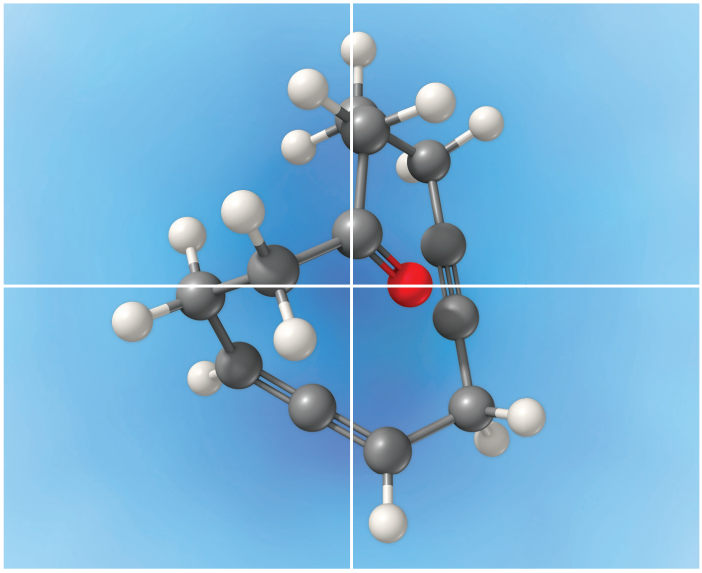
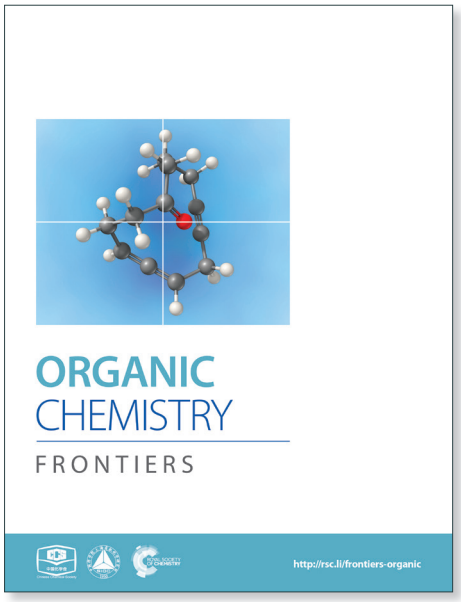
ORGANIC CHEMISTRY

FRONTIERS



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.

Journal Name

RSCPublishing

ARTICLE

Asymmetric Synthesis of Poly-Substituted Spirocyclohexane Oxindoles via Squaramide Catalyzed Cascade Michael-Michael-Aldol Sequence

Qiang-Sheng Sun, Xiao-Yang Chen, Hua Zhu, Hua Lin, Xing-Wen Sun* and Guo-Qiang Lin

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

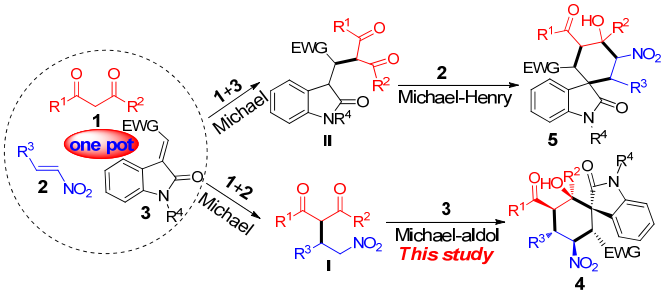
www.rsc.org/

A squaramide-catalyzed Michael-Michael-aldol cascade sequence of three readily accessible substrates (1,3-dicarbonyl compounds, nitroalkenes and methyleneindolinones) was developed. The reactions led to a series of enantioenriched spirocyclohexane oxindoles bearing six contiguous stereocenters in good yields (up to 85%) and with excellent stereoselectivities (>20:1 dr, >99% ee).

Introduction

The prevalence of spirocyclic oxindoles architecture in a variety of natural products and synthetic bioactive compounds has underlined the importance of general asymmetric methods for their efficient construction.[1] Particularly, spirocyclohexane oxindoles have intrigued the chemistry community for years, with a unique synthetic challenge. Significant efforts have been contributed to the stereoselective construction of the requisite all-carbon spiroquaternary and other multiple stereocenters for such complex structures.[2] Recently, a number of elegant asymmetric assemblies of spirocyclohexane oxindoles[3,4] were accomplished by means of organocatalytic domino reactions,[5] in which small organic molecules are used to mediate multiple chemical transformations in a consecutive and protecting group free fashion. The reactions are conducted under mild conditions with remarkable step, atom and redox economy. Notably, these established methods are mainly based on chiral amine catalyzed syntheses through cascade reactions[3] or Diels-Alder reactions.[4] Nevertheless, to the best of our knowledge, the asymmetric synthesis of spirocyclohexane oxindoles bearing six contiguous stereocenters is rare to date. The steric hindrance arising from the multiple crowded groups of cyclohexane, in combination with the difficulties in constructing the all-carbon spiroquaternary stereocenter with excellent stereocontrol, presents an extremely hard task to design highly stereoselective approaches towards fully substituted spirocyclohexane oxindoles. Therefore, new strategies for the efficient and stereospecific synthesis of fully substituted spirocyclohexane oxindoles from readily available starting materials are still in great demand.

Previously, we reported several organocatalyzed cascade reactions for the asymmetric preparation of densely substituted six-membered rings bearing contiguous stereocenters using easily accessible starting materials.[6] Inspired and encouraged by these results, we realized that 1,3-dicarbonyl compounds **1** not only could undergo Michael addition with both nitroalkenes **2** and methyleneindolinones **3** but also could serve as electrophiles for an intramolecular aldol or Henry reaction. The conjugated additions of dicarbonyl compounds to nitroalkenes or oxindoles catalyzed by bifunctional catalysts have been well studied.[7] As such, these Michael adducts (**I**, **II**) would attack another Michael acceptor under the identical condition in the following step. Consequently, two types of multifunctional spirocyclic oxindoles (**4**, **5**) would be generated from these simple substrates through a cascade reaction (Scheme 1). We herein disclose an organocatalytic cascade Michael/Michael/aldol sequence for the construction of spirocyclohexane oxindole bearing six adjacent stereocenters in a highly efficient and stereospecific manner using β-dicarbonyl compounds, nitroalkenes and methyleneindolinones under mild conditions. It is worth noting that Enders and co-workers reported the synthesis of spiropyrazolones using a similar strategy while this manuscript was in preparation.[8]



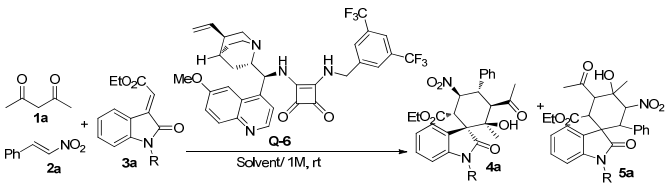
Scheme 1 Asymmetric organocatalytic cascade strategy for privileged six-membered rings

Results and discussion

Initially, the cascade Michael-Michael-aldol sequence was set up in one-pot fashion using acetylacetone **1a**, nitroalkene **2a** and unprotected methyleneindolinone **3a** in DCM at room temperature with 5 mol% of chiral squaramide as catalyst. Unfortunately, no

desired spirocyclohexane oxindoles was obtained but the Michael adduct of 1,3-diketone and nitroalkene was isolated in nearly quantitative yield after 24 hours (Table 1, entry 1). Then, different protecting groups on *N* atom of methyleneindolinone were tested. *N*-Methyl and *N*-benzyl protected substrates showed less reactivity in this cascade reaction (Table 1, entries 2, 3). *N*-Acetyl methyleneindolinone furnished the desired product in 15% yield with 1:1 dr and >99% ee (Table 1, entry 4). To our delight, when *N*-Boc protected methyleneindolinone was examined, the desired product **4a** was obtained in 25% yield with >20:1 dr and >99% ee. However the chemoselectivity (**4a**:**5a** = 1:2.5) and the diastereoselectivity of **5a** (2.5:1) were very low (Table 1, entry 5). To improve the yield and selectivities, the cascade reaction was performed in stepwise-fashion by adding *N*-Boc-protected methyleneindolinone after nitroalkene was consumed completely.[9] Gratifyingly, much higher yield (85%) of **4a** was achieved, along with excellent stereoselectivity (*>20:1 dr, >99% ee*) and chemoselectivity (**4a**: **5a** >20:1) (Table 1, entry 6). Other solvents, such as $CHCl_3$, CCl_4, THF and toluene, gave slightly lower yields compared to DCM (Table 1, entries 7-10). Taken together, the proposed cascade reaction could be realized by adding *N*-Boc-protected methyleneindolinone after the first Michael addition was completed in the presence of 5 mol% **Q-6** in DCM at room temperature. (The reaction of isolated Michael addition adducts with methyleneindolinone catalyzed by achiral base, see ESI).

Table 1 Optimization of cascade reaction conditions [a]

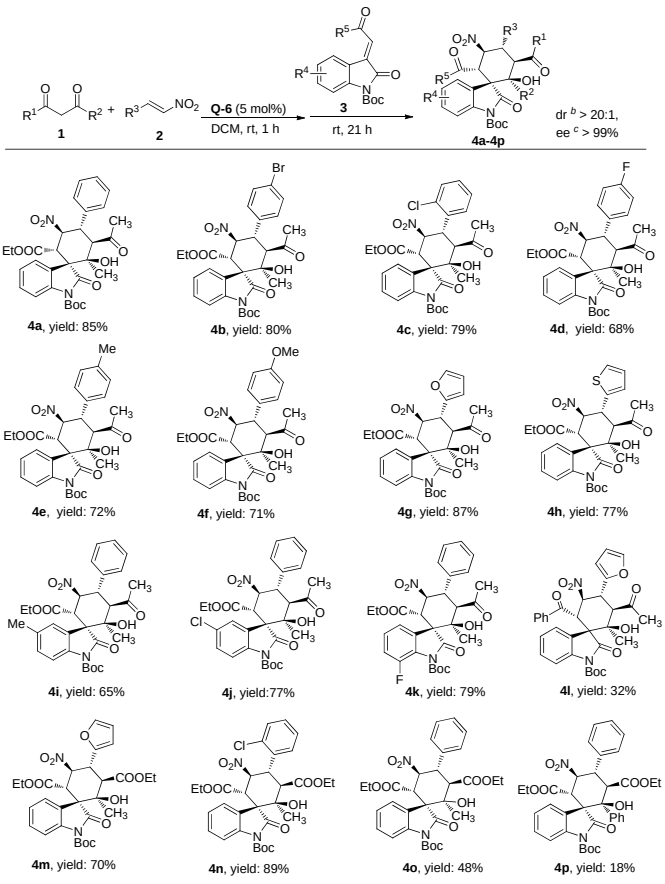


Entry	R	Time (h)	Solvent	Yield (%)[b](**4a**)	dr[c]	ee (%)[d]
1	H	24	DCM	-	-	-
2	Me	24	DCM	-	-	-
3	Bn	24	DCM	-	-	-
4	Ac	24	DCM	15%	1:1	>99%
5[e]	Boc	24	DCM	25%	>20:1	>99%
6[f]	Boc	1+21	DCM	85%	>20:1	>99%
7[f]	Boc	1+21	$CHCl_3$	78%	>20:1	>99%
8[f]	Boc	1+30	CCl_4	73%	>20:1	>99%
9[f]	Boc	1+21	THF	71%	>20:1	>99%
10[f]	Boc	1+30	toluene	76%	>20:1	>99%

[a] The reaction was performed using 0.22 mmol of **1a**, 0.2 mmol of **2a**, 5 mol% of **Q-6**, and 0.3 mmol of **3a** in solvent (1.0 M) at room temperature. Results of other catalysts and bases see ESI. [b] Isolated yield of **4a**. [c,d] dr was determined by chiral HPLC. [e] **4a**:**5a** = 1:2.5, (**5a**, 2.5:1 dr, 96% ee). [f] **3a** was added after **2a** was consumed completely.

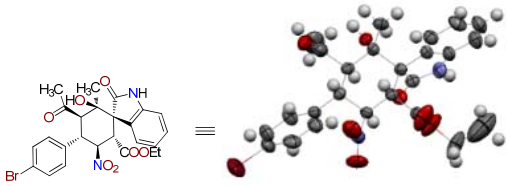
With the optimized conditions in hand, the substrate scope was explored as summarized in Figure 1. In general, the reaction could produce the corresponding products in moderate to good yields (up to 85%) and with excellent stereoselectivities (>20:1 dr, >99% ee, in all cases). Aryl substituted nitroalkenes bearing either electron-withdrawing or electron-donating groups on phenyl ring were well tolerated (Figure 1, **4a** - **4f**), affording the desired compounds in high yields (71 - 85%). Nitroalkenes with alkyl substitutions proven to be not good substrates gave moderate yields but poor selectivities (see SI for details). Desirable results (77-87% yields) were obtained when nitroalkenes bearing heteroaromatic rings were employed (Figure 1, **4g**, **4h)**. Additionly, this cascade reaction was amenable to various *N*-Boc protected methyleneindolinones, providing the desired products in moderate to good yields (32-79%) (Figure 1, **4i** - **4l**). It is worth noting that the employment of ethyl acetoacetate (Figure 1, **4m** - **4o**) and ethyl benzoylacetate (Figure 1, **4p**) also afforded the expected spirocyclic oxindoles with excellent stereoselectivities (>20:1 dr, >99% ee). The absolute configuration of the cascade Michael-Michael-aldol reaction product was unambiguously assigned based on the single-crystal X-ray analysis of the *N*-Boc-deprotected product of **4b** (Figure 2).[10]

Figure 1 Substrate scope [a]

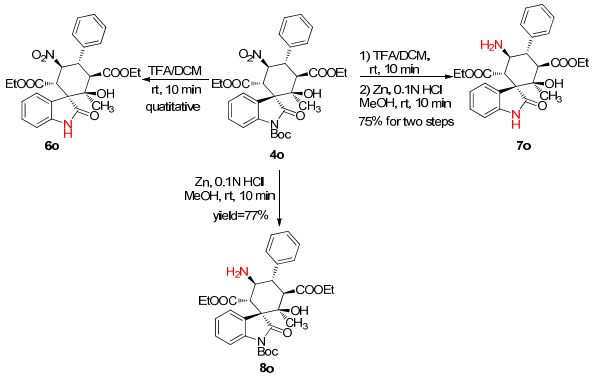


[a] Reaction conditions: the reaction was performed using 0.22 mmol of **1**, 0.20 mmol of **2**, 5 mol% of **Q-6** and 0.3 mmol of **3** in DCM (1.0 M) at room temperature. Isolated yield. [b] dr was determined by crude ^{1}H NMR. [c] ee value of the major product was determined by chiral HPLC.

Figure 2 X-ray structure of *N*-Boc-deprotected product of **4b**[11]

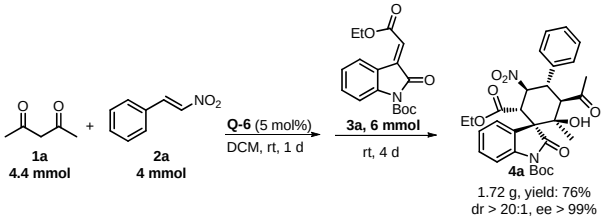


Encouraged by the above results, we next sought to diversify the six-membered spirocyclic oxindoles by reducing the nitro-group or removing the *N*-Boc-group of the obtained products selectively (Scheme 2). The reactions proceeded smoothly to afford the desired compounds (Scheme 2, **6o**, **7o**, **8o**). Notably, the newly formed amine groups in the products **7o** and **8o** could serve as a convenient handle for its further transformations.



Scheme 2 Transformations of the obtained spirocyclohexane oxindoles

To further demonstrate the practicality and efficiency of this cascade Michael-Michael-Aldol sequence, a gram-scale synthesis of poly-substituted spirocyclohexane oxindole was achieved in 76% yield with excellent stereoselectivity (>20:1 dr, >99% ee) (Scheme 3). Albeit prolonged reaction time was needed, this result illustrated a very promising outlook for the applicability of this cascade reaction. When lower catalyst loading (2 mol%) was applied in gram-scale synthesis, high dr (>20:1) and excellent ee (>99%) was achieved but lower yield was observed regretfully (see SI for details).



Scheme 3 Gram-scale cascade reaction

Conclusions

In summary, we have developed an organocatalytic Michael-Michael-aldol sequence that generated a series of polysubstituted spirocyclohexane oxindoles using bifunctional squaramide as the catalyst. These structurally complex scaffolds were obtained in good yields (up to 85%) and with excellent stereoselectivities (>20:1 dr, >99% ee in all cases), featuring the efficient formation of three C-C bonds and six contiguous stereocenters including one all-carbon spiroquaternary stereocenter. We envision that these important skeletons would show great promise in the further synthesis of bioactive molecules.

Acknowledgements

Financial support from the National Natural Science Foundation of China (21302020, 21342009 and 21472019) is gratefully acknowledged.

Notes and references

** Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433 (China) E-mail: sunxingwen@fudan.edu.cn*
Fax/Tel: +86 21 6564 2406.

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 For selected reviews on spirocyclic oxindoles, see: (a) R. M. Williams and R. J. Cox, *Acc. Chem. Res.*, 2003, **36**, 127; (b) H. Lin and S. J .Danishefsky, *Angew. Chem., Int. Ed.*, 2003, **42**, 36; (c) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (d) J. Yang, X. Z. Wearing, P. W. Le Quesne, J. R. Deschamps and J. M. Cook, *J. Nat. Prod.*, 2008, **71**, 1431; (e) G. S. Singh and Z. Y. Desta, *Chem. Rev.* 2012, **112**, 6104; For selected examples on spirocyclic oxindoles, see: (f) J.-J. Liu and Z. Zhang, (Hoffmann-La Roche AG) PCT Int. Appl. WO2008/055812, 2008; (g) T. Onishi, P. R. Sebahar and R. M. Williams, *Org. Lett.*, 2003, **5**, 3135; (h) B. M. Trost, N. Cramer and H. Bernsmann, *J. Am. Chem. Soc.*, 2007, **129**, 3086; (i) X. Zhou, T. Xiao, Y. Iwama and Y. Qin, *Angew. Chem., Int. Ed.*, 2012, **51**, 4909; (j) B. M. Trost, D. A. Bringley, T. Zhang and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135,** 16720; (k) Y.-L. Liu, X. Wang, Y.-L. Zhao, F. Zhu, X.-P. Zeng, L. Chen, C.-H. Wang, X.-L. Zhao and J. Zhou, *Angew. Chem., Int. Ed.*, 2013, **52**, 13735.

2 For selected examples and reviews on synthesis of spirocyclohexane oxindoles, see: (a) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, **12**, 2209; (b) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, **18**, 3003; (c) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (d) J. J. Badillo, N. V. Hanhan and A. K. Franz, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 758; (e) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247; (f) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165; (g) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023; (h) Y. Liu, H. Wang and J. Wan, *Asian J. Org. Chem.*, **2013**, *2*, 374; (i) G. Zhu, W. Sun, C. Wu, G. Li, L. Hong and R. Wang, *Org. Lett.*, 2013, **15**, 4988; (j) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas III, *ACS Catal.*, 2014, **4**, 743; (k) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390.

3 For selected examples on cascade organocatalytic asymmetric synthesis of spirocyclohexane oxindoles, see: (a) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7200; (b) K. Jiang, Z.-J. Jia, S. Chen, L. Wu and Y.-C. Chen, *Chem.-Eur. J.*, 2010, **16**, 2852; (c) K. Jiang, Z.-J. Jia, X. Yin, L. Wu and Y.-C. Chen, *Org. Lett.*, 2010, **12**, 2766; (d) Y.-B. Lan, H. Zhao, Z.-M. Liu, G.-G. Liu, J.-C. Tao and X.-W. Wang, *Org. Lett.*, 2011, **13**, 4866; (e) K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2012, **134**, 12943; (f) X.-F. Huang, Z.-M. Liu, Z.-C. Geng, S.-Y. Zhang, Y. Wang and X.-W. Wang, *Org. Biomol. Chem.*, 2012, **10**, 8794; (g) A. K. Ghosh, and B. Zhou, *Tetrahedron Lett.*, 2013, **54**, 2311; (h) B. Zhou, Y. Yang, J. Shi, Z. Luo and Y. Li, *J. Org. Chem.*, 2013, **78**, 2897; (i) S. Roy, M. Amireddy and K. Chen, *Tetrahedron*, 2013, **69**, 8751.

4 For selected D-A strategy involved examples for the asymmetric synthesis of spirocyclohexane oxindoles, see: (a) Q. Wei and L.-Z. Gong, *Org. Lett.*, 2010, **12**, 1008; (b) G. Li, T. Liang, L. Wojtas and J. C. Antilla, *Angew. Chem., Int. Ed.*, 2013, **52**, 4628; (c) Q.-Q. Zhou, X. Yuan, Y.-C. Xiao, L. Dong and Y.-C. Chen, *Tetrahedron*, 2013, **69**, 10369; (d) P.-Q. Chen, Y.-C. Xiao, C.-Z. Yue and Y.-C. Chen, *Org. Chem. Front.*, 2014, **1**, 490.

5 For selected reviews or book on synthesis of spirocyclohexane oxindoles via domino reactions, see: (a) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem. Int. Ed.*, 2006, **45**, 7134; (b) L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions*

in Organic Synthesis, Wiley-VCH, Weinheim, 2006; (c) D. Enders, C. Grondal and M. R. M. Hűttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (d) X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037; (e) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (f) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (g) Ł. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 8492; (h) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703; (i) S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature*, 2011, **475**, 183; (j) L.-Q. Lu, J.-R. Chen and W.-J. Xiao, *Acc. Chem. Res.*, 2012, **45**, 1278; (k) C. C. J. Loh and D. Enders, *Chem. –Eur. J.*, 2012, **18**, 10212; (l) A. Grossmann and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 314; (m) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237; (n) P. Chauhan and S. S. Chimni, *Tetrahedron: Asymmetry*, 2013, **24**, 343; (o) I. Chatterjee, D. Bastida and P. Melchiorrea, *Adv. Synth. Catal.*, 2013, **355**, 3124; (p) Z. Du and Z. Shao, *Chem. Soc. Rev.*, 2013, **42**, 1337; (q) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442; (r) X. Zeng, *Chem. Rev.*, 2013, **113**, 6864; (s) X. Zeng, Q. Ni, G. Raabe, D. Enders, *Angew. Chem., Int. Ed.*, 2013, **52**, 2977; (t) P. Chauhan and D. Enders, *Angew. Chem., Int. Ed.*, 2014, **53**, 1485.

6 (a) H. Lin, Y. Tan, X.-W. Sun and G.-Q. Lin, *Org. Lett.*, 2012, **14**, 3818; (b) H. Lin, Y. Tan, W.-J. Liu, Z.-C. Zhang, Sun, X.-W. and G.-Q. Lin, *Chem. Commun.*, 2013, **49**, 4024; (c) H. Lin, X.-W. Sun and G.-Q. Lin, *Org. Lett.*, 2014, **16**, 752; (d) Y. Tan, H.-L. Luan, H. Lin, X.-W. Sun, X.-D. Yang, H.-Q. Dong and G.-Q. Lin, *Chem. Commun.*, 2014, **50**, 10027; (e) Y. Tan. Y.-J. Chen, H. Lin, H.-L. Luan, X.-W. Sun, X.-D. Yang and G.-Q. Lin, *Chem. Commun.*, 2014, **50**, 15913.

7 For selected examples on Michael addition catalyzed by bifunctional squaramide, see: (a) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416; (b) H. Y. Bae, S. J. Some, S. Oh, Y. S. Lee and C. E. Song, *Chem. Commun.*, 2011, **47**, 9621; (c) S.-W. Duan, H.-H. Lu, F.-G. Zhang, J. Xuan, J.-R. Chen and W.-J. Xiao, *Synthesis*, 2011, **12**, 1847; (d) Y.-F. Wang, R.-X. Chen, K. Wang, B.-B. Zhang, Z.-B. Lib and D.-Q. Xu, *Green Chem.*, 2012, **14**, 893; (e) O. Baslé, W. Raimondi, M. M. S. Duque, D. Bonne, T. Constantieux and J. Rodriguez, *Org. Lett.*, 2010, **12**, 5246; (f) W. Raimondi, M. M. S. Duque, S. Goudedranche, A. Quintard, T. Constantieux, X. Bugaut, D. Bonne and J. Rodriguez, *Synthesis*, 2013, **12**, 1659.

8 P. Chauhan, S. Mahajan, C. C. J. Loh, G. Raabe and D. Enders, *Org. Lett.*, 2014, **16**, 2954.

9 (a) A. Noole, K. Ilmarinen, I. Järving, M. Lopp and T. Kanger, *J. Org. Chem.*, 2013, **78**, 8117; (b) A. Quintavalla, F. Lanza, E. Montroni, Marco. Lombardo and C. Trombini, *J. Org. Chem.*, 2013, **78**, 12049.

10 CCDC 1007247 (for *N*-Boc-deprotected product of **4b**).

11 The proposed transition states for the explanation of stereochemistry outcome.