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Versatile Enantioselective [3+2] Cyclization between Imines and Allenoates Catalyzed by Dipeptide-Based Phosphines**

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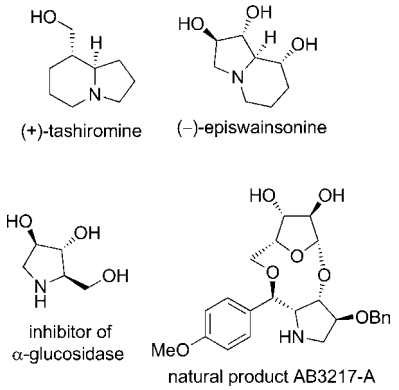
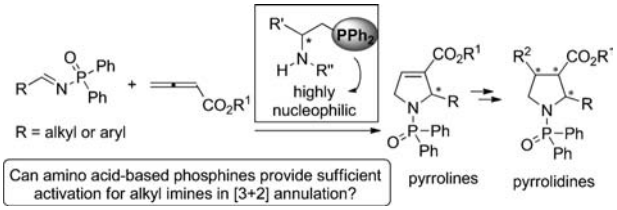
Optically pure five-membered N-heterocycles are valuable intermediates in chemical synthesis, and they are also prevalent structural motifs in bioactive molecules and natural products.[1] Over the past decade, many synthetic methods have been devised for the construction of such ring systems.[2] In this context, [3+2] cyclization of imines with allenes or alkynes is one of the most straightforward and efficient methods for the creation of pyrrolines[3] and pyrrolidines,[4] which are classes of compounds that are of synthetic and biological importance. In 1997, Xu and Lu disclosed the [3+2] cycloadditions between imines and alkynes or allenes for the synthesis of pyrroline rings.[5] However, asymmetric variants of these phosphine-catalyzed [3+2] cyclizations only appeared almost a decade later. The groups of Marinetti and Gladysz independently reported chiral-phosphine-triggered asymmetric [3+2] annulations of allenes with N-tosyl imines, thus affording functionalized 3-pyrrolines with moderate enantioselectivity.[6] The breakthrough came when Fang and Jacobsen introduced phosphinothiourea catalysis of the imine–allene cyclization; by utilizing diphenylphosphinoyl (DPP) imines,[7] substituted 2-aryl-2,5-dihydropyrroles were formed in good yields and with excellent enantioselectivities.[8] Despite all the above advances, the utilization of aliphatic imines in phosphine-catalyzed [3+2] cycloaddition reaction remains elusive.[9] Aliphatic imines are challenging substrates because of their isomerizable nature[10] and relative instability. Nonetheless, their synthetic value is remarkable. Apparently, accessing five-membered N-heterocycles through cycloaddition reactions of aliphatic imines holds significant synthetic utility. As illustrated in Scheme 1, pyrrolidines with 2-alkyl substituents are very common substructures in bioactive molecules and natural products.[11]

We recently embarked on an exciting adventure of developing amino-acid-based bifunctional phosphines and their applications in asymmetric organic transformations.[12] We showed that highly enantioselective aza-Morita–Baylis–Hillman (MBH) and MBH reactions could be realized by using L-threonine-derived phosphine sulfonamides[13] and phosphine thioureas,[14] respectively. We also demonstrated that dipeptide-derived phosphines were powerful catalysts for promoting enantioselective [3+2] cycloadditions of allenes to acrylates or acrylamides.[15] Very recently, we discovered that L-threonine-derived phosphine thioureas were capable of promoting MBH carbonates as C_3 synthons in the [3+2] cyclization.[16] Given the relative instability of aliphatic imines, we reasoned that highly reactive phosphines are probably necessary for their effective activations in the cycloaddition reaction, since potential decomposition of imines may be avoided. It is noteworthy that our amino-acid-based phosphines possess remarkably high nucleophilicity. We hypothesized that employment of highly nucleophilic bifunctional phosphines may result in a practical asymmetric [3+2] annulation protocol in which alkyl imines can be conveniently utilized (Scheme 2).



Scheme 1. Pyrrolidine-containing bioactive molecules. Bn = benzyl.

The [3+2] cycloaddition between the DPP imine **1a** and *tert*-butyl allenoate **2** was selected as a model reaction for the initial explorations (Table 1). For the catalysts, we chose to focus on dipeptide-based bifunctional phosphines, which were shown to be highly efficient in our previous studies.[15a] To our



Scheme 2. Phosphine-triggered [3+2] cyclization of imines with allenoates.

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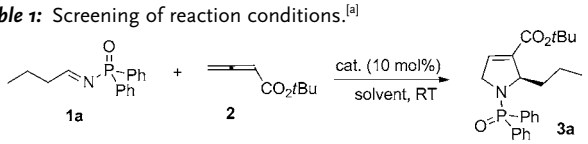
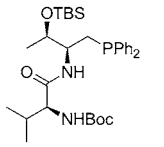
Table 1: Screening of reaction conditions.[a]

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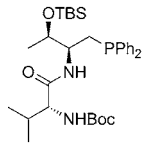
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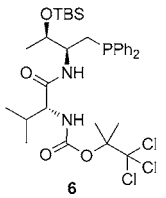
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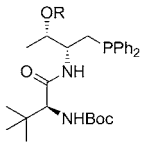

7a: R = TBS; **7b**: R = TDS; **7c**: R = TIPS; **7d**: R = TBDPS

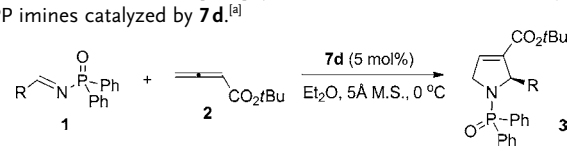
Entry	Cat.	Solvent	*t* [min]	Yield [%][b]	*ee* [%][c]
1	**4**	toluene	3	88	−11
2	**5**	toluene	3	91	−88
3	**6**	toluene	3	86	−82
4	**7a**	toluene	3	91	92
5	**7b**	toluene	3	90	85
6	**7c**	toluene	3	88	89
7	**7d**	toluene	3	90	92
8	**7a**	THF	3	85	86
9	**7a**	Et_2O	3	91	93
10	**7a**	DME	3	87	91
11	**7d**	Et_2O	3	92	94
12[d]	**7d**	Et_2O	10	91	95
13[d,e]	**7d**	Et_2O	20	89	96
14[e,f]	**7d**	Et_2O	12	81	92
15[d,g]	**7d**	Et_2O	30	92	96

[a] Reaction conditions: **1a** (0.05 mmol), **2** (0.075 mmol), and the catalyst (0.005 mmol) in toluene (0.5 mL) at room temperature. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] 5 Å molecular sieves were added. [e] The reaction was performed at 0 °C. [f] H_2O (20 mol%) was added. [g] The catalyst loading was 5 mol%. Boc = *tert*-butoxycarbonyl, DME = dimethyl ether, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TDS = thexyldimethylsilyl, THF = tetrahydrofuran, TIPS = triisopropylsilyl.

delight, all the phosphines examined displayed remarkable catalytic effects, thus affording the desired 3-pyrrolines in just a few minutes. While the L-Thr-L-Val-derived phosphine **4** induced very low enantioselectivity, the catalyst **5** consisting of L-Thr and D-Val subunits turned out to be very effective in asymmetric induction (entries 1–2), thus suggesting that the chirality matching is very important in our catalytic system. The structures of the catalysts were optimized by introducing *tert*-Leu as the second amino acid residue and varying the carbamate group on the N-terminal of the dipeptide, and it was discovered that the O-TBDPS-D-Thr-L-*tert*-Leu-based **7d** was the best catalyst (entries 4–7). To additionally improve the enantioselectivity of the reaction, solvent screening[17] was performed and diethyl ether was found to be the best solvent (entries 8–10). Notably, the addition of water to the reaction system accelerated the reaction, however, the enantioselectivity was descreased (entry 14).[18] When the reaction was carried out at 0 °C for 30 minutes in the presence of 5 mol% of **7d** and molecular sieves, the imine–allene cycloaddition product was obtained in 92% yield with 96% *ee* (entry 15).

Having established the optimal reaction conditions for the preparation of 3-pyrroline, the substrate scope for **7d**-catalyzed [3+2] cyclization was then investigated (Table 2). A wide range of alkyl imines could be employed, and the enantioselectivity of the reaction was independent to the alkyl

Table 2: Enantioselective [3+2] cycloaddition of allenoates with aliphatic DPP imines catalyzed by **7d**.[a]

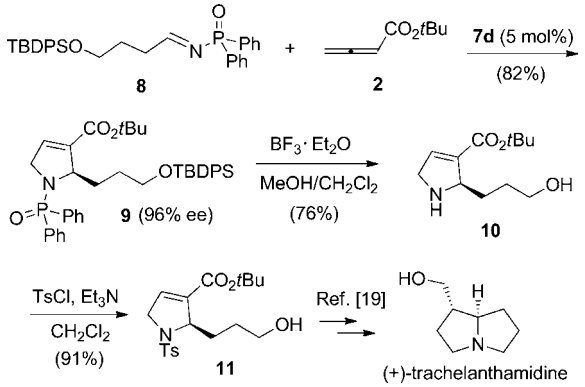


Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	H_3C	**3b**	75	95
2		**3c**	78	96
3		**3d**	80	97
4		**3e**	84	97
5		**3f**	85	97
6		**3g**	82	96
7	Ph	**3h**	81	95
8		**3i**	90	95
9		**3j**	81	99
10		**3k**	83	99
11	Ph	**3l**	81	96

[a] Reactions conditions: **1** (0.1 mmol), **2** (0.15 mmol), and **7d** (0.005 mmol) in Et_2O (1 mL) containing 5 Å molecular sieves at 0 °C for 30 min. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. M.S. = molecular sieves.

substituents of the imines. The reaction was applicable to α-methyl-substituted imine, which tends to form isomeric enamide readily (entry 1). α-Unbranched alkyl imines were found to be excellent substrates; not only were simple linear alkyl groups of different length applicable, but also the alkyl imine bearing a phenyl group at the end was suitable (entries 2–7). The reaction also tolerated branched alkyl imines, and the cycloaddition proceeded remarkably well with imines bearing *sec*-butyl, isopropyl, or cyclohexyl groups (entries 8–10). Furthermore, the imine with a vinylic substituent also proved to be a suitable substrate. Notably, only 5 mol% catalyst was sufficient to promote the allenoate–imine cyclizations, thus affording the 3-pyrrolines in good to excellent yields, and with nearly perfect enantioselectivities. Moreover, the reactions were very fast, and all the cyclizations could be completed in less than 30 minutes. The absolute configuration of [3+2] products were determined by comparing the optical rotation of a **3j** derivative with the value reported in the literature.[19]

2-Alkyl-substituted chiral 3-pyrrolines are structures of high synthetic value, and can potentially be elaborated into many biologically useful molecules.[11] As an illustration, a formal synthesis of pyrrolizidine alkaloid (+)-trachelanthamidine using our cyclization protocol as a key step was performed (Scheme 3). The [3+2] cycloaddition between imine **8** and allenoate **2** occurred smoothly in the presence of **7d** to afford the functionalized pyrroline **9** in 82% yield and 96% *ee*. Treatment of **9** with boron trifluoride resulted in



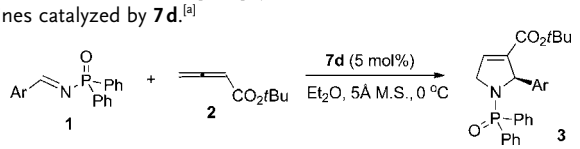
Scheme 3. A formal synthesis of (+)-trachelanthamidine. Ts = 4-toluenesulfonyl.

simultaneous removal of the DPP group and cleavage of the silyloxy group, thus giving the intermediate **10** in good yield. Installation of a tosyl group on the free NH yielded N-tosyl sulfonylamide **11**, which can be converted into (+)-trachelanthamidine using the procedures described in the literature.[20]

The broad applicability of dipeptide-based phosphine-catalyzed [3+2] annulations to various alkyl imines suggested that such enantioselective process should be applicable to aryl imines. We therefore investigated the imine–allenoate cyclization using aryl imines (Table 3). Under the optimized reaction conditions and in the presence of phosphine **7d**, the [3+2] cycloadditions of aryl imines with allenes were completed within one hour, and the desired products were obtained in high yields and excellent enantioselectivities. The reaction was applicable to aryl imines having different electronic characteristics and substitution patterns on the aromatic rings. 2-Naphthyl and heteroaryl imines were also found to be suitable.

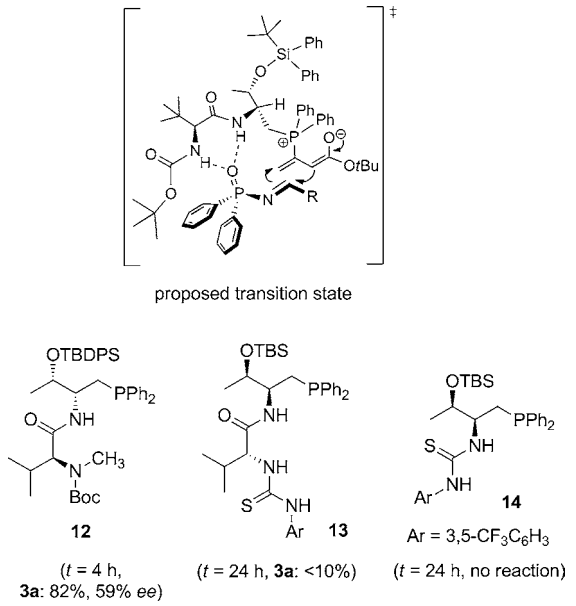
We propose that amide and carbamate portions of the catalyst interact with imines through hydrogen-bonding interactions, which contribute significantly to the key transition state leading to the formation of the major stereoisomer (Scheme 4). The preferential adoption of an s-cis conformation by DPP imines[8] facilitates the intramolecular delivery of the phosphonium enolate to the imine. The catalytic effects of the N-methylated catalyst **12** were examined, and cyclization product **3a** was obtained in 82% yield after 4 hours, but with only 59% *ee*. In comparison, similar catalysts having a free carbamate (**5** and **7d** in Table 1) afforded products in excellent yield and with around a 90% *ee* in just a few minutes. These results clearly support the importance of the

Table 3: Enantioselective [3+2] cycloaddition of allenoates with aromatic imines catalyzed by **7d**.[a]



Entry	Ar	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**3m**	82	95
2	4-BrC_6H_4	**3n**	83	95
3	3-BrC_6H_4	**3o**	85	96
4	4-$OMeC_6H_4$	**3p**	94	98
5	3-CNC_6H_4	**3q**	78	93
6	2-naphthyl	**3r**	86	96
7	2-furyl	**3s**	83	94
8	2-thienyl	**3t**	78	95

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), and **7d** (0.005 mmol) in Et_2O (1 mL) containing 5 Å molecular sieves at 0 °C for 1 h. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase.



Scheme 4. Proposed transition state (top) and the [3+2] annulations between **1a** and **2** in toluene when promoted by different catalysts (bottom).

hydrogen-bond donor groups in our catalytic systems. Thioureas are known to provide excellent activation and stereochemical control for reactions involving imines, as demonstrated by Fang and Jacobsen.[8] However, the dipeptide- or threonine-based phosphine thiourea **13** or **14** was found to be completely ineffective in our reactions.[21]

In conclusion, we have developed a highly enantioselective [3+2] cyclization between imines and allenoates by employing dipeptide-based chiral phosphines as catalysts. Notably, this is the first time that alkyl imines have been applied successfully in the asymmetric [3+2] cycloaddition. Moreover, such an enantioselective cyclization is versatile and worked equally well for aryl imines. The synthetic value

of our method has been demonstrated by using the imine–allene annulation as a key step in a concise formal synthesis of (+)-trachelanthamidine. We are currently investigating the reaction mechanism and applying the described methodology to the synthesis of biologically important molecules.

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Keywords: allenes · cycloadditions · heterocycles · nucleophilic catalysis · phosphines

[1] For selected reviews, see: a) F. C. Biaggio, A. R. Rufino, M. H. Zaim, C. Y. H. Zaim, M. A. Bueno, A. Rodrigues, *Curr. Org. Chem.* **2005**, *9*, 419; b) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825; c) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765; d) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484.

[2] For selected examples, see: a) Z.-H. Chen, Y.-Q. Tu, S.-Y. Zhang, F.-M. Zhang, *Org. Lett.* **2011**, *13*, 724; b) R. A. Bauer, C. M. DiBlasi, D. S. Tan, *Org. Lett.* **2010**, *12*, 2084; c) J. Toueg, C. R. A. Godfrey, J. E. Wibley, *Synlett* **2010**, 2721; d) J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400; e) J. Yu, L. He, X.-H. Chen, J. Song, W.-J. Chen, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4946.

[3] a) B. E. Segelstein, T. T. Wager, W. M. Welch (Pfizer), U.S. Patent Appl. 2005272800, **2005**; *Chem. Abstr.* **2005**, *144*, 51439; b) J. M. Humphrey, T. A. Chappie (Pfizer), WO 05115976, **2005**; *Chem. Abstr.* **2005**, *144*, 36250; c) T. T. Wager, W. Welch, B. T. O'Neill (Pfizer Products Inc.), WO 2004/110996, **2004**; d) Z. Wang, S. Castellano, S. S. Kinderman, C. E. Argueta, A. B. Beshir, G. Fenteany, O. Kwon, *Chem. Eur. J.* **2011**, *17*, 649; For the [2+2] cycloadditions of allenoates and imines, see: e) J.-B. Denis, G. Masson, P. Retailleau, J. Zhu, *Angew. Chem.* **2011**, *123*, 5468; *Angew. Chem. Int. Ed.* **2011**, *50*, 5356.

[4] For selected examples, see: a) M. Shibano, S. Kitagawa, G. Kusano, *Chem. Pharm. Bull.* **1997**, *45*, 505; b) S. H. Kang, H. Choi, *Chem. Commun.* **1996**, 1521.

[5] a) Z. Xu, X. Lu, *Tetrahedron Lett.* **1997**, *38*, 3461; b) Z. Xu, X. Lu, *J. Org. Chem.* **1998**, *63*, 5031.

[6] For the initial and recent reports from the Marinetti group, see: a) L. Jean, A. Marinetti, *Tetrahedron Lett.* **2006**, *47*, 2141; b) N. Fleury-Brégeot, L. Jean, P. Retailleau, A. Marinetti, *Tetrahedron* **2007**, *63*, 11920; c) N. Pinto, N. Fleury-Bregeot, A. Marinetti, *Eur. J. Org. Chem.* **2009**, 146; d) M. Schuler, D. Duvvuru, P. Retailleau, J.-F. Betzer, A. Marinetti, *Org. Lett.* **2009**, *11*, 4406; For the report from the Gladysz group, see: e) A. Scherer, J. A. Gladysz, *Tetrahedron Lett.* **2006**, *47*, 6335.

[7] a) S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712; b) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777.

[8] Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660.

[9] In the nonchiral version of [3+2] annulations reported by Xu and Lu, only a trace amount of product was detected when aliphatic N-tosylimine was used; See Ref. [5]. Fang and Jacobsen observed decomposition of aliphatic imines under their reaction conditions; See Ref. [8].

[10] a) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4439; *Angew. Chem. Int. Ed.* **2005**, *44*, 4365; b) B. M. Trost, J. Jaratjaroonphong, V. Reutrakul, *J. Am. Chem. Soc.* **2006**, *128*, 2778; c) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048; d) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 3985.

[11] a) J. C. Conrad, J. Kong, B. N. Laforteza, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640; b) W.-H. Chiou, Y.-H. Lin, G.-T. Chen, Y.-K. Gao, Y.-C. Tseng, C.-L. Kao, J. C. Tsai, *Chem. Commun.* **2011**, *47*, 3562; c) N. Ikota, A. Hanaki, *Chem. Pharm. Bull.* **1987**, *35*, 2140; d) N. Ikota, A. Hanaki, *Heterocycles* **1987**, *26*, 2369; e) M. Nakata, T. Tamai, T. Kamio, M. Kinoshita, K. Tatsuta, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3057; f) M. Nakata, T. Tamai, T. Kamio, M. Kinoshita, K. Tatsuta, *Tetrahedron Lett.* **1994**, *35*, 3099; g) J. Toueg, C. R. A. Godfrey, J. E. Wibley, *Synlett* **2010**, 2721.

[12] For a recent account on our work, see: a) S.-X. Wang, X. Han, F. Zhong, Y. Wang, Y. Lu, *Synlett* **2011**, 2766; For reviews on phosphine catalysis, see: b) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535; c) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035; d) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140; e) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102; f) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102; g) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174; For selected examples of phosphine-mediated asymmetric cycloadditions, see: h) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836; i) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1454; *Angew. Chem. Int. Ed.* **2006**, *45*, 1426; j) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988; k) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *J. Am. Chem. Soc.* **2008**, *130*, 14030; l) H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang, G. Zhao, *Angew. Chem.* **2010**, *122*, 4569; *Angew. Chem. Int. Ed.* **2010**, *49*, 4467; m) M. Sampath, T.-P. Loh, *Chem. Sci.* **2010**, *1*, 739; n) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672.

[13] F. Zhong, Y. Wang, X. Han, K.-W. Huang, Y. Lu, *Org. Lett.* **2011**, *13*, 1310.

[14] X. Han, Y. Wang, F. Zhong, Y. Lu, *Org. Biomol. Chem.* **2011**, *9*, 6734.

[15] a) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726; b) X. Han, S.-X. Wang, F. Zhong, Y. Lu, *Synthesis* **2011**, 1859.

[16] F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem.* **2011**, *123*, 7983; *Angew. Chem. Int. Ed.* **2011**, *50*, 7837.

[17] For complete solvent screening results, see the Supporting Information.

[18] The rate enhancement is consistent with Jacobsen's observation (Ref. [8]). The decreased enantioselectivity suggested the importance of hydrogen bonding interaction in the *ee* determining step, which was slightly disrupted by water molecules.

[19] See the Supporting Information for details.

[20] S. Ishikawa, F. Noguchi, A. Kamimura, *J. Org. Chem.* **2010**, *75*, 3578.

[21] Since catalysts **13** and **14** are conformationally flexible, we believe the thiourea group of the catalyst preferentially stabilizes the phosphonium enolate, rather than the DPP imines, through hydrogen-bonding interactions.

