

ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

COMMUNICATION

Peroxide promoted tunable decarboxylative alkylation of cinnamic acids to form alkenes or ketones under metal-free conditions

Cite this: DOI: 10.1039/x0xx00000x

Received 00th February 2015,
Accepted 00th February 2015

Jing Ji, Ping Liu and Peipei Sun*

DOI: 10.1039/x0xx00000x

www.rsc.org/

A tunable decarboxylative alkylation of cinnamic acids with alkanes was developed to form alkenes or ketones under transition metal-free conditions. In the presence of DTBP or DTBP/TBHP, the reaction gave alkenes and ketones respectively via a radical mechanism in moderate to good yields.

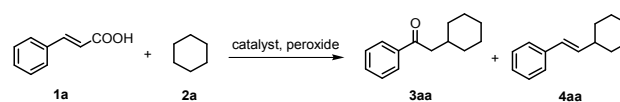
The use of simple alkane as the coupling partner has been aroused great attention in view of green and sustainable chemistry, as well as in economic terms.¹ This approach opened the conspicuous field for development of low-cost hydrocarbons direct into complex organic compounds without prefunctionalization. A series of C–C bond, as well as C–heteroatom bond formation methods were established by the direct C(sp³)–H bond activation of alkanes recently under transition-metal catalysis or metal-free conditions.² To look for the further synthetic application of alkanes is continuously a challenging task for organic chemists.

On the other hand, carboxylic acids served as versatile connection points via extrusion of CO₂, which gave access to various valuable product classes in the last decade.³ These reactions mainly focused on arylation, vinylation, conjugate additions and carbon–heteroatom bond forming reactions. Generally, to loss of CO₂ from most carboxylic acids requires harsh conditions and the addition of a transition metal mediator, *e.g.*, Cu,⁴ Ag,⁵ Pd,⁶ Rh,⁷ Au,⁸ *etc.* Specially, the decarboxylative cross coupling of cinnamic acids catalyzed by Cu,⁹ Fe,¹⁰ Pd,¹¹ Ir,¹² Ru,¹³ *etc.* provided styryl group, which was used for the synthesis of various olefin derivatives. Ni-catalyzed decarboxylative cross-couplings of cinnamic acids with ether or amide to give aryl ketones were also reported.¹⁴ It is noteworthy that the coupling reaction under metal-free conditions provided a new opportunity for organic synthesis, especially in pharmaceutical synthesis.¹⁵ A range of encouraging works using this strategy were developed in recent years, and brought out great vitality for the synthesis of many useful compounds. Several decarboxylative cross couplings of monocarboxylic acids in the absence of metal were reported recently to construct C–C, C–O and C–N bonds.¹⁶ As the continuous study of our group on C–H bond functionalization, especially the oxidative coupling in the absence of metal,^{2f,17} herein we want to disclose a decarboxylative cross coupling of cinnamic acids with alkanes under metal-free conditions,

and the ketones or alkenes were obtained simply in the presence of peroxide.

Initially, we performed the reaction of cinnamic acid **1a** with cyclohexane **2a** in the presence of CuCl and di-*tert*-butyl peroxide (DTBP, 2.0 equiv.) at 120 °C under N₂ for 24 h, and the decarboxylative alkylation product (*E*)-(2-cyclohexylvinyl)benzene (**4aa**) was obtained in 74% yield (Table 1, entry 1). Other Cu salts, such as CuI or Cu(OTf)₂, showed no obvious difference (entries 2 and 3). To our delight, the 75% yield was obtained even without any metal catalyst (entry 4). Then we decided to carry out the reaction under transition metal-free conditions. Some other representative peroxides, such as *tert*-Butyl peroxybenzoate (TBPB), dicumyl peroxide (DCP) or *tert*-butyl hydroperoxide (TBHP) were also screened, and the reaction did not work well under the same conditions (entries 5-7). To our surprise, the product **4aa** was obtained in only a very low yield, accompanied with a 13% yield of decarboxylative carbonylation coupling product 2-cyclohexyl-1-phenylethan-1-one (**3aa**) when 2.0 equiv. DTBP combined with 1.0 equiv. TBHP were used (entry 8). The addition of 4A molecular sieves was helpful to the formation of ketone product and improved the yield to 36% (entry 9). Increasing the amount of TBHP promoted the transformation, and the product **3aa** was achieved in 65% yield in the presence of 2.0 equiv. DTBP and 4.0 equiv. TBHP (entries 10 and 11); further increasing the amount of TBHP had no enhancement (entry 12). Increasing DTBP to 4.0 equiv. brought a slight increase of **4aa** and decrease of **3aa** (entry 13), however, decreasing DTBP to 1.0 equiv. improved the yield of **3aa** to 68%, and only trace **4aa** was detected (entry 14). Performing the reaction under air or at 130 °C did not give better results (entries 15 and 16); yet a very low yield of **3aa** was obtained when lowered the temperature to 100 °C (entry 17). Thus, the general reaction conditions were established for the generation of **3aa** and **4aa** respectively.

Table 1 Optimization of reaction conditions^a

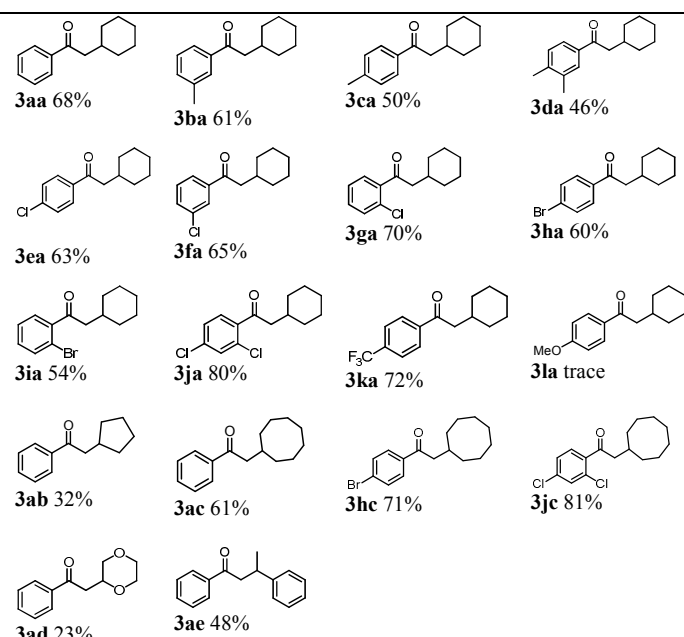
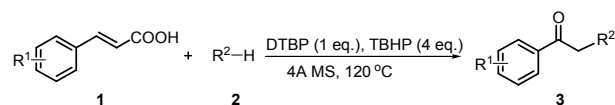


Entry	Catalyst	Peroxide (equiv.)	T (°C)	Yield (%) ^b	
				3aa	4aa
1	CuCl	DTBP (2.0)	120	0	74
2	CuI	DTBP (2.0)	120	0	71
3	Cu(OTf) ₂	DTBP (2.0)	120	0	76
4	-	DTBP (2.0)	120	trace	75
5	-	TBHP (2.0)	120	0	trace
6	-	DCP (2.0)	120	0	30
7	-	TBHP (2.0)	120	<10	trace
8	-	DTBP (2.0)	120	13	<10
9 ^c	-	DTBP (2.0)	120	36	<10
		/TBHP (1.0)			
10 ^c	-	DTBP (2.0)	120	47	<10
		/TBHP (2.0)			
11 ^c	-	DTBP (2.0)	120	65	<5
		/TBHP (4.0)			
12 ^c	-	DTBP (2.0)	120	67	<5
		/TBHP (6.0)			
13 ^c	-	DTBP (4.0)	120	60	<10
		/TBHP (4.0)			
14 ^c	-	DTBP (1.0)	120	68	trace
		/TBHP (4.0)			
15 ^{c,d}	-	DTBP (1.0)	120	58	<5
		/TBHP (4.0)			
16 ^c	-	DTBP (1.0)	130	64	<5
		/TBHP (4.0)			
17 ^c	-	DTBP (1.0)	100	18	<5
		/TBHP (4.0)			

^aUnless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.5 mmol), **2a** (2 mL), catalyst (20 mol%) and peroxide under N₂ for 24 h. ^bIsolated yield, based on **1a**. ^c4A MS (200 mg) was added. ^dUnder air.

Using the optimized reaction conditions, we firstly tested the scope of the decarboxylative alkylation coupling of cinnamic acid derivatives with alkanes to form aryl ketones, as shown in Table 2. The electron-donating substituents on the benzene ring of cinnamic acids seemed to be disadvantageous to the reaction. For example, using cyclohexane as the coupling partner, the *meta*- or *para*-methyl substrates were compatible with the process and afforded ketone products in moderate yields (**3ba-3da**), but the reactant with a methoxy group only gave trace amount of the product (**3la**). On the contrary, the *ortho*-, *meta*- or *para*-halogenated substrates were tolerated, and the reaction proceeded smoothly and gave moderate to high yields (**3ea-3ja**). The strong electron-withdrawing group trifluoromethyl seemed to be favorable to this transformation and gave the desired product in 72% yield (**3ka**), which might due to the formation of more stable radical intermediates. Several other cycloalkanes were then examined as the coupling partners, and similar reactivity was found from cyclooctane (**3ac**, **3hc**, **3jc**). However, cyclopentane which has low boiling-point showed less reactive and led to a lower yield (**3ab**). Surprisingly, the reaction of 1,4-dioxane only gave 23% yield (**3ad**). To our delight, the reaction of ethylbenzene was uneventful, and furnished the ketone product at α -position with high regioselectivity (**3ae**).

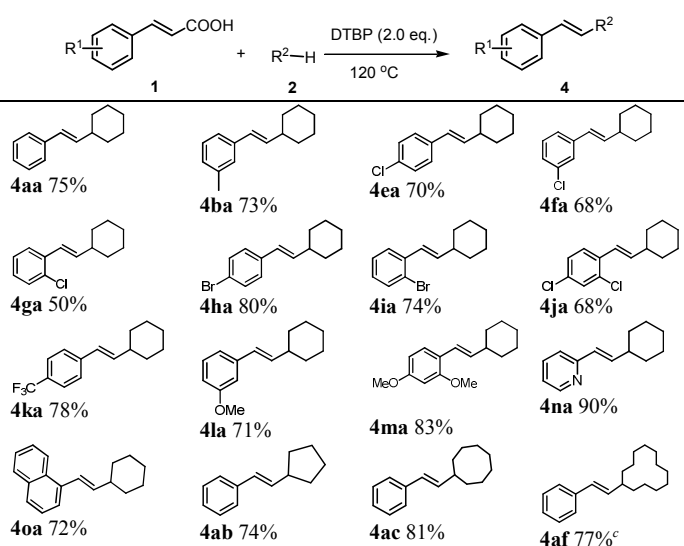
Table 2 Decarboxylative alkylation of cinnamic acids to form ketones^{a,b}

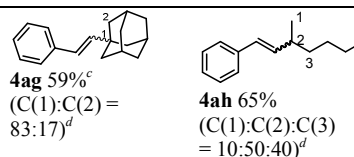


^aReaction conditions: **1** (0.5 mmol), **2** (2.0 mL), DTBP (1.0 equiv.), TBHP (4.0 equiv.), 70% aqueous solution) and 4A MS (200 mg) in a sealed tube under N₂ at 120 °C for 24 h. ^bThe yields are isolated one based on cinnamic acids.

Unlike the above decarboxylative carbonylation, only in the presence of DTBP, cinnamic acids reacted with alkanes to form alkenes via the decarboxylative alkylation. To most of the cinnamic acids we used, the reaction gave the corresponding coupling results in moderate to good yields and exactly with (*E*)-configuration (Table 3). The results showed that the presence of electron-donating group methoxy on benzene ring did not act as a disincentive to this transformation (**4la** and **4ma**). Specially, the heterocyclic derivative, 3-(pyridin-2-yl)acrylic acid also gave a high yield of 90% (**4na**). When adamantane (**2g**) was used as the coupling partner, a mixture of coupling on 3° (C(1)) and 2° (C(2)) carbon was obtained, and the ratio was determined by ¹H NMR to be 83:17 (**4ag**). A mixture was also obtained for the decarboxylative coupling of cinnamic acid (**1a**) with hexane (**2h**) in a total yield of 65% (**4ah**).

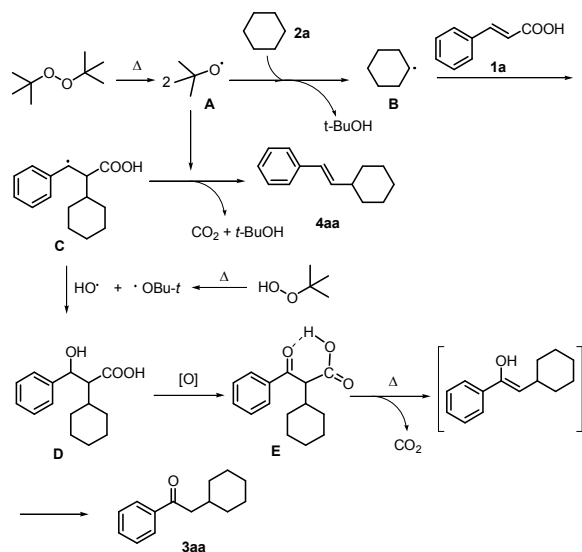
Table 3 Decarboxylative alkylation of cinnamic acids to form alkenes^{a,b}





^aReaction conditions: **1** (0.5 mmol), **2(a-c)** (2.0 mL), DTBP (2.0 equiv.) in a sealed tube under N₂ at 120 °C for 24 h. ^bThe yields are isolated one based on cinnamic acids. ^c**2(f and g)** (3.0 equiv.) in DCE (2.0 mL). ^dThe ratio was determined by ¹H NMR.

The presence of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) had obvious suppression to both reactions above. CO₂ was detected via GC-FTIR in the gas generated from the reaction using air as blank (see electronic supplementary information). And also, from compound **4aa**, we did not observe the formation of **3aa** under the standard reaction conditions which were used to form **3aa** from cinnamic acid. Based on above results and the related reports,^{9,14} we proposed the mechanism referring to radical oxidative coupling process (Scheme 1). Initially, thermal homolysis of DTBP produced *tert*-butoxyl radical **A**, which could abstract a hydrogen radical from cyclohexane and generated cyclohexanyl radical **B**, followed by addition to cinnamic acid **1a** and produced radical intermediate **C**. Next, decarboxylative alkenylation took place to form **4aa** with the aid of another *tert*-butoxyl radical. The combination of radical intermediate **C** and hydroxyl radical which was generated from thermal homolysis of TBHP, afforded the intermediate **D**, which could be further converted to α -carbonyl acid intermediate **E** under oxidative condition. Finally, thermal decarboxylation gave another desired product **3aa** and released CO₂. A LC-MS analysis for the reaction mixture detected the presences of the possible intermediate products **D** and **E** for a reaction time of 8 h (see electronic supplementary information).



Scheme 1 Plausible mechanisms for the two different oxidative coupling reactions.

In summary, we have developed a tunable method for the synthesis of alkenes and ketones via the oxidative alkylation of cinnamic acids with alkanes under transition metal-free conditions. Peroxide DTBP and TBHP/TBHP were proved to be efficient oxidants respectively for these transformations. Alkanes and various substituents on the aryl ring of cinnamic acids tolerated the reactions and gave the corresponding products in moderate to good yields.

Further studies on the cascade addition reaction of cinnamic acids with other radical sources and the mechanism are in progress in our group.

This work was supported by the National Natural Science Foundation of China (Project 21272117) and the Priority Academic Program Development of Jiangsu Higher Education Institutions. The authors also thank Mr. Zilie Liu for the determination of HRMS.

Notes and references

College of Chemistry and Materials Science, Nanjing Normal University; Jiangsu Provincial Key Laboratory of Material Cycle Processes and Pollution Control; Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Nanjing 210097, China
E-mail: sunpei@njnu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c000000x/

- (a) C. Liu, H. Zhang, W. Shi and A. W. Lei, *Chem. Rev.*, 2011, **111**, 1780. (b) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061. (c) S. A. Girard, T. Knauber and C. J. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 74.
- Partial recent examples: (a) M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi and W. Nakanishi, *Science*, 2011, **332**, 448. (b) A. P. Antonchick and L. Burgmann, *Angew. Chem. Int. Ed.*, 2013, **52**, 3267. (c) B. L. Tran, B. J. Li, M. Driess and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 2555. (d) Y. Zhu and Y. Wei, *Chem. Sci.*, 2014, **5**, 2379. (e) W. Sha, J. T. Yu, Y. Jiang, H. Yang and J. Cheng, *Chem. Commun.*, 2014, **50**, 9179. (f) B. Du, B. Jin and P. Sun, *Org. Lett.*, 2014, **16**, 3032. (g) J. Zhao, H. Fang, P. Qian, J. Han and Y. Pan, *Org. Lett.*, 2014, **16**, 5342. (h) Z. Li, F. Fan, J. Yang and Z. Q. Liu, *Org. Lett.*, 2014, **16**, 3396. (i) Z. Li, Y. Zhang, L. Zhang and Z. Q. Liu, *Org. Lett.*, 2014, **16**, 382. (j) H. Zhang, C. Pan, N. Jin, Z. Gu, H. Hu and C. Zhu, *Chem. Commun.*, 2015, **51**, 1320. (k) C. Y. Wang, R. J. Song, W. T. Wei, J. H. Fan and J. H. Li, *Chem. Commun.*, 2015, **51**, 2361. (l) J. Zhao, H. Fang, R. Song, J. Zhou, J. Han and Y. Pan, *Chem. Commun.*, 2015, **51**, 599.
- (a) N. Rodriguez and L. J. Goossen. *Chem. Soc. Rev.*, 2011, **40**, 5030. (b) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291. (c) R. Shang and L. Liu, *Sci. China Chem.*, 2011, **54**, 1670.
- (a) L. J. Goossen, W. R. Thiel, N. Rodriguez and C. Linder, *Adv. Synth. Catal.*, 2007, **349**, 2241. (b) L. J. Goossen, F. Manjolinho, B. A. Khan and N. Rodriguez, *J. Org. Chem.*, 2009, **74**, 2620. (c) R. Shang, Y. Fu, Y. Wang, Q. Xu, H. Z. Yu and L. Liu, *Angew. Chem. Int. Ed.*, 2009, **48**, 9350. (d) G. Cahiez, A. Moyeux, O. Gager and M. Poizat, *Adv. Synth. Catal.*, 2013, **355**, 790.
- (a) L. J. Goßen, C. Linder, N. Rodriguez, P. P. Lange and A. Fromm, *Chem. Commun.*, 2009, 7173. (b) J. Cornella, C. Sanchez, D. Banawa and I. Larrosa, *Chem. Commun.*, 2009, 7176. (c) P. Lu, C. Sanchez, J. Cornella and I. Larrosa, *Org. Lett.*, 2009, **11**, 5710. (d) F. Yin, Z. Wang, Z. Li and C. Li, *J. Am. Chem. Soc.*, 2012, **134**, 10401. (e) Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li and C. Li, *J. Am. Chem. Soc.*, 2012, **134**, 4258.
- (a) D. Tanaka, S. P. Romeril and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 10323. (b) P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey and F. Bilodeau, *J. Am. Chem. Soc.*, 2006, **128**,

11350. (c) J. Cornella, P. Lu and I. Larrosa, *Org. Lett.*, 2009, **11**, 5506. (d) J. –B. Rouchet, C. Schneider, C. Spitz, J. Lefvre, G. Dupas, C. Fruit and C. Hoarau, *Chem. Eur. J.*, 2014, **20**, 3610.
- 7 (a) Z. M. Sun and P. Zhao, *Angew. Chem. Int. Ed.*, 2009, **48**, 6726. (b) Z. M. Sun, J. Zhang and P. Zhao, *Org. Lett.*, 2010, **12**, 992. (c) S. Mochida, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 5776.
- 8 (a) S. Dupuy, F. Lazreg, A. M. Z. Slawin, C. S. J. Cazin and S. P. Nolan, *Chem. Commun.*, 2011, **47**, 5455. (b) S. Dupuy and S. P. Nolan, *Chem. Eur. J.*, 2013, **19**, 14034. (c) J. Cornella, M. Rosillo-Lopez and I. Larrosa, *Adv. Synth. Catal.*, 2011, **353**, 1359. (d) S. Dupuy, L. Crawford, M. Buhl and S. P. Nolan, *Chem. Eur. J.*, 2015, **21**, 1.
- 9 (a) Z. He, T. Luo, M. Hu, Y. Cao and J. Hu, *Angew. Chem. Int. Ed.*, 2012, **51**, 3944. (b) H. Yang, P. Sun, Y. Zhu, H. Yan, L. Lu, X. Qu, T. Li and J. Mao, *Chem. Commun.*, 2012, **48**, 7847. (c) Z. Cui, X. Shang, X. F. Shao and Z. Q. Liu, *Chem. Sci.*, 2012, **3**, 2853. (d) Z. Li, Z. Cui and Z. Q. Liu, *Org. Lett.*, 2013, **15**, 406. (e) S. Cadot, N. Rameau, S. Mangematin, C. Pinel and L. Djakovitch, *Green Chem.*, 2014, **16**, 3089. (f) H. Yan, L. Lu, G. Rong, D. Liu, Y. Zheng, J. Chen and J. Mao, *J. Org. Chem.*, 2014, **79**, 7103. (g) B. V. Rokade and K. R. Prabhu, *Org. Biomol. Chem.*, 2013, **11**, 6713. (h) W. P. Mai, G. Song, G. C. Sun, L. R. Yang, J. W. Yuan, Y. M. Xiao, P. Mao and L. B. Qu, *RSC Adv.*, 2013, **3**, 19264.
- 10 (a) H. Yang, H. Yan, P. Sun, Y. Zhu, L. Lu, D. Liu, G. Rong and J. Mao, *Green Chem.*, 2013, **15**, 976. (b) J. Zhao, H. Fang, J. Han and Y. Pan, *Beilstein J. Org. Chem.*, 2013, **9**, 1718. (c) J. Zhao, W. Zhou, J. Han, G. Li and Y. Pan, *Tetrahedron Lett.*, 2013, **54**, 6507.
- 11 M. Yamashita, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 592.
- 12 P. Xu, A. Abdukader, K. Hu, Y. Cheng and C. Zhu, *Chem. Commun.*, 2014, **50**, 2308.
- 13 H. Huang, K. Jia, and Y. Chen, *Angew. Chem. Int. Ed.*, 2015, **54**, 1881.
- 14 (a) J. X. Zhang, Y. J. Wang, W. Zhang, N. X. Wang, C. B. Bai, Y. L. Xing, Y. H. Li and J. L. Wen, *Sci. Rep.*, 2014, **4**, 7446. (b) J. X. Zhang, Y. J. Wang, N. X. Wang, W. Zhang, C. B. Bai, Y. H. Li and J. L. Wen, *Synlett*, 2014, **25**, 1621.
- 15 C. L. Sun and Z. J. Shi, *Chem. Rev.*, 2014, **114**, 9219.
- 16 (a) S. Manna, S. Jana, T. Saboo, A. Maji and D. Maiti, *Chem. Commun.*, 2013, **49**, 5286. (b) K. Kiyokawa, S. Yahata, T. Kojima and S. Minakata, *Org. Lett.*, 2014, **16**, 4646. (c) X. J. Shang, Z. Li and Z. Q. Liu, *Tetrahedron Lett.*, 2015, **56**, 233.
- 17 (a) B. Du, B. Jin and P. Sun, *Org. Biomol. Chem.*, 2014, **12**, 4586. (b) C. He, X. Qian and P. Sun, *Org. Biomol. Chem.*, 2014, **12**, 6072.