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Cyanomethylation of alkenes with C–H bond activation of acetonitrile: *in situ* generated diazonium salts as promoters without transition-metals†

Zhangqin Ni, Xin Huang, Jichao Wang and Yuanjiang Pan*

Diazonium salts, which were *in situ* generated from *p*-anisidine and *tert*-butyl nitrite, could be used as a novel radical promoter for the C_{sp^3}–H functionalization of acetonitrile. The cyanomethylation of alkenes could be performed without the use of transition-metal salts or photocatalyst and the functionalized oxindoles could be obtained with simple operation in moderate to good yields. This process tolerates a variety of functional groups and provides an alternative procedure for the synthesis of functionalized oxindoles.

Nitriles and alkenes are essential materials in the chemical industry and also widely exist in nature.[1] The functionalization of alkenes, the C–H bond activation of acetonitrile and many important chemical transformations of these compounds have achieved much attention from chemists.[2–5] A wide range of transition metals, such as Ir, Rh, Ni, Fe, *etc.* have been applied to the C–H bond activation of acetonitrile while stoichiometric amounts of these transition metals are needed in most cases.[6] Although several examples of α-C–H functionalization of acetonitrile using a catalytic amount of transition-metal have been developed, there are still some limitations. As acetonitrile has a high pK_a value [pK_a (MeCN) ≈ 31.3, DMSO], a strong base is required for the deprotonation.[7] Therefore, it is of great interest to develop new environment-benign method for the C–H functionalization of acetonitrile. In previous studies, Liu reported a Pd-catalyzed oxidative alkylarylation of alkene involving α-C–H activation of acetonitrile with the aid of stoichiometric amount of $PhI(OCOtBu)_2$ and AgF (Fig. 1, eqn (1)).[8] Very recently, the alkylarylation of alkene with the C–H activation of acetonitrile through a radical process have been well documented. Li used diazonium salts as a promoter for cyanomethylation of alkenes by visible-light catalyst (Fig. 1, eqn (2)).[9] Zhao and Tang reported cascade arylalkylation of activated alkene using phenylboronic acid as radical initiator (Fig. 1, eqn (3)).[10] Sheng developed DIAD as a promoter for cyanomethylation of alkenes by Cu catalyst (Fig. 1, eqn (4)).[11] Nevertheless, catalytic or stoichiometric amount of transition metals are still required in forementioned examples. Metal contamination is a serious issue in the pharmaceutical industry. Transition-metal-free reactions are of great interest in terms of atom economy, environmental impact, and cost reduction. It would still be highly desirable to develop a method for cyanomethylation of alkenes using environmental-friendly condition. As our continuing interests in the researches involving the *in situ* generated diazonium salts,[12] we describe a novel cyanomethylation of alkenes using *in situ* generated diazonium salts as promoter without transition-metals or photocatalyst (Fig. 1, eqn (5)).

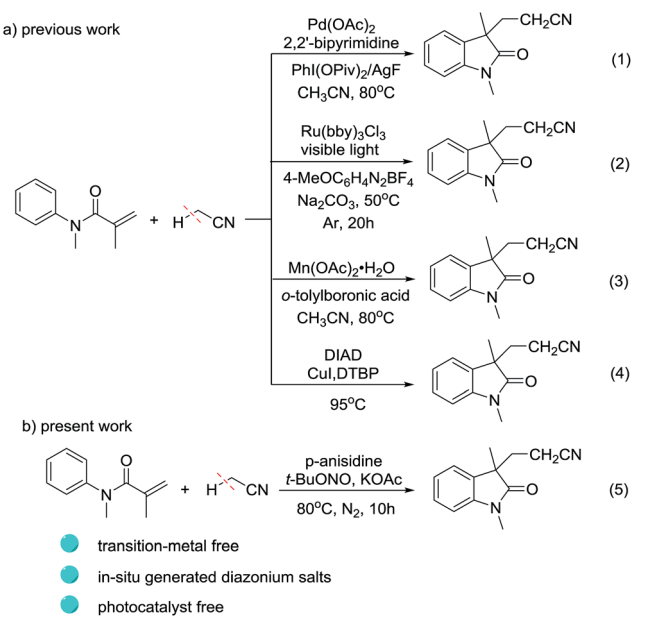

Fig. 1 Oxidative cyanomethylation of alkene with C–H bond activation of acetonitrile.

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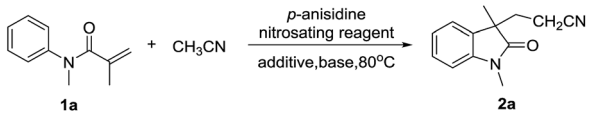
Table 1 The optimization of the reaction conditions[a]

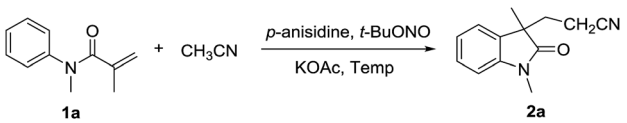


Entry	Nitrosating reagent	Additive	Base	Yield[b] (%)
1	*t*-BuONO	BPO[c]	NaOAc	27
2	*t*-BuONO	BPO[c]	K_3PO_4	Trace
3	*t*-BuONO	BPO[c]	K_2CO_3	Trace
4	*t*-BuONO	BPO[c]	$NaHCO_3$	15
5	*t*-BuONO	—	NaOAc	37
6	*t*-BuONO	—	KOAc	43
7	*t*-BuONO	—	LiOAc	29
8	*t*-BuONO	—	CsOAc	29

[a] Reaction conditions: **1a** (0.5 mmol), *p*-anisidine (1.0 mmol), *t*-BuONO (1.0 mmol), base (2 equiv.), CH_3CN (3 mL), 10 h. [b] Isolated yield. [c] 0.05 mmol BPO was added.

We initiated our investigation using *N*-methyl-*N*-phenylmethacrylamide (**1a**) and acetonitrile as substrates under various conditions and the result was summarized in Tables 1 and 2. When we performed the reaction under the following conditions [**1a** (0.5 mmol), *p*-anisidine (2.0 equiv.), benzoyl peroxide (BPO) (0.1 equiv.), *tert*-butyl nitrite (*t*-BuONO) (2.0 equiv.), NaOAc (2 equiv.), CH_3CN (3 mL), 80 °C, 10 h], our desired product **2a** could be isolated in 27% yield and the structure was confirmed by MS and NMR spectra. Then several different bases were applied to our reaction, a higher yield could be gained using NaOAc (Table 1, entries 1–4). It was interesting to find that a higher yield with 37% was obtained when the reaction was carried out in the absence of BPO (Table 1, entry 5). As acetate was more effective than other bases, some other acetates were screened to improve the yield (Table 1, entries 5–8). Among the acetates tested, KOAc provided the best yield with 43%. Further optimizations were focused on the ratio and the concentration of reactants, while the reaction temperature was also optimized (Table 2). When **1a** (0.5 mmol), *p*-anisidine (0.75 mmol), *t*-BuONO (0.75 mmol) were used, the yield decreased obviously (Table 2, entry 1). This phenomenon indicated that the concentration of reactant had a significant effect on the reaction. When 2 mL of acetonitrile was used as the solvent, the target product could be obtained with only 21% yield (Table 2, entry 2). Once we increased the amount of acetonitrile to 4 mL, the reaction was

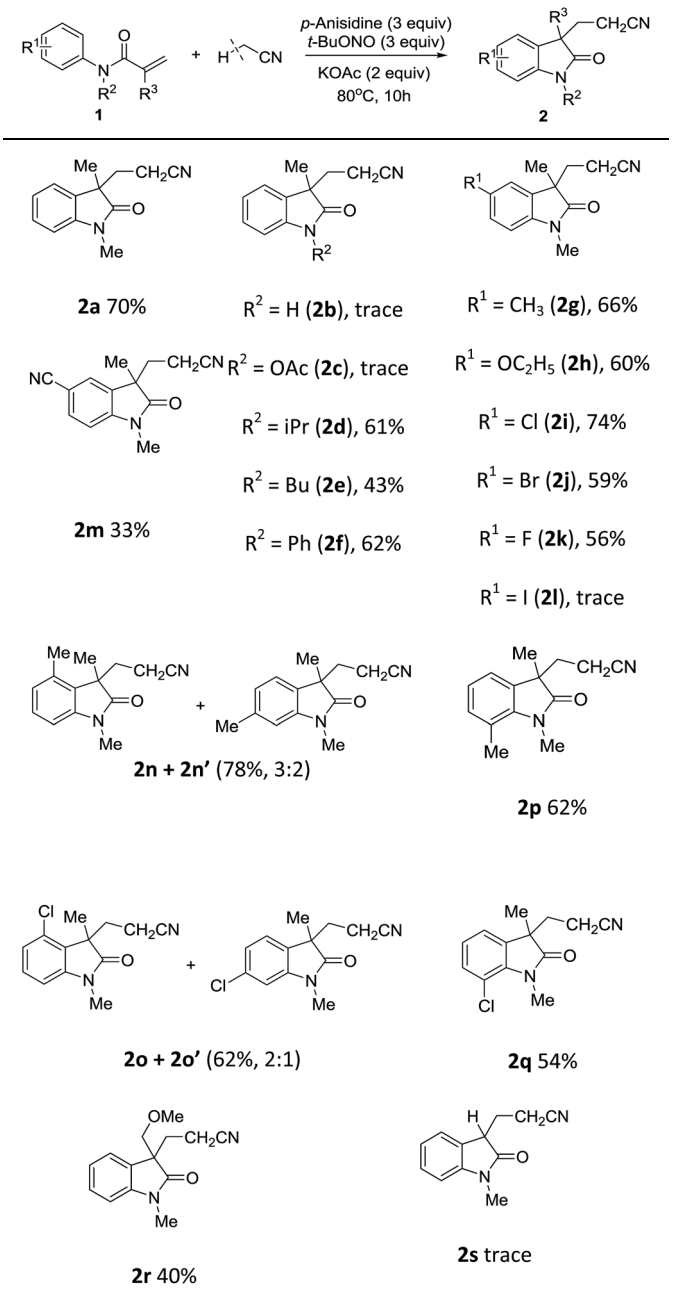
Table 2 The optimization of the reaction conditions[a]



Entry	Ratio[b]	Concentration[c]	Temp	Yield[d] (%)
1	1 : 1.5 : 1.5	0.167 M	80 °C	24
2	1 : 1.5 : 1.5	0.250 M	80 °C	21
3	1 : 1.5 : 1.5	0.125 M	80 °C	50
4	**1 : 3 : 3**	**0.125 M**	**80 °C**	**70**
5	1 : 3 : 3	0.125 M	75 °C	63
6	1 : 3 : 3	0.125 M	85 °C	55
7[e]	1 : 3 : 3	0.125 M	80 °C	22

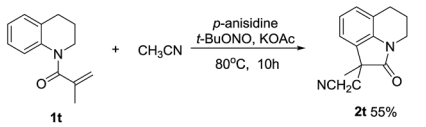
[a] Reaction conditions: **1a** (0.5 mmol), KOAc (2 equiv.), CH_3CN (3 mL), 10 h. [b] The ratio of *N*-arylacrylamide, *p*-anisidine and *t*-BuONO. [c] Concentration refers to **1a**. [d] Isolated yield. [e] Under air.

Table 3 The investigation of the reaction scope

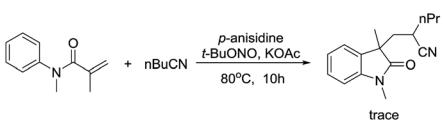


promoted to 50% yield (Table 2, entry 3). Fortunately, when we further increased the ratio of reactants [**1a** (0.5 mmol), *p*-anisidine (1.5 mmol), *t*-BuONO (1.5 mmol)], the desired product was isolated in 70% (Table 2, entry 4). The yield could not be improved when the reaction was performed in either a higher or lower temperature (Table 2, entries 5–6). The inert atmosphere was necessary for this transformation as only 22% could be obtained when the reaction was carried out under air (Table 2, entry 7).

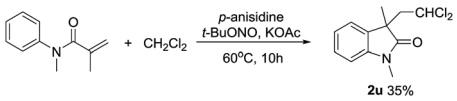
With the optimized reaction condition in hand, we investigated the scope and limitations of substituted *N*-arylacrylamides **1** with acetonitrile and the results were summarized in Table 3. It was interesting to find that the substituted group on the N atom had an obvious influence on the yield. The unprotected *N*-arylacrylamide (R^2 = H) or *N*-arylacrylamide with acetyl group were less efficient in the cyclization (**2b** and **2c**). Whereas, *N*-arylacrylamide substituted with isopropyl, *n*-butyl or phenyl groups could afford the desired products in acceptable yields (**2d**, **2e** and **2f**). Then we set out to investigate the effect of the substituted groups on the phenyl ring. A wide range of substituents at different positions of the aromatic ring were discussed. The electronic character of the substituent groups at *para*-position of aromatic ring had little influence on this reaction. The substrates with electron-donating or electron-withdrawing groups could all give the desired products in moderate to good yields (**2g–2k**). The halogen groups (Cl, Br, F) could be tolerated in this transformation and they might be used for further functionalization. It is a pity that desired product could not be obtained because of the high reactivity of iodine group (**2l**). *N*-Arylacrylamide substituted with cyano group at *para*-position could afford the target product in slightly lower yield (**2m**). As anticipated, a mixture of two products were detected when the substrates were substituted at *meta*-position of phenyl ring (**2n** and **2o**). Besides, the steric hindrance decreased the reactivity. Although the desired products with substituents at *ortho*-position of phenyl ring could be obtained in acceptable yields, they are slightly lower than that with the same substituents at *para*-position (**2p** and **2q**). In addition, desired product was formed in 40% yield when R^3 = OMe (**2r**), but no product could not be obtained when the R^3 = H (**2s**).



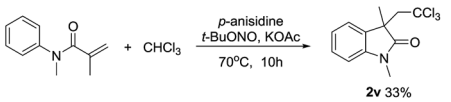
(6)



(7)



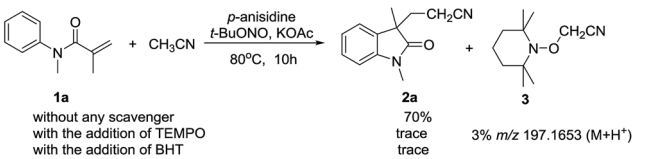
(8)



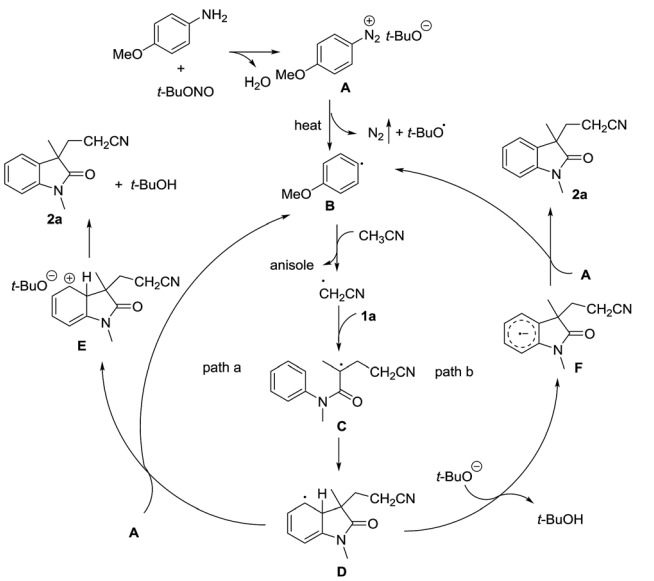
(9)

It was interesting to find that this strategy could also be applied to synthesize more complex oxindoles. When *N*-arylacrylamide **1t** was used as substrate, the desired product polycyclic oxindole **2t** could be obtained in 55% yield (eqn (6)). We also tried to utilize this strategy to other kinds of aliphatic nitriles. However, it failed to get the target product when *n*-butyronitrile was used under the standard reaction condition (eqn (7)). When we used CH_2Cl_2 or $CHCl_3$ as the solvent, the C–H bond of CH_2Cl_2 or $CHCl_3$ could be activated and the target product **2u** or **2v** could be obtained with 35% or 33%, respectively (eqn (8) and (9)).

To investigate the mechanism of this cascade reaction, some control experiments were performed (Scheme 1). The corresponding oxindole **2a** could be obtained with 70% yield when the reaction was conducted under standard reaction condition. When radical scavenger 2,2,6,6-tetramethylpoperdine-1-oxyl



Scheme 1 The control experiments.



Scheme 2 Proposed mechanism for the synthesis of oxindoles.

radical (TEMPO) or butylated hydroxytoluene (BHT) were added to the reaction system, the desired product **2a** could not be obtained. 2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)acetonitrile **3** was obtained with 3% by GC-MS and verified by HRMS. It indicated that the acetonitrile radical was trapped by TEMPO and this reaction might go through a radical pathway.

Based on control experiments and previous literatures,[9–13] a possible mechanism for the cyanomethylation of *N*-arylcarylamides was proposed (Scheme 2). Firstly, the diazonium salt **A** is *in situ* formed by the reaction between *p*-anisidine and *tert*-butyl nitrite. Radical intermediate **B** is then generated by the homolysis of diazonium salt **A** under heat. Radical **B** can abstracte a hydrogen atom from acetonitrile to generate $^{\bullet}CH_2CN$. The resulting $^{\bullet}CH_2CN$ adds to the C=C bond of **1a** to give intermediate **C**. Through the cyclization of intermediate **C**, intermediate **D** is generated. By reacting with another molecule of diazonium salt **A**, intermediate **E** will be given and radical **B** will be regenerated. Finally, the final product can be obtained by counterion, *tert*-butoxide, abstracting a proton from the carbocation. An alternative reaction pathway includes a base promoted homolytic aromatic substitution step is also possible. Intermediate **D** is deprotonated by *tert*-butanolate derived from *tert*-butyl nitrite and radical anion **F** is formed. By reacting with another molecule of diazonium salt **A**, final product is given and radical **B** is regenerated.

Conclusions

We have developed a novel cyanomethylation of alkenes using *in situ* generated diazonium salts as promoter. It is interesting to find that the *in situ* generated diazonium salts could be used as a novel radical promoter without the use of transition-metal salts or photocatalyst for the C_{sp^3}–H functionalization of acetonitrile. In most cases, the target products could be obtained with simple operation in moderate to good yields. This process tolerates a variety of functional groups and provides an alternative procedure for the synthesis of functionalized oxindoles. A radical-involved mechanism was also proposed to give deeper understanding of the transformation.

Acknowledgements

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Notes and references

1 (*a*) G. W. Coates, P. D. Hustad and S. Reinartz, *Angew. Chem., Int. Ed.*, 2002, **41**, 2236–2257; (*b*) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902–7917; (*c*) F. Fleming, *Nat. Prod. Rep.*, 1999, **16**, 597–606.

2 Review on acrylamides as radical acceptors in cascade reactions: R.-J. Song, Y. Liu, Y.-X. Xie and J.-H. Li, *Synthesis*, 2015, 1195–1209.

3 For selected papers on metal-catalyzed cyclization reactions of activated alkenes, see: (*a*) A. Pinto, Y. Jia, L. Neuville and J. Zhu, *Chem.–Eur. J.*, 2007, **13**, 961–967; (*b*) T. Piou, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2012, **51**, 11561–11565; (*c*) T. Wu, X. Mu and G. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 12578–12581; (*d*) X. Mu, T. Wu, H. Wang, Y. Guo and G. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 878–881; (*e*) G. An, W. Zhou, G. Zhang, H. Sun, J. Han and Y. Pan, *Org. Lett.*, 2010, **12**, 4482–4485; (*f*) S. Jaegli, J. Dufour, H. Wei, T. Piou, X. Duan, J. Vors, L. Neuville and J. Zhu, *Org. Lett.*, 2010, **12**, 4498–4501.

4 For selected papers on radical-mediated cyclization/functionalization reactions of activated alkenes, see: (*a*) W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie and J.-H. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 3638–3641; (*b*) M.-B. Zhou, R.-J. Song, X.-H. Ouyang, Y. Liu, W.-T. Wei, G.-B. Deng and J.-H. Li, *Chem. Sci.*, 2013, **4**, 2690–2694; (*c*) H. Wang, L.-N. Guo and X.-H. Duan, *Adv. Synth. Catal.*, 2013, **355**, 2222–2226; (*d*) J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng and C. Zhu, *Chem. Commun.*, 2013, **49**, 5672–5674; (*e*) S.-L. Zhou, L.-N. Guo, H. Wang and X.-H. Duan, *Chem.–Eur. J.*, 2013, **19**, 12970–12973; (*f*) H. Wang, L.-N. Guo and X.-H. Duan, *Chem. Commun.*, 2013, **49**, 10370–10372; (*g*) T. Shen, Y. Yuan and N. Jiao, *Chem. Commun.*, 2014, **50**, 554–556; (*h*) S. G. Newman and M. Lautens, *J. Am. Chem. Soc.*, 2011, **133**, 1778–1780; (*i*) X. Li, X. Xu, P. Hu, X. Xiao and C. Zhou, *J. Org. Chem.*, 2013, **78**, 7343–7348; (*j*) X.-H. Wei, Y.-M. Li, A.-X. Zhou, T.-T. Yang and S.-D. Yang, *Org. Lett.*, 2013, **15**, 4158–4161; (*k*) Z. Li, Y. Zhang, L. Zhang and Z.-Q. Liu, *Org. Lett.*, 2014, **16**, 382–385; (*l*) S. Tang, D. Zhou and Y.-C. Wang, *Eur. J. Org. Chem.*, 2014, 3656–3661; (*m*) W. Fu, F. Xu, Y. Fu, M. Zhu, J. Yu, C. Xu and D. Zou, *J. Org. Chem.*, 2013, **78**, 12202–12206; (*n*) W. Kong, M. Casimiro, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2013, **135**, 14480–14483; (*o*) N. Fuentes, W. Kong, L. Fernandez-Sanchez, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2015, **137**, 964–973.

5 For selected papers on the reaction between acetonitrile and alkenes, see: (*a*) A. Bunescu, Q. Wang and J. Zhu, *Chem.–Eur. J.*, 2014, **20**, 14633–14636; (*b*) A. Bunescu, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2015, **54**, 3132–3135.

6 (*a*) F. Denes, A. Perez-luna and F. Chemla, *Chem. Rev.*, 2010, **110**, 2366–2447; (*b*) A. Bunescu, Q. Wang and J. Zhu, *Chem.–Eur. J.*, 2014, **20**, 14633–14636; (*c*) N. Kumagai, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 13632–13633; (*d*) D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 9330–9331.

7 (*a*) S. D. Ittel, C. A. Tolman, A. D. English and J. P. Jesson, *J. Am. Chem. Soc.*, 1978, **100**, 7577–7585; (*b*) H. J. Heeres, A. Meetsma and J. H. Teuben, *Angew. Chem., Int. Ed.*, 1990, **29**, 420–422; (*c*) D. Churchill, J. H. Shin, T. Hascall, J. M. Hahn, B. M. Bridgewater and G. Parkin, *Organometallics*, 1999, **18**, 2403–2406; (*d*) M. E. Evans, T. Li, A. J. Vetter, R. D. Rieth and W. D. Jones, *J. Org. Chem.*, 2009, **74**, 6907–6914.

8 T. Wu, X. Mu and G. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 12578–12581.

9 J.-H. Li, G.-F. Jiang, J.-L. Zhang, Y. Liu and R.-J. Song, *Synlett*, 2014, 1031–1035.
10 X. Li, J. Xu, Y. Gao, H. Fang, G. Tang and Y. Zhao, *J. Org. Chem.*, 2015, **80**, 2621–2626.
11 S. Tang, S. H. Li, Z. H. Li, D. Zhou and R. Sheng, *Tetrahedron Lett.*, 2015, **56**, 1423–1426.
12 Z. Ni, S. Wang, X. Huang, J. Wang and Y. Pan, *Tetrahedron Lett.*, 2015, **56**, 2512–2516.
13 (*a*) M. Hartmann, C. G. Daniliuc and A. Studer, *Chem. Commun.*, 2015, **51**, 3121–3123; (*b*) A. Studer and D. P. Curran, *Angew. Chem., Int. Ed.*, 2011, **50**, 5018–5022; (*c*) A. Studer and D. P. Curran, *Angew. Chem., Int. Ed.*, 2015, **54**, 2–47; (*d*) A. Studer and D. P. Curran, *Nat. Chem.*, 2014, **6**, 765–773.