ORGANIC LETTERS

2012
Vol. 14, No. 12
3226–3229

Enantioselective Intramolecular Formal [2 + 4] Annulation of Acrylates and α,β-Unsaturated Imines Catalyzed by Amino Acid Derived Phosphines

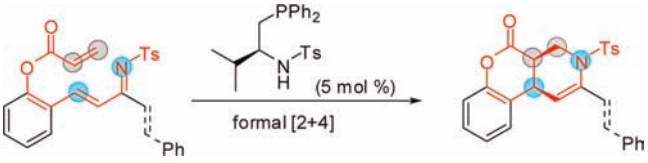
Zhichao Jin, Ruojie Yang, Yu Du, Bhoopendra Tiwari, Rakesh Ganguly, and Yonggui Robin Chi*

Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

robinchi@ntu.edu.sg

Received May 17, 2012

ABSTRACT



The first chiral phosphine-catalyzed activation of acrylates for intramolecular formal [2 + 4] reactions with unsaturated imines is described. The catalytic reactions afford *N*-heterocycles with exceptionally high diastereo- and enantioselectivities. The [2 + 4] products are amenable for further transformations to useful molecules such as chiral piperidines and multicyclic structures.

Nitrogen-containing heterocycles are common motifs in natural and synthetic molecules of pharmaceutical and agrochemical significance.[1] Inverse-electron-demand Diels–Alder reactions and their formal [4 + 2] variants are attractive protocols to prepare such *N*-heterocycles.[2] Over the years, asymmetric (formal) [4 + 2] reactions have mainly been realized with Lewis acid catalysis[3] and recently enamine and iminium-based organocatalysis *via* LUMO or HOMO activations.[4] Phosphines[5] and *N*-Heterocyclic Carbenes (NHCs),[6] as nucleophilic catalysts, hold great potential for enantioselective [4 + 2] and other cycloaddition reactions. In particular, phosphines have long been examined as useful catalysts since Rauhut and Currier's pioneering work in 1963.[7] In recent years, asymmetric cycloadditions using phosphine catalysts have focused on allenoates or their

(1) For selected reviews, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (c) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

(2) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.

(3) For selected reviews, see: (a) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 4351. (b) Kobayashi, S. *Pure Appl. Chem.* **1998**, *70*, 1019. (c) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365. (d) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839. (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2010**, *33*, 325.

(4) For selected reviews and examples, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (d) Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2008**, *47*, 9971. (e) Han, B.; He, Z.-Q.; Li, J. -L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474. (f) Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6418. (g) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20618. (h) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(5) For selected reviews on phosphine catalysis, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Ye, L.-Wu; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (d) Kwong, C. K.-W.; Fu, M. Y.; Lam, C. S.-L.; Toy, P. H. *Synthesis* **2008**, 2307. (e) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. (f) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (g) Wang, S.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, 2766.

(6) For selected reviews on NHC catalysis, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130. (c) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (d) Chiang, P. C.; Bode, J. W. *TCI Mail* **2011**, *149*, 2. (e) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (f) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53.

(7) (a) Rauhut, M. M.; Currier, H. (American Cyanamid Co.) U.S. Patent 307,499,919,630,122, 1963; *Chem. Abstr.* **1963**, *58*, 11224a. For reviews and examples of the Rauhut–Currier reactions, see: (b) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069 and references cited therein.

(8) Lu's pioneering work:Zhang, F. C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.

10.1021/ol3013588
Published on Web 06/07/2012

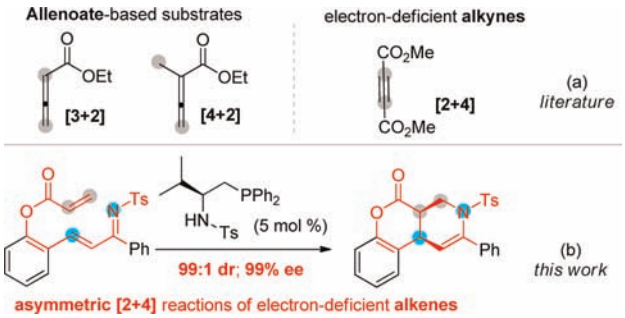
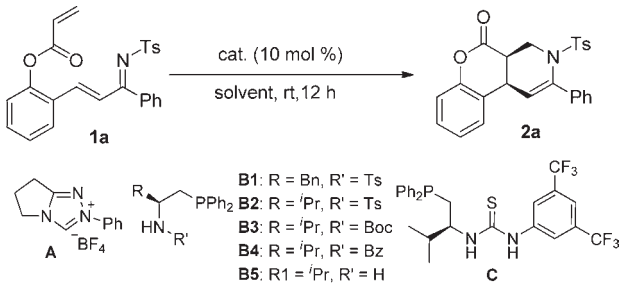


Figure 1. Phosphine-catalyzed (formal) [3 + 2] and [2 + 4] reactions.

equivalents as three carbon synthons for Lu's [3 + 2] reactions.[8−10] The related [4 + 2] reactions using phosphine or nucleophilic NHC catalysts, on the other hand, are much less developed. In 2003, Kown and co-workers initiated the use of α-substituted allenoates as four carbon synthons in [4 + 2] reactions to make tetrahydropyridines (Figure 1a).[11] Further variants, including enantioselective reactions of the Kown-type [4 + 2] cycloadditions based on α-substituted allenoates, were realized by the groups of Fu,[12a] Kown,[12b,c,e,g] Zhao,[12f] and Lu.[12h] In 2008, Waldmann, Kumar and co-workers released the first report of phosphine-catalyzed activation of electron-deficient alkynes (nonallenoate-based substrates) for [2 + 4] reactions with oxo-dienes (Figure 1a);[13] no asymmetric versions of such [2 + 4] reactions have been reported. Here we report the first chiral phosphine-catalyzed activation of electron-deficient alkenes[14] for intramolecular formal [2 + 4] reactions with α,β-unsaturated imines (Figure 1b). The bicyclic *N,O*-containing compounds were obtained as essentially a single diastereomer with 99% ee. Asymmetric transformations of the catalytic products led to potentially useful molecules such as functionalized pyridines and piperidines.

We started by first identifying suitable catalysts for the activation of acrylates as two carbon building blocks for (formal) [2 + 4] intramolecular reactions with unsaturated imines (Table 1). Our efforts with *N*-heterocyclic carbenes (such as **A**)[15] and cinchona alkaloid-based nucleophilic

Table 1. Catalyst and Condition Optimization[a]



entry	cat.	solvent	yield (%)[b]	ee (%)[c]
1	**A**[d]	CH_2Cl_2	0	–
2	PPh_3	CH_2Cl_2	51	–
3	**B1**	CH_2Cl_2	49	97
4	**B2**	CH_2Cl_2	55	99
5	**B3**	CH_2Cl_2	62	93
6	**B4**	CH_2Cl_2	61	98
7	**B5**	CH_2Cl_2	10	64
8	**C**	CH_2Cl_2	22	75
9	**B2**	THF	43	97
10	**B2**	dioxane	39	97
11	**B2**	toluene	61	99
12	**B2**	Et_2O	50	98
13	**B2**	MeCN	70	93
14	**B2**	EtOH	14	77
15	**B2**	hexane	6	93
16	**B2**	DMF	50	88
17	**B2**[e]	toluene	80	99

[a] Unless otherwise noted, all the reactions were carried out at rt using **1a** (0.10 mmol), 10 mol % of catalyst, and 0.5 mL of solvent. [b] Isolated yield. [c] Enantiomeric excess of **2a**, determined *via* chiral HPLC. [d] 20 mol % of Et_3N was added. [e] 5.0 mol % of catalyst was used.

(9) Zhang reported the first chiral version of Lu's [3 + 2] cycloaddition; see: (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. Miller pioneered the use of amino acid derived chiral phosphines as organocatalyst; see: (b) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. Jacobsen introduced the first chiral bifunctional phosphine-thiourea catalyst in this type of [3 + 2] reaction, see: (c) Fang, Y. Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660.

(10) For other elegant examples on asymmetric phosphine catalyzed [3 + 2] reactions, see: (a) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006** *45*, 1426. (b) Voituriez, A.; Panossian, A.; Fleury-Bregeot, N.; Retailleau P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (c) Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467. (d) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293. (e) Han, X.; Wang, S.-X.; Zhong, F.; Lu, Y. *Synthesis* **2011**, 1859. (f) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (g) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (h) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726. (i) Zhao, Q.-Y.; Han, X.; Wei, Y.; Shi, M.; Lu, Y. *Chem. Commun.* **2012**, *48*, 970. (j) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767.

(11) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.

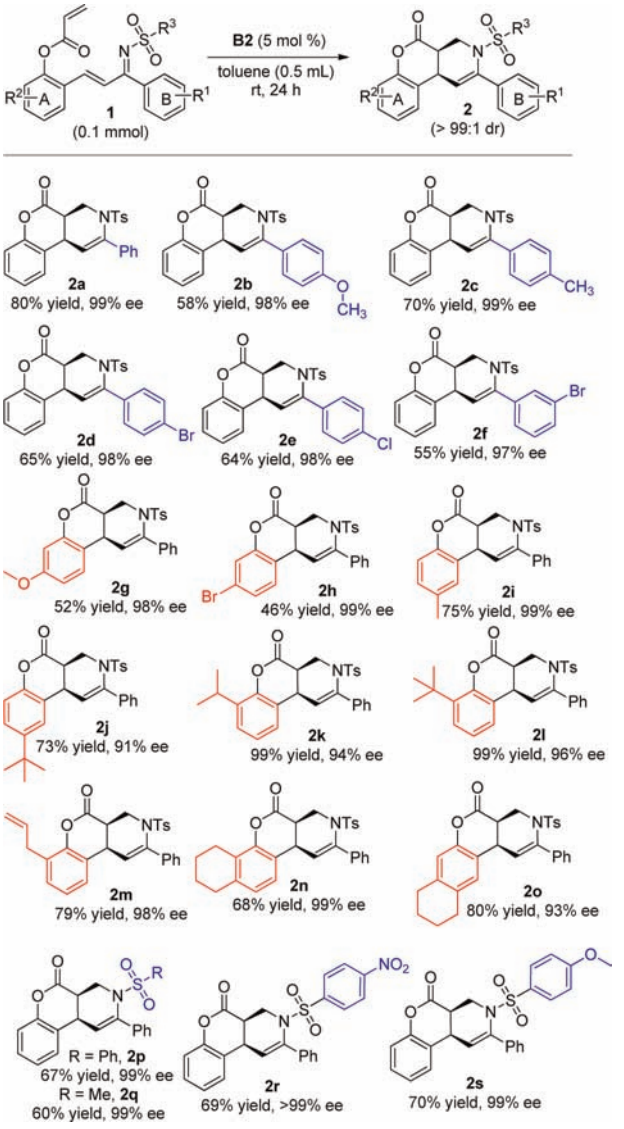
(12) (a) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (b) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (c) Guo, H.; Xu, Q.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318. (d) Wang, T.; Ye, S. *Org. Lett.* **2010**, *12*, 4168. (e) Tran, Y. S.; Martin, T. J.; Kwon, O. *Chem.—Asian J.* **2011**, *6*, 2101. (f) Xiao, H.; Chai, Z.; Wang, H.-F.; Wang, X.-W.; Cao, D.-D.; Liu, W.; Lu, Y.-P.; Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2011**, *11*, 10562. (g) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (h) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231.

(13) (a) Waldmann, H.; Khedhar, V.; Duckert, H.; Schurmann, M.; Oppel, I. M.; Kumar, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6869. (b) Duckert, H.; Khedkar, V.; Waldmann, H.; Kumar, K. *Chem.—Eur. J.* **2011**, *17*, 5130. For a related enantioselective [2 + 3] reaction based on electron-deficient alkynes, see: (c) Sampath, M.; Loh, T.-P. *Chem. Sci.* **2010**, *1*, 739.

(14) During the preparation of this manuscript, Sasai et al. reported an excellent chiral phosphine-catalyzed enantioselective intramolecular Rauhut−Currier reaction of electron-deficient alkenes; see: Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423.

(15) For *N*-heterocyclic carbene-catalyzed Baylis−Hillman-type reactions, see: (a) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466. (b) He, L.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Synthesis* **2008**, 2825. For examples of our efforts on NHC catalyzed-reactions, see: (c) Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910. (d) Fang, X.; Chen, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708. (e) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782. (f) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154.

Scheme 1. Scope of the Reactions[a]



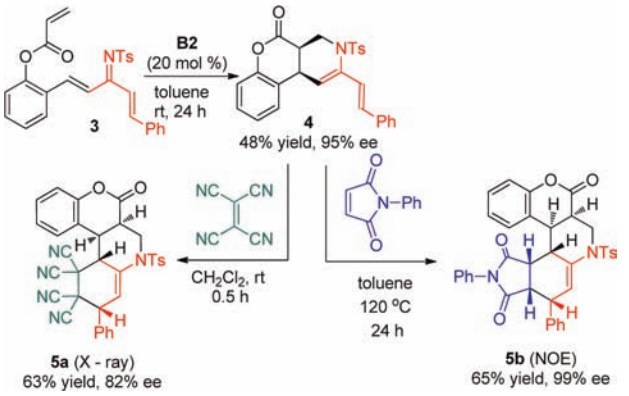
[a] Isolated yields via SiO_2 column chromatography. Ee was determined *via* chiral phase HPLC. Absolute configurations of the products were established *via* the X-ray structure of **2d** (see the Supporting Information).

catalysts[16] failed (entry 1). Later by using Ph_3P, a common catalyst used for Baylis–Hillman and the related Rauhut–Currier reactions,[17] the desired [2 + 4] addition product **2a** was obtained in 51% isolated yield as essentially a single diastereomer (entry 2). Simple phosphine catalysts derived from amino acids, first pioneered by Miller and co-workers,[9b] offered good yields and

(16) With DABCO (10 mol %) as a catalyst, the desired product could be obtained in 62% yield; using 9-amino (9-deoxy) epiquinine or its simple derivatives bearing thiourea motifs as the catalysts, there was no detectable formation of product **2a**.

(17) For selected examples of asymmetric phosphine-catalyzed Rauhut–Currier reactions, see: (a) Gong, J.; Li, T.; Pan, K.; Wu, X. *Chem. Commun.* **2011**, *47*, 1491. For selected examples of asymmetric phosphine-catalyzed MBH reactions, see: (b) Zhong, F.; Wang, Y.; Han, X.; Huang, K.-W.; Lu, Y. *Org. Lett.* **2011**, *13*, 1310. (c) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *Org. Biomol. Chem.* **2011**, *9*, 6734. (d) Song, H.; Yuan, K.; Wu, X. *Chem. Commun.* **2011**, *47*, 1012.

Scheme 2. Catalytic Synthesis of **4** Containing a Diene, and Asymmetric Transformation of **4** to Multicyclic Adduct **5**[a]



[a] **5a** and **5b** were obtained as essentially single diastereomers (> 99:1 dr).

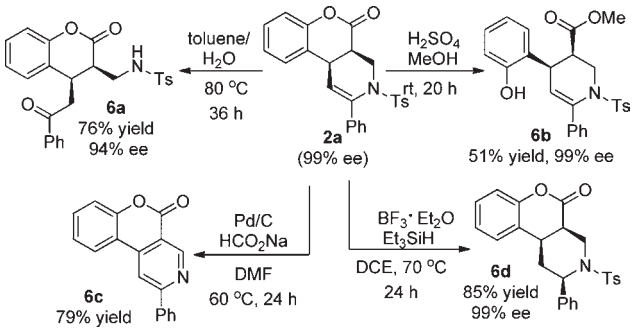
93–98% ee in our reactions (entries 3–6). Replacing the amide moiety of the catalysts with an amino (**B5**) or a thiourea group (**C**) led to a significant drop in yields and ee's (entries 7–8). Further studies (entries 9–17) showed that toluene was an optimal solvent, and the reaction mediated by 5 mol % **B2** afforded product **2a** in 80% isolated yield and 99% ee. All the reactions in Table 1 were highly diastereoselective, and essentially only one diastereomer was obtained. The absolute configuration of **2a** (and all other products) was assigned *via* the X-ray structure of **2d** (Scheme 1, see the Supporting Information).

Having established optimal conditions, the scope of the reactions was examined (Scheme 1). Variations on the aryl unit (B ring) of the α,β-unsaturated imine moiety were well-tolerated, with either electron-donating (**2b** and **2c**) or -withdrawing (**2d**–**f**) substituents on the phenyl rings. Similarly, the introduction of different substituents to the A ring of the substrates did not significantly affect the reaction outcomes (**2g**–**o**): acceptable to excellent yields and excellent ee's were obtained. The *N*-protecting groups of the imine moieties could be changed from Ts to Ms (**2q**) and other $ArSO_2$-substituents (**2p**, **2r**, and **2s**) without affecting the reaction yields or ee's. Installing a β-substituent (Me, Ph, vinyl) to the acrylate moieties of the substrates (**1**) led to no formation of the products.

Notably, the aromatic B ring of substrate **1** could be switched to a vinyl substituent (**3**), with the formation of the corresponding formal [2 + 4] reaction product **4** in 48% yield and 95% ee without much further optimization of the conditions (Scheme 2). Compounds such as **4** contain the necessary functional groups (dienes) for additional useful transformations.[18] For example, reaction of **4** with electron-deficient alkenes afforded fused cyclic Diels–Alder products (e.g., **5a** and **5b**) with good isolated yields and

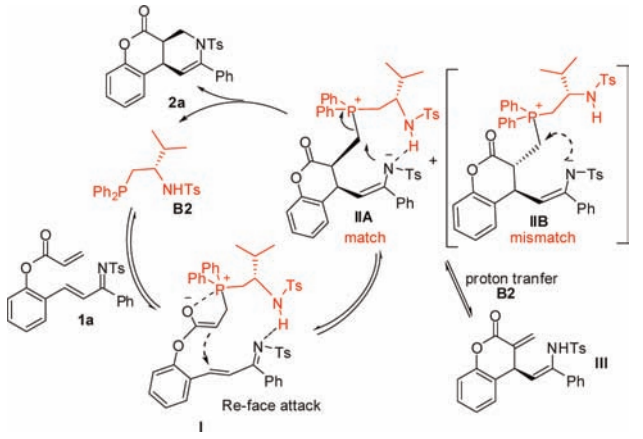
(18) (a) Saito, T.; Kimura, H.; Sakamaki, K.; Karakasa, T.; Moriyama, S. *Chem. Commun.* **1996**, 811. (b) Kobayashi, S.; Furuya, T.; Otani, T.; Saito, T. *Tetrahedron* **2008**, *64*, 9705. (c) Kobayashi, S.; Semabs, T.; Takahashi, T.; Yoshida, S.; Dai, K.; Otani, T.; Saito, T. *Tetrahedron* **2009**, *65*, 920.

Scheme 3. Synthetic Transformations of **2a**[a]



[a] **6a**, **6b**, and **6d** were obtained as essentially single diastereomers (> 99:1 dr).

Scheme 4. Postulated Reaction Mechanism



excellent ee's. These impressive multicyclic products (**5a** and **5b**) containing up to six chiral centers were obtained as a single diastereomer (Scheme 2).

The chiral model product **2a** was amenable to further transformations by employing simple protocols (Scheme 3).[19] For example, the enamide moiety of **2a** could be hydrolyzed to give the corresponding cyclic δ-amino ketone **6a** as a single diastereomer in 76% yield with a little optical purity erosion. Trans-esterification on the phenol ester group of **2a** under acidic conditions led to **6b** in 51% yield and 99% ee. Aromatization of the enamide ring of **2a** led to functional pyridine **6c**. Stereoselective reduction of the enamide afforded chiral piperidine **6d** as a single diastereomer in 85% yield and 99% ee.

The catalytic reaction is postulated to go through a tandem Rauhut–Currier/S_N2-substitution sequence (Scheme 4).[7,17] The high diastereoselectivity (essentially a single diastereomer was obtained) likely resulted from a favorable S_N2 reaction of intermediate **IIA** and a reversible interconversion between intermediate **IIA/IIB** and the Rauhut–Currier adduct **III**. The Rauhut–Currier adduct **III** could be isolated in ~20% yield when Ph_3P was used as the catalyst; over a longer reaction time under the catalysis of Ph_3P or **B2**, **III** was completely transferred to [2 + 4] product **2a**.

In summary, we have described the first chiral phosphine-catalyzed intramolecular aza formal [2 + 4] reaction between α,β-unsaturated imines and electron-deficient alkenes. The nitrogen-containing heterocyclic products were obtained in excellent enantioselectivities as essentially single diastereomers. The optically pure products containing multiple functional groups could undergo further transformations, such as Diels–Alder reactions with electron-deficient alkenes, to give sophisticated multicyclic products with up to six chiral centers. Intermolecular variants of this type of reactions *via* phosphine or NHC-mediated activation of alkenes are under development in our laboratory.

Acknowledgment. We thank the generous financial supports from Singapore National Research Foundation (NRF), Singapore Economic Development Board (EDB), GlaxoSmithKline (GSK), and Nanyang Technological University (NTU).

Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Li, J.-L.; Zhou, S.-L.; Han, B.; Wu, L.; Chen, Y.-C. *Chem. Commun.* **2010**, *46*, 2665.

The authors declare no competing financial interest.