



CrossMark
click for updates

Cite this: *Chem. Sci.*, 2017, 8, 1238

A new approach to the asymmetric Mannich reaction catalyzed by chiral *N,N'*-dioxide–metal complexes†

Xiangjin Lian, Lili Lin, Kai Fu, Baiwei Ma, Xiaohua Liu and Xiaoming Feng*

Received 31st August 2016
Accepted 2nd October 2016

DOI: 10.1039/c6sc03902b

www.rsc.org/chemicalscience

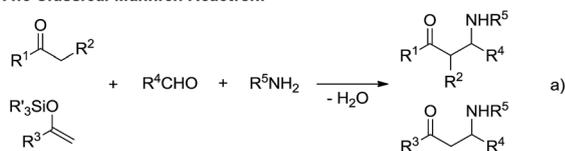
A highly efficient asymmetric Mannich-type reaction between α -tetralone-derived β -keto esters/amides and 1,3,5-triaryl-1,3,5-triazinanes was realized in the presence of chiral *N,N'*-dioxide–Ni(II) or Mg(II) complex. A variety of optically active β -amino compounds with all-carbon quaternary stereocenters were obtained in good yields with excellent enantioselectivities. A possible transition state was proposed based on these experiments and previous reports.

Because the resulting nitrogen-containing compounds are widely distributed in nature and include many biologically important molecules,¹ the Mannich reaction has received a lot of attention since its discovery in the early 20th century (Scheme 1a).² It has become one of the most efficient methods to construct C–C bonds.³ Despite its important synthetic value, the development of the classical intermolecular

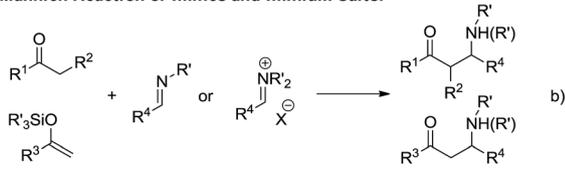
Mannich reaction has been plagued by a number of serious disadvantages such as the undesired side products formed in many cases, and the ability to control the regio- and stereo-selectivity is generally unsatisfactory.⁴ The first catalytic enantioselective approach was reported by Kobayashi using a novel chiral zirconium catalyst in 1997.⁵ To overcome the drawbacks of the classical Mannich reaction, preformed Mannich reagents such as imines and iminium salts have been developed (Scheme 1b).⁶ Subsequently, the catalytic asymmetric Mannich reaction has received a certain amount of development.⁷ However, such preformed Mannich reagents also have some defects such as low activity, sensitivity to moisture and instability, and therefore the development of new Mannich reagents is desirable.

1,3,5-Triaryl-1,3,5-triazinanes, which are conveniently prepared through the condensation of paraformaldehyde and aromatic amines,⁸ can generate the corresponding imines in solvent, which can be used as Mannich reagents. Very recently, Krische reported investigations on the hydroaminomethylation of allenes and 1,3-dienes with 1,3,5-triaryl-1,3,5-triazinanes catalyzed by ruthenium.⁹ Inspired by Krische's work, we think that the *in situ* generated imines from 1,3,5-triaryl-1,3,5-triazinanes might be used as Mannich reagents. On the other hand, all-carbon quaternary stereocenters are widely present in natural products and to build such structures is still a challenge, especially in a catalytic enantioselective manner.¹⁰ In recent years, our group has been committed to utilizing *N,N'*-dioxide–metal complexes as catalysts and has achieved a series of catalytic asymmetric reactions, including the construction of compounds with chiral all-carbon quaternary stereocenters.¹¹ Herein, we report the first asymmetric Mannich reaction employing 1,3,5-triaryl-1,3,5-triazinanes as new Mannich reagents catalyzed by *N,N'*-dioxide–metal complexes, and a variety of optically active β -amino compounds, each with an all-carbon quaternary stereocenter, were obtained.

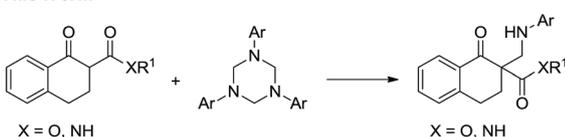
The Classical Mannich Reaction:



Mannich Reaction of Imines and Iminium Salts:



This Work:



Scheme 1 Classical Mannich-type reaction and the new approach.

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China. E-mail: xmfeng@scu.edu.cn; Fax: +86 28 85418249; Tel: +86 28 85418249

† Electronic supplementary information (ESI) available. CCDC 1448521 and 1480808. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc03902b



In our preliminary screening, the α -tetralone-derived β -keto ester **1a** and 1,3,5-triphenyl-1,3,5-triazinane **3a** were chosen as the model substrates to optimize the reaction conditions (Table 1). Initially, the performance of various metal salts was evaluated when combined with the chiral N,N' -dioxide ligand **L-PrPh**, which is derived from *L*-proline, and the reactions were performed in CH_2Cl_2 at 30 °C (Table 1, entries 1–5). Lanthanides, the N,N' -dioxide complexes of which have proved to be efficient catalysts for many reactions,¹¹ can only provide the desired product **4a** with low ee values or as a racemate, although the yields were good (Table 1, entries 1–3). The complex of $\text{Mg}(\text{OTf})_2$ could give the desired product in 85% yield but with only 18% ee (Table 1, entry 4). To our delight, the complex of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ provided **4a** with a better ee value (44% ee, Table 1, entry 5 *versus* entries 1–4). Increasing the steric hindrance of the amide substituents on the chiral N,N' -dioxide ligand further improved the enantioselectivity. Chiral N,N' -dioxide **L-PrPr₂** with a more sterically hindered *i*-Pr at the *ortho*-positions of aniline improved the enantioselectivity to 53% ee (Table 1, entry 6 *versus* entry 5). Then we investigated the effect of the chiral

backbone moiety, the (*S*)-pipercolic acid derived N,N' -dioxide **L-PiPr₂** (Table 1, entry 8) was superior to *L*-proline derived **L-PrPr₂** and *L*-ramipril-derived **L-RaPr₂** (Table 1, entries 6 and 7), giving the product in 94% yield with 96% ee. In addition, lowering the temperature to 0 °C improved the enantioselectivity to 99% ee albeit with a lower yield (Table 1, entry 9). Remarkably, upon reducing the catalyst loading to 5 mol% the yield improved to 97% with the enantioselectivity maintained (Table 1, entry 10). When the α -tetralone-derived β -keto amide **2a** was employed in this reaction instead of **1a**, the desired product **5a** was obtained in good yield but with unsatisfactory enantioselectivity (Table 1, entry 11). Then we replaced the metal salt with $\text{Mg}(\text{OTf})_2$ and got comparable results (Table 1, entry 12).

With the optimized reaction conditions in hand, we firstly investigated the scope of the reactions between α -tetralone-derived β -keto esters and 1,3,5-triaryl-1,3,5-triazinanes (Table 2). Delightfully, the electronic nature and the positions of the substituents on the β -keto esters had little influence on both the yields and enantioselectivities (83–98% yield, 81–99% ee; **4a–4f**). Next, the 1,3,5-triaryl-1,3,5-triazinanes were varied. As it shown in Table 2 (**4g–4k**), the positions of the substituents have a certain influence on the yields, but the enantioselectivities were good in all cases. Generally, the 2-substituted 1,3,5-triaryl-

Table 1 Optimization of the reaction conditions

1a: X = O
2a: X = NH
3a: 1,3,5-triaryl-1,3,5-triazinane
4a: X = O
5a: X = NH

L-PrPh: R = C₆H₅, n = 1
L-PrPr₂: R = 2,6-*i*Pr₂C₆H₃, n = 1
L-PiPr₂: R = 2,6-*i*Pr₂C₆H₃, n = 2

Entry ^a	Substrate	Metal salt	Ligand	Yield ^b (%)	ee ^c (%)
1	1a	Sc(OTf) ₃	L-PrPh	83	0
2	1a	Yb(OTf) ₃	L-PrPh	84	0
3	1a	La(OTf) ₃	L-PrPh	90	13
4	1a	Mg(OTf) ₂	L-PrPh	85	18
5	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PrPh	97	44
6	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PrPr₂	67	53
7	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-RaPr₂	87	87
8	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	94	96
9 ^d	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	87	99
10 ^{d,e}	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	97	99
11 ^{d,e}	2a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	95	61
12 ^{d,f}	2a	Mg(OTf) ₂	L-PiPr₂	98	97

^a Unless otherwise noted, the reactions were performed with **1a** or **2a** (0.10 mmol), **3a** (0.034 mmol), ligand (0.01 mmol), and metal salt (0.01 mmol) in 1.0 mL CH_2Cl_2 at 30 °C for 8 h. ^b Isolated yield of the product. ^c Determined by HPLC analysis on a chiral stationary phase. ^d The reaction was performed at 0 °C for 12 h. ^e 5 mol% **L-PiPr₂** (0.005 mmol) and 5 mol% $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.005 mmol) were used. ^f The reaction was performed with **L-PiPr₂** (0.005 mmol) and $\text{Mg}(\text{OTf})_2$ (0.005 mmol).

Table 2 Substrate scope for β -keto esters^d

1: α -tetralone-derived β -keto ester
3: 1,3,5-triaryl-1,3,5-triazinane
4: β -keto ester product

4a: 97% yield^[b], 99% ee^[c]
4b: 83% yield, 98% ee
4c: 90% yield, 91% ee
4d: 90% yield, 92% ee
4e: 84% yield, 96% ee
4f: 98% yield, 81% ee
4g: 96% yield, 95% ee
4h: 91% yield, 94% ee
4i: 95% yield, 98% ee
4j: 82% yield, 99% ee
4k: 50% yield, 91% ee
4l: 99% yield, 93% ee

^a The reactions were performed with **1** (0.10 mmol), **3** (0.034 mmol), **L-PiPr₂** (0.005 mmol), and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.005 mmol) in 1.0 mL CH_2Cl_2 at 0 °C for 12 h. ^b Isolated yield of the product. ^c Determined by HPLC analysis on a chiral stationary phase.



1,3,5-triazinanes showed a slight decrease in yield compared with the 4-substituted ones. What's more, 1-adamantanol substituted β -keto ester **1l** was also a suitable substrate for this reaction and the corresponding product **4l** was obtained in 99% yield with 93% ee (Table 2, **4l**). Additionally, the absolute configuration of **4a** was determined to be *R* by X-ray crystallography¹² and the configurations of the others were determined to be *R* by circular dichroism (for details see the ESI†).

Subsequently, we turned our attention to investigate the substrate scope of the reactions between α -tetralone-derived β -keto amides and 1,3,5-triaryl-1,3,5-triazinanes (Table 3). To our delight, a variety of β -keto amides with different substituents were tolerated and gave the corresponding products with excellent enantioselectivities (Table 3, 93–98% ee; **5a–5f**). Then the scope of 1,3,5-triaryl-1,3,5-triazinanes was examined. The results are different from the results for the reactions of the β -keto esters, and both 2- and 4-substituted 1,3,5-triazinanes afforded the corresponding products in excellent yields and enantioselectivities (95–99% yields, 95–99% ee, **5g, 5i** and **5j**) except the 4-MeO substituted 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane, which gave the corresponding product in 84% ee. Besides this, five- and seven-membered

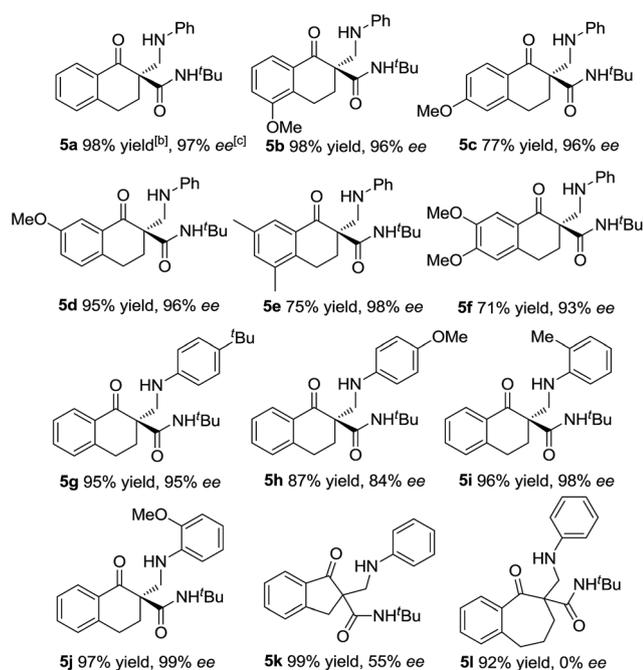
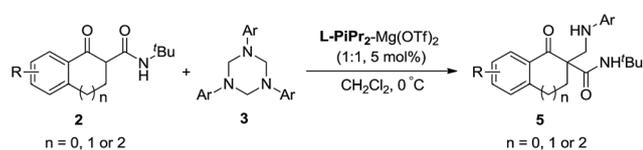
β -keto amide substrates were also examined. Unfortunately, the five-membered β -keto amide gave the corresponding product **5k** with only 55% ee, while the seven-membered β -keto amide gave a racemic product **5l** though the yields were excellent under the standard conditions. A cyclohexanone-derived β -keto amide was also tested under the standard reaction conditions, but the reaction didn't occur. Meanwhile, the absolute configuration of **5a** was determined to be *R* by X-ray crystallography analysis¹² and configurations of the others were also determined to be *R* by circular dichroism (for details see the ESI†).

To evaluate the synthetic value of this catalytic system, gram-scale reactions were performed (Scheme 2). In the presence of the **L-PiPr₂-Ni(ClO₄)₂·6H₂O** complex (5 mol%), the starting material **1a** (4.0 mmol) reacted with **3a** (1.3 mmol, 1.0 equivalent) smoothly, and the corresponding product **4a** was obtained in 92% yield with 99% ee (Scheme 2a). In the system of α -tetralone-derived β -keto amides and 1,3,5-triaryl-1,3,5-triazinanes, the reaction between 0.98 g **2a** and 0.42 g **3a** was performed under the optimized reaction conditions, affording 1.34 g (95% yield) of the corresponding product **5a** with 97% ee (Scheme 2b).

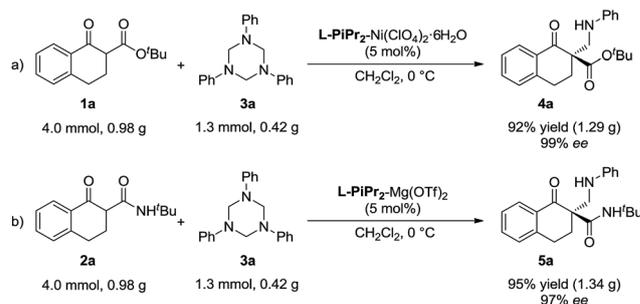
On the other hand, the product **4a** could be efficiently converted into useful β -hydroxyl ester **6** through reduction using NaBH₄ as a reducing agent (Scheme 3). The diastereomer of the product **6** was determined to be *trans*- using NOESY spectra (see the ESI† for details). The product **4h** could be converted into *N*-Boc- β -amino ester **7** by deprotection with cerium ammonium nitrate (CAN) followed by Boc protection of the amino group with Boc₂O (see the ESI† for details).

To gain insight into the mechanism, the relationship between the ee value of the ligand **L-PiPr₂** and that of **4a** was investigated under the optimal reaction conditions.¹³ A linear effect was observed (see the ESI† for details), which suggested that a monomeric catalyst may be the main catalytically active species in the reaction system. Based on the experiments and our previous work¹¹ as well as the absolute configuration of the products, a possible transition state model is proposed in Fig. 1 to elucidate the origin of the asymmetric induction. In the transition state, the oxygens of the *N,N'*-dioxides and the amide oxygens coordinate to Ni(II) in a tetradentate manner. The β -keto ester **1a** could be activated after coordinating to the nickel atom in a bidentate fashion. The *Si*-face of β -keto ester **1a** is effectively shielded by the amide moiety and the piperidine ring on the underside of the ligand **L-PiPr₂**. In contrast, the *Re*-face is

Table 3 Substrate scope for β -keto amides^a

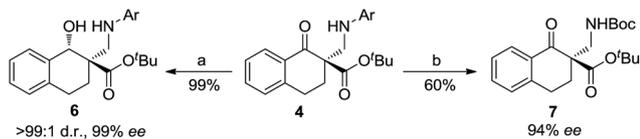


^a The reactions were performed with **2** (0.10 mmol), **3** (0.034 mmol), **L-PiPr₂** (0.005 mmol), and Mg(OTf)₂ (0.005 mmol) in 1.0 mL CH₂Cl₂ at 0 °C for 12 h. ^b Isolated yield of the product. ^c Determined by HPLC analysis on a chiral stationary phase.



Scheme 2 Gram-scale version of the reaction.





Scheme 3 Transformations of the product **4** into other derivatives; reaction conditions: (a) NaBH₄ and MeOH/CH₂Cl₂ (1 : 1), 0 °C (**4a**: Ar = Ph, 99% ee); (b) CAN, CH₃CN/H₂O; then Et₃N and Boc₂O (**4h**: Ar = 4-MeOC₆H₄, 94% ee). Boc = *tert*-butyloxycarbonyl.

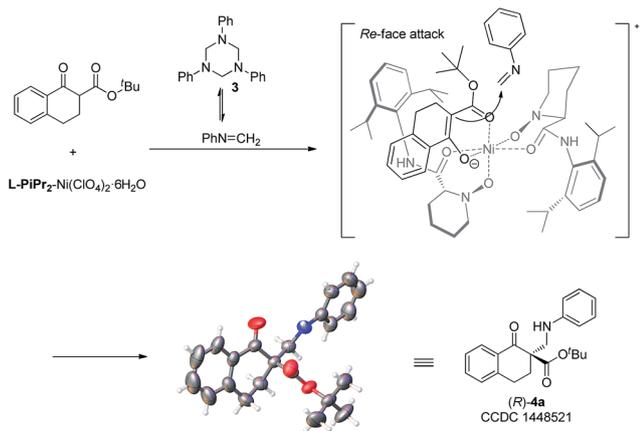


Fig. 1 Proposed transition state and the absolute configuration of **4a**.

located in a relatively open space. The highly selective approach of the *in situ* generated *N*-methylethaniline toward the *Re*-face of the bidentate-coordinated β -keto ester leads to the desired product with an *R* configuration, which is consistent with the observed absolute configuration of the product.

Conclusions

In summary, a highly enantioselective Mannich-type reaction between α -tetralone-derived β -keto esters/amides and 1,3,5-triaryl-1,3,5-triazinanes was realized. In the presence of chiral *N,N'*-dioxide-Ni(II) or *N,N'*-dioxide-Mg(II) complex, a variety of corresponding β -amino compounds each with an all-carbon quaternary stereocenter were obtained in good to excellent enantioselectivities (up to 99% ee) and good to excellent yields (up to 99%). In particular, this is the first time that 1,3,5-triaryl-1,3,5-triazinanes were used as electrophilic reagents in the catalytic asymmetric Mannich reaction. Further studies focused on the reactions of 1,3,5-triaryl-1,3,5-triazinanes are under way.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 21372162, 21432006 and 21321061) for financial support.

Notes and references

1 M. Arend, B. Westermann and N. Rish, *Angew. Chem., Int. Ed.*, 1998, **37**, 1044.

- 2 C. Mannich and W. Krosche, *Arch. Pharm.*, 1912, **250**, 647.
- 3 M. Tramontini and L. Angiolini, *Tetrahedron*, 1990, **46**, 1791.
- 4 For reviews, see: (a) M. Tramontini and L. Angiolini, *Mannich-Bases, Chemistry and Uses*, CRC, F. L. Boca Raton, 1994; (b) M. Tramontini, L. Angiolini and N. Ghedeni, *Polymer*, 1988, **29**, 771; (c) M. Tramontini, *Synthesis*, 1973, 703; (d) H. Hellmann and G. Opitz, *α -Aminoalkylierung*, Verlag Chemie, Weinheim, 1960; (e) B. Reichert, *Die Mannich reaktion*, Springer, Berlin, 1959; (f) F. F. Blicke, *Org. React.*, 1942, **1**, 303.
- 5 (a) H. Ishitani, M. Ueno and S. Kobayashi, *J. Am. Chem. Soc.*, 1997, **119**, 7153; (b) For an early review, see: S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069.
- 6 For examples, see: (a) H. J. Ha and Y. G. Ahn, *Synth. Commun.*, 1995, **25**, 969; (b) A. R. Katritzky, S. Rachwal and G. J. Hitchings, *Tetrahedron*, 1991, **47**, 2683; (c) S. Kobayashi, H. Ishitani, S. Komiyama, D. C. Oniciu and A. R. Katritzky, *Tetrahedron Lett.*, 1996, **37**, 3731; (d) P. C. B. Page, S. M. Allin, E. W. Collington and R. A. E. Carr, *J. Org. Chem.*, 1993, **58**, 6902; (e) A. R. Katritzky, N. Shobana and P. A. Harris, *Tetrahedron Lett.*, 1990, **31**, 3999; (f) A. R. Katritzky and P. A. Harris, *Tetrahedron*, 1990, **46**, 987; (g) D. Enders, D. Ward, J. Adam and G. Raabe, *Angew. Chem., Int. Ed.*, 1996, **35**, 981; (h) U. Jahn and W. Schroth, *Tetrahedron Lett.*, 1993, **34**, 5863.
- 7 For reviews of asymmetric Mannich reactions, see: (a) A. Cordova, *Acc. Chem. Res.*, 2004, **37**, 102; (b) A. G. Wenzel and E. N. Jacobsen, *Enantioselective Synthesis of β -Amino Acids*, ed. E. Juaristi and V. Soloshonok, Wiley-VCH, New York, 2005, ch. 4; (c) A. Ting and S. E. Schaus, *Eur. J. Org. Chem.*, 2007, **2007**, 5797; (d) J. M. M. Verkade, L. J. C. von Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29; (e) B. Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656; (f) B. Karimi, D. Enders and E. Jafari, *Synthesis*, 2013, **45**, 2769.
- 8 (a) C. A. Bischoff and F. Reinfeld, *Chem. Ber.*, 1903, **36**, 41; (b) A. G. Giumanini, G. Verardo, E. Zangrando and L. Lassiani, *J. Prakt. Chem.*, 1987, **329**, 1087; (c) A. G. Giumanini, N. Toniutti, G. Verardo and M. Merli, *Eur. J. Org. Chem.*, 1999, 141; (d) H. J. Ha, C. J. Choi and W. K. Lee, *Synth. Commun.*, 2002, **32**, 1495; (e) M. I. P. Reis, G. A. Romeiro, R. Damasceno, F. de C. da Silva and V. F. Ferreira, *Rev. Virtual Quim.*, 2013, **5**, 283; (f) G. O. Jones, J. M. García, H. W. Horn and J. L. Hedrick, *Org. Lett.*, 2014, **16**, 5502.
- 9 (a) S. Oda, B. Sam and M. J. Krische, *Angew. Chem., Int. Ed.*, 2015, **54**, 8525; (b) S. Oda, J. Franke and M. J. Krische, *Chem. Sci.*, 2016, **7**, 136.
- 10 (a) K. Fuji, *Chem. Rev.*, 1993, **93**, 2037; (b) E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388; (c) J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591; (d) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363; (e) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (f) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369; (g) M. Bella and T. Gasperi, *Synthesis*, 2009, 1583; (h) C. Hawner and



- A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295; (i) J. P. Das and I. Marek, *Chem. Commun.*, 2011, **47**, 4593.
- 11 For reviews of *N,N'*-dioxide–metal complexes in asymmetric reactions, see: (a) X. H. Liu, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2011, **44**, 574; (b) K. Zheng, L. L. Lin and X. M. Feng, *Acta Chim. Sin.*, 2012, **70**, 1785; (c) “Chiral Scandium Complexes in Catalytic Asymmetric Reactions”: X. M. Feng and X. H. Liu, *Scandium: Compounds, Productions and Applications*, ed. V. A. Greene, Nova Science, New York, 2011, p. 1; (d) X. H. Liu, L. L. Lin and X. M. Feng, *Org. Chem. Front.*, 2014, **1**, 298. For recent examples, see: ; (e) W. Li, F. Tan, X. Y. Hao, G. Wang, Y. Tang, X. H. Liu, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2015, **54**, 1608; (f) J. L. Zhang, Y. L. Zhang, L. L. Lin, Q. Yao, X. H. Liu and X. M. Feng, *Chem. Commun.*, 2015, **51**, 10554.
- 12 CCDC 1448521 (**4a**) and CCDC 1480808 (**5a**) contain the supplementary crystallographic data for this paper.
- 13 (a) T. Satyanarayana, S. Abraham and H. B. Kagan, *Angew. Chem., Int. Ed.*, 2009, **48**, 456; (b) D. Guillaneux, S. H. Zhao, O. Samuel, D. Rainford and H. B. Kagan, *J. Am. Chem. Soc.*, 1994, **116**, 9430; (c) C. Girard and H. B. Kagan, *Angew. Chem., Int. Ed.*, 1998, **37**, 2922.

