Journal Name RSCPublishing

COMMUNICATION

Oxidative N-Heterocyclic Carbene Catalyzed Diastereoselective Annulation of Simple Aldehydes and 5-Alkenyl Thiazolones: Facile Asymmetric Synthesis of Chiral Thiazolo Pyrones†

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Li Lin,‡[a]* Yuhong Yang,‡[a] Mei Wang,[a] Luhao Lai,[a] Yarong Guo[a] and Rui Wang[ab]*

A highly diastereoselective annulation of simple aldehydes and 5-alkenyl thiazolones, via oxidative NHC catalysis has been developed. This stategy provides facile access to a diverse library of functionalized chiral thiazolo pyrones. Aerobic oxygen can also be applied as a secondary oxidant to avoid the use of stoichiometric organic or inorganic oxidants.

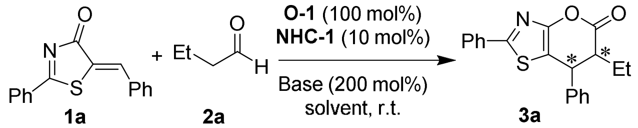
N-Heterocyclic Carbene (NHC) catalysis has been brought forward and developed since middle of 20th century.[1] However, asymmetric NHC catalysis has only gained popularity over the last decade resulting in further development of this research area. [2] Beside the benzoin condensation and the Stetter reaction,[3] oxidative NHC catalysis *via* the Breslow intermediate is the most widely applied model due to its broad applicability allowing for diverse transformations.[4] The Breslow intermediate can be converted to the related positively-charged NHC intermediate (acyl azolium) via a redox process involving an α-ring-fused or α-halo aldehydes,[5-6] enals,[7] and alkynals.[8] Phenol esters,[9] ketenes,[10] and acids[11] as well as acyl fluorides[12] can also be transformed to the acyl azolium intermediate. Aside from these methods, it is preferable to generate the positivly-charged NHC intermediate directly from an unactivated aldehyde via an oxidative process with external oxidants.[13] Stoichiometric or excess quantities of various organic or inorganic oxidants are generally explored. However, molecular oxygen[4][14] has been rarely employed as an electron-transferring oxidant in asymmetric oxidative NHC catalysis.

The generation of the key acyl azolium intermediate from simple aliphatic aldehydes is hughly desirable. Recently, the groups of Rovis [15a] and Chi[15b] sepreately disclosed the asymmetric annulation of aliphatic aldehydes with simple α,β-unsaturated ketimines and ketones. As the commonly used 3,3',5,5'-(^{t}Bu)$_4$-diphenoquinone (**O-1**) did not work in Rovis' work, they exploited riboflavin tetra acetate (**O-2**) and phenazine instead. (§) However, Chi et al.[14b] achieved their annulation of aliphatic aldehydes with simple chalcones when using **O-1** as the oxidant. Although they report the use of catalytic quantities of **O-1** in combination of MnO_2 can afford similar result, a highly excess amount of MnO_2 was essential. Besides, the electrophile in reported works is limited to simple ketimines and chalcones. Asymmetric transformations of simple alaphatic aldehyde with other electrophiles rather than ketimines and chalcones are unknown. Protocols affording more complex structural motifs are highly desired.

Thiazoles skeletons are found in many drug as well as bioactive compounds. In order to further exploit the bioactivities of such compounds, the development of new methodologies towards the synthesis of such scaffolds has always been an attractive field. The most attractive way to make highly functionalized chiral thiazolo pyrones is via an asymmetric annulation of 5-alkenyl thiazolones with the requisite aldehyde, via an oxidative NHC protocol. Herein, we report the highly stereoselective annulation of aliphatic aldehydes with 5-alkenyl thiazolone via oxidative NHC catalysis. A series of chiral thiazolo pyrones were obtained. Most note-worthy, in presence of aerobic oxygen, excellent stereoselectivity and moderate yield can also be achieved using the oxidant quinone **O-1** in catalytic amount.

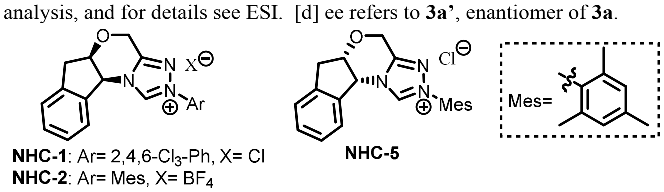
In our initial studies, 5-alkenyl thiazolone **1a** and butyraldehyde **2a** were used in the model reaction to optimize the reaction conditions. Stoichiometric **O-1** was exploited to optimize the reaction conditions, involving solvent and base. Detailed optimization studies are shown in ESI (†). Note worthily, when using Et_3N as the base and catalyzed by **NHC-1**, the highest yield (85%) of **3a** was obtained, along with excellent diastereoselectivity (>20:1) and high ee of 92% (Table 1, entry 1). The ee value was increased to 95% when using NaOAc, and excellent d.r. (>20:1) also resulted (Table 1, entry 2). Thus, NaOAc was realized as the optimal base in for this system, and used in the following studies. Variety of NHC pre-catalysts (**NHC1~8**) was also examined (For details see ESI†). The reactivity was greatly affected by the aryl substitutes in the carbene ring. Interestingly, the two enantiomers of **3a** and **3a'** were respectively obtained, while using **NHC-2** and its opposite enantiomer **NHC-5** (Table 1, entry 3 and 4). The absolute configurations of (*R*, *R*)-**3a** and (*S*, *S*)-**3a'** were confirmed via X-ray crystallography (Scheme 1) (†), which clearly indicated that the reaction give the chiral thiazolo pyrone in *cis*-conformation. Therefore, in order to get the chiral thiazolo pyrones in the desired high yield with excellent stereoselectivity, pre-catalyst **NHC-2** and stoichiometric amount of **O-1** were explored in the following studies.

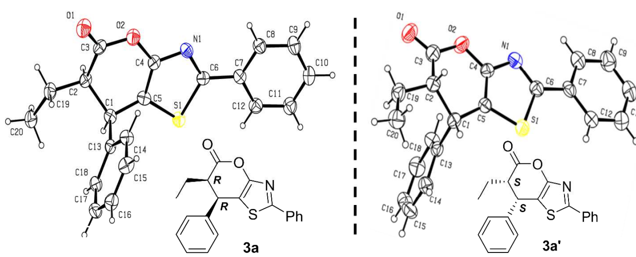
Table 1. Representative screening studies on base and NHC pre-catalyst.[a]



entry	pre-catalyst	base	yield%[b]	ee%[c]	d.r. [c]
1	**NHC-1**	Et_3N	85	92	>20:1
2	**NHC-1**	NaOAc	74	95	>20:1
3	**NHC-2**	NaOAc	80	>99	>20:1
4	**NHC-5**	NaOAc	82	>-99[d]	>20:1

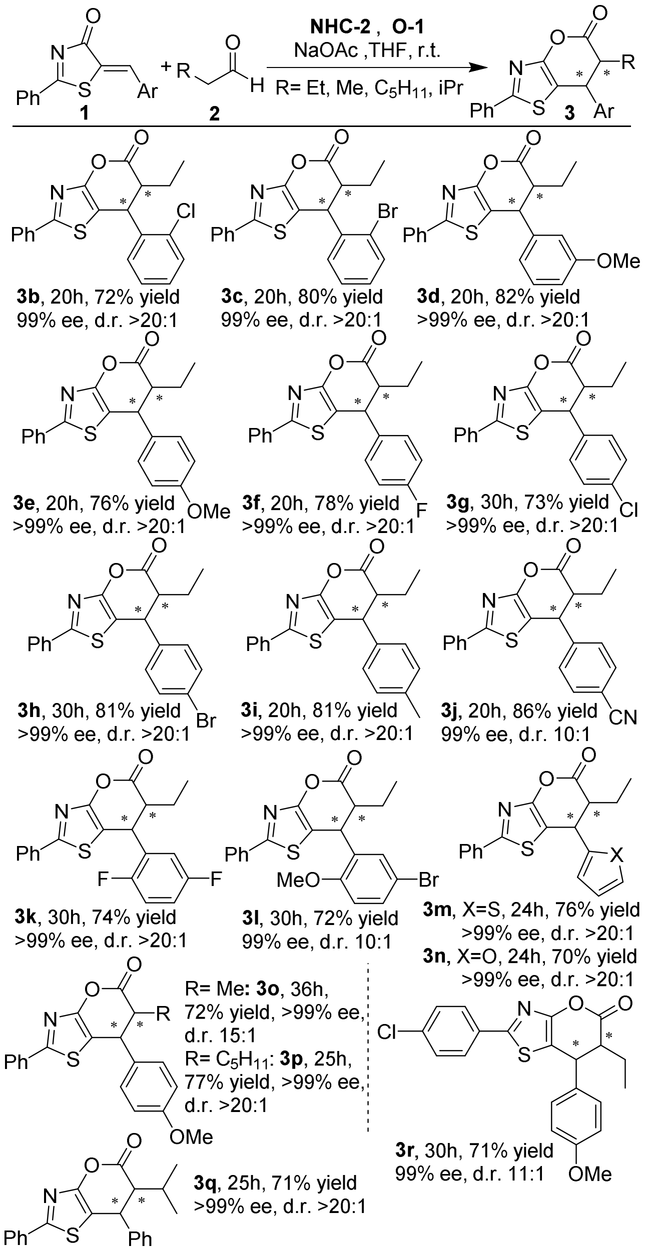
[a] In freshly distilled THF, all the reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), Base (0.4 mmol), **O-1** (0.2 mmol), and **NHC** (0.02 mmol) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis, and for details see ESI. [d] ee refers to **3a'**, enantiomer of **3a**.





Scheme 1. X-ray structure of **3a** and **3a'.**

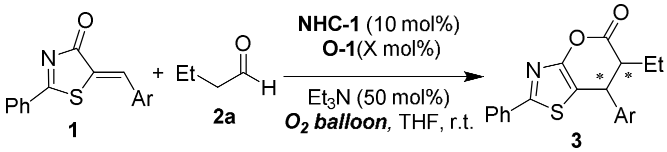
Under the optimal conditions, the reaction scope was investigated with a variety of 5-alkenyl thiazolones with simple aliphatic aldehydes. As shown in Scheme 2, both electron-deficient and electron-rich aryl substitutes of 5-alkenyl thiazolones were well tolerated in the asymmetric annulation. The desired chiral thiazolo pyrones were afforded in moderate to good yields with excellent enantioselectivities (>99%) and diastereoselectivities being observed. Different substituents at the phenyl ring of the 5-alkenyl in compound **1** exerted a limited influence during the annulation (**3b-3i**, and **3k**). The decreased diastereoselectivity observed in the case of **3j** (d.r. 10:1), may be a due to the strong electron-withdrawing effect of the nitrile group. The hindrance of the *o*-MeO substitute may lead to the decreasing of the d.r. of **3l** to 10:1. The chiral thiazolo pyrone containing either a thienyl (**3m)** or a furyl (**3n)** motif was also successfully afforded in good yield with excellent ee (>99%) and diastereoselectivity (d.r. >20:1). In addition, other simple aliphatic aldehydes as well as 5-alkenyl thiazolone were also tolerated. The reaction of **1e** with either propanal or heptanal proceeded successfully to afford the annulation product **3o** or **3p** in good yields, and with excellent ee and d.r. values. While using isovaleraldehyde, excellent stereoselectivity of **3q** was also observed. In contrast with Scheidt's work,[16] the substitute in the 2-aryl group of thiazolone did not affect the reactivity or the stereoselectivity of the annulation. Product **3r** was obtained in good yield with 99% ee and high d.r. of 11:1. This result indicated that the present protocol could lead to more diverse chiral thiazolo pyrones, which can be utilized in medicinal chemistry.



Scheme 2. Diastereoselective [4+2] annulation catalyzed by **NHC-2.** See the Supporting Information for details. All the reactions were carried out in THF at room tempeature for the cited hours, using different 5-alkenyl thiazolone (0.2 mmol), simple aldehyde (0.4 mmol), NaOAc (0.2 mmol), **O-1** (0.2 mmol), and **NHC-2** (0.02 mmol). The yield refers to isolated yield. The ee value and diastereomeric ratio (d.r.) were determined by HPLC analysis, and for details see ESI.

As commonly known, 3,3',5,5'-(^{t}Bu)$_4$-biphenyl-4,4'-diol (**O-1**$^{\mathbf{R}}$) is the reduced form of the oxidant **O-1**. The phenol **O-1**$^{\mathbf{R}}$ can also be oxidized to **O-1** by molecular oxygen, during which would generate one molecular of H_2O.[17] However, no report exploiting catalytic amount of **O-1** in combination of oxygen has been disclosed. Therefore, we attempted to develop an oxidative NHC catalysis in catalytic use of **O-1**. According to the initial studies, the product was obtained in the highest yield while the reaction was catalyzed by **NHC-1** and using Et_3N as the base (Table 1, entry 1), **NHC-1**/Et_3N catalytic system was then exploited to further screen the required amount of **O-1** in presence of molecular oxygen (Table 2).

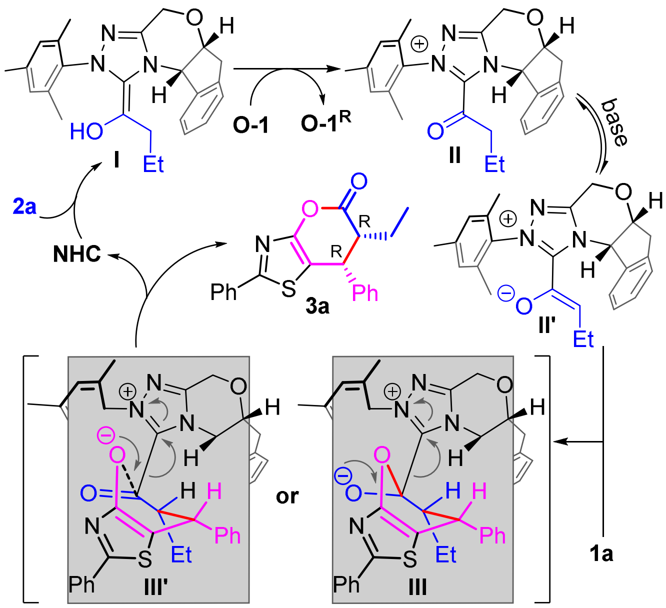
Table 2. Oxidative NHC catalysis using catalytic amount of **O-1**.[a]



entry	product	X mol%	yield(%)[b]	ee(%)[c]	d.r.[c]
1	**3i**	0	trace	ND[d]	ND[d]
2	**3i**	100	81	>99	>20:1
3	**3i**	20	83[e]	>99	>20:1
4	**3i**	10	80[e]	>99	>20:1
5	**3i**	5	75[e]	>99	>20:1
6	**3i**	2	74[e]	>99	>20:1
7	**3d**	2	75[e]	>99	14:1
8	**3f**	2	73[e]	>99	>20:1

[a] All the reactions were carried out with **1** (0.2 mmol), **2a** (0.4 mmol), Et_3N (0.1 mmol), **O-1** (X mmol), and **NHC-1** (0.02 mmol) in THF (2.0 mL) at room temperature. O_2 balloon was used. [b] Isolated yield. [c] Determined by HPLC analysis, and for details see ESI. [d] Not determined. [e] Based on the recovered starting material (**1**), generally in 30% to 40%.

Without using **O-1**, the model reaction gave the thiazolo pyrone **3i** in poor yield with complex by-products (Table 2, entry 1). Surprisingly, no decrease in either enantioselectivity or diastereoselectivity was observed while reducing the amount of **O-1** from 100 mol% to 5 mol% (Table 2, entry 2-5). But the conversion was affected catalytically using **O-1**. Excitingly, the quinone **O-1** can even be reduced to 2 mol% without losing stereoselectivity (Table 2, entry 6). When using 2 mol% of **O-1**, chiral thiazolo pyrones **3d** and **3f** were also obtained in moderate yield with excellent ee (>99%) and high d.r. (14:1 and >20:1, respectively) (Table 2, entry 7-8). But corresponding **1d** and **1f** can be recovered in 30% to 40%. The exact reason for the starting material being not fully convereted remains unkown. The in-situ generation of H_2O might be a possible influence on the reaction outcome. Although the desired products were obatined in moderate yield while using catalytic amount of **O-1**, this work indicates the oxidant **O-1** in combination of molecular oxygen can be an efficient and green oxidation system in oxidative NHC catalysis.



Scheme 3. Proposed mechanism.

A catalytic model is proposed and shown in Scheme 3. Firstly, the in-situ generated free carbene catalyst **NHC** can react with the aldehyde **2a** to form the Breslow intermediate **I**. The acyl azolium **II** is then generated via oxidizing Breslow intermediate **I** by **O-1**. The enolate form of acyl azolium (**II'**), which is the real active species, can be easily formed in the presence of base. Subsequently, enolate intermediate **II'** in combination of the alkenyl thiazolone will undergo the [4+2]-annulation or Michael addition to construct the new six-member ring intermediates (**III** and **III'**, respectively). To simplify the figure, a gray panel was used to block the frameworks behind the surface. The product as well as the free carbene **NHC** can be afforded from the zwitterion intermediate **III** or **III'**. If in the presence of molecular oxygen, the quinone **O-1** can be re-generated via oxidation of **O-1**^{R}, during which one molecular of H_2O is generated. However, the in-situ generated H_2O may affect the formation of the enolate intermediate **II'** as well as the annulation process. Therefore, when using catalytic amount of **O-1**, the in-situ generated H_2O may caused the lower yield.

In conclusion, we have developed an oxidative NHC-catalyzed annulation of 5-alkenyl thiazolones with simple aliphatic aldehydes under mild conditions. A broad substrate scope was tolerated in the present method. Thus, a series of structural diverse chiral thiazolo pyrones were obtained in good yield with excellent enantioselectivity as well as diastereoselectivity. It was also found the common oxidant quinone **O-1** can be used in catalytic amount and be re-generated in the presence of molecular oxygen, which indicates this method is a more efficient and greener oxidation system for oxidative NHC catalysis.

We gratefully acknowledge financial support from NSFC (nos. 21002043 and 21272107), the National S&T Major Project of China (2012ZX09504-001-003), and Fundamental Research Funds for the Central Universities (lzujbky-2013-166).

Notes and references

[a] Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China. E-mail: linli@lzu.edu.cn, wangrui@lzu.edu.cn; Fax: (+86) 0931-8912567

[b] State key Laboratory of Chiroscience, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China.

† Electronic Supplementary Information (ESI) available. CCDC 1040952 (**3a**) and CCDC 1040953 (**3a'**) contain the supplementary crystallographic data for this paper. For ESI and crystallographic data in CIF or other electronic format see See DOI: 10.1039/c000000x/

‡ These two authors contributed equally.

§ Although Rovis group (ref. 14a) reported a 74% yield obtained in the model reaction when using catalytic riboflavin tetra acetate (Riboflavin-Ac_4 or **O-2** in Scheme 2) under "rigorous exclusion of oxygen" condition, it was confused to find that the reaction resulted in only low yield (<20%) under oxygen. However, they did not give a clear and reasonable discussion.

1 R. Breslow, *J. Am. Chem. Soc.* 1958, **80**, 3719.

2 Selected reviews: a) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem. Int. Ed.* 2007, **46**, 2988; b) V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.* 2008, **37**, 2691; c) J. Moore and T. Rovis, in *Asymmetric Organocatalysis, Vol. 291* (Ed.: B. List), Springer Berlin Heidelberg, 2009, pp. 118; d) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.* 2011, **44**, 1182; e) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose and V. Sreekumar, *Chem. Soc. Rev.* 2011, **40**, 5336; f) X. Bugaut and F. Glorius, *Chem. Soc. Rev.* 2012, **41**, 3511; g) D. T. Cohen and K. A. Scheidt, *Chem. Sci.* 2012, **3**, 53; h) A. Grossmann and D. Enders, *Angew. Chem. Int. Ed.* 2012, **51**, 314; i) J.

Izquierdo, G. E. Hutson, D. T. Cohen and K. A. Scheidt, *Angew. Chem. Int. Ed.* 2012, **51**, 11686; j) H. U. Vora, P. Wheeler and T. Rovis, *Adv. Synth. Catal.* 2012, **354**, 1617; k) X.-Y. Chen and S. Ye, in *Stereoselective Organocatalysis*, John Wiley & Sons, Inc., 2013, pp. 231; l) M. Fevre, J. Pinaud, Y. Gnanou, J. Vignolle and D. Taton, *Chem. Soc. Rev.* 2013, **42**, 2142; m) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.* 2013, **42**, 4906; n) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature* 2014, **510**, 485; o) J. Mahatthananchai and J. W. Bode, *Acc. Chem. Res.* 2014, **47**, 696.

3 a) D. Enders, J. Han and A. Henseler, *Chem. Commun.* 2008, 3989; b) Q. Liu, S. Perreault and T. Rovis, *J. Am. Chem. Soc.* 2008, **130**, 14066; c) T. Jousseaume, N. E. Wurz and F. Glorius, *Angew. Chem. Int. Ed.* 2011, **50**, 1410; d) J. Zhang, C. Xing, B. Tiwari and Y. R. Chi, *J. Am. Chem. Soc.* 2013, **135**, 8113; e) J. Xu, C. Mou, T. Zhu, B.-A. Song and Y. R. Chi, *Org. Lett.* 2014, **16**, 3272.

4 Reviews see: a) C. E. I. Knappke, A. Imami and A. Jacobi von Wangelin, *Chemcatchem* 2012, **4**, 937; b) S. De Sarkar, A. Biswas, R. C. Samanta and A. Studer, *Chem. Eur. J.* 2013, **19**, 4664.

5 Z. Q. Rong, W. Zhang, G. Q. Yang and S. L. You, *Curr. Org. Chem.* 2011, **15**, 3077.

6 Recent examples: a) Q. Ni, H. Zhang, A. Grossmann, C. C. J. Loh, C. Merkens and D. Enders, *Angew. Chem. Int. Ed.* 2013, **52**, 13562; b) S. R. Yetra, T. Kaicharla, S. S. Kunte, R. G. Gonnade and A. T. Biju, *Org. Lett.* 2013, **15**, 5202; c) H.-R. Zhang, Z.-W. Dong, Y.-J. Yang, P.-L. Wang and X.-P. Hui, *Org. Lett.* 2013, **15**, 4750; d) C. Zheng, W. Yao, Y. Zhang and C. Ma, *Org. Lett.* 2014, **16**, 5028.

7 Recent examples: a) L.-H. Sun, L.-T. Shen and S. Ye, *Chem. Commun.* 2011, **47**, 10136; b) K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. H. Y. Cheong and K. A. Scheidt, *J. Am. Chem. Soc.* 2014, **136**, 76; c) R. C. Johnston, D. T. Cohen, C. C. Eichman, K. A. Scheidt and P. Ha-Yeon Cheong, *Chem. Sci.* 2014, **5**, 1974; d) M. Wang, Z.-Q. Rong and Y. Zhao, *Chem. Commun.* 2014, **50**, 15309.

8 Selected examples: a) D. Du, Z. Hu, J. Jin, Y. Lu, W. Tang, B. Wang and T. Lu, *Org. Lett.* 2012, **14**, 1274; b) B. Zhou, Z. Luo and Y. Li, *Chem. Eur. J.* 2013, **19**, 4428; c) Y. Zhang, Y. Lu, W. Tang, T. Lu and D. Du, *Org. Biomol. Chem.* 2014, **12**, 3009.

9 Selected examples: a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao and Y. R. Chi, *Org. Lett.* 2012, **14**, 2154; b) J. Cheng, Z. Huang and Y. R. Chi, *Angew. Chem. Int. Ed.* 2013, **52**, 8592; c) Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong and Y. R. Chi, *Nat Chem* 2013, **5**, 835; d) J. Xu, Z. Jin and Y. R. Chi, *Org. Lett.* 2013, **15**, 5028.

10 a) H. Lv, X.-Y. Chen, L.-h. Sun and S. Ye, *J. Org. Chem.* 2010, **75**, 6973; b) T.-Y. Jian, P.-L. Shao and S. Ye, *Chem. Commun.* 2011, **47**, 2381; c) X.-N. Wang, L.-T. Shen and S. Ye, *Chem. Commun.* 2011, **47**, 8388.

11 Selected examples: a) X.-Y. Chen, Z.-H. Gao, C.-Y. Song, C.-L. Zhang, Z.-X. Wang and S. Ye, *Angew. Chem. Int. Ed.* 2014, **53**, 11611; b) A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra and K. A. Scheidt, *J. Am. Chem. Soc.* 2014, **136**, 10589.

12 a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* 2011, **133**, 4694; b) L. Candish and D. W. Lupton, *J. Am. Chem. Soc.* 2012, **135**, 58; c) L. Candish, C. M. Forsyth and D. W. Lupton, *Angew. Chem. Int. Ed.* 2013, **52**, 9149.

13 Recent examples: a) J. M. Mo, X. K. Chen and Y. R. Chi, *J. Am. Chem. Soc.* 2012, **134**, 8810; b) J. Mo, L. Shen and Y. R. Chi, *Angew. Chem. Int. Ed.* 2013, **52**, 8588; c) S. Bera, R. C. Samanta, C. G. Daniliuc and A. Studer, *Angew. Chem. Int. Ed.* 2014, **53**, 9622; d) N. A. White and T. Rovis, *J. Am. Chem. Soc.* 2014, **136**, 14674; e)F. Li, Z. Wu and J. Wang, *Angew. Chem. Int. Ed.* 2015, **54**, 656.

14 S. W. Youn, H. S. Song and J. H. Park, *Org. Lett.* 2014, **16**, 1028. Achiral examples: a) E. G. Delany, C.-L. Fagan, S. Gundala, K. Zeitler and S. J. Connon, *Chem. Commun.* 2013, **49**, 6513; b) J. F. Zhao, C. Muck-Lichtenfeld and A. Studer, *Adv. Synth. Catal.* 2013, **355**, 1098; c) O. Bortolini, C. Chiappe, M. Fogagnolo, P. P. Giovannini, A. Massi, C. S. Pomelli and D. Ragno, *Chem. Commun.* 2014, **50**, 2008; d) S. W. Youn, H. S. Song and J. H. Park, *Org. Biomol. Chem.* 2014, **12**, 2388.

15 a) X. D. Zhao, K. E. Ruhl and T. Rovis, *Angew. Chem. Int. Ed.* 2012, **51**, 12330; b) J. M. Mo, R. J. Yang, X. K. Chen, B. Tiwari and Y. R. Chi, *Org. Lett.* 2013, **15**, 50.

16 E. O. McCusker and K. A. Scheidt, *Angew. Chem. Int. Ed.* 2013, **52**, 13616.

17 a) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.* 1957, **22**, 1439; b) S. V. Bukharov, L. K. Fazlieva, N. A. Mukmeneva, R. M. Akhmadullin and V. I. Morozov, *Russ. J. General Chem.* 2002, **72**, 1805.

