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Aminals as powerful XAT-reagents: activation of fluorinated alkyl chlorides†

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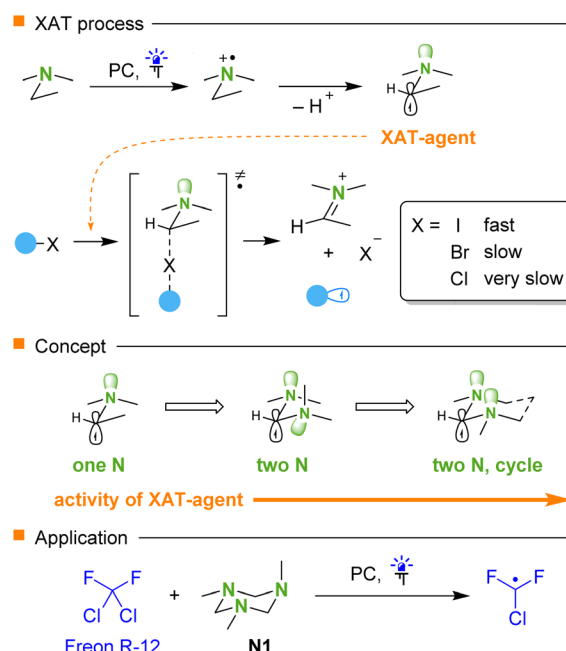
Readily available 1,3,5-trimethyl-1,3,5-triazinane serves as an efficient reagent for halogen atom transfer. Under photocatalytic conditions, the triazinane generates an α -aminoalkyl radical, which can activate the C–Cl bond of fluorinated alkyl chlorides. The hydrofluoroalkylation reaction between fluorinated alkyl chlorides and alkenes is described. The efficiency of the diamino-substituted radical derived from the triazinane is associated with stereoelectronic effects defined by a six-membered cycle forcing the anti-periplanar arrangement of the radical orbital and lone pairs of adjacent nitrogen atoms.

Introduction

The activation of the carbon–halogen bond is a widely used pathway for the generation of organic radicals.¹ The advent of photocatalysis^{2–5} has made a notable breakthrough in this area leading to the development of more efficient approaches to the application of organic halides, which allowed to escape from classic organotin based reagents.⁶ In a series of conventional alkyl halides, iodides are activated most easily, while chlorides are the least reactive, though methods for the activation of the carbon–chlorine bond have been described.⁷ Thus, organometallic and related reagents capable of direct abstraction of the chlorine by virtue of strong a chlorine–element bond^{8–10} or transition metals^{11–13} may be used. Another approach is based on photoredox promoted single electron reduction. However, this step requires catalysts having strongly reducing excited states,^{14–18} which in some cases may be accessed *via* a two-photon absorption mechanism.^{19,20}

Recently, a concept involving halogen atom transfer (XAT)^{21,22} by using α -aminoalkyl radicals was introduced by Leonori²³ (Scheme 1). These radicals are generated from readily available tertiary amines by single electron oxidation followed by proton loss. These α -aminoalkyl radicals effectively activate alkyl iodides^{23,24} and fluorinated bromides,²⁵ while reactions with chlorides are rare.²⁶ We proposed that switching from amines to aminals may provide more effective XAT reagents due to the additional donor effect of the second nitrogen on the radical center. Herein, we report that 1,3,5-triazinane **N1** exhibits very high reactivity in

XAT processes owing to its cyclic structure. The observed phenomenon is based on stereoelectronic effects originating from the fixation of the nitrogen lone pairs in a proper spatial arrangement with respect to the singly occupied orbital.^{27,28} We demonstrate the application of cyclic amine **N1** for the activation of the carbon–chlorine bond of dichlorodifluoromethane (CF₂Cl₂, Freon R-12) and other fluorinated chlorides. In fact, Freon R-12 is one of the most readily available commodity chemicals, and it was used as a refrigerant, aerosol spray propellant, and fire retardant.^{29,30} Apparently, it would be attractive to use this relatively unreactive chemical for the synthesis of valuable organofluorine



Scheme 1 Reactions of α -aminoalkyl radicals.

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compounds,^{31,32} while there are only a few limited radical based methods affording CF₂Cl-compounds.^{33,34}

Results and discussion

4-Phenylbut-1-ene (**1a**) was selected as a model substrate and its reaction with Freon R-12 (**2a**) was evaluated (Table 1). A typical carbazole-type photocatalyst (4CzIPN)³⁵ was used under blue light irradiation. *tert*-Butyl thiol in catalytic amounts (10%) was added as a mediator of hydrogen atom transfer.^{36–39} A series of amines **N1–N5**, which can serve both as XAT-type activating agents and as a source of the hydrogen atom, were evaluated. Triazinanes **N1** and **N2** were found to be optimal (entries 1 and 5), while acyclic amination **N3** was less efficient, and conventional tertiary amines were notably less reactive (entries 8 and 9). Acetonitrile was routinely used as a solvent in this process, though dimethylsulfoxide and dichloromethane performed similarly. Without *tert*-butyl thiol the reaction was slower, and by-products were formed (entry 4). Gaseous **2a** was used in excess (3 equiv.), while the decrease of its amount twice led to some decrease of the product yield (entry 10). Interestingly, the reaction slowly proceeded even without the photocatalyst (entry 11). Finally, the use of 2 equiv. of triazinane **N1** gave higher conversion, and hydrofluoroalkylation product **3a** was

isolated in 92% yield (entry 7). Between triazinanes **N1** and **N2**, we selected the former for further experiments because of the atom efficiency issue. It should also be noted that reagent **N1** is commercially available or can be easily obtained from cheap one-carbon precursors – methylamine and paraform.

Under the optimized conditions, a series of alkenes were fluoroalkylated using Freon R-12 and other fluorinated chlorides (Scheme 2). Typically, hydrofluoroalkylation products **3–5** were obtained in high yields. The reaction tolerates a wide variety of functional groups in the alkene component including keto (**4d**), cyano (**4k**), ester (**3b**, **g**, **k**, **m**, and **4m**), free hydroxyl group (**3f**), free carboxylic acid (**5d**), and diverse protecting groups (silyl, benzyl, PMP, and MEM), *N*-Boc protected amine (**4p**), phosphonate (**4g**), boryl (**4h**), acetal (**4o**) and sulfide (**3j** and **l**) fragments. Besides terminal alkenes, 1,1-, 1,2-disubstituted and trisubstituted alkenes were also successfully involved (products **4i**, **4j**, and **4s**, respectively). Even a fully substituted alkene gave the desired product (**4t**) though in a decreased yield. In some cases (products **3l**, **n**, and **4t**), an increase of the *tert*-butyl thiol additive to 20% was needed to suppress the formation of by-products, which according to NMR and GC-MS analysis was tentatively ascribed to the alkenes (*m/z* values less by 2 relative to that of expected products). It is worth noting that reagent **N1** is very selective and activates only Freon R-12 and tolerates the C–Cl bond of compounds **3**, as no by-products arising from the interaction of **3** with alkenes **1** were observed. Other fluorinated chlorides were found to be good reaction partners such as ethyl 4-chloro-2,2,3,3-tetrafluoropropionate (products **4**), methyl chlorodifluoroacetate (products **5a** and **b**), and higher polyfluorinated chlorides (products **5c–e**). We also evaluated chloroform as a non-fluorinated chloride, which afforded the desired product **5g**, though the reaction required higher loadings of triazinane and the photocatalyst.

While reactions were typically performed on a 0.5 mmol scale, they can be readily scaled-up, as was demonstrated by the synthesis of gram quantities of products **3a** and **5a** starting from 20 and 10 mmol of **1a**, respectively (Scheme 3). Importantly, these products were isolated without chromatography by distillation of the crude material. In these experiments, only 0.25 mol% of the photocatalyst, that is half of the standard amount, was used. Compound **5a** was further converted into alcohol **6** and amide **7** by reactions typical for the ester group.

The fluoroalkylation was successfully applied to difluorinated bromide **8** affording product **5g** in good yield (Scheme 4). At the same time, difluorinated iodide **9** gave a complex mixture containing traces of the desired product **5h**. We may propose that for the iodide, after the radical addition step, the secondary alkyl radical undergoes fast iodine atom transfer to give alkyl iodide followed by dehydroiodination (a series of alkenes were observed by GC-MS analysis). While products **3** are inactive under typical conditions (see above), isolated compound **3a** could be coupled with another alkene by using a different photocatalyst and more powerful purple irradiation (400 nm). As a result, product **10** was assembled from two alkenes and Freon R-12 as a source of the difluoromethylene fragment (Scheme 4, bottom equation).

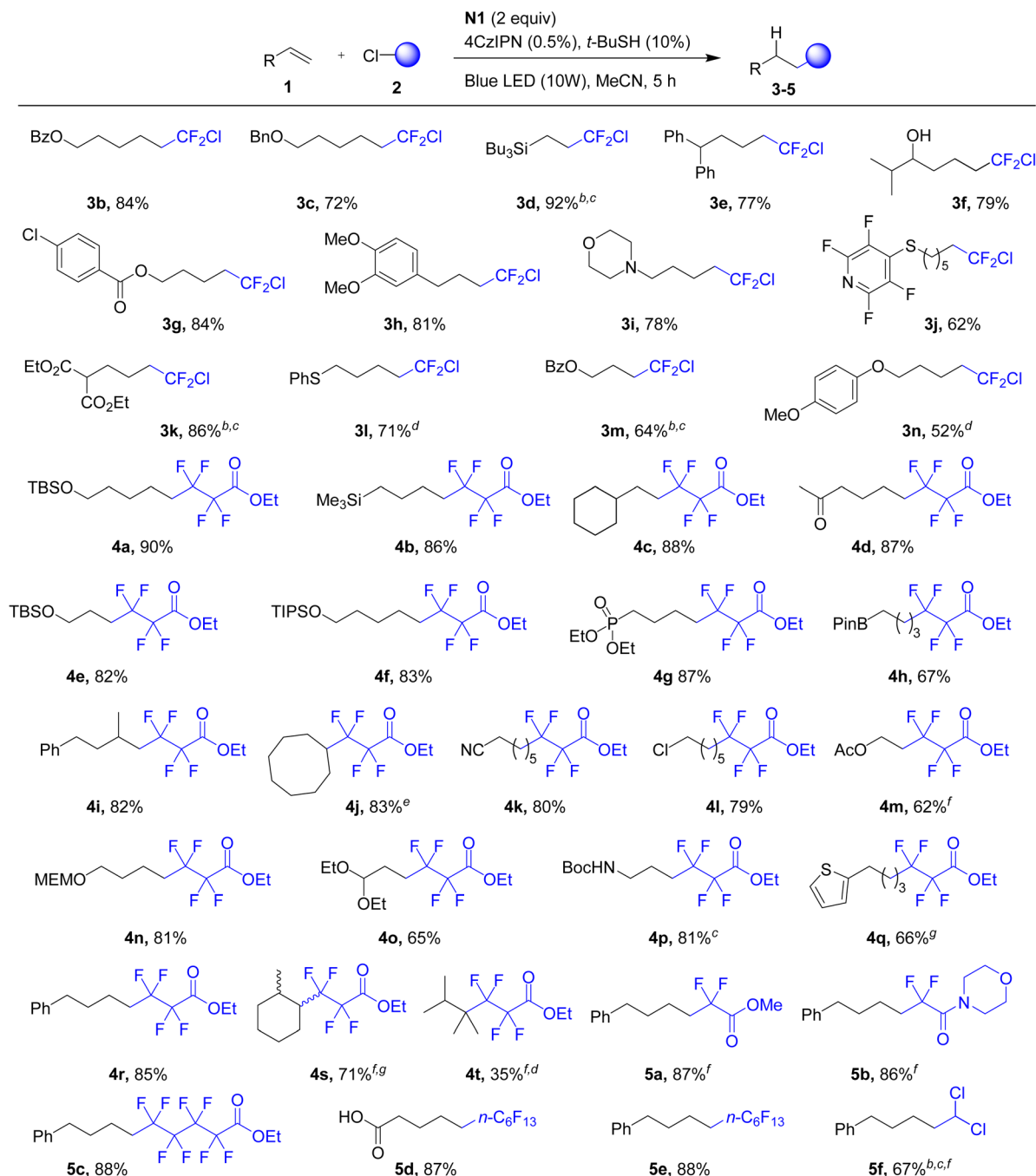
The radical character of the fluoroalkylation was supported by a radical clock experiment involving diallylmalonate, which

Table 1 Optimization studies

Entry	XAT reagent (equiv.)	Solv.	Ratio 3a : 1a ^a
1	N1 (1.5)	MeCN	97 : 3
2	N1 (1.5)	DMSO	96 : 4
3	N1 (1.5)	DCM	97 : 3
4 ^b	N1 (1.5)	MeCN	28 : 72
5	N2 (1.5)	MeCN	95 : 5
6	N3 (1.5)	MeCN	71 : 29
7	N1 (2)	MeCN	> 99 : 1 (92%)
8	N4 (2)	MeCN	5 : 95
9	N5 (2)	MeCN	26 : 74
10 ^d	N1 (2)	MeCN	76 : 24
11 ^e	N1 (2)	MeCN	14 : 86

^a Determined by GC-MS. ^b Without *t*-BuSH. ^c Isolated yield of **3a**. ^d 1.5 equiv. of CF₂Cl₂. ^e Without 4CzIPN.





^a Amounts: **1** (0.5 mmol); chlorides **2**: for CF₂Cl₂ (**2a**) and CHCl₃ (3 equiv); for other chlorides (1.75 equiv). Solvent MeCN (0.5 M). ^b 4 equiv of **2**, 3 equiv of **N1**. ^c 1% of 4CzIPN. ^d 20% of *t*-BuSH. ^e 2 equiv **2**. ^f Reaction time 10 h. ^g 2.5 equiv of **2**.

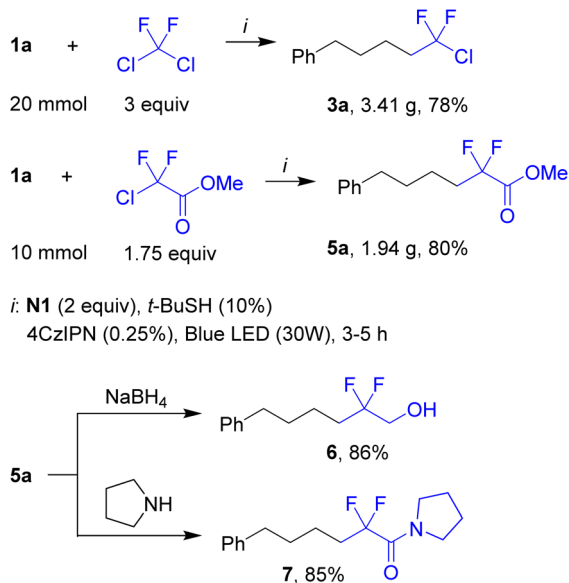
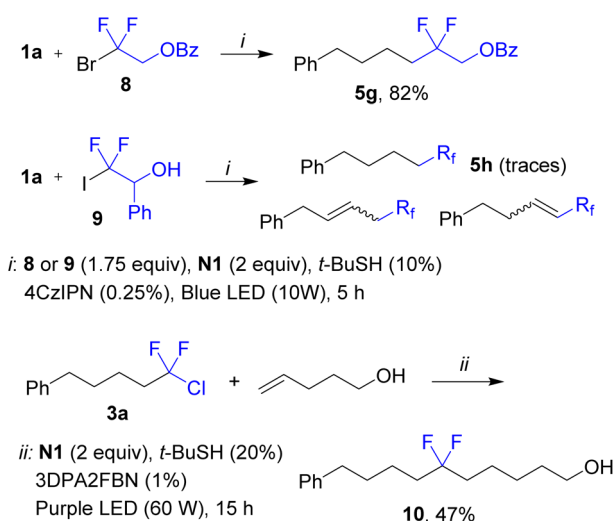
Scheme 2 Fluoroalkylation of alkenes.^a

afforded product **11**, likely *via* rapid 5-*exo* cyclization of the intermediate addition radical (Scheme 5A). Reactions performed in acetonitrile are accompanied by precipitation of a white solid. This precipitate was isolated and identified as previously known iminium salt **12**, which is formed from triazinane **N1** almost quantitatively (Scheme 5B). Performing Stern-Volmer analysis suggested strong quenching of the fluorescence of photoexcited 4CzIPN by triazinane **N1**, while there is virtually no quenching by ethyl 4-chloro-2,2,3,3-tetrafluoropropionate and other components.

Taking into account that the redox potential of triazinane **N1** of +0.94 V (vs. SCE)⁴⁰ matches well the potential of the excited state of 4CzIPN (+1.43 V vs. SCE),³⁵ the single electron oxidation of **N1** by the photocatalyst seems likely. The reaction quantum yield was found to be 0.44, thereby suggesting that the process is either non-chain or has a chain character with short propagating efficiency.

The proposed mechanism is shown in Scheme 6. Triazinane **N1** is oxidized by an excited photocatalyst followed by loss of a proton with the generation of a triazinanyl radical **T1**. The XAT event



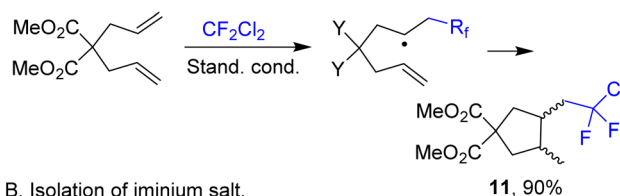
Scheme 3 Gram-scale experiments and reactions of **5a**.

Scheme 4 Scope of difluorinated halides.

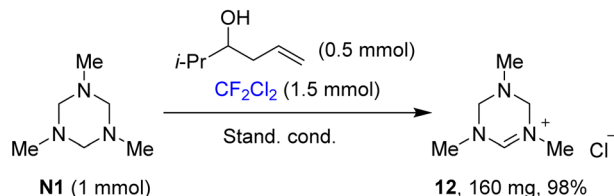
generates the fluorinated radical, which attacks the double bond. Finally, the secondary alkyl radical undergoes hydrogen atom transfer from the thiol. The thiol radical is either reduced by the photocatalyst (path a) or abstracts the hydrogen atom from triazinane to regenerate an aminoalkyl radical **T1** (path b). The latter pathway may contribute to a chain character of the reaction, and it may be responsible for the slow reaction without the photocatalyst (Table 1, entry 11). The interaction of radical **T1** with fluoroalkyl halide may be realized *via* single-electron reduction, but it is difficult to distinguish between these two mechanisms.

To explain the efficiency of triazinane **N1** compared to other amines in the XAT process, the interaction of various aminoalkyl radicals with CF_2Cl_2 was evaluated by DFT calculations (Fig. 1). Thus, the activation free energies for the reactions of radicals **T5** and **T3** derived from monoamine and acyclic amination differ only by

A. Radical clock experiment

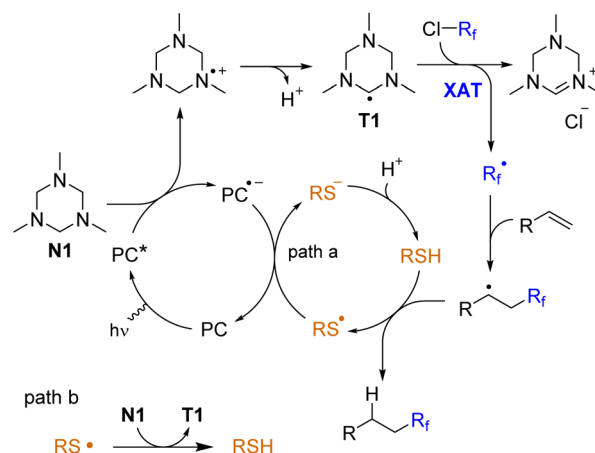


B. Isolation of iminium salt.



Scheme 5 Mechanistic experiments.

0.5 kcal mol^{−1}. However, for the triazinane-derived radical **T1**, the activation energy decreases further by 4.5 kcal mol^{−1}, which corresponds to three orders of magnitude in the rate constant. To rationalize this trend in transition state energies, we analyzed the conformations of aminoalkyl radicals. Thus, for triazinane system **T1** we may consider three structures **C1**–**C3** with various orientations of nitrogen lone pairs, based on the well-studied conformational behavior of triazinanes.^{41–43} The most stable is structure **C1** having two lone pairs of adjacent nitrogens arranged in anti-orientation with respect to the radical. For the diamine-type radical **T3**, the most stable structure has one *anti* and one *gauche* arrangement of lone pairs with respect to the radical, which resemble that of structure **C2**. Interestingly, attempts to locate the **T3** structure with a double *anti* arrangement similar to **C1** (shown in parentheses) was unsuccessful, with the optimization leading to the most stable structure *via* rotation around the C–N bond (see the ESI† for relaxed potential energy scan). As follows from NBO analysis, the interactions of nitrogen lone pairs with the adjacent carbon singly occupied orbital are stronger for the double *anti* arrangement [net energies are shown in brackets in Fig. 1].



Scheme 6 Proposed mechanism.



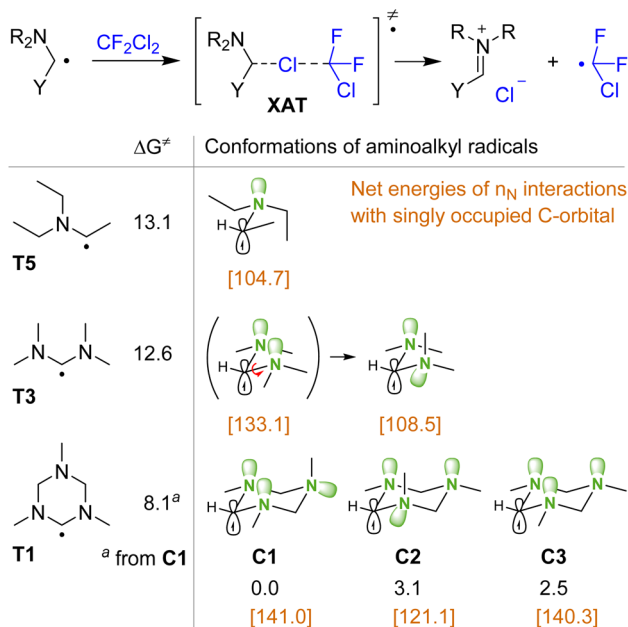


Fig. 1 Activation free energies for the XAT process and conformations of aminoalkyl radicals. Method: uwB97xd/def2svp-CPCM(MeCN). In brackets, energies obtained from second order perturbation theory in NBO analysis are shown (for radicals **T3** and **C1**–**C3**, the sum of interactions for the two lone pairs is given). All energies are in kcal mol^{−1}.

This analysis demonstrates that the ability of the cycle to freeze the rotation and stabilize the structure having two lone pairs anti to the free radical is a key factor responsible for the observed reactivity of the triazinane **N1**.

Conclusions

In summary, an application of a readily available amine-based reagent for an effecting XAT process under photocatalytic conditions is described. Triazinane serves as a precursor of the α -aminoalkyl radical capable of activating the carbon–chlorine bond of various chlorofluoro organic compounds. The enhanced reactivity of the cyclic radical derived from triazinane compared to acyclic mono- and diamino-based analogues is associated with stereo-electronic effects. The cyclic aminals may be considered as promising reagents for the generation of alkyl radicals.

Data availability

Procedures, characterization data, NMR spectra, details of DFT calculations, and Stern–Volmer plots are available in the ESI.†

Author contributions

V. S. Kostromitin and A. O. Sorokin: investigation; V. V. Levin: investigation, conceptualization, and writing; A. D. Dilman: conceptualization and writing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 P. Renaud and M. P. Sibi, *Radicals in Organic Synthesis*, Wiley-VCH, 2001.
- 2 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363.
- 3 J. W. Tucker and C. R. J. Stephenson, *J. Org. Chem.*, 2012, **77**, 1617–1622.
- 4 D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**, 1239176.
- 5 L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem., Int. Ed.*, 2018, **57**, 10034–10072.
- 6 S. Crespi and M. Fagnoni, *Chem. Rev.*, 2020, **120**, 9790–9833.
- 7 M. Cybularczyk-Cecotka, J. Szczepanik and M. Giedyk, *Nat. Catal.*, 2020, **3**, 872–886.
- 8 Z.-Q. Zhang, Y.-Q. Sang, C.-Q. Wang, P. Dai, X.-S. Xue, J. L. Piper, Z.-H. Peng, J.-A. Ma, F.-G. Zhang and J. Wu, *J. Am. Chem. Soc.*, 2022, **144**, 14288–14296.
- 9 T. Kawamoto and I. Ryu, *Org. Biomol. Chem.*, 2014, **12**, 9733–9742.
- 10 X. Wu, W. Hao, K.-Y. Ye, B. Jiang, G. Pombar, Z. Song and S. Lin, *J. Am. Chem. Soc.*, 2018, **140**, 14836–14843.
- 11 M. Claros, F. Ungeheuer, F. Franco, V. Martin-Diaconescu, A. Casitas and J. Lloret-Fillol, *Angew. Chem., Int. Ed.*, 2019, **58**, 4869–4874.
- 12 J. Aragón, S. Sun, D. Pascual, S. Jaworski and J. Lloret-Fillol, *Angew. Chem., Int. Ed.*, 2022, **61**, e202114365.
- 13 V. S. Kostromitin, A. A. Zemtsov, V. V. Levin and A. D. Dilman, *Adv. Synth. Catal.*, 2021, **363**, 5336–5340.
- 14 N. Noto and S. Saito, *ACS Catal.*, 2022, **12**, 15400–15415.
- 15 D. Wei, X. Li, L. Shen, Y. Ding, K. Liang and C. Xia, *Org. Chem. Front.*, 2021, **8**, 6364–6370.
- 16 H. Yin, Y. Jin, J. E. Hertzog, K. C. Mullane, P. J. Carroll, B. C. Manor, J. M. Anna and E. J. Schelter, *J. Am. Chem. Soc.*, 2016, **138**, 16266–16273.
- 17 M. Giedyk, R. Narobe, S. Weiss, D. Touraud, W. Kunz and B. König, *Nat. Catal.*, 2020, **3**, 40–47.
- 18 M. W. Campbell, V. C. Polites, S. Patel, J. E. Lipson, J. Majhi and G. A. Molander, *J. Am. Chem. Soc.*, 2021, **143**, 19648–19654.
- 19 I. Ghosh, T. Ghosh, J. I. Bardagi and B. König, *Science*, 2014, **346**, 725–728.
- 20 I. A. MacKenzie, L. Wang, N. P. R. Onuska, O. F. Williams, K. Begam, A. M. Moran, B. D. Dunietz and D. A. Nicewicz, *Nature*, 2020, **580**, 76–80.
- 21 F. Juliá, T. Constantin and D. Leonori, *Chem. Rev.*, 2022, **122**, 2292–2352.



- 22 T. Constantin, B. Górski, M. J. Tilby, S. Chelli, F. Juliá, J. Llaveria, K. J. Gillen, H. Zipse, S. Lakhdar and D. Leonori, *Science*, 2022, **377**, 1323–1328.
- 23 T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Julia and D. Leonori, *Science*, 2020, **367**, 1021–1026.
- 24 N. Sanosa, B. Peñín, D. Sampedro and I. Funes-Ardoiz, *Eur. J. Org. Chem.*, 2022, **2022**, e202200420.
- 25 W.-J. Yue, C. S. Day, A. J. Brenes Rucinski and R. Martin, *Org. Lett.*, 2022, **24**, 5109–5114.
- 26 Y. Cheng, Z. Qu, S. Chen, X. Ji, G.-J. Deng and H. Huang, *Adv. Synth. Catal.*, 2022, **364**, 1573–1579.
- 27 I. V. Alabugin, *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*, John Wiley & Sons, 2016.
- 28 I. V. Alabugin, L. Kuhn, N. V. Krivoschapov, P. Mehaffy and M. G. Medvedev, *Chem. Soc. Rev.*, 2021, **50**, 10212–10252.
- 29 A. J. Sicard and R. T. Baker, *Chem. Rev.*, 2020, **120**, 9164–9303.
- 30 A. K. Vuppalladadiyam, E. Antunes, S. S. V. Vuppalladadiyam, Z. T. Baig, A. Subiantoro, G. Lei, S.-Y. Leu, A. K. Sarmah and H. Duan, *Sci. Total Environ.*, 2022, **823**, 153670.
- 31 M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633–10640.
- 32 Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467.
- 33 D. Meng, L. Li, A. Brown, J.-N. Desrosiers, S. Duan, C. M. Hayward, Z. He, J. Hu, T. Makowski, M. Maloney, S. Monfette, H. Perfect, J. L. Piper, M. Zhou and D. W. Widlicka, *Cell Rep. Phys. Sci.*, 2021, **2**, 100394.
- 34 S. Kawamura, C. J. Henderson, Y. Aoki, D. Sekine, S. Kobayashi and M. Sodeoka, *Chem. Commun.*, 2018, **54**, 11276–11279.
- 35 E. Speckmeier, T. G. Fischer and K. Zeitler, *J. Am. Chem. Soc.*, 2018, **140**, 15353–15365.
- 36 S. Escoubet, S. Gastaldi, N. Vanthuyne, G. Gil, D. Siri and M. P. Bertrand, *J. Org. Chem.*, 2006, **71**, 7288–7292.
- 37 Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies and D. W. C. MacMillan, *Science*, 2017, **358**, 1182–1187.
- 38 D. B. Vogt, C. P. Seath, H. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2019, **141**, 13203–13211.
- 39 V. S. Kostromitin, V. V. Levin and A. D. Dilman, *J. Org. Chem.*, 2022, DOI: [10.1021/acs.joc.2c00712](https://doi.org/10.1021/acs.joc.2c00712).
- 40 S. F. Nelsen and P. J. Hintz, *J. Am. Chem. Soc.*, 1972, **94**, 7114–7117.
- 41 J. G. Jewett, J. J. Breyear, J. H. Brown and C. H. Bushweller, *J. Am. Chem. Soc.*, 2000, **122**, 308–323.
- 42 C. H. Bushweller, M. Z. Lourandos and J. A. Brunelle, *J. Am. Chem. Soc.*, 1974, **96**, 1591–1593.
- 43 V. J. Baker, I. J. Ferguson, A. R. Katritzky, R. Patel and S. Rahimi-Rastgoo, *J. Chem. Soc., Perkin Trans. 2*, 1978, 377–381.

