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A general and green fluoroalkylation reaction promoted *via* noncovalent interactions between acetone and fluoroalkyl iodides†

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The first example of visible light promoted fluoroalkylation reactions initiated *via* noncovalent interactions between acetone and fluoroalkyl iodides is presented. The reaction system features synthetic simplicity, mild reaction conditions without any photoredox catalyst, and high functional group tolerance. A wide range of substrate scopes such as alkenes, alkynes and (hetero)arenes were all compatible with the reaction system.

Fluorinated compounds have attracted much attention as candidates for pharmaceuticals and functional materials because of their superior lipophilicity, binding selectivity, bioavailability, and metabolic stability compared to their nonfluoroalkylated analogs.¹ Consequently, to meet the increasing demand for these materials in the life sciences and materials science, the development of more practical, economical and environmentally friendly methods enabling the efficient construction of fluorine-containing organic compounds has been one of the most important research topics in organofluorine chemistry.

In the past ten years, numerous methods have been developed to synthesize fluoroalkylated compounds with high efficiency, and major improvements were made *via* transition-metal catalysts or photo-excited catalysts.² Very recently, noncovalent interaction (EDA complexes or halogen bond) initiated radical fluoroalkylations have emerged as an attractive and useful strategy to directly introduce fluorinated groups into organic molecules.³ In such transformations, the noncovalent interaction usually occurs between excess amounts of amines or substrates and R_FI. We envision that noncovalent interactions might also occur between

the solvent and R_FI, and a radical intermediate could be generated under the irradiation of visible light if the driving force is strong enough, thus leading to the discovery of unprecedented transformations.

Acetone is one of the most common solvents. We assumed that a noncovalent interaction between the carbonyl group and C–I bond might occur, which could induce radical intermediates under the irradiation of visible light. To test the hypothesis above, we began our investigations by treating alkenes with R_FI in acetone to study the atom transfer radical addition (ATRA) reaction. Usually, this protocol was realized by using radical initiators, such as peroxide,⁴ Na₂S₂O₄,⁵ Et₃B,⁶ or UV light.⁷ Recently, transition-metal⁸ and photoredox catalysis⁹ have emerged as more effective alternatives, and the utilization of amines,¹⁰ phenols¹¹ or phosphines¹² as catalysts has also been developed in the past several months (Scheme 1). Herein, we report the first example of visible light promoted fluoroalkylation reactions *via* noncovalent interactions between the solvent and R_FI. A variety of substrate scopes such as alkenes, alkynes and (hetero)arenes were all compatible with the reaction system.

Accordingly, we conducted this reaction by treating *tert*-butyl allylcarbamate **1a** and ethyl iododifluoroacetate **2a** (1.5 equiv.) as model substrates. To our delight, 74% yield of the desired product **3a** was obtained when the reaction was performed with K₂CO₃ (1.0 equiv.) in acetone and irradiated by blue LEDs for 16 hours. Further optimization of the inorganic bases demonstrated that other bases were less effective, and the desired product **3a** was

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Scheme 1 Methods for 1,2-addition of fluoroalkyl iodides to alkenes and alkynes.

Table 1 Representative results for the optimization of the visible-light-promoted difluoroalkylation of allylcarbamate **1a**^a

Entry	LEDs (nm)	Solvent	Base (equiv.)	Yield ^b (%)
1	Blue (430–490)	Acetone	K ₂ CO ₃ (1)	74
2	Blue (430–490)	Acetone	KOAc (1)	64
3	Blue (430–490)	Acetone	K ₂ CO ₃ (2)	99 (93)
4	Blue (430–490)	Acetone	Na ₂ CO ₃ (2)	81
5	—	Acetone	K ₂ CO ₃ (2)	0
6	Blue (430–490)	Acetone	—	49
7	Blue (450–455)	Acetone	K ₂ CO ₃ (2)	93
8	Blue (470–475)	Acetone	K ₂ CO ₃ (2)	91
9	Blue (490–495)	Acetone	K ₂ CO ₃ (2)	72
10	Green (510–515)	Acetone	K ₂ CO ₃ (2)	67
11	Green (545–550)	Acetone	K ₂ CO ₃ (2)	52
12	Blue (430–490)	S-1	K ₂ CO ₃ (2)	82
13	Blue (430–490)	S-2	K ₂ CO ₃ (2)	0
14	Blue (430–490)	S-3	K ₂ CO ₃ (2)	0
15	Blue (430–490)	Dioxane	K ₂ CO ₃ (2)	0
16	Blue (430–490)	MeCN	K ₂ CO ₃ (2)	68
17	Blue (430–490)	DMA	K ₂ CO ₃ (2)	26
18	Blue (430–490)	DMSO	K ₂ CO ₃ (2)	5

S-1:		S-2:		S-3:	
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^a Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv.), **2a** (0.45 mmol, 1.5 equiv.), acetone (2.0 mL), room temperature, 16 h. ^b NMR yield determined by ¹⁹F NMR using fluorobenzene as an internal standard and the number in parentheses is yield of isolated product.

isolated in 93% yield when 2.0 equiv. of K₂CO₃ was used (Table 1, entries 1–4). No desired product was observed when control experiments were carried out in the dark, confirming the photochemical nature of the transformation (Table 1, entry 5). To our surprise, the product **3a** at 49% yield was still obtained without bases (Table 1, entry 6). Finally, various short-wavelength LEDs were used as light sources to examine the influence of optical wavelength on the reaction, comparable yields were still obtained when LEDs with wavelengths between 425 and 475 nm were used, and the yields decreased with longer wavelengths (Table 1, entries 7–11). For other ketones, 82% yield was still obtained when 3-pentanone was used, and no reaction was observed using ketones with larger substituents (Table 1, entries 12–14). Those results indicate that the interactions between the solvent and fluoroalkyl iodides were decreased with the increase of the steric hindrance. Other solvents were also examined (Table 1, entries 15–18); no reaction occurred when the reaction was performed in dioxane or toluene, and 68% yield was obtained when MeCN was used as the solvent. The major products come from the atom transfer radical addition–elimination (ATRE) reaction when conducted in DMA or DMSO. We reason that noncovalent interactions also occurred between the solvent and R_FI (Table 1, entries 17 and 18, for details, see the ESI[†]).

With the optimized reaction conditions in hand, the scope of this photochemical atom transfer radical addition was evaluated using abundant structurally diverse terminal alkenes.¹⁰ As shown in Table 2, functional groups such as amine, esters, naphthyl and methoxy were well-tolerated and provided difluoroalkylated ATRA

Table 2 Scope of the 1,2-addition reaction of fluoroalkyl iodides to alkenes^{a,b}

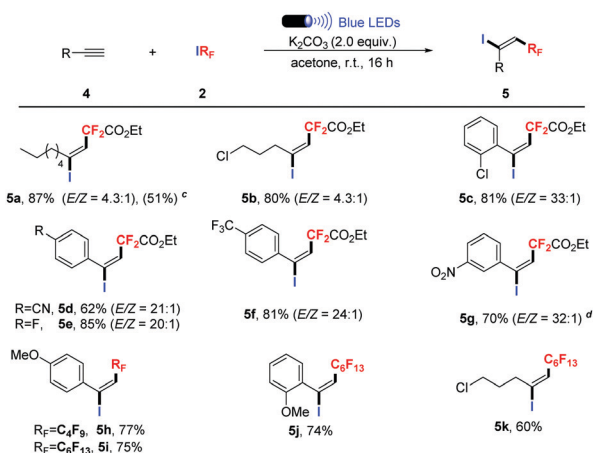
1	2	3
3a , 93% (80%) ^c	3b , 78%	3c , 85%
3d , 96%	3e , 73% ^d	3f , 84%
3g , 91%	R _F =C ₄ F ₉ , 3h , 72% ^d R _F =C ₆ F ₁₃ , 3i , 70% ^d	R _F =C ₄ F ₉ , 3j , 76% ^d R _F =C ₆ F ₁₃ , 3k , 72% ^d
R _F =C ₄ F ₉ , 3l , 79% ^d R _F =C ₆ F ₁₃ , 3m , 79% ^d	3n , 84%	3o , 68%
3p , 72% ^e	3q , 55% ^e	3r , 41% ^e

^a Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.45 mmol, 1.5 equiv.), K₂CO₃ (0.6 mmol, 2.0 equiv.) in acetone (2.0 mL), room temperature, 12 W blue LEDs (430–490 nm), 16 h. ^b Yield of isolated product. ^c **1a** (10 mmol, 1.0 equiv.), **2a** (15 mmol, 1.5 equiv.), K₂CO₃ (2.0 equiv.), acetone (40 mL), room temperature, 24 W blue LED (430–490 nm), 48 h. ^d **2** (2.0 equiv.) was used. ^e CF₃I (5.0 equiv.) was used.

products in good to excellent yields (Table 2, **3a–g**). This reaction system is also amenable to the use of other commercial perfluoroalkyl iodides, such as C₄F₉I and C₆F₁₃I, and the corresponding products were obtained in moderate to good yields (Table 2, **3h–o**). CF₃I was less reactive, and moderate to good yields could be provided when 5.0 equiv. of CF₃I was used (Table 2, **3p–r**). Remarkably, when the reaction was performed on a gram scale (**3a**), an 80% yield was still obtained, demonstrating the synthetic utility of the protocol.

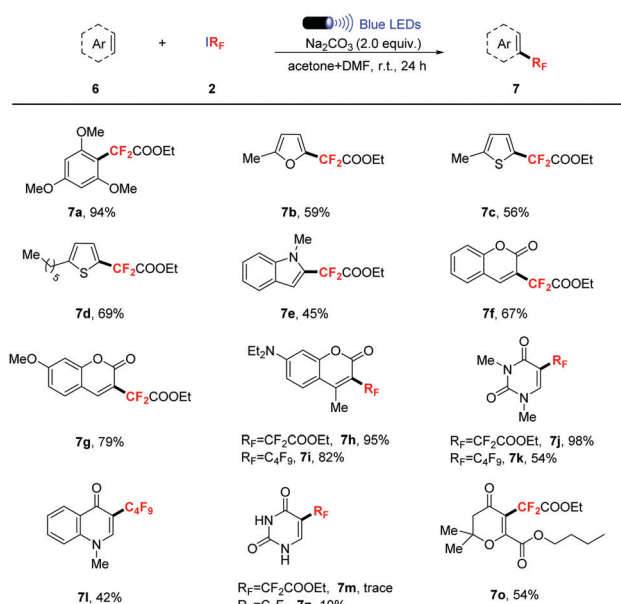
Then, we extended the substrate scope to a variety of terminal alkynes. Many important functional groups, such as halide, cyano, methoxy trifluoromethyl and even nitro underwent the process smoothly (Table 3). For aliphatic alkynes, high yield with low stereoselectivity was provided (Table 3, **5a–b**). Phenylacetylenes were suitable substrates, and high stereoselectivity could be obtained (Table 3, **5c–g**). Moreover, we found that the transformation presented good reactivity when C₄F₉I and C₆F₁₃I were employed, and provided the desired products in good yields (Table 3, **5h–k**).

Encouraged by the results of the 1,2-addition of R_FI to alkenes and alkynes, we proceeded to investigate direct fluoroalkylation of arenes.¹³ Pleasingly, by using DMF as a co-solvent, a wide range of arenes and heteroarenes underwent the catalyst-free fluoroalkylation smoothly. 94% yield was obtained when 1,3,5-trimethoxybenzene was treated (Table 4, **7a**). Five membered heteroarenes such as furan, thiophene and pyrrole were relatively inert reaction partners, and only moderate yields were given (Table 4, **7b–e**). Coumarins and 1,3-dimethyluracil were also suitable substrates

Table 3 Scope of the 1,2-addition reaction of fluoroalkyl iodides to alkynes^{a,b}

^a Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.45 mmol, 1.5 equiv.), K₂CO₃ (0.6 mmol, 2.0 equiv.) in acetone (2.0 mL), room temperature, 12 W blue LEDs (430–490 nm), 16 h. ^b Yield of isolated product. ^c Without K₂CO₃. ^d **2** (2.0 equiv.) was used.

for this transformation, delivering the desired products in good to excellent yields (Table 4, **7f–h**, **7j**). In addition, the C–H perfluoroalkylation of heteroarenes with C₄F₉I was also investigated, and moderate to good yields were still obtained (Table 4, **7i**, **7k–l**). Unprotected uracil failed to give satisfactory results (Table 4, **7m–n**), which indicated that the mechanism of this transformation is different from our previous report.^{3f} Moreover, butopyronoxyl was also a suitable substrate, and 54% yield was obtained (Table 4, **7o**).

Table 4 Direct fluoroalkylation of arenes and heterocycles^{a,b}

^a Reaction conditions: **6** (0.3 mmol, 1.0 equiv.), **2** (0.9 mmol, 3.0 equiv.), Na₂CO₃ (0.6 mmol, 2.0 equiv.), acetone (1.0 mL) + DMF (1.0 mL), room temperature, 12 W blue LEDs (430–490 nm), 24 h. ^b Yield of isolated product.

**Fig. 1** Optical absorption spectra studies.

To gain insight into the mechanism of this transformation, a series of experiments were conducted. The reaction was suppressed by the addition of a radical scavenger TEMPO (100 mol%) and only 15% yield of **3a** was obtained, which suggests that the involvement of radical intermediates is likely during the reaction (for details, see the ESI[†]). A radical clock experiment employing alpha-cyclopropylstyrene **8** as a substrate produced the ring-opening product **9** in 82% yield (for details, see the ESI[†]). Optical absorption spectra of the reactants found that the absorption was clearly strengthened when **2a** and acetone were mixed, and those results indicate that non-covalent interactions occurred between acetone and **2a** (Fig. 1, for details, see the ESI[†]). In addition, this conclusion was further confirmed by a Job's plot. Finally, the light–dark experiment was performed using alternative intervals of light and dark, and the formation of the product was both feasible during periods of irradiation and dark, which is suggestive of a radical chain process (for details, see the ESI[†]).

Based on these preliminary results, a plausible mechanism for this transformation was proposed in Scheme 2. First, non-covalent interactions occurred between acetone and the fluoroalkyl iodides. Then, a fluoroalkyl radical was generated under the irradiation of blue LEDs. Subsequent regioselective addition of •R_F to alkenes or alkynes (**1** or **4**) lead to the carbon-radical intermediate (**B**), which abstracted an iodine atom from R_FI to afford the desired product **3** or **5** and regenerated the R_F radical. For arenes, cation species were generated *via* a SET process from an intermediate **C**, and the fluoroalkylated products (**7**) were obtained by further deprotonation.

In summary, we have developed a simple, mild, and efficient protocol for photochemical fluoroalkylation reactions *via* non-covalent interactions between acetone and fluoroalkyl iodides. The significant advantages of this method are high atom economy, excellent functional group tolerance, and synthetic simplicity, thus providing a facile route for further application in pharmaceuticals and life sciences. Mechanistic studies indicate that the reaction

**Scheme 2** Proposed plausible reaction mechanism.

was initiated *via* non-covalent interactions between acetone and carbon-iodine bonds.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- For selected reviews, see: (a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (d) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719; (e) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (f) C. S. Burgey, K. A. Robinson, T. A. Lyle, P. E. J. Sanderson, S. Dale Lewis, B. J. Lucas, J. A. Krueger, R. Singh, C. Miller-Stein, R. B. White, B. Wong, E. A. Lyle, P. D. Williams, C. A. Coburn, B. D. Dorsey, J. C. Barrow, M. T. Stranieri, M. A. Holahan, G. R. Sitko, J. J. Cook, D. R. McMasters, C. M. McDonough, W. M. Sanders, A. A. Wallace, F. C. Clayton, D. Bohn, Y. M. Leonard, T. J. Detwiler, Jr, J. J. Lynch, Jr, Y. Yan, Z. Chen, L. Kuo, S. J. Gardell, J. A. Shafer and J. P. Vacca, *J. Med. Chem.*, 2003, **46**, 461; (g) G. L. Grunewald, M. R. Seim, J. Lu, M. Makboul and K. R. Criscione, *J. Med. Chem.*, 2006, **49**, 2939; (h) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529.
- For selected reviews, see: (a) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (b) C. Alonso, E. M. Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847; (c) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (d) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513; (e) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731; (f) Z. Feng, Y.-L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264; (g) T. Chatterjee, N. Iqbal, Y. You and E. J. Cho, *Acc. Chem. Res.*, 2016, **49**, 2284; (h) D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem. – Eur. J.*, 2017, **23**, 14676; (i) J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes and B. Koksche, *Chem. Rev.*, 2019, **119**, 10718; (j) X. Shao, C. Xu, L. Lu and Q. Shen, *Acc. Chem. Res.*, 2015, **48**, 1227; (k) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470.
- For representative papers, see: (a) M. Nappi, G. Bergonzini and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2014, **53**, 4921; (b) V. M. Fernández-Alvarez, M. Nappi, P. Melchiorre and F. Maseras, *Org. Lett.*, 2015, **17**, 2676; (c) S. R. Kandukuri, A. Bahamonde, I. Chatterjee, I. D. Jurberg, E. C. Escudero-Adán and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2015, **54**, 1485; (d) Q. Guo, M. Wang, H. Liu, R. Wang and Z. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 4747; (e) Y. Wang, J. Wang, G.-X. Li, G. He and G. Chen, *Org. Lett.*, 2017, **19**, 1442; (f) Y. Huang, Y.-Y. Lei, L. Zhao, J. Gu, Q. Yao, Z. Wang, X.-F. Li, X. Zhang and C.-Y. He, *Chem. Commun.*, 2018, **54**, 13662; (g) Y. Liu, X.-L. Chen, K. Sun, X.-Y. Li, F.-L. Zeng, X.-C. Liu, L.-B. Qu, Y.-F. Zhao and B. Yu, *Org. Lett.*, 2019, **21**, 4019; (h) H.-Y. Tu, S. Zhu, F.-L. Qing and L. Chu, *Chem. Commun.*, 2018, **54**, 12710; (i) G.-R. Park, Y. Choi, M. G. Choi, S.-K. Chang and E. J. Cho, *Asian J. Org. Chem.*, 2017, **6**, 436; (j) Y. Cheng, X. Yuan, J. Ma and S. Yu, *Chem. – Eur. J.*, 2015, **21**, 8355; (k) D. Zheng and A. Studer, *Org. Lett.*, 2019, **21**, 325; For review, see: (l) A. Postigo, *Eur. J. Org. Chem.*, 2018, 6391.
- X. Fang, X. Yang, X. Yang, S. Mao, Z. Wang, G. Chen and F. Wu, *Tetrahedron*, 2007, **63**, 10684.
- A.-R. Li and Q.-Y. Chen, *Synthesis*, 1997, 333.
- (a) Y. Takeyama, Y. Ichinose, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, 1989, **30**, 3159; (b) Y. Li, H. Li and J. Hu, *Tetrahedron*, 2009, **65**, 478.
- (a) K. Tsuchii, M. Imura, N. Kamada, T. Hirao and A. Ogawa, *J. Org. Chem.*, 2004, **69**, 6658; (b) R. Beniazza, L. Remisse, D. Jardel, D. Lastecoueres and J.-M. Vincent, *Chem. Commun.*, 2018, **54**, 7451.
- (a) T. Xu, C. W. Cheung and X. Hu, *Angew. Chem., Int. Ed.*, 2014, **53**, 4910; (b) G. Wu and A. J. von Wangelin, *Chem. Sci.*, 1795, 2018, 9.
- (a) T. Yajima and M. Ikegami, *Eur. J. Org. Chem.*, 2017, 2126; (b) F. Sladojevich, E. McNeill, J. Börgel, S.-L. Zheng and T. Ritter, *Angew. Chem., Int. Ed.*, 2015, **54**, 3712; (c) G. Magagnano, A. Gualandi, M. Marchini, L. Mengozzi, P. Ceroni and P. G. Cozzi, *Chem. Commun.*, 2017, **53**, 1591; (d) J. D. Nguyen, J. W. Tucker, M. D. Konieczynska and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2011, **133**, 4160; (e) Y. Du, R. M. Pearson, C.-H. Lim, S. M. Sartor, M. D. Ryan, H. Yang, N. H. Damrauer and G. M. Miyake, *Chem. – Eur. J.*, 2017, **23**, 10962; (f) R. Beniazza, R. Atkinson, C. Absalon, F. Castet, S. A. Denisov, N. D. McClenaghan, D. Lastecoueres and J.-M. Vincent, *Adv. Synth. Catal.*, 2016, **358**, 2949; (g) S. Kim, G. Park, E. J. Cho and Y. You, *J. Org. Chem.*, 2016, **81**, 7072.
- C. Rosso, J. D. Williams, G. Filippini, M. Prato and C. O. Kappe, *Org. Lett.*, 2019, **21**, 5341.
- E. Zhu, X.-X. Liu, A.-J. Wang, T. Mao, L. Zhao, X. Zhang and C.-Y. He, *Chem. Commun.*, 2019, **55**, 12259.
- (a) L. Zhao, Y. Huang, Z. Wang, E. Zhu, T. Mao, J. Jia, J. Gu, X.-F. Li and C.-Y. He, *Org. Lett.*, 2019, **21**, 6705; (b) L. Helmecke, L. Spittler, K. Baumgarten and C. Czekelius, *Org. Lett.*, 2019, **21**, 7823.
- For recent examples on direct fluoroalkylation of arenes and heteroarenes, see: (a) M. J. Hossain, T. Ono, K. Wakiya and Y. Hisaeda, *Chem. Commun.*, 2017, **53**, 10878; (b) L. Wang, X.-J. Wei, W.-L. Jia, J.-J. Zhong, L.-Z. Wu and Q. Liu, *Org. Lett.*, 2014, **16**, 5842; (c) W. Yu, X.-H. Xu and F.-L. Qing, *Org. Lett.*, 2016, **18**, 5130; (d) J. Jung, E. Kim, Y. You and E. J. Cho, *Adv. Synth. Catal.*, 2014, **356**, 2741; (e) X. Wang, S. Zhao, J. Liu, D. Zhu, M. Guo, X. Tang and G. Wang, *Org. Lett.*, 2017, **19**, 4187; (f) C.-H. Qu, G.-T. Song, J. Xu, W. Yan, C.-H. Zhou, H.-Y. Li, Z.-Z. Chen and Z.-G. Xu, *Org. Lett.*, 2019, **21**, 8169; (g) S. Zhang, N. Rotta-Loria, F. Weniger, J. Rabeah, H. Neumann, C. Taeschler and M. Beller, *Chem. Commun.*, 2019, **55**, 6723; (h) B. Yang, D. Yu, X.-H. Xu and F.-L. Qing, *ACS Catal.*, 2018, **8**, 2839; (i) C. Yuan, L. Zhu, Y. Lan and Y. Zhao, *Angew. Chem., Int. Ed.*, 2018, **57**, 1277; (j) C.-Y. He, J. Kong, X. Li, X. Li, Q. Yao and F.-M. Yuan, *J. Org. Chem.*, 2017, **82**, 910.