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Catalyst-free direct arylsulfonylation of *N*-arylacrylamides with sulfinic acids: a convenient and efficient route to sulfonated oxindoles†

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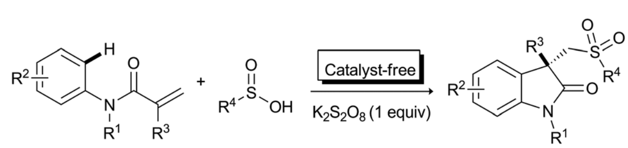
A simple, efficient and catalyst-free procedure has been developed for the construction of sulfonated oxindoles *via* the direct arylsulfonylation of *N*-arylacrylamides with sulfinic acids. The present protocol, which simply utilizes cheap oxidants, readily-available starting materials, and catalyst-free conditions, provides an alternative and highly attractive approach to a series of sulfonated oxindoles with high atom efficiency and excellent functional group tolerance.

Oxindoles are an important class of heterocycles with unique biological activity that are frequently found in many natural products and biologically active compounds.[1] In particular, the functionalized oxindoles have elicited considerable synthetic interest because of their important applications in asymmetric synthesis, library design and drug discovery.[2] So far, a number of effective synthetic methods have been established, among them the recently developed transition-metal catalyzed or metal-free oxidative difunctionalization of activated alkenes offer particularly appealing approaches to various functional oxindoles.[3–9] Through this methodology, many functional groups such as cyano,[3] carbonyl,[4] hydroxyl,[5] phosphoryl,[6] trifluoromethyl,[7] azidyl,[8] and nitro[9] groups have been successfully incorporated into the oxindole framework. Gracefully successive as these recent studies on difunctionalization of activated alkenes could be, there is still a great demand for the development of a simple, convenient, efficient and highly atom-economic oxidative difunctionalization system to offer other important functionalized oxindoles.

The sulfone functionality, as the key structural motif, widely exists in a variety of natural products, clinical pharmaceuticals, and synthetic intermediates.[10] The incorporation of sulfone groups into organic molecules has drawn increasing attention from chemists in view of their important biological properties and widespread synthetic applications for various organic transformations.[11] So far, various sulfonylating agents such as sulfonyl chlorides, sulfinates, sulfonyl selenides, sulfonyl cyanides, sulfonylazides and sulfonyl hydrazides have been used for the construction of organic sulfone compounds.[12]

Nevertheless, most sulfonylation reactions usually suffer from low atom-efficiency and relatively harsh or complex reaction conditions. Recently, sulfinic acids as stable and readily available sulfonylating agents have alternatively emerged for constructing sulfone compounds with high atom-efficiency.[13] For example, Lei and co-workers described pyridine mediated aerobic oxysulfonylation of alkenes with arylsulfinic acids leading to β-hydroxysulfones.[13a] In 2013, Li *et al.* reported KI/18-crown-6 (20 mol%) catalyzed oxidative arylsulfonylation of activated alkenes with *p*-toluenesulfonylhydrazide ($TsNHNH_2$) in the presence of 3 equiv. TBHP.[14] To the best of our knowledge, there are no examples describing the direct arylsulfonylation of alkenes to access sulfonated oxindoles using sulfinic acids as sulfonylating reagents. Owing to our continued interest in the construction of sulfone-containing organic compounds,[13c,15] herein, we wish to report a new and efficient catalyst-free direct arylsulfonylation of arylacrylamides with sulfinic acids towards sulfonated oxindoles by simply using the cheap $K_2S_2O_8$ (1 equiv.) as the oxidant (eqn (1)). The present methodology provides a convenient and highly attractive approach to a diverse range of sulfonated oxindoles in moderate to high yields with high atom efficiency and excellent functional group tolerance.



(1)

Initially, the model reaction of *N*-arylacrylamide **1a** with benzenesulfinic acid **2a** was conducted in $CH_3CN–H_2O$ (1 : 2) at 80 °C under air (Table 1, entry 1). To our delight, the desired sulfonated oxindole **3aa** was obtained in 58% yield.

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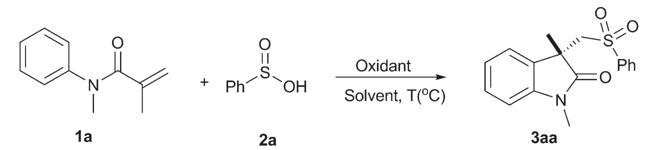
Table 1 Optimization of the reaction conditions[a]



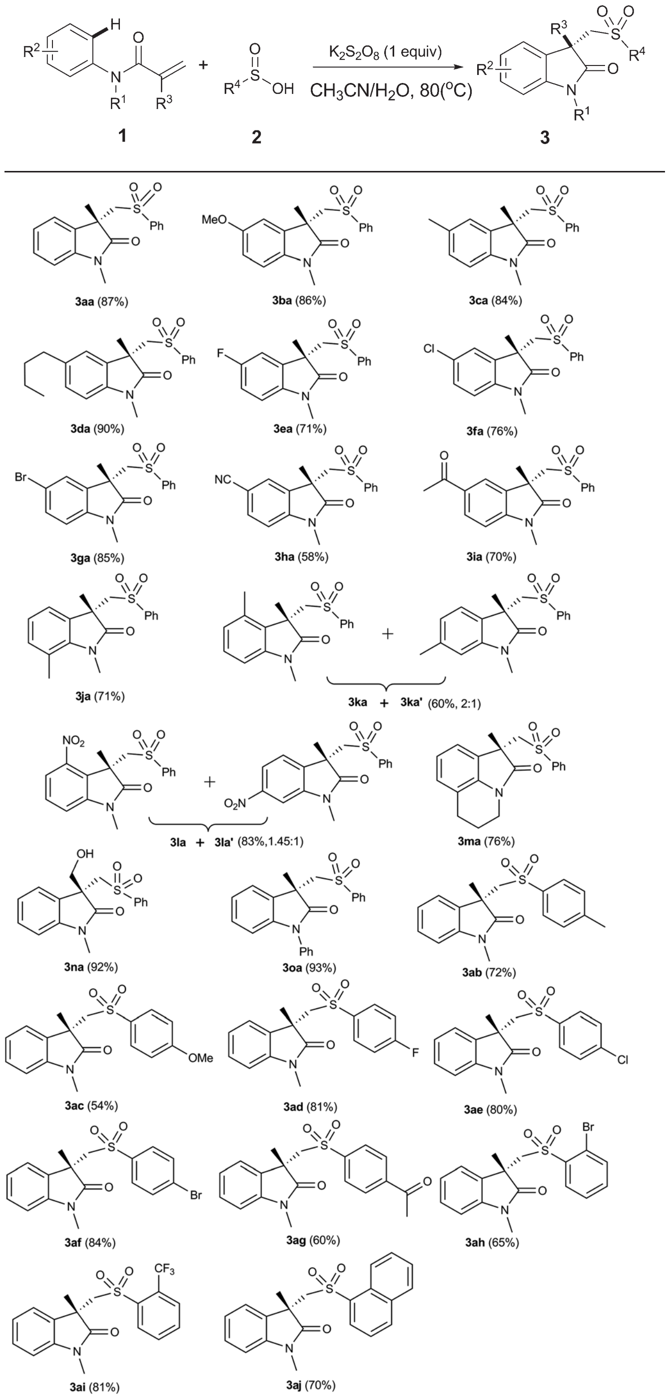
Entry	Oxidant	Solvent	Yield[b] (%)
1	Air (O_2)	CH_3CN–H_2O (1/2)	58
2	$(NH_4)_2S_2O_8$ (1)	CH_3CN–H_2O (1/2)	81
3	$Na_2S_2O_8$(1)	CH_3CN–H_2O (1/2)	80
4	**$K_2S_2O_8$(1)**	**CH_3CN–H_2O (1/2)**	**87**
5	TBHP (1)	CH_3CN–H_2O (1/2)	63
6	DTBP (1)	CH_3CN–H_2O (1/2)	57
7	H_2O_2 (1)	CH_3CN–H_2O (1/2)	28
8	$K_2S_2O_8$ (1)	DCE–H_2O (1/2)	83
9	$K_2S_2O_8$ (1)	DME–H_2O (1/2)	70
10	$K_2S_2O_8$ (1)	DMSO–H_2O (1/2)	77
11	$K_2S_2O_8$ (1)	DMF–H_2O (1/2)	64
12	$K_2S_2O_8$ (1)	1,4-Dioxane–H_2O (1/2)	69
13	$K_2S_2O_8$ (1)	DMA–H_2O (1/2)	64
14	$K_2S_2O_8$ (1)	Toluene–H_2O (1/2)	63
15	$K_2S_2O_8$ (1)	NMP–H_2O (1/2)	65
16	$K_2S_2O_8$ (1)	CH_3CN–H_2O (1/1)	73
17	$K_2S_2O_8$ (1)	CH_3CN–H_2O (2/1)	66
18	$K_2S_2O_8$ (1)	CH_3CN–H_2O (1/4)	82
19	$K_2S_2O_8$ (1)	H_2O	66
20	$K_2S_2O_8$ (1)	CH_3CN	42
21	$K_2S_2O_8$ (1.5)	CH_3CN–H_2O (1/2)	81
22	$K_2S_2O_8$ (2)	CH_3CN–H_2O (1/2)	80
23	$K_2S_2O_8$ (1)	CH_3CN–H_2O (1/2)	Trace[c]
24	$K_2S_2O_8$ (1)	CH_3CN–H_2O (1/2)	76[d]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), oxidant (1–2 equiv.), solvent (3 mL), 80 °C, 12 h, under air. TBHP: *tert*-butyl hydroperoxide, 70% solution in water; DTBP: di-*tert*-butyl peroxide; DCE: 1,2-dichloroethane; DME: 1,2-dimethoxyethane; DMA: *N*,*N*-dimethylacetamide; NMP: *N*-methyl-2-pyrrolidone. [b] Isolated yields based on **1a**. [c] 25 °C. [d] 60 °C.

Then, the effects of other oxidants (1 equiv.) such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, $K_2S_2O_8$, TBHP, DTBP and H_2O_2 were investigated. The results showed that this arylsulfonylation reaction could also occur in the presence of the above oxidants, while the reactivity of $K_2S_2O_8$ was better than others to form the desired product in 87% yield (Table 1, entries 2–7). Further optimization of solvents showed that the reaction performed in CH_3CN–H_2O (1 : 2) was found to be superior for the formation of **3aa** (Table 1, entries 8–18). Notably, this arylsulfonylation reaction was also conducted effectively in water (Table 1, entry 19). In contrast, product **3aa** was obtained in relatively low yield when the reaction was performed in sole CH_3CN (Table 1, entry 20). Increasing the amount of $K_2S_2O_8$ did not improve this reaction yield (Table 1, entries 21 and 22). Only a trace amount of **3aa** was detected at room temperature, and the best yield was isolated when the reaction was conducted at 80 °C (Table 1, entries 4, 23–24).

Under the optimized conditions, the scope and limitations of the reaction of various *N*-arylacrylamides with sulfinic acids were investigated and the results are shown in Table 2. In general, *N*-arylacrylamides containing electron-donating or -withdrawing groups on the aryl rings were suitable for this protocol, and the corresponding products were obtained in moderate to good yields (**3aa–3la**). A wide range of functionalities such as halogen, carbonyl, and cyano groups were all tolerated in this reaction, thereby facilitating possible further modifications (**3ea–3ia**). *ortho*-Substituted arylacryl-

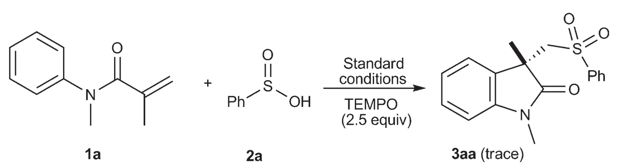
Table 2 Results for catalyst-free arylsulfonylation of *N*-arylacrylamide with sulfinic acids[a,b]



[a] Reaction conditions: **1** (0.25 mmol), **2** (0.75 mmol), $K_2S_2O_8$ (1 equiv.), CH_3CN–H_2O (3 mL, 1/2), 80 °C, 12–24 h. [b] Isolated yields based on **1**.

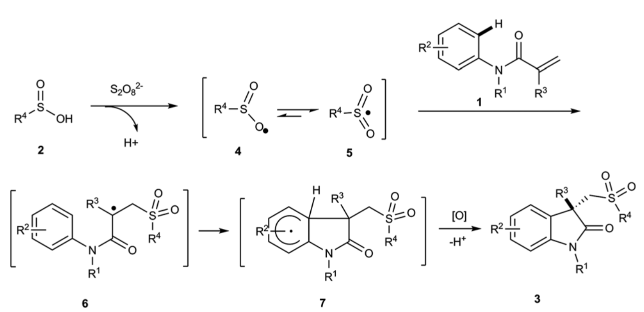
amide, which could not be effectively used in the previous reported system,[14] was compatible with this reaction, affording the desired product **3ja** in good yield. The substituent group at the *meta*-position of the phenyl ring afforded a mixture of two regioselective products (**3ka**/**3ka′**) and (**3la**/**3la′**) and 4-substituted indolinones were obtained as the major products (**3ka** and **3la**). It is noteworthy that the cyclization of tetrahydroquinoline could afford tricyclic oxindole **3ma** in 76% yield. *N*-Arylacrylamides with different functional groups such as alcohol could also be used in the reaction to give the expected product **3na** in 92% yield. Investigations of different N-protection groups showed that substrates bearing both alkyl and aryl protecting groups on the nitrogen are suitable for this reaction (**3aa–3oa**), whereas N-free and acetyl *N*-arylacrylamides failed to afford the desired products. In addition to benzenesulfinic acid, various substituted benzenesulfinic acids bearing either electron-rich or electron-deficient groups were all suitable for this reaction to give the corresponding products in good yields (**3ab–3ag**). The sterically-hindered substituted arylsulfinic acids such as 2-bromobenzenesulfinic acid and 2-(trifluoromethyl)benzenesulfinic acid were also tolerated in this process, leading to the desired products in good yields (**3ah** and **3ai**). Naphthalene-1-sulfinic acid could also be used in the reaction to give the desired product **3aj** in 70% yield.

A radical pathway was proposed in the oxidative addition reaction of sulfinic acids to alkenes leading to β-hydroxysulfones by Lei,[13a] the corresponding mechanism was proved by radical trapping experiments with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well-known radical scavenger). As shown in eqn (2), when TEMPO was added in this reaction system, the arylsulfonylation reaction was extremely inhibited, which suggested that a radical process might be involved in the present reaction.



(2)

On the basis of the above results and referring to the related literature,[13–16] a possible reaction pathway was thus proposed as depicted in Scheme 1. Initially, arylsulfinic acid **2** was converted into an oxygen-centered radical **4** resonating with the sulfonyl radical **5** *via* the single electron transfer (SET) and deprotonation process in the presence of $K_2S_2O_8$.[16] Subsequently, the addition of the sulfonyl radical **5** to *N*-arylacrylamide **1** generated the alkyl radical **6**. Intramolecular cyclization of intermediate **6** with an aryl ring would lead to the formation of radical intermediate **7**. Finally, the oxidation of **7** afforded the corresponding carbocation, which lost H^+ to produce the sulfonated oxindole **3**.



Scheme 1 Postulated reaction pathway.

In summary, a convenient and efficient method has been developed for the construction of sulfonated oxindoles *via* a catalyst-free direct arylsulfonylation reaction of arylacrylamides with sulfinic acids using the simple and cheap $K_2S_2O_8$ as the oxidant. Taking into account the combination of desirable features, such as operation simplicity, product diversity, catalyst-free conditions, and high atom efficiency, this reaction system is expected to provide an alternative and attractive approach to a series of biologically important sulfonated oxindoles from sulfinic acids. The detailed scope, mechanism, and synthetic application of this reaction are under investigation.

Acknowledgements

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References

1 For some selected reviews, see: (*a*) H. Lin and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2003, **42**, 36; (*b*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209; (*c*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*d*) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247; (*e*) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104; (*f*) K. Shen, X. Liu, L. Lin and X. Feng, *Chem. Sci.*, 2012, **3**, 327; (*g*) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165; (*h*) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023.

2 For some selected examples, see: (*a*) J. E. M. N. Klein and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2011, 6821; (*b*) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2010, 4527; (*c*) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (*d*) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003; (*e*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*f*) E. J. Hennessy and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084; (*g*) Y.-X. Jia and E. P. Kündig, *Angew. Chem., Int. Ed.*, 2009, **48**, 1636; (*h*) S. Ueda, T. Okada and H. Nagasawa, *Chem.*

Commun., 2010, **46**, 2462; (*i*) A. Beyer, J. Buendia and C. Bolm, *Org. Lett.*, 2012, **14**, 3948; (*j*) T. Piou, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2012, **51**, 11561.

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

4 (*a*) 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; (*b*) H. Wang, L-N. Guo and X-H. Duan, *Adv. Synth. Catal.*, 2013, **355**, 2222.

5 L.-N. Guo, H. Wang and X.-H. Duan, *Chem. Commun.*, 2013, **49**, 7540.

6 Y.-M. Li, M. Sun, H.-L. Wang, Q.-P. Tia and S.-D. Yang, *Angew. Chem., Int. Ed.*, 2013, **52**, 3972.

7 (*a*) X. Mu, T. Wu, H. Y. Wang, Y. L. Guo and G. S. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 878; (*b*) H. Egami, R. Shimizu, S. Kawamura and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4000; (*c*) P. Xu, J. Xie, Q. C. Xue, C. D. Pan, Y. X. Cheng and C. J. Zhu, *Chem. – Eur. J.*, 2013, **19**, 14039; (*d*) W. Kong, M. Casimiro, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2013, **135**, 14480; (*e*) W. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem., Int. Ed.*, 2013, **52**, 13086.

8 X. H. Wei, Y. M. Li, A. X. Zhou, T. T. Yang and S. D. Yang, *Org. Lett.*, 2013, **15**, 4158.

9 (*a*) Y.-M. Li, X.-H. Wei, X.-A. Li and S.-D. Yang, *Chem. Commun.*, 2013, **49**, 11701; (*b*) T. Shen, Y. Z. Yuan and N. Jiao, *Chem. Commun.*, 2014, **50**, 554.

10 For selected examples, see: (*a*) W. M. Wolf, *J. Mol. Struct.*, 1999, **474**, 113; (*b*) K. G. Petrov, Y. Zhang, M. Carter, G. S. Cockerill, S. Dickerson, C. A. Gauthier, Y. Guo, R. A. Mook, D. W. Rusnak, A. L. Walker, E. R. Wood and K. E. Lackey, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4686; (*c*) R. Ettari, E. Nizi, M. E. Di Francesco, M.-A. Dude, G. Pradel, R. Vicik, T. Schirmeister, N. Micale, S. Grasso and M. Zappala, *J. Med. Chem.*, 2008, **51**, 988; (*d*) S. Kotha and A. S. Chavan, *J. Org. Chem.*, 2010, **75**, 4319; (*e*) N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, 1993.

11 For selected examples, see: (*a*) C. Cassani, L. Bernardi, F. Fini and A. Ricci, *Angew. Chem., Int. Ed.*, 2009, **48**, 5694; (*b*) V. Sikervar, J. C. Fleet and P. L. Fuchs, *Chem. Commun.*, 2012, **48**, 9077; (*c*) V. Sikervar, J. C. Fleet and P. L. Fuchs, *J. Org. Chem.*, 2012, **77**, 5132; (*d*) E. A. Rodkey, D. C. McLeod, C. R. Bethel, K. M. Smith, Y. Xu, W. Chai, T. Che, P. R. Carey, R. A. Bonomo, F. Akker and J. D. Buynak, *J. Am. Chem. Soc.*, 2013, **135**, 18358; (*e*) E. J. Emmett, B. R. Hayter and M. C. Willis, *Angew. Chem., Int. Ed.*, 2013, **52**, 12679.

12 For selected examples, see: (*a*) R. P. Nair, T. H. Kim and B. J. Frost, *Organometallics*, 2009, **28**, 4681; (*b*) V. Nair, A. Augustine, T. G. George and L. G. Nair, *Tetrahedron Lett.*, 2001, **42**, 6763; (*c*) V. Nair, A. Augustine and T. D. Suja, *Synthesis*, 2002, 2259; (*d*) V. Nair, A. Augustine, S. B. Panicker, T. D. Suja and S. Mathai, *Res. Chem. Intermed.*, 2003, **29**, 213; (*e*) H. Qian and X. Huang, *Synlett*, 2001, 1913; (*f*) N. Taniguchi, *Synlett*, 2012, 1245; (*g*) R.-J. Song, Y. Liu, Y.-Y. Liu and J.-H. Li, *J. Org. Chem.*, 2011, **76**, 1001; (*h*) L. R. Reddy, B. Hu, M. Prashad and K. Prasad, *Angew. Chem., Int. Ed.*, 2009, **48**, 172; (*i*) H.-H. Li, D.-J. Dong, Y.-H. Jin and S.-K. Tian, *J. Org. Chem.*, 2009, **74**, 9501; (*j*) M. Yoshimatsu, M. Hayashi, G. Tanabe and O. Muraoka, *Tetrahedron Lett.*, 1996, **37**, 4161; (*k*) J.-M. Fang and M.-Y. Chen, *Tetrahedron Lett.*, 1987, **28**, 2853; (*l*) N. Mantrand and P. Renaud, *Tetrahedron*, 2008, **64**, 11860; (*m*) X. Li, X. Xu and Y. Tang, *Org. Biomol. Chem.*, 2013, **11**, 1739.

13 (*a*) Q. Lu, J. Zhang, G. Zhao, Y. Qi, H. Wang and A. W. Lei, *J. Am. Chem. Soc.*, 2013, **135**, 11481; (*b*) Q. Lu, J. Zhang, F. Wei, Y. Qi, H. Wang, Z. Liu and A. W. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 7156; (*c*) W. Wei, J. Li, D. Yang, J. Wen, Y. Jiao, J. You and H. Wang, *Org. Biomol. Chem.*, 2014, **12**, 1861.

14 X. Li, X. Xu, P. Hu, X. Xiao and C. Zhou, *J. Org. Chem.*, 2013, **78**, 7343.

15 W. Wei, C. Liu, D. Yang, J. Wen, J. You, Y. Suo and H. Wang, *Chem. Commun.*, 2013, **49**, 10239.

16 (*a*) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 13194; (*b*) Y. Wei, J. Tang, X. Cong and X. Zeng, *Green Chem.*, 2013, **15**, 3165.

