ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d1cc03466a

Received 29th June 2021,
Accepted 29th July 2021

DOI: 10.1039/d1cc03466a

rsc.li/chemcomm

N-Hydroxyphthalimide-catalyzed chemoselective intermolecular benzylic C–H amination of unprotected arylalkanols†

Masatoshi Shibuya,* Takayuki Orihashi, Yamei Li and Yoshihiko Yamamoto

***N*-Hydroxyphthalimide-catalyzed chemoselective benzylic C(sp^3)–H amination of unprotected arylalkanols using bis(2,2,2-trichloroethyl)-azodicarboxylate has been developed. The use of 1,1,1,3,3,3-hexafluoropropan-2-ol as a solvent plays a critical role in chemoselectivity. The conversion of an aminated product to the corresponding free amino alcohol was also demonstrated.**

C(sp^3)–H amination is a powerful reaction for the synthesis of nitrogen compounds.[1,2] The C–H amination of alkanols facilitates the synthesis of amino alcohols, which are important components of biologically active compounds (Fig. 1a).[3,4] The intramolecular C–H amination of alkanol derivatives (*e.g.* carbamates, sulfamates, and imidates) shows promise for preparing 1,2- and 1,3-amino alcohols (Fig. 1b).[5–7] In addition, Chang and coworkers reported the intermolecular C–H amination of a terminal CH_3 group directed by ketoxime producing 1,2-amino alcohol derivatives.[8] More recently, Zuo and coworkers reported δ-selective amination of alkanols by photoinduced ligand-to-metal charge transfer (LMCT) catalysis, which enables the synthesis of 1,4-amino alcohols.[9] These are effective strategies for the preparation of amino alcohols that possess specific chain lengths between hydroxy and amino groups. In contrast, the non-directed regioselective intermolecular C(sp^3)–H amination of alkanols facilitates the preparation of amino alcohols possessing a diverse range of chain lengths between hydroxy and amino groups. In particular, the reaction of unprotected alkanols is a promising method for the straightforward preparation of free amino alcohols; however, the C–H bond proximal to the hydroxy group is susceptible to yielding a non-desired product under amination conditions.[10] Although protected alkanols are often used to examine the scope of C–H amination reactions,[2g,11] a general strategy toward the successful C(sp^3)–H amination of unprotected alkanols has not been established to the best of our knowledge. Focusing on the potential usefulness of this reaction, we have developed a chemoselective intermolecular benzylic C(sp^3)–H amination of unprotected arylalkanols (Fig. 1c).

In 2012, Kamijo, Inoue and coworkers reported on C(sp^3)–H amination using *N*-hydroxyphthalimide (NHPI) and dialkyl azodicarboxylate, which enabled C–H amination across a broad range of substrates with high efficiency.[11] Despite the

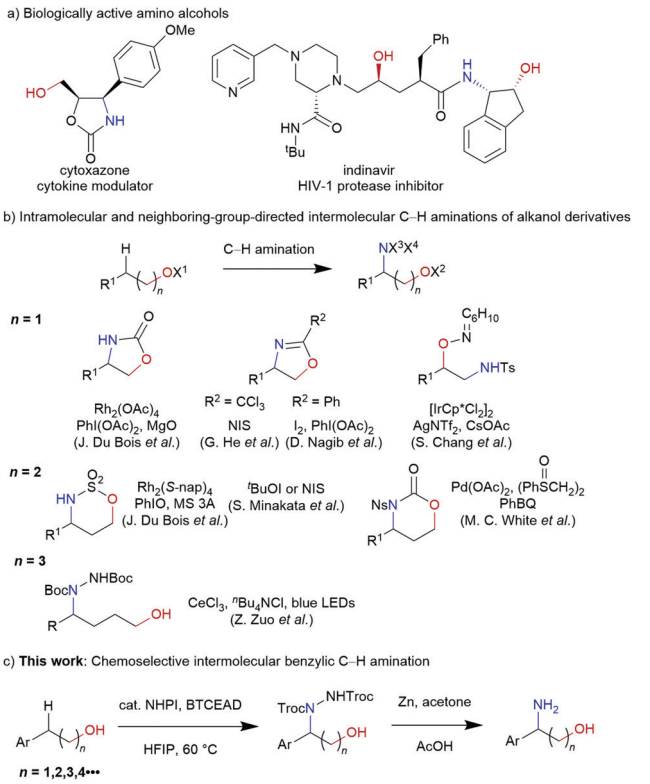


Fig. 1 Biologically active amino alcohols and the C–H amination of alkanols or its derivatives.

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan
E-mail: m-shibu@ps.nagoya-u.ac.jp

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1cc03466a

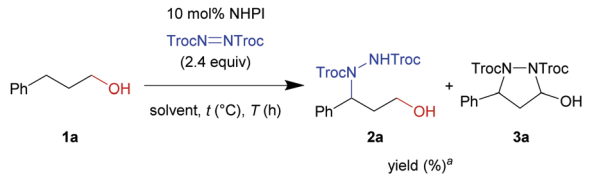
demonstration of benzylic C–H amination of protected phenylalkanols (*e.g.* benzoates and a TBDPS ether), the reaction of an unprotected phenylalkanol was not examined. Hence, our research commenced with the application of their C–H amination method to an unprotected phenylalkanol. We examined the reaction of 4-phenylbutanol using NHPI (20 mol%) and diethyl azodicarboxylate (DEAD) (2.4 equiv.) in DCE (Table S1, ESI†). The reaction was hampered by side reactions, resulting in a moderate yield (42%) of the desired product. After initial solvent screening to improve the yield, we found that 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) was an optimal solvent for the chemoselective benzylic C(sp^3)–H amination. The conversion of the aminated product to the corresponding free amino alcohol, however, had failed (Scheme S1, ESI†).[11,12] Bis(2,2,2-trichloroethyl)azodicarboxylate (TrocN=NTroc, BTCEAD) instead of DEAD was chosen as a nitrogen source and an oxidant for the regeneration of phthalimide *N*-oxyl (PINO) (for the reaction mechanism; see Fig. S1, ESI†), under the expectation that the corresponding aminated products would convert to free amino alcohols.[11]

We treated **1a** with NHPI (10 mol%) and BTCEAD (2.4 equiv.) in HFIP at 60 °C for 5 h. The C–H amination efficiently proceeded to afford the desired product **2a** in 89% yield (Table 1, entry 1). The same reaction was then administered in DCE. **2a** was produced in 43% yield with 11% of **1a** remaining unaffected. A small amount of pyrazolidine **3a** was also produced through alcohol oxidation alongside several unidentified side products (entry 2). Although **1a** was fully consumed after prolonging the reaction time to 24 h, the yield of **2a** had decreased to 24%. In contrast, the yield of **3a** increased to 19%. Small amounts of **4a** and **5** which were formed from the condensation of **2a** and BTCEAD, and/or the condensation of **1a** and BTCEAD and the subsequent C–H amination, were also produced (entry 3). The reaction in HFIP after 24 h yielded only trace amounts of **3a** and no trace of either **4a** or **5**, although the yield of **2a** had slightly decreased (entry 4). These results suggest that alcohol oxidation, as well as the condensation of **2a** and/or **1a** with BTCEAD, are suppressed in HFIP.

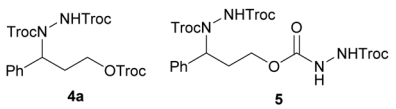
Having developed an effective protocol for the chemoselective benzylic C–H amination, the reactions of ω-phenylalkanols with various alkyl chain lengths were examined (Fig. 2). The benzylic C–H bonds of ω-phenylalkanols, including the long alkyl chain bearing **1e**, were efficiently aminated to produce the desired products **2b–2e**. Note that the amination of **1b** bearing a hydroxy group adjacent to the benzylic C–H bond also proceeded with high chemoselectivity to provide **2b** in 83% yield.

Next, a variety of 3-arylpropanols were subjected to the reaction to examine the effects of substituents bonded to an aromatic ring (Fig. 3). The reactions of 4-*tert*-butyl-, 4-phenyl- and 4-fluoro-substituted phenylpropanols (**1f–1h**) produced **2f–2h** in high yields (80–95%). The moderately electron-withdrawing 4-chloro and 4-bromo-substituted phenylpropanols (**2i** and **2j**) were also obtained in high yields (85%). Although the reactions of strongly electron-withdrawing 4-trifluoromethyl- and 4-methoxycarbonyl-substituted phenyl propanols (**1k** and **1l**) provided small amounts of pyrazolidines **3k** and **3l** (6% and 10% yields), the desired products **2k** and **2l** were obtained in 66% and 65% yields, respectively. The reaction of 1-naphthylpropanol (**1m**) produced 28% yield of **6** which was aminated on its aromatic ring along with the desired product **2m** (23% yield), as HFIP enhanced the aromatic amination process.[13] We found that benzylic C–H amination of **1m** selectively occurred in the mixed solvent of HFIP and DCE (1 : 1) to produce **2m** in 70% yield. The mixed solvent was also effective for the chemoselective amination of 2-naphthylpropanol (**1n**) and strongly electron-donating methoxy-substituted phenylpropanols (**1o–1q**), and the desired products (**2n–2q**) were afforded in good to high yields (64–93%). The reaction of acetanilide **1r** produced **2r** in 46% yield along with 14% of trichloroethyl carbonate **4r**; however, the reason for the formation of **4r** remains unclear. When the reaction of **1r** was operated using the less amount of BTCEAD (1.5 equiv.) in HFIP, **2r** was produced in higher yield (63%).

Table 1 Benzylic C–H amination of 3-phenylpropanol (**1a**) using NHPI and BTCEAD in HFIP and DCE



				Yield[a] (%)	
Entry	Solvent	t (°C)	T (h)	**2a**	**3a**
1	HFIP	60	5	89	0
2[b]	DCE	80	2	43	2
3[c]	DCE	80	24	24	19
4	HFIP	60	24	72	Trace



[a] Isolated yields. [b] **1a** (11%) was recovered. [c] **4a** (6%) and **5** (4%) were obtained. Troc = 2.2.2-trichloroethoxycarbonyl.

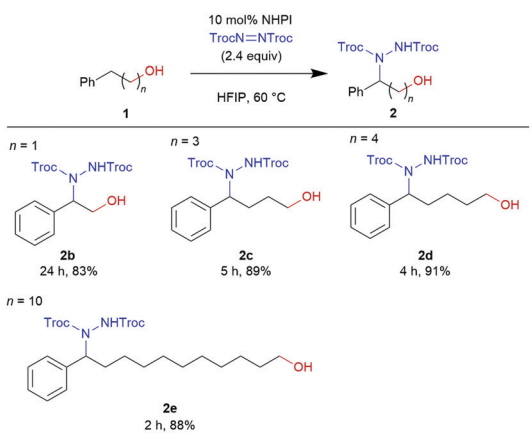


Fig. 2 C–H amination of ω-phenylalkanols.

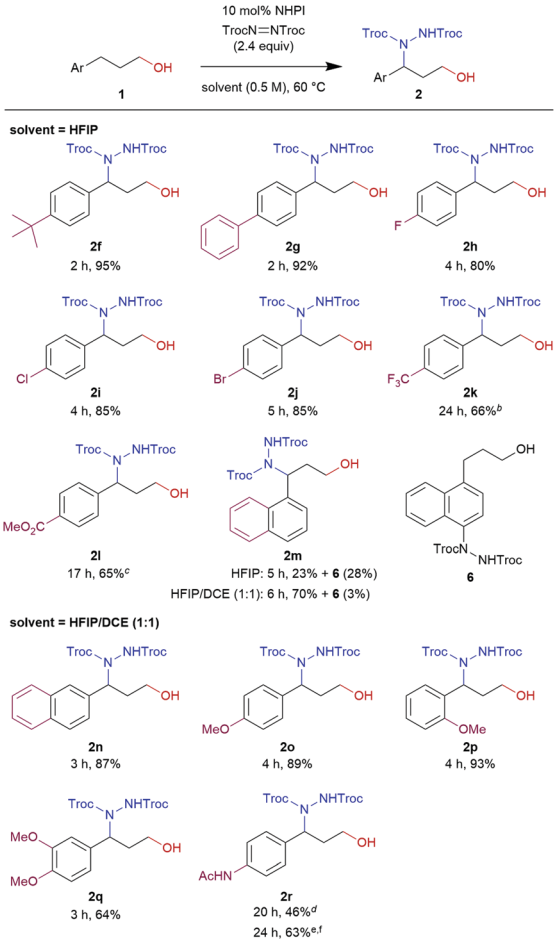
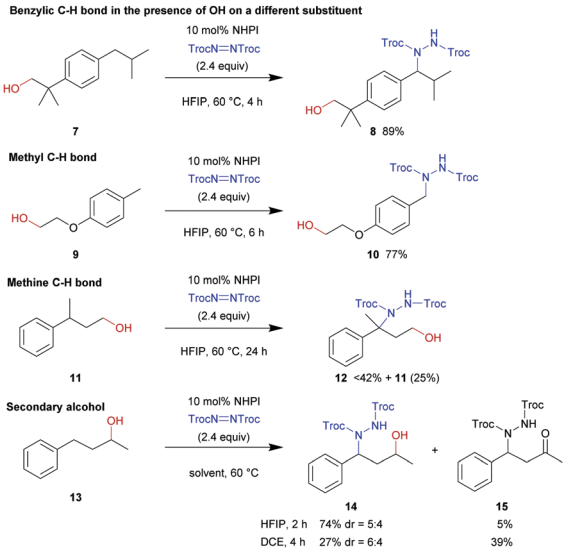


Fig. 3 Scope on the aromatic ring of 3-arylpropanols for the benzylic C–H amination. [a]Isolated yields. [b]**3k** was obtained in 6% yield. [c]**3l** was obtained in 10% yield. [d]**4r** was produced in 14% yield (NMR). [e]BTCEAD (1.5 equiv.) was used and the reaction was operated in HFIP. [f]**4r** was produced in 5% yield (NMR).

We additionally examined the C–H aminations of four substrates to probe the substrate scope (Scheme 1). **7** bearing a remote hydroxy group in a different substituent on its aromatic ring, underwent the desired reaction to provide **8** in 89% yield. Methylarene **9** was also efficiently aminated to provide **10** in 77% yield without overamination products affecting the methylene C–H bond of **10**. The amination of the methine C–H bond in **11** was slow, and **12** was formed in moderate yield (<42%) with inseparable unidentified byproducts after 24 h. Even though the BDE of the C–H bond proximal to a secondary hydroxy group is generally higher than that of the C–H bond proximal to a primary hydroxy group,[10a] the benzylic C–H amination of secondary alkanol **13** proceeded with high chemoselectivity to produce **14** in 74% yield with a small amount of the aminated ketone **15** (5% yield). The reaction of **13** was examined in DCE as a control experiment, which was completed after 4 h to produce **15** as a major product (39% yield) along with **14** (27% yield). As a side note, the benzylic C–H amination of 1,1-dimethyl-3-phenylpropanol (**S3**) which is a tertiary alkanol having no C–H bond proximal



Scheme 1 Additional scope of benzylic C–H amination.

to a hydroxy group afforded the desired product in 88% yield (Scheme S2, ESI†).

To gain insight into the effects of HFIP, ^{13}C NMR spectra of a solution at different ratios of **1c** and HFIP in $CDCl_3$ were collected (Fig. 4a).[14] The signal assigned to the α-carbon of **1c** was shifted downfield as the HFIP to **1c** ratio increased.

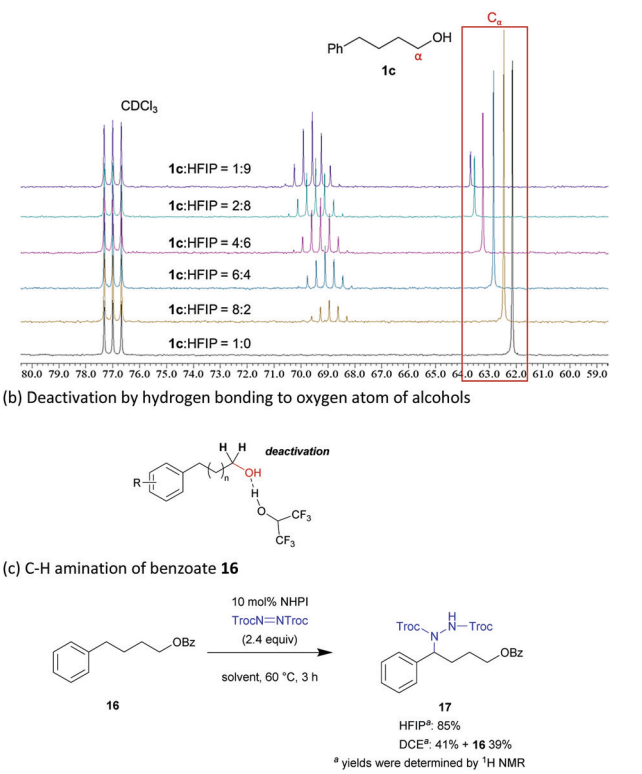
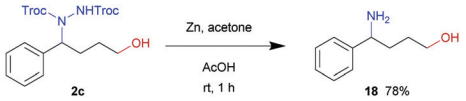


Fig. 4 Control experiments to get insight into the effect of HFIP. (a) ^{13}C NMR spectra of a **1c** and HFIP mixture in $CDCl_3$. (b) Deactivation by hydrogen bonding to the oxygen atom of alcohols. (c) C–H amination of benzoate **16**.



Scheme 2 Preparation of free amino alcohol **18** from **2c**.

These results indicate the presence of hydrogen bonding from HFIP to the oxygen atom of alcohol substrates (Fig. 4b), which deactivates the proximal C–H bonds toward a hydrogen atom abstraction by PINO.[15,16] A similar deactivation effect on the C–H bond proximal to a hydroxy group of HFIP was reported by Costas and coworkers.[17] They reported that Mn-catalyzed C–H oxidation of hydrocarbons produced the corresponding alcohols in HFIP, while the reaction in MeCN produced the corresponding ketones. Pappo and coworkers also reported the NHPI-catalyzed selective oxidation of methylarenes to the corresponding benzaldehydes in HFIP which deactivates the formic C–H bond to suppress the overoxidation to the corresponding carboxylic acids.[18]

We examined the C–H aminations of benzoate **16** in HFIP and DCE, respectively, to compare the reaction rates (Fig. 4c and Fig. S2, ESI†). The reaction in HFIP was completed within 3 h to produce **17** with 85% yield, whereas the reaction in DCE produced **17** in 41% yield and a 39% yield of **16** remained after the same reaction time. These results suggest that C–H amination is accelerated by HFIP. The hydrogen bonding of HFIP to BTCEAD enhances the addition of a benzyl radical intermediate to BTCEAD (Fig. S3, ESI†).

To demonstrate the usefulness of this method, **2c** was treated with Zn in AcOH in the presence of acetone, with a free amino alcohol **18** being obtained in 78% yield (Scheme 2).

In conclusion, we have developed a method of NHPI-catalyzed chemoselective benzylic C(sp^3)–H amination of unprotected arylalkanols. HFIP solvent deactivates the C–H bonds proximal to a hydroxy group, enabling the chemoselective hydrogen atom abstraction at the benzylic position. Benzylic C–H bonds of primary alkanols as well as a secondary alkanol were chemoselectively aminated. Benzylic methylene C–H bonds, as well as a benzylic methyl C–H bond, were also efficiently aminated. Aminated products can be converted to the corresponding free amino alcohols *via* zinc reduction. Chemoselective amination enables a direct conversion of arylalkanols to the corresponding amino alcohols without the use of a protective group, which facilitates a step- and atom-economic synthesis toward producing pharmaceutically important amino alcohols.

This work was partially supported by JSPS KAKENHI (no. JP19K06973), and Platform Project for Supporting Drug Discovery and Life Science Research (BINDS, no. JP21am0101099) from AMED. We thank Shin-ichi Suzuki for experimental help.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960–9009; (*b*) D. Hazelard, P.-A. Nocquet and P. Compain, *Org. Chem. Front.*, 2017, **4**, 2500–2521; (*c*) Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301; (*d*) H. Hayashi and T. Uchida, *Eur. J. Org. Chem.*, 2020, 909–916.
2 (*a*) Y. Kohmura and T. Katsuki, *Tetrahedron Lett.*, 2001, **42**, 3339–3342; (*b*) Z. Ni, Q. Zhang, T. Xiong, Y. Zheng, Y. Li, H. Zhang, J. Zhang and Q. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 1244–1247; (*c*) X. Huang, T. M. Bergsten and J. T. Groves, *J. Am. Chem. Soc.*, 2015, **137**, 5300–5303; (*d*) C. K. Prier, R. K. Zhang, A. R. Buller, S. Brinkmann-Chen and F. H. Arnold, *Nat. Chem.*, 2017, **9**, 629–634; (*e*) A. Wang, N. J. Venditto, J. W. Darcy and M. H. Emmert, *Organometallics*, 2017, **36**, 1259–1268; (*f*) G. X. Li, C. A. Morales-Rivera, F. Gao, Y. Wang, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2017, **8**, 7180–7185; (*g*) J. R. Clark, K. Feng, A. Sookezian and M. C. White, *Nat. Chem.*, 2018, **10**, 583–591; (*h*) S. E. Suh, S. J. Chen, M. Mandal, I. A. Guzei, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2020, **142**, 11388–11393; (*i*) Z. W. Hou, D. J. Liu, P. Xiong, X. L. Lai, J. Song and H. C. Xu, *Angew. Chem., Int. Ed.*, 2021, **60**, 2943–2947.
3 P. Gupta and N. Mahajan, *New J. Chem.*, 2018, **42**, 12296–12327.
4 (*a*) M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325–2327; (*b*) B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schleif, J. C. Quintero, J. H. Lin, I.-W. Chen, M. K. Holloway, P. M. D. Fitzgerald, M. G. Axel, D. Ostovic, P. S. Anderson and J. R. Huff, *J. Med. Chem.*, 1994, **37**, 3443–3451; (*c*) H. Kakeya, M. Morishita, K. Kobinata, M. Osono, M. Ishizuka and H. Osada, *J. Antibiot.*, 1998, **51**, 1126–1128.
5 (*a*) C. G. Espino and J. Du Bois, *Angew. Chem., Int. Ed.*, 2001, **40**, 598–600; (*b*) G. T. Rice and M. C. White, *J. Am. Chem. Soc.*, 2009, **131**, 11707–11711; (*c*) R. Ma, J. Young, R. Promontorio, F. M. Dannheim, C. C. Pattillo and M. C. White, *J. Am. Chem. Soc.*, 2019, **141**, 9468–9473.
6 (*a*) D. N. Zalatan and J. Du Bois, *J. Am. Chem. Soc.*, 2008, **130**, 9220–9221; (*b*) K. Kiyokawa, S. Nakamura, K. Jou, K. Iwaida and S. Minakata, *Chem. Commun.*, 2019, **55**, 11782–11785.
7 (*a*) X. Q. Mou, X. Y. Chen, G. Chen and G. He, *Chem. Commun.*, 2018, **54**, 515–518; (*b*) L. M. Stateman, E. A. Wappes, K. M. Nakafuku, K. M. Edwards and D. A. Nagib, *Chem. Sci.*, 2019, **10**, 2693–2699.
8 T. Kang, H. Kim, J. G. Kim and S. Chang, *Chem. Commun.*, 2014, **50**, 12073–12075.
9 A. H. Hu, J. J. Guo, H. Pan, H. M. Tang, Z. B. Gao and Z. W. Zuo, *J. Am. Chem. Soc.*, 2018, **140**, 1612–1616.
10 (*a*) Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, 2007, pp. 19–134; (*b*) L. M. Reid, T. Li, Y. Cao and C. P. Berlinguette, *Sustainable Energy Fuels*, 2018, **2**, 1905–1927.
11 Y. Amaoka, S. Kamijo, T. Hoshikawa and M. Inoue, *J. Org. Chem.*, 2012, **77**, 9959–9969.
12 P. Magnus, N. Garizi, K. A. Seibert and A. Ornholt, *Org. Lett.*, 2009, **11**, 5646–5648.
13 R. J. Tang, T. Milcent and B. Crousse, *Eur. J. Org. Chem.*, 2017, 4753–4757.
14 (*a*) J. P. Begue, D. Bonnet-Delpon and B. Crousse, *Synlett*, 2004, 18–29; (*b*) A. Shuklov, N. V. Dubrovina and A. Boerner, *Synthesis*, 2007, 2925–2943.
15 M. Bietti, *Angew. Chem., Int. Ed.*, 2018, **57**, 16618–16637.
16 The reaction of **1a** in hexafluoroisopropyl methyl ether afforded **3a** in low yield (<35%); see Scheme S3 (ESI†).
17 V. Dantignana, M. Milan, O. Cusso, A. Company, M. Bietti and M. Costas, *ACS Cent. Sci.*, 2017, **3**, 1350–1358.
18 E. Gaster, S. Kozuch and D. Pappo, *Angew. Chem., Int. Ed.*, 2017, **56**, 5912–5915.

