COMMUNICATION

Photoinduced metal-free trifluoro/perfluoroalkylation of heteroarenes†

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A practical and straightforward protocol to access trifluoromethyl-ated/perfluoroalkylated heteroarenes *via* radical-type nucleophilic substitution rather than typical radical-type electrophilic substitution is described here. The substrate scope was observed to be broad and diverse—covering arenes, heteroarenes (containing N, O, S), bioactive cores, and allylic cores. Mechanistic studies confirmed a radical-mediated reaction pathway.

Over several decades, strategies for synthesizing fluorinated scaffolds have seen an incredible transformation and even today constitute a subject of immense interest.[1] This unparalleled interest is attributed to the major influence of the fluorine group on the physiochemical and biological activities of organic molecules.[2] Organofluoro compounds are widely used in the fields of materials science[3a–c] and agriculture[3d] (Scheme 1A). The ability to add trifluoromethyl and/or perfluoroalkyl groups to arenes and heteroarenes is thus important—but has become a specific bottleneck in efforts at effecting easy translation of the above strategies into commercially viable methods. Derivatizing arenes and heteroarenes with trifluoromethyl and/or perfluoroalkyl groups is also important industrially as such processes are necessary for generating the precursors used to manufacture commercial medications such as mapracorat,[4a] fluoxetine,[4b] and penthiopyrad.[4c]

To address the above-described bottleneck, various attempts at designing methods for the practical synthesis of trifluoromethylated/perfluoroalkylated motifs have been reported. Most methods involving heteroarene trifluoromethylation documented in the literature involve the use of metals such as Pd,[5] Ag,[6] Cu,[7] Ru,[8] Ir,[9] and Ni.[10] These approaches, though elegant, suffer from various limitations including the need to carry out pre-functionalizations such as with halides

or boronic acids the need to use directing groups, and by-product formation. In addition, some of the traditional strategies also exploit oxidative trifluoromethylation using corrosive gaseous, namely CF_3I[11] and CF_3SO_2Cl,[12] electrophiles such as Umemoto's reagent,[13] Togni reagent,[14] and Shibata's reagent,[15] nucleophiles such as Rupert-Prakash reagent (CF_3SiMe_3),[16] *etc*. In addition to these methods being impractical due to their use of expensive metals and designer trifluoromethylating reagents, they also display limited utilization due to functional group intolerance for various classes of heterocycles.

Recently, visible light photoredox catalysis has emerged as a powerful tool for achieving easy activation of C–C bonds. Photoredox-mediated radical trifluoromethylation protocols complement the traditional approaches. In pioneering work reported by Nagib and Macmillan, they showcased photolytic
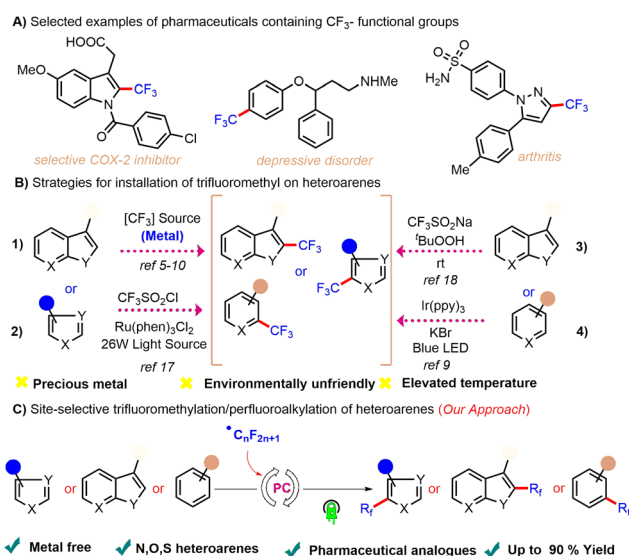
Scheme 1 (A) Biologically relevant trifluoromethylated scaffolds. (B) Previous strategies for trifluoromethylation. (C) Our work: trifluoromethylation/perfluoroalkylation of heteroarenes.

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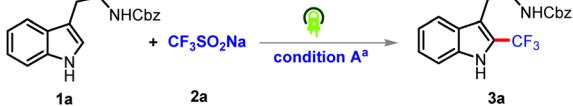†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ob00511b

trifluoromethylation of heteroarenes using trifluorosulfonyl chloride (CF₃SO₂Cl).[17] Baran *et al.* presented a direct C–H trifluoromethylation of a heterocycle using CF₃SO₂Na as a CF₃ radical precursor.[18] Li *et al.* disclosed trifluoromethylation of heteroarenes using CF₃SO₂Na and UV light irradiation.[19] Bottecchia *et al.* developed a trifluoromethylation protocol of heteroarenes using CF₃I and 5,5′-bis(((2-trifluoromethyl) phenyl)ethynyl)-2,2′bithiophene as a photocatalyst.[20] Díaz Díaz *et al.* presented trifluoromethylation of heteroarenes using CF₃SO₂Cl and Ir(ppy)₃ as a photocatalyst.[21] Xiao disclosed trifluoromethylation of heteroarenes *via* trifluoro-methylsulfonyl-pyridinium salts (TFSP) in the presence of Ir (ppy)₃ photocatalyst.[9] However, note that similar to the traditional procedures involving metal catalysis, these strategies are also impractical as they too use either expensive/toxic metal catalysts or are restricted to just a few select fluoro-methylation products due to narrow substrate scopes (Scheme 1B). Therefore, there remains a dire need to develop a straightforward, environmentally benign, scalable and economical method that enables the synthesis of various classes of trifluoromethylated/perfluoroalkylated heterocycles.

To develop a protocol addressing the trifluoromethylation gap, the indole-ring-containing motif was chosen as the heterocycle. Of the important classes of pharmaceutically relevant scaffolds, alkaloids such as tryptamines,[22] which contain each an indole ring as a core nucleus, holds an important place in synthetic organic chemistry. The tryptamine skeleton serves as the basis for many synthetic, semi-synthetic, and naturally occurring pharmacological medications. Our interest[23] and previous work on heteroarene[24] motifs led us to hypothesize that the relatively low energy required for the activation of heteroaromatic C–H in the tryptamine skeleton can be easily provided by a photoredox reaction, allowing us to investigate a mild strategy for achieving trifluoromethylation and perfluoroalkylation (Scheme 1C).

We commenced our initial investigation with NHCbz-tryptamine **1a** and bench-stable Langlois reagent **2a** under photoredox conditions. After extensive tests, the optimal conditions were established to be **1a** (1.0 equiv.), **2a** (3.0 equiv.), eosin Y (2.5 mol%), and (NH₄)₂S₂O₈ (2.0 equiv.) in MeCN (0.1 M), under photoirradiation (12 W blue LED irradiation (525 nm)) and stirring at rt for 12 h. The reaction conditions achieved the desired coupling, which afforded **3a** in 72% isolated yield (Table 1, entry 1).

Control experiments demonstrated that the exclusion of any component in the reaction, specifically light, photocatalyst or oxidant, failed to give the desired product (Table 1, entries 2–5). A screening of various photocatalysts revealed eosin Y as optimal and high yielding; others were less effective (Table 1, entries 6–9). A survey of various solvents indicated MeCN to be the optimal solvent, and replacing it led to a significant decrease in reactivity (Table 1, entries 10–12). Note that inclusion of additives did not result in any significant increase in the yield of the desired product (Table 1, entry 13). After successfully optimizing the reaction conditions for NHCbz -tryptamine, we then investigated the tolerance of our protocol

Table 1 Optimization of C–H trifluoromethylation of NHCbz-tryptamine (**1a**) with Langlois reagent (**2a**)[a]

Entry	Deviation from "condition A"	Yield[b] (%)
1	None	72
2	Absence of light(dark)	N.D.
3	Np photcatalyst	N.D.
4	No oxidant	N.D.
5	No inert atmosphere	N.D.
6	TPT instead of Eosin Y	11
7	[Mes-Arc-Me⁺]BF₄⁻ instead of Eosin Y	60
8	RoseBengal instead of Eosin Y	25
9	[Ru(bpy)₃] instead of Eosin Y	68
10	DCM instead of MeCN	60
11	DCE instead of MeCN	35
12	Dioxance instead of MeCN	65
13	With DIPEA as additive	69

[a] Reactions were carried out with **1a** (0.2 mmol), CF₃SO₂Na **2a** (0.6 mmol), (NH₄)₂S₂O₈ (3 equiv.), eosin Y (2.5 mol%) in 2 mL MeCN under 12 W green LED irradiation at room temperature for 12 h. [b] Isolated yield. MeCN = acetonitrile, DCM = dichloromethane, DIPEA = diisopropyl ethyl amine, ND: no reaction.

for trifluoromethylation of functional indole cores and other classes of heteroarenes (Table 2). Boc-protected tryptamine derivative performed well, affording C-2 product in excellent yield (Table 2, **3b**).

Furthermore, the broad scope of this protocol was validated by the observation of heteroarenes bearing sensitive functional groups (such as aldehyde and nitro groups) providing C-2 products in moderate yields (Table 2, **3c–3d**). The electron-withdrawing cyano group was tolerated, affording the desired C-2 adduct in good yield (Table 2, **3e**). We found that the reaction proceeded with high substrate generality as aliphatic cyclic chain substituents afforded the respective desired C-2 adducts in good yields (Table 2, **3f–3g**). Additionally, trifluoromethyl-ation of indole cores bearing bioactive scaffolds and redox-active component substrates were also felicitous and gave corresponding C-2 adducts in good to excellent yields (Table 2, **3h–3i**). Similarly, a hydrolysis-prone hexafluoro-isopropanol-derived ester component was well tolerated in this C–H trifluoromethylation, giving product with a good yield (Table 2, **3j**). Interestingly, an unsymmetrical heteroarene bearing multiple sites of reaction also provided site-selective C-5-coupled products in excellent yield (Table 2, **3k**). Subsequently, imidazo[1,2-α]pyridine and benzothiophene 3-carbaldehyde scaffolds were tested; they performed well, and the corresponding adducts were formed in good to excellent yields (Table 2, **3l–3m**). We next turned our attention towards arene functionalization, due to it offering the possibility of a valuable pharmaceutically active core. Delightfully our protocol demonstrated complementary reactivity for trifluoromethyl-ation of an arene in a site-selective fashion in moderate to good yields (Table 2, **3n**). The nonsteroidal drug indomethacin
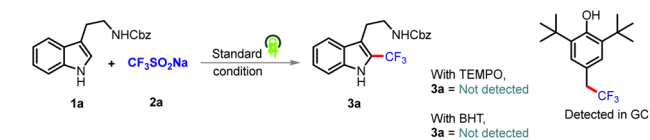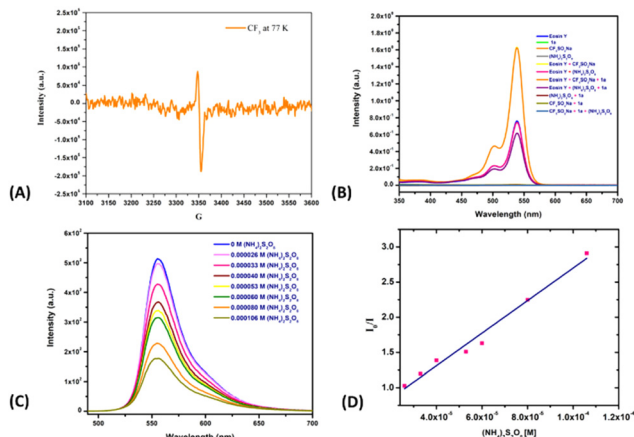
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Table 2 Scope of heteroarene trifluoromethylation/perfluoroalkylation[a,b,c]

3a (72 %) 3b (67 %) 3c (50 %) 3d (45 %) 3e (52 %)

3f (69 %) 3g (64 %) 3h (85 %) 3i (55 %)

3j (60 %) 3k (90 %) 3l (88 %) 3m (79 %) 3n (70 %)[c]

3o (45 %) 3p (90 %) 3q (75 %) 3r (65 %)

3s (66 %) 3t (60 %) 3u (53 %)

[a] Reactions were carried out with **1** (0.2 mmol), **2** (0.6 mmol), $(NH_4)_2S_2O_8$ (3 equiv.), eosin Y (2.5 mol%) in 2 mL solvent under 12 W green LED irradiation at room temperature for 12 h. [b] Isolated yield. [c] GC-determined yield.

Scheme 2 Mechanistic studies.

Fig. 1 (A) EPR experiment. (B) UV-visible studies. (C) Fluorescence quenching with $(NH_4)_2S_2O_8$. (D) Stern–Volmer plot for $(NH_4)_2S_2O_8$.

was directly functionalized and yielded a C-4-trifluoromethylated adduct in moderate yield (Table 2, **3o**). A highly reactive bromo-derived MBH ester scaffold also reacted efficiently under the optimized protocol, yielding the corresponding trifluoromethylated adduct in excellent yield (Table 2, **3p**). The generality of the methodology was further established by extending the reaction to coumarin and *N*-benzyl quinoxalinone. These reactions afforded C-3-trifluoromethylated adducts in good yields (Table 2, **3q–3r**). We next evaluated whether the transformation could be performed with other perfluoroalkyl sulfinate salts. Gratifyingly, our protocol was found to tolerate a wide range of perfluoroalkyl substituents and resulted in C-2-perfluoroalkylated tryptamine adducts in good yields (Table 2, **3s–3u**).
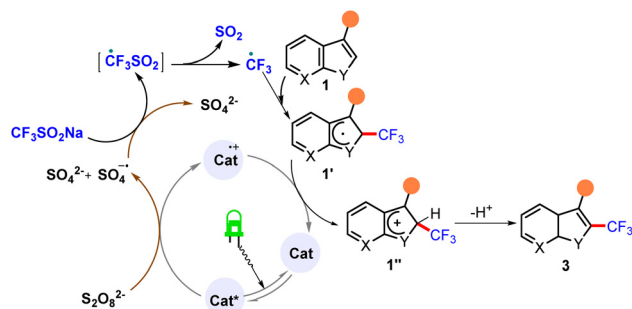
To gain mechanistic insights into this coupling reaction, radical scavengers 2,2,6,6-tetramethyl-1-peperidyloxy (TEMPO) and BHT were added; they suppressed the reactivity and the corresponding radical adduct was detected using GC-MS (Scheme 2). Based on putting together these pieces of experimental evidence, the reaction was concluded to proceed *via* a radical mechanism. Note that *in situ* EPR studies of the corresponding reaction mixture also indicated the presence of a radical intermediate in the reaction system (Fig. 1A). To elim-

inate the possibility of an interaction between eosin Y and the substrates during the catalytic cycle and to observe the ground/excited state of the reactants, experiments involving UV studies were performed. These studies revealed a lack of formation of electron donor–acceptor (EDA) complex (see the ESI†), indicating no possibility of an EDA complex in the reaction medium (Fig. 1B). Based on the established mechanism of action for such photoactive dyes, it was speculated that eosin Y, on being irradiated with green light, would undergo excitation with it further undergoing single-electron oxidation with $(NH_4)_2S_2O_8$ to produce oxidized eosin $Y^{•+}$ and corresponding sulfate dianion (SO_4^{2-}) and sulfate radical anion $(SO_4^{•-})$, which would then oxidize the Langlois reagent to generate the reactive CF_3 radical. To further validate our hypothesis, fluorescence quenching experiments were carried out with **1a**, **2a** and $(NH_4)_2S_2O_8$. A fluorescence quenching effect was witnessed in the presence of $(NH_4)_2S_2O_8$ (Fig. 1C). The corresponding Stern–Volmer plot indicated that the excited state of eosin Y was quenched by $(NH_4)_2S_2O_8$ and an increase in quenching was noticed with an increasing oxidant concentration (see the ESI†).

Furthermore, quenching constants were determined by carrying out Stern–Volmer analyses (Fig. 1D).

Based on the information in the literature and the observations made in the present study (see ESI†), a plausible mechanism was derived for this reaction. According to this proposed mechanism, photoirradiation of eosin Y* with green light followed by single-electron oxidation of catalyst resulted in the formation of sulfate dianion (SO_4^{2-}), which in turn oxi-

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Scheme 3 Plausible mechanism.

dized CF_3SO_2Na to generate a trifluoromethyl radical. This radical was intercepted by heteroarenes **1** to form **1′**, which subsequently underwent single-electron oxidation (SET) and protonation to ultimately afford the desired compounds **3** (Scheme 3).

Conclusions

In summary, we have developed a transition-metal-free, visible-light-mediated trifluoromethylation/perfluoroalkylation of heteroarenes. This simple protocol employs bench-stable, easy-to-handle and inexpensive sodium triflinate (Langlois reagent) as a CF_3 source and eosin Y as a photoredox catalyst. This strategy allows direct installation of both trifluoromethyl and perfluoroalkyl groups into various classes of heterocycles, thus providing an opportunity for a one-step direct functionalization of heteroarenes, and exhibits excellent functional group tolerance, and is thus suited for late-stage functionalization of natural products and pharmaceuticals.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

References

1 (*a*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477; (*b*) M. G. Campbell and T. Ritter, *Chem. Rev.*, 2015, **115**, 612–633; (*c*) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme and J.-F. Paquin, *Chem. Rev.*, 2015, **115**, 9073–9174; (*d*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264.

2 (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886; (*b*) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637–643; (*c*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (*d*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.

3 (*a*) F. Babudri, G. M. Farinola, F. Naso and R. Ragni, *Chem. Commun.*, 2007, 1003–1022; (*b*) R. Milad, J. Shi, A. Aguirre, A. Cardone, B. Milián-Medina, G. M. Farinola, M. Abderrabba and J. Gierschner, *J. Mater. Chem. C*, 2016, **4**, 6900–6906; (*c*) M. Pagliaro and R. Ciriminna, *J. Mater. Chem.*, 2005, **15**, 4981–4991; (*d*) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467.

4 (*a*) Y. Yanase, H. Katsuta, K. Tomiya, M. Enomoto and O. Sakamoto, *J. Pest Sci.*, 2013, **38**, 167–168; (*b*) C. J. Wenthur, M. R. Bennett and C. W. Lindsley, *ACS Chem. Neurosci.*, 2014, **5**, 14–23; (*c*) M. Baiula and S. Spampinato, *Inflammation Allergy: Drug Targets*, 2014, **13**, 289–298.

5 (*a*) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648–3649; (*b*) M. Miura, C.-G. Feng, S. Ma and J.-Q. Yu, *Org. Lett.*, 2013, **15**, 5258–5261; (*c*) K. Natte, R. V. Jagadeesh, L. He, J. Rabeah, J. Chen, C. Taeschler, S. Ellinger, F. Zaragoza, H. Neumann, A. Brückner and M. Beller, *Angew. Chem., Int. Ed.*, 2016, **55**, 2782–2786; (*d*) Q. Zhao, T. Besset, T. Poisson, J.-P. Bouillon and X. Pannecoucke, *Eur. J. Org. Chem.*, 2016, 76–82.

6 (*a*) Y. Ye, S. H. Lee and M. S. Sanford, *Org. Lett.*, 2011, **13**, 5464–5467; (*b*) G. Shi, C. Shao, S. Pan, J. Yu and Y. Zhang, *Org. Lett.*, 2015, **17**, 38–41.

7 (*a*) L. Chu and F.-L. Qing, *J. Am. Chem. Soc.*, 2010, **132**, 7262–7263; (*b*) T. D. Senecal, A. T. Parsons and S. L. Buchwald, *J. Org. Chem.*, 2011, **76**, 1174–1176; (*c*) L. Chu and F.-L. Qing, *Org. Lett.*, 2012, **14**, 2106–2109; (*d*) Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034–9037; (*e*) S. Arimori and N. Shibata, *Org. Lett.*, 2015, **17**, 1632–1635; (*f*) J. Lei, X. Wu and Q. Zhu, *Org. Lett.*, 2015, **17**, 2322–2325.

8 N. Iqbal, S. Choi, E. Kim and E. J. Cho, *J. Org. Chem.*, 2012, **77**, 11383–11387.

9 F. Xiao, J.-H. Lin, F. Hao, X. Zheng, Y. Guo and J.-C. Xiao, *Org. Chem. Front.*, 2022, **9**, 1982–1985.

10 (*a*) Y. Wu, H.-R. Zhang, R.-X. Jin, Q. Lan and X.-S. Wang, *Adv. Synth. Catal.*, 2016, **358**, 3528–3533; (*b*) S. Deolka, R. Govindarajan, E. Khaskin, R. R. Fayzullin, M. C. Roy and J. R. Khusnutdinova, *Angew. Chem., Int. Ed.*, 2021, **60**, 24620–24629.

11 T. Kino, Y. Nagase, Y. Ohtsuka, K. Yamamoto, D. Uraguchi, K. Tokuhisa and T. Yamakawa, *J. Fluor. Chem.*, 2010, **131**, 98–105.

12 H. Chachignon, H. Guyon and D. Cahard, *Beilstein J. Org. Chem.*, 2017, **13**, 2800–2818.

13 (*a*) C. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 6580–6589; (*b*) S. Tsujibayashi, Y. Kataoka, S. Hirano and H. Matsubara, *Org. Biomol. Chem.*, 2018, **16**, 4517–4526.

This journal is © The Royal Society of Chemistry 2024

Org. Biomol. Chem., 2024, **22**, 4072–4076 | **4075**

14 (a) M. S. Wiehn, E. V. Vinogradova and A. Togni, *J. Fluor. Chem.*, 2010, **131**, 951–957; (b) E. Mejía and A. Togni, *ACS Catal.*, 2012, **2**, 521–527.

15 N. Shibata, A. Matsnev and D. Cahard, *Beilstein J. Org. Chem.*, 2010, **6**, 65.

16 (a) P. Ramaiah, R. Krishnamurti and G. K. S. Prakash, in *Organic Syntheses*, 2003, pp. 232–232; (b) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack and G. A. Olah, *Science*, 2012, **338**, 1324–1327.

17 D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224–228.

18 Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 14411–14415.

19 L. Li, X. Mu, W. Liu, Y. Wang, Z. Mi and C.-J. Li, *J. Am. Chem. Soc.*, 2016, **138**, 5809–5812.

20 C. Bottecchia, R. Martín, I. Abdiaj, E. Crovini, J. Alcazar, J. Orduna, M. J. Blesa, J. R. Carrillo, P. Prieto and T. Noël, *Adv. Synth. Catal.*, 2019, **361**, 945–950.

21 B. Maiti, A. Abramov, R. Pérez-Ruiz and D. Díaz Díaz, *Acc. Chem. Res.*, 2019, **52**, 1865–1876.

22 B. E. Blough, A. Landavazo, A. M. Decker, J. S. Partilla, M. H. Baumann and R. B. Rothman, *Psychopharmacology*, 2014, **231**, 4135–4144.

23 S. Singh, K. S. Naskar, A. Kundu and R. P. Singh, *Synthesis*, 2023, 3685–3692.

24 (a) K. N. Tripathi, S. Singh, N. Akhtar, K. Manna and R. P. Singh, *Chem. Commun.*, 2022, **58**, 9674–9677; (b) S. Singh and R. P. Singh, *Org. Biomol. Chem.*, 2022, **20**, 7891–7895; (c) S. Singh, K. N. Tripathi and R. P. Singh, *Org. Biomol. Chem.*, 2022, **20**, 5716–5720.

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