Organic LETTERS

Letter

pubs.acs.org/OrgLett

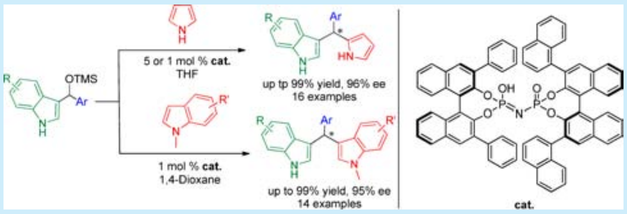
Enantioselective Synthesis of Triarylmethanes by Chiral Imidodiphosphoric Acids Catalyzed Friedel–Crafts Reactions

Ming-Hua Zhuo, Yi-Jun Jiang,* Yan-Sen Fan, Yang Gao, Song Liu, and Suoqin Zhang*

College of Chemistry, Jilin University, 2699 Qianjin Street, Changchun 130012, China

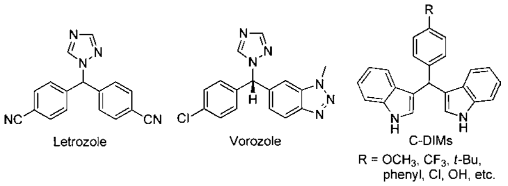
S *Supporting Information*

ABSTRACT: The first enantioselective synthesis of pyrrolyl-substituted triarylmethanes has been accomplished using a novel imidodiphosphoric acid catalyst, which is derived from two (*R*)-BINOL frameworks with different 3,3′-substituents. This strategy was also expanded to the synthesis of bis(indolyl)-substituted triarylmethanes with high enantioselectivities, which could only be obtained with moderate ee values in previous reports. These two efficient Friedel–Crafts alkylation processes feature low catalyst loading, broad functional group compatibilities, and the potential to provide practical pathways for the synthesis of enantioenriched bioactive triarylmethanes.

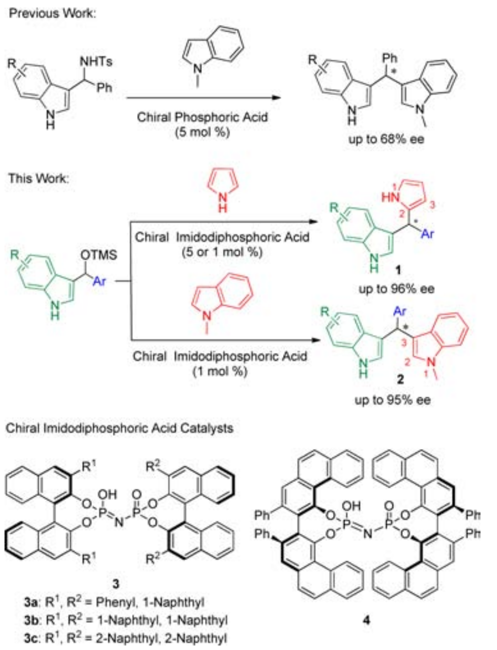


Triarylmethanes are attractive molecules which have been widely used in medicinal and material sciences.[1] Heteroaryl-substituted triarylmethanes present privileged architectural units frequently found in pharmaceuticals and bioactive molecules.[2−4] For example, Letrozole, Vorozole, and *para*-phenyl-substituted diindolylmethanes (C-DIMs) have proven to be very effective drugs in the treatment of cancer (Scheme 1). The absolute configurations of these molecules or their derivatives are shown to further modulate the biological activities.[2a,c,e] It is therefore of high importance to introduce asymmetry at the methanetriyl group in the heteroaryl-substituted triarylmethane molecules with high enantiocontrol. However, the enantioselective synthesis of triarylmethanes has until recently remained a challenge and only a few examples have been reported.[5] In addition, the enantioselective synthesis of pyrrolyl-substituted triarylmethanes has not been developed.

Scheme 1. Pharmaceutically Relevant Triarylmethanes



Scheme 2. Chiral Imidodiphosphoric Acids Catalyzed Highly Enantioselective Syntheses of Two Different Types of Triarylmethanes 1 and 2



Friedel–Crafts-type arylations of diarylmethanols or diarylmethylamines have been the most common method for the synthesis of unsymmetric triarylmethanes.[4,5b,6] However, only one enantioselective protocol toward the synthesis of bis(indolyl)methanes has been reported by You and co-workers with only moderate enantioselectivities (Scheme 2).[5b] Compared with You's work, the synthesis of enantioenriched pyrrolyl-substituted triarylmethanes **1** is more challenging since pyrroles always give lower enantioselectivities than indoles in enantioselective Friedel–Crafts alkylations.[7] It is probably because of the higher reactivity of pyrroles and the difficulty in enantiofacial differentiation caused by the smaller size of the pyrroles.

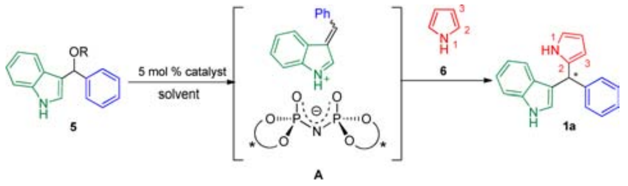
Recently, imidodiphosphoric acids have been first reported by List and co-workers as new efficient chiral Brønsted acids in catalytic enantioselective reactions.[8] We have also reported

Received: December 19, 2013
Published: February 3, 2014

their syntheses and applications, independently (Scheme 2).[9] In view of the efficiency of imidodiphosphoric acids in enantioselective transformations of small substrates,[8a,b] we expected that this new type of chiral Brønsted acids could also promote the Friedel−Crafts reactions of pyrrole with high enantioselectivities. Herein, we will first report the enantioselective synthesis of pyrrolyl-substituted triarylmethanes **1** through chiral imidodiphosphoric acids catalyzed Friedel−Crafts reactions of pyrrole with trimethylsilyl protected 3-arylindolylmethanols with high enantioselectivities and a low catalyst loading (Scheme 2). Moreover, this strategy was also expanded to the synthesis of bis(indolyl)triarylmethanes **2** successfully with high enantioselectivities.

We initially investigated our triarylmethane synthesis strategy by using 3-indolylphenylmethanol **5** and pyrrole **6** in the presence of 5 mol % of catalyst **3** or **4** in toluene (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



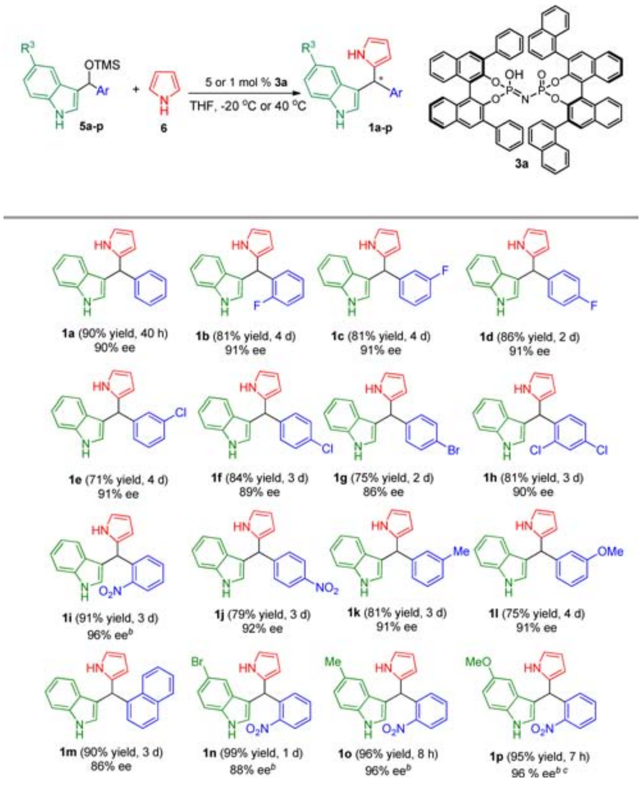
entry	R	cat.	solvent	temp, *t*	yield (%)[b]	ee (%)[c]
1	H	**3a**	toluene	rt, 0.5 h	60	65
2	H	**3b**	toluene	rt, 0.5 h	55	43
3	H	**3c**	toluene	rt, 6 h	42	11
4	H	**4**	toluene	rt, 0.5 h	56	33
5	TMS	**3a**	toluene	rt, 0.5 h	74	80
6	TMS	**3a**	CH_2Cl_2	rt, 2 h	73	77
7	TMS	**3a**	1,4-dioxane	rt, 35 h	73	83
8	TMS	**3a**	THF	rt, 18 h	80	88
9	TMS	**3a**	THF	0 °C, 33 h	86	88
10	TMS	**3a**	THF	−20 °C, 40 h	90	90
11	TMS	**3a**	THF	−30 °C, >72 h	63	90

[a] Reactions were performed with 0.1 mmol of **5**, 0.1 mmol of **6**, and 5 mol % of the catalyst in 1 mL of solvent. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a Chiralcel AD-H column.

Imidodiphosphoric acid catalyst **3** or **4** could promote the dehydration of substrate **5** and generate an alkylideneindolenine intermediate[10] which could form a stable chiral ion pair **A** with the chiral imidodiphosphoric acid.[8a,11,12] This chiral ion pair may add the nucleophilic reagent pyrrole in a regio- and stereoselective fashion. Since the C-2 position of pyrrole **6** was more nucleophilic,[13] it attacked substrate **5** at the C-2 position and produced triarylmethane **1a** as the main product. Interestingly, catalyst **3a** derived from two (*R*)-BINOL frameworks with different 3,3′-substituents gave a higher yield and enantioselectivity (60% yield, 65% ee, Table 1, entry 1) than other symmetric imidodiphosphoric acid catalysts (Table 1, entries 2−4). Our first notable improvement was the use of a trimethylsilyl protection group on 3-arylindolylmethanols. This change resulted in a dramatic increase in the chemo- and enantioselectivity of the reaction (74% yield, 80% ee, Table 1, entry 5). Besides, the trimethylsilyl protected 3-arylindolylmethanol substrates are easy to store since they are less sensitive to air and light compared with the unprotected 3-arylindolylmethanols. It might be because the weak acidity of the H atom on the hydroxyl group in unprotected substrate **5** could also promote the dehydration of other molecules of **5** and the subsequent addition of pyrrole **6**. This possible problem could not only consume unprotected substrate **5** and lead to a lower yield but also result in a decrease of the ee value of product **1a**. Thus, protecting the hydroxyl group with the trimethylsilyl group might largely prevent these disadvantages from happening. An improvement to 88% ee was observed when the solvent was changed from toluene to tetrahydrofuran (THF) (Table 1, entry 8). Lowering of the reaction temperature further improved the chemo- and enantioselectivity (Table 1, entries 9 and 10) until the reaction was below −20 °C (Table 1, entry 11). Thus, the best result was observed when the reaction was run at −20 °C in THF by using 5 mol % of catalyst **3a** (Table 1, entry 10).

Under our optimized conditions (Table 1, entry 10), we observed a broad scope with respect to the trimethylsilyl protected 3-arylindolylmethanols **5** (Scheme 3). Substrates bearing either electron-withdrawing (**5b**−**j**) or electron-donating groups (**5k** and **5l**) on the phenyl moiety reacted to form the corresponding triarylmethanes **1b**−**l** in high yields with excellent enantioselectivities (71−91% yield, 86−96% ee). The substrate **5m**, containing the naphthyl substituent, also reacted smoothly and afforded the triarylmethanes **1m** in high yield with good enantioselectivity (90% yield, 86% ee). Besides, we were pleased to find that the reaction of substrate **5i** could proceed with 1 mol % of catalyst **3a** under an increased reaction

Scheme 3. Scope of Synthesis of 1-(Aryl)-1-(indolyl)-1-(pyrrolyl)methanes 1[a]

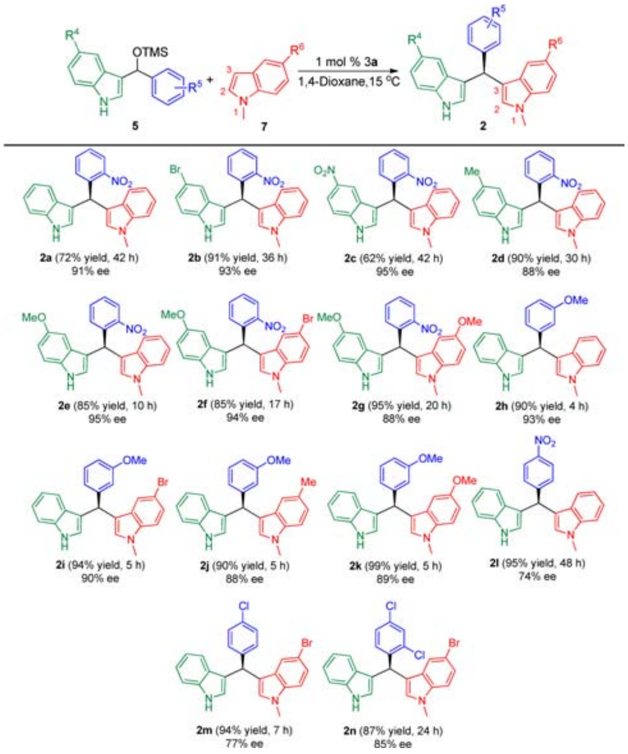


[a] Reactions were performed with 0.1 mmol of **5**, 0.1 mmol of **6**, and 5 mol % of catalyst **3a** in 1 mL of THF at −20 °C. Yield of the isolated product. Ee value was determined by HPLC analysis on Chiralcel AD-H or OD-H column. [b] Reactions were run at 40 °C with 1 mol % of catalyst **3a**. [c] The reaction was carried out on a 1 g (2.7 mmol) scale of **5p**.

temperature (40 °C) and generated triarylmethane **1i** in high yield with excellent ee (91% yield, 96% ee). Further, variation of the indole substituents was also tested (Scheme 3, **5n**−**p**) with 1 mol % of catalyst **3a** at 40 °C. An electron-withdrawing group on the 5-position of indole slightly decreased the enantioselectivity (Scheme 3, **1n**). Electron-donating substituents on the 5-position of the indole rings were more favorable, and triarylmethanes **1o** and **1p** were synthesized in high yields (96% and 95%) with excellent enantioselectivities (96% ee). As illustrated in the synthesis of enantioenriched triarylmethane **1p**, the method is also amenable to gram scale.

Our next challenge was to apply this method to synthesize enantioenriched triarylmethanes **2**. Although similar work has been reported by You and co-workers by using chiral phosphoric acid catalysts and different substrates (3-indolyl)-methanamines, only moderate ee values (45 to 68% ee) were obtained.[5b] Gratifyingly, imidodiphosphoric acid catalyst **3a** was found to be more effective and triarylmethanes **2** have been synthesized with high enantioselectivities. When a range of substituted 1-methyl-indoles **7** were selected as the nucleophilic reagents, their more nucleophilic C-3 positions[13] attacked substrates **5** and produced triarylmethanes **2** as the main products. The reaction conditions were optimized, and the best result was obtained in a 1,4-dioxane at 15 °C with 1 mol % of catalyst **3a**. The scope of the substrates was explored under the optimized reaction conditions. Substrates with electron-withdrawing or -donating groups at the *ortho* or *meta* position of the phenyl rings gave rise to the triarylmethane products in good yields with high levels of enantioselectivities (Scheme 4, **2a**−**k**, 62−99% yield, 88−95% ee), including the highly symmetric triarylmethanes **2a**, **2g**, and **2h**. Substrates with substituents on the *para* position of the phenyl rings and other substitution patterns also underwent Friedel−Crafts reactions to yield triarylmethanes **2l**−**n** in high yields with good enantioselectivities (87−95% yield, 74−85% ee). Besides, in these processes, our catalyst loading (1 mol %) was much lower than that reported by You et al. (5 mol %). Combined with the high enantioselectivities, our reaction was more efficient and the imidodiphosphoric acid catalyst showed more extraordinary chiral-control ability compared with the phosphoric acid catalyst.[5b]

Scheme 4. Scope of Synthesis of 1-(Aryl)-1,1′-bis(indolyl)methanes 2[a]



[a]Reactions were performed with 0.1 mmol of **5**, 0.1 mmol of **7**, and 1 mol % of catalyst **3a** in 2 mL of 1,4-dioxane at 15 °C. Yield of the isolated product. Ee value was determined by HPLC analysis on Chiralcel AD-H or OD-H column.

The absolute configuration of the optically active **2b** was established to be *R* by X-ray crystallographic analysis (Figure 1).[14] It is noteworthy that the highly enantioselective synthesis of triarylmethanes **2** would provide more opportunities for further biological activity studies of the analogs of cancer treating drug C-DIMs (Scheme 1).[3]

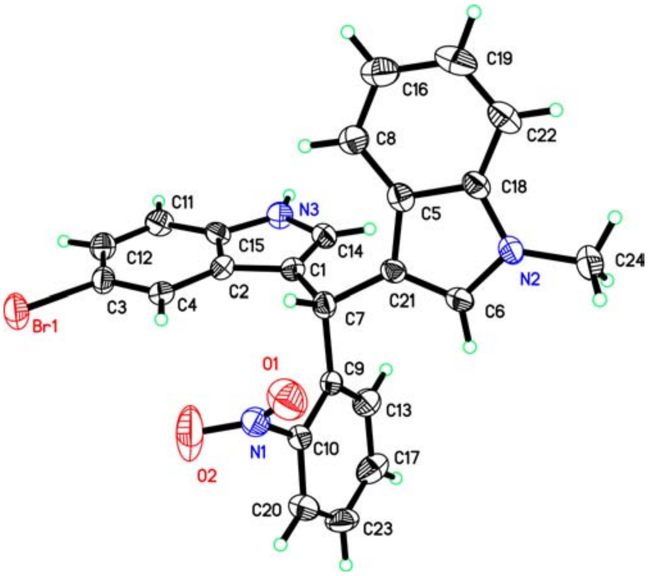


Figure 1. X-ray crystallographic structure of enantiopure triarylmethane **2b**.

In summary, we have disclosed the chiral imidodiphosphoric acids catalyzed highly efficient and enantioselective Friedel−Crafts-type alkylations for the construction of two different types of chiral triarylmethanes **1** and **2**. The novel imidodiphosphoric acid catalyst **3a** derived from two (*R*)-BINOL frameworks with different 3,3′-substituents developed in our previous work showed excellent catalytic activity and stereocontrolled ability in both of these two catalyses. A range of highly enantioenriched and versatile triarylmethanes **1** and **2** were synthesized in high yields (up to 99%) with excellent enantioselectivities (up to 96% and 95% ee, respectively) with a low catalyst loading (as low as 1 mol %) unprecedentedly. Remarkably, enantioenriched triarylmethanes **1** have been synthesized for the first time. We believe that the protocol presented in this work will be appealing to practitioners of medicinal chemistry. Studies aimed at further exploration of the synthetic potential of this approach are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Single crystal X-ray crystallography data for triarylmethane **2b**, experimental procedures, and complete characterizations (NMR spectra, HPLC traces of both racemic and enantioenriched triarylmethanes products, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jiangyijun@jlu.edu.cn.
*E-mail: suoqin@jlu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21202059), the China Postdoctoral Science Foundation (2013M541287), and the Jilin Province Science & Technology Development Program (20100538, 20110436, 201215033) for financial support.

■ REFERENCES

(1) (a) Duxbury, D. F. *Chem. Rev.* **1993**, *93*, 381. (b) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003**, *32*, 170. (c) Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731. (d) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250.

(2) For selected examples of Letrozole and Vorozole type triarylmethanes, see: (a) Bossche, H. V.; Willemsens, G.; Roels, I.; Bellens, D.; Moereels, H.; Coene, M.-C.; Jeune, L. L.; Lauwers, W.; Janssen, P. A. *Biochem. Pharmacol.* **1990**, *40*, 1707. (b) Recanatini, M.; Cavalli, A.; Valenti, P. *Med. Res. Rev.* **2002**, *22*, 282. (c) Wood, P. M.; Woo, L. L.; Labrosse, J.-R.; Trusselle, M. N.; Abbate, S.; Longhi, G.; Castiglioni, E.; Lebon, F.; Purohit, A.; Reed, M. J. *J. Med. Chem.* **2008**, *51*, 4226. (d) Takahashi, K.; Yamagishi, G.; Hiramatsu, T.; Hosoya, A.; Onoe, K.; Doi, H.; Nagata, H.; Wada, Y.; Onoe, H.; Watanabe, Y.; Hosoya, T. *Bioorg. Med. Chem.* **2011**, *19*, 1464. (e) Wood, P. M.; Woo, L. W.; Thomas, M. P.; Mahon, M. F.; Purohit, A.; Potter, B. V. *ChemMedChem* **2011**, *6*, 1423.

(3) For selected examples of *para*-phenyl-substituted diindolylmethane type triarylmethanes, see: (a) Cho, S. D.; Yoon, K.; Chintharlapalli, S.; Abdelrahim, M.; Lei, P.; Hamilton, S.; Khan, S.; Ramaiah, S. K.; Safe, S. *Cancer Res.* **2007**, *67*, 674. (b) Inamoto, T.; Papineni, S.; Chintharlapalli, S.; Cho, S. D.; Safe, S.; Kamat, A. M. *Mol. Cancer Ther.* **2008**, *7*, 3825. (c) Cho, S. D.; Lee, S. O.; Chintharlapalli, S.; Abdelrahim, M.; Khan, S.; Yoon, K.; Kamat, A. M.; Safe, S. *Mol. Pharmacol.* **2010**, *77*, 396. (d) Yoon, K.; Lee, S. O.; Cho, S. D.; Kim, K.; Khan, S.; Safe, S. *Carcinogenesis* **2011**, *32*, 836.

(4) For thiophene containing triarylmethanes, see: Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289.

(5) (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) Sun, F.-L.; Zheng, X.-J.; Gu, Q.; He, Q.-L.; You, S.-L. *Eur. J. Org. Chem.* **2010**, 47. (c) Taylor, B. L.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790. (d) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303.

(6) (a) Katritzky, A. R.; Toader, D. *J. Org. Chem.* **1997**, *62*, 4137. (b) Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem.* **2006**, *118*, 645. (c) He, Q.-L.; Sun, F.-L.; Zheng, X.-J.; You, S.-L. *Synlett* **2009**, 1111. (d) Thirupathi, P.; Kim, S. S. *Tetrahedron* **2010**, *66*, 2995. (e) Thirupathi, P.; Kim, S. S. *J. Org. Chem.* **2010**, *75*, 5240.

(7) For reviews: (a) Wang, Y.; Ding, K.-L. *Chin. J. Org. Chem.* **2001**, *21*, 763. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (d) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (e) Sheng, Y.-F.; Zhang, A. J.; Zheng, X.-J.; You, S.-L. *Chin. J. Org. Chem.* **2008**, *28*, 605. (f) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (g) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (h) You, S.-L.; Zeng, M. *Synlett* **2010**, 1289.

(8) (a) Čorić, I.; List, B. *Nature* **2012**, *483*, 315. (b) Liao, S.; Čorić, I.; Wang, Q.; List, B. *J. Am. Chem. Soc.* **2012**, *134*, 10765. (c) Kim, J. H.; Čorić, I.; Vellalath, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 4474.

(9) (a) Chen, Y.-Y.; Jiang, Y.-J.; Fan, Y.-S.; Sha, D.; Wang, Q.; Zhang, G.; Zheng, L.; Zhang, S. *Tetrahedron: Asymmetry* **2012**, *23*, 904. (b) Wu, K.; Jiang, Y. J.; Fan, Y. S.; Sha, D.; Zhang, S. *Chem.—Eur. J.* **2013**, *19*, 474. (c) An, D.; Fan, Y.-S.; Gao, Y.; Zhu, Z.-Q.; Zheng, L.-Y.; Zhang, S. *Eur. J. Org. Chem.* **2014**, 301.

(10) Palmieri, A.; Petrini, M.; Shaikh, R. R. *Org. Biomol. Chem.* **2010**, *8*, 1259.

(11) (a) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593. (b) Guo, Q.-X.; Peng, Y.-G.; Zhang, J.-W.; Song, L.; Feng, Z.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4620. (c) Sun, F.-L.; Zeng, M.; Gu, Q.; You, S.-L. *Chem.—Eur. J.* **2009**, *15*, 8709. (d) Liang, T.; Zhang, Z.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 9734. (e) Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732. (f) Wang, S.-G.; Han, L.; Zeng, M.; Sun, F.-L.; Zhang, W.; You, S.-L. *Org. Biomol. Chem.* **2012**, *10*, 3202. (g) Song, L.; Guo, Q.-X.; Li, X.-C.; Tian, J.; Peng, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 1899. (h) Čorić, I.; Kim, J. H.; Vlaar, T.; Patil, M.; Thiel, W.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 3490.

(12) (a) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (b) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518.

(13) Pratihar, S.; Roy, S. *J. Org. Chem.* **2010**, *75*, 4957.

(14) CCDC 948305 (2b) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambrige Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.