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Chiral Brønsted Acid Catalyzed Enantioselective Phosphonylation of Allylamine via Oxidative Dehydrogenation Coupling

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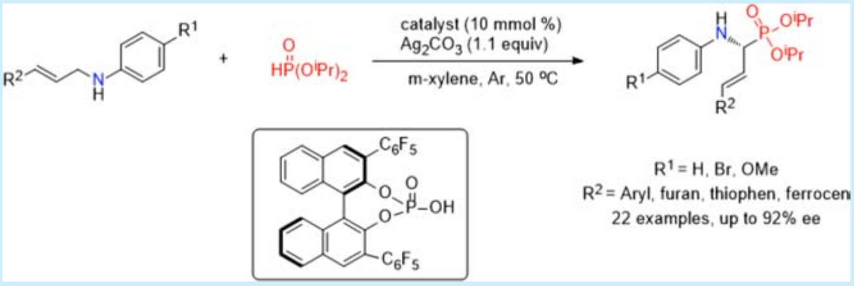
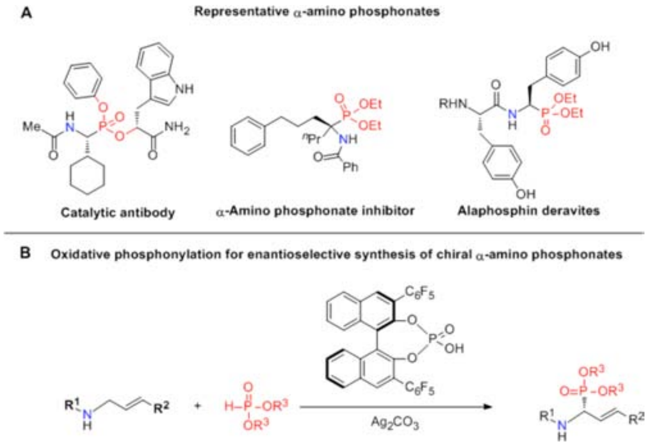
Ⓢ *Supporting Information*



ABSTRACT: A new strategy for the synthesis of chiral α-amino phosphonates by enantioselective C−H phosphonylation of allylamine with phosphite in the presence of a chiral Brønsted acid catalyst has been developed. This protocol successfully integrates direct C−H oxidation with asymmetric phosphonylation and exhibits high enantioselectivity.

Chiral α-amino phosphonates have attracted considerable attention in modern pharmaceutical chemistry due to their intriguing biological activities such as anti-HIV (human immunodeficiency virus)[1] and antibacterial activities[2] as well as protease[3] and phosphatase inhibitory properties[4] (Scheme 1A). Because biological activity depends on their absolute configuration at the α-carbon atom, the development of an efficient way for the preparation of optically pure α-amino phosphonates is highly desired. The most straightforward strategy for the enantioselective synthesis of chiral α-amino phosphonates is the asymmetric addition of phosphites to imines (aza-Pudovik reaction).[5−7] Another widely used approach is the asymmetric Kabachnik−Fields reaction.[8] For example, the List group developed a direct catalytic asymmetric Kabachnik−Fields reaction to furnish β-branched α-amino phosphonates using chiral phosphoric acid as catalyst.[8b] More recently, the Feng group also reported a selective approach for the preparation of α-amino phosphonates using a chiral scandium-*N*,*N*′-dioxide complex.[8c] To date, the development of an alternative protocol, which enables efficient synthesis of chiral α-amino phosphonates, remains requisite. Over the past few decades, Li's cross-dehydrogenative coupling (CDC) reactions provided a highly efficient and versatile protocol for the construction of C−C and C−heteroatom bonds via reactive imine intermediates generated from C−H oxidations,[9] which has also been proven to be an economical alternative route for the synthesis of α-amino phosphonates.[10] In the past several years, inspired by the first asymmetric CDC reaction of Cu(I)-catalyzed alkynylation of *N*-phenyltetrahydroisoquinoline,[11] asymmetric CDC reactions involving in different chiral control strategies have been disclosed and made significant progress.[12] These processes fulfill the ideals of efficiency as well as green chemistry, and they represent cutting-edge synthetic technology in modern organic chemistry. Herein, we report a general chiral phosphoric acid catalyzed enantioselective synthesis of unsaturated α-amino phosphonates via aerobic sp^3 C−H oxidations. This protocol starts from readily availble allylamine, uses a simple catalytic system, and provides access to a series of

Scheme 1. New Strategy for the Synthesis of Chiral α-Amino Phosphonate



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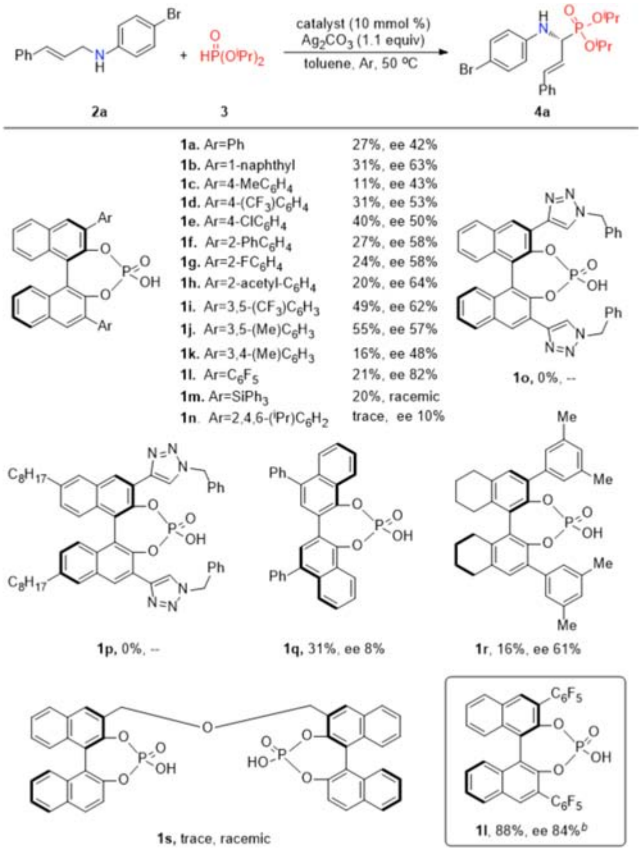
chiral allylic α-amino phosphonates which are difficult to obtain from known process (Scheme 1B).

Initially, we studied the oxidative phosphonylation reaction of diisopropyl phosphite (2.0 equiv) with 4-bromo-*N*-cinnamylaniline (**2a**) in the presense of Ag_2CO_3 (1.1 equiv) and the chiral phosphoric acid **1a** (10 mmol %) in toluene at 50 °C under an Ar atmosphere. Fortunately, target product **4a** was obtained in 27% yield with 42% ee after 72 h (Scheme 2).

Scheme 2. Screening of Catalysts for Enantioselective Phosphonylation of Allylamine[a]

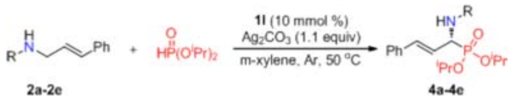


[a]All reactions were carried out in the presence of 0.1 mmol of **2a** and 0.2 mmol of **3** in 2.0 mL of toluene under an Ar atmosphere for 72 h unless otherwise specified. Yield of isolated product. The ee was determined by HPLC analysis using chiral columns. [b]Reaction was carried out in the presence of 0.1 mmol of **2a** and 0.1 mmol of **3** in 1.5 mL of *m*-xylene under an Ar atmosphere for 168 h.

Encouraged by this result, a series of substituted chiral phosphoric acids (**1b**−**1s**) were synthesized to catalyze the reaction. When using **1b** instead of **1a**, the reaction proceeded smoothly and achieved better enantioselectivity (63% ee). It was demonstrated that the substituents on the skeleton were vital to improve enantioselectivity. Next, we examined various aryl substituents at the 3,3′-positions of the chiral phosphoric acids (**1c**−**1e**). When the substituents 4-MeC_6H_4, $4\text{-CF}_3C_6H_4$, and 4-ClC_6H_4 were at the 3,3′-positions of the chiral phosphoric acid, ee values were only slightly increased and electron-withdrawing $4\text{-CF}_3C_6H_4$ and 4-ClC_6H_4 were superior to electron-donating 4-MeC_6H_4 to obtain higher yields and enantioselectivities. Subsequently when the substituents were changed to 2-PhC_6H_4, 2-FC_6H_4, and 2-acetyl-C_6H_4 (**1f**−**1h**), the results remained unsatisfying. Next, multisubstituted aryls such as $3,5\text{-CF}_3C_6H_3$, $3,5\text{-MeC}_6H_3$, and $3,4\text{-MeC}_6H_3$ (**1i**−**1k**) were also examined, and the best result was obtained in 49% yield with 62% ee. Further screening revealed that the pentafluorobenzene substituted chiral phosphoric acid (**1l**) improved the ee value to 82%, although the yield was unsatisfying. Whereas, using a larger substituent such as triphenylsilyl- (**1m**) and 2,4,6-triisopropylbenzene (**1n**), we respectively obtained a racemic product and lower enantioselectivity. Other complicated chiral phosphoric acids screening has still not afforded good results (**1o**−**1s**). Based on foregoing results, it was proven that electron-withdrawing substituents were superior to electron-donating substituents and small steric hindrance groups were superior to large steric hindrance groups to obtain higher enantioselectivity. Finally, we selected **1l** as the catalyst for further screening, including various solvents, concentrations, and reaction times. To our delight, by using **1l** (10 mmol %) as catalyst and Ag_2CO_3 (1.1 equiv) as oxidant in 1.5 mL of *m*-xylene for 0.1 mmol of **2a** with 0.1 mmol of diisopropyl phosphite at 50 °C under an argon atmosphere for 168 h (see Supporting Information for more details), the desired product of **4a** was obtained in 88% yield with 84% ee.

With the optimized conditions in hand, we explored the scope of the reaction. We first screened the influence of the *N*-substituent on the allylamine (Table 1). Results showed that the presence of *p*-methoxy decreased the enantioselectivity (Table 1, entry 2). Moreover, when using Ts (*p*-Toluenesulfonate) and CBZ (Carbobenzoxy) as the *N*-protecting group, the corresponding product was not obtained (Table 1, entries 4−5). These results demonstrated that the electrical of *N*-substituent on the allylamine was vital for reaction activity and high enantioselectivity.

Table 1. Effect of *N*-Substituent[a]



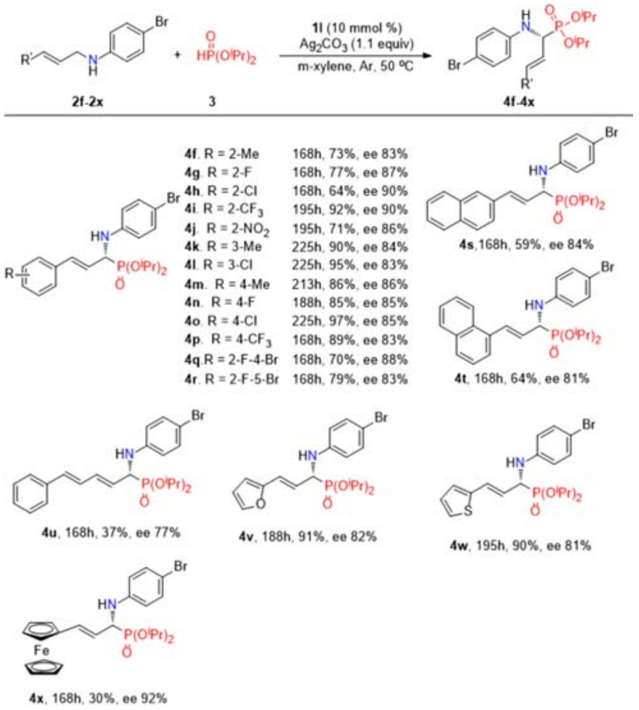
entry	R	product	reaction time (h)	yield (%)	ee (%)
1	4-BrC_6H_4	**4a**	168	88	84
2	4-OMeC_6H_4	**4b**	92	75	64
3	C_6H_5	**4c**	120	85	71
4	Ts	**4d**	120	N.R.	−
5	CBZ	**4e**	120	N.R.	−

[a]All reactions were carried out in the presence of 0.1 mmol of allylamine and 0.1 mmol of diisopropyl phosphite in 1.5 mL of solvent under an Ar atmosphere unless otherwise specified. Yield of isolated product. The ee was determined by HPLC analysis using chiral columns. N.R. = No Reaction.

A broad range of aromatic as well as heteroaromatic allylamines are suitable substrates for the asymmetric reaction. High enantioselectivities and yields were obtained (Scheme 3).

We first explored the scope in terms of aromaticity. Electron-withdrawing or -donating groups as well as halogen substituents were well tolerated (**4f**−**4p**), especially when allylamine with a 2-trifluoromethylbenezne substituent was used, we obtained the desired product in 92% yield with 90% ee (**4i**). The reaction with a multisubstituted aromatic also afforded higher enantioselectivities (**4q**−**4r**). When using a naphthalene substituent instead of a benzene substituent, the products could be isolated in moderate yields and high enantioselectivities (**4s**−**4t**). However, when the long chain substituent was tested, the desired product was obtained in a lower yield and

Scheme 3. Scope of Allylamine[a]

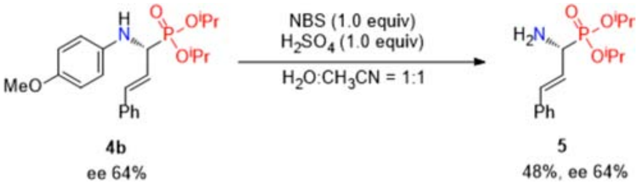


[a] All reactions were carried out in the presence of 0.1 mmol of **2f**−**2x** and 0.1 mmol of **3** in 1.5 mL of solvent under an Ar atmosphere. Yield of isolated product. The ee was determined by HPLC analysis using chiral columns.

enantioselectivity (**4u**). To our delight, heteroaromatic substituents were suitable substrates for our enantioselective phosphonylation reaction. The corresponding heteroaromatic phosphonates **4v** and **4w** could be isolated in good yields and high enantioselectivities. The allylamine with a ferrocene substituent could be used as a substrate in the reaction to obtain **4x** in 92% ee although the yield was unsatisfying.

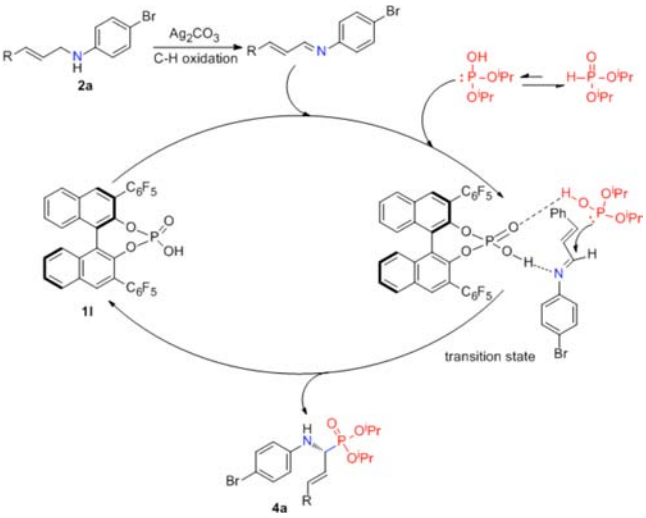
The optical phosphonylation data and HPLC analysis data of phosphonate **4b** were found to be in good agreement with those reported in the literature; thus, the absolute configuration could be determined by comparison.[7b] The product **4b** also can be converted to the corresponding α-amino phosphonate without loss of enantioselectivity (Scheme 4).

Scheme 4. Deprotection of *N*-substituent



A proposed mechanism for the chiral Brønsted acid catalyzed enantioselective phosphonylation of allylamine is presented in Scheme 5. Initially, allylimine could be generated in situ from allylamine via C−H oxidation. Next, a chiral Brønsted acid actives the phosphite and the allylimine to form a nine-membered transition state,[7b] wherein the chiral phosphoric acid works as a bifunctional catalyst.[13] It promotes the phosphite to attack the allylimine from the *re* face and increases the enantioselectivity by proximity effect. Finally, protonation gives rise to the desired product and the catalytic cycle completes.

Scheme 5. Plausible Reaction Mechanism



In summary, we have reported the first general chiral Brønsted acid catalyzed oxidative phosphonylation of an sp^3 C−H bond. This protocol benefits from easily accessible starting material and a simple catalytic system and offers easy and high efficient access to synthesize bioactive chiral α-amino phosphonates with high enantioselectivities. Further studies related to C−H bond oxidative functionalization are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01514.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Alonso, E.; Solis, A.; Pozo, C. D. *Synlett* **2000**, 698.

(2) (a) Smith, A. B.; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879. (b) Pratt, R. F. *Science* **1989**, *246*, 917.

(3) Hirschmann, R.; Smith, A. B., III.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.

(4) Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, J. *Bioorg. Med. Chem.* **1996**, *4*, 1693.

(5) For review, see: (a) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195. (b) Groger, H.; Hammer, B. *Chem.*

- *Eur. J.* **2000**, *6*, 943. (c) Ordóñez, M.; Rojas-cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17. (d) Ma, J.—A. *Chem. Soc. Rev.* **2006**, *35*, 630. (e) Albrecht, Ł.; Albrecht, A.; Krawczyk, H.; Jørgensen, K. A. *Chem. - Eur. J.* **2010**, *16*, 28. (f) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757. (g) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410. (h) Davis, F. A.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 7249. (i) Davis, F. A.; Lee, S. H.; Xu, H. *J. Org. Chem.* **2004**, *69*, 3774.

(6) For chiral metal complex catalytic hydrophosphonylation of imine, see: (a) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (b) Gröger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291. (c) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (d) Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818. (e) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978. (f) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Tetrahedron* **2007**, *63*, 8199. (g) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 10521. (h) Ingle, G. K.; Liang, Y.; Mormino, M. G.; Li, G.; Fronczek, F. R.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2054.

(7) For organocatalytic hydrophosphonylation of imine, see: (a) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (c) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209. (d) Zhao, D.-P.; Wang, Y.; Mao, L.-J.; Wang, R. *Chem. - Eur. J.* **2009**, *15*, 10983. (e) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240. (f) Bhadury, P. S.; Zhang, Y.; Zhang, S.; Song, B.; Yang, S.; Hu, D.; Chen, Z.; Xue, W.; Jin, L. *Chirality* **2009**, *21*, 547. (g) Xu, W.; Zhang, S.; Yang, S.; Jin, L.-H.; Bhadury, P. S.; Hu, D.-Y.; Zhang, Y. *Molecules* **2010**, *15*, 5782. (h) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269. For a theoretical study on the chiral phosphoric acid catalyzed hydrophosphonylation, see: (i) Yamanaka, M.; Hirata, T. *J. Org. Chem.* **2009**, *74*, 3266. (j) Akiyama, T.; Morita, H.; Bachu, P.; Mori, K.; Yamanaka, M.; Hirata, T. *Tetrahedron* **2009**, *65*, 4950.

(8) For the asymmetric Kabachnik—Fields reaction, see: (a) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978. (b) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079. (c) Zhou, X.; Shang, D.; Zhang, Q.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2009**, *11*, 1401. (d) Ohara, M.; Nakamura, S.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3285. (e) Wang, L.; Cui, S.; Meng, W.; Zhang, G.; Nie, J.; Ma, J. *Chin. Sci. Bull.* **2010**, *55*, 1729. (f) Wan, D.; Wu, M.; Ma, J. *Youji Huaxue* **2012**, *32*, 13. (g) Sreekanth, R. P.; Krishna, R. M. V.; Govardhana, R. P. V. *Chin. Chem. Lett.* **2016**, *27*, 943.

(9) For example, see: (a) Li, Z.; Bohle, D.; Li, C.-J. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 8928. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (d) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931. (e) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648. (f) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (g) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (h) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169. (i) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953. (j) Wang, M.-Z.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. - Eur. J.* **2010**, *16*, 5723. (k) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (l) Salman, M.; Zhu, Z.-Q.; Huang, Z.-Z. *Org. Lett.* **2016**, *18*, 1526. (m) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214. (n) Zhu, Z.-Q.; Bai, P.; Huang, Z.-Z. *Org. Lett.* **2014**, *16*, 4881. (o) Xie, J.; Li, H.; Zhou, J.; Cheng, Y.; Zhu, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1252. (p) Scheuermann, C. J. *Chem. - Asian J.* **2010**, *5*, 436. (q) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (r) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (s) Rohlmann, R.; Mancheño, O. G. *Synlett* **2012**, *24*, 6.

(10) For oxidative phosphonylation, see: (a) Baslé, O.; Li, C. *Chem. Commun.* **2009**, 4124. (b) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 6023. (c) Han, W.; Mayer, P.; Ofial, A. R. *Adv. Synth. Catal.* **2010**, *352*, 1667. (d) Rueping, M.; Zhu, S.-Q.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 8679. (e) Hari, D. P.; Konig, B. *Org. Lett.* **2011**, *13*, 3852. (f) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Tetrahedron Lett.* **2012**, *53*, 1456. (g) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem. - Eur. J.* **2012**, *18*, 5160. (h) Xie, J.; Li, H.; Xue, Q.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.* **2012**, *354*, 1646.

(11) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997.

(12) (a) Zhang, G.; Ma, Y.; Wang, S.; Kong, W.; Wang, R. *Chem. Sci.* **2013**, *4*, 2645. (b) Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429. (c) Zhang, G.; Ma, Y.; Wang, S.; Zhang, Y.; Wang, R. *J. Am. Chem. Soc.* **2012**, *134*, 12334. (d) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044. (e) Zhang, J.; Tiwari, B.; Xing, C.; Chen, X.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 3649. (f) Bergonzini, G.; Schindler, C. S.; Wallentin, C.-J.; Jacobsen, E. N.; Stephenson, C. R. J. *Chem. Sci.* **2014**, *5*, 112. (g) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590. (h) Sun, S.; Li, C.; Floreancig, P. E.; Lou, H.; Liu, L. *Org. Lett.* **2015**, *17*, 1684. (i) Liu, X.; Sun, S.; Meng, Z.; Lou, H.; Liu, L. *Org. Lett.* **2015**, *17*, 2396. (j) Liu, X.; Meng, Z.; Li, C.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 6012. (k) Wei, X.-H.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.* **2015**, *51*, 832. (l) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010. (m) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem.* **2008**, *73*, 5859. (n) Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558. (o) Wan, M.; Meng, Z.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13845.

(13) For a bifunctional catalyst, see: Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3. (b) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511. (c) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865. (d) Gröger, H. *Chem.-Eur. J.* **2001**, *7*, 5247. (e) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (f) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (g) Shibasaki, M. *Chemtracts-Organic Chemistry* **1999**, *12*, 979. (h) Shibasaki, M. *Enantiomer* **1999**, *4*, 513. (i) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.