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Sulfonamide formation from sodium sulfinates and amines or ammonia under metal-free conditions at ambient temperature†

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A novel, practical and highly efficient method for the construction of a variety of sulfonamides mediated by I_2 was demonstrated. The reaction proceeds readily at room temperature using a variety of sodium sulfinates and amines or ammonia in water in a metal-, base-, ligand-, or additive-free protocol. Primary, secondary and tertiary sulfonamides were obtained in good to excellent yields with a broad range of functional group tolerability.

Sulfonamides are a common structural motif in biologically active compounds and pharmaceutical interesting molecules owing to their well-known anticonvulsant, antibacterial, anticancer, antitumor, anti-inflammatory and HIV protease inhibitory activities (Fig. 1).[1–7] In addition, sulfonamides are a good type of amine protection group due to their easy removability.[8,9] Consequently, many endeavors have been made towards the construction of sulfonamides. The traditional method for the formation of sulfonamides stems from sulfonyl chloride and amino compounds,[10,11] and later a transition metal catalyzed alternative method was developed between primary sulfonamides and aryl halides[12–17] or arylboronic acids.[18] Very recently, Jiang and co-workers developed an efficient method to build up sulfonamides between sodium sulfinates and amines *via* copper-catalyzed aerobic oxidative conditions.[19] Kim et. al. reported a mild copper catalyzed Chan-Lam type coupling by using sulfonyl azide and boronic acids at room temperature (Scheme 1).[20] Although great progress has been achieved on the synthesis of sulfonamides, there are still many drawbacks existing in the current methods, such as hazardous starting materials (mutagenic sulfonyl chlorides or precautious-handling organic azides), harsh reaction conditions, long reaction time, poor functional group tolerability and transition metal usage, which might cause pollution in the final product, and so on. Therefore, development of a general, practical and efficient method for the construction of sulfonamides under mild conditions is still a challenge, and such a method is highly desirable.

Herein, we report transition metal-free sulfonamide formation between sodium sulfinates and amines mediated by I_2 at room temperature. There are several obvious advantages of the present method: (1) Cheap and readily available I_2 emerges as an efficient catalyst and oxidant as well, instead of a

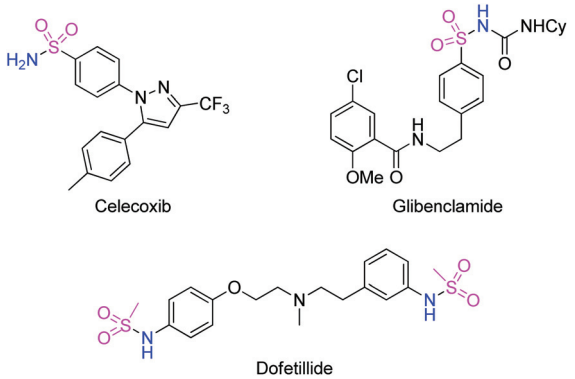
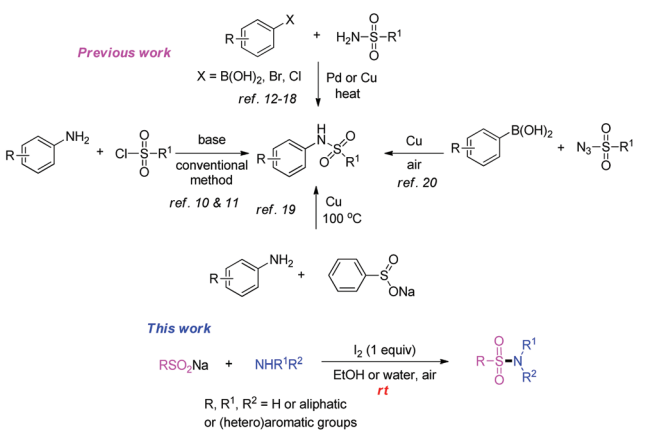


Fig. 1 Drugs with sulfonamide structure motif.



Scheme 1 Overview of the synthetic approach for sulfonamides.

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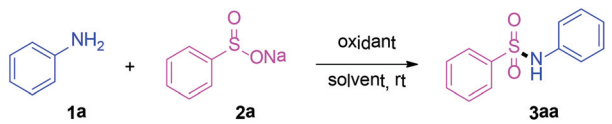
transition-metal catalyst, which is usually quite expensive and must be completely removed from products, particularly during the process of drug synthesis. (2) The reaction shows broad substrate scopes and generality: various sodium sulfinates, including aromatic, heteroaromatic or aliphatic ones and numerous amines, such as aromatic, heteroaromatic or aliphatic, naturally occurring amino ester, or even aqueous ammonia, are well tolerable under the standard conditions and the desired sulfonamide compounds are obtained at room temperature in open air smoothly within 3 h. Therefore, we have reasons to believe that pharmaceutical molecules and bioactive compounds could be manipulated by this strategy. (3) The I_2/EtOH or water system is low cost, easily handled and mild with high efficiency and safety.

In our previous research, we found that I_2 could function as a surrogate for CuI in the process of acylation of benzothiazoles with acetophenones.[21] This reaction inspired us, and since sulfonamide could be formed under a copper-catalyzed aerobic oxidative condition between sodium sulfinates and amines, we propose that I_2 should replace copper salt, yet just play the same role in the reaction between sodium sulfinates and amines, thus making the reaction take place under transition metal-free conditions (Scheme 1).

In order to verify the hypothesis, aniline (**1a**) and sodium benzenesulfinate (**2a**) were chosen as the substrates in the model reaction (Table 1). To our delight, the desired product **3aa** was formed in 60% yield (Table 1, entry 4) with 1 equivalent of I_2 in CH_3CN at just room temperature in an open flask! This reaction condition was much milder than the copper-catalyzed one. Further oxidant screening revealed that I_2 was the superior oxidant to NBS, NCS, NIS, $K_2S_2O_8$, DDQ and DTBP (Table 1, entries 1–4, 6–8), which was also better than the catalytic amount of I_2 with one equivalent of TBHP (70% in water) (Table 1, entry 5). The solvent effect was also investigated (Table 1, entries 8–14), and both water and EtOH showed optimal influence on the reaction and afforded desired products in 73% and 75% yields, respectively (Table 1, entries 9 and 14), indicating this reaction was environmentally benign. Gratifyingly, shortening the reaction time from 18 hours to 3 hours did not reduce the efficiency of the reaction, and 76% of the desired product was obtained correspondingly (Table 1, entry 15). However, a decrease in the amount of I_2 to 0.2 equivalents did cause a decrease in the yield of desired product from 76% to 23% (Table 1, entries 16 and 17). Notably, the catalytic amount of I_2 (20 mol%) with TBHP (70% in water) did not bring a satisfactory yield; only 19% of desired product was obtained after an 18 hour reaction time. Based on the above results, EtOH was the optimal solvent for this reaction and water could be an alternative one for this transformation. It is well known that both EtOH and water are environmentally benign solvents and there are many advantages with EtOH and water as solvents over other organic ones. This property makes the whole process quite green and sustainable. Together with mild reaction conditions, the process might be used in late-stage manipulation of complex molecules.

Table 1 Condition screening[a]



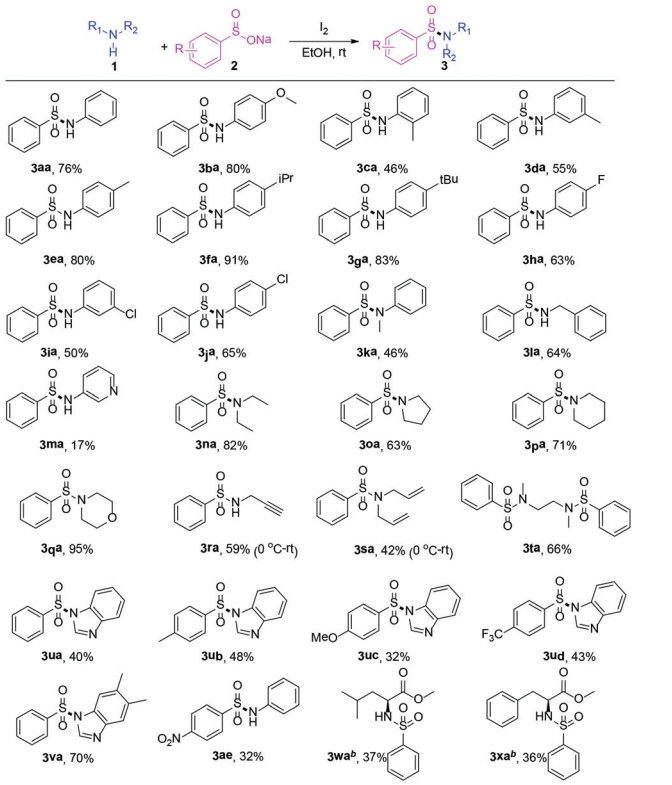
1a **2a** **3aa**

Entry	Oxidant (equiv.)	Solvent (mL)	Time (h)	Yield[c] (%)
1	NBS (1)	CH_3CN	18	21
2	NCS (1)	CH_3CN	18	37
3	NIS (1)	CH_3CN	18	12
4	I_2 (1)	CH_3CN	18	60
5	I_2 (0.1) + TBHP (1)	CH_3CN	18	8
6	$K_2S_2O_8$ (1)	CH_3CN	18	Trace
7	DDQ (1)	CH_3CN	18	Trace
8	DTBP (1)	CH_3CN	18	0
9	I_2 (1)	DCM	18	69
10	**I_2 (1)**	**H_2O**	**18**	**73**[d]
11	I_2 (1)	THF	18	49
12	I_2 (1)	Dioxane	18	27
13	I_2 (1)	DCE	18	68
14	I_2 (1)	Toluene	18	59
15	I_2 (1)	EtOH	18	75[d]
16[b]	**I_2 (1)**	**EtOH**	**3**	**76**[d]
17[b]	I_2 (0.2)	EtOH	3	23
18	I_2 (0.2) + TBHP (2)	EtOH	18	19

[a] Reaction condition: aniline (**1a**) (0.5 mmol), sodium benzenesulfinate (**2a**) (1 mmol), oxidant (0.5 mmol), solvent (2 mL), air, rt. [b] I_2 and sodium benzenesulfinate (**2a**) were mixed up and stirred at rt for 20 min, then EtOH (2 mL) and aniline (**1a**) were added, the mixture was continued to stir at rt for 3 h. [c] GC yields. [d] Isolated yields.

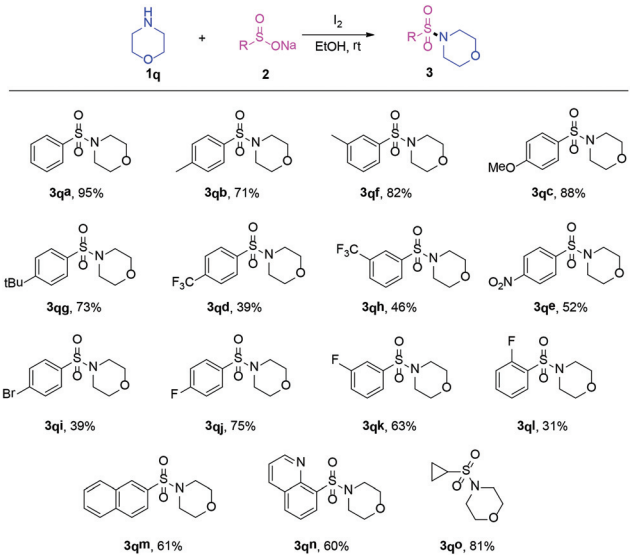
With the optimized reaction conditions in hand, the substrate scope of amines were explored first (Table 2). As listed in Table 2, both aromatic amines, such as aniline derivatives and aliphatic amines, worked well under the mild reaction conditions. The electronic property of the substituents on the aromatic rings of anilines had some effect on yields, with electron-deficient substitutions usually giving lower yields of the sulfonamides in comparison to electron-rich substitutions (Table 2, **3ba–3ja**), perhaps as a result of the lower nucleophilic property of the electron-deficient ones. Secondary anilines, such as *N*-methylaniline, also reacted well with sodium benzenesulfinate and gave the corresponding sulfonamide **3ka**, albeit with a slightly lower yield. All aliphatic amines showed good reactivity in this novel transformation. Notably, both terminal alkyne and alkene functionalities were tolerable in this reaction (Table 2, **3ra** and **3sa**) and provide feasibility for further structural manipulation. Interestingly, a bis-sulfonamide **3ta** was obtained in 66% yield with a diamine as the substrate. A special aromatic secondary amine, benzoimidazole, which reacted with a variety of sulfonamides, was also applicable in the standard reaction condition to give the desired products in moderate to good yields (Table 2, **3ua–3ud**, **3va**). Remarkably, the naturally occurring amino esters, which are bioactive molecules, were also proven to be compatible with this reaction and generated the corresponding products in reasonable yields (Table 2, **3wa–3xa**), which showed our method's potential application in late stage modification of complex molecule synthesis.

Table 2 I_2 mediated synthesis of sulfonamides from amines **1** and sodium sulfinate **2**[a]



[a] Reaction condition: I_2 (0.5 mmol) and sodium sulfinate **2** (1.0 mmol) were mixed up and stirred at rt for 20 min, then EtOH (2 ml) and amine **1** (0.5 mmol) were added, the mixture was continued to stir at rt for 3 h. [b] Et_3N (1 equiv.) was added due to the starting materials amino esters exist in HCl salt.

Table 3 I_2 mediated synthesis of sulfonamides from morpholine (**1q**) and sodium sulfinate **2**[a]



[a] Reaction condition: I_2 (0.5 mmol) and sodium sulfinate **2** (1.0 mmol) were mixed up and stirred at rt for 20 min, then EtOH (2 ml) and morpholine (**1q**) (0.5 mmol) were added, the mixture was continued to stir at rt for 3 h.

The scope of sodium sulfinates was investigated by reaction with morpholine (**1q**) under the standard conditions (Table 3). Both electron-rich and electron-deficient substituents on the aromatic ring of sodium benzenesulfinates were tolerant under the novel transformation (Table 3, **3qb–3ql**), yet the latter ones usually showed lower efficiencies than the former ones in terms of the isolated yields, which might be explained by the electron-inductive effect. The different position of substituents on the aromatic ring of sodium benzenesulfinates does have an effect on the efficiency of the reaction, with the *ortho* position having lower yield compared with the *meta* and *para* positions, which might be explained by the steric hindrance of the *ortho* position. In Table 3, these phenomena are clearly shown by compounds **3qj**, **3qk** and **3ql**. 2-Naphthyl sodium sulfinate was also a good reactant for this reaction (Table 3, **3qm**). Intriguingly, the quinolinyl group survived in the standard conditions and gave the corresponding product **3qn** in 60% yield. Gratifyingly, this reaction was applicable to aliphatic sodium sulfinates as well, and cyclopropyl sodium sulfinate was a good candidate for this novel metal-free reaction with 81% isolated yield (Table 3, **3qo**).

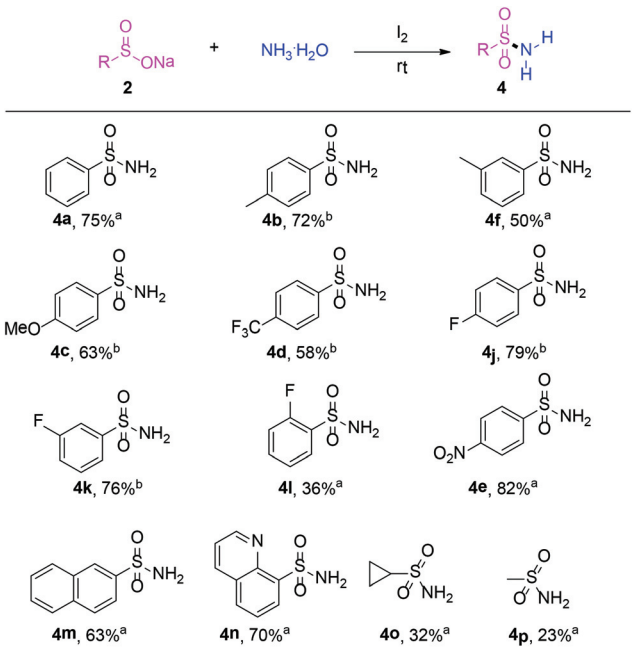
Intrigued by the above results, we further applied the same conditions to ammonia in water. Delightfully, primary benzenesulfonamide was obtained in 75% yield when sodium benzenesulfinate was reacted with aqueous ammonia under the standard conditions (Table 4, **4a**). Without optimization, numerous primary sulfonamides were found to be formed through various sodium sulfinates with ammonia in water in moderate to good yields under the standard conditions (Table 4), with a similar substrate scope as the examples list in Table 3.

Primary sulfonamide is a type of very useful building block, which can be used as a starting material in the cross coupling reaction for polysubstituted sulfonamide synthesis as well as key scaffolds in many bioactive molecules and pharmaceutical compounds. Additionally, this reaction shows a very wide range of functional group tolerability, and all primary, secondary and tertiary sulfonamides can be generated under the standard conditions smoothly. Therefore, this is a universal method for the formation of sulfonamides in a transition-metal-free, ligand-, base- and additive-free conditions at ambient temperature.

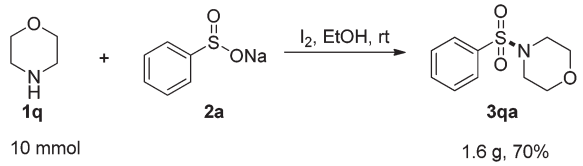
To our delight, this reaction could be easily scaled up to 10 mmol without dramatically losing the efficiency. As shown below, morpholine (**1a**) and sodium benzenesulfinate (**2a**) were reacted with each other under the standard conditions to generate desired product **3qa** in 70% yield (1.6 gram) (Scheme 2), which might suggest a potential application in industry.

Control experiments were performed in order to understand and gain insight into the mechanism (Scheme 3). When

Table 4 I_2 mediated synthesis of sulfonamides from ammonia in water and sodium sulfinate **2**



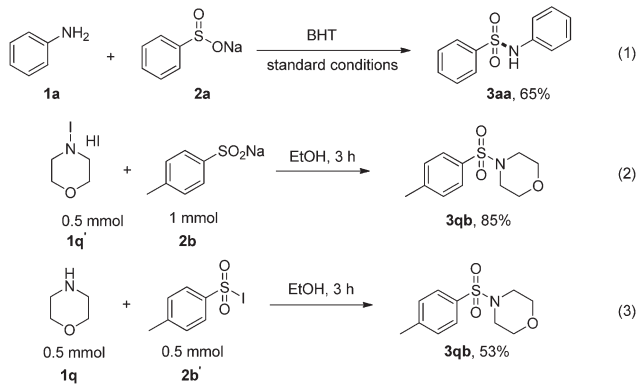
[a] Reaction condition: I_2 (0.5 mmol) and sodium sulfinate **2** (0.5 mmol) were mixed up and stirred at rt for 20 min, then ammonia (1 mL) was added, the mixture was continued to stir at rt for 3 h. [b] I_2 (0.5 mmol) and sodium sulfinate **2** (0.5 mmol) were mixed up and stirred at rt for 20 min, then ammonia (1 mL) and EtOH (1 mL) were added, the mixture was continued to stir at rt for 3 h.



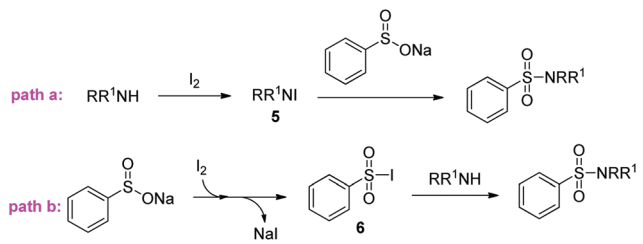
Scheme 2 Scale up reaction with morpholine (**1q**) and sodium benzenesulfinate (**2a**).

a radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol) was added to the reaction system, 65% of desired product **3aa** was obtained (Scheme 3, eqn (1)), with almost no significant influence on the reaction. Furthermore, no radical intermediate was trapped by the radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl). These two reactions suggested that a radical reaction might not be involved in the reaction. *N*-Iodomorpholine (**1q′**) and 4-methylbenzene sulfinyl iodide (**2b′**) were prepared according to methods in the literature,[22,23] and they were used as the substrates with 4-methylbenzene sodium sulfinate and morpholine, correspondingly, under the standard conditions. Remarkably, the desired product was obtained in 85% and 53% yields, respectively. These two reactions suggested that **1q′** and **2b′** might be the key intermediates for this novel and sustainable reaction.

On the basis of the above results, two tentative reaction mechanisms for this I_2-mediated sulfonamide formation are



Scheme 3 Control experiments.



Scheme 4 Plausible reaction mechanisms for sulfonamide formation.

given in Scheme 4. In **path a**, amine might be activated in the presence of iodine to give *N*-iodoamine **5**, which reacts with sodium benzenesulfinate to give the sulfonamide with the release of HI. or in **path b**, sodium benzenesulfinate reacts first with I_2 to give benzenesulfonyl iodide **6**, which further reacts with an amine to afford the desired sulfonamide product.

Conclusions

In summary, a highly efficient, practical, and chemoselective sulfonamide synthesis method has been developed. All types of sulfonamides, such as primary, secondary and tertiary sulfonamides, could be generated in good to excellent yields. A wide substrate scope compatibility and mild reaction conditions plus transition-metal-, base-, ligand- and additive-free features suggest that this method might be applied to the synthesis of bioactive compounds and medically important compounds and also could be used in late-stage structural manipulation of complex molecules. This method will widely expand the utility of sodium sulfinates in organic synthesis.

Notes and references

1 A. Scozzafava, T. Owa, A. Mastrolorenzo and C. T. Supuran, *Curr. Med. Chem.*, 2003, **10**, 925–953.
2 C. T. Supuran, A. Casini and A. Scozzafava, *Med. Res. Rev.*, 2003, **23**, 535–558.

3 M. Banerjee, A. Poddar, G. Mitra, A. Surolia, T. Owa and B. Bhattacharyya, *J. Med. Chem.*, 2004, **48**, 547–555.
4 A. Natarajan, Y. Guo, F. Harbinski, Y.-H. Fan, H. Chen, L. Luus, J. Diercks, H. Aktas, M. Chorev and J. A. Halperin, *J. Med. Chem.*, 2004, **47**, 4979–4982.
5 N. S. Reddy, M. R. Mallireddigari, S. Cosenza, K. Gumireddy, S. C. Bell, E. P. Reddy and M. V. R. Reddy, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4093–4097.
6 N. Siddiqui, S. N. Pandeya, S. A. Khan, J. Stables, A. Rana, M. Alam, M. F. Arshad and M. A. Bhat, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 255–259.
7 M. Basanagouda, K. Shivashankar, M. V. Kulkarni, V. P. Rasal, H. Patel, S. S. Mutha and A. A. Mohite, *Eur. J. Med. Chem.*, 2010, **45**, 1151–1157.
8 W. Yuan, K. Fearon and M. H. Gelb, *J. Org. Chem.*, 1989, **54**, 906–910.
9 S. Chandrasekhar and S. Mohapatra, *Tetrahedron Lett.*, 1998, **39**, 695–698.
10 M. Harmata, P. Zheng, C. Huang, M. G. Gomes, W. Ying, K.-O. Ranyanil, G. Balan and N. L. Calkins, *J. Org. Chem.*, 2006, **72**, 683–685.
11 R. Sridhar, B. Srinivas, V. P. Kumar, M. Narender and K. R. Rao, *Adv. Synth. Catal.*, 2007, **349**, 1873–1876.
12 J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 6043–6048.
13 G. Burton, P. Cao, G. Li and R. Rivero, *Org. Lett.*, 2003, **5**, 4373–4376.
14 B. R. Rosen, J. C. Ruble, T. J. Beauchamp and A. Navarro, *Org. Lett.*, 2011, **13**, 2564–2567.
15 W. Deng, L. Liu, C. Zhang, M. Liu and Q.-X. Guo, *Tetrahedron Lett.*, 2005, **46**, 7295–7298.
16 J. Baffoe, M. Y. Hoe and B. B. Touré, *Org. Lett.*, 2010, **12**, 1532–1535.
17 D. Audisio, S. Messaoudi, J.-F. o. Peyrat, J.-D. Brion and M. d. Alami, *J. Org. Chem.*, 2011, **76**, 4995–5005.
18 P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon and P. K. Jadhav, *Tetrahedron Lett.*, 2001, **42**, 3415–3418.
19 X. Tang, L. Huang, C. Qi, X. Wu, W. Wu and H. Jiang, *Chem. Commun.*, 2013, **49**, 6102–6104.
20 S.-Y. Moon, J. Nam, K. Rathwell and W.-S. Kim, *Org. Lett.*, 2014, **16**, 338–341.
21 Q. Feng and Q. Song, *Adv. Synth. Catal.*, 2014, **356**, 2445–2452.
22 T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner and B. J. Nachtsheim, *Org. Lett.*, 2011, **13**, 3754–3757.
23 L. K. Liu, Y. Chi and K.-Y. Jen, *J. Org. Chem.*, 1980, **45**, 406–410.