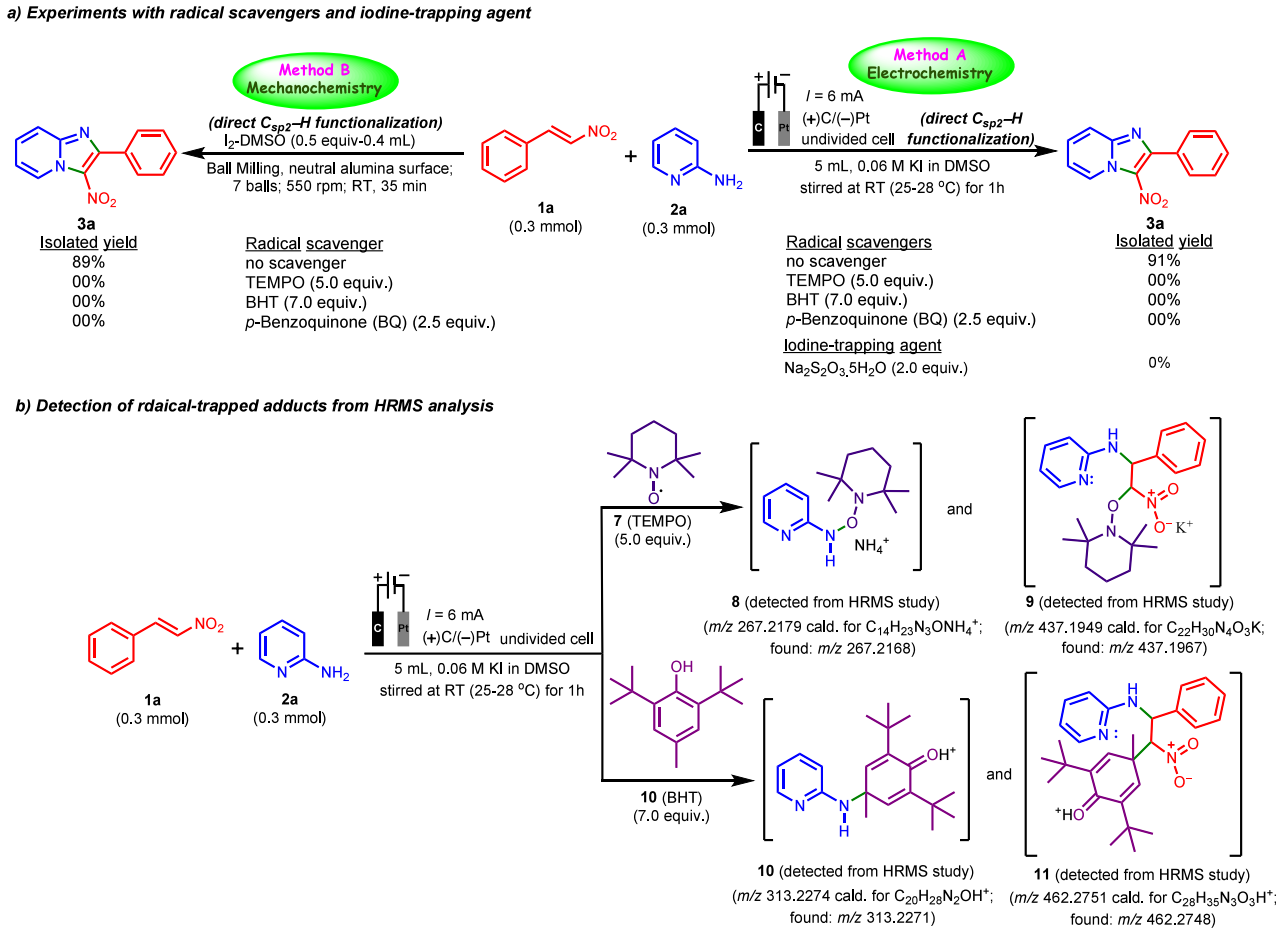
Scheme 3. Control Experiments



with a 5 s break at 5 min intervals) at 550 rpm in the presence of 0.5 equiv of I_2 as an additive and DMSO (0.4 mL) as the solvent, from where we isolated **3a** in an excellent yield of 89% (Table 2, entry 5). All of these results are summarized in Table 2.

Scheme 4 illustrates our proposed mechanism for this ball-mill-assisted mechanochemical transformation. Under ball-milling, an iodine molecule generates two iodine radicals, one of which snatches a hydrogen radical from the amino ($-NH_2$) group of 2-aminopyridines **2** to form amino radical **2″** (detected from the HRMS study), which in turn attacks at the α-carbon of the olefinic double bond of β-nitrostyrenes **1** in a regioselective manner to furnish a secondary carbon radical **4** (also detected by HRMS study). Another iodine radical adds to this carbon radical intermediate **4** to iodo-adduct **5**, which undergoes rapid intramolecular ring-closure via an energetically favorable 5-*exo-tet* process to form the cyclized species **6**. This intermediate **6**, in the final step, undergoes an oxidative aromatization by molecular iodine oxidant under the reaction conditions, thus furnishing desired product **3** (Scheme 4). The hydroiodic acid, formed during the reaction, is converted to molecular iodine once again upon reacting with alumina under ball-milling conditions.

Thus, we have now explored a dual approach for accessing biologically promising functionalized 3-nitro-imidazo-[1,2-*a*]-pyridines by using an electrosynthetic strategy (method A) and mechanochemical design (method B), both of which are effective and useful as the alternative synthetic routes (Scheme 1). Having optimized reaction conditions for both methods, we planned to explore the scope of the developed protocols and compare their efficacies in terms of respective yields and reaction times. As part of this endeavor, we first performed a set of eight reactions by treating various β-nitrostyrene derivatives (**1b**–**1i**), containing phenyl rings substituted with both electron-donating and electron-withdrawing functionalities (such as methyl, dimethyl, methoxy, 3,4-methylenedioxy, bromo, chloro, and fluoro) and 2-furyl as a heteroaryl ring, with pyridin-2-amine (**2a**) separately under the optimized conditions for electrosynthesis (method A) and the mechanochemical process (method B). All of the reactions took place smoothly in both methods, furnishing the desired 3-nitro-imidazo-[1,2-*a*]pyridines derivatives (**3b**–**3i**) in good yields ranging from 68–88% in the electrochemical and 66–86% in the mechanochemical method, within respective reaction times of 0.75–4 h and 35–45 min (Table 3, compounds **3b**–**3i**). We further extended the scope of both methods by conducting a set of 25 more reactions between diversely substituted β-nitrostyrenes (**1a**–**1c** and **1e**–**1l**) and 2-aminopyridines (viz., 4-methylpyridin-2-amine **2b**, 5-methylpyridin-2-amine **2c**, and 6-methylpyridin-2-amine **2d**) under identical reaction conditions using both strategies. Gratifyingly, all of these varieties of reactions proceeded efficiently, and the targeted products **3j**–**3z** and **3a′** were isolated with good to excellent yields ranging from 64–83% within 0.75–4 h under the electrochemical method and ranging from 62–80% within 35–45 min under the ball-milling method (Table 3, compounds **3j**–**3z** and **3a′**). Encouraged by these experimental outcomes, we synthesized another set of seven more functionalized 3-nitro-

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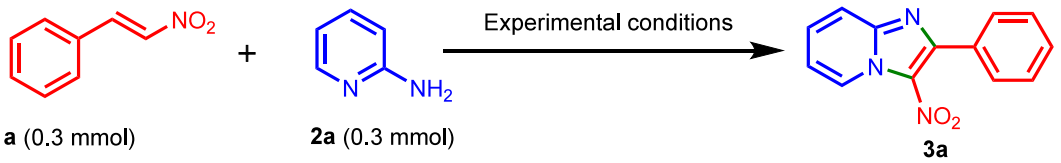
Table 2. Optimization of Reaction Conditions under Ball-Milling[a]

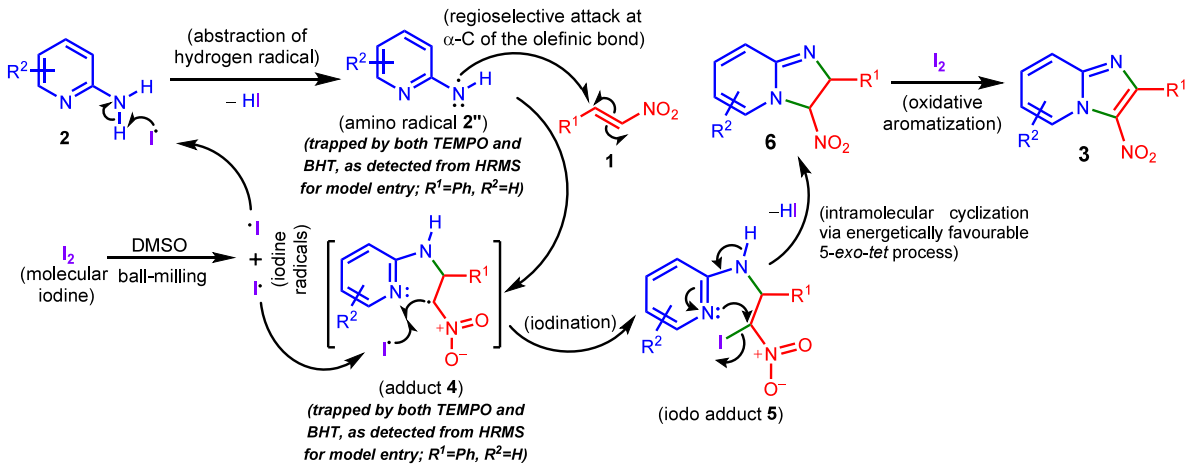


1a (0.3 mmol) **2a** (0.3 mmol) **3a**

entry	solvent (mL)	surface (2 g)	I_2 (equiv)	condition	no. of balls/rpm	time (min)	yield (%)[a,b]
1	DMSO (0.4)		I_2 (0.5)	ball-milling	7/550	60	28
2	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	10	34
3	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	20	48
3	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	10	34
4		basic alumina	I_2 (0.5)	ball-milling	7/550	60	trace
5	DMSO (0.4)	**basic alumina**	**I_2(0.5)**	**ball-milling**	7/550	**35**	**89**
6	DMSO (0.3)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	25
7	DMSO (0.5)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	46
8	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	29
9	DMSO (0.4)	basic alumina	I_2 (1.0)	ball-milling	7/550	35	60
10	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	8/550	35	88
11	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	6/550	35	86
12	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/450	35	72
13	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/600	35	66
14	DMSO (0.4)	neutral alumina	I_2 (0.5)	ball-milling	7/550	35	25
15	DMSO (0.4)	acidic alumina	I_2 (0.5)	ball-milling	7/550	35	
16	DMSO (0.4)	silica	I_2 (0.5)	ball-milling	7/550	35	
17	DMSO (0.4)	NaCl	I_2 (0.5)	ball-milling	7/550	35	
18	CH_3CN (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	85
19	THF (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
20	1,4-dioxane (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
21	EtOH (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	45
22	DMF (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
23	H_2O (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
24	DMSO (3 mL)		I_2 (0.5)	stirring at rt		120	
25	DMSO (3 mL)	basic alumina	I_2 (0.5)	stirring at rt		360	60
26[c]	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	88

[a]Reaction conditions: A mixture of (*E*)-(2-nitrovinyl)benzene (**1a**; 0.3 mmol) and pyridin-2-amine (**2a**; 0.3 mmol) was reacted either under ball-milling (using a 25 mL stainless-steel jar and balls of 10 mm in diameter, and rotation in an inverted direction with a break of 5 s at each 5 min interval) in the presence or absence of additives or by simple stirring with iodine in various solvents (2 mL) at room temperature (25−28 °C). [b]Isolated yields. [c]Using tungsten carbide jar and balls.

Scheme 4. Proposed Mechanism for the Mechanochemical Synthesis of 3-Nitro-imidazo-[1,2-*a*]pyridines 3



imidazo-[1,2-*a*]pyridines **3b′−3h′** from the reactions between substituted *β*-nitrostyrenes and 4-ethylpyridin-2-amine (**2e**) by both methods (methods A and B) keeping all of the reaction parameters intact. The products **3b′−3h′** were obtained in good yields of 69−84% within 2−4 h in method A and 67−83% within 35−45 min in method B (Table 3, compounds **3b′−3h′**). 7-Ethyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-*a*]pyridine (**3i′**) and 7-ethyl-2-(naphthalen-2-yl)-3-nitroimidazo[1,2-*a*]pyridine

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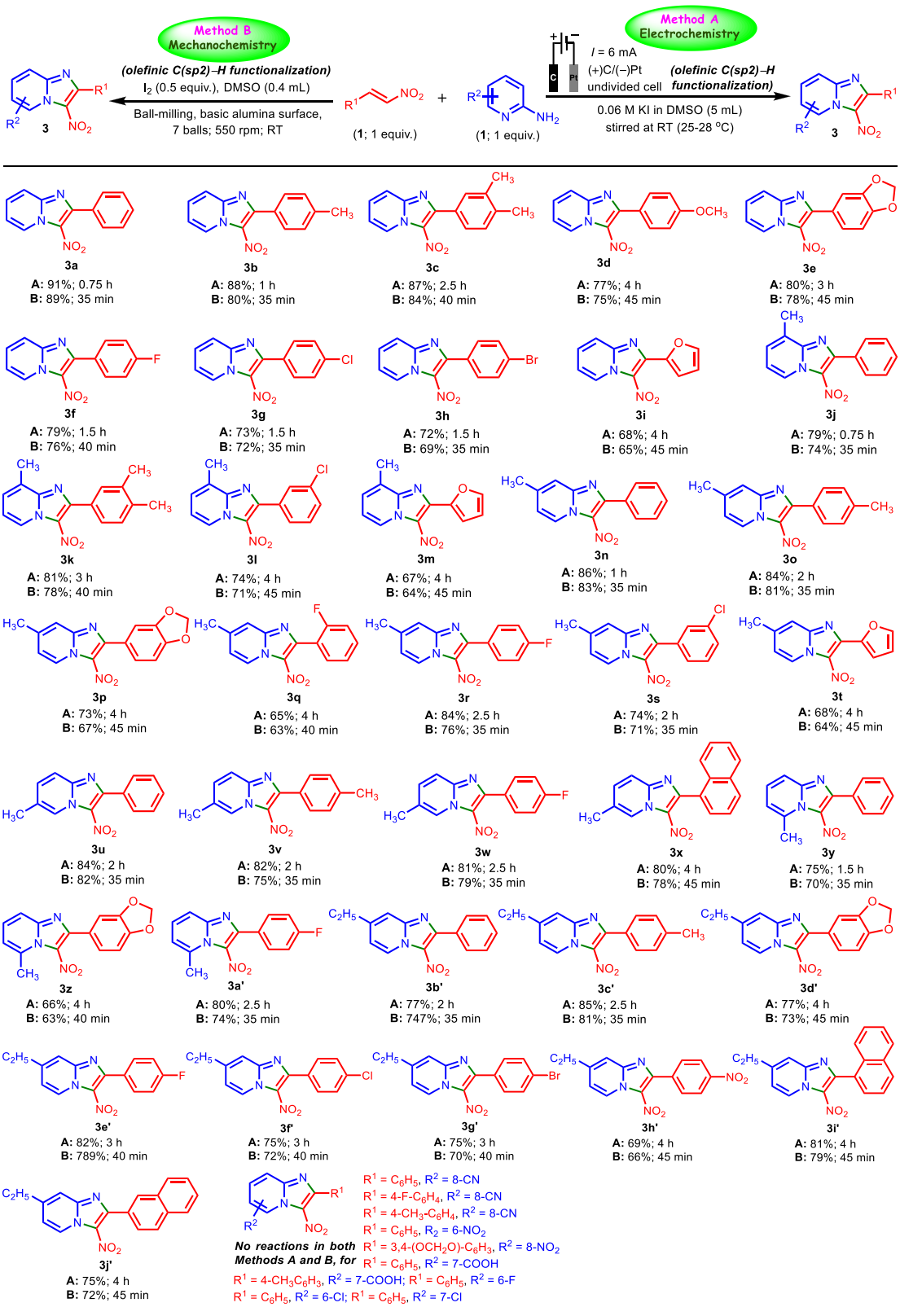
Table 3. Electrochemical and Mechanochemical Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines (3)[a,b]



[a]Standard conditions: Method A: Graphite plate as anode and platinum plate as cathode placed in an undivided cell at 0.5 cm distance, electrode size: 0.7 cm × 0.7 cm × 0.2 cm, constant current (I = 6 mA), β-nitrostyrene derivatives **1** (0.3 mmol), 2-aminopyridines **2** (0.3 mmol), KI (0.06 M), DMSO (5.0 mL), rt (28−30 °C). Method B: A mixture of β-nitrostyrene derivatives **1** (0.3 mmol) and 2-aminopyridines **2** (0.3 mmol) was reacted under ball-milling using seven stainless steel balls (10 mm in diameter) within a 25 mL stainless-steel jar at 550 rpm (rotation in an inverted direction with a break of 5 s at each 5 min interval) in the presence of 0.5 equiv of I_2 and 0.4 mL of DMSO using a solid basic alumina surface. [b]Isolated yields.

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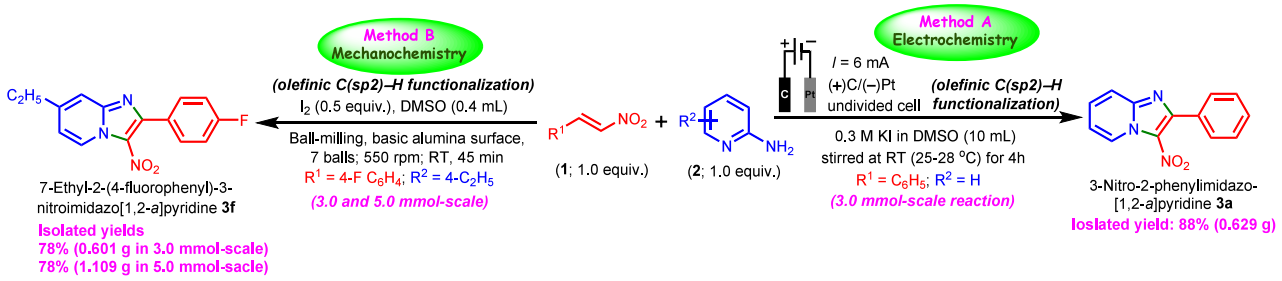
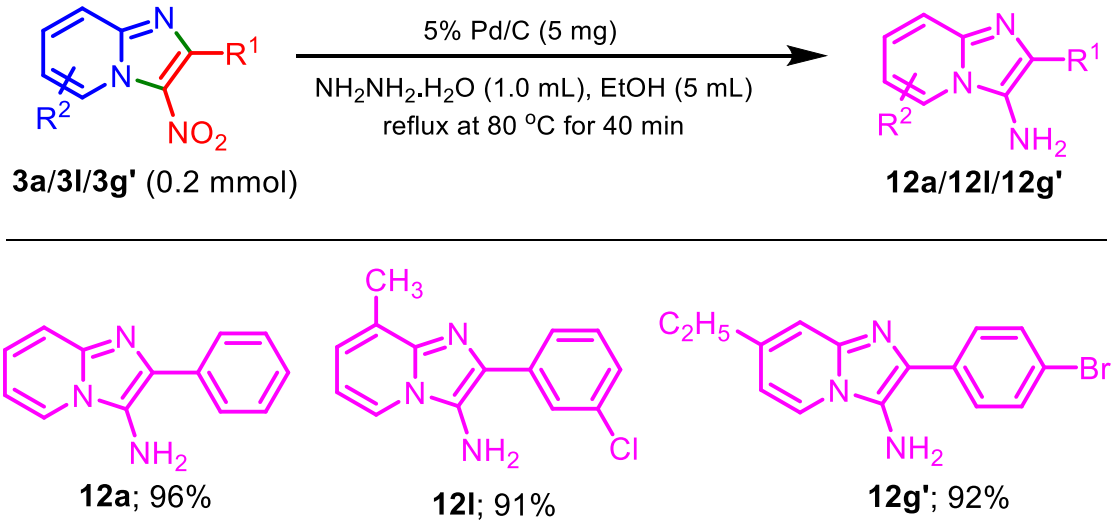
Scheme 5. Larger-Scale Synthetic Application at the Electrochemical Cell and Ball-Milling Conditions



Scheme 6. Reduction to 3-Amino-2-aryl-immidazo[1,2-*a*]pyridines (12)[a]



[a](a) Reaction conditions: A mixture of 3-nitro-2-aryl-immidazo[1,2-*a*]pyridine (**3a**/**3l**/**3g**′; 0.2 mmol), hydrazine hydrate (1.0 mL, 80% solution in water), a catalytic amount (5 mg) of 5% palladium on activated charcoal, and ethanol (5 mL) was refluxed for 40 min, and upon completion of each reaction, the desired product (**12a**/**12l**/**12g**′) was isolated following standard procedure.[11] (b) Isolated yields.

(**3j**′), the two more 3-nitro-imidazo-[1,2-*a*]pyridine derivatives, were successfully synthesized from the reaction of 4-ethyl-pyridin-2-amine (**2e**), respectively, with (*E*)-1-(2-nitrovinyl)-naphthalene (**1l**) and (*E*)-2-(2-nitrovinyl)naphthalene (**1m**), in the respective yields of 81% and 75% at 4 h under the electrochemical process (method A), and 79% and 72% yields, respectively, under ball-milling (method B) (Table 3, compounds **3i**′ and **3j**′). However, 2-aminopyridine derivatives containing electron-withdrawing groups, such as 3-CN, 5-NO_2, 4-COOH, 5-F, 4-Cl, and 5-Cl, did not undergo the reaction with varying *β*-nitrostyrenes in both electrochemical (method A) and mechanochemical (method B) processes. The presence of electron-withdrawing groups within the 2-aminopyridine nucleus possibly retards the generation and stabilization of amino radical cation **2**′ in the initial mechanistic step (Schemes 2 and 4). All of these experimental results are shown in Table 3.

Column chromatographic purification (see Experimental Section) was required to purify all of the synthesized products **3** (**3a**−**3z** and **3a**′−**3j**′ in both methods). All are new compounds except **3a**−**3e**, **3g**−**3j**, **3u**, and **3y**. Each synthesized compound was fully characterized based on their detailed spectral studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **3f**, **3q**, **3r**, **3w**, **3a**′, and **3e**′), 2D-NMR (for **3u**), and HRMS (see Experimental Section).

To verify the efficacy of both methods for somewhat higher-scale synthetic applications, we performed larger-scale reactions in each case (see Experimental Section). First, we carried out a 3.0 mmol scale (10-fold enhancement) reaction with the model entry under the electrochemical method and successfully obtained the desired 3-nitro-2-phenylimidazo-[1,2-*a*]pyridine **3a** in almost similar yield (88%; 0.629 g) compared to the submillimolar scale (Table 3, entry 1); although this reaction was completed with 1.0 equiv of KI (dissolved in 10 mL of DMSO solvent), it required substantially more time (4 h) than that for the submillimolar. Afterward, we conducted two larger-scale reactions (3.0 and 5.0 mmol; 10-fold and 16.7-fold enhancements, respectively) with a representative entry under the mechanochemical process, and delightfully, we isolated the target product, 7-ethyl-2-(4-fluorophenyl)-3-nitroimidazo[1,2-*a*]pyridine **3f**, with almost identical yields (78% yield in both cases) and time (45 min), compared to the respective submillimolar scale (Table 3, entry 5), with the optimized conditions. Scheme 5 delineates the experimental observations.

To extend the synthetic application of our synthesized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines, we then planned to reduce a set of three representative compounds, such as **3a**, **3l**, and **3g**′, to their respective amino derivatives, following the standard N_2H_4/Pd−C procedure[11] when we isolated the targeted aromatic primary amines product **12a**/**12l**/**12g**′ in excellent yields (Scheme 6), which may find many applications as synthones.

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3. CONCLUSIONS

We have developed practical and straightforward alternative synthetic protocols for diversely functionalized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines (**3**) based on electrochemical and mechanochemical strategies as a dual approach from the reaction between *β*-nitrostyrenes (**1**) and 2-aminopyridines (**2**). The transformation involves direct olefinic C(sp^2)−H functionalization of *β*-nitrostyrenes and an intramolecular ring closure. The electrochemical method exploits iodide salt as an electrolyte, redox-mediator, and oxidizing agent in an efficient manner. At the same time, the mechanochemical process also uses molecular iodine as an effective catalyst and oxidant under high-speed ball-milling conditions. Thus, both methods avoid using transition metals and additional oxidants. The key advantages of the newly developed methods are mild and energy-efficient reaction conditions that use electrochemical cells and ball-mill as green tools, avoidance of transition metal catalysts, external heating and additional oxidants, shorter reaction times, good to excellent yields, broad substrate scope and tolerance of various functional groups, scalability, operational simplicity, and eco-friendliness. Furthermore, a few representatives of the synthesized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines were reduced to their corresponding amino derivatives, which may find possible applications as valuable intermediates for some organic reactions.

4. EXPERIMENTAL SECTION

4.1. General. All chemicals (analytical grade) were purchased from reputed companies and used without further purification. All of the starting *β*-nitrostyrene derivatives used in this study were synthesized following the previously reported methods.[12] ^{1}H, ^{13}C, and ^{19}F NMR spectra were collected at 400, 100, and 376 MHz, respectively, on a Bruker DRX spectrometer using $CDCl_3$ as the solvent. Chemical shifts were reported in *δ* (ppm), relative to the internal standard TMS. The signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants are reported as *J* value in Hz. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments. Mass spectrometry was obtained using a Waters (G2-XS Q-TOF) high-resolution mass spectrometer. Cyclic voltammetry was carried out in a conventional three-electrode electrochemical cell with a Metrohm Autolab potentiostat (type: PGSTAT204; serial no. AUT52241). The melting points were recorded on a Chemiline CL-725 melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using 60 F254 (Merck) silica gel plates. A DC-regulated power supply machine (brand: Metravi; model: RPS-3005; power details − input: 220/110 V 10%, 50−60 Hz, variable output: 0−30 V DC, variable output current: 0−5 A), and Pt, graphite (C), stainless steel (SS) Ag, Zn, and Cu plate-electrodes were used to perform the electrochemical cell reactions. A PM 100, Retsch GmbH, Germany, ball-milling apparatus was used for mechanochemical reactions. Safety statement of the procedure: We did not detect/encounter any unexpected, new, and/or significant hazards or risks associated with the reported work.

4.2. General Procedure for the Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines (3) under Electrochemical Cell. *β*-Nitrostyrenes (**1**; 0.3 mmol), 2-aminopyridines (**2**; 0.3 mmol), 5 mL of 0.06 M potassium iodide (KI) electrolyte solution in DMSO, and a magnetic stir bar were successively sequentially transferred into an oven-dried glass-vessel. The reaction vessel was then capped with the graphite electrodes plate as an anode (dimensions of 0.7 × 0.7 × 0.2 cm) and platinum plate as a cathode (dimensions of 0.7 × 0.7 × 0.7 × 0.01 cm) with a distance of 0.5 cm, constructing an undivided electrochemical cell. Here, an uninterrupted flow of direct current (6 mA) was maintained through the reaction mixture with stirring at ambient temperature (25−28 °C) for 0.75−4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, 20 mL of a mixture of ethyl acetate and saturated aqueous sodium thiosulfate solution in a proportion of 3:1 (v/v) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the crude mass, which was then subjected to column chromatographic purification using an EtOAc−hexane mixture as eluent to obtain the desired products **3** (**3a**−**3z** and **3a′**−**3j′**). The synthesized compounds were fully characterized by spectroscopic studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F-NMR (**3f**, **3q**, **3r**, **3w**, **3a′**, and **3e′**), 2D-NMR (**3u**), and HRMS; the physical and spectral data for known compounds (viz. **3a**−**3e**, **3g**−**3j**, **3u**, and **3y**) are well-matched with those reported earlier[8] (see the Supporting Information).

4.3. General Procedure for the Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines (3) under Ball-Milling. *β*-Nitrostyrenes (**1**; 0.3 mmol), 2-aminopyridines (**2**; 0.3 mmol), in the presence of molecular iodine (0.5 equiv) and DMSO (0.4 mL) and basic alumina (1.5 g) used as the solid surface, was subjected to ball-milling at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) of the same material for 35−45 min. The ball-milling operation was performed using an inverted rotation direction, with an interval of 5 min and taking a break of 5 s. On completion of the reaction (monitored by TLC), 30 mL of ethyl acetate and saturated aqueous sodium thiosulfate solution in a proportion of 3:1 (v/v) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to obtain a white crude mass, which was then subjected to column chromatographic purification using EtOAc−hexane mixture as eluent to have pure products of 3-nitro-imidazo-[1,2-*a*]pyridines **3** (**3a**−**3z** and **3a′**−**3j′**).

4.4. Physical and Spectral Data of the Synthesized 3-Nitro-imidazo-[1,2-*a*]pyridine 3 (Including the Model Compound 3a and All of the New Compounds; These Data for Known Compounds 3b, 3c, 3d, 3e, 3g, 3h, 3i, 3j, 3u, and 3y Are Given in the Supporting Information) and the Reduced Amino Derivatives 12a, 12l, and 12g′. *3-Nitro-2-phenylimidazo[1,2-a]pyridine (**3a**).* Pale yellow solid; yield: 91% (65 mg, 0.3 mmol scale, electrochemistry), yield: 89% (64 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 170−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 9.52 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.92−7.89 (m, 2H, Ar−H), 7.84 (d, 1H, *J* = 8.8 Hz, Ar−H), 7.66−7.64 (m, 1H, Ar−H), 7.52−7.50 (m, 3H, Ar−H), 7.30−7.27 (m, 1H, Ar−H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* = 150.4 (*C*), 145.3 (*C*), 131.9 (*C*), 131.0 (CH), 130.4 (CH), 130.2 (2 × CH), 128.9 (*C*), 128.3 (CH), 128.3 (2 × CH), 118.5 (CH), 116.6 (CH) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_9N_3O_2H^+$, 240.0773; found, *m*/*z* 240.0765.

*2-(4-Fluorophenyl)-3-nitroimidazo[1,2-a]pyridine (**3f**).* Pale yellow solid; yield: 79% (61 mg, 0.3 mmol scale, electrochemistry), yield: 76% (59 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 9.51 (d, 1H, *J* = 6.8 Hz, Ar−H), 7.95−7.92 (m, 2H, Ar−H), 7.83 (d, 1H, *J* = 8.8 Hz, Ar−H), 7.69−7.65 (m, 1H, Ar−H), 7.31−7.26 (m, 1H, Ar−H), 7.21−7.17 (m, 2H, Ar−H), ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* = 164.1 (d, J^1_{C-F} = 249 Hz, *C*), 149.4 (*C*), 145.3 (*C*), 143.1 (*C*), 132.5 (d, J^3_{C-F} = 8 Hz, 2 × CH), 131.2 (CH), 128.4 (CH), 118.4 (CH), 116.7 (CH), 116.2 (d, J^2_{C-F} = 22 Hz, *C*), 115.5 (d, J^2_{C-F} = 22 Hz, 2 × CH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): *δ* = −109.88 ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8FN_3O_2H^+$, 258.0673; found, *m*/*z* 258.0660.

*2-(3,4-Dimethylphenyl)-8-methyl-3-nitroimidazo[1,2-a]pyridine (**3k**).* Dark brown semisolid; yield: 81% (68 mg, 0.3 mmol scale, electrochemistry); yield: 78% (66 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 9.35 (d, 1H, *J* = 6.8 Hz, Ar−H), 7.68−7.64 (m, 2H, Ar−H), 7.42 (d, 1H, *J* = 7.2, Ar−H), 7.27−7.25 (s, 1H, Ar−H), 7.14 (t, 1H, *J* = 6.8 Hz, Ar−H), 2.71 (s, 3H, Ar−CH_3), 2.34 (d, 6H, *J* = 4 Hz, 2 × Ar−CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* = 149.2 (*C*), 144.3 (*C*), 138.1 (*C*), 135.5 (2 × *C*), 130.1 (CH), 128.9 (CH), 128.7 (*C*), 128.5 (CH), 127.5 (*C*), 126.7 (CH), 125.0 (CH), 115.4

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(*C*H), 18.9 (2 × Ar−*C*H$_3$), 15.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3O_2H^+$, 282.1237; found, *m*/*z* 282.1221.

*2-(3-Chlorophenyl)-8-methyl-3-nitroimidazo[1,2-a]pyridine (**3l**).* Yellow solid; yield: 74% (64 mg, 0.3 mmol scale, electrochemistry); yield: 71% (61 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 93:7; mp = 175−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.89 (s, 1H, Ar−H), 7.80−7.78 (m, 1H, *J* = 1.2 Hz, Ar−H), 7.47−7.41 (m, 3H, Ar−H), 7.22−7.18 (m, 1H, Ar−H), 2.72 (s, 3H, Ar−CH_3, Ar−H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 147.1 (*C*), 144.2 (*C*), 133.2 (*C*), 133.0 (*C*), 129.2 (*C*H), 129.2 (*C*H), 129.2 (*C*H), 128.5 (*C*H), 127.9 (2 × *C*), 127.5 (*C*H), 124.9 (*C*H), 115.9 (*C*H), 15.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}ClN_3O_2H^+$, 288.0534; found, *m*/*z* 288.0520.

*2-(Furan-2-yl)-8-methyl-3-nitroimidazo[1,2-a]pyridine (**3m**).* Greenish yellow solid; yield: 67% (49 mg, 0.3 mmol scale, electrochemistry); yield: 64% (47 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 184−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.91 (d, 1H, *J* = 3.2 Hz, Ar−H), 7.76 (d, 1H, *J* = 1.2 Hz, Ar−H), 7.46 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.18−7.15 (m, 1H, Ar−H), 6.66 (qt, 1H, *J* = 1.6 Hz, *J* = 3.6 Hz, Ar−H), 2.76 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 146.1 (*C*), 146.1 (*C*), 145.9 (*C*H), 137.8 (*C*), 130.7 (*C*H), 126.1 (*C*H), 118.4 (*C*H), 116.5 (*C*H), 115.5 (*C*), 112.6 (*C*H), 109.7 (*C*), 14.1 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9N_3O_3H^+$, 244.0717; found, *m*/*z* 244.0701.

*7-Methyl-3-nitro-2-phenylimidazo[1,2-a]pyridine (**3n**).* Pale yellow solid; yield: 86% (65 mg, 0.3 mmol scale, electrochemistry); yield: 83% (63 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 164−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.92−7.89 (m, 2H, Ar−H), 7.59 (br s, 1H, Ar−H), 7.49 (t, 3H, *J* = 3.2 Hz, Ar−H), 7.11−7.09 (m, 1H, Ar−H), 2.55 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.8 (*C*), 145.8 (*C*), 143.1 (2*C*), 132.2 (*C*), 130.3 (*C*H), 130.2 (2 × *C*H), 128.2 (2 × *C*H), 127.6 (*C*H), 119.0 (*C*H), 117.2 (*C*H), 21.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_3O_2H^+$, 254.0924; found, *m*/*z* 254.0918.

*7-Methyl-3-nitro-2-(p-tolyl)imidazo[1,2-a]pyridine (**3o**).* Yellowish white solid, 84% yield (67 mg, 0.3 mmol scale, electrochemistry), 81% yield (65 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 148−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.82 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.58 (s, 1H, Ar−H), 7.30 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.09−7.08 (m, 1H, Ar−H), 2.54 (s, 3H, Ar−C*H*$_3$), 2.44 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.9 (*C*), 145.8 (*C*), 143.2 (*C*), 140.6 (2C), 130.1 (2 × *C*H), 129.2 (*C*), 128.9 (2 × *C*H), 127.6 (*C*H), 118.9 (*C*H), 117.1 (*C*H), 21.7 (Ar−*C*H$_3$), 21.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_3O_2H^+$, 268.1081; found: *m*/*z* 268.1070.

*2-(Benzo[d][1,3]dioxol-5-yl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3p**).* Yellow solid; yield: 73% (65 mg, 0.3 mmol scale, electrochemistry); yield: 67% (60 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 162−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.56 (s, 1H, Ar−H), 7.52−7.49 (m, 1H, Ar−H), 7.42−7.41 (m, 1H, Ar−H), 7.08 (dd, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz, Ar−H), 6.92 (d, 1H, *J* = 8.0 Hz, Ar−H), 6.04 (s, 2H, Ar−H), 2.53 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 149.5 (*C*), 147.5 (*C*), 145.7 (*C*), 143.4 (*C*), 127.6 (*C*H), 126.7 (*C*), 125.7 (*C*), 125.2 (*C*H), 122.9 (*C*), 118.9 (*C*H), 116.9 (*C*H), 110.6 (*C*H), 108.2 (*C*H), 101.6 (*C*H$_2$), 21.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}N_3O_4H^+$, 298.0822; found, *m*/*z* 298.0810.

*2-(2-Fluorophenyl)-5-methyl-3-nitroimidazo[1,2-a]pyridine (**3q**).* Yellowish brown viscous oil; yield: 65% (53 mg, 0.3 mmol scale, electrochemistry); yield: 63% (51 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9; mp = 160−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.37 (d, 1H, *J* = 6.8, Ar−H), 7.68−7.64 (m, 1H, Ar−H), 7.62 (s, 1H, Ar−H), 7.53−7.47 (m, 1H, Ar−H), 7.30 (d, 1H, *J* = 7.6, Ar−H), 7.23−7.19 (m, 1H, Ar−H), 7.13 (qt, 1H, *J* = 6.8 and 1.2, Ar−H), 2.56 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 160.7 (d, J^1_{C-F} = 250 Hz, *C*), 142.9 (2 × *C*), 135.1 (2 × *C*), 131.9 (d, J^3_{C-F} = 8 Hz, *C*H), 131.2 (d, J^3_{C-F} = 3 Hz, CH), 130.1 (*C*), 127.1 (*C*H), 124.3 (d, J^3_{C-F} = 3 Hz, *C*H), 119.2 (*C*H), 117.3 (*C*H), 115.9 (d, J^2_{C-F} = 21 Hz, *C*H), 21.8 (Ar−*C*H$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −109.99 ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, *m*/*z* 272.0824.

*2-(4-Fluorophenyl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3r**).* Yellowish white solid; yield: 84% (68 mg, 0.3 mmol scale, electrochemistry); yield: 76% (62 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9; mp = 160−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 7.2, Ar−H), 7.95−7.91 (m, 2H, Ar−H), 7.59−7.58 (m, 1H, Ar−H), 7.21−7.16 (m, 2H, Ar−H), 7.13−7.10 (m, 1H, Ar−H), 2.55 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.1 (d, J^1_{C-F} = 249 Hz, *C*), 149.8 (*C*), 143.4 (*C*), 132.5 (d, J^3_{C-F} = 9 Hz, 2 × *C*H), 128.2 (*C*), 127.6 (*C*H), 124.8 (*C*), 123.2 (*C*), 119.1 (*C*H), 117.2 (*C*H), 115.4 (d, J^2_{C-F} = 22 Hz, 2 × *C*H), 21.7 (Ar−*C*H$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −109.99 ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, *m*/*z* 272.0831.

*2-(3-Chlorophenyl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3s**).* Gray solid; yield: 74% (64 mg, 0.3 mmol scale, electrochemistry); yield: 71% (61 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 93:7; mp = 183−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 6.8 Hz, Ar−H), 7.89 (s, 1H, Ar−H), 7.79 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.64 (s, 1H, Ar−H), 7.49−7.41 (m, 2H, Ar−H), 7.15 (d, 1H, *J* = 7.2 Hz, Ar−H), 2.56 (s, 3H, Ar−CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 148.6 (*C*), 145.4 (*C*), 143.8 (*C*), 134.2 (*C*), 133.4 (*C*), 131.9 (*C*), 130.5 (*C*H), 130.2 (*C*H), 129.6 (*C*H), 128.5 (*C*H), 127.5 (*C*H), 119.5 (*C*H), 117.1 (*C*H), 21.8 (Ar−CH_3) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}ClN_3O_2H^+$, 288.0534; found, *m*/*z* 288.0519.

*2-(Furan-2-yl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3t**).* Greenish brown solid; yield: 68% (50 mg, 0.3 mmol scale, electrochemistry); yield: 64% (47 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 222−224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.93 (d, 1H, *J* = 3.6 Hz, Ar−H), 7.73 (d, 1H, *J* = 1.2 Hz, Ar−H), 7.59 (s, 1H, Ar−H), 7.08 (dd, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz, Ar−H), 6.66 (dd, 1H, *J* = 3.6 Hz, *J* = 1.6 Hz, Ar−H), 2.54 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 146.3 (*C*), 145.9 (*C*H), 143.9 (*C*), 140.4 (2 × *C*), 138.4 (*C*), 127.5 (*C*H), 118.9 (*C*H), 118.7 (*C*H), 117.0 (*C*H), 112.7 (*C*H), 21.8 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9N_3O_3H^+$, 244.0717; found, *m*/*z* 244.0709.

*6-Methyl-3-nitro-2-(p-tolyl)imidazo[1,2-a]pyridine (**3v**).* Greenish yellow solid, 82% yield (66 mg, 0.3 mmol scale, electrochemistry); 75% yield (60 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 172−174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1H, Ar−H), 7.80 (d, 2H, *J* = 8.0 Hz, Ar−H), 7.72 (d, 1H, *J* = 8.8 Hz, Ar−H) 7.49 (dd, 1H, *J* = 8.8 Hz, *J* = 1.6 Hz, Ar−H), 7.30 (d, 2H, *J* = 8.0 Hz, Ar−H), 2.50 (s, 3H, Ar−C*H*$_3$), 2.43 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.5 (*C*), 144.3 (*C*), 140.5 (2*C*), 138.8 (*C*), 133.8 (*C*H), 130.1 (2 × *C*H), 128.9 (*C*H), 126.4 (*C*H), 125.1 (*C*), 117.6 (*C*H), 116.7 (*C*H), 21.7 (Ar−CH_3), 18.8 (Ar−CH_3) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_3O_2H^+$, 268.1081; found, *m*/*z* 268.1071.

*2-(4-Fluorophenyl)-6-methyl-3-nitroimidazo[1,2-a]pyridine (**3w**).* Gray amorphous powder, 81% (66 mg, 0.3 mmol scale, electrochemistry); 79% (64 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9; mp = 196−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1H, Ar−H), 7.94−7.90 (m, 2H, Ar−H), 7.72 (d, 1H, *J* = 9.2 Hz, Ar−H), 7.51 (dd, 1H, *J* = 8.8 Hz, *J* = 1.2 Hz, Ar−H), 7.20−7.16 (m, 2H, Ar−H), 2.52 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.0 (d, J^1_{C-F} = 248 Hz, *C*), 149.3 (*C*), 144.3 (*C*), 138.9 (*C*), 134.0 (*C*H), 133.0 (d, J^3_{C-F} = 9 Hz, *C*), 132.4 (d, J^3_{C-F} = 8 Hz, 2 × *C*H), 126.4 (*C*H), 117.6 (*C*H), 116.2 (d, J^2_{C-F} = 22 Hz, *C*), 115.4 (d, J^2_{C-F} = 21 Hz, 2 × *C*H), 18.8 (Ar−

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CH_3)ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.17 ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, m/z 272.0825.

*6-Methyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-a]pyridine (**3x**).* Yellow solid; yield: 80% (73 mg, 0.3 mmol scale, electrochemistry); yield: 78% (71 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 198−200 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.37 (s, 1H, Ar−H), 7.99 (d, 1H, J = 8.0 Hz, Ar−H), 7.93 (d, 1H, J = 8.4 Hz, Ar−H), 7.77 (d, 1H, J = 8.8 Hz, Ar−H), 7.71−7.69 (m, 2H, Ar−H), 7.60−7.57 (m, 1H, Ar−H), 7.60−7.57 (m, 1H, Ar−H), 7.52−7.48 (m, 1H, Ar−H), 7.44 (t, 1H, J = 7.2 Hz, Ar−H), 2.51 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.2 (2 × C), 144.3 (C), 133.8 (CH), 133.5 (C), 131.3 (C), 130.2 (CH), 128.7 (CH), 128.3 (CH), 127.2 (2 × C), 126.9 (CH), 126.1 (CH), 126.0 (CH), 125.1 (CH), 124.9 (CH), 117.7 (CH), 21.8 (Ar−CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{13}N_3O_2H^+$, 304.1081; found, m/z 304.1065.

*2-(Benzo[d][1,3]dioxol-5-yl)-5-methyl-3-nitroimidazo[1,2-a]-pyridine (**3z**).* Brown viscous oil; yield: 66% (59 mg, 0.3 mmol scale, electrochemistry); yield: 63% (56 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (s, 1H, Ar−H), 7.56 (d, 1H, J = 8.8 Hz, Ar−H), 7.49−7.46 (m, 2H, Ar−H), 7.18−7.14 (m, 1H, Ar−H), 7.88 (d, 1H, J = 8.0 Hz, Ar−H), 6.63 (d, 1H, J = 6.8 Hz, Ar−H), 5.99 (s, 2H, Ar−H), 2.61 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 148.2 (C), 147.7 (C), 145.9 (C), 145.3 (C), 134.4 (C), 127.9 (C), 125.4 (C), 120.1 (CH), 114.6 (CH), 111.9 (CH), 108.8 (CH), 106.8 (CH), 104.8 (CH), 101.3 (CH_2), 18.9 (Ar−CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{11}N_3O_4H^+$, 298.0822; found, m/z 298.0821.

*2-(4-Fluorophenyl)-5-methyl-3-nitroimidazo[1,2-a]pyridine (**3a′**).* Yellow viscous oil; yield: 80% (65 mg, 0.3 mmol scale, electrochemistry); yield: 74% (60 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1H, Ar−H), 7.67 (s, 1H, Ar−H), 7.55 (d, 1H, J = 8.0 Hz, Ar−H), 7.18−7.08 (m, 3H, Ar−H), 6.64 (d, 1H, J = 6.0 Hz, Ar−H), 2.60 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.8 (d, J^1_{C-F} = 245 Hz, C), 146.1 (2 × C), 144.6 (C), 134.6 (C), 129.9 (C), 127.9 (d, J^3_{C-F} = 7 Hz, 2 × CH), 125.5 (CH), 115.8 (d, J^2_{C-F} = 22 Hz, CH), 114.8 (CH), 112.0 (CH), 105.2 (CH), 18.9 (Ar−CH_3)ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −113.98 ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, m/z 272.0830.

*7-Ethyl-3-nitro-2-phenylimidazo[1,2-a]pyridine (**3b′**).* Yellow amorphous solid, yield: 77% (62 mg, 0.3 mmol scale, electrochemistry); yield: 74% (59 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 90:10; mp = 150−152 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, 1H, J = 7.2 Hz, Ar−H), 7.91−7.89 (m, 2H, Ar−H), 7.61 (s, 1H, Ar−H) 7.49 (t, 3H, J = 7.2 Hz, Ar−H), 7.13−7.11 (m, 1H, Ar−H), 2.83 (qt, 2H, J = 7.2 Hz, Ar−CH_2CH_3), 1.35 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.7 (C), 148.1 (2 × C), 144.9 (C), 131.1 (C), 129.2 (CH), 129.1 (2 × CH), 127.2 (2 × CH), 126.7 (CH), 117.0 (CH), 114.7 (CH), 27.6 (Ar−CH_2CH_3), 13.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_3O_2H^+$, 268.1081; found, m/z 268.1057.

*7-Ethyl-3-nitro-2-(p-tolyl)imidazo[1,2-a]pyridine (**3c′**).* Pale yellow solid, 85% yield (72 mg, 0.3 mmol scale, electrochemistry); 81% yield (68 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 90:10; mp = 115−117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, 1H, J = 6.8 Hz, Ar−H), 7.82 (d, 2H, J = 8.4 Hz, Ar−H), 7.60 (s, 1H, J = 8.4 Hz, Ar−H), 7.30 (d, 2H, J = 8.0 Hz, Ar−H) 7.17−7.10 (m, 1H, Ar−H), 2.84 (q, 2H, J = 7.6 Hz, Ar−CH_2CH_3), 2.44 (s, 3H, Ar−CH_3) 1.35 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.1 (C), 140.6 (C), 130.3 (C), 130.2 (2 × CH), 129.2 (C), 129.0 (2 × CH), 127.8 (CH), 124.1 (C), 119.6 (C), 117.9 (CH), 115.7 (CH), 28.7 (Ar−CH_2CH_3), 21.7 (Ar−CH_3) 14.2 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_3O_2H^+$, 282.1237; found, m/z 282.1243.

*2-(Benzo[d][1,3]dioxol-5-yl)-7-ethyl-3-nitroimidazo[1,2-a]-pyridine (**3d′**).* Yellow solid; yield: 77% (72 mg, 0.3 mmol scale, electrochemistry); yield: 73% (68 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 134−136 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, 1H, J = 6.8 Hz, Ar−H), 7.56 (s, 1H, Ar−H), 7.51−7.49 (m, 1H, J = 8.0 Hz, Ar−H), 7.41 (d, 1H, J = 1.2 Hz, Ar−H), 7.11−7.08 (m, 1H, Ar−H), 6.91 (d, 1H, J = 8.0 Hz, Ar−H), 6.03 (s, 2H, Ar−H), 2.84−2.79 (m, 2H, Ar−CH_2CH_3), 1.34 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.4 (C), 148.5 (2 × C), 148.2 (C), 146.5 (C), 144.8 (C), 126.8 (CH), 124.7 (C), 124.2 (CH), 116.9 (CH), 114.5 (CH), 109.6 (CH), 107.2 (CH), 100.6 (CH_2), 27.6 (Ar−CH_2CH_3), 13.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{16}H_{13}N_3O_4H^+$, 312.0979; found, m/z 312.0976.

*7-Ethyl-2-(4-fluorophenyl)-3-nitroimidazo[1,2-a]pyridine (**3e′**).* Yellow solid, 82% (70 mg, 0.3 mmol scale, electrochemistry), 79% (68 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 89:11; mp = 145−147 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, 1H, J = 7.2 Hz, Ar−H), 7.95−7.92 (m, 2H, Ar−H), 7.61 (s, 1H, Ar−H), 7.23−7.13 (m, 3H, Ar−H), 2.87−2.82 (m, 2H, Ar−CH_2CH_3), 1.38−1.34 (m, 3H, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 164.1 (d, J^1_{C-F} = 249 Hz, C), 149.3 (2 × C), 132.4 (d, J^3_{C-F} = 8 Hz, 2 × CH), 127.8 (CH), 127.1 (C), 119.0 (C), 118.1 (CH), 116.2 (C), 115.7 (CH), 115.5 (CH), 115.3 (CH), 28.7 (Ar−CH_2CH_3), 14.2 (Ar−CH_2CH_3)ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.17 ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}FN_3O_2H^+$, 286.0986; found, m/z 286.0966.

*2-(4-Chlorophenyl)-7-ethyl-3-nitroimidazo[1,2-a]pyridine (**3f′**).* Reddish gray solid; yield: 75% (68 mg, 0.3 mmol scale, electrochemistry); yield: 72% (65 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 115−117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.37 (d, 1H, J = 7.2 Hz, Ar−H), 7.85 (d, 2H, J = 8.4 Hz, Ar−H), 7.59 (s, 1H, Ar−H), 7.45 (d, 1H, J = 7.6 Hz, Ar−H), 7.15−7.12 (m, 1H, Ar−H), 2.83 (q, 2H, J = 7.6 Hz, Ar−CH_2CH_3, Ar−H), 1.34 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3, Ar−H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.4 (2 × C), 145.8 (C), 136.4 (C), 131.9 (CH), 131.6 (CH), 130.5 (2 × C), 129.2 (CH), 128.5 (CH), 127.7 (CH), 118.2 (CH), 115.7 (CH), 28.6 (Ar−CH_2CH_3), 14.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}ClN_3O_2H^+$, 302.0691; found, m/z 302.0679.

*2-(4-Bromophenyl)-7-ethyl-3-nitroimidazo[1,2-a]pyridine (**3g′**).* Orangish brown solid; 75% (78 mg, 0.3 mmol scale, electrochemistry); yield: 70% (73 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 105−107 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, 1H, J = 7.2 Hz, Ar−H), 7.78 (d, 2H, J = 8.4 Hz, Ar−H), 7.61 (d, 3H, J = 8.8 Hz, Ar−H), 7.13 (dd, 1H, J = 8.0 Hz, J = 7.2 Hz, Ar−H), 2.83 (q, 2H, J = 7.6 Hz, Ar−CH_2CH_3), 1.36−1.32 (m, 3H, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.4 (2 × C), 145.9 (C), 132.2 (C), 131.8 (2 × CH), 131.4 (2 × CH), 130.9 (C), 127.7 (CH), 124.9 (C), 118.2 (CH), 115.7 (CH), 28.6 (Ar−CH_2CH_3), 14.1 (Ar−CH_2CH_3) ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}BrN_3O_2H^+$, 346.0186; found, m/z 346.0173.

*7-Ethyl-3-nitro-2-(4-nitrophenyl)imidazo[1,2-a]pyridine (**3h′**).* Gray amorphous powder, yield: 69% (65 mg, 0.3 mmol scale, electrochemistry); yield: 66% (62 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 172−174 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.40 (d, 1H, J = 7.2 Hz, Ar−H), 8.35 (d, 2H, J = 7.2 Hz, Ar−H), 8.08 (d, 2H, J = 8.8 Hz, Ar−H), 7.65 (s, 1H, Ar−H) 7.21−7.19 (m, 1H, Ar−H), 2.89−2.84 (m, 2H, Ar−CH_2CH_3), 1.37 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.7 (C), 147.9 (C), 131.3 (2 × CH), 127.9 (C), 127.6 (C), 124.3 (CH), 123.4 (2 × CH), 121.6 (C), 118.8 (CH), 116.0 (CH), 115.5 (C), 28.7 (Ar−CH_2CH_3), 14.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_4O_4H^+$, 313.0931; found, m/z 313.0922.

*7-Ethyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-a]pyridine (**3i′**).* Brown solid; yield: 81% (77 mg, 0.3 mmol scale, electrochemistry); yield: 79% (75 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 82−84 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.47 (d, 1H, J = 7.2 Hz, Ar−H), 8.00 (d, 1H, J =

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8.0 Hz, Ar−H), 7.94 (d, 1H, J = 7.2 Hz, Ar−H), 7.72−7.68 (m, 3H, Ar−H), 7.61−7.56 (m, 1H, Ar−H), 7.53−7.49 (m, 1H, Ar−H), 7.46−7.42 (m, 1H, Ar−H), 7.21−7.19 (m, 1H, Ar−H), 2.87 (q, 2H, J = 7.6 Hz, Ar−CH_2CH$_3$), 1.38 (t, 3H, J = 7.6 Hz, Ar−CH$_2$$CH_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.7 (*C*), 149.2 (2 × *C*), 145.9 (*C*), 133.5 (*C*), 131.3 (*C*), 130.3 (*C*H), 130.2 (*C*), 128.7 (*C*H), 128.3 (*C*H), 127.5 (*C*H), 126.9 (*C*H), 126.2 (*C*H), 125.1 (*C*H), 125.0 (*C*H), 118.2 (*C*H), 115.8 (*C*H), 28.7 (Ar−CH_2CH$_3$), 14.2 (Ar−CH$_2$$CH_3$) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{15}N_3O_2H^+$, 318.1237; found, m/z 318.1225.

*7-Ethyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-a]pyridine (**3j′**).* Yellowish brown solid; yield: 75% (71 mg, 0.3 mmol scale, electrochemistry), yield: 72% (69 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 91−93 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.41 (d, 1H, J = 7.2 Hz, Ar−H), 8.46 (s, 1H, Ar−H), 7.98−7.93 (m, 3H, Ar−H), 7.89 (d, 1H, J = 7.6 Hz, Ar−H), 7.64 (s, 1H, Ar−H), 7.56−7.52 (m, 2H, Ar−H), 7.14−7.12 (m, 1H, Ar−H), 2.83 (q, 2H, J = 7.6 Hz, Ar−CH_2CH$_3$), 1.35 (t, 3H, J = 7.6 Hz, Ar−CH$_2$$CH_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 155.9 (*C*), 150.8 (*C*), 149.3 (*C*), 145.9 (*C*), 134.1 (*C*), 132.9 (*C*), 130.4 (*C*H), 129.4 (*C*), 129.0 (*C*H), 127.8 (*C*H), 127.7 (2 × *C*H), 127.4 (*C*H), 126.9 (*C*H), 126.5 (*C*H), 118.1 (*C*H), 115.7 (*C*H), 28.6 (Ar−CH_2CH$_3$), 14.1 (Ar−CH$_2$$CH_3$) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{15}N_3O_2H^+$, 318.1237; found, m/z 318.1230.

*2-Phenylimidazo[1,2-a]pyridin-3-amine (**12a**).* Brown solid; yield: 96% (40 mg, 0.2 mmol scale); mp = 100−102 °C. ^1H NMR (400 MHz, $CDCl_3$): d = 7.99−7.95 (m, 3H, Ar−H), 7.53 (d, 1H, J = 8.8 Hz, Ar−H), 7.45 (t, 2H, J = 7.6 Hz, Ar−H), 7.33−7.29 (m, 1H, Ar−H), 7.12−7.08 (m, 1H, Ar−H), 6.79 (t, 1H, J = 6.8 Hz, Ar−H), 3.43 (s, 2H, Ar−NH_2) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.0 (*C*), 134.4 (2 × *C*), 128.9 (2 × *C*H), 127.3 (*C*H), 127.2 (2 × *C*H), 123.5 (*C*H), 122.8 (*C*), 121.9 (*C*H), 117.4 (*C*H), 111.9 (*C*H) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}N_3H^+$, 210.1026; found, m/z 210.1007.

*2-(3-Chlorophenyl)-8-methylimidazo[1,2-a]pyridin-3-amine (**12l**).* Brown semisolid; yield: 91% (47 mg, 0.2 mmol scale). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1H, Ar−H), 7.89−7.85 (m, 2H, Ar−H), 7.37−7.33 (m, 2H, Ar−H), 6.94 (d, 1H, J = 6.8 Hz, Ar−H), 6.76 (t, 1H, J = 6.8 Hz, Ar−H), 3.47 (s, 2H, Ar−NH_2), 2.60 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.7 (*C*), 135.4 (*C*), 134.7 (2 × *C*), 129.9 (*C*H), 127.4 (*C*), 127.3 (*C*H), 126.9 (*C*), 125.5 (*C*H), 123.9 (*C*H), 120.2 (*C*H), 113.1 (*C*H), 112.8 (*C*H), 16.9 (Ar−CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{12}ClN_3H^+$, 258.0793; found, m/z 258.0780.

*2-(4-Bromophenyl)-7-ethylimidazo[1,2-a]pyridin-3-amine (**12g′**).* Yellow solid; yield: 92% (58 mg, 0.2 mmol scale); mp = 134−136 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94−7.86 (m, 3H, J = 7.2 Hz, Ar−H), 7.52 (d, 1H, J = 7.2 Hz, Ar−H), 7.29−7.26 (m, 2H, Ar−H), 6.68 (d, 1H, J = 5.2 Hz, Ar−H), 3.35 (s, 1H, Ar−NH_2), 2.70−2.65 (m, 2H, Ar−CH_2CH$_3$), 1.25 (s, 3H, Ar−CH$_2$$CH_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.4 (*C*), 133.3 (*C*), 131.8 (*C*H), 129.9 (*C*), 128.8 (*C*H), 128.6 (*C*H), 127.3 (*C*), 127.2 (*C*H), 122.3 (*C*), 121.5 (*C*H), 114.2 (*C*H), 114.0 (*C*), 113.9 (*C*H), 28.5 (Ar−CH_2CH$_3$), 14.5 (Ar−CH$_2$$CH_3$) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{14}BrN_3H^+$, 316.0444; found, m/z 316.0424.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00881.

Experimental procedures, compound characterization data for known molecules, and scanned copies of respective ^1H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **3f**, **3q**, **3r**, **3w**, **3a′**, and **3e′**), 2D NMR (for one representative compound, **3u**), and HRMS (all new compounds) spectra for all of the synthesized compounds, along with those of cyclic voltammograms (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a−3z**, **3a′−3j′**, and **12a**, **12l**, and **12g′** (ZIP)

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Notes

The authors declare no competing financial interest.

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Mechanochemical Solvent-Free One-Pot Synthesis of Poly-Functionalized 5-(Arylselanyl)-1*H*-1,2,3-triazoles Through a Copper(I)-Catalyzed Click Reaction

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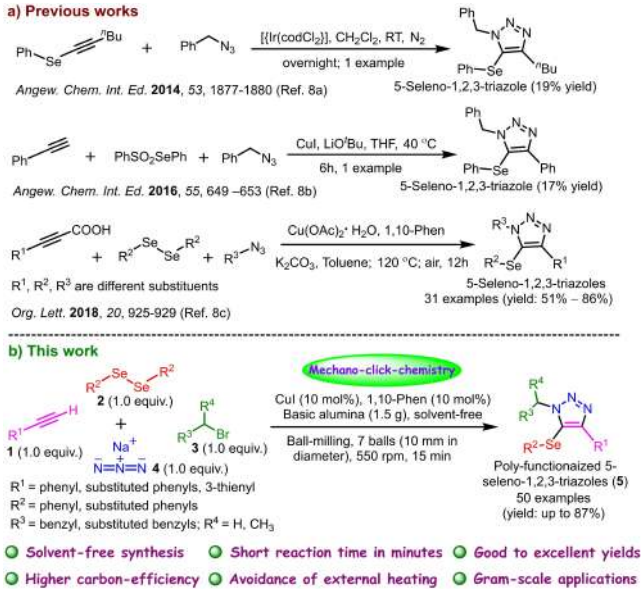
A mechanochemistry-driven practical and efficient synthetic protocol for accessing diverse series of biologically relevant poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles through copper(I)-catalyzed click reaction between aryl/heteroaryl acetylenes, diaryl diselenides, benzyl bromides, and sodium azide has been accomplished under high-speed ball-milling. Advantages of this method include operational simplicity, avoidance of using solvent and external heating, one-pot synthesis, short reaction time in minutes, good to excellent yields, broad substrate scope, and gram-scale applications. Furthermore, synthesized organoselenium compounds were synthetically diversified to biologically promising selenones.

Introduction

Organoselenium compounds hold a significant position among bioactive natural and synthetic analogs.[1] Many such molecules are used in organic syntheses as essential building blocks,[2] medicinal and agro-chemistry,[3] material sciences,[4] and many other related fields.[5] As a result, recent times have seen a good deal of synthetic endeavors for diverse organoselenium compounds.[6] On the other hand, the 1,2,3-triazole moiety is well-regarded as an important class of *N*-heterocycles, possessing useful applications in the domain of synthetic organic, medicinal, pharmaceutical and agricultural chemistry, and material sciences.[7] Hence, the design and synthesis of seleno-triazoles with a motto to couple the essence of these two structural motifs in one molecular architecture that may show extended biological, pharmacological, and materials applications is warranted. A literature survey revealed only three such previous reports (Scheme 1a). In 2014, Ding *et al.*[8a] first reported the synthesis of one such compound, 1-benzyl-4-butyl-5-(phenylselanyl)-1*H*-1,2,3-triazole through an iridium-catalyzed azide–alkyne cycloaddition reaction (IrAAC), and another such entry (*viz.* 1-benzyl-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole) by Wang *et al.*[8b] in 2016 following copper(I)-catalyzed interrupted click reaction. Later, in 2018, Yan-Li Xu and co-workers[8c] reported a more generalized protocol involving a Cu-catalyzed decarboxylative click reaction to access a series of 1,4-disubstituted 5-arylselanyl-1,2,3-triazoles by heating the reaction mixture of propiolic acids, diselenides, and azides at 120 °C in toluene for 12 h in the presence of additive and base. As part of our ongoing research endeavors in designing and developing greener and advanced synthetic protocols for biologically relevant organic scaffolds,[9] we were motivated to design an alternative methodology for such important organoselenium compounds, which would be more practical to operate and attributed with several other greener aspects. To our delight, we have now developed a ball mill-driven mechanochemical synthetic protocol to prepare a diverse series of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles (**5**) through copper(I)-catalyzed click reaction of the reaction mixture containing aryl/heteroaryl acetylenes (**1**), diaryl diselenides (**2**), benzyl bromides (**3**) and sodium azide (**4**) under solvent-free conditions



Scheme 1. (a) Earlier reports on the synthesis of 5-seleno-1,2,3-triazoles. (b) Mechanochemical one-pot synthesis of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles through CuI/1,10-Phen-catalyzed click reaction

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(Scheme 1b). The major advantages of this method include one-pot synthesis without any pre-functionalization, solvent-free synthesis, short reaction time in minutes, good to excellent yields, broad substrate scope, higher carbon-efficiency, avoidance of external heating, and gram-scale applications. Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, independently developed by Sharpless[10] and Meldal,[11] is much well-known technique in synthesizing diverse 1,4-disubstituted-1,2,3-triazoles in facile and a regioselective manner.[12] This pioneering work has recently been recognized with the Nobel Prize in Chemistry for the year 2022. Furthermore, mechanochemical synthesis has emerged as one of the fascinating green techniques in modern organic synthesis.[13]

Results and Discussion

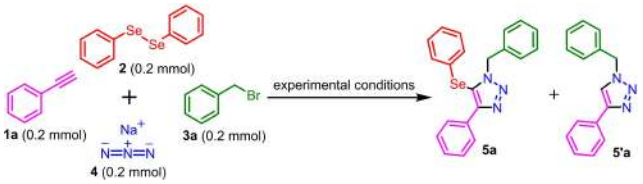
We started our endeavor with our model reaction between phenylacetylene (**1 a**), diphenyl diselenide (**2 a**), benzyl bromide (**3 a**) and sodium azide (NaN_3; **4**), targeting the desired product, 1-benzyl-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole (**5 a**), through solvent-free ball-milling under various conditions. All such results are summarized in Table 1. In our very first attempt, when the mixture of **1 a**, **2 a**, **3 a** and NaN_3 (**4**) was milled over a basic alumina surface (1.5 g, pH = 8.01) using seven stainless steel balls (10 mm in diameter) at 550 rpm in the absence of any other catalysts and additives, no reaction took place even at 1 h (with 10 s break at 10 min intervals) (Table 1, entry 1), while we isolated the phenylselanyl product **5 a** and the non-phenylselanyl product **5′a** in 72% and 21% yields, respectively, at 1 h, upon using 10 mol% of CuI as the catalyst (Table 1, entry 2). Most strikingly, the conversion was successfully implemented when we just added 10 mol% of 1,10-phenanthroline (1,10-Phen) and isolated **5 a** in 87% yield and **5′a** in 13% yield within 15 min on ball-milling (using 7 stainless steel balls with 10 mm in diameter, and rotation in an inverted direction at 550 rpm with 30 sec break at 7.30 min interval) the model reaction mixture containing 10 mol% of CuI as the catalyst and basic alumina (1.5 g) as the surface (Table 1, entry 3). We then performed a series of reactions with the model entry under ball-milling (Table 1, entries 4–31) to explore the best optimum reaction conditions upon varying the amount of CuI catalyst (entries 4 & 5) and 1,10-Phen additive (entries 6 & 7), other copper-catalysts (such as CuBr, CuCl, $CuCl_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, $Cu(NO_3)_2$, $CuSO_4$, CuO, Cu-powder, and $[Cu(PPh_3)_2]BH_4$; entries 8–17) and additives (such as ethylene diamine, DABCO and DBU; entries 18–20), the effect of the acid-base property of alumina surface using acidic and neutral alumina (entries 21 & 22), and the milling-parameters such as the number of balls, frequency and milling-time (entries 23–31). We also checked the transformation without ball-milling upon stirring the reaction mixture in two different solvents, such as DMSO (entry 32) and CH_3CN (entry 33), overnight (12 h) at ambient conditions when **5 a** was found not to be formed. From the detailed experimental outcomes, we appeared at the optimum reaction conditions for this click-reaction as to ball-mill the reaction mixture of **1 a** (0.2 mmol), **2 a** (0.2 mmol), **3 a** (0.2 mmol), and **4** (0.2 mmol) with 7 stainless-steel balls at 550 rpm for 15 min in the presence of CuI (10 mol%) as a catalyst, 1,10-Phen (10 mol%) as an additive, and basic alumina (1.5 g, pH = 8.01) as a surface to afford the desired product **5 a** in its best-isolated yield of 87% (entry 3). We observed that the proportion of the non-phenylselanyl product **5′a** enhances with an increase in ball-milling time (entry 30: **5 a**:**5′a** 60:26 at 25 min; entry 31: **5 a**:**5′a** 33:68 at 35 min), thereby indicating the ball-milling time of 15 min is crucial for the obtaining the best-yield of **5 a** (87%) under the optimized ball-mill conditions. The pure products **5 a** and **5′a** were isolated using flash column chromatography and characterized based on their detailed spectral studies. Both are known compounds, and their physical and spectral properties are well-matched with those reported in the literature.[8c]

Once we came across the optimized reaction conditions, we planned to explore the substrate scopes with diversely substituted phenylacetylenes **1** and benzyl bromides **3**. A set of eleven different phenylacetylenes (**1 b**-**1 l**) having substitutions at the *para*-position of the phenyl ring with both electron-donating (such as Me, Et, *n*-Pr, *t*-Bu, OMe, OEt, Br) and electron-withdrawing (such as F, CF_3, Ph, OPh) groups were tested first. To our delight, all of these phenylacetylene derivatives **1 b**–**1 l** afforded the expected 4-aryl-1-benzyl-5-(phenylselanyl)-1*H*-1,2,3-triazoles (**5 b**–**5 l**) upon reacting with diphenyl diselenide (**2 a**), benzyl bromide (**3 a**) and sodium azide under the optimized conditions with moderate to good yields ranging from 46%-84% (Table 2). Two more phenylacetylene derivatives, 3-aminophenylacetylene (**1 m**) and 1-(3-thienyl)acetylene (**1 n**) were also found to produce 3-(1-benzyl-5-(phenylselanyl)-1H-1,2,3-triazol-4-yl)aniline (**5 m**) and 1-benzyl-5-(phenylselanyl)-4-(thiophen-3-yl)-1*H*-1,2,3-triazole (**5 n**) with respective yields of 51% and 70% (Table 2).

With these successful results in hand, we then performed the solvent-free mechano-click-reaction for a set of ten more entries from the reaction between varying phenylacetylenes (**1 a**–**1 c**, **1 f**, **1 j**–**1 l** and **1 n**), diphenyl diselenide (**2 a**), 4-methylbenzyl bromide (**3 b**)/3-chlorobenzyl bromide (**3 c**) and sodium azide under the identical reaction conditions. To our delight, all the reactions proceeded smoothly and furnished the functionalized 4-aryl-1-benzyl-5-(phenylselanyl)-1*H*-1,2,3-triazoles (**5 o**–**5 x**) within 15 min with the isolated yields ranging from 42%–77% (Table 2). We then carried out five more reactions with 1-naphthylmethyl bromide (**3 d**) and successfully isolated the substituted 1-(naphthalen-1-ylmethyl)-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole derivatives (**5 y**–**5 c′**) with good yields (65%–74%; Table 2). In addition, 1-methyl-1-phenyl-methylbromide (**3 e**) took part in this reaction and yielded the desired product, 1-(1-(naphthalen-1-yl)ethyl)-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole (**5 d′**) in 68% yield within 15 min upon ball-milling with phenylacetylene, diphenyl diselenide (**2 a**), 1-methyl-1-phenyl-methylbromide (**3 e**) and sodium azide under the optimized conditions.

We then turned our attention to extending the scope of diphenyl diselenides **2**. For this purpose, we first screened a set of six differently substituted diaryl diselenides, such as di-*o*-tolyl diselenide (**2 b**), di-*m*-tolyl diselenide (**2 c**), di-*p*-tolyl diselenide

Table 1. Optimization of reaction conditions.[a]

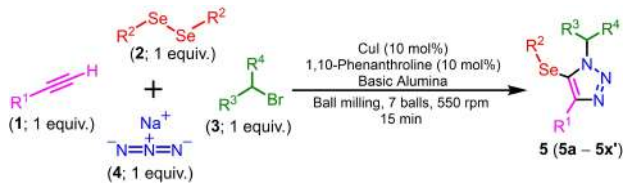


Entry	Catalyst (mol%)	Additive (mol%)	Surface (Alumina)	No. of balls/rpm	Time (min)	% yield[b] **5a**	% yield[b] **5′a**
1	–	–	Basic	7/550	60	–	–
2	CuI (10)	–	Basic	7/550	60	72	21
3	**CuI** (10)	**1,10-Phen** (10)	**Basic**	**7/550**	**15**	**87**	**13**
4	CuI (20)	1,10-Phen (10)	Basic	7/550	15	86	13
5	CuI (5)	1,10-Phen (10)	Basic	7/550	20	67	13
6	CuI (10)	1,10-Phen (20)	Basic	7/550	15	85	11
7	CuI (10)	1,10-Phen (5)	Basic	7/550	20	60	17
8	CuBr (10)	1,10-Phen (10)	Basic	7/550	60	67	26
9	CuCl (10)	1,10-Phen (10)	Basic	7/550	60	41	51
10	$CuCl_2$ (10)	1,10-Phen (10)	Basic	7/550	60	38	43
11	$Cu(OAc)_2$ (10)	1,10-Phen (10)	Basic	7/550	60	60	26
12	$Cu(OTf)_2$ (10)	1,10-Phen (10)	Basic	7/550	45	49	26
13	$Cu(NO_3)_2$ (10)	1,10-Phen (10)	Basic	7/550	60	28	21
14	$CuSO_4$(10)	1,10-Phen (10)	Basic	7/550	60	38	30
15	CuO (10)	1,10-Phen (10)	Basic	7/550	60	41	21
16	Cu powder (10)	1,10-Phen (10)	Basic	7/550	30	62	26
17	$[Cu(PPh_3)_2]$ BH_4 (10)	–	Basic	7/550	60	Trace	47
18	CuI (10)	EN (10)	Basic	7/550	60	–	–
19	CuI (10)	DABCO (10)	Basic	7/550	60	54	30
20	CuI (10)	DBU (10)	Basic	7/550	60	49	38
21	CuI (10)	1,10-Phen (10)	Acidic	7/550	60	38	43
22	CuI (10)	1,10-Phen (10)	Neutral	7/550	60	41	55
23	CuI (10)	1,10-Phen (10)	Basic	9/550	15	77	17
24	CuI (10)	1,10-Phen (10)	Basic	5/550	25	67	26
25	CuI (10)	1,10-Phen (10)	Basic	3/550	30	23	09
26	CuI (10)	1,10-Phen (10)	Basic	0/550	30	–	-
27	CuI (10)	1,10-Phen (10)	Basic	7/600	15	82	17
28	CuI (10)	1,10-Phen (10)	Basic	7/450	20	67	30
29	CuI (10)	1,10-Phen (10)	Basic	7/550	10	28	09
30	CuI (10)	1,10-Phen (10)	Basic	7/550	25	60	26
31	CuI (10)	1,10-Phen (10)	Basic	7/550	35	33	68
32[c]	CuI (10)	1,10-Phen (10)	Basic	–	720	Trace	17
33[d]	CuI (10)	1,10-Phen (10)	Basic	–	720	Trace	13

[a] Reaction conditions: A mixture of phenylacetylene (**1a**; 0.2 mmol), diphenyl diselenide (**2**; 0.2 mmol), benzyl bromide (**3a**; 0.2 mmol) and sodium azide (**4**; 0.2 mmol) was ball-milled (using a 25 mL of stainless-steel jar and stainless-steel 5–9 balls of 10 mm in diameter) in presence/absence of catalysts, additives and surface without the aid of any solvent. [b] Isolated yields. [c, d] Reaction conditions: Stirring the reaction mixture at ambient conditions (25–28 °C), respectively, in DMSO and CH_3CN. pH was measured (1.5 g of acidic/neutral/basic alumina suspended in 5 mL of distilled water, followed by stirring for 10 min and then leaving undisturbed for 1 h) for acidic alumina as 6.13, neutral alumina as 7.07, and acidic alumina as 8.01. 1,10-Phen = 1,10-phenanthroline; EN = ethylene diamine.

(**2d**), di-*p*-ethylphenyl diselenide (**2e**), di-*p*-trifluoromethylphenyl diselenide (**2f**), and di-*p*-fluorophenyl diselenide (**2g**), and performed a series of twenty individual mechano-click-reactions with diverse aryl acetylenes (**1a**, **1b**, **1f**, **1g**, **1j**, **1k**, **1l**, and **1n**), benzyl bromides (**3a** and **3b**) and sodium azide (4) under the identical reaction conditions. All these reactions

Table 2. Mechanochemical synthesis of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles.[a,b]



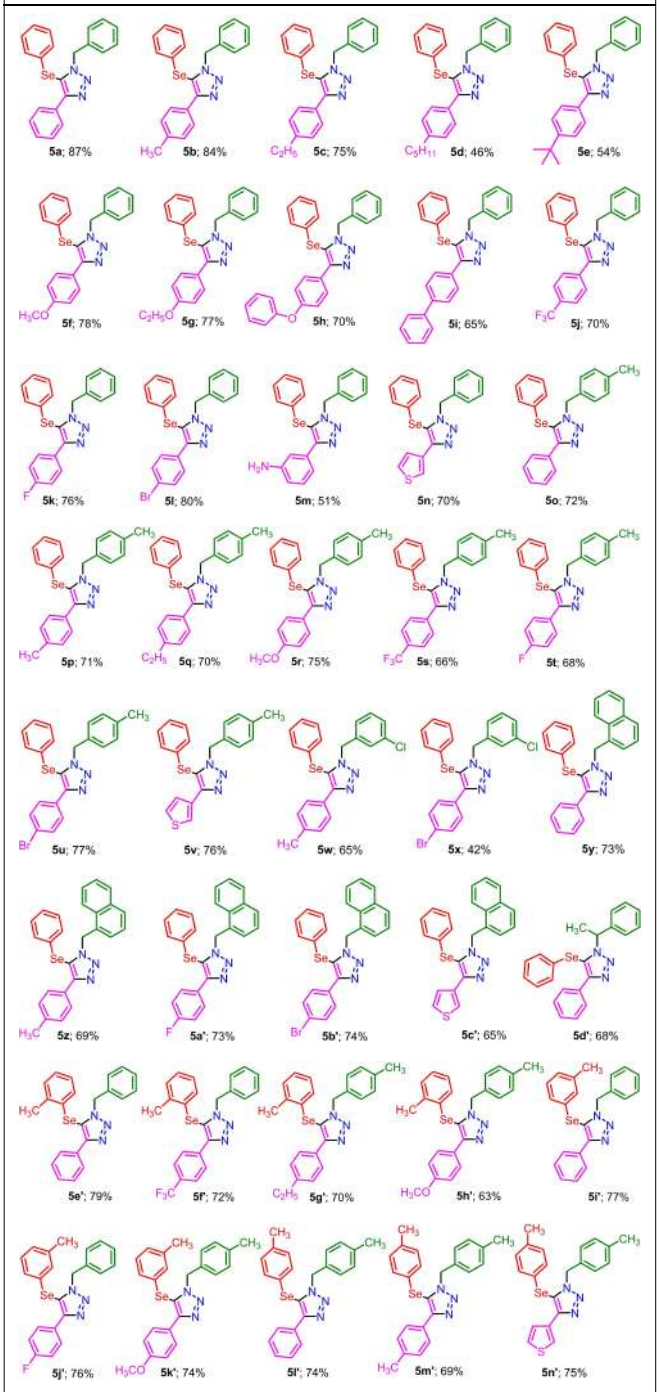
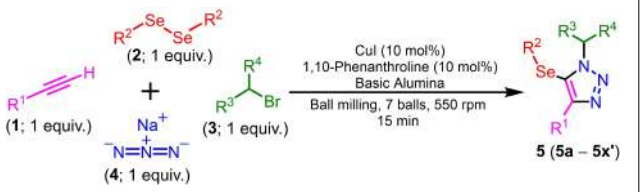
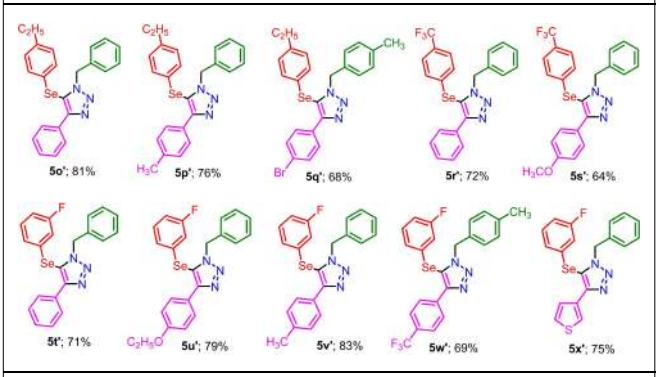


Table 2. continued





[a] Reaction conditions: A mixture of aryl acetylenes (**1**; 0.2 mmol), diaryl diselenides (**2**; 0.2 mmol), benzyl bromides (**3**; 0.2 mmol) and sodium azide (**4**; 0.2 mmol) was ball-milled under neat-conditions using 7 stainless-steel balls (10 mm in diameter) within a 25 mL of stainless-steel jar at 550 rpm for 15 min (with 30 sec breaks upon 7.30 min interval) in the presence of CuI (10 mol%) as the catalyst and 1,10-Phenanthroline (10 mol%) as an additive. [b] Isolated yields.

proceeded efficiently, resulting in the targeted products **5e'**-**5x'** with good yields ranging from 63–81% within 15 min (Table 2). The overall experimental observations are summarized in Table 2. All the products were isolated in their pure state using flash column chromatography, followed by their characterization based on elemental analyses and detailed spectral studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **5j**, **5k**, **5s**, **5t** and **5a'**), and HRMS (*see Experimental*). To our delight, we were also successful in developing suitable crystals for one representative entry, 1-benzyl-4-(4-ethoxyphenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (**5g**, Table 2), and its single crystal X-ray analysis (CCDC 2283663; unit cell parameters: a = 9.32 Å, b = 9.923 Å, c = 22.579 Å, α = 86.953(4)°, β = 86.606(4)°, γ = 75.878(4)°; Space Group: P-1) documented in this present communication (see the Supporting Information) is in full structural agreement. The ORTEP diagram of the molecule is represented in Figure 1.

Based on literature reports[14] and the results of our control experiments (Scheme 2), we herein proposed a possible mechanism for this ball-mill-driven one-pot four-component click reaction as outlined in Scheme 3. That the reaction follows an ionic pathway received evidential support from the radical-scavenging experiments where none of the radical scavengers (*viz.* TEMPO, BQ, and BHT) could influence the conversion (Scheme 2a). An active Cu(I)-coordination complex **A** is first formed from the interaction between CuI and 1,10-phenanthroline ligand, which then binds with arylacetylene molecule (**1**) to form the copper(I)-complex **10**. Upon reacting with diaryl diselenide (**2**), the intermediate **10** generates a copper(II)-

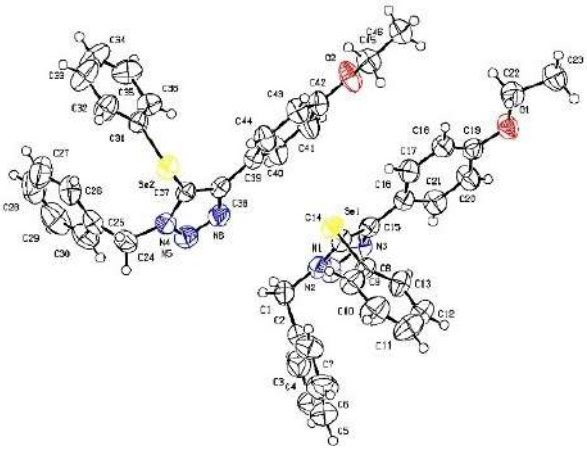
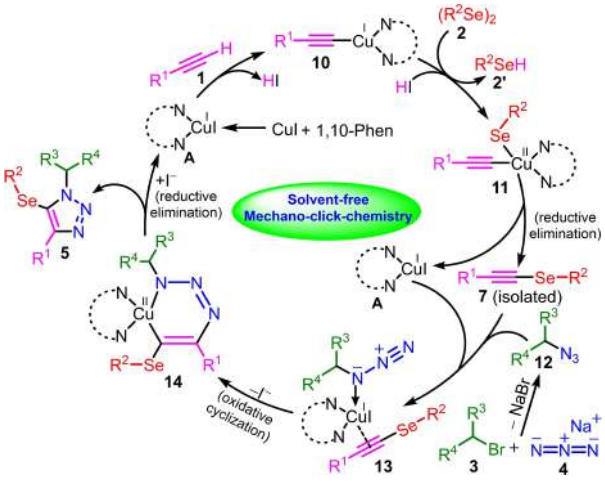
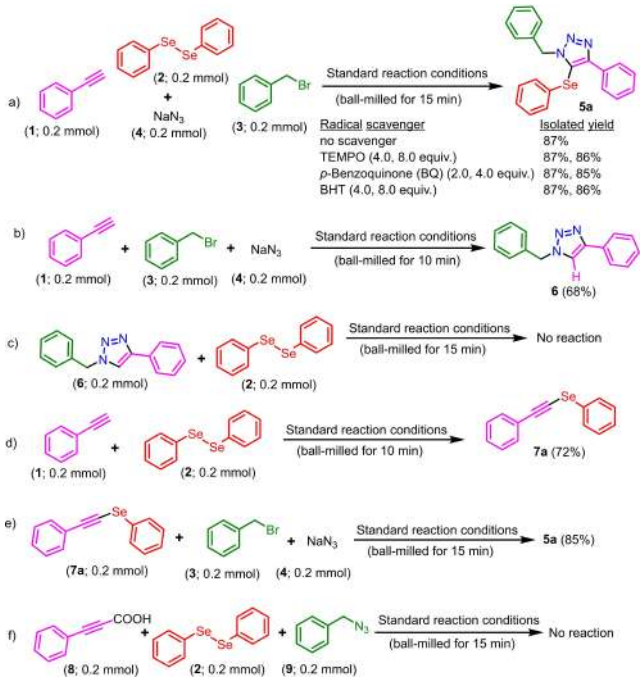


Figure 1. ORTEP view of the molecule **5g**, showing the atom-labelling scheme (displacement ellipsoids are drawn at the 50% probability level, and H atoms are shown as small spheres of arbitrary radii).



Scheme 3. Proposed mechanism.



Scheme 2. Control experiments.

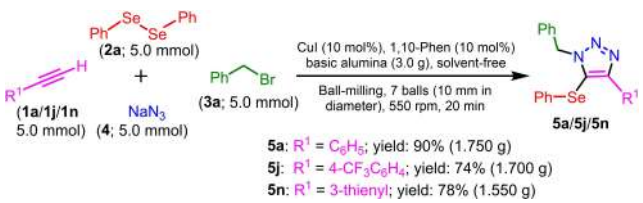
complex **11**, which then undergoes reductive elimination, thereby producing aryl(arylethynyl)selane intermediate (**7**; **7a** was isolated; Scheme 2d) and the Cu(I)-coordination complex **A** is regenerated. In the next step, an intermediate **13** is formed by the interaction between Cu(I)-coordination complex **A**, *in-situ*-generated intermediate **7**, and benzyl azide **12** (formed *in-situ* by the reaction between benzyl bromide **3** and sodium azide **4** under the reaction conditions), which in turn takes part in an oxidative cyclization to form a six-membered Cu(II)-coordination complex **14**. In the final step, complex **14** collapses to the desired product **5**, having a 1,2,3-triazole nucleus, and Cu(I)-coordination complex **A** that enters into the next catalytic cycle (Scheme 3).

To check the efficacy of our method, we performed gram-scale syntheses (5.0 mmol scale; 25-fold enhancement; Scheme 4) for three different entries **5a**, **5j** and **5n**. To our delight, all three gram-scale reactions proceeded smoothly, resulting in satisfactory respective yields of 90%, 74% and 78% within 20 min (*see Experimental*). The yield and time in each gram-scale synthesis were found to be almost identical to those for the millimolar scale.

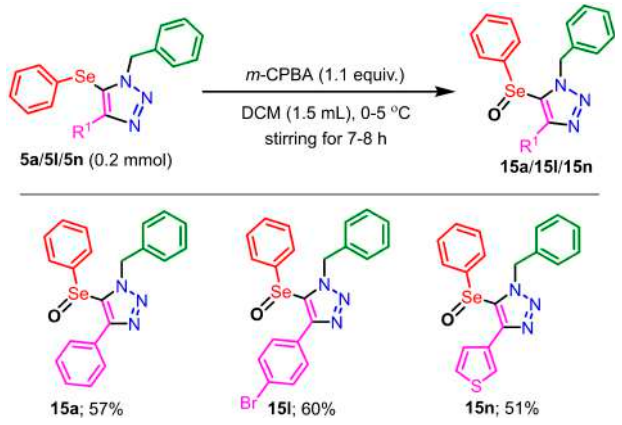
We then planned to extend the synthetic application of our synthesized selenotriazole compounds. For this purpose, we synthetically diversified a set of three representative synthesized compounds, such as **5a**, **5l**, and **5n**, to selonones by facile and controlled oxidation by *m*-chloroperbenzoic acid (*m*-CPBA) to produce selenoxides **15** (Scheme 5) in good yields, following the standard procedure.[15] Selenones are interesting organoselenium compounds that find immense application as building blocks for a handful of natural and synthetic bioactive molecules[16] and exhibit numerous biological activities.[17]

Conclusions

In conclusion, we have developed a practical and straightforward mechanochemistry-driven synthetic route for accessing diverse series of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles (**5**) through copper(I)-catalyzed click reaction between aryl/heteroaryl acetylenes (**1**), diaryl diselenides (**2**), benzyl bromides (**3**) and sodium azide (**4**) under high-speed ball-



Scheme 4. Gram-scale synthetic applications.



Scheme 5. *m*-CPBA-mediated controlled oxidation of **5 a**, **5 l** and **5 n** to corresponding selenoxides **15**.[a,b] [a] Reaction conditions: A mixture of 5-(arylselanyl)-1*H*-1,2,3-triazoles (**5 a**/**5 l**/**5 n**; 0.2 mmol) and *m*-chloroperbenzoic acid (*m*-CPBA; 1.1 equiv.) dissolved in 1.5 mL of dichloromethane (DCM) was stirred for 7–8 h at 0–5 °C, and upon completion of each reaction, the desired product (**15 a**/**15 l**/**15 n**) was isolated following standard procedure.[15] [b] Isolated yields.

milling. One-pot synthesis without any pre-functionalizations, avoidance of using solvent and external heating, short reaction time in minutes, good to excellent yields, broad substrate scope and tolerance of various functional groups, higher carbon efficiency, and facile gram-scale applications, operational simplicity and use of ball-mill as a green tool are the key features of this present method. Furthermore, certain representative organoselenium compounds were synthetically diversified to biologically promising selenone derivatives.

Experimental Section

General method

All chemicals (analytical grade) except starting diaryldiselenide derivatives used in this experiment were purchased from reputed companies and used without further purification. Diaryldiselenide **2 b**–**2 g** used as substrates in this study were synthesized as per the previously reported method.[8c] ^{1}H, ^{13}C, ^{19}F, ^{77}Se NMR spectra were collected at 400, 100, 376, and 76 MHz, respectively, on a Bruker DRX spectrometer using $CDCl_3$ as solvent. Chemical shifts were reported in δ (ppm), relative to the internal standard, TMS. The signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants are reported as *J* value in Hz. Mass spectrometry was obtained using a Microtek Q-TOF Micro YA 263 Waters high-resolution mass spectrometer. X-ray single crystallographic data were collected on X'Calibur CCD area-detector diffractometer. Elemental analyses were performed using a Perkin Elmer 2400 Series II analyzer instrument. The melting points were recorded on a Chemiline CL-725 melting point apparatus and are uncorrected. Thin Layer Chromatography (TLC) was performed using silica gel 60 F_{254} (Merck) plates. A PM 100, Retsch GmbH, Germany, ball-milling apparatus was used for all reactions.

General procedure for the synthesis of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles 5 (5 a–5 z and 5 a′–5 x′)

A mixture of aryl acetylenes (**1**; 0.2 mmol), diaryldiselenides (**2**; 0.2 mmol), benzyl bromides (**3**; 0.2 mmol) and sodium azide (**4**; 0.2 mmol) was ball-milled under neat-conditions using 7 stainless-steel balls (10 mm in diameter) within a 25 mL of stainless-steel jar at 550 rpm for 15 in the presence of CuI (10 mol%) as the catalyst and 1,10-Phenanthroline (10 mol%) as an additive. The ball-milling operation was performed in an inverted rotation direction, with 30 sec break at 7.30 min interval. On completion of the reaction (confirmed by TLC upon ceasing the grinding operation), 20 mL of ethyl acetate and aqueous solution in a proportion of 3:1 (*v*/*v*) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was then removed under reduced pressure to obtain a white crude mass, which was then subjected to column chromatographic purification using EtOAc-hexane mixtures as eluents, to have pure products of **5** (**5 a**–**5 z** and **5 a**′–**5 x**′). All the structures of the synthesized compounds were confirmed by spectroscopic studies, including ^{1}H-NMR, ^{13}C-NMR, DEPT-135, ^{19}F-NMR and HRMS (*see Supporting Information*). The physical and spectral data of all the synthesized compounds **5** (**5 a**–**5 z**, **5 a**′–**5 x**′, **15 a**, **15 l**, and **15 n**) are given below.

1-Benzyl-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole (**5 a**):[8c] White solid; yield 87% (68 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97.5:2.5; mp 125–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05-8.03 (m, 2H, Ar–H), 7.42–7.38 (m, 2H, Ar–H), 7.36–7.33 (m, 1H, Ar–H), 7.23 (s, 5H, Ar–H), 7.17–7.08 (m, 3H, Ar–H), 6.98–6.96 (m, 2H, Ar–H), 5.66 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.72 (*C*), 134.91 (*C*), 130.61 (*C*), 129.81 (2×*C*H), 129.71 (*C*), 129.32 (2×*C*H), 128.79 (2×*C*H), 128.68 (*C*H), 128.59 (2×*C*H), 128.31 (*C*H), 128.03 (2×*C*H), 127.58 (2×*C*H), 127.36 (*C*H), 117.92 (*C*), 53.27 (–NCH_2Ar) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 227.86 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_3SeH$; 392.0666; found, 392.0691.

1-Benzyl-5-(phenylselanyl)-4-(*p*–tolyl)-1*H*-1,2,3-triazole (**5 b**):[8c] White solid; yield 84% (68 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 98:2; mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.22–7.19 (m, 7H, Ar–H), 7.14–7.08 (m, 3H, Ar–H), 6.98–6.95 (m, 2H, Ar–H), 5.64 (s, 2H, –NCH_2Ar), 2.36 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.82 (*C*), 138.56 (*C*), 134.95 (*C*), 129.84 (*C*), 129.76 (2×*C*H), 129.28 (2×*C*H), 129.21 (2×*C*H), 128.73 (2×*C*H), 128.25 (*C*H), 128.00 (2×*C*H), 127.42 (2×*C*H), 127.24 (*C*H), 126.18 (*C*), 117.47 (*C*), 53.20 (–NCH_2Ar), 21.41 (Ar–CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 226.91 ppm. Elemental analysis: calcd (%) for $C_{22}H_{19}N_3Se$: C, 65.35; H, 4.74; N, 10.39. Found: C, 65.51; H, 4.81; N, 10.52.

1-Benzyl-4-(4-ethylphenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (**5 c**): White solid; yield 84% (68 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 98:2; mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.22–7.19 (m, 7H, Ar–H), 7.14–7.08 (m, 3H, Ar–H), 6.98–6.95 (m, 2H, Ar–H), 5.64 (s, 2H, - NCH_2Ar), 2.36 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.82 (*C*), 138.56 (*C*), 134.95 (*C*), 129.84 (*C*), 129.76 (2×*C*H), 129.28 (*C*H), 129.21 (2×*C*H), 128.73 (2×*C*H), 128.25 (*C*H), 128.00 (2×*C*H), 127.42 (2×*C*H), 127.24 (2×*C*H), 126.18 (*C*), 117.47 (*C*), 53.20 (–NCH_2Ar), 21.41 (Ar–CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 227.43 ppm. Elemental analysis: calcd (%) for $C_{23}H_{21}N_3Se$: C, 66.03; H, 5.06; N, 10.04. Found: C, 66.24; H, 5.13; N, 10.17.

1-Benzyl-4-(4-pentylphenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole(**5 d**): White solid; yield 46% (42 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96.5:3.5; mp 136–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.22–

7.20 (m, 7H, Ar–H), 7.17–7.08 (m, 3H, Ar–H), 6.98–6.96 (m, 2H, Ar–H), 5.65 (s, 2H, –NCH_2Ar), 2.61 (t, 2H, J = 7.6 Hz, Ar–CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.65–1.58 (m, 2H, Ar–CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 1.33–1.30 (m, 4H, Ar–CH$_2$CH$_2$CH_2CH_2CH$_3$), 0.88 (t, 3H, J = 6.8 Hz, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.87 (*C*), 143.62 (*C*), 134.97 (*C*), 129.90 (*C*), 129.78 (2×*C*H), 129.20 (2×*C*H), 128.74 (2×*C*H), 128.66 (2×*C*H), 128.25 (*C*H), 128.00 (2×*C*H), 127.93 (*C*), 127.40 (2×*C*H), 127.24 (*C*H), 117.43 (*C*), 53.21 (–NCH$_2$Ar), 35.83 (Ar–CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.57 (Ar–CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.10 (Ar–CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 22.65 (Ar–CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 14.16 (Ar–CH$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 227.47 ppm. Elemental analysis: calcd (%) for $C_{26}H_{27}N_3Se$: C, 67.82; H, 5.91; N, 9.13. Found: C, 67.97; H, 5.96; N, 9.01.

1-Benzyl-4-(4-(*tert*-butyl)phenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 e): White solid; yield 54% (48 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, 2H, J = 8.4 Hz, Ar–H), 7.42 (d, 2H, J = 8.4 Hz, Ar–H), 7.21 (s, 5H, Ar–H), 7.17–7.09 (m, 3H, Ar–H), 6.98–6.96 (m, 2H, Ar–H), 5.64 (s, 2H, –NCH_2Ar), 1.32 (s, 9H, -C(CH_3)$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.82 (*C*), 151.75 (*C*), 134.98 (*C*), 129.97 (*C*), 129.82 (2×*C*H), 129.11 (2×*C*H), 128.76 (2×*C*H), 128.27 (*C*H), 128.01 (2×*C*H), 127.72 (*C*), 127.22 (*C*H), 127.20 (2×*C*H), 125.57 (2×*C*H), 117.41 (*C*), 53.23 (–NCH$_2$Ar), 34.80 (Ar–*C*(CH$_3$)$_3$), 31.38 (Ar–C(CH_3)$_3$)ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_3SeH$; 448.1292; found, 448.1286.

1-Benzyl-4-(4-methoxyphenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 f):[8c] White solid; yield 78% (65 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96.5:3.5; mp 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, 2H, J = 8.8 Hz, Ar–H), 7.22 (s, 5H, Ar–H), 7.16–7.08 (m, 3H, Ar–H), 6.97–6.91 (m, 4H, Ar–H), 5.64 (s, 2H, –NCH_2Ar), 3.81 (s, 3H, Ar–OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.99 (*C*), 151.65 (*C*), 134.98 (*C*), 129.87 (*C*), 129.79 (2×*C*H), 129.17 (2×*C*H), 128.86 (2×*C*H), 128.76 (2×*C*H), 128.26 (*C*H), 128.03 (2×*C*H), 127.26 (*C*H), 123.20 (*C*), 116.99 (*C*), 114.02 (2×*C*H), 55.37 (Ar–OCH$_3$), 53.23 (–NCH$_2$Ar) ppm. Elemental analysis: calcd (%) for $C_{22}H_{19}N_3OSe$: C, 62.86; H, 4.56; N, 10.00. Found: 62.98; H, 4.61; N, 10.11.

1-Benzyl-4-(4-ethoxyphenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 g): White solid; yield 77% (67 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, 2H, J = 8.8 Hz, Ar–H), 7.22 (s, 5H, Ar–H), 7.16–7.08 (m, 3H, Ar–H), 6.97–6.95 (m, 2H, Ar–H), 6.91 (d, 2H, J = 8.8 Hz, Ar–H), 5.64 (s, 2H, –NCH_2Ar), 4.07–4.01 (m, 2H, Ar–OCH_2CH$_3$), 1.43–1.39 (m, 3H, Ar–OCH$_2$CH_3)ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.36 (*C*), 151.67 (*C*), 134.98 (*C*), 129.87 (*C*), 129.76 (2×*C*H), 129.17 (2×*C*H), 128.81 (2×*C*H), 128.73 (2×*C*H), 128.23 (*C*H), 127.99 (2×*C*H), 127.23 (*C*H), 123.01 (*C*), 116.92 (*C*), 114.51 (2×*C*H), 63.51 (Ar–OCH$_2$CH$_3$), 53.20 (–NCH$_2$Ar), 14.91 (Ar–OCH$_2$CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 226.12 ppm.Elemental analysis: calcd (%) for $C_{23}H_{21}N_3OSe$: C, 63.59; H, 4.87; N, 9.67. Found: C, 63.78; H, 4.91; N, 9.59.

1-Benzyl-4-(4-phenoxyphenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 h): Yellowish semi-solid; yield 70% (68 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97.5:2.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, 2H, J = 8.8 Hz, Ar–H), 7.45 (t, 2H, J = 8.0 Hz, Ar–H), 7.36–7.33 (m, 5H, Ar–H), 7.28–7.18 (m, 4H, Ar–H), 7.15–7.11 (m, 4H, Ar–H), 7.08–7.06 (m, 2H, Ar–H), 5.76 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.86 (*C*), 156.77 (*C*), 151.24 (*C*), 134.87 (*C*), 129.88 (2×*C*H), 129.79 (2×*C*H), 129.68 (*C*), 129.15 (2×*C*H), 129.03 (2×*C*H), 128.76 (2×*C*H), 128.29 (*C*H), 128.01 (2×*C*H), 127.30 (*C*H), 125.49 (*C*), 123.68 (*C*H), 119.37 (2×*C*H), 118.57 (2×*C*H), 117.38 (*C*), 53.24 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 227.07 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}N_3OSeH$; 484.0928; found, 484.0923.

4-([1,1′-Biphenyl]-4-yl)-1-benzyl-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 i):[8c] White solid; yield 65% (61 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, 2H, J = 8.4 Hz, Ar–H), 7.65–7.61 (m, 4H, Ar–H), 7.36–7.33 (m, 2H, Ar–H), 7.18–7.09 (m, 3H, Ar–H), 7.01–6.99 (m, 2H, Ar–H), 5.67 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.37 (*C*), 141.32 (*C*), 140.66 (*C*), 134.93 (*C*), 129.87 (2×*C*H), 129.74 (*C*), 129.58 (*C*), 129.32 (2×*C*H), 128.93 (2×*C*H), 128.82 (2×*C*H), 128.34 (*C*H), 128.06 (2×*C*H), 127.87 (2×*C*H), 127.59 (*C*H), 127.40 (*C*H), 127.29 (2×*C*H), 127.15 (2×*C*H), 117.91 (*C*), 53.30 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 228.40 ppm. Elemental analysis: calcd (%) for $C_{27}H_{21}N_3Se$: C, 69.53; H, 4.54; N, 9.01. Found: C, 69.72; H, 4.61; N, 9.14.

1-Benzyl-5-(phenylselanyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (5 j):[8c] White solid; yield 70% (64 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, 2H, J = 8.4 Hz, Ar–H), 7.64 (d, 2H, J = 8.0 Hz, Ar–H), 7.24 (s, 4H, Ar–H), 7.19–7.09 (m, 4H, Ar–H), 6.96 (d, 2H, J = 7.2 Hz, Ar–H), 5.68 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.13 (*C*), 134.37 (J^2_{C-F} = 58 Hz, *C*), 130.43 (J^2_{C-F} = 32 Hz, *C*), 129.96 (2×*C*H), 129.39 (2×*C*H), 129.19 (*C*), 128.87 (2×*C*H), 128.47 (2×*C*H), 128.09 (*C*H), 127.65 (3×*C*H), 126.49 (*C*), 125.59 (d, J^3_{C-F} = 3 Hz, *C*H), 125.52 (d, J^3_{C-F} = 3 Hz, *C*H), 121.51 (J^1_{C-F} = 267 Hz, -*C*F$_3$), 118.87 (*C*), 53.39 (–NCH$_2$Ar) ppm.^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.68 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 229.76 ppm. Elemental analysis: calcd (%) for $C_{22}H_{16}F_3N_3Se$: C, 57.65; H, 3.52; N, 9.17. Found: C, 57.81; H, 3.56; N, 9.13.

1-Benzyl-4-(4-fluorophenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 k):[8c] White solid; yield 76% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 127–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.01 (m, 2H, Ar–H), 7.23 (s, 4H, Ar–H), 7.18–7.06 (m, 6H, Ar–H), 6.96–6.94 (m, 2H, Ar–H), 5.66 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.04 (d, J^1_{C-F} = 246 Hz, *C*), 150.83 (*C*), 134.80 (*C*), 133.80 (*C*), 129.84 (2×*C*H), 129.36 (d, J^3_{C-F} = 7 Hz, 2×*C*H), 129.25 (2×*C*H), 128.79 (2×*C*H), 128.34 (*C*H), 128.04 (2×*C*H), 127.42 (*C*H), 126.78 (*C*), 117.71 (*C*), 115.58 (d, J^2_{C-F} = 22 Hz, 2×*C*H), 53.29 (–NCH$_2$Ar) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −112.89 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 227.01 ppm. Elemental analysis: calcd (%) for $C_{21}H_{16}FN_3Se$: C, 61.77; H, 3.95; N, 10.29. Found: C, 61.96; H, 3.99; N, 10.41.

1-Benzyl-4-(4-bromophenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 l): White solid; yield 80% (75 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97.5:2.5; mp 99–100°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, 2H, J = 8.4 Hz, Ar–H), 7.51 (d, 2H, J = 8.4 Hz, Ar–H), 7.23 (s, 5H, Ar–H), 7.18–7.09 (m, 3H, Ar–H), 6.96–6.94 (m, 2H, Ar–H), 5.66 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.56 (*C*), 134.79 (*C*), 133.04 (*C*), 132.02 (*C*), 131.79 (2×*C*H), 129.91 (2×*C*H), 129.34 (2×*C*H), 129.02 (2×*C*H), 128.84 (2×*C*H), 128.41 (*C*H), 128.08 (2×*C*H), 127.54 (*C*H), 122.97 (*C*), 118.11 (*C*), 53.34 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 228.14 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}N_3SeBrH$; 469.9771; found, 469.9766.

4-(1-Benzyl-5-(phenylselanyl)-1*H*-1,2,3-triazol-4-yl)aniline (5 m): White semi-solid; yield 51% (41 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 98.5:1.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 2H, Ar–H), 7.37–7.34 (m, 5H, Ar–H), 7.32–7.28 (m, 3H, Ar–H), 7.15–7.11 (m, 1H, Ar–H), 6.88 (d, 1H, J = 7.6 Hz, Ar–H), 6.78–6.77 (m, 1H, Ar–H), 4.33 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.05 (*C*), 139.09 (2 *C*), 129.65 (2×*C*H), 129.35 (*C*H), 129.17 (*C*), 128.98 (2×*C*H), 128.84 (2×*C*H), 127.62 (2×*C*H), 127.50 (*C*H), 127.12 (*C*H), 123.86 (*C*), 121.34 (*C*H), 115.58 (*C*H), 113.72 (*C*H), 103.73 (*C*), 48.26 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 271.35 ppm. Elemental analysis: calcd (%) for $C_{21}H_{18}N_4Se$: C, 62.22; H, 4.48; N, 13.82. Found: C, 62.81; H, 4.52; N, 13.76.

1-Benzyl-5-(phenylselanyl)-4-(thiophen-3-yl)-1*H*-1,2,3-triazole (5 n):[8c] White solid; yield 70% (57 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.99 (m, 1H, Ar–H), 7.86–7.84 (m, 1H, Ar–H), 7.35–7.33 (m, 1H, Ar–H), 7.21 (s, 5H, Ar–H), 7.17–7.08 (m, 3H, Ar–H), 6.99–6.98 (m, 2H, Ar–H), 5.65 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.48 (*C*), 134.83 (*C*), 131.45 (*C*),129.80 (2×*C*H), 129.38 (*C*), 129.16 (2×*C*H), 128.71 (2×*C*H), 128.24 (*C*H), 127.89 (2×*C*H), 127.32 (*C*H), 126.71 (*C*H), 125.79 (*C*H), 123.11 (*C*H), 117.26 (*C*), 53.13 (–NCH_2Ar) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 223.67 ppm. Elemental analysis: calcd (%) for $C_{19}H_{15}N_3SSe$: C, 57.57; H, 3.81; N, 10.60. Found: C, 57.78; H, 3.86; N, 10.73.

1-(4-Methylbenzyl)-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 o):[8c] White solid; yield 72% (58 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 98:2; mp 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, 2H, *J* = 7.2 Hz, Ar–H), 7.42–7.34 (m, 3H, Ar–H), 7.15–7.09 (m, 5H, Ar–H), 7.02 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.97 (d, 2H, *J* = 7.2 Hz, Ar–H), 5.62 (s, 2H, –NCH_2Ar), 2.28 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.70 (*C*), 138.08(*C*), 131.91 (*C*), 130.63 (*C*), 129.74 (2×*C*H), 129.40 (*C*H), 129.23 (2×*C*H), 128.62 (2×*C*H), 128.55 (2×*C*H), 128.04 (2×*C*H), 127.54 (2×*C*H), 127.17 (*C*H), 126.29(*C*), 117.71 (*C*), 53.10 (–NCH_2Ar), 21.19 (Ar–CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 228.11 ppm. Elemental analysis: calcd (%) for $C_{22}H_{19}N_3Se$: C, 65.35; H, 4.74; N, 10.39. Found: C, 65.54; H, 4.80; N, 10.28.

1-(4-Methylbenzyl)-5-(phenylselanyl)-4-(*p*–tolyl)-1*H*-1,2,3-triazole (5 p): White solid; yield 71% (59 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 98.5:1.5; mp 91–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.21 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.15–7.08 (m, 5H, Ar–H), 7.01 (d, 2H, *J* = 7.6 Hz, Ar–H), 6.97–6.95 (m, 2H, Ar–H), 5.61 (s, 2H, –NCH_2Ar), 2.36 (s, 3H, Ar–CH_3), 2.28 (s, 3H, –NCH$_2$ArCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.83 (*C*), 138.50 (*C*), 138.03 (*C*), 131.95 (*C*), 129.94 (*C*), 129.71 (2×*C*H), 129.37 (2×*C*H), 129.26 (2×*C*H), 129.14 (2×*C*H), 128.03 (2×*C*H), 127.77 (*C*), 127.40 (2×*C*H), 127.08 (*C*H), 117.29 (*C*), 53.05 (–NCH_2Ar), 21.40 (Ar–CH_3), 21.17 (–NCH$_2$ArCH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 226.85 ppm. Elemental analysis: calcd (%) for $C_{23}H_{21}N_3Se$: C, 66.03; H, 5.06; N, 10.04. Found: C, 66.21; H, 5.11; N, 10.15.

4-(4-Ethylphenyl)-1-(4-methylbenzyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 q): White solid; yield 70% (61 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96.5:3.5; mp 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.19 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.12–7.03 (m, 5H, Ar–H), 6.96 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.93–6.91 (m, 2H, Ar–H), 5.56 (s, 2H, –NCH_2ArCH$_3$), 2.62 (q, 2H, *J* = 7.6 Hz, Ar–CH_2CH$_3$), 2.23 (s, 3H, Ar–CH_3), 1.19 (t, 3H, *J* = 7.6 Hz, Ar–CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.80 (*C*), 144.77 (*C*), 137.97 (*C*), 131.91 (*C*), 129.92 (*C*), 129.68 (2×*C*H), 129.33 (2×*C*H), 129.03 (2×*C*H), 128.04 (2×*C*H), 127.99 (2×*C*H), 127.42 (2×*C*H), 127.02 (*C*H), 126.20 (*C*), 117.20 (*C*), 53.01 (–NCH$_2$ArCH$_3$), 28.72 (Ar–CH_2CH$_3$), 21.16 (–NCH$_2$ArCH_3), 15.50 (Ar–CH$_2$CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 227.56 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_3SeH$; 434.1135; found, 434.1130.

4-(4-Methoxyphenyl)-1-(4-methylbenzyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 r): White solid; yield 75% (65 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 95:5; mp 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.15–7.08 (m, 5H, Ar–H), 7.01 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.96–6.91 (m, 4H, Ar–H), 5.59 (s, 2H, –NCH_2ArCH$_3$), 3.82 (s, 3H, Ar–OCH_3), 2.27 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.99 (*C*), 138.09 (*C*), 132.03 (*C*), 130.00 (*C*),129.77 (*C*H), 129.67 (*C*), 129.42 (2×*C*H), 129.13 (2×*C*H), 128.88 (2×*C*H), 128.07 (2×*C*H), 127.97 (*C*), 127.13 (*C*H), 123.28 (*C*), 114.01 (3×*C*H), 55.39 (Ar–OCH$_3$), 53.11 (–NCH$_2$ArCH$_3$), 21.22 (Ar–CH$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 225.69 ppm. Elemental analysis: calcd (%) for $C_{23}H_{21}N_3OSe$: C, 63.59; H, 4.87; N, 9.67. Found: C, 63.74; H, 4.91; N, 9.61.

1-(4-Methylbenzyl)-5-(phenylselanyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (5 s): White solid; yield 66% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4; mp 99–100°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.64 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.19–7.09 (m, 5H, Ar–H), 7.03 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.97–6.94 (m, 2H, Ar–H), 5.64 (s, 2H, –NCH_2Ar), 2.28 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.12 (*C*), 138.30 (*C*), 134.13 (*C*), 130.37 (d, J^2_{C-F} = 32 Hz, *C*), 131.69 (*C*), 129.91 (2×*C*H), 129.73 (*C*), 129.50 (2×*C*H), 129.32 (2×*C*H), 128.12 (2×*C*H), 127.63 (2×*C*H), 127.48 (2×*C*H), 125.52 (d, J^3_{C-F} = 4 Hz, *C*H), 121.53 (d, J^1_{C-F} = 264 Hz, -CF_3), 118.68 (*C*), 53.24 (–NCH_2Ar), 21.20 (CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.62 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 229.33 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}N_3F_3SeH$; 474.0696; found, 474.0691.

4-(4-Fluorophenyl)-1-(4-methylbenzyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 t): White solid; yield 68% (57 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.00 (m, 2H, Ar–H), 7.18–7.05 (m, 7H, Ar–H), 7.02 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.96–6.94 (m, 2H, Ar–H), 5.62 (s, 2H, –NCH_2Ar), 2.28 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.00 (d, J^1_{C-F} = 247 Hz, *C*), 150.81 (*C*), 138.13 (*C*), 131.81 (*C*), 129.78 (2×*C*H), 129.56 (*C*), 129.39 (d, J^3_{C-F} = 4 Hz, 2×*C*H), 129.30 (2×*C*H), 129.18 (2×*C*H), 128.04 (2×*C*H), 127.26 (*C*H), 126.79 (d, J^4_{C-F} = 2 Hz, *C*), 117.53 (*C*), 115.54 (d, J^2_{C-F} = 21 Hz, 2×*C*H), 53.14 (–NCH_2Ar), 21.17 (Ar–CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −112.87 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 226.93 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}N_3FSeH$; 424.0728; found, 424.0723.

4-(4-Bromophenyl)-1-(4-methylbenzyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 u): White solid; yield 77% (74 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.51 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.18–7.09 (m, 5H, Ar–H), 7.02 (d, 2H, *J* = 8 Hz, Ar–H), 6.94 (d, 2H, *J* = 7.2 Hz, Ar–H), 5.62 (s, 2H, –NCH_2Ar), 2.28 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.57 (*C*), 138.22 (2 *C*), 131.75 (2×*C*H), 129.85 (2×*C*H), 129.59 (*C*), 129.46 (2×*C*H), 129.26 (*C*H), 129.00 (2×*C*H), 128.09 (2×*C*H), 127.37 (2×*C*H), 122.91 (2 *C*), 117.91 (*C*), 53.18 (–NCH_2Ar), 21.22 (Ar–CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 228.05 ppm. Elemental analysis: calcd (%) for $C_{22}H_{18}BrN_3Se$: C, 54.68; H, 3.75; N, 8.70. Found: 54.82; H, 3.78; N, 8.64.

1-(4-Methylbenzyl)-5-(phenylselanyl)-4-(thiophen-3-yl)-1*H*-1,2,3-triazole (5 v): White solid; yield 76% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96.5:3.5; mp 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.98 (m, 1H, Ar–H), 7.84–7.83 (m, 1H, Ar–H), 7.35–7.33 (m, 1H, Ar–H), 7.19–7.14 (m, 1H, Ar–H), 7.13–7.09 (m, 4H, Ar–H), 7.01–6.97 (m, 4H, Ar–H), 5.61 (s, 2H, –NCH_2Ar), 2.27 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.53 (*C*), 138.06 (*C*), 131.89 (*C*), 131.53 (*C*), 129.78 (2×*C*H), 129.51 (*C*), 129.38 (2×*C*H), 129.15 (2×*C*H), 127.94 (2×*C*H), 127.20 (*C*H), 126.75 (*C*H), 125.77 (*C*H), 123.10 (*C*H), 117.12 (*C*), 53.03 (–NCH_2Ar), 21.17 (Ar–CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 223.15 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}N_3SSeH$; 412.0387; found, 412.0381.

1-(3-Chlorobenzyl)-5-(phenylselanyl)-4-(*p*–tolyl)-1*H*-1,2,3-triazole (5 w): White solid; yield 65% (57 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4; mp 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.22 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.16–7.07 (m, 7H, Ar–H), 6.96–6.94 (m, 2H, Ar–H), 5.61 (s, 2H, –NCH_2Ar), 2.37 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.03 (*C*), 138.73 (*C*), 136.68 (*C*), 134.58 (*C*), 130.00 (*C*H), 129.78 (2×*C*H), 129.55 (*C*), 129.36 (2×*C*H), 129.08 (2×*C*H), 128.45 (*C*H), 128.15 (*C*H), 127.56 (*C*), 127.39 (3×*C*H), 126.13 (*C*H), 117.52 (*C*),

52.55 (–NCH$_2$Ar), 21.45 (Ar–CH$_3$) ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 226.46 ppm. HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{22}H_{18}N_3ClSeH$; 440.0433; found, 440.0427.

4-(4-Bromophenyl)-1-(3-chlorobenzyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 x): White solid; yield 42% (40 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 108–109 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.98 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.55 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.19–7.09 (m, 7H, Ar–H), 6.97–6.94 (m, 2H, Ar–H), 5.65 (s, 2H, –NC*H*$_2$Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 152.21 (*C*), 136.54 (2 *C*), 131.89 (2×*C*H), 130.21 (2 *C*), 130.11 (*C*H), 129.95 (2×*C*H), 129.23 (2×*C*H), 129.02 (2×*C*H), 128.63 (*C*H), 128.23 (*C*H), 127.69 (*C*H), 127.66 (*C*), 126.19 (*C*H), 117.28 (*C*), 52.70 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 226.70 ppm. HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{21}H_{15}N_3BrClSeH$; 503.9381; found, 503.9376.

1-(Naphthalen-1-ylmethyl)-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole(5 y):[8c] White solid; yield 73% (64 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96.5:3.5; mp 110–111 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.20 (d, 1H, *J* = 8.4 Hz, Ar–H), 8.15–8.12 (m, 2H, Ar–H), 7.89–7.87 (m, 1H, Ar–H), 7.77 (d, 1H, *J* = 8.4 Hz, Ar–H), 7.62–7.49 (m, 3H, Ar–H), 7.47–7.38 (m, 3H, Ar–H), 7.29–7.26 (m, 1H, Ar–H), 7.17–7.13 (m, 1H, Ar–H), 7.10–7.06 (m, 3H, Ar–H), 6.99–6.97 (m, 2H, Ar–H), 6.16 (s, 2H, –NC*H*$_2$Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 151.64 (*C*), 133.74 (*C*), 130.89 (*C*), 130.65 (*C*), 130.55 (*C*), 129.69 (2×*C*H), 129.54 (*C*), 129.47 (2×*C*H), 129.06 (*C*H), 128.95 (*C*H), 128.70 (*C*H), 128.61 (2×*C*H), 127.59 (2×*C*H), 127.38 (*C*H), 126.82 (*C*H), 126.59 (*C*H), 126.10 (*C*H), 125.26 (*C*H), 123.03 (*C*H), 122.82 (*C*), 118.47 (*C*), 51.14 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 230.43 ppm. Elemental analysis: calcd (%) for $C_{25}H_{19}N_3Se$: C, 68.18; H, 4.35; N, 9.54. Found: C, 68.32; H, 4.39; N, 9.43.

1-(Naphthalen-1-ylmethyl)-5-(phenylselanyl)-4-(*p*–tolyl)-1*H*-1,2,3-triazole (5 z): White solid;yield 73% (64 mg,0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96.5:3.5; mp 112–113°C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.19 (d, 1H, *J* = 8.0 Hz, Ar–H), 8.02 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.95–7.85 (m, 2H, Ar–H), 7.75 (d, 1H, *J* = 8.4 Hz, Ar–H), 7.66–7.51 (m, 3H, Ar–H), 7.32–7.28 (m, 1H, Ar–H), 7.24 (s, 1H, Ar–H), 7.08–7.04 (m, 3H, Ar–H), 6.97–6.95 (m, 2H, Ar–H), 6.14 (s, 2H, –NC*H*$_2$Ar), 2.39 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 151.74 (*C*), 138.60 (*C*), 133.71 (*C*), 130.86 (*C*), 130.58 (*C*), 129.64 (2×*C*H), 129.37 (2×*C*H), 129.31 (2×*C*H), 129.00 (*C*H), 128.90 (*C*H), 127.45 (2×*C*H), 127.28 (*C*H), 126.77 (*C*H), 126.54 (*C*H), 126.06 (*C*H), 125.38 (*C*), 125.24 (*C*H), 123.01 (*C*H), 122.82 (*C*), 118.04 (*C*), 51.07 (–NCH$_2$Ar), 21.42 (Ar–C*H*$_3$)ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 229.38 ppm. Elemental analysis: calcd (%) for $C_{25}H_{19}N_3Se$: C, 68.18; H, 4.35; N, 9.54. Found: C, 68.32; H, 4.39; N, 9.43.

4-(4-Fluorophenyl)-1-(naphthalen-1-ylmethyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 a′): White solid;yield 70% (64 mg,0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 135–136 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.17 (d, 1H, *J* = 8.0 Hz, Ar–H), 8.08–8.05 (m, 2H, Ar–H), 7.84 (d, 1H, *J* = 8.4 Hz Ar–H), 7.73 (d, 1H, *J* = 8.0 Hz, Ar–H), 7.56–7.49 (m, 2H, Ar–H), 7.32–7.28 (m, 1H, Ar–H), 7.23 (d, 1H, *J* = 7.6 Hz, Ar–H), 7.12–7.02 (m, 6H, Ar–H), 6.92–6.91 (m, 2H, Ar–H), 6.12 (s, 2H, –NC*H*$_2$Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.11 (J^1_{C-F} = 247 Hz, *C*), 150.78 (*C*), 133.76 (*C*), 130.89 (*C*), 130.44 (*C*), 129.75 (2×*C*H), 129.44 (J^3_{C-F} = 3 Hz, *C*H), 129.41 (J^3_{C-F} = 5 Hz, *C*H), 129.14 (*C*), 129.14 (*C*H), 128.96 (*C*H), 127.48 (*C*H), 126.86 (2×*C*H), 126.69 (*C*H), 126.13 (2×*C*H), 125.24 (2×*C*H), 123.01 (*C*H), 122.82 (*C*), 118.30 (*C*), 115.62 (J^2_{C-F} = 21 Hz, *C*H), 51.22 (–NCH$_2$Ar) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = −112.84 ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 229.36 ppm. HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{25}H_{18}FN_3SeH$; 460.0728; found, 460.0743.

4-(4-Bromophenyl)-1-(naphthalen-1-ylmethyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 b′): White solid;yield 75% (78 mg,0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 137–138 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.21 (d, 1H, *J* = 8.0 Hz, Ar–H), 8.03–8.01 (m, 2H, Ar–H), 7.89–7.87 (m, 1H, Ar–H), 7.77 (d, 1H, *J* = 8.0 Hz, Ar–H), 7.59–7.52 (m, 4H, Ar–H), 7.29–7.28 (m, 1H, Ar–H), 7.18–7.14 (m, 1H, Ar–H), 7.12–7.06 (m, 3H, Ar–H), 6.96–6.94 (m, 2H, Ar–H), 6.16 (s, 2H, –NC*H*$_2$Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 150.47 (*C*), 133.75 (*C*), 132.93 (*C*), 132.11 (*C*), 131.99 (*C*), 131.78 (2×*C*H), 130.88 (*C*), 130.37 (*C*), 129.77 (2×*C*H), 129.48 (2×*C*H), 129.16 (*C*H), 129.03 (2×*C*H), 128.96 (*C*H), 127.54 (*C*H), 126.87 (*C*H), 126.69 (*C*H), 126.14 (*C*H),125.24 (*C*H), 122.99 (*C*H), 118.65 (*C*), 51.21 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 230.46 ppm. Elemental analysis: calcd (%) for $C_{25}H_{18}BrN_3Se$: C, 57.82; H, 3.49; N, 8.09. Found: C, 57.98; H, 3.51; N, 8.16.

1-(Naphthalen-1-ylmethyl)-5-(phenylselanyl)-4-(thiophen-3-yl)-1*H*-1,2,3-triazole (5 c′): White solid;yield 65% (58 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97.5:2.5; mp 109–110 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.15 (d, 1H, *J* = 8.0 Hz, Ar–H), 8.04–7.99 (m, 2H, Ar–H), 7.88–7.80 (m, 1H, Ar–H), 7.71 (d, 1H, *J* = 8.0 Hz, Ar–H), 7.57–7.48 (m, 2H, Ar–H), 7.43–7.35 (m, 1H, Ar–H), 7.24–7.20 (m, 1H, Ar–H), 7.12 (t, 1H, *J* = 7.2 Hz, Ar–H), 7.06–7.02 (m, 3H, Ar–H), 6.96–6.94 (m, 2H, Ar–H), 6.12 (s, 2H, –NC*H*$_2$Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 148.52 (*C*), 133.73 (*C*), 131.57 (*C*), 130.84 (*C*), 130.54 (*C*), 129.96 (*C*), 129.75 (2×*C*H), 129.40 (2×*C*H), 129.06 (*C*H), 128.94 (*C*H), 127.42 (*C*H), 126.82 (2×*C*H), 126.51 (*C*H), 126.10 (*C*H), 125.85 (*C*H), 125.24 (2×*C*H), 123.23 (*C*H), 122.98 (*C*H), 122.79 (*C*), 117.88 (*C*), 51.11 (–NCH$_2$Ar) ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 225.57 ppm. HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{23}H_{17}N_3SSeH$; 448.0387; found, 448.0357.

4-Phenyl-1-(1-phenylethyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 d′):[8c] White solid; yield 68% (55 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4; mp 96–97 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.04–8.01 (m, 2H, Ar–H), 7.39–7.32 (m, 3H, Ar–H), 7.25–7.22 (m, 2H, Ar–H), 7.21–7.18 (m, 2H, Ar–H), 7.14–7.05 (m, 3H, Ar–H), 6.95–6.93 (m, 2H, Ar–H), 6.03–5.98 (m, 1H, –NC*H*(CH$_3$)Ar), 2.49 (d, 3H, J = 7.2 Hz, –NCH(C*H*$_3$)Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 151.40 (*C*), 140.54 (*C*), 130.37 (*C*), 129.98 (*C*), 129.74 (2×*C*H), 129.15 (2×*C*H), 128.72 (2×*C*H), 128.57 (*C*H), 128.51 (2×*C*H), 128.04 (*C*H), 127.70 (2×*C*H), 127.21 (*C*H), 126.76 (2×*C*H), 117.86 (*C*), 59.70 (–NCH(CH$_3$)Ar), 22.45 (–NCH(CH$_3$)Ar)ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 225.59 ppm. Elemental analysis: calcd (%) for $C_{22}H_{19}N_3Se$: C, 65.35; H, 4.74; N, 10.39. Found: C, 65.49; H, 4.78; N, 10.31.

1-Benzyl-4-phenyl-5-(*o*–tolylselanyl)-1*H*-1,2,3-triazole (5 e′):[8c] Yellow semi-solid; yield 79% (64 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.01–7.99 (m, 2H, Ar–H), 7.40–7.33 (m, 3H, Ar–H), 7.21 (br s, 5H, Ar–H), 7.23 (d, 1H, *J* = 7.6 Hz, Ar–H), 7.06 (t, 1H, *J* = 7.2 Hz, Ar–H), 6.82 (t, 1H, *J* = 7.6 Hz, Ar–H), 6.48 (d, 1H, *J* = 7.6 Hz, Ar–H), 5.62 (s, 2H, –NC*H*$_2$Ar), 2.37 (s, 2H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 152. 18 (*C*), 136.62 (*C*), 134.88 (*C*), 130.72 (*C*H), 130.65 (*C*), 130.63 (*C*), 128.76 (2×*C*H), 128.67 (*C*H), 128.58 (2×*C*H), 128.39 (*C*H), 128.31 (*C*H), 128.04 (2×*C*H), 127.56 (2×*C*H), 127.42 (*C*H), 127.12 (*C*H), 117.34 (*C*), 53.29 (–NCH$_2$Ar), 21.42 (Ar–C*H*$_3$) ppm. ^{77}Se NMR (76 MHz, CDCl$_3$): δ = 198.66 ppm. Elemental analysis: calcd (%) for $C_{22}H_{19}N_3Se$: C, 65.35; H, 4.74; N, 10.39. Found: 65.51; H, 4.78; N, 10.30.

1-Benzyl-5-(*o*–tolylselanyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (5 f′): White solid; yield 72% (68 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 98:2; mp 130–132 °C.^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.14 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.63 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.14 (d, 1H, *J* = 7.2 Hz, Ar–H), 7.09–7.05 (m, 1H, Ar–H), 6.84–6.80 (m, 1H, Ar–H), 6.44 (d, 1H, *J* = 7.6 Hz, Ar–H), 5.65 (s, 2H, –NC*H*$_2$Ar), 2.38 (s, 2H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 150.58 (*C*), 136.69 (*C*), 134.61 (*C*), 134.12 (*C*), 130.90 (*C*H), 130.61 (*C*), 130.29 (*C*), 130.10 (*C*), 128.82 (*C*H), 128.45 (*C*H), 128.31

(*C*H), 128.09 (*C*H), 127.63 (*C*H), 127.51 (*C*H), 127.39 (*C*H), 125.59 (*C*H), 125.55 (*C*H), 125.51 (*C*H), 125.47 (*C*H), 122.87 (*C*), 118.28 (*C*), 53.40 (–N*C*H$_2$Ar), 21.41 (Ar–*C*H$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.69 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 220.14 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}F_3N_3SeH$; 474.0696; found, 474.0708.

4-(4-Ethylphenyl)-1-(4-methylbenzyl)-5-(*o*–tolylselanyl)-1*H*-1,2,3-triazole (5 g′): White semi-solid; yield 70% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.21 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.13–7.09 (m, 3H, Ar–H), 7.07–7.03 (m, 1H, Ar–H), 6.99 (d, 2H, *J* = 7.6 Hz, Ar–H), 6.80 (t, 1H, *J* = 7.6 Hz, Ar–H), 6.46 (d, 1H, *J* = 8.0 Hz, Ar–H), 5.57 (s, 2H, –NC*H*$_2$Ar), 2.68–2.62 (m, 2H, Ar–C*H*$_2$CH$_3$), 2.37 (s, 2H, Ar–C*H*$_3$), 2.26 (s, 2H, Ar–C*H*$_3$), 1.23 (s, 2H, Ar–CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.40 (*C*), 144.86 (*C*), 138.07 (*C*), 136.50 (*C*), 131.99 (*C*), 130.90 (*C*), 130.65 (*C*H), 129.65 (*C*), 129.39 (2×*C*H), 128.33 (*C*H), 128.08 (3×*C*H), 127.98 (*C*), 127.52 (2×*C*H), 127.37 (2×*C*H), 126.89 (*C*H), 53.14 (–NCH$_2$Ar), 28.80 (Ar–*C*H$_2$CH$_3$), 21.39 (Ar–*C*H$_3$), 21.19 (Ar–*C*H$_3$), 15.49 (Ar–CH$_2$*C*H$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 198.17 ppm. Elemental analysis: calcd (%) for $C_{25}H_{25}N_3Se$: C, 67.26; H, 5.64; N, 9.41. Found: C, 67.41; H, 5.70; N, 9.33.

4-(4-Methoxyphenyl)-1-(4-methylbenzyl)-5-(*o*–tolylselanyl)-1*H*-1,2,3-triazole (5 h′): White solid; yield 63% (56 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4; mp 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.13–7.09 (m, 3H, Ar–H), 7.07–7.03 (m, 1H, Ar–H), 6.99 (d, 2H, *J* = 7.6 Hz, Ar–H), 6.86 (d, 2H, *J* = 8.8 Hz, Ar–H), 6.82–6.78 (m, 1H, Ar–H), 6.43 (d, 1H, *J* = 8.0 Hz, Ar–H), 5.56 (s, 2H, –NC*H*$_2$Ar), 3.80 (s, 3H, Ar–OC*H*$_3$), 2.37 (s, 3H, Ar–C*H*$_3$), 2.26 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.99 (*C*), 152.15 (*C*), 138.06 (*C*), 136.39 (*C*), 131.92 (*C*), 130.64 (*C*H), 129.36 (2×*C*H), 128.83 (2×*C*H), 128.10 (2×*C*H), 128.06 (2×*C*H), 127.35 (*C*H), 126.83 (*C*H), 123.26 (*C*), 116.17 (*C*), 114.00 (*C*H), 55.37 (Ar–OCH$_3$), 53.12 (–NCH$_2$Ar), 21.38 (Ar–*C*H$_3$), 21.20 (Ar–*C*H$_3$), 21.06 (Ar–*C*H$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 196.68 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_3OSeH$; 450.1085; found, 450.1093.

1-Benzyl-4-phenyl-5-(*m*–tolylselanyl)-1*H*-1,2,3-triazole (5 i′):[8c] White semi-solid; yield 77% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–8.02 (m, 2H, Ar–H), 7.42–7.32 (m, 4H, Ar–H), 7.23 (br s, 4H, Ar–H), 7.00 (t, 1H, *J* = 7.6 Hz, Ar–H), 6.94 (d, 1H, *J* = 7.2 Hz, Ar–H), 6.81 (d, 1H, *J* = 7.6 Hz, Ar–H), 6.72 (br s, 1H, Ar–H), 5.66 (s, 2H, –NC*H*$_2$Ar), 2.14 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.71 (*C*), 139.83 (*C*), 135.03 (2×*C*), 130.75 (*C*), 129.95 (*C*H), 129.56 (*C*H), 128.74 (2×*C*H), 128.64 (*C*H), 128.57 (2×*C*H), 128.29 (2×*C*H), 128.06 (2×*C*H), 127.65 (2×*C*H), 126.48 (*C*H), 118.11 (*C*), 53.26 (–NCH$_2$Ar), 21.36 (Ar–*C*H$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 227.32 ppm. Elemental analysis: calcd (%) for $C_{22}H_{19}N_3Se$: C, 65.35; H, 4.74; N, 10.39. Found: 65.46; H, 4.77; N, 10.48.

1-Benzyl-4-(4-fluorophenyl)-5-(*m*–tolylselanyl)-1*H*-1,2,3-triazole (5 j′): White solid; yield 76% (64 mg,0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 125–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.99 (m, 2H, Ar–H), 7.23 (s, 5H, Ar–H), 7.08 (t, 2H, *J* = 8.8 Hz, Ar–H), 7.01 (t, 1H, *J* = 7.6 Hz Ar–H), 6.95 (d, 1H, *J* = 7.6 Hz, Ar–H), 6.79 (d, 1H, *J* = 7.6 Hz, Ar–H), 6.69 (s, 1H, Ar–H), 5.66 (s, 2H, –NC*H*$_2$Ar), 2.14 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.92 (J^3_{C-F} = 5 Hz, *C*), 150.90 (*C*), 139.93 (*C*), 134.97 (*C*), 129.93 (*C*H), 129.64 (*C*H), 129.53 (*C*H), 129.44 (2×*C*H), 128.80 (2×*C*H), 128.39 (J^3_{C-F} = 3 Hz, *C*H), 128.11 (2×*C*H), 126.45 (2×*C*H), 121.14 (J^1_{C-F} = 235 Hz, *C*), 118.30 (*C*), 115.60 (J^2_{C-F} = 22 Hz, *C*H), 114.32 (*C*), 53.35 (–NCH$_2$Ar), 21.39 (Ar–*C*H$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −113.03 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}FN_3SeH$; 424.0728; found, 424.0740.

4-(4-Methoxyphenyl)-1-(4-methylbenzyl)-5-(*m*–tolylselanyl)-1*H*-1,2,3-triazole (5 k′): White solid; yield 74% (66 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 95:5; mp 107–108 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.13 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.02–6.99 (m, 3H, Ar–H), 6.95–6.92 (m, 3H, Ar–H), 6.81 (d, 1H, *J* = 7.6 Hz, Ar–H), 6.67 (br s, 1H, Ar–H), 5.61(s, 2H, –NC*H*$_2$Ar), 3.81 (s, 3H, Ar–OC*H*$_3$), 2.27 (s, 3H, Ar–C*H*$_3$), 2.14 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.90 (*C*), 151.61 (*C*), 139.66 (*C*), 137.93 (*C*), 131.98 (*C*), 129.66 (*C*), 129.58 (*C*H), 129.44 (*C*H), 129.30 (2×*C*H), 128.85 (2×*C*H), 128.04 (2×*C*H), 127.96 (*C*H), 126.13 (*C*H), 123.29 (*C*), 116.89 (*C*), 113.94 (2×*C*H), 55.32 (Ar–OCH$_3$), 53.03 (–NCH$_2$Ar), 21.27 (Ar–*C*H$_3$), 21.15 (Ar–*C*H$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 224.99 ppm. Elemental analysis: calcd (%) for $C_{24}H_{23}N_3OSe$: C, 64.28; H, 5.17; N, 9.37. Found: C, 64.42; H, 5.23; N, 9.31.

1-(4-Methylbenzyl)-4-phenyl-5-(*p*–tolylselanyl)-1*H*-1,2,3-triazole (5 l′):[8c] White solid; yield 74% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4; mp 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.05 (m, 2H, Ar–H), 7.42–7.33 (m, 3H, Ar–H), 7.13 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.04 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.94–6.88 (m, 4H, Ar–H), 5.61 (s, 2H, –NC*H*$_2$Ar), 2.29 (s, 3H, Ar–C*H*$_3$), 2.25 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.45 (*C*), 138.00 (*C*), 137.41 (*C*), 132.03 (*C*), 130.74 (*C*), 130.49 (2×*C*H), 129.69 (2×*C*H), 129.37 (2×*C*H), 128.53 (*C*H), 128.51 (2×*C*H), 127.97 (2×*C*H), 127.58 (2×*C*H), 125.90 (*C*), 118.22 (*C*), 53.01 (–NCH$_2$Ar), 21.19 (Ar–CH$_3$), 21.04 (Ar–*C*H$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 222.54 ppm. Elemental analysis: calcd (%) for $C_{23}H_{21}N_3Se$: C, 66.03; H, 5.06; N, 10.04. Found: C, 66.18; H, 5.10; N, 10.13. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_3SeH$; 434.1135; found, 434.1130.

1-(4-Methylbenzyl)-4-(*p*–tolyl)-5-(*p*–tolylselanyl)-1*H*-1,2,3-triazole (5 m′): White solid; yield 69% (60 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4; mp 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.21 (d, 2H, *J* = 7.6 Hz, Ar–H), 7.11 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.02 (d, 2H, *J* = 7.6 Hz, Ar–H), 6.93–6.87 (m, 4H, Ar–H), 5.59 (s, 2H, –NC*H*$_2$Ar), 2.36 (s, 3H, Ar–C*H*$_3$), 2.29 (s, 3H, Ar–C*H*$_3$), 2.25 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.63 (*C*), 138.45 (*C*), 138.00 (*C*), 137.35 (*C*), 132.11 (*C*), 130.50 (2×*C*H), 129.63 (2×*C*H), 129.37 (2×*C*H), 129.26 (2×*C*H), 128.00 (2×*C*H), 127.90 (*C*), 127.48 (2×*C*H), 126.07 (*C*), 117.83 (*C*),53.01 (–NCH$_2$Ar), 21.42 (Ar–CH$_3$), 21.21 (Ar–*C*H$_3$), 21.06 (Ar–CH$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 221.56 ppm.

1-(4-Methylbenzyl)-4-(thiophen-3-yl)-5-(*p*–tolylselanyl)-1*H*-1,2,3-triazole (5 n′): White solid; yield 75% (64 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96:4; mp 113–114 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, 1H, *J* = 2.0 Hz, Ar–H), 7.84 (d, 1H, *J* = 4.8 Hz, Ar–H), 7.35–7.33 (m, 1H, Ar–H), 7.09 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.02 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.94–6.89 (m, 4H, Ar–H), 5.59 (s, 2H, –NC*H*$_2$Ar), 2.28 (s, 3H, Ar–C*H*$_3$), 2.25 (s, 3H, Ar–C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.35 (*C*), 138.05 (*C*), 137.49 (2×*C*), 132.05 (*C*), 131.67 (*C*), 130.58 (2×*C*H), 129.64 (2×*C*H), 129.40 (2×*C*H), 127.92 (2×*C*H), 126.84 (*C*H), 125.73 (*C*H), 123.10 (*C*H), 117.67 (*C*), 52.99 (–NCH$_2$Ar), 21.20 (Ar–*C*H$_3$), 21.07 (Ar–CH$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 217.98 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}N_3SSeH$; 426.0543; found, 426.0539.

1-Benzyl-5-((4-ethylphenyl)selanyl)-4-phenyl-1*H*-1,2,3-triazole (5 o′):[8c] White solid; yield 81% (68 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 52–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, 2H, *J* = 7.2 Hz, Ar–H), 7.42–7.33 (m, 3H, Ar–H), 7.22 (br s, 5H, Ar–H), 6.95–6.91 (m, 4H, Ar–H), 5.65(s, 2H, –NC*H*$_2$Ar), 2.57–2.51 (m, 2H, Ar–C*H*$_2$CH$_3$), 1.17 (t, 3H, *J* = 7.6 Hz, Ar–CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.51 (*C*), 143.90 (*C*), 135.06 (*C*), 130.76 (*C*), 129.88 (2×*C*H), 129.42 (2×*C*H), 128.76 (2×*C*H), 128.61 (*C*H), 128.57 (2×*C*H), 128.23 (*C*H), 127.99 (2×*C*H), 127.63 (2×*C*H), 126.07 (*C*), 118.43 (*C*), 53.19 (–NCH$_2$Ar), 28.46

(Ar–CH_2CH_3), 15.52 (Ar–CH_2CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 222.28 ppm. Elemental analysis: calcd (%) for $C_{23}H_{21}N_3Se$: C, 66.03; H, 5.06; N, 10.04. Found: C, 66.17; H, 5.11; N, 10.12.

1-Benzyl-5-((4-ethylphenyl)selanyl)-4-(*p*–tolyl)-1*H*-1,2,3-triazole (5 p′): White solid; yield 76% (66 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97.5:2.5; mp 65–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.21 (br s, 7H, Ar–H), 6.95–6.90 (m, 4H, Ar–H), 5.64 (s, 2H, –NCH_2Ar), 2.56–2.51 (m, 2H, Ar–CH_2CH$_3$), 2.37 (s, 3H, Ar–CH_3), 1.17 (t, 3H, *J* = 7.6 Hz, Ar–CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.68 (*C*), 143.85 (*C*), 138.53 (*C*), 135.16 (*C*), 129.84 (2×*C*H), 129.43 (2×*C*H), 129.31 (2×*C*H), 128.77 (2×*C*H), 128.23 (*C*H), 128.03 (2×*C*H), 127.96 (*C*), 127.55 (2×*C*H), 126.27 (*C*), 118.05 (*C*), 53.19 (–NCH$_2$Ar), 28.49 (Ar–CH_2CH$_3$), 21.46 (Ar–CH_3), 15.56 (Ar–CH$_2$CH_3) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 221.41 ppm. Elemental analysis: calcd (%) for $C_{24}H_{23}N_3Se$: C, 66.66; H, 5.36; N, 9.72. Found: 66.81; H, 5.41; N, 9.83.

4-(4-Bromophenyl)-5-((4-ethylphenyl)selanyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole (5 q′): White solid; yield 68% (70 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 94:6; mp 100–101 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.51 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.12 (d, 2H, *J* = 7.6 Hz, Ar–H), 7.03 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.95 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.89 (d, 2H, *J* = 8.4 Hz, Ar–H), 5.61 (s, 2H, –NCH_2Ar), 2.55 (q, 2H, *J* = 7.6 Hz, Ar–CH_2CH$_3$), 2.28 (s, 3H, Ar–CH_3), 1.17 (t, 3H, *J* = 7.6 Hz, Ar–CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.37 (*C*), 144.08 (*C*), 138.18 (*C*), 131.99 (*C*), 131.77 (2×*C*H), 129.89 (2×*C*H), 129.81 (*C*), 129.49 (4×*C*H), 129.12 (2×*C*H), 128.09 (2×*C*H), 125.89 (*C*), 122.87 (*C*), 118.52 (*C*), 53.15 (–NCH$_2$Ar), 28.49 (Ar–CH$_2$CH$_3$), 21.26 (Ar–CH$_3$), 15.53 (Ar–CH$_2$CH$_3$) ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 222.54 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}BrN_3SeH$; 512.0241; found, 512.0264.

1-Benzyl-4-phenyl-5-((4-(trifluoromethyl)phenyl)selanyl)-1*H*-1,2,3-triazole (5 r′):[8c] White solid; yield 72% (66 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 97:3; mp 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, 2H, *J* = 7.2 Hz, Ar–H), 7.49–7.38 (m, 4H, Ar–H), 7.35–7.33 (m, 2H, Ar–H), 7.24–7.22 (m, 4H, Ar–H), 7.01 (d, 2H, *J* = 8.0 Hz, Ar–H), 5.76 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.40 (*C*), 134.85 (*C*), 134.47 (*C*), 130.31 (*C*), 129.04 (*C*), 128.99 (*C*H), 128.78 (2×*C*H), 128.74 (2×*C*H), 128.62 (2×*C*H), 128.44 (*C*H), 128.02 (2×*C*H), 127.50 (2×*C*H), 126.38 (2×*C*H), 122.57 (*C*F$_3$), 116.50 (*C*), 53.56 (–NCH$_2$Ar) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.85 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 238.24 ppm. Elemental analysis: calcd (%) for $C_{22}H_{16}F_3N_3Se$: C, 57.65; H, 3.52; N, 9.17. Found: 57.77; H, 3.54; N, 9.26.

1-Benzyl-4-(4-methoxyphenyl)-5-((4-(trifluoromethyl)phenyl)selanyl)-1*H*-1,2,3-triazole (5 s′): White solid; yield 64% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 95.5:4.5; mp 106–108 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.42–7.39 (m, 2H, Ar–H), 7.32–7.28 (m, 4H, Ar–H), 7.08 (d, 4H, *J* = 8.4 Hz, Ar–H), 5.82 (s, 2H, –NCH_2Ar), 3.96 (s, 3H, Ar–OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.27 (*C*), 152.31 (*C*), 135.02 (*C*), 134.54 (*C*), 129.02 (*C*), 128.92 (*C*), 128.80 (2×*C*H), 128.75 (2×*C*H), 128.51 (2×*C*H), 128.39 (*C*H), 128.02 (2×*C*H), 126.39 (J_{C-F} = 3 Hz, *C*H), 126.31 (J_{C-F} = 3 Hz, *C*H), 122.87 (−*C*F$_3$), 115.57 (*C*), 114.19 (2×*C*H), 55.40 (Ar–OCH$_3$), 53.52 (–NCH$_2$Ar) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.82 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 236.74 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}F_3N_3OSeH$; 490.0645; found, 490.0610.

1-Benzyl-5-((3-fluorophenyl)selanyl)-4-phenyl-1*H*-1,2,3-triazole (5 t′):[8c] Yellow semi-solid; yield 71% (58 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 95.5:4.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 2H, Ar–H), 7.43–7.39 (m, 2H, Ar–H), 7.38–7.33 (m, 1H, Ar–H), 7.21 (br s, 5H, Ar–H), 7.07–7.01 (m, 1H, Ar–H), 6.84–6.79 (m, 1H, Ar–H), 6.71–6.69 (m, 1H, Ar–H), 6.59–6.57 (m, 1H, Ar–H), 5.68 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.03 (J^1_{C-F} = 249 Hz, *C*), 152.04 (*C*), 134.70 (*C*), 131.42 (J^3_{C-F} = 7 Hz, *C*), 130.94 (J^3_{C-F} = 9 Hz, *C*H), 130.40 (*C*), 128.83 (*C*H), 128.77 (*C*H), 128.63 (2×*C*H), 128.39 (2×*C*H), 127.98 (2×*C*H), 127.54 (2×*C*H), 124.59 (J^4_{C-F} = 3 Hz, *C*H), 117.13 (*C*), 116.14 (J^2_{C-F} = 24 Hz, *C*H), 114.37 (J^2_{C-F} = 21 Hz, *C*H), 53.43 (–NCH$_2$Ar) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.50 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 237.63 ppm. Elemental analysis: calcd (%) for $C_{21}H_{16}FN_3Se$: C, 61.77; H, 3.95; N, 10.29. Found: C, 61.93; H, 3.98; N, 10.40.

1-Benzyl-4-(4-ethoxyphenyl)-5-((3-fluorophenyl)selanyl)-1*H*-1,2,3-triazole (5 u′): White solid; yield 79% (71 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 94:6; mp 92–94 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.14 (m, 2H, Ar–H), 7.42–7.36 (m, 4H, Ar–H), 7.24–7.07 (m, 3H, Ar–H), 7.02–7.87 (m, 2H, Ar–H), 6.79–6.75 (m, 1H, Ar–H), 5.87–5.82 (m, 2H, –NCH_2Ar), 4.27–4.21 (m, 2H, Ar–OCH_2CH$_3$), 1.63-1.57 (m, 3H, Ar–OCH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.99 (J^1_{C-F} = 254 Hz, *C*), 159.53 (*C*), 151.96 (*C*), 134.80 (*C*), 131.59 (*C*), 130,89 (J^3_{C-F} = 6 Hz, *C*), 128.80 (2×*C*H), 128.69 (J^3_{C-F} = 5 Hz, *C*H), 128.30 (2×*C*H), 127.92 (J_{C-F} = 2 Hz, 2×*C*H), 124.49 (*C*H), 122.82 (*C*), 116.03 (J^4_{C-F} = 24 Hz, *C*H), 114.61 (J_{C-F} = 5 Hz, 2×*C*H), 114.24 (J^2_{C-F} = 21 Hz, *C*H), 63.54 (Ar–OCH$_2$CH$_3$), 53.34 (–NCH$_2$Ar), 14.86 (Ar–OCH$_2$CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.54 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 236.34 ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}FN_3OSeH$; 454.0834; found, 454.0834.

5-((3-Fluorophenyl)selanyl)-1-(4-methylbenzyl)-4-(*p*–tolyl)-1*H*-1,2,3-triazole (5 v′): White semi-solid; yield 83% (71 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 96.5:3.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.20 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.10 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.06–7.01 (m, 1H, Ar–H), 6.98 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.83–6.78 (m, 1H, Ar–H), 6.70–6.68 (m, 1H, Ar–H), 6.53–6.50 (m, 1H, Ar–H), 5.63(s, 2H, –NCH_2Ar), 2.36 (s, 3H, Ar–CH_3), 2.26 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.06 (J^1_{C-F} = 249 Hz, *C*), 152.27 (*C*), 138.76 (*C*), 138.21 (*C*), 131.74 (J^3_{C-F} = 8 Hz, *C*), 130.85 (J^3_{C-F} = 7 Hz, *C*H), 129.64 (*C*), 129.42 (2×*C*H), 129.36 (2×*C*H), 128.04 (2×*C*H), 127.62 (*C*), 127.45 (2×*C*H), 124.49 (J^4_{C-F} = 2 Hz, *C*H), 116.53 (*C*), 116.05 (J^2_{C-F} = 24 Hz, *C*H), 114.09 (J^2_{C-F} = 22 Hz, *C*H), 53.32 (–NCH$_2$Ar), 21.43 (Ar–CH$_3$), 21.14 (Ar–CH$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.79 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 236.55 ppm. Elemental analysis: calcd (%) for $C_{23}H_{20}FN_3Se$: C, 63.30; H, 4.62; N, 9.63. Found: C, 63.44; H, 4.65; N, 9.56.

5-((3-Fluorophenyl)selanyl)-1-(4-methylbenzyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (5 w′): White solid; yield 69% (68 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 94:6; mp 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.65 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.12 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.09–7.03 (m, 1H, Ar–H), 7.00 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.85–6.81 (m, 1H, Ar–H), 6.69 (d, 1H, *J* = 7.6 Hz, Ar–H), 6.51–6.48 (m, 1H, Ar–H), 5.66 (s, 2H, –NCH_2Ar), 2.26 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.07 (J^1_{C-F} = 250 Hz, *C*H), 150.56 (*C*), 138.46 (*C*), 133.91 (*C*), 131.45 (*C*), 131.06 (J^3_{C-F} = 9 Hz, *C*H), 130.95 (*C*), 130.45 (*C*), 129.76 (*C*), 129.51 (2×*C*H), 128.09 (2×*C*H), 127.66 (2×*C*H), 125.63 (J_{C-F} = 4 and 3 Hz, 2×*C*H), 124.55 (J^4_{C-F} = 2 Hz, *C*H), 117.81 (*C*F$_3$), 116.13 (J^2_{C-F} = 24 Hz, *C*H), 114.47 (J^2_{C-F} = 21 Hz, *C*H), 53.48 (–NCH$_2$Ar), 21.15 (Ar–CH$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.71 and −110.33 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 238.05 ppm. Elemental analysis: calcd (%) for $C_{23}H_{17}F_4N_3Se$: C, 56.34; H, 3.49; N, 8.57. Found: C, 56.46; H, 3.53; N, 8.52.

1-Benzyl-5-((3-fluorophenyl)selanyl)-4-(thiophen-3-yl)-1*H*-1,2,3-triazole (5 x′): White solid; yield 75% (62 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 93:7; mp 78–80 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.97 (m, 1H, Ar–H), 7.82–

7.81 (m, 1H, Ar–H), 7.36–7.34 (m, 1H, Ar–H), 7.19 (s, 5H, Ar–H), 7.08–7.02 (m, 1H, Ar–H), 6.84–6.79 (m, 1H, Ar–H), 6.72 (m, 1H, Ar–H), 6.61–6.58 (m, 1H, Ar–H), 5.66 (s, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.05 (J^1_{C-F} = 249 Hz, *C*), 148.87 (*C*), 134.71 (*C*), 131.31 (*C*), 131.19 (*C*) 131.00 (J^3_{C-F} = 8 Hz, *C*H), 128.77 (2×*C*H), 128.39 (*C*H), 127.92 (2×*C*H), 126.70 (*C*H), 125.97 (*C*H), 124.55 (J^4_{C-F} = 3 Hz, *C*H), 123.33 (*C*H), 116.55 (*C*), 116.10 (J^2_{C-F} = 24 Hz, *C*H), 114.43 (J^2_{C-F} = 21 Hz, *C*H), 53.38 (–NCH_2Ar) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = yM- > 110.79 ppm. ^{77}Se NMR (76 MHz, $CDCl_3$): δ = 236.55 ppm. Elemental analysis: calcd (%) for $C_{19}H_{14}FN_3SSe$: C, 55.08; H, 3.41; N, 10.14. Found: C, 55.21; H, 3.45; N, 10.19.

1-Benzyl-4-phenyl-5-(phenylseleninyl)-1*H*-1,2,3-triazole (15 a): White solid; yield 57% (46 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 70:30; mp 116–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, 2H, *J* = 6.4 Hz, Ar–H), 7.49–7.48 (m, 2H, Ar–H), 7.36–7.29 (m, 6H, Ar–H), 7.19–7.18 (m, 3H, Ar–H), 7.09–7.08 (m, 2H, Ar–H), 5.94-5.78 (m, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.44 (*C*), 139.41 (*C*), 134.68 (*C*), 131.73 (*C*H), 129.96 (2×*C*H), 129.57 (*C*H), 129.29 (*C*), 129.18 (2×*C*H), 128.70 (2×*C*H), 128.51 (2×*C*H), 128.25 (2×*C*H), 127.93 (2×*C*H), 126.28 (*C*H), 119.46 (*C*), 53.08 (–NCH_2Ar) ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_3SeOH$; 408.0615; found, 408.0603.

1-Benzyl-4-(4-bromophenyl)-5-(phenylseleninyl)-1*H*-1,2,3-triazole (15 l): White solid; yield 60% (58 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 70:35; mp 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.47 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.24–7.23 (m, 1H, Ar–H), 7.19–7.07 (m, 7H, Ar–H), 7.01–6.99 (m, 2H, Ar–H), 5.83–5.65 (m, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.48 (*C*), 138.83 (*C*), 134.55 (*C*), 132.25 (2×*C*H), 131.85 (*C*H), 130.04 (2×*C*H), 129.95 (2×*C*H), 129.19 (*C*), 128.86 (2×*C*H), 128.50 (2×*C*H), 128.21 (*C*), 127.94 (2×*C*H), 126.21 (*C*H), 123.90 (*C*), 53.35 (–NCH_2Ar) ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}BrN_3OSeH$; 485.9720; found, 485.9349; *m/z* $[M+H+2]^+$ calcd for $C_{21}H_{16}BrN_3OSeH$; 487.9700; found, 487.9308.

1-Benzyl-5-(phenylseleninyl)-4-(thiophen-3-yl)-1*H*-1,2,3-triazole (15 n): White solid; yield 51% (42 mg, 0.2 mmol scale); eluent used for flash column was hexane/EtOAc 73:27; mp 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, 2H, *J* = 5.2 Hz, Ar–H), 7.43–7.41 (m, 1H, Ar–H), 7.35–7.27 (m, 5H, Ar–H), 7.19–7.14 (m, 3H, Ar–H), 7.08 (d, 2H, *J* = 6.8 Hz, Ar–H), 5.93–5.73 (m, 2H, –NCH_2Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.16 (*C*), 139.10 (*C*), 134.69 (*C*), 131.75 (*C*H), 130.07 (*C*), 129.95 (2×*C*H), 128.82 (2×*C*H), 128.39 (2×*C*H), 128.23 (*C*), 127.91 (2×*C*H), 127.18 (*C*H), 127.04 (*C*H), 126.15 (*C*H), 125.23 (*C*H), 53.21 (–NCH_2Ar) ppm. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}N_3SeOSH$; 414.0179; found, 414.0172.

Supporting Information

Scanned copies of respective ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **5 j**, **5 k**, **5 s**, **5 t**, **5 a′**, **5F′**, **5 j′**, and **5 r′**–**5 x′**), ^{77}Se NMR, and HRMS spectra for the synthesized compounds (**5 a**–**5 z**, **5 a′**–**5 x′**, **15 a**, **15 l**, and **15 n**) and single-crystal X-ray analysis for a representative entry, 1-benzyl-4-(4-ethoxyphenyl)-5-(phenylselanyl)-1*H*-1,2,3-triazole (5 g) (PDF).

Deposition Number 2283663 (for **5 g**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material. The Supporting Information is available free of charge on the Publisher's website.

Keywords: click reaction · mechanochemistry · one-pot synthesis · selenotriazoles · solvent-free synthesis

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C(sp)−C(sp^3) Bond Formation through Ligand- and Additive-Free CuO-Mediated Decarboxylative Direct Cross-Coupling of Coumarin-/Chromone-3-carboxylic Acids and Terminal Alkynes

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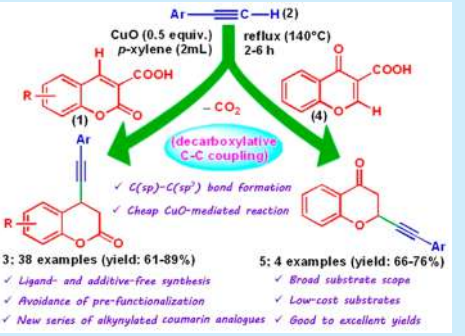
ABSTRACT: A practical and efficient method for the synthesis of functionalized 4-(aryl-/heteroaryl-ethynyl)chroman-2-ones and 2-(aryl-/heteroaryl-ethynyl)chroman-4-ones through copper-catalyzed decarboxylative direct cross-coupling of coumarin-/chromone-3-carboxylic acids with terminal alkynes, leading to the formation of C(sp)−C(sp^3) bonds, has been unearthed. Advantages of this protocol include avoidance of any ligands and bases, a broad substrate scope, tolerance of diverse functional groups, and good to excellent yields.



Carbon−carbon cross-coupling reactions are essential for synthetic organic chemists to prepare bioactive natural products and their analogues, drug molecules, agrochemicals, organic materials, fine chemicals, and many other valuable synthones.[1] In modern organic chemistry, the transition-metal-mediated direct C−C cross-coupling reactions have drawn significant interest as a result of the avoidance of pre-activation of both coupling components, making the system operationally simple, economically viable, and environmentally benign.[2] In 1975, the Sonogashira reaction[3] was first introduced to install an alkyne moiety into organic scaffolds, and since its discovery, it has become a powerful tool for alkynylation. The formation of *C*-alkynyl bonds has several benefits associated with transformation into diverse chemical structures, including synthetic intermediates,[4] precursors for natural products,[5] and metathesis and cycloaddition reactions.[6] Even though C(sp)−C(sp^2) bond formation has great success, the construction of direct C(sp)−C(sp^3) bonds is still limited. Recently, readily available and less-expensive copper salts or complexes have been given much attention in direct C(sp)−C(sp^3) coupling reactions.[7]

On the other hand, the coumarin scaffold is an important class of basic structural motifs of naturally occurring compounds and has privileged medicinal properties.[8] The C-4 alkynyl coumarin compounds have been found to act as synthetically very useful precursors[9] for complex organic molecules as well as organic electronic materials.[10] Therefore, developing efficient and practical methods for incorporating the alkynyl group into the coumarin moiety is an important topic. Upon a literature survey, we found that Yang's group in 2001 performed C(sp)−C(sp^2) bond formation by direct cross-coupling reaction of 4-tosylcoumarins (prepared from 4-hydroxycoumarin) and terminal alkynes under a dual-catalytic system of Pd(0)/Cu(I) and base in acetonitrile (Scheme 1a).[11a] There is also another report by Wu's group in 2009, where 4-hydroxycoumarins and terminal alkynes are reacted under Pd(0) catalysis in the presence of a base and an additive in acetonitrile (Scheme 1a).[11b] In both strategies, an expensive $PdCl_2(PPh_3)_2$ catalyst, base, and additive are required. In 2019, a further report by Knochel and his group came out on the $NiCl_2(PPh_3)_2$-catalyzed cross-coupling of alkynylzinc pivalates with pre-functionalized 4-hydroxycoumarin (Scheme 1a).[11c] Substrate scopes of all of these processes are very limited. Under this purview and our ongoing endeavors to develop advantageous synthetic protocols for functionalized coumarin analogues,[12] we have been motivated to undertake the present work. Accordingly, we herein report ligand- and additive-free CuO-mediated C(sp)−C(sp^3) bond formation through decarboxylative direct cross-coupling of coumarin-3-carboxylic acids/chromone-3-carboxylic acid (**1**/**4**) and terminal alkynes (**2**) just by refluxing the reactants in *p*-xylene to access a new series of diversely substituted 4-(aryl-/heteroaryl-ethynyl)-chroman-2-ones/2-(aryl-/heteroaryl-ethynyl)chroman-4-ones (**3**/**5**) with good to excellent yields (Scheme 1b). The key

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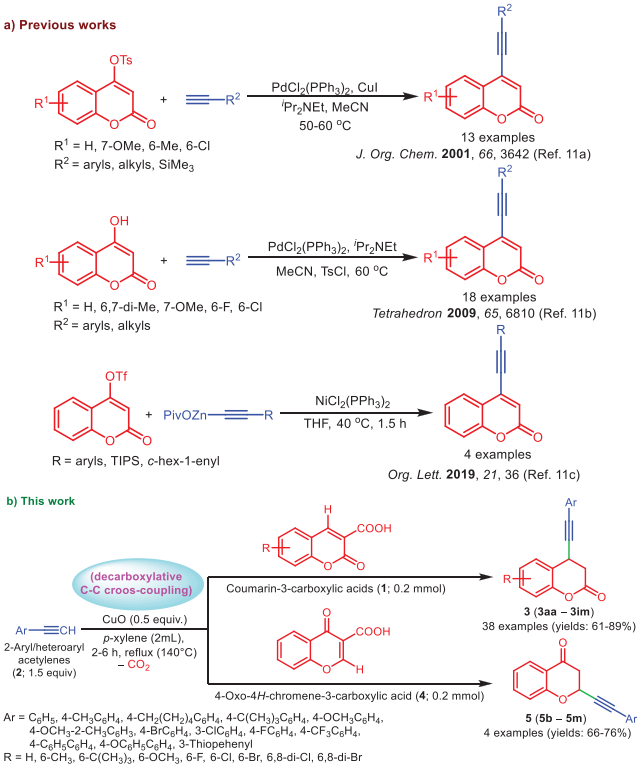
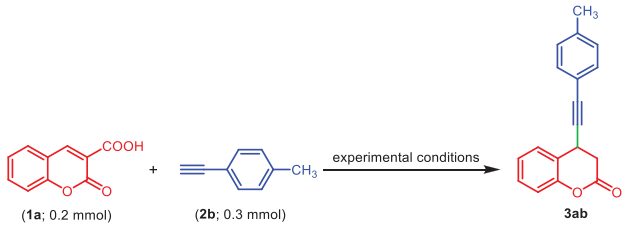
Scheme 1. (a) Earlier Reports on 4-Alkynylated Coumarins via the C−C Cross-Coupling Reaction and (b) Decaroboxylative Direct Cross-Coupling of Coumarin-3-carboxylic Acids with Terminal Alkynes



advantages of this present protocol are the avoidance of any ligands and additives, a broad substrate scope, tolerance of diverse functional groups, good to excellent yields within a reasonable time frame, and larger scale applicability.

Initially, we examined this two-component reaction between coumarin-3-carboxylic acid (**1a**) and 1-ethynyl-4-methylbenzene (**2b**) as our model entry, using 0.5 equiv of $Cu(OAc)_2$ as the catalyst and 1,4-dioxane as the solvent. The reaction did not proceed at room temperature (28 °C) even after 10 h; in contrast, the decarboxylative C-4 $C(sp^2)$−H functionalized C−C cross-coupling product **3ab** was observed in a moderate yield of 61% when refluxed at 120 °C for 6 h (entries 1 and 2 in Table 1, respectively). Following this encouraging result, we then performed a series of trial reactions by varying the equivalency of copper acetate (0.25−0.75 equiv) and solvents, such as 1,4-dioxane, CH_3CN, dimethylformamide (DMF), ethanol, toluene, and *p*-xylene (entries 3−9 in Table 1). We observed no further improvement, except when the reaction was carried out in *p*-xylene at 140 °C, isolating product **3ab** in a 67% yield at 6 h (entry 9 in Table 1). We also checked for other Cu(II) salts [viz., $CuCl_2$, $CuBr_2$, $CuSO_4$, and $Cu(OTf)_2$] and Cu(I) salts (viz., CuCl and CuI) by carrying out the conversion in *p*-xylene under reflux at 140 °C (entries 10−15 in Table 1); none of these copper salts appeared to be suitable (only $CuSO_4$ gave a poor yield of 48%; entry 12 in Table 1). We then envisioned running the model reaction using CuO (0.5 equiv) in *p*-xylene under reflux (140 °C), and we were delighted to isolate the desired product **3ab** in an excellent yield of 82% within 3 h (entry 16 in Table 1). Lowering the equivalency of CuO (0.25 equiv) resulted in a lower yield (42%; entry 17 in Table 1), while using the catalyst with a higher equivalency of 0.75 equiv neither showed any superiority in percent yield or time (entry 18 in Table 1). The heating condition at 100 °C did not work (entry 19 in Table 1). Palladium acetate was also found not to exert any catalytic influence on this reaction (entry 20 in Table 1). Finally, we arrived at the best suited conditions for this decarboxylative C−C cross-coupling reaction to access 4-(*p*-tolylethynyl)chroman-2-one (**3ab** in 82% yield) when coumarin-3-carboxylic acid (**1a**, 0.2 mmol) in *p*-xylene (2 mL) was refluxed with 1-ethynyl-4-methylbenzene (**2b**, 0.3 mmol) at 140 °C for 3 h in the presence of CuO (0.5 equiv) as the catalyst (entry 12 in Table 1). The pure product was isolated using a column chromatography technique. Compound **3ab** was characterized on the basis of detailed spectral [^1H and ^{13}C nuclear magnetic resonance (NMR), distortionless enhancement by polarization transfer (DEPT)-135, and high-resolution mass spectrometry (HRMS)] studies. The overall experimental results are summarized in Table 1.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (equiv)	solvent (2 mL)	temperature	time (h)	yield (%)[b]
1	$Cu(OAc)_2$ (0.5)	1,4-dioxane	rt	10	
2	$Cu(OAc)_2$ (0.5)	1,4-dioxane	reflux	6	61
3	$Cu(OAc)_2$ (0.75)	1,4-dioxane	reflux	6	61
4	$Cu(OAc)_2$ (0.25)	1,4-dioxane	reflux	10	32
5	$Cu(OAc)_2$ (0.5)	CH_3CN	reflux	10	
6	$Cu(OAc)_2$ (0.5)	DMF	reflux	10	51
7	$Cu(OAc)_2$ (0.5)	EtOH	reflux	10	
8	$Cu(OAc)_2$ (0.5)	toluene	reflux	10	11
9	$Cu(OAc)_2$ (0.5)	*p*-xylene	reflux	6	67
10	$CuCl_2$ (0.5)	*p*-xylene	reflux	10	trace
11	$CuBr_2$ (0.5)	*p*-xylene	reflux	10	trace
12	$CuSO_4$ (0.5)	*p*-xylene	reflux	10	48
13	$Cu(OTf)_2$ (0.5)	*p*-xylene	reflux	10	
14	CuCl (0.5)	*p*-xylene	reflux	10	trace
15	CuI (0.5)	*p*-xylene	reflux	10	trace
16	CuO (0.5)	*p*-xylene	reflux	3	82
17	CuO (0.25)	*p*-xylene	reflux	6	42
18	CuO (0.75)	*p*-xylene	reflux	3	82
19	CuO (0.5)	*p*-xylene	100 °C	10	
20	$Pd(OAc)_2$ (0.5)	*p*-xylene	reflux	10	

[a]Reaction conditions: A mixture of coumarin-3-carboxylic acid (**1a**, 0.2 mmol) and 1-ethynyl-4-methylbenzene (**2b**, 0.3 mmol) in varying solvents was stirred at room temperature (rt) or reflux temperature in the presence of different copper salts/palladium acetate as catalysts. [b]Isolated yields.

With the optimized conditions in hand, we turned our attention to explore the substrate scope of this decarboxylative $C(sp^2)$−H functionalization of coumarin-3-carboxylic acids (**1**) at the C-4 position with 2-aryl-/heteroaryl acetylenes (1-ethynyl arenes, **2**). We conducted a set of 11 such reactions of coumarin-3-carboxylic acid (**1a**) with simple 2-phenylacetylene (**2a**) and its diverse derivatives (**2c**−**2l**) having the phenyl group substituted with both electron-donating (viz., methyl, *n*-

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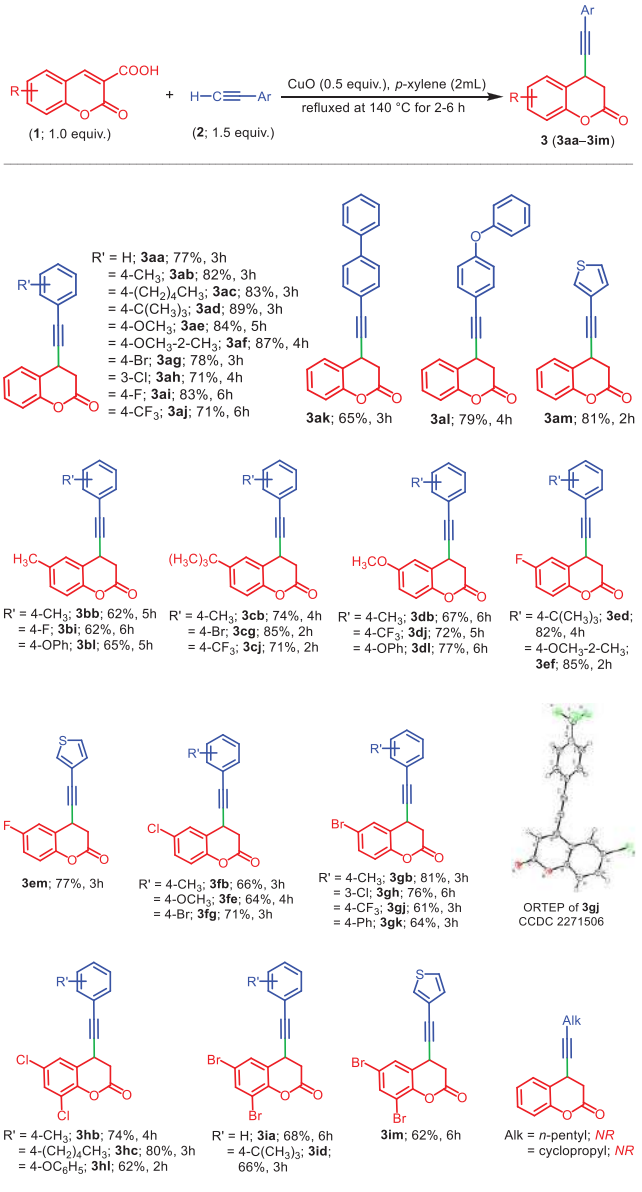
pentyl, *tert*-butyl, and bromo) and electron-withdrawing (viz., chloro, fluoro, methoxyl, trifluoromethyl, phenyl, and phenyloxyl) groups under the standard reaction conditions. All of the reactions went smoothly, giving rise to the desired products, such as 4-(phenylethynyl)chroman-2-one (**3aa**), 4-((4-pentylphenyl)ethynyl)chroman-2-one (**3ac**), 4-((4-(*tert*-butyl)phenyl)ethynyl)chroman-2-one (**3ad**), 4-((4-methoxyphenyl)ethynyl)chroman-2-one (**3ae**), 4-((4-methoxy-2-methylphenyl)ethynyl)chroman-2-one (**3af**), 4-((4-bromophenyl)ethynyl)chroman-2-one (**3ag**), 4-((3-chlorophenyl)ethynyl)-chroman-2-one (**3ah**), 4-((4-fluorophenyl)ethynyl)chroman-2-one (**3ai**), 4-((4-(trifluoromethyl)phenyl)ethynyl)chroman-2-one (**3aj**), 4-([1,1′-biphenyl]-4-ylethynyl)chroman-2-one (**3ak**), and 4-((4-phenoxyphenyl)ethynyl)chroman-2-one (**3al**), in 77, 83, 89, 84, 87, 78, 71, 83, 71, 65, and 79% yields, respectively, within 3−6 h. 3-Thiopheneylacetylene (**2m**) was found to take part in the reaction under identical reaction conditions, producing 4-(thiophen-3-ylethynyl)-chroman-2-one (**3am**) in a good yield of 81% at 2 h.

Motivated by these preliminary encouraging results, we then tried to extend the scope of the reaction further with substituted coumarin-3-carboxylic acids. For this purpose, we screened 6-methyl-coumarin-3-carboxylic acid (**1b**), 6-*tert*-butyl-coumarin-3-carboxylic acid (**1c**), 6-methoxy-coumarin-3-carboxylic acid (**1d**), 6-fluoro-coumarin-3-carboxylic acid (**1e**), 6-chloro-coumarin-3-carboxylic acid (**1f**), 6-bromo-coumarin-3-carboxylic acid (**1g**), 6,8-dichloro-coumarin-3-carboxylic acid (**1h**), and 6,8-dibromo-coumarin-3-carboxylic acid (**1i**). All of these versions of substituted coumarin-3-carboxylic acids (**1b−1i**) reacted efficiently with the diverse series of 2-aryl-/heteroaryl acetylenes (**2**) under the same reaction conditions to furnish the desired products **3bb−3im** with good to excellent yields ranging from 61 to 85% within 2−6 h. However, 2-alkanyl acetylenes, such as 2-*n*-pentyl acetylene and 2-cyclopropyl acetylene, did not take part in the reaction. All of these experimental outcomes are shown in Table 2.

To our delight, when we replaced coumarin-3-carboxylic acid (**1a**) with 4-oxo-4*H*-chromene-3-carboxylic acid (**4**), the latter participated in the decarboxylative cross-coupling reaction with a set of five different 2-aryl-/heteroaryl acetylenes (**2b**, **2e**, **2i**, and **2m**) under the identical reaction conditions, thereby affording the target products, 2-(aryl-/heteroaryl-ethynyl)chroman-4-ones (**5**) in good yields ranging from 66 to 76% within 2−6 h (Table 3; compounds **5b**, **5e**, **5i**, and **5m**).

All of the synthesized products **3** (**3aa−3im**) and **5** (**5b**, **5e**, **5i**, and **5m**) were purified by dint of the column chromatography technique (see the experimental procedures in the Supporting Information). All are new compounds and were fully characterized on the basis of their detailed spectral studies, including ^{1}H and ^{13}C NMR, DEPT-135, ^{19}F NMR (for compounds **3ai**, **3aj**, **3bi**, **3cj**, **3dj**, **3ed**, **3ef**, **3el**, **3gj**, and **5i**), HRMS, and elemental analyses. Further confirmation of the structural framework was taken up from single-crystal X-ray analysis for a representative entry, 6-bromo-4-((4-(trifluoromethyl)phenyl)ethynyl)chroman-2-one (**3gj**; CCDC 2271506; see the Supporting Information). To check the proficiency of this method, we carried out two representative reactions on a larger scale (2.0 mmol; 10-fold enhancement) that proceeded smoothly and afforded satisfactory results in isolating the products **3ab** and **3gb** in 78 and 76% yields,

Table 2. Synthesis of Functionalized 4-(Aryl-/Heteroarylethynyl)chroman-2-ones (3)[a,b]



[a]Reaction conditions: A mixture of coumarin-3-carboxylic acids (**1**, 0.2 mmol) and 2-aryl-/heteroaryl acetylenes (**2**, 0.3 mmol) in 2 mL of varying *p*-xylene was refluxed at 140 °C in the presence of CuO (0.5 equiv). [b]Isolated yields. NR = no reaction.

respectively (see the experimental procedures in the Supporting Information).

On the basis of the literature precedents,[13] we herein suggest a possible mechanism for this CuO-mediated decarboxylative C−C cross-coupling reaction (Scheme 2). Initially, CuO reacts with 1-ethynyl arene **2** to form a bis(arylethynyl)copper complex (**A**) upon removal of one molecule of H_2O. The alkynyl copper species, thus formed, in turn, attacks coumarin-3-carboxylic acid **1** to generate an intermediate organo-copper complex **6**. This intermediate species **6** reacts with another molecule of 1-ethynyl arene **2** to form the alkynyl copper species **A** again and an intermediate **7**. In the next step, intermediate **7** undergoes tautomerization to give intermediate

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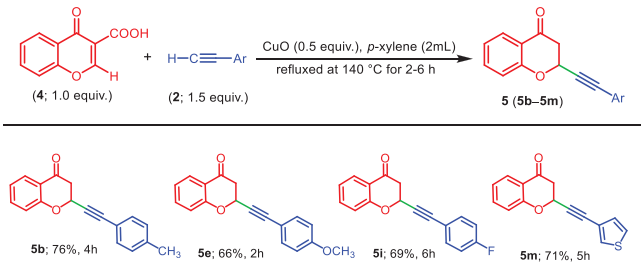
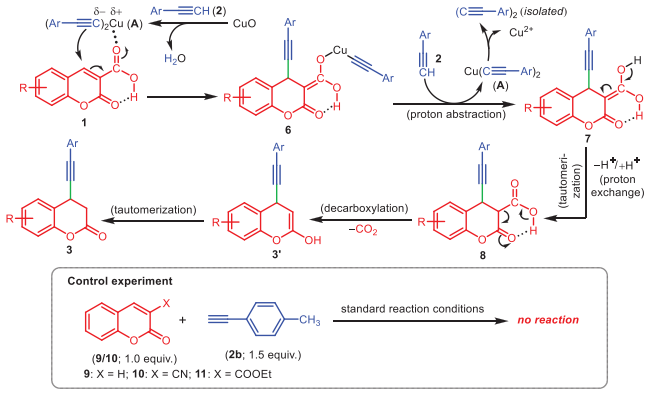
Table 3. Synthesis of Functionalized 2-(Aryl-/Heteroarylethynyl)chroman-4-ones (5)[a,b]



[a]Reaction conditions: A mixture of 4-oxo-4*H*-chromene-3-carboxylic acid (**4**, 0.2 mmol) and 2-aryl-/heteroaryl acetylenes (**2**, 0.3 mmol) in 2 mL of varying *p*-xylene was refluxed at 140 °C in the presence of CuO (0.5 equiv). [b]Isolated yields.

Scheme 2. Proposed Mechanism



8, which takes parts in a decarboxylation process, followed by isomerization to afford the desired product **3**. To examine the role of the carboxylic acid group within the coumarin moiety, we conducted a set of control experiments (Scheme 2, control experiment) with unsubstituted coumarin **9** and coumarins substituted with other functionalities at the 3 position (viz., 3-cyanocoumarin **10** and ethyl coumarin-3-carboxylate **11**); we observed no reaction to take place in all of these cases under the optimized conditions. Such observations support our presumption that the coumarin nucleus must bear a C_3–COOH group that is crucial in initiating the reaction through hydrogen bonding.

In conclusion, we have developed a facile and straightforward synthetic route for accessing a new series of biorelevant 4-(aryl-/heteroaryl-ethynyl)chroman-2-ones (**3**) and 2-(aryl-/heteroaryl-ethynyl)chroman-4-ones (**5**) through CuO-mediated C(sp)–C(sp^3) bond formation upon decarboxylative direct cross-coupling of coumarin-3-carboxylic acids (**1**) and chromone-3-carboxylic acid (**4**), respectively, with terminal alkynes (**2**). The significant advantages of this method are the avoidance of using any ligands and additives, a broad substrate scope, tolerance of diverse functional groups, good to excellent yields within a reasonable time frame, and larger scale applicability.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02369.

Experimental procedures, compound characterization, and scanned copies of respective ^{1}H and ^{13}C NMR, DEPT-135, and ^{19}F NMR (for compounds **3ai**, **3aj**, **3bi**, **3cj**, **3dj**, **3ed**, **3ef**, **3em**, **3gj**, and **5i**), HRMS spectra for the synthesized compounds (**3aa**–**3im** and **5b**–**5m**), and single-crystal X-ray analysis for a representative entry, 6-bromo-4-((4-(trifluoromethyl)phenyl)ethynyl)-chroman-2-one (**3gj**) (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa**–**3im** and **5b**–**5m** (ZIP)

Accession Codes

CCDC 2271506 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Visible Light-Induced and Singlet Oxygen-Mediated Photochemical Conversion of 4-Hydroxy-α-benzopyrones to 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides/carboxylates Using Rose Bengal as a Photosensitizer

Goutam Brahmachari* and Indrajit Karmakar

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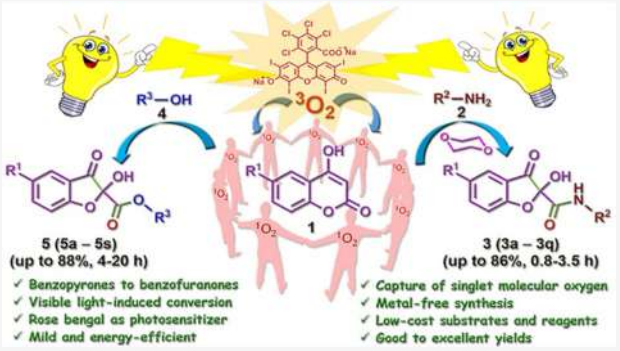
ABSTRACT: Development of a visible light-induced and singlet oxygen-mediated green protocol has been accomplished for the first time for the photochemical transformation of 4-hydroxy-α-benzopyrones to a new series of biorelevant 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides and 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates using rose bengal as a triplet photosensitizer at ambient temperature. Metal-free one-pot synthesis, broader substrate scope, good-to-excellent yields, use of cost-effective and eco-friendly starting materials and photosensitizer, and energy efficiency are the salient features of this newly developed method.



1. INTRODUCTION

Benzofuranones represent a key structural motif found in a plethora of natural products as well as their synthetic analogues with a broad range of biological and pharmacological activities.[1] In addition, benzofuranones are also regarded as useful building blocks in synthesizing certain desired natural products and their derivatives.[2] Among the benzofuranone family of compounds, benzofuran-3(2*H*)-ones serve as an important member,[3] and particularly, 2,2-disubstituted derivatives of this scaffold are ubiquitous in potentially bioactive natural products with multifaceted pharmaceutical properties that include antibiotic, antioxidant, antipsychotic, antidiabetic, anticancer, anti-HIV, and many more.[4] Figure 1 offers a glimpse of such naturally occurring bioactive 2,2-disubstituted benzofuran-3(2*H*)-ones.

Such useful pharmaceutical behavior and diverse biological properties of this class of molecules drew the attention of the chemists recently to develop a handful of synthetic methodologies to access 2,2-disubstituted benzofuranone-type compounds;[2c,5] however, most of these reported methodologies suffer from many shortcomings such as multistep procedures, toxic reagents and solvents, expensive catalysts, and harsh reaction conditions. Hence, the design and synthesis of this class of biologically relevant molecules in a facile, cost-effective, and greener route is deeply warranted.

A literature survey revealed that there is still no report on the synthesis of 2-hydroxybenzofuran-3(2*H*)-ones, although the presence of a hydroxyl function at C-2 is very much frequent in naturally occurring bioactive 2,2-disubstituted benzofuran-3(2*H*)-ones.[4a−c] Under this purview, we were motivated to undertake the challenge to develop an efficient protocol for this particular series of compounds as a part of our ongoing research endeavors.[6] Accordingly, we herein report a visible light-induced green and efficient protocol to access a new series of diversely substituted 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (**3**) and 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (**5**), for the first-time, using rose bengal as a triplet photosensitizer for molecular oxygen (O_2) at room temperature (25−28 °C); the overall results are outlined in Scheme 1. In addition to inducing a hydroxy group at the C-2 position of the benzofuran-3(2*H*)-one moiety, the present method came out to be successful in installing either an ester or amide functionality at the same position, thereby offering an additional flavor to the anticipated biological profiles of the synthesized molecules, as both ester and amide functionalities are known to exert positive impacts to the pharmacological efficacy of their derivatives.[7] As per our knowledge, this is the first report on the chemical transformation of a 4-hydroxy-α-benzopyrone motif to the 2-hydroxy-3-oxo-2,3-dihydrobenzo-

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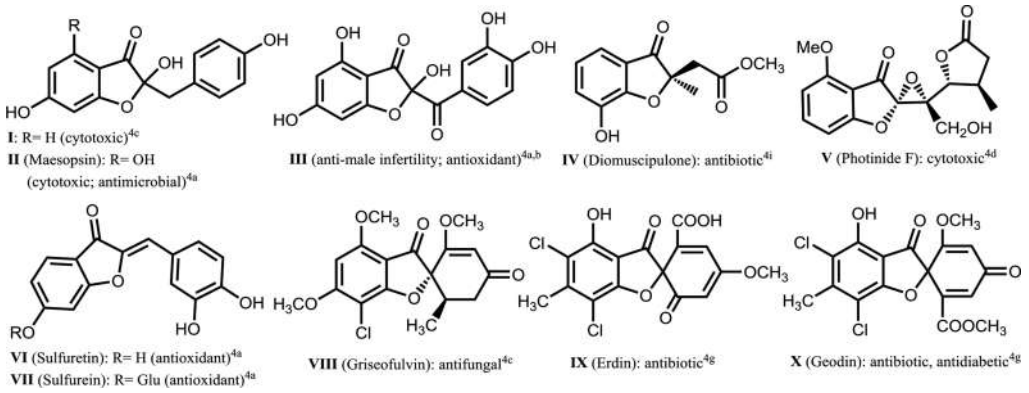


Figure 1. Selected examples of naturally occurring bioactive 2,2-disubstituted benzofuran-3(2*H*)-ones.

Scheme 1. Visible light-Induced Synthesis of Diversely Substituted 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (3) and 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (5)

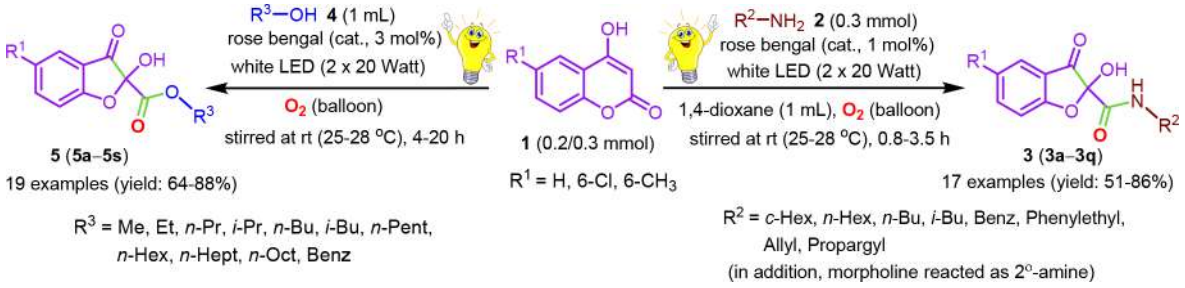
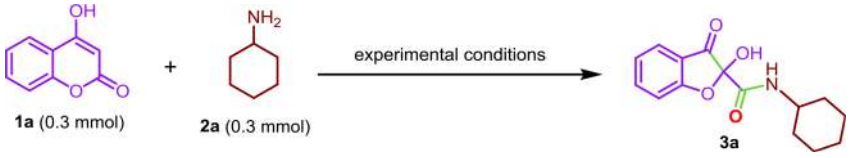


Table 1. Optimization of Reaction Conditions for the Synthesis of Diversely Substituted 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (3)



entry	photocatalyst	visible light (power)	atmosphere	solvent (1 mL)	time (h)	yield (%)[a,b]
1		sunlight (diffused)	aerial (open)	1,4-dioxane	8	
2		white LED (2 × 20 W)	oxygen	1,4-dioxane	8	
3	rose bengal (3 mol %)	dark	oxygen	1,4-dioxane	8	
4	rose bengal (3 mol %)	white LED (2 × 20 W)	oxygen	1,4-dioxane	2	65
5	rose bengal (5 mol %)	white LED (2 × 20 W)	oxygen	1,4-dioxane	2	65
6	eosin Y (3 mol %)	white LED (2 × 20 W)	oxygen	1,4-dioxane	3	58
7	rhodamine B (3 mol %)	white LED (2 × 20 W)	oxygen	1,4-dioxane	8	
8	fluorescence (3 mol %)	white LED (2 × 20 W)	oxygen	1,4-dioxane	8	
9	eosin B (3 mol %)	white LED (2 × 20 W)	oxygen	1,4-dioxane	8	
10	**rose bengal (1 mol %)**	**white LED (2 × 20 W)**	**oxygen**	**1,4-dioxane**	**2**	**65**
11	rose bengal (1 mol %)	white LED (2 × 20 W)	aerial (open)	1,4-dioxane	4	59
12	rose bengal (1 mol %)	green LED (2 × 12 W)	oxygen	1,4-dioxane	2.5	59
13	rose bengal (1 mol %)	blue LED (2 × 12 W)	oxygen	1,4-dioxane	3	53
14	rose bengal (1 mol %)	white LED (2 × 20 W)	nitrogen	1,4-dioxane	8	
15	rose bengal (1 mol %)	sunlight (diffused)	oxygen	1,4-dioxane	8	
16	rose bengal (1 mol %)	white LED (2 × 20 W)	oxygen	CH_3CN	5	51
17	rose bengal (1 mol %)	white LED (2 × 20 W)	oxygen	DCM	8	
18	rose bengal (1 mol %)	white LED (2 × 20 W)	oxygen	DMF	8	
19	rose bengal (1 mol %)	white LED (2 × 20 W)	oxygen	DMSO	8	
20	rose bengal (1 mol %)	white LED (2 × 20 W)	oxygen	H_2O	8	

[a]Reaction conditions: 4-hydroxycoumarin (**1a**; 0.3 mmol) was reacted with *c*-hexylamine (**2a**; 0.3 mmol) under the influence of different visible lights and atmospheres using varying photocatalysts in the presence of solvent(s) at room temperature (25−28 °C). [b]Isolated yields.

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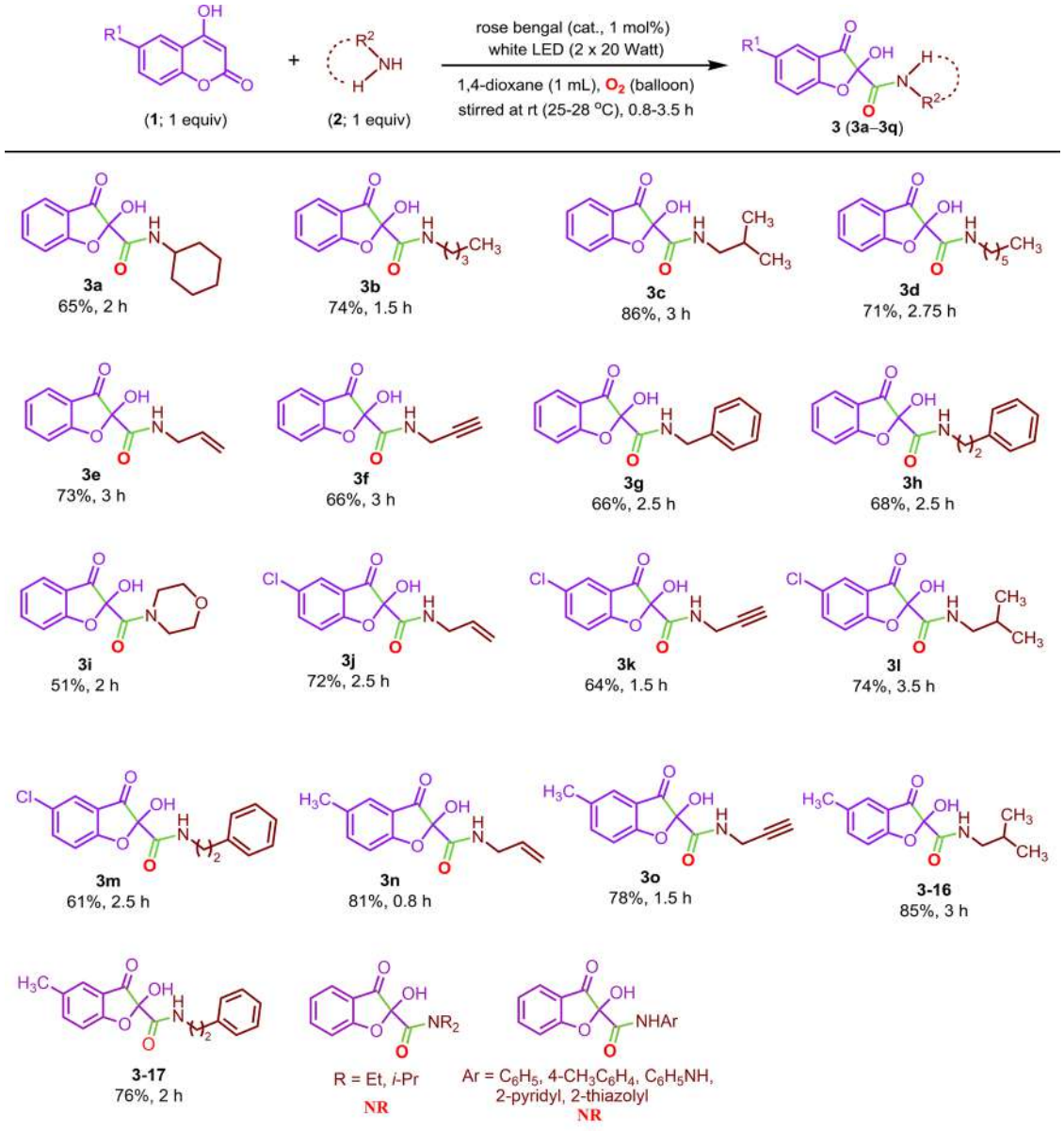
Table 2. Synthesis of Diversely Functionalized 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (3)[a,b]



[a]Reaction conditions: 4-hydroxycoumarins (**1**; 0.3 mmol) and amines (**2**; 0.3 mmol) in 1 mL of 1,4-dioxane under the influence of visible light (white LED; 2 × 20 W) in the presence of rose bengal (1 mol %) as a photocatalyst under an oxygen atmosphere (in balloon) at room temperature (25−28 °C). [b]Isolated yields. NR = no reaction.

furan-2-carboxamide/carboxylate scaffold. The key advantages of this present protocol are the broader substrate scope, insertion of molecular oxygen, metal-free synthesis, use of commercially available, cheap and eco-friendly catalyst, and energy efficiency. Visible light-mediated photoredox catalysis to drive chemical reactivity has now become a powerful tool in modern synthetic chemistry and finds useful applications, both in academia and industry, due to low-energy consumption, mildness, and environmental friendliness.[8] Rose bengal also finds wide-spread applications as a triplet photosensitizer in organic synthesis due to its efficacy, nontoxicity, low cost, and ecofriendliness.[9]

2. RESULTS AND DISCUSSION

To elicit the optimized reaction conditions, we commenced our studies by performing a series of trial reactions between 4-hydroxycoumarin (**1a**) and cyclohexyl amine (**2a**), as our model reaction, in the presence or absence of varying photocatalysts (viz., rose bengal, eosin B, eosin Y, fluorescence, and rhodamine), visible lights (diffused sunlight, white/blue/green LED bulbs), and solvents (viz., 1,4-dioxane, acetonitrile, dichloromethane, dimethyl sulfoxide, dimethylformamide, and water) at room temperature under aerial/nitrogen/oxygen environments (Table 1, entries 1−20). These experimental results revealed that rose bengal and eosin Y (entry 6), among the photocatalysts tried with, are capable of carrying out the transformation only either in 1,4-dioxane or acetonitrile (entry 16) under the influence of visible light irradiation in an oxygen

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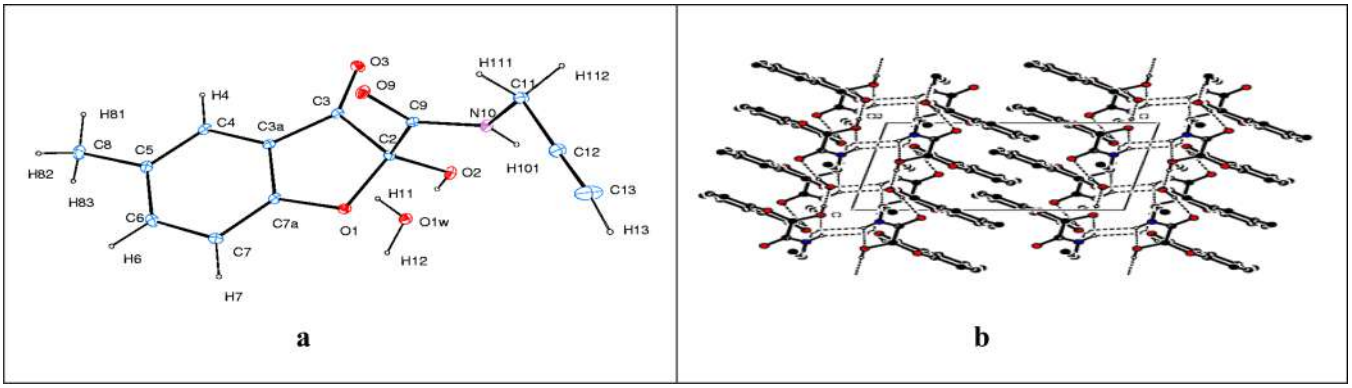

Figure 2. (a) *ORTEP* view of the molecule **3o**, showing the atom-labelling scheme (displacement ellipsoids are drawn at the 40% probability level, and H atoms are shown as small spheres of arbitrary radii). (b) The packing arrangement of **3o** viewed along the *b*-axis.

(balloon) atmosphere; however, rose bengal (1 mol %) appeared as the best-suited photocatalyst, while white LED (2 × 20 Watt) and 1,4-dioxane came out as the best-supporting light source and solvent, respectively, in terms of reaction time and product yield (Table 1, entry 10). This is also to be mentioned herein that the reaction did not undergo in a nitrogen atmosphere and also in solvents such as dichloromethane, dimethyl sulfoxide, dimethylformamide, and water. Finally, we were able to establish the optimum reaction conditions for this conversion and isolate a pure product of *N*-cyclohexyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3a**) in 65% yield within 2 h upon irradiating the mixture of 4-hydroxycoumarin (**1a**; 0.3 mmol) and cyclohexyl amine (**2a**, 0.3 mmol) in 1,4-dioxane (1 mL) with white LED (2 × 20 Watt) in the presence of rose bengal (1 mol %) as a photocatalyst at room temperature under oxygen atmosphere (Table 1, entry 10). To our delight, we eventually unearthed a visible light-induced photocatalytic reaction, for the first-time as per our knowledge, for the conversion of a 4-hydroxy-α-benzopyrone motif to 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide. Compound **3a** was characterized by the conventional spectral (^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, and HRMS) studies. The overall results are summarized in Table 1.

With the optimized reaction conditions in hand, we then proceeded to check the viability of this newly developed protocol by carrying out the conversion of 4-hydroxycoumarin (**1a**; 0.3 mmol) using a set of five varying aliphatic primary amines (0.3 mmol for each) such as *n*-butyl amine (**2b**), isobutyl amine (**2c**), *n*-hexyl amine (**2d**), allyl amine (**2e**), and propargyl amine (**2f**) in 1 mL of 1,4-dioxane using 1 mol % rose bengal as the photocatalyst, a white LED (2 × 20 Watt) as the visible light source, and an oxygen atmosphere (balloon) at room temperature; all the reactions took place efficiently furnishing the expected products, viz., 2-hydroxy-*N*-propyl-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3b**), 2-hydroxy-*N*-isobutyl-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3c**), 2-hydroxy-*N*-hexyl-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3d**), *N*-allyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3e**), and 2-hydroxy-3-oxo-*N*-(prop-2-yn-1-yl)-2,3-dihydrobenzofuran-2-carboxamide (**3f**) in 74, 86, 71, 73, and 66% yields, respectively, within 1.5−3 h. Two more reactions were successfully carried out with benzyl amine (**2g**) and phenylethyl amine (**2h**) under identical reaction conditions to have the corresponding products such as *N*-benzyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3g**) and 2-hydroxy-3-oxo-*N*-phenethyl-2,3-dihydrobenzofuran-2-carboxamide (**3h**) in respective yields of 66 and 68% at 2.5 h. Morpholine (**2i**), as a 2°-amine, was also found to undergo this reaction with 4-hydroxycoumarin to furnish 2-hydroxy-2-(morpholine-4-carbonyl)benzofuran-3(2*H*)-one (**3i**) at 2 h but with a moderate yield of 51%. However, both the secondary amines, diethylamine and di-isopropylamine, were found not undergoing the reaction. In case of piperidine, we also could not isolate the corresponding product due to the very slow reaction rate.

With these results in hand, we then performed another set of eight different reactions between substituted 4-hydroxycoumarins (viz., 6-chloro-4-hydroxycoumarin **1b** and 4-hydroxy-6-methylcoumarin **1c**) and varying amines under the optimized reaction conditions. All these reactions were found to be implemented smoothly, thereby affording the desired 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides **3j−3q** with good-to-excellent yields ranging from 64 to 85% at 0.8−3 h (Table 2). This is to mention herein that aromatic amines (such as aniline, *p*-toluidine, *N*-methylaniline, 2-aminopyridine, 2-aminothiazole, and phenyl hydrazine) did not take part in the reaction; this is probably due to reluctancy of the aromatic amino group to undergo the homolytic cleavage of the N−H bond under the reaction conditions.[10] Table 2 summarizes the overall results. The synthesized products (**3a−3q**) were purified using column chromatography (see the Experimental Section). All are new compounds and were fully characterized on the basis of their detailed spectral studies including ^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, and HRMS. We also validated the present protocol for a somewhat larger scale (1.0 mmol; 3.3-fold) reaction for one representative entry (Table 2, entry 3); the reaction proceeded quite satisfactory furnishing the desired product **3c** in an almost similar yield but required an extended reaction time of 1 h compared to the submillimolar scale (see the Experimental Section).

To our delight, we were successful in developing suitable crystals for 2-hydroxy-5-methyl-3-oxo-*N*-(prop-2-yn-1-yl)-2,3-dihydrobenzofuran-2-carboxamide (**3o**, Table 2), and its single crystal X-ray analysis (CCDC1974786; unit cell parameters: a = 11.7637(7) Å, b = 14.5153(8) Å, c = 7.3338(4) Å, α = 90°, β = 101.923(5)°, γ = 90°, $P21/c$) documented in this present communication (see the Supporting Information) is in full structural agreement. The *ORTEP* and packing diagram of the molecule are represented in Figure 2.

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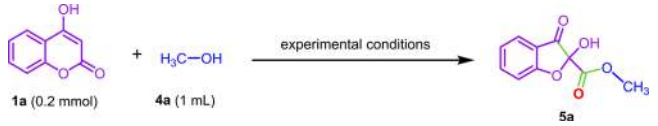
Table 3. Optimization of Reaction Conditions for the Synthesis of Diversely Substituted 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (5)



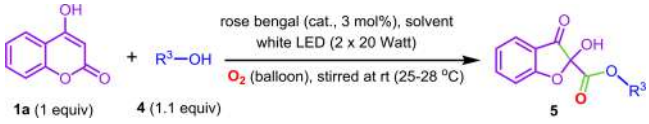
entry	photocatalyst	visible light (power)	atmosphere	time (h)	yield (%)[a,b]
1		sunlight (diffused)	aerial (open)	10	
2		white LED (2 × 20 W)	oxygen	10	
3	rose bengal (1 mol %)	dark	oxygen	10	
4	rose bengal (1 mol %)	white LED (2 × 20 W)	aerial (open)	7	76
5	rose bengal (1 mol %)	white LED (2 × 20 W)	oxygen	5.5	71
6	rose bengal (2 mol %)	white LED (2 × 20 W)	oxygen	4.5	79
7	**rose bengal (3 mol %)**	**white LED (2 × 20 W)**	**oxygen**	**4**	**84**
8	rose bengal (4 mol %)	white LED (2 × 20 W)	oxygen	4	84
9	rose bengal (4 mol %)	white LED (1 × 20 W)	oxygen	5	79
10	rose bengal (3 mol %)	white LED (2 × 20 W)	nitrogen	10	
11	rose bengal (3 mol %)	blue LED (2 × 12 W)	oxygen	7	89
12	rose bengal (3 mol %)	green LED (2 × 12 W)	oxygen	10	74
13	rose bengal (3 mol %)	CFL (2 × 27 W)	oxygen	7	79
14	eosin Y (3 mol %)	white LED (2 × 20 W)	oxygen	7	50
15	rhodamine B (3 mol %)	green LED (2 × 12 W)	oxygen	10	
16	rose bengal (4 mol %)	white LED (1 × 20 W)	oxygen	10	79

[a]Reaction conditions: 4-hydroxycoumarin (**1a**, 0.2 mmol) was reacted with methanol (**4a**, 1 mL) under the influence of different visible lights and atmospheres using varying photocatalysts in the absence of any added solvent at room temperature (25−28 °C). [b]Isolated yields.

Encouraged with these successful results, we then turned our attention to explore whether this technique could be fruitfully applicable in replacing amines just with alcohols to obtain a new series of substituted 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates. Accordingly, we performed a series of trial reactions (Table 3, entries 1−16) with 4-hydroxycoumarin (**1a**, 0.2 mmol) and methanol (**4a**, 1 mL) under varying conditions. To our delight, we eventually isolated the target product, methyl 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5a**), in 84% yield within 4 h under the optimal reaction conditions (Table 3, entry 7) that involve the use of rose bengal (3 mol %) as a photocatalyst, a white LED (2 × 20 W) as a visible light source, and an oxygen (balloon) atmosphere in the absence of any added solvent. Compound **5a** was characterized based on spectroscopic (^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, and HRMS) studies. To verify the optimal reaction conditions, we studied the effects of various solvents (e.g., acetonitrile, dichloroethane, 1,4-dioxane, dimethyl sulfoxide, and tetrahydrofuran) other than the reacting alcohol(s) with three different sets of reactions (Table 4). From the experimental results, it was evident that all the reactions, in general, proceeded well only when the reacting alcohols act as the solvents. The overall results are described in Table 4.

Furthermore, we studied the effects of other alcohols as solvents over the reacting alcohol(s). For this purpose, we performed four different sets of reactions (Table 5) between 4-hydroxycoumarin (**1a**, 1 equiv) and EtOH (**4b**, 1.1 equiv)/*n*-PrOH (**4c**; 1.1 equiv)/*n*-BuOH (**4e**; 1.1 equiv) using a different alcohol (1 mL) as the solvent in each respective case retaining other conditions intact; interestingly, we found that the isolated ester products (**5a**/**5b**/**5c**/**5e**) in all the four sets are the resultants of not from the stoichiometrically used alcohols but out of the alcohols used as solvents in a relatively large excess. Table 5 summaries these experimental observations. We then checked the finally optimized conditions in case

Table 4. Effect of Solvents Other than Reacting Alcohols (4)



entry	R^3	solvent (1 mL)	time (h)	yield (%)[a]
1	Me	CH_3CN	6	61
2	Me	DCE	10	
3	Me	1,4-dioxane	10	
4	Me	DMSO	10	
5	Me	THF	10	27
6	Et	CH_3CN	9	47
7	*n*-Pr	CH_3CN	12	37

[a]Isolated yields.

of a somewhat larger scale (1.0 mmol; 5-fold) for the model reaction (Table 3, entry 1); the reaction proceeded quite satisfactory furnishing the desired product **5a** in an almost similar yield within the reasonable time frame (see the Experimental Section).

With the optimized conditions established for the visible light-induced synthesis of 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (**5**), we then investigated on enhancing the substrate scope for this protocol. We carried out a total of 19 sets of such reactions with 4-hydroxycoumarin/5-chloro-4-hydroxycoumarin/5-methyl-4-hydroxycoumarin and varying alcohols (e.g., methanol **4a**, ethanol **4b**, *n*-propanol **4c**, *i*-propanol **4d**, *n*-butanol **4e**, *i*-butanol **4f**, *n*-pentanol **4g**, *n*-hexanol **4h**, *n*-heptanol **4i**, *n*-octanol **4j**, and benzyl alcohol **4k**) under the influence of white visible light (white LED, 2 × 20 Watt) in the presence of 3 mol % rose bengal as a photocatalyst and an oxygen atmosphere (balloon) at room temperature, to obtain a series of substituted 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (**5a**−**5s**) with good-to-

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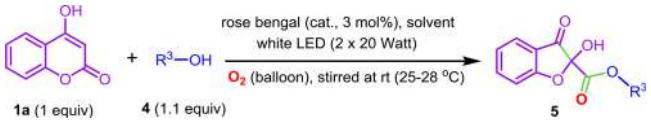
Table 5. Effect of Other Alcohols as Solvents over Reacting Alcohols (4)



entry	R^3	solvent (1 mL)	time (h)	product	yield (%)[a]
1	Et	methanol	4	**5a**	83
2	*n*-Pr	methanol	4	**5a**	83
3	*n*-Bu	methanol	4	**5a**	83
4	Me	ethanol	7	**5b**	67
5	*n*-Pr	ethanol	7	**5b**	68
6	*n*-Bu	ethanol	7	**5b**	68
7	Me	*n*-propanol	11	**5c**	72
8	Et	*n*-propanol	11	**5c**	73
9	*n*-Bu	*n*-propanol	11	**5c**	73
10	Me	*n*-butanol	12	**5e**	69
11	Et	*n*-butanol	12	**5e**	70
12	*n*-Pr	*n*-butanol	12	**5e**	73

[a]Isolated yields.

excellent yields ranging from 64 to 88% within the time frame of 4−20 h. However, *tert*-butanol, trifluoroethanol, and *p*-cresol were found not to undergo the reaction. Thiophenol also did not take part in this reaction. All the products **5** were purified using column chromatography and fully characterized on the basis of their detailed spectral studies including ^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, and HRMS (see the Experimental Section). The overall results are shown in Table 6.

We herein propose a possible mechanism for this visible light-induced and rose bengal-photosensitized synthesis of substituted 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (**3**)/2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (**5**), as depicted in Scheme 2, in the presence of molecular oxygen under the optimized conditions. Initially, rose bengal (RB), a triplet sensitizer,[11] gets activated (RB*) upon irradiation with visible light (white LED, 2 × 20 W), which is responsible for generation of singlet oxygen ($^1O_2$) by transferring its energy to the ground-state triplet oxygen ($^3O_2$)[12] in a cyclic manner. The in situ generation of singlet oxygen from its triplet state under the reaction conditions received experimental confirmation from the fact that no product was detected when two representative reactions (Table 7, 0% yields for **3a** and **5a**) were performed in the presence of DABCO, which serves as an effective quencher for singlet oxygen.[13] This $^1O_2$ then undergoes a rapid [2 + 2]-cycloaddition across the enolic double bond of the tautomer **1′** of hydroxycoumarin (**1**)[14] to form dioxetane intermediate **6** (non-isolable), which in turn generates a radical species **7** as results of homolytic cleavages of both the bonds "***a***" and "***b***".[15] In the next step, formation of hydroperoxide intermediate **8** (non-isolable) is anticipated due to participation of **7** in the radical recombination process, both intramolecularly (leading to the five-membered furan ring) and intermolecularly with the alkoxy/aminoalkyl and hydrogen radicals generated in situ from alcohols (**2**)/amines (**3**)[16] under the reaction conditions. Finally, the removal of a molecule of water from the hydroperoxide **8** furnishes the desired product **3**/**5**.

In support of our proposition for this radical pathway, we conducted sets of control experiments with our model reactions in the presence of radical-trapping reagents (*p*-benzoquinone, TEMPO, and BHT) (Table 7). It was observed that the formations of both the desired products **3a** and **5a** were completely prohibited in all three cases upon using at least 1 equiv of the trapping agents, thereby suggesting the involvement of a radical process in the transformation.[17] This is to mention herein that the possibility of formation of a superoxide radical anion ($O_2^{\cdot-}$) under the reaction conditions was discarded as we did not detect any H_2O_2 in the reaction mixture using a KI/starch indicator.[18]

3. CONCLUSIONS

In conclusion, we accomplished a visible light (white LED)-induced facile, straightforward, and efficient synthetic protocol for a new series of pharmaceutically interesting functionalized 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (**3**) and 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (**5**) from the reaction, respectively, between 4-hydroxycoumarins (**1**) and amines (**2**) in 1,4-dioxane and between 4-hydroxycoumarins (**1**) and alcohols (**4**) in the absence of any added solvent, making the good use of singlet oxygen in the presence of rose bengal as the photosensitizer at ambient temperature (25−28 °C). As per our knowledge, this is the first report on the chemical transformation of a 4-hydroxy-α-benzopyrone motif to the 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide/carboxylate scaffold. The notable advantages of this present protocol include the use of commercially available low-cost starting materials, low-energy visible light source, cheap and eco-friendly photosensitizer, broader substrate scope, insertion of molecular oxygen, metal-free synthesis, good-to-excellent yields, and energy efficiency.

4. EXPERIMENTAL SECTION

4.1. General Method. All chemicals (analytical grade) were purchased from reputed companies and used without further purification. ^{1}H and ^{13}C NMR spectra were collected at 400 and 100 MHz, respectively, on a Bruker DRX spectrometer using DMSO-d_6 and $CDCl_3$ as solvents. Chemical shifts were reported in δ (ppm), relative to the internal standard, TMS. The signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants are reported as J value in hertz (Hz). Mass spectrometry was obtained using a Bruker maXis Impact (Q-TOF) high-resolution mass spectrometer. X-ray single-crystallographic data were collected on an X′Calibur CCD area-detector diffractometer. The melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. Thin-layer chromatography (TLC) was performed using silica gel $60F_{254}$ (Merck) plates. Philips 20W Standard B22 white LED bulbs (Manufacturer: PHILIPS; Model and other details: LED Lamp B22 Crystal White, 20 W, F6500, Lumen 2000 lm, 0.090 A, 220−240 Vac, 5 C Hz) were used as the light source.

4.2. General Procedure for the Synthesis of Substituted 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (3). An oven-dried tripod standard-joint glass-vessel was charged with 4-hydroxycoumarins (**1**; 0.3 mmol), a rose bengal photocatalyst (1.0 mol %, 3 mg), amines (**2**; 0.3 mmol) dissolved in 1 mL of 1,4-dioxane, and a magnetic stir bar in a sequential manner. Oxygen (O_2) was bubbled through the reaction mixture for about 10 s, and the reaction vessel was then capped with a stopper having a vertical channel fitted with an O_2 balloon. This reaction system was now placed (at a distance of 2 cm from the light source) under the influence of white LEDs (2 × 20 W) within a specially designed wooden box. After then, the reaction mixture was started to stir at room temperature for stipulated time frame (0.8−3.5 h) with occasional TLC monitoring to judge the progress of the reaction. On completion of the reaction, 20 mL of EtOAc−H_2O (3:1 v/v) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated

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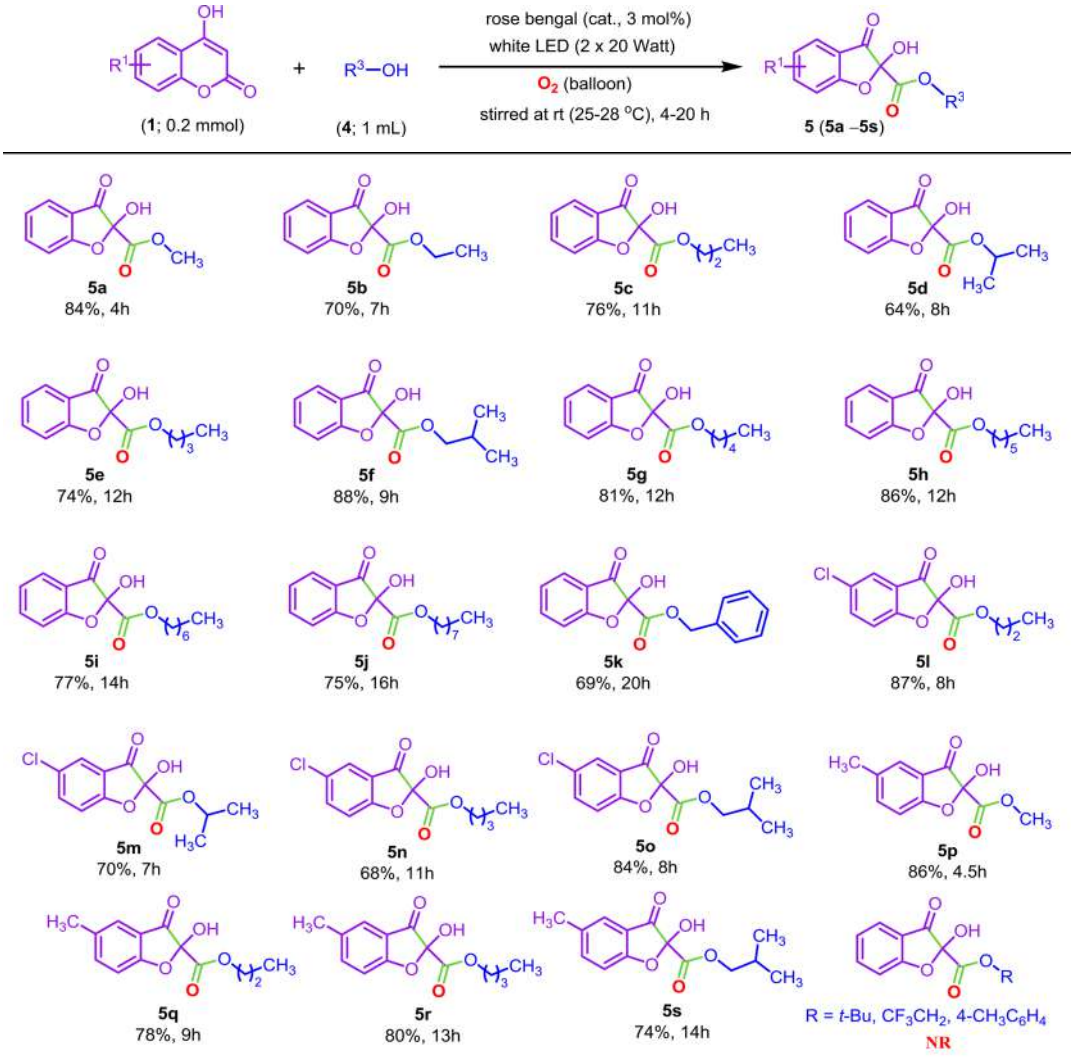
Table 6. Synthesis of Diversely Functionalized 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (5)[a,b]



[a]Reaction conditions: 4-hydroxycoumarin (**1**; 0.2 mmol) in 1 mL of alcohols (**4**) was reacted under the influence of visible light (white LED; 2 × 20 W) in the presence of rose bengal (3 mol %) as a photocatalyst under an oxygen atmosphere (in balloon) at room temperature (25−28 °C). [b]Isolated yields, NR = no reaction.

out, dried in sodium sulfate, and the organic solvent was then removed under reduced pressure to obtain a crude mass, which was finally purified by means of column chromatography using mixtures of EtOAc−hexane as eluents, to furnish the desired hydroxybenzofuranone carboxymides **3** (**3a**−**3q**). All the structures of the synthesized compounds were confirmed by spectroscopic studies including ^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, and HRMS. Further structural confirmation for a representative entry, 2-hydroxy-5-methyl-3-oxo-*N*-(prop-2-yn-1-yl)-2,3-dihydrobenzofuran-2-carboxamide (**3o**), based on single X-ray crystallographic studies was also supplemented (see the Supporting Information). The amount of reactants used for the 0.3 mM-scale reaction: 4-hydroxycoumarin (**1a**, 49 mg), 6-chloro-4-hydroxycoumarin (**1b**, 59 mg), 4-hydroxy-6-methylcoumarin (**1c**, 53 mg), cyclohexyl amine (**2a**, 30 mg), *n*-butyl amine (**2b**, 22 mg), isobutyl amine (**2c**, 22 mg), *n*-hexyl amine (**2d**, 30 mg), allyl amine (**2e**, 17 mg), propargyl amine (**2f**, 17 mg), benzyl amine (**2 g**, 32 mg), phenylethyl amine (**2 h**, 36 mg), and morpholine (**2i**, 26 mg).

4.3. Larger (Millimolar) Scale Synthesis of Compound 3c. An oven-dried tripod standard-joint glass vessel was charged with 4-hydroxycoumarin (**1a**; 1.0 mmol; 162 mg), rose bengal photocatalyst (1 mol %, 10 mg), isobutyl amine (**2c**; 1.0 mmol; 73 mg) dissolved in 3 mL of 1,4-dioxane, and a magnetic stir bar in a sequential manner. Oxygen (O_2) was bubbled through the reaction mixture for about 10 s, and the reaction vessel was then capped with a stopper having a vertical channel fitted with an O_2 balloon. This reaction system was now placed (at a distance of 2 cm from the light source) under the influence of white LEDs (2 × 20 W) fitted within the wooden box. After then, the reaction mixture was started to stir at room temperature for 4 h to complete the conversion (monitored by TLC), followed by work-up of the resulting crude product mixture in a similar fashion as described for the General Method. Upon drying, pure **3c** was isolated in 83% yield (206 mg), the physical and spectral properties (see the Supporting Information) of which were found identical with those obtained in 0.3 mmol-scale reaction (Table 2, entry 3).

4.4. Physical and Spectral Data of all the Synthesized Compounds 3 (3a−3q) Are Given below. *4.4.1. N-Cyclohexyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3a**).* White amorphous solid; yield: 65% (54 mg; 0.3 mmol scale); mp = 159 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.81 (s, 1H, −O*H*), 8.05 (d, 1H, *J* = 8.4 Hz, −N*H*), 7.77−7.73 (m, 1H, Ar−H), 7.62 (d, 1H, *J* = 7.6 Hz, Ar−H), 7.21 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.16 (t, 1H, *J* = 7.6 and 7.2 Hz, Ar−H), 3.56−3.48 (m, 1H,

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Scheme 2. Proposed Mechanism for the Visible Light-Induced Rose Bengal-Photosensitized Synthesis of Substituted 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides (3) and 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (5) in the Presence of Molecular Oxygen

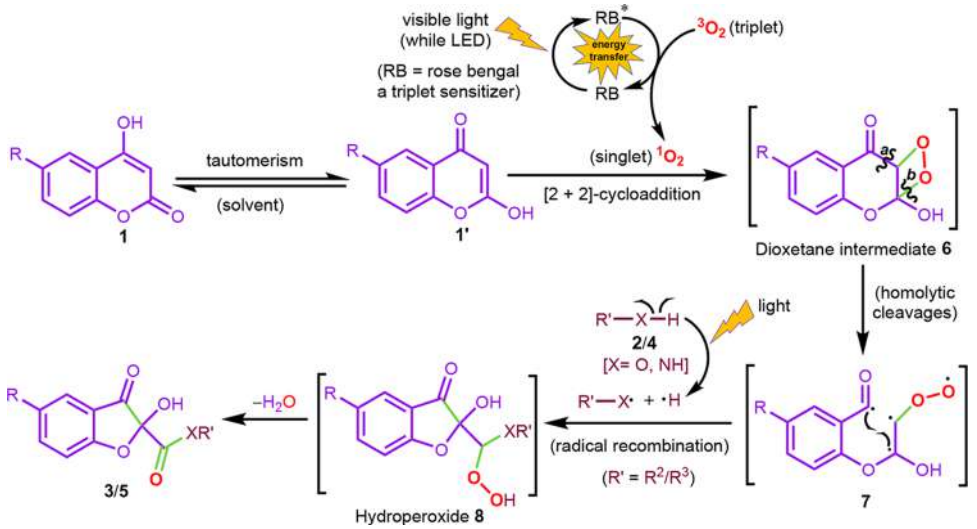
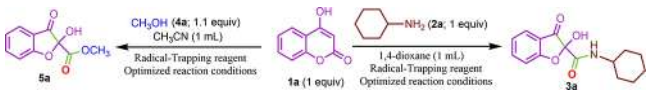


Table 7. Results of Control Experiments[a,b]



5a (% yield)	Time (h)	Amount (equiv)	Radical-Trapping reagent	Amount (equiv)	Time (h)	3a (% yield)
84	4	0.0		0.0	2	65
Trace	4	0.25		0.25	2	Trace
0	4	0.5		0.5	2	0
0	4	1.0		1.0	2	0
0	4	1.5	*p*-Benzoquinone	1.5	2	0
84	4	0.0		0.0	2	65
22	4	0.5		0.5	2	26
0	4	1.0		1.0	2	0
0	4	1.5	TEMPO	1.5	2	0
84	4	0.0		0.0	2	65
7	4	0.5		0.5	2	29
0	4	1.0		1.0	2	Trace
0	4	1.5	BHT	1.5	2	0
0	4	1.0		1.0	2	0
			DABCO			

[a]Reaction conditions: 4-hydroxycoumarin (**1a**; 1.0 equiv.) was added with cyclohexylamine (**2a**; 1.0 equiv) dissolved in 1 mL of 1,4-dioxane or with methanol (**4a**; 1.1 equi) in 1 mL of acetonitrile under the optimized reaction conditions in the presence of varying radical-trapping reagents, viz., BQ, TEMPO, BHT, and DABCO. [b]Isolated yields.

–CONHC*H*<), 1.69–1.64 (m, 4H, 2 × cyclohexyl CH_2), 1.57–1.54 (m, 1H, cyclohexyl C*H*), 1.41–1.31 (m, 2H, cyclohexyl CH_2), 1.28–1.19 (m, 2H, cyclohexyl CH_2), 1.13–1.03 (m, 1H, cyclohexyl C*H*) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6,100 MHz): δ = 197.3 (*C*O), 171.3 (*C*), 164.1 (amide carbonyl), 139.1 (*C*H), 124.4 (*C*H), 122.3 (*C*H), 119.2 (*C*), 113.2 (*C*H), 100.5 (>*C*(OH)–), 48.1 (–CONHC*H*<), 31.9 (2C, CH_2), 25.0 (CH_2), 24.8 (2C, CH_2) ppm. 2D NMR: COSY-45, HMQC and HMBC interactions are shown in the Supporting Information. HRMS (ESI): *m*/*z* 298.1050 $[M + Na]^+$ calcd for $C_{15}H_{17}NO_4Na$, found: *m*/*z* 298.1062.

*4.4.2. N-Butyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3b**).* Pale yellow oil; yield: 74% (55 mg; 0.3 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (t, 1H, *J* = 8.0 and 7.6 Hz, Ar–H), 7.56 (d, 1H, *J* = 7.6 Hz, Ar–H), 7.09–7.05 (m, 2H, Ar–H), 6.71 (br s, 1H, –N*H*), 3.17–3.13 (m, 2H, –CONHC$H_2C_3H_7$), 1.47–1.39 (m, 2H, –CONHCH$_2$CH_2C$_2$H$_5$), 1.32–1.23 (m, 2H, –CONH(CH$_2$)$_2$CH_2CH$_3$), 0.87 (t, 3H, *J* = 7.2 Hz, –CONH-(CH$_2$)$_3$CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 196.3 (*C*O), 171.9 (*C*), 165.2 (amide carbonyl), 139.5 (*C*H), 125.4 (*C*H), 122.9 (*C*H), 118.7 (*C*), 113.7 (*C*H), 99.8 (>*C*(OH)–), 39.8 (CONHC$H_2C_3H_7$), 31.2 (CONHCH$_2$CH_2C$_2$H$_5$), 19.9 (CONH-(CH$_2$)$_2$CH_2CH$_3$), 13.7 (CONH(CH$_2$)$_3$CH_3) ppm. HRMS (ESI): *m*/*z* 272.0893 $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4Na$, found: *m*/*z* 272.0901.

*4.4.3. 2-Hydroxy-N-isobutyl-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3c**).* Reddish white amorphous solid; yield: 86% (64 mg; 0.3 mmol scale); mp = 142 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.63–7.59 (m, 1H, Ar–H), 7.56–7.55 (m, 1H, Ar–H), 7.09–7.05 (m, 2H, Ar–H), 6.73 (br s, 1H, –N*H*), 2.99–2.96 (m, 2H, –CONHCH_2CH(CH$_3$)$_2$), 1.77–1.67 (m, 1H, –CONHCH$_2$C*H*(CH$_3$)$_2$), 0.85 (d, 3H, *J* = 1.6 Hz, –CONHCH$_2$CH-(CH_3)$_2$), 0.83 (d, 3H, *J* = 1.6 Hz, –CONHCH$_2$CH(CH_3)$_2$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 196.3 (*C*O), 171.9 (*C*), 165.3 (amide carbonyl), 139.4 (*C*H), 125.4 (*C*H), 122.9 (*C*H), 118.7 (*C*), 113.7 (*C*H), 99.9 (>*C*(OH)–), 47.2 (CONHCH$_2$CH(CH$_3$)$_2$), 28.4 (CONHCH$_2$CH(CH$_3$)$_2$), 19.9 (2C, CONHCH$_2$CH(CH_3)$_2$) ppm. HRMS (ESI): *m*/*z* 372.0893 $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4Na$, found: *m*/*z* 372.0897.

*4.4.4. N-Hexyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3d**).* White amorphous solid; yield: 71% (59 mg; 0.3 mmol scale); mp = 88 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.61 (t, 1H, *J* = 8.0 and 7.6 Hz, Ar–H), 7.54 (d, 1H, *J* = 7.6 Hz, Ar–H), 7.08–7.04 (m, 2H, Ar–H), 6.73 (br s, 1H, –N*H*), 3.14–3.09 (m, 2H, –CONHC$H_2C_5H_{11}$), 1.47–1.39 (m, 2H, –CONHCH$_2$CH_2C$_4$H$_9$), 1.30–1.21 (m, 6H, –CONH(CH$_2$)$_2$(CH_2)$_3$CH$_3$), 0.85 (t, 3H, *J* = 6.8 Hz, –CONH(CH$_2$)$_5$CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 196.3 (*C*O), 171.9 (*C*), 165.2 (amide carbonyl), 139.3 (*C*H), 125.4 (*C*H), 122.9 (*C*H), 118.7 (*C*), 113.6 (*C*H), 99.8 (>*C*(OH)–), 40.1 (CONHC$H_2C_5H_{11}$), 31.4 (CONHCH$_2$CH$_2$C$_4$H$_9$), 29.1 (CONH(CH$_2$)$_2$CH$_2$C$_3$H$_7$), 26.4 (CONH(CH$_2$)$_3$CH$_2$C$_2$H$_5$), 22.6 (CONH(CH$_2$)$_4$CH$_2$CH$_3$), 14.1 (CONH(CH$_2$)$_5$CH$_3$) ppm. HRMS (ESI): *m*/*z* 300.1206 $[M + Na]^+$ calcd for $C_{15}H_{19}NO_4Na$, found: *m*/*z* 300.1204.

*4.4.5. N-Allyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3e**).* Reddish oil; yield: 73% (51 mg; 0.3 mmol scale). ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.82 (s, 1H, –O*H*), 8.59–8.56 (m, 1H, –N*H*), 7.78–7.74 (m, 1H, Ar–H), 7.64 (dd, 1H, *J* = 8.0, 1.2 and 0.8 Hz, Ar–H), 7.22 (d, 1H, *J* = 8.4 Hz, Ar–H), 7.16 (t, 1H, *J* = 7.6 and 7.2 Hz, Ar–H), 5.83–5.74 (m, 1H, —NH—CH$_2$—C*H*=CH$_2$),

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5.14−5.13 (m, 2H, —NH—CH_2—CH═CH_2), 3.73−3.69 (m, 2H, —NH—CH_2—CH═CH_2) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6,100 MHz): δ = 197.2 (*C*O), 171.3 (*C*), 164.9 (amide carbonyl), 139.2 (*C*H), 134.5 (NH—CH_2—*C*H═CH_2), 124.4 (*C*H), 122.4 (*C*H), 119.0 (*C*), 115.1 (NH—CH_2—CH═CH_2), 113.2 (*C*H), 100.6 (>*C*(OH)−), 40.9 (NH—CH_2—CH═CH_2) ppm. HRMS (ESI): *m*/*z* 256.0580 $[M + Na]^+$ calcd for $C_{12}H_{11}NO_4Na$, found: *m*/*z* 256.0589.

*4.4.6. 2-Hydroxy-3-oxo-N-(prop-2-yn-1-yl)-2,3-dihydrobenzofuran-2-carboxamide (**3f**).* Pale yellow solid; yield: 66% (46 mg; 0.3 mmol scale); mp = 171 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.86 (s, 1H, −O*H*), 8.85−8.82 (m, 1H, −N*H*), 7.79−7.74 (m, 1H, Ar−H), 7.64 (d, 1H, *J* = 7.6 Hz, Ar−H), 7.23 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.17 (t, 1H, *J* = 7.6 and 7.2 Hz, Ar−H), 3.87−3.84 (m, 2H, —NH—CH_2—C≡CH), 3.08 (t, 1H, *J* = 2.4 Hz, —NH—CH_2—C≡*C*H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): δ = 196.8 (*C*O), 171.2 (*C*), 165.0 (amide carbonyl), 139.3 (*C*H), 124.5 (*C*H), 122.5 (*C*H), 118.9 (*C*), 113.2 (*C*H), 100.4 (>*C*(OH)−), 80.7 (NH—CH_2—*C*≡CH), 72.8 (NH—CH_2—C≡*C*H), 28.2 (NH—CH_2—C≡*C*H) ppm. HRMS (ESI): *m*/*z* 254.0424 $[M + Na]^+$ calcd for $C_{12}H_9NO_4Na$, found: *m*/*z* 254.0421.

*4.4.7. N-Benzyl-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3g**).* White amorphous solid; yield: 66% (56 mg; 0.3 mmol scale); mp = 164 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.68−7.64 (m, 2H, Ar−H), 7.35−7.31 (m, 2H, Ar−H), 7.29−7.27 (m, 1H, Ar−H), 7.25−7.23 (m, 2H, Ar−H), 7.15−7.11 (m, 2H, Ar−H), 6.67 (br s, 1H, −N*H*), 4.46 (d, 2H, *J* = 6.0 Hz, −NHC$H_2C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 195.7 (*C*O), 171.8 (*C*), 165.1 (amide carbonyl), 139.6 (*C*H), 136.9 (*C*), 128.9 (2 × *C*H), 128.0 (*C*H), 127.8 (2 × *C*H), 125.6 (*C*H), 123.4 (*C*H), 118.7 (*C*), 113.8 (*C*H), 99.5 (>*C*(OH)−), 44.2 (NH$CH_2C_6H_5$) ppm. HRMS (ESI): *m*/*z* 306.0737 $[M + Na]^+$ calcd for $C_{16}H_{13}NO_4Na$, found: *m*/*z* 306.0736.

*4.4.8. Hydroxy-3-oxo-N-phenethyl-2,3-dihydrobenzofuran-2-carboxamide (**3h**).* White amorphous solid; yield: 68% (61 mg; 0.3 mmol scale); mp = 164 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.63−7.56 (m, 2H, Ar−H), 7.28−7.24 (m, 2H, Ar−H), 7.22−7.18 (m, 1H, Ar−H), 7.13−7.11 (m, 2H, Ar−H), 7.09−7.05 (m, 2H, Ar−H), 6.63−6.61 (m, 1H, −N*H*), 3.45−3.39 (m, 2H, −NHC$H_2CH_2C_6H_5$), 2.75 (t, 2H, *J* = 7.2 and 6.8 Hz, −NHCH$_2$C$H_2C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 195.9 (*C*O), 171.7 (*C*), 165.2 (amide carbonyl), 139.5 (*C*H), 138.2 (*C*), 128.9 (2 × *C*H), 128.8 (2 × *C*H), 126.8 (*C*H), 125.5 (*C*H), 123.1 (*C*H), 118.7 (*C*), 113.6 (*C*H), 99.7 (>*C*(OH)−), 41.4 (NH*C*H$_2$CH$_2$C$_6$H$_5$), 35.3 (NHCH$_2$*C*H$_2$C$_6$H$_5$) ppm. HRMS (ESI): *m*/*z* 320.0893 $[M + Na]^+$ calcd for $C_{17}H_{15}NO_4Na$, found: *m*/*z* 320.0894.

*4.4.9. Hydroxy-2-(morpholine-4-carbonyl)benzofuran-3(2H)-one (**3i**).* White amorphous solid; yield: 51% (40 mg; 0.3 mmol scale); mp = 163 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.94 (br s, 1H, −O*H*), 7.77−7.73 (m, 1H, Ar−H), 7.66−7.64 (m, 1H, Ar−H), 7.21 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.17 (t, 1H, *J* = 7.6 Hz, Ar−H), 3.99−3.84 (m, 2H, −CH_2), 3.64−3.46 (m, 6H, 3 × −CH_2) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): δ = 195.7 (*C*O), 169.5 (*C*), 163.3 (amide carbonyl), 139.0 (*C*H), 124.6 (*C*H), 122.7 (*C*H), 118.9 (*C*), 113.3 (*C*H), 102.2 (>*C*(OH)−), 66.3 (−O*C*H$_2$−), 66.0 (−O*C*H$_2$−), 46.4 (−N*C*H$_2$−), 42.6 (−N*C*H$_2$−) ppm. HRMS (ESI): *m*/*z* 386.0686 $[M + Na]^+$ calcd for $C_{13}H_{13}NO_5Na$, found: *m*/*z* 386.0693.

*4.4.10. N-Allyl-5-chloro-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3j**).* Pale yellow jelly; yield: 72% (58 mg; 0.3 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.57 (d, 1H, *J* = 8.8 Hz, Ar−H), 7.52 (br s, 1H, Ar−H), 7.05 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.82 (br s, 1H, −N*H*), 5.79−5.70 (m, 1H, —NH—CH_2—*C*H═CH_2), 5.19−5.14 (m, 2H, —NH—CH_2—CH═*C*H_2), 3.80 (br s, 2H, —NH—*C*H_2—CH═CH_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 195.1 (*C*O), 170.1 (*C*), 164.9 (amide carbonyl), 139.2 (*C*H), 132.6 (NH—CH_2—*C*H═CH_2), 128.6 (*C*), 124.7 (*C*H), 119.8 (*C*), 117.5 (NH—CH_2—CH═*C*H_2), 115.1 (*C*H), 100.6 (>*C*(OH)−), 42.3 (NH—CH_2—CH═CH_2) ppm. HRMS (ESI): *m*/*z* 290.0191 $[M + Na]^+$ calcd for $C_{12}H_{10}ClNO_4Na$, found: *m*/*z* 290.0188.

*4.4.11. 5-Chloro-2-hydroxy-3-oxo-N-(prop-2-yn-1-yl)-2,3-dihydrobenzofuran-2-carboxamide (**3k**).* Pale yellow semisolid; yield: 64% (51 mg; 0.3 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (dd, 1H, *J* = 8.8 and 2.4 Hz, Ar−H), 7.55 (d, 1H, *J* = 2.0 Hz, Ar−H), 7.09 (d, 1H, *J* = 8.8 Hz, Ar−H), 6.97−6.95 (t, 1H, −N*H*), 4.02−4.00 (m, 2H, —NH—*C*H_2—C≡CH), 2.28 (br s, 1H, —NH—CH_2—C≡*C*H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 194.8 (*C*O), 170.1 (*C*), 164.6 (amide carbonyl), 139.4 (*C*H), 128.8 (*C*), 124.8 (*C*H), 119.7 (*C*), 115.1 (*C*H), 100.3 (>*C*(OH)−), 78.1 (NH—CH_2—*C*≡CH), 72.9 (NH—*C*H_2—C≡*C*H), 29.9 (NH—CH_2—C≡*C*H) ppm. HRMS (ESI): *m*/*z* 288.0034 $[M + Na]^+$ calcd for $C_{12}H_8ClNO_4Na$, found: *m*/*z* 288.0038.

*4.4.12. 5-Chloro-2-hydroxy-N-isobutyl-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3l**).* White amorphous solid; yield: 74% (63 mg; 0.3 mmol scale); mp = 171 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.58 (dd, 1H, *J* = 8.8 and 2.4 Hz, Ar−H), 7.53 (d, 1H, *J* = 2.4 Hz, Ar−H), 7.06 (d, 1H, *J* = 8.8 Hz, Ar−H), 6.64−6.61 (m, 1H, −N*H*), 3.01 (t, 2H, *J* = 6.8 and 6.4 Hz, −CONHCH_2CH(CH$_3$)$_2$), 1.79−1.69 (m, 1H, −CONHCH$_2$*C*H(CH$_3$)$_2$), 0.87 (d, 6H, *J* = 6.8 Hz, 2 × −CONHCH$_2$CH(*C*H$_3$)$_2$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 195.0 (*C*O), 170.2 (*C*), 164.9 (amide carbonyl), 139.2 (*C*H), 128.6 (*C*H), 124.7 (*C*H), 119.9 (*C*), 115.1 (*C*H), 100.5 (>*C*(OH)−), 47.4 (CONHCH$_2$CH(CH$_3$)$_2$), 28.5 (CONHCH$_2$*C*H(CH$_3$)$_2$), 19.9 (2C, CONHCH$_2$CH(*C*H$_3$)$_2$) ppm. HRMS (ESI): *m*/*z* 306.0509 $[M + Na]^+$ calcd for $C_{13}H_{14}ClNO_4Na$, found: *m*/*z* 306.0520.

*4.4.13. 5-Chloro-2-hydroxy-3-oxo-N-phenethyl-2,3-dihydrobenzofuran-2-carboxamide (**3m**).* Off white amorphous solid; yield: 61% (61 mg; 0.3 mmol scale); mp = 168 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.96 (br s, 1H, −O*H*), 8.49 (t, 1H, *J* = 6.0 and 5.6 Hz, −N*H*), 7.79 (dd, 1H, *J* = 8.8 and 2.4 Hz, Ar−H), 7.72 (d, 1H, *J* = 2.4 Hz, Ar−H), 7.30−7.27 (m, 3H, Ar−H), 7.21−7.19 (m, 3H, Ar−H), 3.32−3.28 (m, 2H, −NHC$H_2CH_2C_6H_5$), 2.75 (t, 2H, *J* = 7.6 Hz, NHCH$_2$CH_2C$_6$H$_5$) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): δ = 196.2 (*C*O), 169.7 (*C*), 164.6 (amide carbonyl), 139.1 (*C*), 138.6 (*C*H), 128.6 (*C*H), 128.3 (2 × *C*H), 128.3 (*C*H), 126.4 (*C*), 126.1 (*C*H), 123.6 (*C*H), 120.4 (*C*), 115.1 (*C*H), 101.5 (>*C*(OH)−), 40.3 (NHCH$_2$CH$_2$C$_6$H$_5$), 34.7 (NHCH$_2$CH$_2$C$_6$H$_5$) ppm. HRMS (ESI): *m*/*z* 354.0504 $[M + Na]^+$ calcd for $C_{17}H_{14}ClNO_4Na$, found: *m*/*z* 354.0504.

*4.4.14. N-Allyl-2-hydroxy-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3n**).* Pale yellow semisolid; yield: 81% (60 mg; 0.3 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.46−7.44 (m, 1H, Ar−H), 7.37 (br s, 1H, Ar−H), 7.01 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.67 (br s, 1H, −N*H*), 5.81−5.71 (m, 1H, —NH—CH_2—*C*H═CH_2), 5.19−5.11 (m, 2H, NH—*C*H_2—CH═*C*H_2), 3.84−3.82 (m, 2H, —NH—*C*H_2—CH═CH_2), 2.32 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 196.1 (*C*O), 170.3 (*C*), 165.3 (amide carbonyl), 140.8 (*C*H), 132.9 (*C*), 132.8 (NH—CH_2—*C*H═CH_2), 124.9 (*C*H), 118.6 (*C*), 117.3 (NH—CH_2—CH═*C*H_2), 113.3 (*C*H), 99.9 (>*C*(OH)−), 42.4, (NH—CH_2—CH═*C*H_2), 20.7 (Ar−*C*H_3) ppm. HRMS (ESI): *m*/*z* 270.0737 $[M + Na]^+$ calcd for $C_{13}H_{13}NO_4Na$, found: *m*/*z* 270.0735.

*4.4.15. 2-Hydroxy-5-methyl-3-oxo-N-(prop-2-yn-1-yl)-2,3-dihydrobenzofuran-2-carboxamide (**3o**).* Pale yellow amorphous solid; yield: 78% (57 mg; 0.3 mmol scale); mp = 160 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.49 (dd, 1H, *J* = 8.4 and 1.6 Hz, Ar−H), 7.42 (br s, 1H, Ar−H), 7.06 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.70 (br s, 1H, −N*H*), 4.07−4.05 (m, 2H, NH—*C*H_2—C≡CH), 2.35 (s, 3H, Ar−H), 2.26 (br s, 1H, NH—CH_2—C≡*C*H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 195.5 (*C*O), 170.2 (*C*), 165.0 (amide carbonyl), 140.9 (*C*H), 133.3 (*C*), 125.0 (*C*H), 118.5 (*C*), 113.4 (*C*H), 99.6 (>*C*(OH)−), 78.2 (NH—CH_2—*C*≡CH), 72.7 (NH—CH_2—C≡*C*H), 29.9 (NH—CH_2—C≡*C*H), 20.7 (Ar−*C*H_3) ppm. HRMS (ESI): *m*/*z* 268.0580 $[M + Na]^+$ calcd for $C_{13}H_{11}NO_4Na$, found: *m*/*z* 268.0585.

*4.4.16. 2-Hydroxy-N-isobutyl-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxamide (**3p**).* White amorphous solid; yield: 85% (67 mg; 0.3 mmol scale); mp = 162 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45 (dd, 1H, *J* = 8.8, 1.6 and 1.2 Hz, Ar−H), 7.37 (br s, 1H, Ar−H), 7.01 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.58−6.55 (m, 1H, −N*H*), 3.03

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(t, 2H, J = 6.4 Hz, −CONHCH_2CH(CH$_3$)$_2$), 2.33 (s, 3H, Ar−CH_3), 1.79−1.69 (m, 1H, −CONHCH$_2$CH(CH$_3$)$_2$), 0.87 (br s, 3H, −CONHCH_2CH(CH_3)$_2$), 0.85 (br s, 3H, −CONHCH_2CH(CH_3)$_2$) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 196.2 (CO), 170.3 (C), 165.4 (amide carbonyl), 140.7 (CH), 132.9 (C), 124.9 (CH), 118.6 (C), 113.3 (CH), 100.0 (>C(OH)−), 47.3 (CONHCH$_2$CH(CH$_3$)$_2$), 28.4 (CONHCH$_2$CH(CH$_3$)$_2$), 20.7 (Ar−CH$_3$) 19.9 (2C, CONHCH_2CH(CH_3)$_2$) ppm. HRMS (ESI): m/z 286.1050 [M + Na]$^+$ calcd for C$_{14}$H$_{17}$NO$_4$Na, found: m/z 286.1063.

*4.4.17. 2-Hydroxy-5-methyl-3-oxo-N-phenethyl-2,3-dihydrobenzofuran-2-carboxamide (**3q**).* White amorphous solid; yield: 76% (71 mg; 0.3 mmol scale); mp = 180 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.73 (br s, 1H, −OH), 8.41 (t, 1H, J = 6.4 and 5.6 Hz, −NH), 7.57 (dd, 1H, J = 8.4, 2.0 and 1.6 Hz, Ar−H), 7.42 (br s, 1H, Ar−H), 7.31−7.27 (m, 2H, Ar−H), 7.22−7.18 (m, 3H, Ar−H), 7.11 (d, 1H, J = 8.4 Hz, Ar−H), 3.30−3.22 (m, 2H, −NHCH_2CH$_2$C$_6$H$_5$), 2.75 (t, 2H, J = 7.6 Hz, NHCH$_2$CH_2C$_6$H$_5$), 2.32 (s, 3H, Ar−CH_3) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ = 197.1 (CO), 169.7 (C), 165.0 (amide carbonyl), 140.0 (CH), 139.1 (CH), 131.6 (CH), 128.6 (2 × CH), 128.3 (2 × CH), 126.1 (CH), 123.6 (CH), 118.9 (C), 112.8 (CH), 100.7 (>C(OH)−), 40.3 (NHCH$_2$CH$_2$C$_6$H$_5$), 34.8 (NHCH$_2$CH$_2$C$_6$H$_5$), 19.9 (Ar−CH$_3$) ppm. HRMS (ESI): m/z 334.1050 [M + Na]$^+$ calcd for C$_{18}$H$_{17}$NO$_4$Na, found: m/z 334.1051.

4.5. General Procedure for the Synthesis of Substituted 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates (5). An oven-dried tripod standard-joint glass-vessel was charged with 4-hydroxycoumarins (**1**; 0.2 mmol), rose bengal photocatalyst (3 mol %, 6 mg), alcohols (**4**; 1 mL), and a magnetic stir bar in a sequential manner. Oxygen (O_2) was bubbled through the reaction mixture for about 10 s, and the reaction vessel was then capped with a stopper having a vertical channel fitted with an O_2 balloon. This reaction system was now placed (at a distance of 2 cm from the light source) under the influence of white LEDs (2 × 20 W) within a specially designed wooden box. After then, the reaction mixture was started to stir at room temperature for stipulated time frame (4−20 h) with occasional TLC monitoring to judge the progress of the reaction. On completion of the reaction, 20 mL of EtOAc−H$_2$O (3:1 v/v) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated out, dried in sodium sulfate, and the organic solvent was then removed under reduced pressure to obtain a crude mass, which was finally purified by means of column chromatography using mixtures of EtOAc−hexane as eluents, to furnish the desired hydroxybenzofuranone carboxylates **5** (**5a**−**5s**). All the structures of the synthesized compounds were confirmed by spectroscopic studies including ^{1}H NMR, ^{13}C NMR, DEPT-135, 2D NMR, and HRMS. The amount of reactants used for the 0.2 mM-scale reaction: 4-hydroxycoumarin (**1a**, 32 mg), 6-chloro-4-hydroxycoumarin (**1b**, 39 mg), 4-hydroxy-6-methylcoumarin (**1c**, 35 mg).

4.6. Larger (Millimolar) Scale Synthesis of Compound 5a. An oven-dried tripod standard-joint glass-vessel was charged with 4-hydroxycoumarin (**1a**; 1.0 mmol; 162 mg), rose bengal photocatalyst (3 mol %, 31 mg), methanol (**4a**; 2 mL), and a magnetic stir-bar in a sequential manner. Oxygen (O_2) was bubbled through the reaction mixture for about 10 s, and the reaction vessel was then capped with a stopper having a vertical channel fitted with an O_2 balloon. This reaction system was now placed (at a distance of 2 cm from the light source) under the influence of white LEDs (2 × 20 W) fitted within the wooden box. After then, the reaction mixture was started to stir at room temperature for 4.5 h to complete the conversion (monitored by TLC), followed by work-up of the resulting crude product mixture in a similar fashion as described for the General Method. Upon drying, pure **5a** was isolated in 82% yield (171 mg), the physical and spectral properties (see the Supporting Information) of which were found identical with those obtained in 0.2 mmol scale reaction (Table 6, entry 1).

4.7. Physical and Spectral Data of all the Synthesized Compounds 5 (5a−5s) Are Given below. *4.7.1. Methyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5a**).* White amorphous solid; yield: 84% (35 mg; 0.2 mmol scale); mp = 109 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.98 (s, 1H, −OH), 7.82−7.78 (m, 1H, Ar−H), 7.69 (dd, 1H, J = 7.6 and 0.8 Hz, Ar−H), 7.27 (d, 1H, J = 8.8 Hz, Ar−H), 7.24−7.20 (m, 1H, Ar−H), 3.69 (s, 3H, −COOCH_3) ppm. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.69−7.65 (m, 2H, Ar−H), 7.17−7.13 (m, 1H, Ar−H), 7.11 (d, 1H, J = 8.4 Hz, Ar−H), 3.81 (s, 3H, −OCH_3) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 193.8 (CO), 171.4 (C), 167.4 (ester carbonyl), 139.4 (CH), 125.5 (CH), 123.3 (CH), 118.9 (C), 113.6 (CH), 97.8 (>C(OH)−), 54.4 (COOCH_3) ppm. 2D NMR: COSY-45, HMQC and HMBC interactions are shown in the Supporting Information. HRMS (ESI): m/z 231.0264 [M + Na]$^+$ calcd for C$_{10}$H$_8$O$_5$Na, found: m/z 231.0274.

*4.7.2. Ethyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5b**).* Pale yellow jelly; yield: 70% (31 mg; 0.2 mmol scale). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.69−7.64 (m, 2H, Ar−H), 7.16−7.10 (m, 2H, Ar−H), 4.33−4.24 (m, 2H, −OCH_2CH$_3$), 1.22 (t, 3H, J = 7.2 and 6.8 Hz, −OCH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 193.9 (CO), 171.5 (C), 166.9 (ester carbonyl), 139.2 (CH), 125.5 (CH), 123.2 (CH), 118.9 (C), 113.6 (CH), 97.8 (>C(OH)−), 64.1 (OCH$_2$CH$_3$), 13.9 (OCH$_2$CH$_3$) ppm. HRMS (ESI): m/z 245.0420 [M + Na]$^+$ calcd for C$_{11}$H$_{10}$O$_5$Na, found: m/z 245.0406.

*4.7.3. Propyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5c**).* Pale yellow jelly; yield: 76% (36 mg; 0.2 mmol scale). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.69−7.63 (m, 2H, Ar−H), 7.16−7.09 (m, 2H, Ar−H), 4.24−4.14 (m, 2H, −OCH_2C$_2$H$_5$), 1.63−1.55 (m, 2H, −OCH$_2$CH_2CH$_3$), 0.79 (t, 3H, J = 7.6 and 7.2 Hz, −O(CH$_2$)$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 193.9 (CO), 171.5 (C), 167.0 (ester carbonyl), 139.2 (CH), 125.4 (CH), 123.2 (CH), 119.1 (C), 113.5 (CH), 97.9 (>C(OH)−), 69.4 (OCH$_2$C$_2$H$_5$), 21.7 (OCH$_2$ CH$_2$CH$_3$), 9.9 (O(C$_2$H$_4$)$_2$CH$_3$) ppm. HRMS (ESI): m/z 259.0577 [M + Na]$^+$ calcd for C$_{12}$H$_{12}$O$_5$Na, found: m/z 259.0553.

*4.7.4. Isopropyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5d**).* White amorphous solid; yield: 64% (30 mg; 0.2 mmol scale); mp = 94 °C. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.70−7.65 (m, 2H, Ar−H), 7.17−7.11 (m, 2H, Ar−H), 5.16−5.09 (m, 2H, −OCH(CH$_3$)$_2$), 1.22 (br s, 3H, −OCH(CH_3)$_2$), 1.21 (br s, 3H, −OCH(CH_3)$_2$) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 194.0 (CO), 171.6 (C), 166.6 (ester carbonyl), 139.2 (CH), 125.4 (CH), 123.1 (CH), 119.1 (C), 113.6 (CH), 97.7 (>C(OH)−), 72.9 (OCH(CH$_3$)$_2$), 21.5 (OCH(CH$_3$)(CH$_3$)), 21.5 (OCH(CH$_3$)(CH$_3$)) ppm. HRMS (ESI): m/z 259.0577 [M + Na]$^+$ calcd for C$_{12}$H$_{12}$O$_5$Na, found: m/z 259.0572.

*4.7.5. Butyl 2-Hydroxy-3-Oxo-2,3-Dihydrobenzofuran-2-Carboxylate (**5e**).* Pale yellow jelly; yield: 74% (37 mg; 0.2 mmol scale). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.69−7.64 (m, 2H, Ar−H), 7.16−7.09 (m, 2H, Ar−H), 4.28−4.18 (m, 2H, −OCH_2C$_3$H$_7$), 1.58−1.51 (m, 2H, −OCH$_2$CH_2C$_2$H$_5$), 1.25−1.21 (m, 2H, −O(CH$_2$)$_2$CH_2CH$_3$), 0.81 (t, 3H, J = 7.6 and 7.2 Hz, −O(CH$_2$)$_3$CH_3) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 193.9 (CO), 171.5 (C), 167.0 (ester carbonyl), 139.2 (CH), 125.4 (CH), 123.2 (CH), 119.0 (C), 113.5 (CH), 97.9 (>C(OH)−), 67.8 (OCH$_2$C$_3$H$_7$), 30.2 (OCH$_2$CH$_2$C$_2$H$_5$), 18.8 (O(CH$_2$)$_2$CH$_2$CH$_3$), 13.5 (O(CH$_2$)$_3$CH$_3$) ppm. HRMS (ESI): m/z 273.0733 [M + Na]$^+$ calcd for C$_{13}$H$_{14}$O$_5$Na, found: m/z 273.0749.

*4.7.6. Isobutyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5f**).* Pale yellow jelly; yield: 88% (44 mg; 0.2 mmol scale). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.69−7.63 (m, 2H, Ar−H), 7.15−7.09 (m, 2H, Ar−H), 4.04−3.96 (m, 2H, −OCH_2CH(CH$_3$)$_2$), 1.90−1.80 (m, 1H, −OCH$_2$CH(CH$_3$)$_2$), 0.77 (d, 3H, J = 1.6 Hz, −OCH$_2$CH(CH_3)$_2$), 0.76 (d, 3H, J = 1.2 Hz, −OCH$_2$CH(CH_3)$_2$) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz): δ = 194.0 (CO), 171.4 (C), 166.9 (ester carbonyl), 139.2 (CH), 125.4 (CH), 123.2 (CH), 119.1 (C), 113.5 (CH), 98.0 (>C(OH)−), 73.4 (OCH$_2$CH(CH$_3$)$_2$), 27.6 (OCH$_2$CH(CH$_3$)$_2$), 18.6 (2C, OCH$_2$CH(CH$_3$)$_2$) ppm. HRMS (ESI): m/z 273.0733 [M + Na]$^+$ calcd for C$_{13}$H$_{14}$O$_5$Na, found: m/z 273.0734.

*4.7.7. Pentyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5g**).* Yellow jelly; yield: 81% (43 mg; 0.2 mmol scale). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.70−7.64 (m, 2H, Ar−H), 7.16−7.09 (m,

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2H, Ar−H), 4.25−4.19 (m, 2H, $-OCH_2C_4H_9$), 1.59−1.53 (m, 2H, $-OCH_2CH_2C_3H_7$), 1.24−1.14 (m, 4H, 2 × $-OCH_2(CH_2)_2CH_3$), 0.79 (t, 3H, J = 7.2 and 6.8 Hz, $-O(CH_2)_4CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 194.0 (*C*O), 171.5 (*C*), 166.9 (ester carbonyl), 139.2 (*C*H), 125.4 (*C*H), 123.2 (*C*H), 119.1 (*C*), 113.5 (*C*H), 97.9 (>*C*(OH)−), 68.0 ($OCH_2C_4H_9$), 27.9 ($OCH_2CH_2C_3H_7$), 27.6 ($O(CH_2)_2CH_2C_2H_5$), 22.1 ($O(CH_2)_3CH_2CH_3$), 13.9 ($O(CH_2)_4CH_3$) ppm. HRMS: m/z 287.0895 $[M + Na]^+$ calcd for $C_{14}H_{16}O_5Na$, found: m/z 287.0937.

*4.7.8. Hexyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5h**).* Colorless viscous liquid; yield: 86% (44 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.69−7.64 (m, 2H, Ar−H), 7.16−7.09 (m, 2H, Ar−H), 4.25−4.19 (m, 2H, $-OCH_2C_5H_{11}$), 1.59−1.52 (m, 2H, $-OCH_2CH_2C_4H_9$), 1.24−1.17 (m, 6H, $-O(CH_2)_2(CH_2)_3CH_3$), 0.81 (t, 3H, J = 6.8 Hz, $-O(CH_2)_5CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 193.9 (*C*O), 171.5 (*C*), 167.0 (ester carbonyl), 139.2 (*C*H), 125.4 (*C*H), 123.2 (*C*H), 119.1 (*C*), 113.5 (*C*H), 97.9 (>*C*(OH)−), 68.1 ($OCH_2C_5H_{11}$), 31.1 ($OCH_2CH_2C_4H_9$), 28.2 ($O(CH_2)_2CH_2C_3H_7$), 25.1 ($O(CH_2)_3CH_2C_2H_5$), 22.5 ($O(CH_2)_4CH_2CH_3$), 13.9 ($O(CH_2)_5CH_3$) ppm. HRMS (ESI): m/z 301.1052 $[M + Na]^+$ calcd for $C_{15}H_{18}O_5Na$, found: m/z 301.1208.

*4.7.9. Heptyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5i**).* Pale yellow jelly; yield: 77% (45 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.71−7.65 (m, 2H, Ar−H), 7.17−7.10 (m, 2H, Ar−H), 4.25−4.21 (m, 2H, $-OCH_2C_6H_{13}$), 1.60−1.53 (m, 2H, $-OCH_2CH_2C_5H_{11}$), 1.25−1.19 (m, 8H, $-O(CH_2)_2(CH_2)_4CH_3$), 0.84 (t, 3H, J = 7.2 and 6.4 Hz, $-O(CH_2)_6CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 193.9 (*C*O), 171.5 (*C*), 167.1 (ester carbonyl), 139.2 (*C*H), 125.4 (*C*H), 123.2 (*C*H), 119.2 (*C*), 113.6 (*C*H), 97.9 (>*C*(OH)−), 68.1 ($OCH_2C_6H_{13}$), 31.6 ($OCH_2CH_2C_5H_{11}$), 28.7 ($O(CH_2)_2CH_2C_4H_9$), 28.2 ($O(CH_2)_3CH_2C_3H_7$), 25.4 ($O(CH_2)_4CH_2C_2H_5$), 22.5 ($O(CH_2)_5CH_2CH_3$), 14.1 ($O(CH_2)_6CH_3$) ppm. HRMS (ESI): m/z 315.1208 $[M + Na]^+$ calcd for $C_{16}H_{20}O_5Na$, found: m/z 315.1271.

*4.7.10. Octyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5j**).* Pale yellow jelly; yield: 75% (46 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.69−7.63 (m, 2H, Ar−H), 7.15−7.09 (m, 2H, Ar−H), 4.21 (t, 2H, J = 6.8 and 6.4 Hz, $-OCH_2C_7H_{15}$), 1.57−1.54 (m, 2H, $-OCH_2CH_2C_6H_{13}$), 1.24 (br s, 2H, $-O(CH_2)_2CH_2C_5H_{11}$), 1.17 (br s, 8H, $-O(CH_2)_3(CH_2)_4CH_3$), 0.85 (t, 3H, J = 7.2 and 6.8 Hz, $-O(CH_2)_7CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 193.9 (*C*O), 171.5 (*C*), 166.9 (ester carbonyl), 139.2 (*C*H), 125.4 (*C*H), 123.1 (*C*H), 119.1 (*C*), 113.5 (*C*H), 97.9 (>*C*(OH)−), 68.0 ($OCH_2C_7H_{15}$), 31.7 ($OCH_2CH_2C_6H_{13}$), 29.1 ($O(CH_2)_2CH_2C_5H_{11}$), 28.9 ($O(CH_2)_3CH_2C_4H_9$), 28.2 ($O(CH_2)_4CH_2C_3H_7$), 25.4 ($O(CH_2)_5CH_2C_2H_5$), 22.7 ($O(CH_2)_6CH_2CH_3$), 14.1 ($O(CH_2)_7CH_3$) ppm. HRMS (ESI): m/z 329.1359 $[M + Na]^+$ calcd for $C_{17}H_{22}O_5Na$, found: m/z 329.1450.

*4.7.11. Benzyl 2-Hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5k**).* Pale yellow wax; yield: 69% (39 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.70−7.64 (m, 2H, Ar−H), 7.32−7.30 (m, 3H, Ar−H), 7.21−7.19 (m, 2H, Ar−H), 7.17−7.10 (m, 2H, Ar−H), 5.26 (s, 2H, $-OCH_2C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 193.7 (*C*O), 171.5 (*C*), 166.9 (ester carbonyl), 139.3 (*C*H), 134.1 (*C*), 128.8 (2 × *C*H), 128.8 (*C*H), 127.9 (2 × *C*H), 125.5 (*C*H), 123.3 (*C*H), 119.0 (*C*), 113.6 (*C*H), 97.8 (>*C*(OH)−), 69.2 ($OCH_2C_6H_5$) ppm. HRMS (ESI): m/z 307.0582 $[M + Na]^+$ calcd for $C_{16}H_{12}O_5Na$, found: m/z 307.0580.

*4.7.12. Propyl 5-Chloro-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5l**).* Pale yellow jelly; yield: 87% (47 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, 1H, J = 2.4 Hz, Ar−H), 7.61 (dd, 1H, J = 8.8, 2.4 and 2.0 Hz, Ar−H), 7.08 (d, 1H, J = 8.8 Hz, Ar−H), 4.26−4.15 (m, 2H, $-OCH_2C_2H_5$), 1.65−1.56 (m, 2H, $-OCH_2CH_2CH_3$), 0.81 (t, 3H, J = 7.6 Hz, $-O(CH_2)_2CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 192.8 (*C*O), 169.8 (*C*), 166.6 (ester carbonyl), 139.0 (*C*H), 128.7 (*C*), 124.8 (*C*H), 120.2 (*C*), 114.9 (*C*H), 98.6 (>*C*(OH)−), 69.6 ($OCH_2C_2H_5$), 21.8 ($OCH_2CH_2CH_3$), 9.9 ($O(CH_2)_2CH_3$) ppm. HRMS (ESI): m/z 293.0187 $[M + Na]^+$ calcd for $C_{12}H_{11}ClO_5Na$, found: m/z 293.0188.

*4.7.13. Isopropyl 5-Chloro-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5m**).* Pale yellow amorphous solid; yield: 70% (38 mg; 0.2 mmol scale); mp = 82 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, 1H, J = 2.0 Hz, Ar−H), 7.61 (dd, 1H, J = 8.8, 2.4 and 2.0 Hz, Ar−H), 7.08 (d, 1H, J = 8.8 Hz, Ar−H), 5.16−5.10 (m, 1H, $-OCH(CH_3)_2$), 1.23 (br s, 3H, $-OCH(CH_3)_2$), 1.22 (br s, 3H, $-OCH(CH_3)_2$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 192.9 (*C*O), 169.9 (*C*), 166.2 (ester carbonyl), 138.9 (*C*H), 128.7 (*C*), 124.8 (*C*H), 120.2 (*C*), 114.9 (*C*H), 98.5 (>*C*(OH)−), 73.2 ($OCH(CH_3)_2$), 21.5 ($OCH(CH_3)_2$), 21.5 ($OCH(CH_3)_2$) ppm. HRMS: m/z 293.0187 $[M + Na]^+$ calcd for $C_{12}H_{11}ClO_5Na$, found: m/z 293.0195.

*4.7.14. Butyl 5-Chloro-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5n**).* Pale yellow jelly; yield: 68% (39 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (d, 1H, J = 2.4 Hz, Ar−H), 7.61 (dd, 1H, J = 8.4, 2.4 and 2.0 Hz, Ar−H), 7.08 (d, 1H, J = 8.8 Hz, Ar−H), 4.31−4.20 (m, 2H, $-OCH_2C_3H_7$), 1.61−1.54 (m, 2H, $-OCH_2CH_2C_2H_5$), 1.27−1.22 (m, 2H, $-O(CH_2)_2CH_2CH_3$), 0.85 (t, 3H, J = 7.6 and 7.2 Hz, $-O(CH_2)_3CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 192.7 (*C*O), 169.8 (*C*), 166.7 (ester carbonyl), 139.0 (*C*H), 128.8 (*C*), 124.8 (*C*H), 120.2 (*C*), 114.9 (*C*H), 98.5 (>*C*(OH)−), 68.1 ($OCH_2C_3H_7$), 30.3 ($OCH_2CH_2C_2H_5$), 18.8 ($O(CH_2)_2CH_2CH_3$), 13.6 ($O(CH_2)_3CH_3$) ppm. HRMS: m/z 307.0344 $[M + Na]^+$ calcd for $C_{13}H_{13}ClO_5Na$, found: m/z 307.0347.

*4.7.15. Isobutyl 5-Chloro-2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5o**).* Colorless jelly; yield: 84% (48 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, 1H, J = 2.0 Hz, Ar−H), 7.61 (dd, 1H, J = 8.8, 2.4 and 2.0 Hz, Ar−H), 7.08 (d, 1H, J = 8.8 Hz, Ar−H), 4.05−4.00 (m, 2H, $-OCH_2CH(CH_3)_2$), 1.93−1.83 (m, 1H, $-OCH_2CH(CH_3)_2$), 0.80 (d, 3H, J = 1.2 Hz, $-OCH_2CH(CH_3)_2$), 0.78 (d, 3H, J = 1.2 Hz, $-OCH_2CH(CH_3)_2$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 192.8 (*C*O), 169.7 (*C*), 166.6 (ester carbonyl), 139.0 (*C*H), 128.7 (*C*), 124.7 (*C*H), 120.2 (*C*), 114.9 (*C*H), 98.7 (>*C*(OH)−), 73.7 ($OCH_2CH(CH_3)_2$), 27.7 ($OCH_2CH(CH_3)_2$), 18.6 (2C, $OCH_2CH(CH_3)_2$) ppm. HRMS: m/z 307.0344 $[M + Na]^+$ calcd for $C_{13}H_{13}ClO_5Na$, found: m/z 307.0352.

*4.7.16. Methyl 2-Hydroxy-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5p**).* White amorphous solid; yield: 86% (38 mg; 0.2 mmol scale); mp = 123 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.49−7.47 (m, 2H, Ar−H), 7.02−7.00 (m, 1H, Ar−H), 3.81 (s, 3H, $-COOCH_3$), 2.36 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 193.9 (*C*O), 169.9 (*C*), 167.6 (ester carbonyl), 140.5 (*C*H), 133.1 (*C*), 124.9 (*C*H), 118.8 (*C*), 113.2 (*C*H), 98.0 (>*C*(OH)−), 54.3 ($COOCH_3$), 20.7 (Ar−CH_3) ppm. HRMS: m/z 245.0420 $[M + Na]^+$ calcd for $C_{11}H_{10}O_5Na$, found: m/z 245.0425.

*4.7.17. Propyl 2-Hydroxy-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5q**).* Pale yellow jelly; yield: 78% (39 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.48−7.46 (m, 2H, Ar−H), 7.02−6.99 (m, 1H, Ar−H), 4.24−4.14 (m, 2H, $-OCH_2C_2H_5$), 2.35 (s, 3H, Ar−CH_3), 1.64−1.55 (m, 2H, $-OCH_2CH_2CH_3$), 0.80 (t, 3H, J = 7.6 and 7.2 Hz, $-O(CH_2)_2CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 194.1 (*C*O), 169.9 (*C*), 167.2 (ester carbonyl), 140.4 (*C*H), 132.9 (*C*), 124.8 (*C*H), 118.9 (*C*), 113.1 (*C*H), 98.1 (>*C*(OH)−), 69.3 ($OCH_2C_2H_5$), 21.8 ($OCH_2CH_2CH_3$), 20.7 (Ar−CH_3), 9.9 ($O(CH_2)_2CH_3$) ppm. HRMS: m/z 273.0739 $[M + Na]^+$ calcd for $C_{13}H_{14}O_5Na$, found: m/z 273.0729.

*4.7.18. Butyl 2-Hydroxy-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5r**).* Pale yellow jelly; yield: 80% (42 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.49−7.46 (m, 2H, Ar−H), 7.02−6.99 (m, 1H, Ar−H), 4.28−4.18 (m, 2H, $-OCH_2C_3H_7$), 2.36 (s, 3H, Ar−CH_3), 1.59−1.52 (m, 2H, $-OCH_2CH_2C_2H_5$), 1.26−1.21 (m, 2H, $-O(CH_2)_2CH_2CH_3$), 0.83 (t, 3H, J = 7.6 and 7.2 Hz, $-O(CH_2)_3CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 194.0 (*C*O), 169.9 (*C*), 167.2 (ester carbonyl), 140.4 (*C*H), 132.9 (*C*), 124.8 (*C*H), 118.9 (*C*), 113.1 (*C*H), 98.1 (>*C*(OH)−), 67.8 ($OCH_2C_3H_7$), 30.3 ($OCH_2CH_2C_2H_5$), 20.7 (Ar−CH_3), 18.8 (O-

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$(CH_2)_2CH_2CH_3$), 13.6 ($O(CH_2)_3CH_3$) ppm. HRMS: m/z 287.0890 $[M + Na]^+$ calcd for $C_{14}H_{16}O_5Na$, found: m/z 287.0915.

*4.7.19. Isobutyl 2-Hydroxy-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**5s**).* Colorless jelly; yield: 74% (39 mg; 0.2 mmol scale). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.48−7.46 (m, 2H, Ar−H), 7.51 (d, 1H, J = 8.8 Hz, Ar−H), 4.03−3.99 (m, 2H, $-OCH_2CH(CH_3)_2$), 2.36 (s, 3H, $Ar-CH_3$), 1.92−1.82 (m, 1H, $-OCH_2CH(CH_3)_2$), 0.79 (d, 3H, J = 1.6 Hz, $-OCH_2CH(CH_3)_2$), 0.78 (d, 3H, J = 1.2 Hz, $-OCH_2CH(CH_3)_2$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 194.0 (CO), 169.9 (C), 167.2 (ester carbonyl), 140.4 (CH), 132.9 (C), 124.8 (CH), 119.0 (C), 113.1 (CH), 98.1 (>C(OH)−), 73.5 ($OCH_2CH(CH_3)_2$), 27.7 ($OCH_2CH(CH_3)_2$), 20.7 ($Ar-CH_3$), 18.7 (2C, $OCH_2CH(CH_3)_2$) ppm. HRMS: m/z 287.0890 $[M + Na]^+$ calcd for $C_{14}H_{16}O_5Na$, found: m/z 287.1008.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00726.

Scanned copies of respective ^1H NMR, ^{13}C NMR, DEPT-135, 2D NMR (for two representative compounds, **3a** and **5a**), and HRMS spectra for all the synthesized compounds **3a−3q** and **5a−5s**, along with X-ray single crystallographic analysis for a representative entry, 2-hydroxy-5-methyl-3-oxo-*N*-(prop-2-yn-1-yl)-2,3-dihydrobenzofuran-2-carboxamide (**3o**) (PDF)

Single X-ray crystallographic data for **3o** (CIF)

NFR FIDs (ZIP)

FAIR data, including the primary NMR FID files, for compounds **3a-3q** and **5a-5s** (ZIP)

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Notes

The authors declare no competing financial interest.

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Catalyst- and Additive-Free Decarboxylative C-4 Phosphorylation of Coumarin-3-Carboxylic Acids at Ambient Conditions

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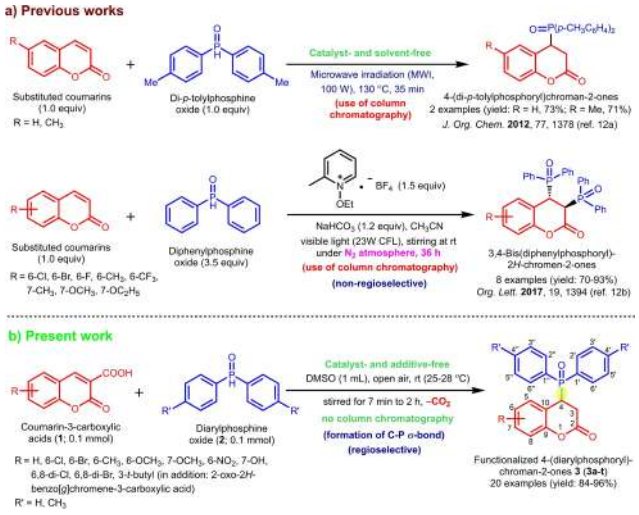
Abstract: A catalyst- and additive-free practical and green synthetic strategy for decarboxylative C-4 phosphorylation of coumarin-3-carboxylic acids, for the first time, has been accomplished to access a series of substituted 4-(diarylphosphoryl)chroman-2-ones at ambient conditions. The developed protocol is successfully applied to large-scale synthesis.

Keywords: coumarin-3-carboxylic acids; decarboxylative C-4 phosphorylation; catalyst- and additive-free; ambient conditions; gram-scale synthetic application

Introduction

Coumarins, an important class of *O*-heterocycles, are already well-established to form the basic structural motif for a plethora of therapeutically promising organic scaffolds of both natural and synthetic origins, finding immense applications in treating multifaceted disease manifestations.[1] Coumarin derivatives are also used as additives in foods and cosmetics,[2] fragrances and perfumes,[3] and agrochemicals,[4] Also, such molecules find extensive applications as fluorescence sensors,[5] optical brighteners,[6] and molecular photonic devices.[7] 3,4-Dihydrcoumarin, *i.e.* chroman-2-one is a sub-class of this group and this interesting structural motif is also potentially found both in natural and their synthetic analogs exhibiting a wide range of biological profiles including antioxidant, cytotoxic, anticancer, immunomodulatory, anti-platelet aggregation, estrogenic, antibacterial and antileishmanial activity.[8] On the other hand, phosphorus-functionalized organic molecules have also found useful applications in the areas of industrial, agricultural, materials, and medicinal chemistry owing to their noteworthy biological and physical properties.[9] The imposition of a phosphoryl group on to diverse kinds of organic skeletons thus remains a valid and active exercise in chemical research.[10] As part of these research endeavors, a good deal of work on the combination of these two units, *i.e.* a coumarin system and a phosphoryl group, so as to open a route to a new class of organophosphorus compounds, has been reported in the recent past.[10b,c,11] However, all these literature reports basically deal with the phosphorylation at C-3 position of a coumarin nucleus, and were implemented under varying reaction conditions, mostly non-ecofriendly.[11] An extensive literature survey revealed just two earlier reports on the direct C-4 phosphorylation of coumarins to access C-4 phosphorylated chroman-2-ones.[12] In 2012, Lenker *et al.*[12a] for the first-time reported the microwave-assisted synthesis of only two such derivatives. Later on, in 2017 Hong and co-investigators[12b] developed a visible-light-induced photocatalytic synthetic protocol for phosphorylated chroman-2-ones; however, their method is non-regioselective and furnished 3,4-bis(diphenylphosphoryl)-2*H*-chromen-2-ones. Scheme 1a overviews these earlier reports along with their merits and demerits.

Based on this background and as part of our research endeavors in developing green synthetic protocols for biologically relevant compounds,[13] we targeted this interesting research problem and envisioned that coumarin-3-carboxylic acid might be a suitable substrate, which would afford the targeted scaffold regioselectively *via* decarboxylative C-4 phosphorylation. To our delight, we now wish to report herein, for the first time, a regioselective decarboxylative C-4 phosphorylation strategy for coumarin-3-carboxylic acids without the aid of any catalyst or additive under ambient conditions (Scheme 1b). The key advantages of this newly developed method are



Scheme 1. Direct phosphorylation of coumarin-3-carboxylic acids.

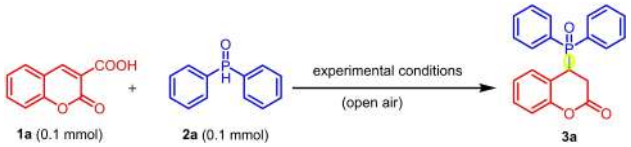
the clean reaction profile, use of no catalyst or additive, DMSO as reaction medium, mild reaction conditions at room temperature, energy-efficiency, no need of column chromatographic purification, high atom-economy, and low E-factor, excellent regioselectivity, good to excellent yields, and large-scale synthetic applicability.

Results and Discussion

To optimize the best-suited reaction conditions, we first performed a series of trial reactions between coumarin-3-carboxylic acid (**1 a**; 0.1 mmol) and diphenylphosphine oxide (**2 a**; 0.1 mmol), as our model reaction, in the absence or presence of various solvents (*viz.* water, dichloromethane, acetonitrile, 1,4-dioxane, ethanol, and dimethyl sulfoxide) in open-air either at room or elevated temperature (Table 1, entries 1–8). Dimethyl sulfoxide (DMSO) came out as the best solvent for this conversion, just at ambient conditions, in terms of yield and time. We thus achieved the best result for our model reaction in preparing the desired product, 4-(diphenylphosphoryl)chroman-2-one (**3 a**), in 92% yield at 10 min (Table 1, entry 7) upon stirring the reactants dissolved in 1 mL of DMSO in the open-air at room temperature (25–28 °C) without any additive and/or catalyst. Compound **3 a** was characterized based on detailed spectroscopic (^{1}H NMR, ^{13}C NMR, DEPT-135, ^{31}P NMR, and HRMS) studies. The overall results are summarized in Table 1.

It seemed that ethanol (Table 1, entry 6), yielding 83% of **3 a** in 30 min under identical reaction conditions, may also be a competitive solvent for this conversion, and to explore this issue, we carried out a set of two more reactions with coumarin-3-carboxylic acids (**1 f**/**1 i**) substituted with electron-donating and

Table 1. Optimization of reaction conditions.



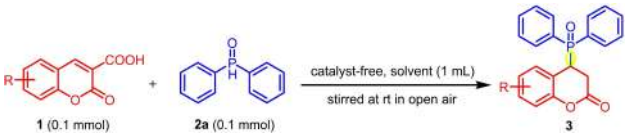
Entry	Solvent (1 mL)	Catalyst	Condition	Time (min)	Yield (%)[a,b]
1	no solvent	–	rt	60	–
2	H_2O	–	rt	60	66
3	CH_2Cl_2	–	rt	240	72
4	CH_3CN	–	rt	30	78
5	1,4-dioxane	–	rt	30	80
6	EtOH	–	rt	30	83
7	**DMSO**	–	**rt**	**10**	**92**
8	DMSO	–	80 °C	10	89

[a] Reaction conditions: coumarin-3-carboxylic acid (**1 a**; 0.1 mmol) was stirred with diphenylphosphine oxide (**2 a**; 0.1 mmol) in the absence or presence of solvent(s) without any additive either at room temperature (25–28 °C) or heating;
[b] Isolated yields.

electron-withdrawing groups, separately in DMSO and ethanol, using the identical reaction conditions, and compared the results (Table 2). These experimental results, as summarized in Table 2, clearly demonstrated that DMSO is the most suitable solvent for the conversion for various substrates in terms of reaction-times and yields of the products (**3 f**/**3 i**).

To check the feasibility as well as the effectiveness of this newly developed protocol, we then carried out a set of three similar reactions with 6-methylcoumarin-3-carboxylic acid (**1 b**), 6-*tert*-butylcoumarin-3-carbox-

Table 2. Selection of solvent.



Entry	R	Solvent	Product	Time (min)	Yield (%)[a,b]
1	H	DMSO	**3 a**	10	92
2	H	EtOH	**3 a**	30	83
3	7-OCH_3	DMSO	**3 f**	15	71
4	7-OCH_3	EtOH	**3 f**	90	42
5	6-NO_2	DMSO	**3 i**	7	76
6	6-NO_2	EtOH	**3 i**	60	43

[a] Reaction conditions: a coumarin-3-carboxylic acid (**1 a**/**1 f**/**1 i**; 0.1 mmol) was stirred with diphenylphosphine oxide (**2 a**; 0.1 mmol) dissolved in 1 mL of DMSO/EtOH in the absence any catalyst at room temperature (25–28 °C);
[b] Isolated yields.

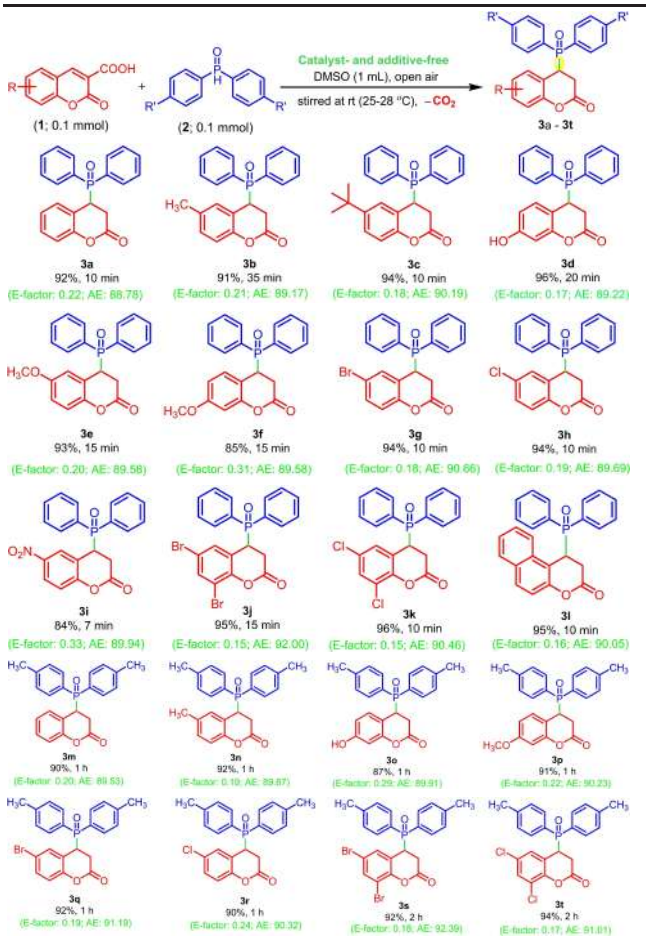
ylic acid (**1 c**) and 7-hydroxycoumarin-3-carboxylic acid (**1 d**) using the optimized reaction conditions; all the three reactions took place efficiently, furnishing the expected products, *viz.* 4-(diphenylphosphoryl)-6-methylchroman-2-one (**3 b**), 6-(*tert*-butyl)-4-(diphenylphosphoryl)chroman-2-one (**3 c**) and 4-(diphenylphosphoryl)-7-hydroxychroman-2-one (**3 d**), in 91%, 94% and 96% yields, respectively, at 35, 10 and 20 min. Encouraged with this satisfactory experimental outcomes, we then planned to extend the substrate scope, and accordingly, another set of seven more reactions with diversely substituted coumarin-3-carboxylic acids (**1 e–1 k**; containing methoxy, bromo, chloro, nitro, dibromo and di-chloro groups) were performed under identical reaction conditions. All these reactions underwent smoothly, thereby affording the desired 4-(diphenylphosphoryl)chroman-2-one derivatives **3 e–3 k** with good to excellent yields ranging from 84–96% just at 7–15 min. To our delight, 3-oxo-3*H*-benzo[*f*]chromene-2-carboxylic acid (**1 l**) also took part in the reaction giving rise to the desired phosphorylated product, 1-(diphenylphosphoryl)-1,2-dihydro-3*H*-benzo[*f*]chromen-3-one (**3 l**) with 95% yield after 10 min.

We then tried to extend the scope of >P(O)H reagent and accordingly, we carried out a set of two reactions between di-*p*-toylphosphine oxide **2 b**, a variant of >P(O)H reagent, and unsubstituted coumarin-3-carboxylic acid **1 a** and with 6-methylcoumarin-3-carboxylic acid **1 b**, under the identical reaction conditions. Both the reactions took place smoothly giving the desired and known compounds, 4-(di-*p*-tolylphosphoryl)chroman-2-one (**3 m**) and 4-(di-*p*-tolylphosphoryl)-6-methylchroman-2-one (**3 n**), respectively, in 90% and 92% yields at 1 h; the physical and spectral data of both the products are in close agreement with those reported in literature.[12a] To our delight, we were also successful in synthesizing another set of six functionalized phosphorylated chroman-2-one derivatives **3 o–3 t** with good to excellent yields ranging from 87–94% within 1–2 h upon the reaction of the phosphorus reagent **2 b** with the diversely substituted coumarin-3-carboxylic acids (**1 d**, **1 f–h**, **1 j**, and **1 k**) under identical reaction conditions. The overall results are shown in Table 3.

However, $(EtO)_3P$, $(PhO)_2P(O)H$ and $(MeO)_2P(O)H$ were found not to take part in the reaction – possibly, because the P–H hydrogen in case of the latter two reagents [$(PhO)_2P(O)H$ and $(MeO)_2P(O)H$] is reluctant to undergo tautomerization required for initiating decarboxylation of the coumaric acid substrate. No decarboxylation occurred upon the addition of either of the three P-reagents with coumaric acid dissolved in DMSO, and hence, there was no reaction at all.

The synthesized compounds **3 a–3 t** were isolated pure just upon filtration, followed by drying in the open-air; no tedious chromatographic purification was required. All the products, except **3 m** and **3 n**, are new

Table 3. Synthesis of substituted 4-(diarylphosphoryl)- chroman-2-ones (3).[a,b]



[a] Reaction conditions: a coumarin-3-carboxylic acid (**1**; 0.1 mmol) was stirred in open air with diarylphosphine oxide (**2**; 0.1 mmol) dissolved in 1 mL of DMSO in the absence any catalyst at room temperature (25–28 °C);
[b] Isolated yields.

and were fully characterized based on their detailed spectral studies including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{31}P NMR, and HRMS. In support of the phosphorylation taking place at C-4 of the coumarin moiety, we further studied 2D-NMR, particularly the HMQC (^{1}H–^{13}C heteronuclear multiple quantum coherence) and HMBC (^{1}H–^{13}C heteronuclear multiple bond correlation) spectral analysis for a representative compound **3 g** (see Supporting Information) – the key HMBC interaction between the multiplet proton signal for H-4 at δ_H 4.64–4.60 (–C*H*P–) and carbon-13 signal for C-6 at δ_C 120.48 confirmed the structure **I** for compound **3 g**, while another possible structure **II** was discarded as no such interaction was observed between either H_a of –CH_2CO– at δ_H 3.18–3.11(m, merged with DMSO-d_6 water peak) or H_b of –CH_2CO– at δ_H 2.57–

2.52 (m) and the C-6 at δ_C 120.48, as depicted in Figure 1.

To evaluate the greenness of this newly developed method, we herein calculated (see Supporting Information) two important green parameters,[14] *i.e.* E-factor (g/g), and atom economy (AE) for all the synthesized compounds (**3a**–**3t**). The calculated E-factors and atom economy are found to be in the range of 0.33–0.15, and 88.78–92.39%, respectively, which are indicative of the considerable greenness of this present method; the respective E-factor and atom economy for each entry is shown in Table 3.

Herein we propose a possible mechanism for this catalyst- and additive-free C-4 phosphorylation of substituted coumarin-3-carboxylic acids (**1**) with diarylphosphine oxide (**2**) in DMSO at ambient conditions, leading to the synthesis of a new series of substituted 4-(diarylphosphoryl)chroman-2-ones (**3**) (Scheme 2). Coumaric acid **1** first gets associated with the phosphorus substrate **2** in the reaction mixture through hydrogen bonding between the carboxylic acidic proton and the oxygen atom of $Ar_2P{=}O$ (**2**), thereby facilitating tautomeric conversion of **2** to **2′**. This less stable P(III) form **2′**, which thus generated from the P (V) form **2** *via* tautomerization in solution phase (DMSO),[15] then takes part in a nucleophilic attack at C-4 of coumarin nucleus through phosphorus (C–P σ-bond formation)[16] to give an adduct **4** (non-isolable) that in turn affords the desired product **3** through a rapid tautomerization, followed by decarboxylation (expulsion of CO_2 was detected during the gram-scale experiment) process.[17] To validate the role of the carboxylic acid group within the coumarin moiety, we performed a set of control experiments (Scheme 2, control experient-1) with unsubstituted coumarin **5** and coumarins substituted with other groups at the 3-position (*viz.* 3-cyanocoumarin **6**, 3-acetylcoumarin **7** and ethyl coumarin-3-carboxylate **8**), and in all these cases no reaction occurred under the optimized conditions. These observations support our presumption that the coumarin nucleus must bear a C_3–COOH group that plays a crucial role in initiating the reaction through hydrogen bonding.

It is thus evident from the mechanistic pathway that during the reaction, C-3 of coumarin-3-carboxylic acids (**1**) becomes saturated by adopting two hydrogen atoms, one from its –COOH group and another from the $Ar_2P(O)H$, not from the water used during work-up. In support of this proposition, we performed an isotope (deuterium)-labeling experiment (Scheme 2, isotope-labeling experiment 2): deuterated coumarin-3-carboxylic acid-*d* (**1a**–d_1; see Supporting Information) upon reaction with diphenylphosphine oxide-*d* (**2a**–d_1)[18] furnished 4-(diphenylphosphoryl)chroman-2-one-3,3-d_2 (**3a**–d_2) solely in similar yield (91%) compared to the normal entry (Table 3, entry 1, **3a**) but with a somewhat elongated time (50 min), as usually expected for deuterated-substrates. The deuterated product **3a**–d_2 was characterized based on ^{1}H-NMR and HRMS (experimental and Supporting Information). That this C-4 phosphorylation reaction follows an ionic path was furthermore documented by performing radical-scavenging experiments (experiment-3 as shown in Scheme 2) where none of the radical scavengers (*viz.* TEMP, BHT, *p*-benzoquinone) used could inhibit the reaction at all (see Supporting Information). The overall mechanistic aspects are shown in Scheme 2.

We checked the effectiveness of this catalyst- and additive-free protocol for a somewhat scaled-up (on the gram scale; 3 mmol scale; 30-fold enhancement) experiment with one representative entry (Table 3; entry 10); the large-scale reaction afforded the target product, 6,8-dibromo-4-(diphenylphosphoryl)chroman-2-one (**3j**), in 93% yield within 17 min (Scheme 3). It has been revealed that the large-scale reaction is almost

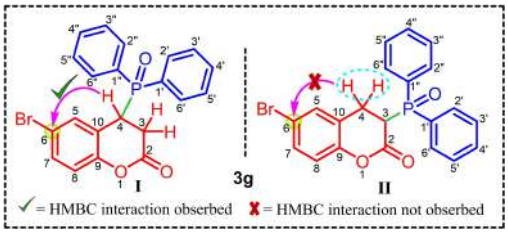
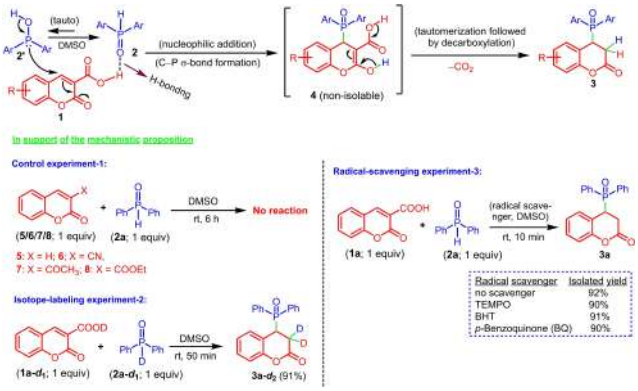


Figure 1. The key HMBC interaction in compound **3g**.



Scheme 2. Proposed mechanism of decarboxylative C-4 phosphorylation of coumarin-3-carboxylic acids.

Scheme 3. Representative gram-scale experiment (30-fold enhancement).

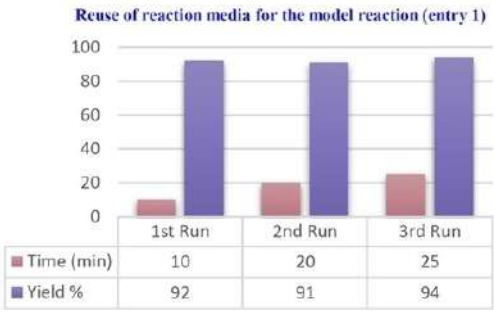


Figure 2. Reusability of reaction media (Table 3, entry 1).

similar to 0.1 mmol scale entry (Table 3, entry 10) in terms of respective yield and time.

Besides, the reaction media containing the residual reactants, solvent (DMSO), and certain portions of the product obtained upon filtration of the reaction mixture after the completion of the reaction, followed by removal of added water (during processing) on boiling at 110 °C for 1 h, was successfully reused up to the third run in the case of a representative entry (Table 3, entry 1), *viz.* reaction between coumarin-3-carboxylic acid and diphenylphosphine oxide. The desired product **3 a** was isolated in 92, 91 and 94% yields, respectively, almost similar to that from the first run, but the time frame was found to be elongated from 10 min (1st run) to 25 min (3rd run), thereby indicating in a gradual decrease in the efficiency of the reused solvent over further uses. The results are graphically represented in Figure 2.

Conclusions

In conclusion, we have accomplished a catalyst- and additive-free practical and green synthetic method to access a new series of 4-(diarylphosphoryl)chroman-2-ones *via* decarboxylative C-4 phosphorylation of coumarin-3-carboxylic acids just under ambient conditions. This is the first report on C-4 phosphorylation of coumarin derivatives by decarboxylation under green conditions. The use of no catalyst or additive, green and reusable reaction media, clean reaction profile, mild reaction conditions at room temperature, energy-efficiency, no column chromatography, thereby avoiding the use of toxic organic solvents, excellent regioselectivity, good to excellent yields within a short reaction time-frame, large-scale synthetic applicability, and high atom-economy and low E-factor are the notable features of this present protocol.

Experimental Section

General information. All chemicals (analytical grade) except starting coumarin-3-carboxylic acids were purchased from reputed companies and used without further purification. All the starting coumarin-3-carboxylic acids (**1 a**–**1 l**) used in this present study were synthesized as per the previous report from our laboratory.[1e] ^{1}H-, ^{13}C-, ^{31}P-NMR spectra were collected at 400, 100 and 162 MHz, respectively, on a Bruker DRX spectrometer using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts were reported in δ (ppm), relative to the internal standard, TMS. The signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants are reported as *J* value in Hz. Mass spectrometry was obtained using a Bruker maXis Impact (Q-TOF) high-resolution mass spectrometer. Elemental analyses were performed with a Perkin Elmer 2400 Series II elemental analyzer instrument. The melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. Thin Layer Chromatography (TLC) was performed using silica gel 60 F_{254} (Merck) plates.

General Procedure for the Synthesis of Functionalized 4-(Diarylphosphoryl)chroman-2-ones (3)

Coumarin-3-carboxylic acids (**1**; 0.10 mmol) and diarylphosphine oxide (**2**; 0.10 mmol) were carefully weighed into an oven-dried open glass-vessel equipped with a magnetic stirrer bar. Then dimethylsulfoxide (DMSO) (1.0 mL) was added to the mixture, and stirred in the open-air under ambient conditions for a stipulated time-frame (7 min to 2 h), with occasional TLC monitoring to judge the progress of the reaction. On completion of the reaction, 2 mL of water was added to the resulting mixture and shaken for a while when the product precipitated out and allowed to settle, and then filtered off using ordinary filter paper. Upon drying in the open-air, the desired products, 4-(diarylphosphoryl)chroman-2-ones **3** (**3 a**–**3 t**), were obtained as pure. The structures of the isolated products were confirmed by elemental analyses and detailed spectral studies including ^{1}H-NMR, ^{13}C-NMR, DEPT-135, ^{31}P-NMR, and HRMS (2D-NMR for one representative entry, **3 g**).

The physical and spectroscopic data of all the compounds **3** (**3 a**–**3 t** and **3 a**-d_2) are given below:

4-(Diphenylphosphoryl)chroman-2-one (3 a). Bright white amorphous solid; yield: 92% (32 mg; 0.1 mmol scale); Mp = 270 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 2H, Ar–H), 7.66–7.62 (m, 1H, Ar–H), 7.60–7.54 (m, 5H, Ar–H), 7.46–7.42 (m, 2H, Ar–H), 7.27–7.24 (m, 1H, Ar–H), 7.05–7.03 (m, 1H, Ar–H), 6.90–6.86 (m, 1H, Ar–H), 6.65–6.62 (m, 1H, Ar–H), 3.96–3.91 (m, 1H, –C*H*P), 3.25–3.19 (m, 1H, H_a of –CH_2CO–), 3.08–2.95 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02–7.97 (m, 2H, Ar–H), 7.75–7.69 (m, 2H, Ar–H), 7.68–7.60 (m, 3H, Ar–H), 7.58–7.54 (m, 1H, Ar–H), 7.49–7.45 (m, 2H, Ar–H), 7.24–7.21 (m, 1H, Ar–H), 7.06–7.04 (m, 1H, Ar–H), 6.85–6.81 (m, 1H, Ar–H), 6.64–6.62 (m, 1H, Ar–H), 4.65 (t, *J* = 6.8 Hz, 1H, –C*H*P), 2.56–2.53 (m, 1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.08 (d, J_{CP} = 4 Hz, lactone *C*O), 152.53 (d, J^{3}_{CP} = 4 Hz), 132.28 (d, J_{CP} = 15 Hz), 131.07 (2 C), 130.99 (2 C), 130.96 (d, J^{1}_{CP} = 93 Hz), 130.92, 130.65 (d, J^{1}_{CP} = 97 Hz), 129.50 (d, J_{CP} = 4 Hz), 129.15 (d, J_{CP} = 12 Hz, 2 C), 128.90, 128.54 (d, J_{CP} = 12 Hz, 2 C), 123.49, 117.99 (d, J_{CP} = 6 Hz), 116.82, 35.25 (d, J^{1}_{CP} = 65 Hz, *C*HP), 28.43 (*C*H_2CO) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 32.21 ppm. HRMS: *m/z* 349.0994 $[M+H]^+$ calcd for $C_{21}H_{17}O_3PH$, found: *m/z*

349.0988; *m/z* 387.0552 $[M+K]^+$ calcd for $C_{21}H_{17}O_3PK$, found: *m/z* 387.0548.

4-(Diphenylphosphoryl)-6-methylchroman-2-one (3 b). White amorphous solid; yield: 91% (33 mg; 0.1 mmol scale); Mp = 269 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03–7.98 (m, 2H, Ar–H), 7.69–7.61 (m, 5H, Ar–H), 7.59–7.55 (m, 1H, Ar–H), 7.49–7.46 (m, 2H, Ar–H), 7.03–7.01 (m, 1H, Ar–H), 6.94–6.92 (m, 1H, Ar–H), 6.33 (br s, 1H, Ar–H), 4.54–4.50 (m, 1H, –C*H*P), 2.56–2.52 (m, 1H, H_b of –CH_2CO–), 1.94 (s, 3H, Ar–CH_3) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.04 (lactone *C*O), 150.40 (d, J^3_{CP} = 4 Hz), 132.21 (d, J_{CP} = 2 Hz), 132.17 (dd, J_{CP} = 26, 3 and 2 Hz), 130.74 (d, J^1_{CP} = 94 Hz), 131.09 (2 C), 131.02 (d, J_{CP} = 2 Hz, 2 C), 130.95 (2 C), 130.68 (d, J^1_{CP} = 97 Hz), 129.96 (d, J_{CP} = 4 Hz), 129.06 (d, J_{CP} = 10 Hz, 2 C), 128.31 (d, J_{CP} = 12 Hz, 2 C), 117.43 (d, J_{CP} = 6 Hz), 116.33 (d, J_{CP} = 2 Hz), 35.41 (d, J^1_{CP} = 64 Hz, *C*HP), 28.40 (*C*H_2CO), 19.95 (Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.35 ppm. HRMS: *m/z* 363.1150 $[M+H]^+$ calcd for $C_{22}H_{19}O_3PH$, found: *m/z* 363.1150; *m/z* 385.0970 $[M+Na]^+$ calcd for $C_{21}H_{19}O_3PNa$; found: *m/z* 385.0981.

6-(*tert*-Butyl)-4-(diphenylphosphoryl)chroman-2-one (3 c). White amorphous solid; yield: 94% (38 mg; 0.1 mmol scale); Mp = 272 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.87 (m, 2H, Ar–H), 7.64–7.60 (m, 1H, Ar–H), 7.58–7.51 (m, 5H, Ar–H), 7.43–7.38 (m, 2H, Ar–H), 7.25–7.22 (m, 1H, Ar–H), 6.97–6.95 (m, 1H, Ar–H), 6.49–6.48 (m, 1H, Ar–H), 3.89–3.84 (m, 1H, –C*H*P), 3.22–3.15 (m, 1H, H_a of –CH_2CO–), 3.07–2.93 (m, 1H, H_b of –CH_2CO–), 1.01 (s, 9H, (CH_3)$_3$C) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.56–8.01 (m, 2H, Ar–H), 7.72–7.63 (m, 5H, Ar–H), 7.56–7.52 (m, 1H, Ar–H), 7.48–7.44 (m, 2H, Ar–H), 7.24–7.20 (m, 1H, Ar–H), 6.96 (d, 1H, *J* = 8.4 Hz, Ar–H), 6.58–6.57 (m, 1H, Ar–H), 4.58 (t, 1H, *J* = 6.8 Hz, –C*H*P), 2.56–2.52 (m, 1H, H_b of –CH_2CO–), 0.94 (s, 9H, (CH_3)$_3$C) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.16 (lactone *C*O), 150.29 (d, J^3_{CP} = 4 Hz), 145.63 (d, J_{CP} = 2 Hz), 132.14 (d, J_{CP} = 36 Hz), 131.16 (2 C), 131.06 (d, J_{CP} = 3 Hz, 2 C), 130.85 (d, J^1_{CP} = 91 Hz), 130.81 (d, J^1_{CP} = 98 Hz), 130.95 (2 C), 129.13 (d, J_{CP} = 10 Hz, 2 C), 128.41 (d, J_{CP} = 12 Hz), 126.6 (d, J_{CP} = 4 Hz), 125.61 (d, J_{CP} = 2 Hz), 116.74 (d, J_{CP} = 6 Hz), 116.08 (d, J_{CP} = 3 Hz), 35.63 (d, J^1_{CP} = 66 Hz, *C*HP), 33.76 (*C*(CH$_3$)$_3$), 30.81 (C(*C*H$_3$)$_3$, 3 C), 28.36 (*C*H$_2$CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.55 ppm. HRMS: *m/z* 405.1620 $[M+H]^+$ calcd for $C_{25}H_{25}O_3PH$, found: *m/z* 405.1616; *m/z* 427.1439 $[M+Na]^+$ calcd for $C_{25}H_{25}O_3PNa$, found: *m/z* 427.1215; *m/z* 443.1178 $[M+K]^+$ calcd for $C_{25}H_{25}O_3PK$, found: *m/z* 443.1166.

4-(Diphenylphosphoryl)-7-hydroxychroman-2-one (3 d). White amorphous powder; yield: 96% (35 mg; 0.1 mmol scale); Mp = 255 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (br s, 1H, –OH), 7.87–7.82 (m, 2H, Ar–H), 7.67–7.61 (m, 3H, Ar–H), 7.59–7.55 (m, 3H, Ar–H), 7.51–7.46 (m, 2H, Ar–H), 6.50 (br s, 1H, Ar–H), 6.43–6.38 (m, 2H, Ar–H), 3.87–3.83 (m, 1H, –C*H*P), 3.04–3.01 (m, 1H, H_a of –CH_2CO–), 2.98–2.96 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.75 (br s, 1H, –OH), 7.99–7.94 (m, 2H, Ar–H), 7.74–7.69 (m, 2H, Ar–H), 7.66–7.58 (m, 3H, Ar–H), 7.57–7.53 (m, 1H, Ar–H), 7.49–7.45 (m, 2H, Ar–H), 6.42–6.39 (m, 2H, Ar–H), 6.22 (dd, 1H, *J* = 8.4, 2.4, 2.0 Hz, Ar–H), 4.48 (t, 1H, *J* = 6.4 Hz, –C*H*P), 3.29–3.19 (m, 1H, H_a of –CH_2CO–), 2.54–2.53 (m, 1H, H_b of –CH_2CO–) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.09 (lactone *C*O, d, J^3_{CP} = 2 Hz), 157.82 (d, J^5_{CP} = 3 Hz), 153.19 (d, J^3_{CP} = 4 Hz), 132.08 (d, J_{CP} = 15 Hz), 131.27 (d, J^1_{CP} = 85 Hz), 131.04 (2 C), 130.94 (2 C), 130.93 (d, J^1_{CP} = 97 Hz), 130.84 (2 C), 129.98 (d, J_{CP} = 4 Hz, 2 C), 129.02 (d, J_{CP} = 11 Hz), 128.43 (d, J_{CP} = 12 Hz), 110.82 (d, J_{CP} = 3 Hz), 107.56 (d, J_{CP} = 6 Hz), 103.56, 34.48 (d, J^1_{CP} = 66 Hz, *C*HP), 28.68 (*C*H$_2$CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.01 ppm. HRMS: *m/z* 365.0943 $[M+H]^+$ calcd for $C_{21}H_{17}O_4PH$, found: *m/z* 365.0941; *m/z* 387.0762 $[M+Na]^+$ calcd for $C_{21}H_{17}O_4PNa$, found: *m/z* 387.0766.

4-(Diphenylphosphoryl)-6-methoxychroman-2-one (3 e). White amorphous solid; yield: 93% (35 mg; 0.1 mmol scale); Mp = 281 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.81 (m, 2H, Ar–H), 7.63–7.51 (m, 6H, Ar–H), 7.45–7.40 (m, 2H, Ar–H), 6.56–6.55 (m, 1H, Ar–H), 6.51–6.48 (m, 1H, Ar–H), 6.43–6.40 (m, 1H, Ar–H), 3.88–3.79 (m, 1H, –C*H*P), 3.76 (s, 3H, Ar–OCH_3), 3.20–3.13 (m, 1H, H_a of –CH_2CO–), 3.03–2.89 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03–7.98 (m, 2H, Ar–H), 7.75–7.70 (m, 2H, Ar–H), 7.67–7.61 (m, 3H, Ar–H), 7.59–7.55 (m, 1H, Ar–H), 7.51–7.47 (m, 2H, Ar–H), 6.99–6.97 (m, 1H, Ar–H), 6.79–6.76 (m, 1H, Ar–H), 6.14–6.13 (m, 1H, Ar–H), 4.59–4.55 (m, 1H, –C*H*P), 3.36 (s, 3H, Ar–OCH_3), 2.55–2.53 (m, 1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.06 (d, J^3_{CP} = 3 Hz, lactone *C*O), 159.58, 154.64 (d, J^3_{CP} = 3 Hz), 132.31 (d, J_{CP} = 2 Hz), 132.08 (d, J_{CP} = 2 Hz), 131.09 (d, J_{CP} = 9 Hz, 2 C), 130.94 (d, J_{CP} = 9 Hz, 2 C), 130.82 (d, J^1_{CP} = 93 Hz), 130.72 (d, J^1_{CP} = 97 Hz), 129.09 (d, J_{CP} = 10 Hz, 2 C), 128.46 (d, J_{CP} = 11 Hz, 2 C), 118.58 (d, J_{CP} = 6 Hz), 117.45, 114.73, 113.85 (d, J_{CP} = 5 Hz), 55.09 (Ar–O*C*H$_3$), 35.59 (d, J^1_{CP} = 65 Hz, *C*HP), 28.21 (*C*H$_2$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.20 ppm. HRMS: *m/z* 378.1021 $[M]^+$ calcd for $C_{22}H_{19}O_4P$, found: *m/z* 378.0150.

4-(Diphenylphosphoryl)-7-methoxychroman-2-one (3 f). White amorphous solid; yield: 85% (32 mg; 0.1 mmol scale); Mp = 251 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.83 (m, 2H, Ar–H), 7.64–7.53 (m, 6H, Ar–H), 7.46–7.41 (m, 2H, Ar–H), 6.94–6.92 (m, 1H, Ar–H), 6.79–6.75 (m, 1H, Ar–H), 6.06–6.05 (m, 1H, Ar–H), 3.89–3.84 (m, 1H, –C*H*P), 3.45 (s, 3H, Ar–OCH_3), 3.23–3.16 (m, 1H, H_a of –CH_2CO–), 3.04–2.89 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.00–7.95 (m, 2H, Ar–H), 7.76–7.71 (m, 2H, Ar–H), 7.65–7.59 (m, 3H, Ar–H), 7.55–7.53 (m, 1H, Ar–H), 7.49–7.45 (m, 2H, Ar–H), 6.66 (d, 1H, *J* = 2.4 Hz, Ar–H), 6.54–6.52 (m, 1H, Ar–H), 6.44–6.41 (m, 1H, Ar–H), 4.58–4.54 (m, 1H, –C*H*P), 3.69 (s, 3H, Ar–OCH_3), 3.33–3.23 (m, 1H, H_a of –CH_2CO–), 2.55–2.52 (m, 1H, H_b of –CH_2CO–) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.97 (lactone *C*O, d, J_{CP} = 3 Hz), 159.60 (d, J^5_{CP} = 2 Hz), 153.36 (d, J^3_{CP} = 5 Hz), 132.14 (dd, J_{CP} = 11 and 2 Hz), 131.14 (d, J^1_{CP} = 92 Hz), 131.02, 130.92 (2 C), 130.82 (2 C), 130.82 (d, J^1_{CP} = 97 Hz), 129.97 (d, J_{CP} = 3 Hz), 129.04 (d, J_{CP} = 10 Hz, 2 C), 128.48 (d, J_{CP} = 11 Hz, 2 C), 109.74 (d, J_{CP} = 3 Hz), 109.40 (d, J_{CP} = 6 Hz), 102.25, 55.43 (Ar–O*C*H$_3$), 34.49 (d, J^1_{CP} = 66 Hz, *C*HP), 28.57 (d, J^2_{CP} = 2 Hz, *C*H$_2$CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6):

δ 32.05 ppm. HRMS: *m/z* 401.0919 $[M+Na]^+$ calcd for $C_{22}H_{19}O_4PNa$; Found: *m/z* 401.0927.

6-Bromo-4-(diphenylphosphoryl)chroman-2-one (3 g). White amorphous solid; yield: 94% (40 mg; 0.1 mmol scale); Mp = 289 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.85 (m, 2H, Ar–H), 7.67–7.63 (m, 1H, Ar–H), 7.60–7.53 (m, 5H, Ar–H), 7.48–7.43 (m, 2H, Ar–H), 7.36–7.33 (m, 1H, Ar–H), 6.93–6.91 (m, 1H, Ar–H), 6.61–6.60 (m, 1H, Ar–H), 3.83–3.78 (m, 1H, –C*H*P), 3.18–3.11 (m, 1H, H_a of –CH_2CO–), 3.04–2.90 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02–7.97 (m, 2H, Ar–H), 7.71–7.63 (m, 5H, Ar–H), 7.61–7.57 (m, 1H, Ar–H), 7.52–7.48 (m, 2H, Ar–H), 7.41–7.38 (m, 1H, Ar–H), 7.04 (d, 1H, *J* = 8.8 Hz, Ar–H), 6.72–6.71 (m, 1H, Ar–H), 4.64–4.60 (m, 1H, –C*H*P), 2.57–2.52 (m, 1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.40 (lactone *C*O), 151.72 (d, J^3_{CP} = 7 Hz), 132.48, 132.16 (dd, J_{CP} = 26, 4 and 2 Hz), 131.39 (d, J_{CP} = 2 Hz), 131.02 (2 C), 130.94 (2 C), 130.23 (d, J_{CP} = 94 Hz), 130.17 (d, J_{CP} = 97 Hz), 129.16 (d, J_{CP} = 11 Hz, 2 C), 128.47 (d, J_{CP} = 12 Hz, 2 C), 120.48 (d, J_{CP} = 6 Hz), 118.79 (d, J_{CP} = 3 Hz, 2 C), 114.88 (d, J_{CP} = 2 Hz), 35.39 (d, J^1_{CP} = 65 Hz, *C*HP), 27.94 (*C*H_2CO) ppm. 2D-NMR: Selected HMQC interactions at δ 3.18–3.11 (m, H_a of –CH_2CO–, merged with DMSO-d_6 water peak) *vs* δ 27.94 (*C*H_2CO), δ 2.57–2.52 (m, H_b of –CH_2CO–) *vs* δ 27.94 (*C*H_2CO), δ 4.64–4.60 (–C*H*P–) *vs* δ 35.39 (*C*HP); HMBC interaction (selected) at δ 4.64–4.60 (–C*H*P–) *vs* δ 120.48 (C-6). ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.63 ppm. HRMS: *m/z* 427.0099 $[M+H]^+$ calcd for $C_{21}H_{16}BrO_3PH$; found: *m/z* 427.0097; *m/z* 448.9918 $[M+Na]^+$ calcd for $C_{21}H_{16}BrO_3PNa$; found: *m/z* 448.9882.

6-Chloro-4-(diphenylphosphoryl)chroman-2-one (3 h). White amorphous solid; yield: 94% (36 mg; 0.1 mmol scale); Mp = 283 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 2H, Ar–H), 7.66–7.63 (m, 1H, Ar–H), 7.59–7.54 (m, 5H, Ar–H), 7.48–7.42 (m, 2H, Ar–H), 7.21–7.18 (m, 1H, Ar–H), 6.98–6.96 (m, 1H, Ar–H), 6.49–6.48 (m, 1H, Ar–H), 3.85–3.80 (m, 1H, –C*H*P), 3.18–3.11 (m, 1H, H_a of –CH_2CO–), 3.04–2.90 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02–7.97 (m, 2H, Ar–H), 7.69–7.59 (m, 6H, Ar–H), 7.49 (br s, 2H, Ar–H), 7.29–7.27 (m, 1H, Ar–H), 7.10–7.08 (m, 1H, Ar–H), 6.59 (br s, 1H, Ar–H), 4.64–4.61 (m, 1H, –C*H*P), 2.57–2.54 (m, 1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.45 (lactone *C*O), 155.65, 132.67, 132.48, 132.31, 131.19 (d, J_{CP} = 8 Hz), 131.02 (2 C), 130.94 (2 C), 130.69 (d, J_{CP} = 8 Hz), 129.22 (2 C), 129.09 (d, J_{CP} = 5 Hz, 2 C), 128.51 (d, J_{CP} = 10 Hz, 2 C), 118.44, 102.03 (d, J_{CP} = 54 Hz), 35.42 (d, J^1_{CP} = 64 Hz, *C*HP), 27.94 (*C*H_2CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.56 ppm. HRMS: *m/z* 383.0604 $[M+H]^+$ calcd for $C_{21}H_{16}ClO_3PH$, found: *m/z* 383.0617; *m/z* 405.0423 $[M+Na]^+$ calcd for $C_{21}H_{16}ClO_3PNa$; found: *m/z* 405.0437; *m/z* 421.0163 $[M+K]^+$ calcd for $C_{21}H_{16}ClO_3PNK$; found: *m/z* 421.0175.

4-(Diphenylphosphoryl)-6-nitrochroman-2-one (3 i). Pale yellow amorphous solid; yield: 84% (33 mg; 0.1 mmol scale); Mp = 288 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12–8.09 (m, 1H, Ar–H), 8.06–8.01 (m, 2H, Ar–H), 7.71–7.65 (m, 4H, Ar–H), 7.57–7.53 (m, 2H, Ar–H), 7.48–7.45 (m, 3H, Ar–H), 7.33–7.31 (m, 1H, Ar–H), 4.85–4.81 (m, 1H, –C*H*P), 2.64–2.58 (m, 1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.76 (lactone *C*O), 157.12, 142.53 (d, J_{CP} = 19 Hz), 132.53 (d, J_{CP} = 23 Hz), 131.08, 130.98 (2 C), 130.88, 129.76 (d, J^1_{CP} = 104 Hz), 129.23 (d, J_{CP} = 11 Hz, 2 C), 129.73 (d, J_{CP} = 97 Hz), 128.91, 128.53 (d, J_{CP} = 12 Hz, 2 C), 125.16 (d, J_{CP} = 5 Hz), 124.54, 119.61 (d, J_{CP} = 6 Hz), 117.93 (d, J_{CP} = 1 Hz), 35.52 (d, J^1_{CP} = 64 Hz, *C*HP), 27.62 (*C*H_2CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 33.10 ppm. HRMS: *m/z* 416.0664 $[M+Na]^+$ calcd for $C_{21}H_{16}NO_5PNa$; found: *m/z* 416.0759.

6,8-Dibromo-4-(diphenylphosphoryl)chroman-2-one (3 j). White amorphous solid; yield: 95% (48 mg; 0.1 mmol scale); Mp = 239–341 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.83 (m, 2H, Ar–H), 7.68–7.64 (m, 1H, Ar–H), 7.62–7.58 (m, 4H, Ar–H), 7.56–7.53 (m, 2H, Ar–H), 7.49–7.47 (m, 2H, Ar–H), 6.55–6.54 (m, 1H, Ar–H), 3.84–3.79 (m, 1H, –C*H*P), 3.17–3.11 (m, 1H, H_a of –CH_2CO–), 3.04–2.90 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03–7.97 (m, 2H, Ar–H), 7.78–7.77 (m, 1H, Ar–H), 7.70–7.66 (m, 5H, Ar–H), 7.59–7.58 (m, 1H, Ar–H), 7.53–7.48 (m, 2H, Ar–H), 6.71–6.70 (m, 1H, Ar–H), 4.69–4.66 (m, 1H, –C*H*P), 2.57–2.53 (m, 1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.69 (d, J^3_{CP} = 3 Hz, lactone *C*O), 148.75 (d, J^3_{CP} = 4 Hz), 133.89 (d, J_{CP} = 3 Hz), 132.58, 132.40 (d, J_{CP} = 2 Hz), 131.55 (d, J_{CP} = 5 Hz), 131.03 (d, J_{CP} = 3 Hz, 2 C), 130.93 (2 C), 129.88 (d, J^1_{CP} = 93 Hz), 129.82 (d, J^1_{CP} = 98 Hz), 129.20 (d, J_{CP} = 12 Hz, 2 C), 128.52 (d, J_{CP} = 12 Hz, 2 C), 122.09 (d, J_{CP} = 5 Hz), 114.95 (d, J_{CP} = 4 Hz), 110.85 (d, J^3_{CP} = 3 Hz), 35.90 (d, J^1_{CP} = 64 Hz, *C*HP), 27.79 (d, J^3_{CP} = 2 Hz, *C*H_2CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.98 ppm. HRMS: *m/z* 526.9023 $[M+Na]^+$ calcd for $C_{21}H_{15}Br_2O_3PNa$, found: *m/z* 526.9013 $[M+Na]^+$, 528.8996 $[M+2+Na]+$ and 530.8978 $[M+4+Na]^+$.

6,8-Dichloro-4-(diphenylphosphoryl)chroman-2-one (3 k). White amorphous solid; yield: 96% (40 mg; 0.1 mmol scale); Mp = 274 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 2H, Ar–H), 7.68–7.64 (m, 1H, Ar–H), 7.62–7.55 (m, 5H, Ar–H), 7.49–7.45 (m, 2H, Ar–H), 7.32–7.31 (m, 1H, Ar–H), 6.39–6.38 (m, 1H, Ar–H), 3.86–3.81 (m, 1H, –C*H*P), 3.18–3.11 (m, 1H, H_a of –CH_2CO–), 3.04–2.91 (m, 1H, H_b of –CH_2CO–) ppm. ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.02–7.98 (m, 2H, Ar–H), 7.72–7.65 (m, 5H, Ar–H), 7.59–7.57 (m, 2H, Ar–H), 7.53–7.48 (m, 2H, Ar–H), 6.57–6.56 (m, 1H, Ar–H), 4.70 (t, 1H, *J* = 6.8 Hz, –C*H*P), 2.59–2.54 (m, 1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.56 (lactone *C*O), 147.30 (d, J^3_{CP} = 4 Hz), 132.49 (d, J_{CP} = 17 Hz), 131.01 (2 C), 130.93 (2 C), 129.88 (d, J^1_{CP} = 94 Hz), 129.83 (d, J^1_{CP} = 98 Hz), 129.52, 129.20 (d, J_{CP} = 12 Hz, 2 C), 128.54 (d, J_{CP} = 12 Hz, 2 C), 128.56 (d, J_{CP} = 3 Hz), 128.00 (d, J_{CP} = 4 Hz), 126.97 (d, J_{CP} = 2 Hz), 121.84 (d, J_{CP} = 5 Hz), 121.38, 35.91 (d, J^1_{CP} = 63 Hz, *C*HP), 27.70 (*C*H_2CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.76 ppm. HRMS: *m/z* 417.0214 $[M+H]^+$ calcd for $C_{21}H_{15}Cl_2O_3PH$, found: *m/z* 417.0219; *m/z* 439.0034 $[M+Na]^+$ calcd for $C_{21}H_{15}Cl_2O_3PNa$; found: *m/z* 439.0046.

1-(Diphenylphosphoryl)-1*H*-benzo[*f*]chromen-3(2*H*)-one (3l). White amorphous solid; yield: 95% (38 mg; 0.1 mmol scale); Mp = 270 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19–8.15 (m, 2H, Ar–H), 7.89 (d, 1H, J = 8.8 Hz, Ar–H), 7.78–7.68 (m, 4H, Ar–H), 7.48 (d, 1H, J = 8.4 Hz, Ar–H), 7.32 (d, 1H, J = 8.8 Hz, Ar–H), 7.27–7.18 (m, 4H, Ar–H), 7.09–7.05 (m, 2H, Ar–H), 7.03–6.99 (m, 1H, Ar–H), 5.10–5.08 (m, 1H, –C*H*P), 2.73–2.67 (m,1H, H_b of –CH_2CO–) ppm (*signal for H_a proton of –CH_2CO– is merged with DMSO-d_6 water peak*). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.19 (d, J^3_{CP} = 2 Hz, lactone *C*O), 150.70 (d, J^3_{CP} = 6 Hz), 132.55, 131.83, 131.58 (d, J^3_{CP} = 9 Hz), 130.99 (d, J^3_{CP} = 9 Hz), 130.78 (d, J^3_{CP} = 97 Hz), 130.76 (d, J^3_{CP} = 101 Hz), 130.69 (d, J^3_{CP} = 3 Hz), 129.95, 129.80 (d, J_{CP} = 2 Hz), 129.14 (d, J_{CP} = 11 Hz, 2 C), 127.94 (2 C), 127.83 (2 C), 125.84, 124.41, 123.86, 122.14, 117.32 (d, J_{CP} = 2 Hz), 111.57 (d, J_{CP} = 7 Hz), 32.76 (d, J^1_{CP} = 64 Hz, *C*HP), 29.26 (*C*H_2CO) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.66 ppm. HRMS: *m/z* 399.1150 $[M+H]^+$ calcd for $C_{25}H_{19}O_3PH$, found: *m/z* 399.1142; *m/z* 421.0970 $[M+Na]^+$ calcd for $C_{25}H_{19}O_3PNa$; found: *m/z* 421.1083.

4-(Di-*p*-tolylphosphoryl)chroman-2-one (3m).[12a] White amorphous powder; yield: 90% (34 mg; 0.1 mmol scale); Mp = 265–268 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 2H, Ar–H), 7.43–7.38 (m, 2H, Ar–H), 7.33–7.31 (m, 2H, Ar–H), 7.23–7.19 (m, 3H, Ar–H), 7.00–6.98 (m, 1H, Ar–H), 6.89–6.86 (m, 1H, Ar–H), 6.85–6.65 (m, 1H, Ar–H), 3.91–3.85 (m, 1H, –C*H*P), 3.24–3.17 (m, 1H, H_a of –CH_2CO–), 3.02–2.89 (m, 1H, H_b of –CH_2CO–), 2.42 (s, 3H, Ar–CH_3), 2.38 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.06 (d, J^3_{CP} = 3 Hz, lactone *C*O), 152.45 (d, J^3_{CP} = 5 Hz), 142.27, 142.03 (d, J_{CP} = 3 Hz), 130.98 (d, J_{CP} = 10 Hz), 130.93 (2 C), 130.88 (d, J_{CP} = 10 Hz), 129.62 (d, J_{CP} = 11 Hz, 2 C), 129.50 (d, J_{CP} = 4 Hz), 129.03 (d, J_{CP} = 12 Hz, 2 C), 128.71 (d, J_{CP} = 2 Hz), 127.94 (d, J_{CP} = 96 Hz), 127.60 (d, J_{CP} = 100 Hz), 123.44, 118.22 (d, J_{CP} = 6 Hz), 116.72 (d, J_{CP} = 3 Hz), 35.34 (d, J^1_{CP} = 65 Hz, *C*HP), 28.43 (*C*H_2CO), 21.08 (Ar–*C*H_3, 2 C) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 32.50 ppm. Elemental analysis: calcd (%) for $C_{23}H_{21}O_3P$: C, 73.40; H, 5.62; Found: C, 73.48; H, 5.69.

4-(di-*p*-tolylphosphoryl)-6-methylchroman-2-one (3n).[12a] White amorphous solid; yield: 92% (36 mg; 0.1 mmol scale); Mp = 274–276 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 2H, Ar–H), 7.42–7.37 (m, 2H, Ar–H), 7.33–7.31 (m, 2H, Ar–H), 7.22–7.19 (m, 2H, Ar–H), 7.02–7.00 (m, 1H, Ar–H), 6.88–6.86 (m, 1H, Ar–H), 6.37 (br s, 1H, Ar–H), 3.82–3.77 (m, 1H, –C*H*P), 3.20–3.14 (m, 1H, H_a of –CH_2CO–), 3.00–2.87 (m, 1H, H_b of –CH_2CO–), 2.42 (s, 3H, Ar–CH_3), 2.83 (s, 3H, Ar–CH_3), 2.07 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.05 (d, J^3_{CP} = 3 Hz, lactone *C*O), 150.49 (d, J^3_{CP} = 5 Hz), 143.21 (d, J_{CP} = 3 Hz, 2 C), 133.49 (d, J_{CP} = 3 Hz), 131.94 (d, J_{CP} = 9 Hz, 2 C), 131.71 (d, J_{CP} = 8 Hz, 2 C), 130.14 (d, J_{CP} = 4 Hz), 129.83, 129.72 (d, J_{CP} = 12 Hz, 2 C), 129.27 (d, J_{CP} = 12 Hz, 2 C), 126.45 (d, J^1_{CP} = 99 Hz), 125.58 (d, J^1_{CP} = 100 Hz), 117.23 (d, J_{CP} = 2 Hz), 116.95 (d, J_{CP} = 4 Hz), 38.08 (d, J^1_{CP} = 65 Hz, *C*HP), 28.93 (*C*H_2CO), 21.76 (2 C, Ar–*C*H_3), 20.64 (Ar–CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.75 ppm. Elemental analysis: calcd (%) for $C_{24}H_{23}O_3P$: C, 73.83; H, 5.94; Found: C, 73.91; H, 5.98.

4-(Di-*p*-tolylphosphoryl)-7-hydroxychroman-2-one (3o). White amorphous powder; yield: 87% (34 mg; 0.1 mmol scale); Mp = 278–279 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.67 (m, 2H, Ar–H), 7.52–7.48 (m, 2H, Ar–H), 7.36–7.34 (m, 2H, Ar–H), 7.29–7.27 (m, 2H, Ar–H), 6.49–6.48 (m, 1H, Ar–H), 6.46–6.39 (m, 2H, Ar–H), 3.81–3.77 (m, 1H, –C*H*P), 3.01–2.99 (m, 1H, H_a of –CH_2CO–), 2.95–2.93 (m, 1H, H_b of –CH_2CO–), 2.43 (s, 3H, Ar–CH_3), 2.41 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.27 (lactone *C*O, d, J^3_{CP} = 3 Hz), 157.77, 153.19 (d, J^3_{CP} = 4 Hz), 142.20 (d, J_{CP} = 2 Hz), 141.97 (d, J_{CP} = 4 Hz), 131.05 (d, J_{CP} = 10 Hz, 2 C), 130.90 (d, J_{CP} = 8 Hz, 2 C), 130.10 (d, J_{CP} = 2 Hz), 129.64 (d, J_{CP} = 11 Hz, 2 C), 129.07 (d, J_{CP} = 12 Hz, 2 C), 128.26 (d, J^1_{CP} = 93 Hz), 127.90 (d, J^1_{CP} = 98 Hz), 110.89, 107.83, 103.57, 34.56 (d, J^1_{CP} = 64 Hz, *C*HP), 28.73 (*C*H_2CO), 21.15 (2 C, Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 29.19 ppm. Elemental analysis: calcd (%) for $C_{23}H_{21}O_4P$: C, 70.40; H, 5.39; Found: C, 70.51; H, 5.42.

4-(Di-*p*-tolylphosphoryl)-7-methoxychroman-2-one (3p). White amorphous solid; yield: 91% (37 mg; 0.1 mmol scale); Mp = 237–238 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 2H, Ar–H), 7.45–7.40 (m, 2H, Ar–H), 7.33–7.30 (m, 2H, Ar–H), 7.23–7.20 (m, 2H, Ar–H), 6.55–6.53 (m, 2H, Ar–H), 6.45–6.42 (m, 1H, Ar–H), 3.85–3.79 (m, 1H, –C*H*P), 3.76 (s, 3H, Ar–OCH_3), 3.21–3.14 (m, 1H, H_a of –CH_2CO–), 3.00–2.86 (m, 1H, H_b of –CH_2CO–), 2.42 (s, 3H, Ar–CH_3), 2.39 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.81 (d, J^3_{CP} = 2 Hz, lactone *C*O), 160.39 (d, J^3_{CP} = 3 Hz), 153.48 (d, J^3_{CP} = 4 Hz), 143.18, 131.91 (d, J^2_{CP} = 9 Hz, 2 C), 131.62 (d, J^2_{CP} = 9 Hz, 2 C), 130.40 (d, J_{CP} = 4 Hz, 2 C), 129.77 (d, J_{CP} = 12 Hz, 2 C), 129.39 (d, J_{CP} = 13 Hz, 2 C), 126.65 (d, J^1_{CP} = 116 Hz), 125.66 (d, J^1_{CP} = 117 Hz), 110.58 (d, J_{CP} = 3 Hz), 108.99 (d, J_{CP} = 4 Hz), 102.75 (d, J_{CP} = 2 Hz), 55.62 (Ar–OCH_3), 37.16 (d, J^1_{CP} = 67 Hz, *C*HP), 29.01 (*C*H_2CO), 21.79 (Ar–*C*H_3, 2 C) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.66 ppm. Elemental analysis: calcd (%) for $C_{24}H_{23}O_4P$: C, 70.93; H, 5.70; Found: C, 70.99; H, 5.78.

6-Bromo-4-(di-*p*-tolylphosphoryl)chroman-2-one (3q). White amorphous solid; yield: 92% (42 mg; 0.1 mmol scale); Mp = 285–286 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.69 (m, 2H, Ar–H), 7.42–7.30 (m, 5H, Ar–H), 7.24–7.22 (m, 2H, Ar–H), 6.88 (d, 1H, J = 8.8 Hz, Ar–H), 6.59 (br s, 1H, Ar–H), 3.80–3.76 (m, 1H, –C*H*P), 3.16–3.09 (m, 1H, H_a of –CH_2CO–), 3.01–2.87 (m, 1H, H_b of –CH_2CO–), 2.44 (s, 3H, Ar–CH_3), 2.39 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.08 (lactone *C*O), 151.74 (d, J^3_{CP} = 5 Hz), 143.59, 132.34 (d, J_{CP} = 3 Hz), 132.13 (d, J_{CP} = 2 Hz), 131.72 (d, J_{CP} = 8 Hz, 2 C), 131.64 (d, J_{CP} = 8 Hz, 2 C), 129.96 (d, J_{CP} = 12 Hz, 2 C), 129.49 (d, J_{CP} = 13 Hz, 2 C), 125.89 (d, J^1_{CP} = 99 Hz), 125.39 (d, J^1_{CP} = 102 Hz), 119.66 (d, J_{CP} = 5 Hz), 119.21 (2 C), 116.32, (d, J_{CP} = 5 Hz), 38.15 (d, J^1_{CP} = 64 Hz, *C*HP), 28.60 (*C*H_2CO), 21.78 (2 C, Ar–CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.98 ppm. Elemental analysis: calcd (%) for $C_{23}H_{20}BrO_3P$: C, 60.68; H, 4.43; Found: C, 60.74; H, 4.46.

6-Chloro-4-(di-*p*-tolylphosphoryl)chroman-2-one (3r). White amorphous solid; yield: 90% (37 mg; 0.1 mmol scale); Mp = 287–288 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.69 (m, 2H, Ar–H), 7.44–7.34 (m, 4H, Ar–H), 7.26–7.22 (m, 2H, Ar–H), 7.19–7.16 (m, 1H, Ar–H), 6.94 (d, 1H, J = 8.8 Hz,

Ar–H), 6.51–6.49 (m, 1H, Ar–H), 3.81–3.77 (m, 1H, –C*H*P), 3.17–3.10 (m, 1H, H_a of –CH_2CO–), 3.01–2.87 (m, 1H, H_b of –CH_2CO–), 2.44 (s, 3H, Ar–CH_3), 2.39 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.18 (d, J = 2 Hz, lactone *C*O), 151.19 (d, J^3_{CP} = 4 Hz), 143.57 (d, J = 2 Hz, 2 C), 131.72 (d, J_{CP} = 9 Hz, 2 C), 131.63 (d, J_{CP} = 9 Hz, 2 C), 129.95 (d, J_{CP} = 12 Hz, 2 C), 129.50 (d, J_{CP} = 12 Hz, 2 C), 129.37 (d, J_{CP} = 4 Hz), 129.24 (d, J_{CP} = 3 Hz), 128.94 (d, J_{CP} = 5 Hz), 125.94 (d, J^l_{CP} = 99 Hz), 125.36 (d, J^l_{CP} = 100 Hz), 119.27 (d, J_{CP} = 5 Hz), 118.87 (d, J_{CP} = 4 Hz), 38.08 (d, J^1_{CP} = 64 Hz, *C*HP), 28.60 (d, J^2_{CP} = 2 Hz, *C*H_2CO), 21.78 (2 C, Ar–CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.88 ppm. Elemental analysis: calcd (%) for $C_{23}H_{20}ClO_3P$: C, 67.24; H, 4.91; Found: C, 67.31; H, 4.99.

6,8-Dibromo-4-(di-*p*-tolylphosphoryl)chroman-2-one (3 s). White amorphous solid; yield: 92% (49 mg; 0.1 mmol scale); Mp = 277–278 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.68 (m, 2H, Ar–H), 7.59–7.58 (m, 1H, Ar–H), 7.43–7.31 (m, 2H, Ar–H), 7.38–7.35 (m, 3H, Ar–H), 7.24–7.23 (m, 1H, Ar–H), 6.54–6.53 (m, 1H, Ar–H), 3.80–3.76 (m, 1H, –C*H*P), 3.16–3.09 (m, 1H, H_a of –CH_2CO–), 3.01–2.88 (m, 1H, H_b of –CH_2CO–), 2.44 (s, 3H, Ar–CH_3), 2.41 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.97 (d, J_{CP} = 3 Hz, lactone *C*O), 148.93 (d, J^3_{CP} = 3 Hz), 143.79 (d, J^3_{CP} = 3 Hz), 135.25 (d, J_{CP} = 3 Hz, 2 C), 131.72 (d, J_{CP} = 10 Hz, 2 C), 131.63 (d, J_{CP} = 9 Hz, 2 C), 131.43 (d, J_{CP} = 5 Hz), 130.05 (d, J_{CP} = 12 Hz, 2 C), 129.58 (d, J_{CP} = 12 Hz, 2 C), 125.50 (d, J^l_{CP} = 100 Hz), 125.07 (d, J^l_{CP} = 101 Hz), 121.09 (d, J_{CP} = 5 Hz), 116.13 (d, J_{CP} = 2 Hz), 112.21 (d, J_{CP} = 3 Hz), 38.66 (d, J^1_{CP} = 64 Hz, *C*HP), 28.60 (*C*H_2CO), 21.80 (2 C, Ar–CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 32.18 ppm. Elemental analysis: calcd (%) for $C_{23}H_{19}Br_2O_3P$: C, 51.71; H, 3.59; Found: C, 51.79; H, 3.61.

6,8-Dichloro-4-(di-*p*-tolylphosphoryl)chroman-2-one (3 t). White amorphous solid; yield: 94% (42 mg; 0.1 mmol scale); Mp = 281–282 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.69 (m, 2H, Ar–H), 7.45–7.40 (m, 2H, Ar–H), 7.37–7.35 (m, 3H, Ar–H), 7.30–7.29 (m, 1H, Ar–H), 7.25–7.24 (m, 1H, Ar–H), 6.41–6.40 (m, 1H, Ar–H), 3.83–3.78 (m, 1H, –C*H*P), 3.18–3.11 (m, 1H, H_a of –CH_2CO–), 3.01–2.88 (m, 1H, H_b of –CH_2CO–), 2.44 (s, 3H, Ar–CH_3), 2.41 (s, 3H, Ar–CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.94 (d, J_{CP} = 3 Hz, lactone *C*O), 143.78 (d, J^3_{CP} = 2 Hz, 2 C), 131.71 (d, J_{CP} = 9 Hz, 2 C), 131.62 (d, J_{CP} = 9 Hz, 2 C), 130.33 (d, J_{CP} = 2 Hz), 130.04 (d, J_{CP} = 12 Hz, 2 C), 129.70, 129.60 (d, J_{CP} = 12 Hz, 2 C), 128.70 (d, J_{CP} = 4 Hz), 127.77 (d, J_{CP} = 3 Hz), 125.61 (d, J^l_{CP} = 98 Hz), 125.13 (d, J^l_{CP} = 102 Hz), 123.41 (d, J_{CP} = 4 Hz), 120.79 (d, J_{CP} = 4 Hz), 38.58 (d, J^1_{CP} = 64 Hz, *C*HP), 28.53 (*C*H_2CO), 21.80 (2 C, Ar–CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.92 ppm. Elemental analysis: calcd (%) for $C_{23}H_{19}Cl_2O_3P$: C, 62.04; H, 4.30; Found: C, 62.11; H, 4.32.

4-(Diphenylphosphoryl)chroman-2-one-3,3-d_2 (3 a-d_2). White amorphous solid; yield: 89% (31 mg; 0.1 mmol scale); Mp = 280 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02–7.97 (m, 2H, Ar–H), 7.75–7.69 (m, 2H, Ar–H), 7.67–7.61 (m, 3H, Ar–H), 7.57–7.54 (m, 1H, Ar–H), 7.49–7.45 (m, 2H, Ar–H), 7.25–7.21 (m, 1H, Ar–H), 7.05 (d, 1H, J = 8.0 Hz, Ar–H), 6.83 (t, 1H, J = 7.6 and 7.2 Hz, Ar–H), 6.63 (d, 1H, J = 7.6 Hz, Ar–H), 4.63 (t, 1H, J = 6.4 Hz, –C*H*P) ppm. HRMS: *m/z* 351.1119 $[M+H]^+$ calcd for $C_{21}H_{15}D_2O_3PH$, found: *m/z* 351.0903; *m/z* 373.0939 $[M+Na]^+$ calcd for $C_{21}H_{15}D_2O_3PNa$; found: *m/z* 373.0689.

Supporting Information

Scanned copies of ^{1}H-NMR, ^{13}C-NMR, DEPT-135, ^{31}P-NMR and HMRS spectra for the synthesized 4-(diarylphosphoryl)chroman-2-one **3** (**3 a**–**3 t** and **3 a**–***d*$_2$**) including 2D-NMR (HMQC and HMBC) for compound **3 g**, synthetic procedures and ^{1}H-NMR spectra for deuterated diphenylphosphine oxide-*d* (**2 a**–***d*$_1$**) and couramin-3-carboxylic acid-*d* (**1 a**–***d*$_1$**), and calculations for atom economy (AE) and E-factors for all the reactions are documented (PDF).

FAIR data, including the primary NMR FID files, for compounds **3 a**–**3 t** (ZIP)

Notes

The author declares no competing financial interest.

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