Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Asymmetric catalytic *aza*-Morita–Baylis–Hillman reaction for the synthesis of 3-substituted-3-aminooxindoles with chiral quaternary carbon centers†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 1921

Received 23rd December 2012,
Accepted 31st January 2013

DOI: 10.1039/c3ob27495k

www.rsc.org/obc

Fang-Le Hu,[a] Yin Wei,[a] Min Shi,*[a,b] Suresh Pindi[c] and Guigen Li*[c,d]

The asymmetric catalytic *aza*-Morita–Baylis–Hillman (*aza*-MBH) reaction of isatin-derived ketimines with MVK has been established by using chiral amino and phosphino catalysts. The reaction resulted in biomedically important 3-substituted 3-amino-2-oxindoles in good yields (>80% for most cases) and with excellent enantioselectivity (90–99% ee). Twenty-eight cases assembled with chiral quaternary stereogenic centers have been examined under convenient systems.

3-Substituted-3-amino-2-oxindoles are core structures in a variety of natural products and biologically active compounds,[1] such as the potent gastrin/CCK-B receptor antagonist AG-041R,[2] the vasopressin VIb receptor antagonist SSR-1494153[3] and the antimalarial drug candidate NITD609.[4] The development of efficient synthetic protocols leading to these products, particularly those assembled with quaternary chiral carbon centers, has been desired and extremely challenging. Recently, significant advances have been achieved in the development of synthetic methodologies for these targets. These methods include organocatalytic and metal-catalyzed asymmetric α-amination,[5] chiral auxiliary-controlled diastereoselective synthesis of chiral 3-substituted 3-aminooxindoles[6] and enantioselective additions of isatin-derived ketimines.[7] Very recently, Wang and co-workers reported the asymmetric addition of 1,3-dicarbonyl compounds onto *N*-alkoxycarbonyl ketimines and the asymmetric *aza*-Friedel–Craft reaction of indoles and pyrroles with *N*-Boc ketimines in the presence of chiral phosphoric acid catalysts;[8] the latter led to the formation of 3-aminooxindoles in good yields and with excellent enantioselectivities.[9]

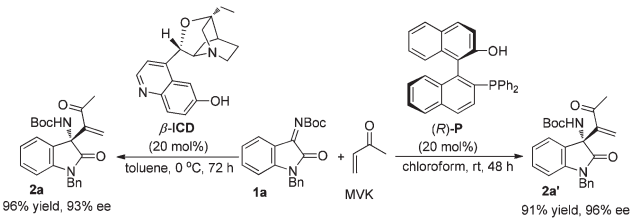
In the meanwhile, the Morita–Baylis–Hillman (MBH) reaction has become a powerful and atom-economic tool for constructing enantiomerically enriched α-hydroxycarbonyl or α-aminocarbonyl compounds. In the past one decade, we and others have extensively studied the Morita–Baylis–Hillman (MBH) reaction and its *aza* versions;[10,11] among that is the MBH reaction of *N*-protected isatin with electron-deficient alkenes leading to the construction of 3-substituted 3-hydroxyoxindoles in good yields and with excellent enantioselectivities.[12] Obviously, the more challenging work is to achieve an asymmetric catalytic *aza*-Morita–Baylis–Hillman approach to chiral 3-aminooxindoles. Herein, we wish to report a highly enantioselective *aza*-MBH reaction of isatin-derived *N*-Boc ketimines with methyl vinyl ketone (MVK) for the efficient synthesis of chiral 3-aminooxindoles.

Inspired by the fact that chiral amino[13,10a] and phosphino[14,15,10c,d] derivatives are commonly utilized for asymmetric MBH and *aza*-MBH reactions, we came up with chiral β-isocupreidine (β-**ICD**) and (*R*)-2′-diphenylphosphanyl-[1,1′]-binaphthalenyl-2-ol ((*R*)-**P**) as the catalyst candidates for the reaction of *N*-Boc ketimine **1a** and MVK for our initial investigation. After the catalytic conditions were screened extensively (for details, see Tables SI-1 and 2 in the ESI†), we found the best condition is as below: 0.10 mmol of **1a** was subjected to reaction with 0.20 mmol of MVK in the presence of the catalyst β-**ICD** (20 mol%) in toluene (2 mL). The reaction occurred to completion at 0 °C in 72 hours to give product **2a** in 96% yield and 93% ee. We also found that when 20 mol% of (*R*)-**P** was employed as the catalyst, the reaction occurred to completion in chloroform (2 mL) within a shorter period of 48 h to afford **2a′** in 91% yield and 96% ee (Scheme 1, numbering **2a** and **2a′** is for outcomes' differentiation).

With the optimized condition in hand, we then turned our attention to the examination of scope and limitations of this reaction using *N*-protected ketimines **1** with different

[a]*Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Mei Long Road, Shanghai 200237, P. R. China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China. E-mail: mshi@mail.sioc.ac.cn*
[c]*Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA. E-mail: guigen.li@ttu.edu*
[d]*Institute of Chemistry & BioMedical Sciences, Nanjing University, Nanjing 210093, P. R. China*

†Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds. CCDC 900656. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob27495k



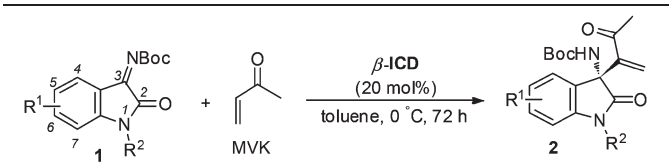
Scheme 1 Chiral amine or phosphine-catalyzed asymmetric *aza*-MBH reaction.

substituents attached to their benzene rings. We found that whether electron-withdrawing or donating groups were attached to the 5-, 6- or 7-position of the benzene ring of *N*-protected ketimines **1**, the reaction can smoothly go to completion to give product **2** in good to high yields (up to 98%) and with excellent enantioselectivities (90%–94% ee) (Table 1, entries 1–11 and entry 17). As for ketimine **1m** with two substituents on its benzene ring, the corresponding *aza*-MBH product **2m** was obtained in 97% yield and 90% ee (Table 1, entry 12). Unfortunately, when the electron-withdrawing or donating substituents were introduced at the 4-position of the benzene ring, no desired products were formed (Table 1, entries 13 and 14), which is presumably due to the steric hindrance between the substituents on the 4-position of the benzene ring and the *N*-Boc group. *N*-Boc ketimines **1p** and **1q** derived from *N*-methyl and *N*-allyl protected isatins, respectively, were also found to be suitable for this reaction, affording *aza*-MBH adducts, **2p** and **2q**, in excellent yields and enantioselectivity (Table 1, entries 15 and 16). However, when the *t*-Bu group of the Boc moiety was replaced by the ethyl group, the yield and ee value decreased remarkably (Table 1, entry 18). In order to resolve the steric problem with 4-substituted substrates in which the *t*-Bu group of the Boc moiety has been replaced by the ethyl group, we also synthesized compound **1t** and used it in this asymmetric *aza*-MBH reaction. However, no desired products were formed under the standard conditions (Table 1, entry 19). The absolute chemistry of this reaction is represented by the unambiguous determination of crystals of product **2e** *via* X-ray diffraction to be "*R*" configuration (see ESI†).

Having examined the β-**ICD**-catalyzed asymmetric *aza*-MBH reaction, we next turned our attention to the chiral phosphine-catalyzed reaction, the results are summarized in Table 2. As compared with the β-**ICD**-catalyzed asymmetric reaction, similar results were obtained, affording *aza*-MBH adducts **2′** in up to 97% yield and 99% ee (Table 2, entries 1–19). The β-**ICD** catalyst resulted in the same absolute "*R*" configuration as that of the (*R*)-**P**-catalyzed *aza*-MBH process.

Furthermore, we also examined the (*S*)-**BINOL**-derived catalyst, (*S*)-**P**,[10d] for this reaction. As expected, (*S*)-**P** catalyzed the present *aza*-MBH reaction similarly to (*R*)-**P** and resulted in (*S*)-**2a** with the opposite enantioselectivity (95% ee) and in 91% yield (Scheme 2).

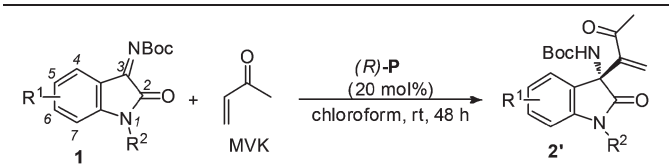
Table 1 β-**ICD**-catalyzed asymmetric *aza*-MBH reaction



Entry[a]	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	**1b**, 5-CH_3	Bn	**2b**, 86	91
2	**1c**, 5-F	Bn	**2c**, 97	94
3	**1d**, 5-Cl	Bn	**2d**, 98	93
4	**1e**, 5-Br	Bn	**2e**, 97	94
5	**1f**, 6-CH_3	Bn	**2f**, 93	92
6	**1g**, 6-Cl	Bn	**2g**, 98	94
7	**1h**, 6-Br	Bn	**2h**, 98	94
8	**1i**, 7-F	Bn	**2i**, 97	92
9	**1j**, 7-Cl	Bn	**2j**, 98	92
10	**1k**, 7-Br	Bn	**2k**, 92	91
11	**1l**, 7-CF_3	Bn	**2l**, 84	91
12	**1m**, 5-Cl, 7-CH_3	Bn	**2m**, 97	90
13	**1n**, 4-CH_3	Bn	Trace	nd[d]
14	**1o**, 4,7-Cl_2	Bn	Trace	nd[d]
15	**1p**, H	Me	**2p**, 85	90
16	**1q**, H	Allyl	**2q**, 96	90
17	**1r**, 5-CH_3O	Bn	**2r**, 80	90
18[e]	**1s**, H	Bn	**2s**, 32	62
19[e]	**1t**, 4,7-Cl_2	Bn	Trace	nd[d]

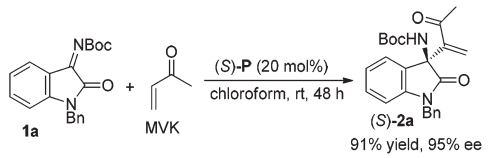
[a] **1** (0.1 mmol), MVK (0.2 mmol) and catalyst (0.02 mmol) were stirred in 2 mL of toluene within 72 h at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Not determined. [e] The *t*-Bu group of the Boc moiety in **1a** was replaced by the ethyl group.

Table 2 (*R*)-**P**-catalyzed asymmetric *aza*-MBH reaction

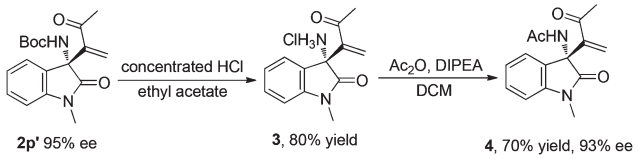


Entry[a]	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	**1b**, 5-CH_3	Bn	**2b′**, 93	95
2	**1c**, 5-F	Bn	**2c′**, 96	93
3	**1d**, 5-Cl	Bn	**2d′**, 91	99
4	**1e**, 5-Br	Bn	**2e′**, 97	>99
5	**1f**, 6-CH_3	Bn	**2f′**, 88	99
6	**1g**, 6-Cl	Bn	**2g′**, 93	96
7	**1h**, 6-Br	Bn	**2h′**, 93	97
8	**1i**, 7-F	Bn	**2i′**, 87	95
9	**1j**, 7-Cl	Bn	**2j′**, 70	99
10	**1k**, 7-Br	Bn	**2k′**, 78	99
11	**1l**, 7-CF_3	Bn	**2l′**, 70	94
12	**1m**, 5-Cl, 7-CH_3	Bn	**2m′**, 86	>99
13	**1n**, 4-CH_3	Bn	Trace	nd[d]
14	**1o**, 4,7-Cl_2	Bn	Trace	nd[d]
	1p, H	Me	**2p′**, 85	95
16	**1q**, H	Allyl	**2q′**, 90	97
17	**1r**, 5-CH_3O	Bn	**2r**, 83	90
18[e]	**1s**, H	Bn	**2s**, 86	70
19[e]	**1t**, 4,7-Cl_2	Bn	Trace	nd[d]

[a] **1** (0.1 mmol), MVK (0.2 mmol) and catalyst (0.02 mmol) were stirred in 2 mL of chloroform within 48 h at rt. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Not determined. [e] The *t*-Bu group of the Boc moiety in **1a** was replaced by the ethyl group.



Scheme 2 (*S*)-**P**-catalyzed asymmetric *aza*-MBH reaction.



Scheme 3 Representative *aza*-MBH product transformation.

For the removal of the *N*-Boc protection group of 3-amino-2-oxindoles, **2p′** was used as an example by treating with HCl (conc.) in ethyl acetate. The cleavage product **3** was obtained in 80% yield without observation of a major side-product. After treating with acetic anhydride, *N*-acyl 3-aminooxindole **4** was generated in 70% yield (Scheme 3). The free amino product **3** would be able to be converted into many other building blocks in future.

The reaction mechanism for the MBH reaction has been extensively investigated by several groups.[16] We have studied the chiral Lewis base (*R*)-**P**-catalyzed asymmetric *aza*-MBH reaction of *N*-sulfonated imines with activated olefins.[10] The key enolate intermediate, which was stabilized by intramolecular hydrogen bonding, has been observed by ^{31}P and ^{1}H NMR spectroscopy.[10d] In order to identify the correlation of the ee values of product **2** with those of catalyst (*R*)-**P** during the present *aza*-MBH process, a series of control experiments were performed by employing **1q** as the substrate and (*R*)-**P** with different ee values as catalysts under standard conditions (for details, see Table SI-3 in the ESI†). It was confirmed that there is no non-linear effect between the ee value of (*R*)-**P** and those of **2q′**, indicating that the exclusive reaction transition state that involves only one molecule of chiral phosphine catalyst played a role in controlling asymmetric induction during the present asymmetric *aza*-MBH reaction.[17]

The corresponding *aza*-MBH reaction using *N*-phosphonyl and *N*-phosphinyl imines for GAP (group-assisted purification) synthesis will be explored in due course.[18]

In conclusion, the asymmetric *aza*-MBH reaction of isatin-derived *N*-Boc ketimines with MVK in the presence of chiral amine and phosphine catalysts has been developed for the first time; this reaction provides an efficient enantioselective tool for the synthesis of 3-amino-2-oxindoles bearing quaternary stereogenic centers. The mechanistic study showed that there is no non-linear effect existing in this asymmetric catalytic process. Further efforts will be focused on applications of this reaction for organic and medicinal synthesis.

Acknowledgements

We thank the Shanghai Municipal Committee of Science and Technology (11JC1402600), NIH (R21DA031860-01), the Robert Welch Foundation (D-1361), the National Basic Research Program of China (973)-2010CB833302, the Fundamental Research Funds for the Central Universities, and the National Natural Science Foundation of China for financial support (21072206, 20472096, 20872162, 20672127, 21121062, 21102166 and 20732008).

Notes and references

1 For reviews, see: (*a*) A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945; (*b*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*c*) G. S. Singh, M. Dhooghe and N. De Kimpe, *Chem. Rev.*, 2007, **107**, 2080; (*d*) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (*e*) K. Shen, X. Liu, L. Lin and X.-M. Feng, *Chem. Sci.*, 2012, **3**, 327; (*f*) J. E. M. N. Klein and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2011, 6821; (*g*) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104.

2 M. Ochi, K. Kawasaki, H. Kataoka and Y. Uchio, *Biochem. Biophys. Res. Commun.*, 2001, **283**, 1118.

3 (*a*) G. Decaux, A. Soupart and G. Vassart, *Lancet*, 2008, **371**, 1624; (*b*) T. Shimazaki, M. Iijima and S. Chaki, *Eur. J. Pharmacol.*, 2006, **543**, 63.

4 M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H. P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175.

5 (*a*) L. Cheng, L. Liu, D. Wang and Y.-J. Chen, *Org. Lett.*, 2009, **11**, 3874; (*b*) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao and J. Zhou, *Chem. Commun.*, 2009, 6753; (*c*) T. Bui, M. Borregan and C. F. Barbas III, *J. Org. Chem.*, 2009, **74**, 4537; (*d*) T. Bui, G. Hernández-Torres, C. Milite and C. F. Barbas III, *Org. Lett.*, 2010, **12**, 5696; (*e*) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 1255; (*f*) Z. Yang, Z. Wang, S. Bai, K. Shen, D. Chen, X. Liu, L. Lin and X.-M. Feng, *Chem.–Eur. J.*, 2010, **16**, 6632; (*g*) K. Shen, X. Liu, G. Wang, L. Lin and X.-M. Feng, *Angew. Chem., Int. Ed.*, 2011, **50**, 4684.

6 (*a*) T. Emura, T. Esaki, K. Tachibana and M. Shimizu, *J. Org. Chem.*, 2006, **71**, 8559; (*b*) G. Lesma, N. Landoni, T. Pilati, A. Sacchetti and A. Silvani, *J. Org. Chem.*, 2009, **74**, 4537; (*c*) H. H. Jung, A. W. Buesking and J. A. Ellman, *Org. Lett.*, 2011, **13**, 3912; (*d*) W.-J. Yan, D. Wang, J.-C. Feng, P. Li and R. Wang, *J. Org. Chem.*, 2012, **77**, 3311.

7 (*a*) Y.-L. Liu, F. Zhou, J.-J. Cao, C.-B. Ji, M. Ding and J. Zhou, *Org. Biomol. Chem.*, 2010, **8**, 3847; (*b*) Q.-X. Guo, Y.-W. Liu, X.-C. Li, L.-Z. Zhong and Y.-G. Peng, *J. Org.*

Chem., 2012, **77**, 3589; (*c*) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi and N. Shibata, *Chem.–Eur. J.*, 2012, **18**, 9276; (*d*) H. Lv, B. Tiwari, J.-M. Mo, C. Xing and Y. G. R. B. Chi, *Org. Lett.*, 2012, **14**, 5412; (*e*) B. Zhang, P. Feng, L.-H. Sun, Y.-X. Cui, S. Ye and N. Jiao, *Chem.–Eur. J.*, 2012, **18**, 9198.

8 W.-J. Yan, D. Wang, J.-C. Feng, P. Li, D.-P. Zhao and R. Wang, *Org. Lett.*, 2012, **14**, 2512.

9 J.-C. Feng, W.-J. Yan, D. Wang, P. Li, Q.-T. Sun and R. Wang, *Chem. Commun.*, 2012, **48**, 8003.

10 (*a*) M. Shi and Y.-M. Xu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4507; (*b*) M. Shi, Y.-M. Xu and Y.-L. Shi, *Chem.–Eur. J.*, 2005, **11**, 1794; (*c*) M. Shi and L.-H. Chen, *Chem. Commun.*, 2003, 1310; (*d*) M. Shi, L.-H. Chen and C.-Q. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3790; (*e*) Y.-L. Shi and M. Shi, *Adv. Synth. Catal.*, 2007, **349**, 2129; (*f*) M.-J. Qi, T. Ai, M. Shi and G. Li, *Tetrahedron*, 2008, **64**, 1181; (*g*) X.-Y. Guan, Y.-Q. Jiang and M. Shi, *Eur. J. Org. Chem.*, 2008, 2150; (*h*) X.-Y. Guan, Y. Wei and M. Shi, *Eur. J. Org. Chem.*, 2010, 4098; (*i*) W. Pei, H.-X. Wei and G. Li, *Chem. Commun.*, 2002, 2412; (*j*) W. Pei, H.-X. Wei and G. Li, *Chem. Commun.*, 2002, 1856.

11 For reviews, see: (*a*) S. E. Drewes and G. H. P. Roo, *Tetrahedron*, 1988, **44**, 4653; (*b*) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001; (*c*) P. Langer, *Angew. Chem., Int. Ed.*, 2000, **39**, 3049; (*d*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811; (*e*) G. Masson, C. Housseman and J.-P. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 4614; (*f*) D. Basavaiah, K. V. Rao and R. J. Reddy, *Chem. Soc. Rev.*, 2007, **36**, 1581; (*g*) Y.-L. Shi and M. Shi, *Eur. J. Org. Chem.*, 2007, 2905; (*h*) V. Singh and S. Batra, *Tetrahedron*, 2008, **64**, 4511; (*i*) V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev.*, 2009, **109**, 1; (*j*) Y. Wei and M. Shi, *Acc. Chem. Res.*, 2010, **43**, 1005.

12 (*a*) X.-Y. Guan, Y. Wei and M. Shi, *Chem.–Eur. J.*, 2010, **16**, 13617; (*b*) Y.-L. Liu, B.-L. Wang, L. Chen, Y.-X. Zhang, C. Wang and J. Zhou, *J. Am. Chem. Soc.*, 2010, **132**, 15176; (*c*) F.-R. Zhong, G.-Y. Chen and Y.-X. Lu, *Org. Lett.*, 2011, **13**, 82.

13 For selected examples, see: (*a*) Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219; (*b*) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.*, 2005, **127**, 3680; (*c*) I. T. Raheem and E. N. Jacobsen, *Adv. Synth. Catal.*, 2005, **347**, 1701; (*d*) N. Abermil, G. Masson and J. Zhu, *J. Am. Chem. Soc.*, 2008, **130**, 12596.

14 For selected examples, see: (*a*) Y.-H. Liu, L.-H. Chen and M. Shi, *Adv. Synth. Catal.*, 2006, **348**, 973; (*b*) F.-R. Zhong, Y.-Q. Wang, X.-Y. Han, K.-W. Huang and Y.-X. Lu, *Org. Lett.*, 2011, **13**, 1310.

15 A. Nakano, M. Ushiyama, Y. Iwabuchi and S. Hatakeyama, *Adv. Synth. Catal.*, 2005, **347**, 1790.

16 For recent mechanistic studies on the MBH reaction: (*a*) L. S. Santos, C. H. Pavam, W. P. Almeida, F. Coelho and M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2004, **43**, 4330; (*b*) K. E. Price, S. J. Broadwater, H. M. Jung and D. T. McQuade, *Org. Lett.*, 2005, **7**, 147; (*c*) V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2005, **44**, 1706; (*d*) R. Robiette, V. K. Aggarwal and J. N. Harvey, *J. Am. Chem. Soc.*, 2007, **129**, 15513.

17 S. Lin and E. N. Jacobsen, *Nat. Chem.*, 2012, **4**, 817.

18 (*a*) A. Kattuboina and G. Li, *Tetrahedron Lett.*, 2008, **49**, 1573; (*b*) P. Kaur, G. Shakya, H. Sun, Y. Pan and G. Li, *Org. Biomol. Chem.*, 2010, **8**, 1091; (*c*) S. Pindi, P. Kaur, G. Shakya and G. Li, *Chem. Biol. Drug Des.*, 2011, **77**, 20; (*d*) P. V. Kattamuri, T. Ai, S. Pindi, Y. Sun, P. Gu, M. Shi and G. Li, *J. Org. Chem.*, 2011, **76**, 2792.

