

RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2018, 5, 1155

Transition metal-free aminofluorination of β,γ -unsaturated hydrazones: base-controlled regioselective synthesis of fluorinated dihydropyrazole and tetrahydropyridazine derivatives†

Juan Zhao, Min Jiang * and Jin-Tao Liu *

Received 8th December 2017,
Accepted 25th January 2018

DOI: 10.1039/c7qo01105a

rsc.li/frontiers-organic

Various base-controlled regioselective reactions of β,γ -unsaturated hydrazones with Selectfluor were achieved under transition metal-free conditions. In the presence of K_2HPO_4 or $NaHCO_3$, the intramolecular aminofluorination reaction took place readily to give the corresponding monofluoromethylated dihydropyrazoles or fluoro-tetrahydropyridazines, respectively. The possible pathways were proposed based on the experimental results.

Introduction

Selective introduction of fluorine or fluorine-containing functional groups into organic molecules is becoming increasingly prevalent with *ca.* 40% of agrochemicals and *ca.* 20% of pharmaceuticals containing at least one fluorine atom.¹ Compounds containing a C–F bond frequently experience dramatic changes of their properties (*i.e.* hydrophobicity, solubility, and metabolic stability) compared to their corresponding C–H counterparts.² In particular, the synthesis of functionalized fluorinated heterocycles has become a very important weapon in the armamentarium of medicinal chemistry.³

Dihydropyrazoles and tetrahydropyridazines are frequently found in natural products and pharmacologically active compounds. Being privileged and valuable N–N bond-containing heterocyclic scaffolds, they also serve as versatile intermediates in organic synthesis.⁴ Consequently, great efforts have been devoted to the development of elegant and creative strategies to construct these nitrogen heterocycles, and most research studies are based on thermal cycloaddition reactions.^{5,6} Recently, a series of hydrazone radical-involved cyclization reactions have emerged as new powerful protocols for their assembly.^{7,8} In these reactions, stoichiometric oxidants

were usually employed to generate the key hydrazone radicals.

It is well known that the intramolecular aminofluorination of alkenes is a straightforward and step-economical protocol to synthesize nitrogen-containing heterocycles with vicinal amino and fluorine moieties.⁹ In 2009, Liu's group developed a Pd-catalyzed intramolecular aminofluorination of alkenes, which provided a variety of fluorinated piperidines.^{9a} Later, further studies were conducted to make other types of fluorinated heterocycles.^{9b–i} However, these elegant studies usually required transition metal catalysts and hypervalent iodine reagents.⁹ Recently, we reported a transition metal-free intramolecular cyclization of alkenyl oximes for the synthesis of monofluoromethylated isoxazolines.¹⁰ As part of our continuing research on the fluorination of unsaturated alkenes, we further studied the transition metal-free intramolecular cyclization/fluorination reaction of β,γ -unsaturated hydrazones. In the reaction, Selectfluor served as both oxidant and fluorine source.^{10,11} It was found that the reaction pathway could be controlled by different base, and the corresponding monofluoromethyl dihydropyrazoles and fluorotetrahydropyridazines were firstly obtained regioselectively in the presence of different bases (Scheme 1). The results are reported in this paper.

Results and discussion

In our initial experiments, β,γ -unsaturated hydrazone **1a** was chosen as the substrate. Based on our previous work,¹⁰ the reaction was carried out with 1.1 equiv. of Selectfluor and

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: jtliu@sioac.ac.cn, jiangmin@sioac.ac.cn; <http://www.sioac.ac.cn>; Fax: +86-21-64166128

† Electronic supplementary information (ESI) available: Experimental, spectral data and copies of spectra. See DOI: 10.1039/c7qo01105a



Scheme 1 Base-controlled regioselective reactions of β,γ -unsaturated hydrazones.

2.0 equiv. of NaHCO_3 in acetonitrile (CH_3CN) at room temperature.

However, only trace amount of desired product monofluoromethylated dihydropyrazole **2a** was observed with a large amount of **1a** being recovered (Table 1, entry 1). Increasing the reaction temperature to 50 °C improved the yield of **2a** to 25% (entry 2). Surprisingly, when the reaction was carried out at above 80 °C, fluorotetrahydropyridazine **3a** was formed as the major product along with a small amount of **2a**. At 100 °C, the reaction could finish in only 1 hour and **3a** was obtained in 54% yield (entries 3–7). Other solvents, such as dimethylformamide (DMF), ethyl acetate (EtOAc), acetone, tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM) or

toluene, were not suitable for this reaction. It is worth mentioning that only **2a** was formed in nitromethane (CH_3NO_2) (entry 8).

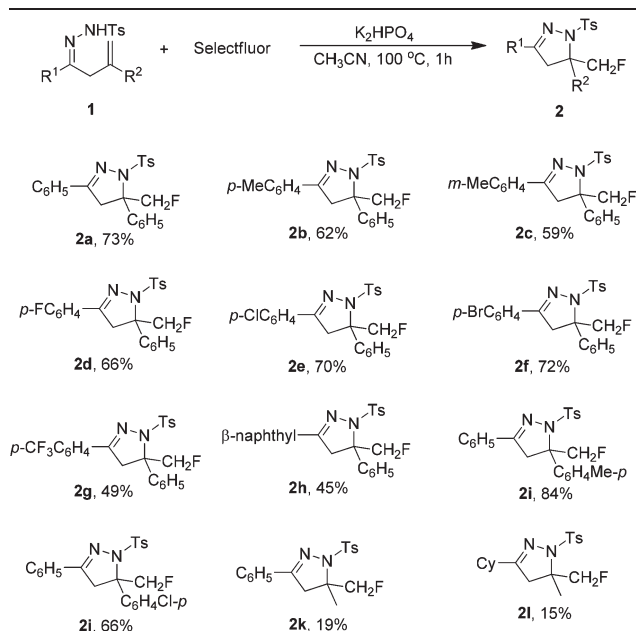
The ratio of **1a** and Selectfluor was then evaluated. It was found that the best result with respect to regioselectivity and the yield of **3a** was obtained with 1.2 equiv. of Selectfluor (entries 9–11). Further screening of bases showed that inorganic bases such as Na_2CO_3 , KHCO_3 , K_2CO_3 , NaOH and Cs_2CO_3 gave both isomers with lower selectivities and yields (entries 13–17). However, it was interesting to find that some phosphates, such as $\text{K}_2\text{HPO}_4 \cdot 3\text{H}_2\text{O}$, KH_2PO_4 , NaH_2PO_4 , K_3PO_4 , Na_2HPO_4 and K_2HPO_4 afforded **2a** as the sole product (entries 18–23), and up to 79% yield of **2a** was achieved in the presence of K_2HPO_4 (entry 23). No desired product was observed when organic bases such as DABCO and triethylamine were used (entries 24 and 25). These results indicated that the regioselectivity of this intramolecular aminofluorination reaction could be controlled by different bases: NaHCO_3 helped to form fluorotetrahydropyridazine **3a** as the major product, while only monofluoromethylated dihydropyrazole **2a** was obtained in the presence of K_2HPO_4 . This might be attributed to the basicity and solubility of the base. NaHCO_3 ($\text{pK}_a = 10.25$) is a medium strength base with good solubility in the reaction system, but K_2HPO_4 ($\text{pK}_a = 12.32$) is poorly soluble in the reaction system.¹²

Under the optimized conditions (Table 1, entry 23), the scope of β,γ -unsaturated hydrazones **1** was first investigated in

Table 1 Optimization of reaction conditions

Entry ^a	1a : [F]	Base	Solvent	<i>t</i> /h	Temp/°C	2a ^b /%	3a ^b /%
1	1 : 1.1	NaHCO_3	CH_3CN	12	rt	3	—
2	1 : 1.1	NaHCO_3	CH_3CN	12	50	25	—
3	1 : 1.1	NaHCO_3	CH_3CN	12	80	10	39
4	1 : 1.1	NaHCO_3	CH_3CN	12	100	10	55
5	1 : 1.1	NaHCO_3	CH_3CN	12	120	16	50
6	1 : 1.1	NaHCO_3	CH_3CN	4	100	12	52
7	1 : 1.1	NaHCO_3	CH_3CN	1	100	11	54
8	1 : 1.1	NaHCO_3	CH_3NO_2	1	100	42	—
9	1 : 1.0	NaHCO_3	CH_3CN	1	100	17	46
10	1 : 1.2	NaHCO_3	CH_3CN	1	100	12	66
11	1 : 1.4	NaHCO_3	CH_3CN	1	100	22	51
12	1 : 1.2	—	CH_3CN	1	100	20	—
13	1 : 1.2	Na_2CO_3	CH_3CN	1	100	26	10
14	1 : 1.2	KHCO_3	CH_3CN	1	100	23	17
15	1 : 1.2	K_2CO_3	CH_3CN	1	100	16	15
16	1 : 1.2	NaOH	CH_3CN	1	100	15	5
17	1 : 1.2	Cs_2CO_3	CH_3CN	1	100	—	—
18	1 : 1.2	$\text{K}_2\text{HPO}_4 \cdot 3\text{H}_2\text{O}$	CH_3CN	1	100	37	—
19	1 : 1.2	KH_2PO_4	CH_3CN	1	100	60	—
20	1 : 1.2	NaH_2PO_4	CH_3CN	1	100	60	—
21	1 : 1.2	K_3PO_4	CH_3CN	1	100	24	—
22	1 : 1.2	Na_2HPO_4	CH_3CN	1	100	64	—
23	1 : 1.2	K_2HPO_4	CH_3CN	1	100	79	—
24	1 : 1.2	DABCO	CH_3CN	1	100	—	—
25	1 : 1.2	NEt_3	CH_3CN	1	100	—	—

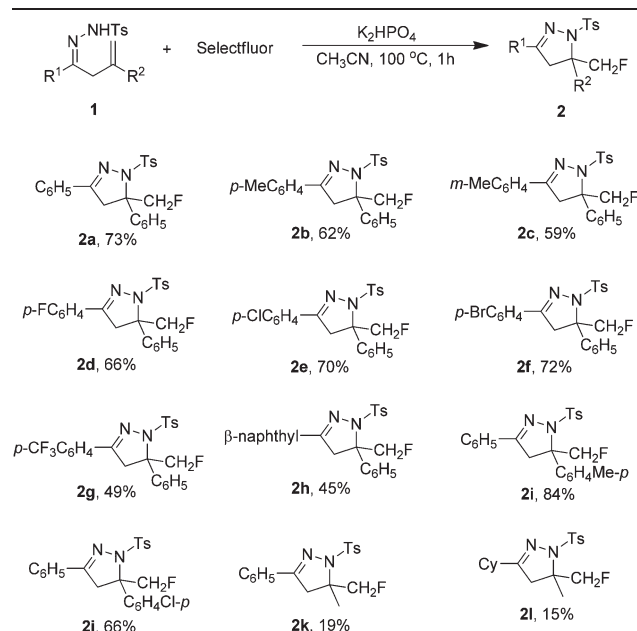
^a Reaction conditions: **1a** (0.2 mmol), Selectfluor (0.2–0.28 mmol), base (0.4 mmol), solvent (4 mL), under a nitrogen atmosphere. ^b Determined by ^{19}F NMR spectroscopy based on **1a** using PhCF_3 as the internal standard.

Table 2 Scope of K_2HPO_4 -promoted intramolecular aminofluorination reaction of β,γ -unsaturated hydrazones^a

^a Reaction conditions: **1** (0.2 mmol), Selectfluor (0.24 mmol), K_2HPO_4 (0.4 mmol), CH_3CN (4 mL), 100 °C, under a nitrogen atmosphere, 1 h. Isolated yields.

the K_2HPO_4 -promoted reaction. As shown in Table 2, various functional groups (R^1) in the hydrazone moiety were compatible with this reaction system. The substituent in the benzene ring, either electron-donating or electron-withdrawing, had a little influence on the yield of **2**. For example, the reaction of **1b** with a *p*-methylphenyl substituent gave desired product **2b** in 62% yield. For hydrazones **1d–f** bearing a halide substituent in the phenyl ring, the corresponding products **2d–f** were obtained in 66–72% yields. Only 49% yield was achieved with hydrazone **1g** containing a strong electron-withdrawing trifluoromethyl group. Hydrazone **1h** with a β -naphthyl group could also react with Selectfluor to give **2h** in 45% yield. However, the reaction was complicated when R^1 was an aliphatic substituent such as cyclohexyl group. Regarding the substituents in the alkene moiety (R^2), it was found that hydrazones bearing an aryl group were suitable substrates for this reaction (**2i** and **2j**), and poor results were obtained again with alkyl substitution (**2k** and **2l**).

The *p*-toluenesulfonyl group in products **2** could be easily removed under mild conditions. The result shown in Scheme 2 indicated that compound **2a** can be efficiently con-

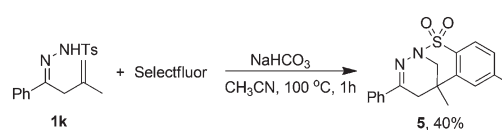
**Scheme 2** Deprotection of **2a**.**Table 3** Scope of $NaHCO_3$ -promoted intramolecular aminofluorination reaction of β,γ -unsaturated hydrazones^a

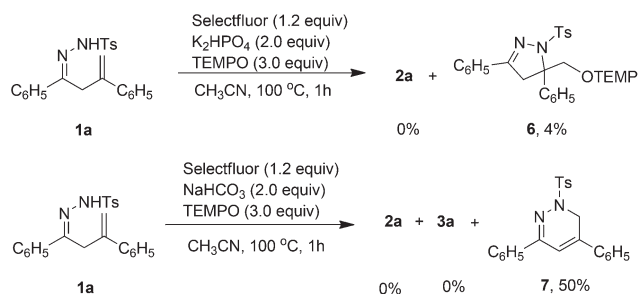
^a Reaction conditions: **1** (0.2 mmol), Selectfluor (0.24 mmol), $NaHCO_3$ (0.4 mmol), CH_3CN (4 mL), 100 °C, under a nitrogen atmosphere, 1 h. Isolated yields of **3**. Ratio determined by ^{19}F NMR spectroscopy.

verted into biologically important monofluoromethyl 3*H*-pyrazole **4a** by treatment with NaOH, and no defluorination reaction was observed in this reaction.

Next, we studied the scope of the $NaHCO_3$ -promoted reaction (Table 1, entry 10). According to the results in Table 3, this protocol also shows a broad substrate scope and functional group tolerance, giving fluorotetrahydropyridazines **3** as the major products. For example, a series of hydrazones bearing an aryl substituent in both hydrazone and alkene moieties reacted well with Selectfluor to give the corresponding products (**3b–f** and **3h–j**) in moderate to good yields along with a small amount of monofluoromethylated dihydropyrazoles **2**. The substitution pattern of the phenyl ring and the electronic property of the substituents had no obvious effect on the reaction. Unfortunately, hydrazone **1k** containing a methyl substituent failed to give the expected cyclic product **3k**, and compound **5** was obtained in 40% yield instead (Scheme 3).

Taking product **3a** as an example, the removal of the Ts group in products **3** was also tried. Unfortunately, the treatment of **3a** with NaOH resulted in the removal of both the Ts group and fluorine atom (see the ESI†). Other reagents, such

**Scheme 3** Reaction of **1k** with Selectfluor in the presence of $NaHCO_3$.



Scheme 4 Control experiments.

as HBr/AcOH and HF/pyridine, did not give the desired deprotection product either.

To gain additional insights into the reaction mechanism, the control experiments were conducted (Scheme 4). When 3.0 equiv. of the radical scavenger TEMPO was added to the K_2HPO_4 -promoted system, the aminofluorination reaction was completely suppressed, and a small amount of aminooxygenation product **6** was observed in the reaction mixture. These results indicated that the fluorination might be a radical process. Similarly, the addition of TEMPO to the $NaHCO_3$ -promoted reaction also inhibited the formation of products **3a** and **2a**. Only 1,6-dihydropyridazine **7** was isolated in 50% yield. According to Xiao's research,¹³ compound **7** might be generated from a N-centered hydrazone radical intermediate.

On the basis of the aforementioned mechanistic studies and related literature,^{10,13,14} plausible mechanisms were proposed for the base-controlled reactions. As shown in Scheme 5, the oxidation of **1** by Selectfluor might initially take place to form cation-radical intermediate **A** (Path A). Subsequent fluorination and cyclization of **A** give intermediate

C, which affords product **2** by hydrogen abstraction. The existence of intermediate **A** and **B** has been confirmed through an ESI mass spectrum by Zhang *et al.*¹⁴ The presence of K_2HPO_4 may accelerate this process due to its compatible basicity. When R^2 is an aryl group, intermediate **A** and **B** are more stable due to its stabilization effect and product **2** is formed in higher yield.

However, in the presence of $NaHCO_3$, the proton atom of NHTs in hydrazones **1** may also be abstracted firstly to give anionic intermediate **D**, which is transformed to N-centred radical **E** by Selectfluor through a SET process (Path B). Then, intermediate **F** and **F'** may be formed from **E** through 5-*exo* radical cyclization and 6-*endo* radical cyclization, respectively. According to the density functional theory (DFT) investigations by Xiao's group,¹³ the 6-*endo* cyclization of the N-radical was more feasible than the 5-*exo* process when R^2 was an aryl group. In the $NaHCO_3$ -promoted reaction, both Path A and Path B may exist as competing reactions, and Path B is the dominant one which affords fluorotetrahydropyridazine **3** as the major product *via* intermediate **F'**.

Conclusions

In summary, we have successfully developed a base-controlled regioselective intramolecular aminofluorination of β,γ -unsaturated hydrazones. Using Selectfluor as the fluorine source, monofluoromethylated dihydropyrazoles and fluorotetrahydropyridazines were synthesized selectively in moderate to good yields in the presence of K_2HPO_4 or $NaHCO_3$, respectively. Good functional group compatibility, scalability, easily available materials, and mild reaction conditions characterize this protocol. Efforts towards an asymmetric variant of this transformation are currently underway in our laboratory.

Conflicts of interest

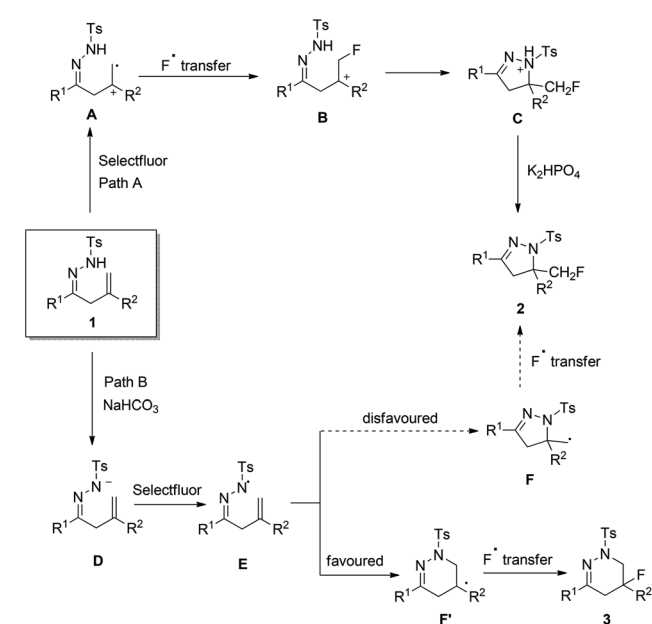
There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation (No. 21572257 and 21502213) and the Science and Technology Commission of Shanghai Municipality (No. 16XD1404400) for generous financial support.

Notes and references

- (a) A. M. Thayer, *Chem. Eng. News*, 2006, **84**, 15; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
- (a) J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; (b) R. E. Banks, B. E. Smart and J. C. Tatlow, *Organofluorine*



Scheme 5 Proposed mechanism for the base-controlled reaction.

- Chemistry: Principles and Commercial Applications*, Plenum Press, New York, 1994; (c) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881.
- 3 (a) D. Cahard, X. Xu, S. Couve-Bonaire and X. Pannecoucke, *Chem. Soc. Rev.*, 2010, **39**, 558; (b) P. Liu, A. Sharon and C.-K. Chu, *J. Fluorine Chem.*, 2008, **129**, 743; (c) K. B. Park, N. R. Kitteringham and P. M. O'Neill, *Annu. Rev. Pharmacol. Toxicol.*, 2001, **41**, 443; (d) A. V. Petrov, *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, John Wiley & Sons, Inc., New York, NY, 2009; (e) V. Gouverneur and K. Miller, *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*, Imperial College Press, London, 2012; (f) D. Barnes-Seeman, J. Beck and C. Springer, *Curr. Top. Med. Chem.*, 2014, **14**, 855.
 - 4 For selected reviews, see: (a) L. M. Blair and J. Sperry, *J. Nat. Prod.*, 2013, **76**, 794; (b) C. G. Wermuth, *MedChemComm*, 2011, **2**, 935; (c) A. Marella, R. Ali, T. Alam, R. Saha, O. Tanwar, M. Akhter, M. Shaquiquzzaman and M. Mumtaz Alam, *Mini-Rev. Med. Chem.*, 2013, **13**, 921; (d) M. Yusuf and P. Jain, *Arab. J. Chem.*, 2014, **7**, 553; (e) J. M. Alex and R. J. Kumar, *J. Enzyme Inhib. Med. Chem.*, 2014, **29**, 427; (f) W. Maison and C. H. Küchenthal, *Synthesis*, 2010, 719. For selected examples, see: (g) B. N. Acharya, D. Saraswat, M. Tiwari, A. K. Shrivastava, R. Ghorpade, S. Bapna and M. P. Kaushik, *Eur. J. Med. Chem.*, 2010, **45**, 430; (h) D. Dardic, G. Lauro, G. Bifulco, P. Laboudie, P. Sakhaei, A. Bauer, A. Vilcinskas, P. E. Hammann and A. Plaza, *J. Org. Chem.*, 2017, **82**, 6032.
 - 5 For selected examples on the synthesis of dihydropyrazoles, see: (a) J. R. Chen, W. R. Dong, M. Candy, F. F. Pan, M. Jorres and C. Bolm, *J. Am. Chem. Soc.*, 2012, **134**, 6924; (b) M. Rueping, M. S. Maji, H. B. Kucuk and I. Atodiresei, *Angew. Chem., Int. Ed.*, 2012, **51**, 12864; (c) X. Hong, H. B. Kucuk, M. S. Maji, Y. F. Yang, M. Rueping and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 13769; (d) C. B. Tripathi and S. Mukherjee, *Org. Lett.*, 2014, **16**, 3368; (e) O. A. Attanasi, L. De Crescentini, G. Favi, F. Mantellini, S. Mantenuto and S. Nicolini, *J. Org. Chem.*, 2014, **79**, 8331; (f) X. Wu, M. Wang, G. Zhang, Y. Zhao, J. Wang and H. Ge, *Chem. Sci.*, 2015, **6**, 5882; (g) D. Y. Zhang, L. Shao, J. Xu and X. P. Hu, *ACS Catal.*, 2015, **5**, 5026; (h) J. Cheng, P. Xu, W. Li, Y. Cheng and C. Zhu, *Chem. Commun.*, 2016, **52**, 11901.
 - 6 For selected examples on the synthesis of tetrahydropyridazines, see: (a) M. C. Tong, X. Chen, J. Li, R. Huang, H. Y. Tao and C. J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4680; (b) J. Li, R. Huang, Y. K. Xing, G. Qiu, H. Y. Tao and C. J. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 10124; (c) L. Wei and C. J. Wang, *Chem. Commun.*, 2015, **51**, 15374; (d) S. M. M. Lopes, M. S. C. Henriques, J. A. Paixao and T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.*, 2015, 6146; (e) X. Zhong, J. Lv and S. Luo, *Org. Lett.*, 2016, **18**, 3150; (f) L. K. B. Garve, M. Petzold, P. G. Jones and D. B. Werz, *Org. Lett.*, 2016, **18**, 564; (g) A. M. Shelke and G. Suryavanshi, *Org. Lett.*, 2016, **18**, 3968; (h) X. L. Yang, X. X. Peng, F. Chen and B. Han, *Org. Lett.*, 2016, **18**, 2070; (i) Y. Deng, C. Pei, H. Arman, K. Dong, X. Xu and M. P. Doyle, *Org. Lett.*, 2016, **18**, 5884; (j) L. Wei, Y. Zhou, Z. M. Song, H. Y. Tao, Z. Lin and C. J. Wang, *Chem. – Eur. J.*, 2017, **23**, 4995; (k) X. R. Zhong, J. Lv and S. Z. Luo, *Org. Lett.*, 2015, **17**, 1561.
 - 7 For selected reviews on N-radical chemistry, see: (a) S. Z. Zard, *Chem. Soc. Rev.*, 2008, **37**, 1603; (b) J. R. Chen, X. Q. Hu, L. Q. Lu and W. J. Xiao, *Chem. Soc. Rev.*, 2016, **45**, 2044; (c) T. Xiong and Q. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 3069.
 - 8 (a) X. Y. Duan, N. N. Zhou, R. Fang, X. L. Yang, W. Yu and B. Han, *Angew. Chem., Int. Ed.*, 2014, **53**, 3158; (b) X. Y. Duan, X. L. Yang, R. Fang, X. X. Peng, W. Yu and B. Han, *J. Org. Chem.*, 2013, **78**, 10692; (c) X. Y. Duan, X. L. Yang, P. P. Jia, M. Zhang and B. Han, *Org. Lett.*, 2015, **17**, 6022; (d) E. Brachet, L. Marzo, M. Selkti, B. König and P. Belmont, *Chem. Sci.*, 2016, **7**, 5002; (e) F. Punner, Y. Sohtome and M. Sodeoka, *Chem. Commun.*, 2016, **52**, 14093.
 - 9 (a) T. Wu, G. Yin and G. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 16354; (b) T. Xu, S. Qiu and G. Liu, *Chin. J. Chem.*, 2011, **29**, 2785; (c) Q. Wang, W. Zhong and X. Wei, *Org. Biomol. Chem.*, 2012, **10**, 8566; (d) T. Wu, J. Cheng, P. Chen and G. Liu, *Chem. Commun.*, 2013, **49**, 8707; (e) H. Huang, T. Lacy, B. Bzachut, G. Ortiz Jr. and Q. Wang, *Org. Lett.*, 2013, **15**, 1818; (f) W. Kong, P. Feige, T. de Haro and C. Nevado, *Angew. Chem., Int. Ed.*, 2013, **52**, 2469; (g) Z. Li, L. Song and C. Li, *J. Am. Chem. Soc.*, 2013, **135**, 4640; (h) D. Lu, G. Liu and C. Zhu, *Org. Lett.*, 2014, **16**, 2912; (i) J. Cui, Q. Jia, R. Feng, S. Liu, T. He and C. Zhang, *Org. Lett.*, 2014, **16**, 1442.
 - 10 J. Zhao, M. Jiang and J. T. Liu, *Adv. Synth. Catal.*, 2017, **359**, 1626.
 - 11 F. Yin, Z.-T. Wang, Z.-D. Li and C.-Z. Li, *J. Am. Chem. Soc.*, 2012, **134**, 10401.
 - 12 C. T. Kenner and K. W. Busch, *Quantitative Analysis*, Macmillan Publishing Co., Inc., New York, NY, 1973.
 - 13 X. Q. Hu, X. T. Qi, J. R. Chen, Q. Q. Zhao, Q. Wei, Y. Lan and W. J. Xiao, *Nat. Commun.*, 2016, **7**, 11188.
 - 14 Q. Zhang, G. F. Zheng, Q. Zhang, Y. Li and Q. Zhang, *J. Org. Chem.*, 2017, **82**, 8258.