Organic LETTERS

Letter

pubs.acs.org/OrgLett

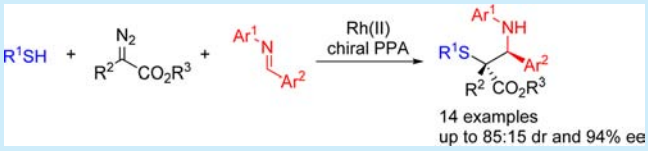
Enantioselective Synthesis of α-Mercapto-β-amino Esters via Rh(II)/Chiral Phosphoric Acid-Cocatalyzed Three-Component Reaction of Diazo Compounds, Thiols, and Imines

Guolan Xiao, Chaoqun Ma, Dong Xing,* and Wenhao Hu*

Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, China

Supporting Information

ABSTRACT: An enantioselective method for the synthesis of α-mercapto-β-amino esters has been developed via a rhodium(II)/chiral phosphoric acid-cocatalyzed three-component reaction of diazo compounds, thiols, and imines. This transformation is proposed to proceed through enantioselective trapping of the sulfonium ylide intermediate generated in situ from the diazo compound and thiol by the phosphoric acid-activated imine. With this method, a series of α-mercapto-β-amino esters were obtained in good yields with moderate to good stereoselectivities.



Chiral sulfur-containing compounds widely exist in a large number of pharmaceuticals and natural products.[1] Nearly one-fifth of the 200 most-prescribed pharmaceutical products in 2011 were sulfur-containing compounds.[2] Among them, sulfur-containing amino acid derivatives are of particular interest because of their diverse biological activities. For example, pseudotripeptides containing an α-mercapto-β-amino acid residue displayed high inhibition of aminopeptidase A,[3] botulinum neurotoxin type B4,[4] and tetanus neurotoxin.[5] Azetidinones derived from α-mercapto-β-amino acids have also been shown to be potent inhibitors of cholesterol absorption.[6] It is further well-known that captopril, one of the amino acid drugs containing a thiol moiety, is effective as an angiotensin-converting enzyme inhibitor.[7] As a result, great effort has been made to synthesize sulfur-containing amino acid derivatives.[8] These methods include ring opening of aziridinium ion intermediates by sulfur-containing nucleophiles,[8a] tandem conjugate addition of homochiral lithium amide to α,β-unsaturated esters followed by electrophilic trapping of the resulting β-amino enolates with sulfur-containing electrophiles,[8b] stereoselective thiolation of iminocarbonates derived from the corresponding amino alcohols,[8c] and Mannich-type reaction between aldimines and sulfonium salts.[8d] Among these methods, however, a catalytic enantioselective transformation to provide chiral sulfur-containing β-amino acid derivatives has not been realized, and the formation of chiral products has been achieved only by starting from chiral starting materials. Therefore, it would be highly desirable to develop a catalytic asymmetric transformation to produce such molecules starting from simple and nonchiral starting materials.

In recent years, multicomponent reactions (MCRs) based on electrophilic trapping of in situ-generated active oxonium or ammonium ylides derived from diazo compounds by various electrophiles have constituted a powerful strategy for the rapid construction of complex molecules.[9−11] By using imines as electrophiles, our research group has developed a series of catalytic asymmetric transformations for such types of MCR to synthesize chiral α-hydroxy-β-amino esters[9a−c] and chiral α-amino-β-amino esters.[10a,b] Following these research efforts, we envisioned that a similar strategy starting from a thiol, diazo compound, and imine would allow efficient electrophilic trapping of the in situ-generated sulfonium ylide species by the imine to produce chiral α-mercapto-β-amino esters. However, given the conceptual feasibility of this design, the sulfonium ylide trapping process may be a great challenge because the strong coordinating ability of the sulfur atom to the transition metal would greatly poison its catalytic ability. On the other hand, the sulfonium ylide intermediate may undergo rapid 1,2-proton transfer instead of being intercepted by the electrophile, generating S−H insertion products.[12] Nonetheless, herein we report an efficient three-component reaction of thiols, diazo compounds, and imines that utilizes a Rh(II)/chiral phosphoric acid (PPA) cocatalytic system (Scheme 1). This transformation represents the first example of electrophilic trapping of sulfonium ylide species and offers an efficient method for the synthesis of chiral α-mercapto-β-amino acid derivatives.

We initiated our exploration by investigating the three-component reaction of 4-methylbenzenethiol (**1a**), methyl phenyldiazoacetate (**2a**), and *N*-phenylbenzaldimine (**3a**) under Rh(II)/phosphoric acid cocatalytic conditions. When 2 mol % $Rh_2(OAc)_4$ and 10 mol % racemic BINOL-derived phosphoric acid *rac*-**5a** were employed, the desired three-component product was obtained in 54% yield with 79:21 dr (Table 1, entry 1). Encouraged by this result, we evaluated a series of chiral BINOL-derived PPA catalysts. Among them, (*R*)-3,3′-bis(4-trifluoromethylphenyl)-BINOL phosphoric acid

Received: October 12, 2016
Published: November 22, 2016

DOI: 10.1021/acs.orglett.6b03075
Org. Lett. 2016, 18, 6086−6089

Scheme 1. Rh(II)/Chiral PPA-Cocatalyzed Enantioselective Trapping of in Situ-Generated Sulfonium Ylide

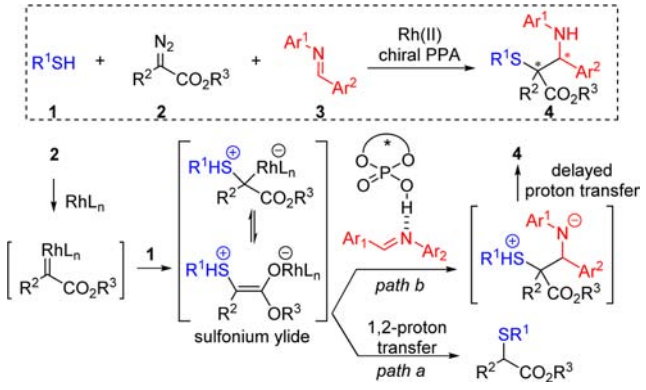
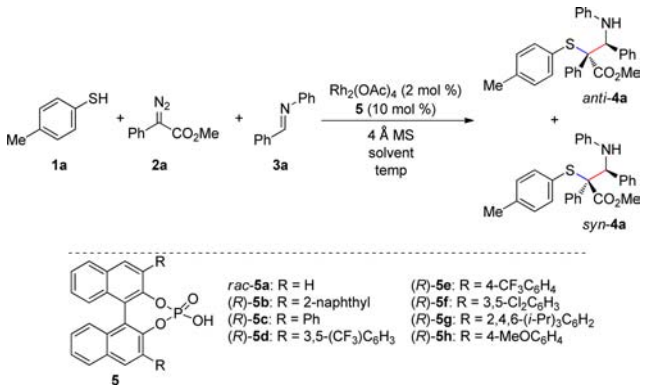


Table 1. Catalyst Screening and Optimization of the Reaction Conditions[a]



entry	solvent	temp (°C)	5	yield (%)[b]	dr (*anti*:*syn*)[c]	ee (%)[d]
1	CH_2Cl_2	0	*rac*-**5a**	54	79:21	–
2	CH_2Cl_2	0	(*R*)-**5b**	52	73:27	73
3	CH_2Cl_2	0	(*R*)-**5c**	52	78:22	71
4	CH_2Cl_2	0	(*R*)-**5d**	62	78:22	64
5	CH_2Cl_2	0	(*R*)-**5e**	66 (47)[e]	71:29	80
6	CH_2Cl_2	0	(*R*)-**5f**	50	73:27	70
7	CH_2Cl_2	0	(*R*)-**5g**	66	72:28	80
8	CH_2Cl_2	0	(*R*)-**5h**	60	79:21	67
9	DCE	0	(*R*)-**5e**	50	68:32	77
10	$CHCl_3$	0	(*R*)-**5e**	52	75:25	82
11	toluene	0	(*R*)-**5e**	36	68:32	78
12	THF	0	(*R*)-**5e**	<5	–	–
13	CH_2Cl_2	rt	(*R*)-**5e**	60	70:30	70

[a] **1a**:**2a**:**3a** = 2.0:2.0:1.0. [b] Total isolated yields of **4a** (*anti* + *syn*). [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d] Enantiomeric excess of *anti*-**4a** as determined by chiral HPLC. [e] The value in parentheses is the isolated yield of *anti*-**4a**.

(*R*)-**5e** was most optimal, yielding the desired three-component product in 66% yield with 73:27 dr and 80% ee (Table 1, entries 2–8). It is worth mentioning that the Mannich-type product from thiol **1a** and imine **3a** was not detected; the only byproduct of this three-component transformation was methyl 2-phenyl-2-(*p*-tolylthio)acetate (**6a**) derived from S–H insertion of **1a** and **2a**. Switching the solvent from CH_2Cl_2 to other halogenated solvents such as 1,2-dichloroethane (DCE) or $CHCl_3$ gave the desired three-component product in comparable yields and stereoselectivities (Table 1, entries 9 and 10). Using toluene as the solvent resulted in a low yield of the product, while the use of THF as the solvent gave only a trace amount of the desired product (Table 1, entries 11 and 12). Raising the reaction temperature to room temperature resulted in no improvement in the stereoselectivity and a slightly decreased yield of the desired three-component product (Table 1, entry 13).

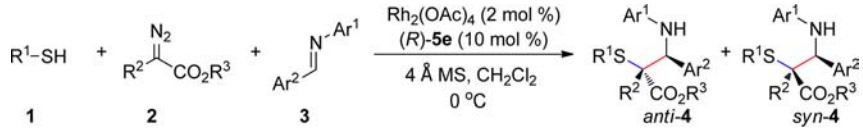
With the optimal reaction conditions in hand, the substrate scope of this Rh(II)/chiral phosphoric acid-cocatalyzed three-component reaction was investigated. A series of substituted imines were first evaluated. Imines derived from electron-deficient amines gave the desired three-component products in comparable yields and diastereoselectivities but with relatively lower enantioselectivities (Table 2, entries 2 and 3). On the other hand, imines bearing electron-withdrawing groups on the C substituent (*C*-Ar) gave the desired three-component products in higher yields with higher enantioselectivities (Table 2, entries 5 and 6 vs entry 4). Aromatic thiols containing electron-donating groups at the *para* position (**1a** and **1b**) or *ortho* position (**1c**) all gave the corresponding three-component products in good yields with good dr and ee (Table 2, entries 7 and 8). The reaction was further extended to a number of substituted diazo compounds. Aryl diazoacetates bearing electron-donating groups on the aryl ring gave higher yields than those bearing electron-withdrawing groups, while the stereoselectivities remained unaffected (Table 2, entries 9–11 vs entry 12). When ethyl diazoacetate (**2f**) was used as the diazo source, the corresponding three-component product **4m** was obtained in a much lower yield with 70:30 dr and 76% ee (Table 2, entry 13). Switching the diazo compound to *tert*-butyl diazoacetate (**2g**) resulted a slightly improved yield of the desired three-component product and much-improved stereoselectivities (85:15 dr and 94% ee) (Table 2, entry 14). Finally, the absolute configuration of the products was assigned to be (2*R*,3*S*) by analogy with that of *anti*-**4e** as determined by single-crystal X-ray diffraction (Figure 1).[13]

This Rh(II)/chiral PPA-cocatalyzed three-component reaction of thiols, diazo compounds, and imines may involve electrophilic trapping of the in situ-generated sulfonium ylide intermediates by PPA-activated imines or a stepwise S–H insertion/Mannich-type reaction pathway. To gain some insights, we carried out a control experiment starting from the suspected intermediate S–H insertion product **6a** and imine **3a**. Under identical reaction conditions, the three-component product **4a** was not observed (Scheme 2, eq 1). Therefore, a stepwise pathway is unlikely to be involved in this transformation. In the absence of $Rh_2(OAc)_4$, the desired three-component product was not observed. On the other hand, in the absence of the chiral PPA, the desired three-component product was obtained in only 27% yield (Scheme 2, eq 2), indicating that the chiral PPA not only induces the enantioselectivity but also facilitates the reactivity of this transformation.[14,15]

In summary, we have developed a catalytic enantioselective three-component reaction of diazo compounds, thiols, and imines in the presence of $Rh_2(OAc)_4$ and chiral phosphoric acid catalysts. This transformation provides a straightforward and efficient route for the synthesis of chiral α-mercapto-β-amino acid derivatives bearing a quaternary carbon stereogenic center. This reaction is proposed to proceed through electrophilic trapping of the active sulfonium ylide intermediate derived from the diazo compound and thiol in the presence of a Rh(II) catalyst. The success of this trapping process also provides

DOI: 10.1021/acs.orglett.6b03075
Org. Lett. 2016, 18, 6086–6089

Table 2. Substrate Scope[a]



1a: R_1 = *p*-$CH_3C_6H_4$
1b: R_1 = *p*-$MeOC_6H_4$
1c: R_1 = *o*-$MeOC_6H_4$

entry	1	R^2/R^3 (2)	Ar^1/Ar^2 (3)	4 (*anti* + *syn*)	yield (%)[b]	dr (*anti*:*syn*)[c]	ee (%)[d]
1	**1a**	Ph/Me (**2a**)	Ph/Ph (**3a**)	**4a**	66 (47)	71:29	80
2	**1a**	Ph/Me (**2a**)	*p*-$CF_3C_6H_4$/Ph (**3b**)	**4b**	61 (46)	75:25	67
3	**1a**	Ph/Me (**2a**)	*p*-$B_rC_6H_4$/Ph (**3c**)	**4c**	60 (43)	71:29	73
4	**1a**	Ph/Me (**2a**)	Ph/*p*-$CH_3C_6H_4$ (**3d**)	**4d**	60 (46)	76:24	74
5	**1a**	Ph/Me (**2a**)	Ph/*p*-FC_6H_4 (**3e**)	**4e**	81 (62)	77:23	82
6	**1a**	Ph/Me (**2a**)	Ph/*p*-CNC_6H_4 (**3f**)	**4f**	84 (65)	77:23	82
7	**1b**	Ph/Me (**2a**)	Ph/Ph (**3a**)	**4g**	65 (49)	75:25	74
8	**1c**	Ph/Me (**2a**)	Ph/Ph (**3a**)	**4h**	65 (46)	71:29	70
9	**1a**	*p*-$CH_3C_6H_4$/Me (**2b**)	Ph/Ph (**3a**)	**4i**	80 (59)	74:26	76
10	**1a**	*p*-$MeOC_6H_4$/Me (**2c**)	Ph/Ph (**3a**)	**4j**	74 (55)	74:26	80
11	**1a**	3,4-$(MeO)_2C_6H_3$/Me (**2d**)	Ph/Ph (**3a**)	**4k**	85 (60)	70:30	74
12	**1a**	*p*-FC_6H_4/Me (**2e**)	Ph/Ph (**3a**)	**4l**	51 (37)	73:27	76
13	**1a**	H/Et (**2f**)	Ph/Ph (**3a**)	**4m**	38 (27)	70:30	76
14	**1a**	H/*t*-Bu (**2g**)	Ph/Ph (**3a**)	**4n**	45 (38)	85:15	94

[a]**1**:**2**:**3** = 2.0:2.0:1.0. [b]Total isolated yields of **4** (*anti* + *syn*). Values in parentheses are isolated yields of the *anti* isomers. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d]Enantiomeric excess of *anti*-**4** as determined by chiral HPLC.

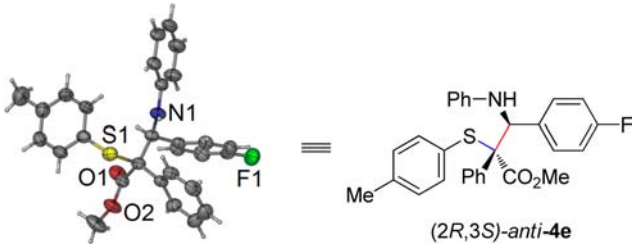
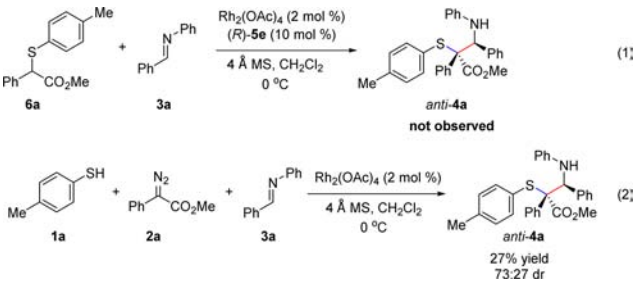


Figure 1. X-ray crystal structure of (2*R*,3*S*)-**4e**.

Scheme 2. Control Experiments



experimental evidence for the involvement of a sulfonium ylide intermediate in the S–H insertion reaction of diazo compounds and thiols. Related research focusing on the expansion to other types of electrophiles is currently 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.6b03075.

Crystallographic data for *anti*-**4e** (CIF)

Experimental procedures and full spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dxing@sat.ecnu.edu.cn.
*E-mail: whu@chem.ecnu.edu.cn.

ORCID

Dong Xing: 0000-0003-3718-4539

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21332003, 21402051) is gratefully acknowledged.

■ REFERENCES

(1) (a) Tisdale, M.; Kemp, S. D.; Parry, N. R.; Larder, B. A. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 5653. (b) Sobal, G.; Menzel, E. J.; Sinzinger, H. *Biochem. Pharmacol.* **2001**, *61*, 373. (c) Halama, A.; Jirman, J.; Boušková, O.; Gibala, P.; Jarrah, K. *Org. Process Res. Dev.* **2010**, *14*, 425. (d) Suhas, R.; Chandrashekar, S.; Gowda, D. C. *Eur. J. Med. Chem.* **2012**, *48*, 179.

(2) Bartholow, M. Top 200 Drugs of 2011. http://www.pharmacytimes.com/publications/issue/2012/July2012/Top-200-Drugs-of-2011 (accessed Sept 27, 2016).

(3) David, C.; Bischoff, L.; Meudal, H.; Mothé, A.; De Mota, N.; DaNascimento, S.; Llorens-Cortes, C.; Fournié-Zaluski, M.-C.; Roques, B. P. *J. Med. Chem.* **1999**, *42*, 5197.

(4) (a) Anne, C.; Turcaud, S.; Quancard, J.; Teffo, F.; Meudal, H.; Fournié-Zaluski, M.-C.; Roques, B. P. *J. Med. Chem.* **2003**, *46*, 4648. (b) Anne, C.; Blommaert, A.; Turcaud, S.; Martin, A.-S.; Meudal, H.; Roques, B. P. *Bioorg. Med. Chem.* **2003**, *11*, 4655. (c) Blommaert, A.; Turcaud, S.; Anne, C.; Roques, B. P. *Bioorg. Med. Chem.* **2004**, *12*,

DOI: 10.1021/acs.orglett.6b03075
Org. Lett. 2016, 18, 6086–6089

3055. (d) Anne, C.; Turcaud, S.; Blommaert, A. G. S.; Darchen, F.; Johnson, E. A.; Roques, B. P. *ChemBioChem* **2005**, *6*, 1375.
(5) Martin, L.; Cornille, F.; Turcaud, S.; Meudal, H.; Roques, B. P.; Fournié-Zaluski, M.-C. *J. Med. Chem.* **1999**, *42*, 515.
(6) McKittrick, B. A.; Ma, K.; Huie, K.; Yumibe, N.; Davis, H., Jr.; Clader, J. W.; Czarniecki, M.; McPhail, A. T. *J. Med. Chem.* **1998**, *41*, 752.
(7) (a) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441. (b) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *16*, 5484. (c) Shimazaki, M.; Hasegawa, J.; Kan, K.; Nomura, K.; Nose, Y.; Kondo, H.; Ohashi, T.; Watanabe, K. M. *Chem. Pharm. Bull.* **1982**, *30*, 3139.
(8) (a) Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555. (b) Candela-Lena, J. I.; Davies, S. G.; Roberts, P. M.; Roux, B.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1135. (c) De Paolis, M.; Blankenstein, J.; Bois-Choussy, M.; Zhu, J.-P. *Org. Lett.* **2002**, *4*, 1235. (d) Kantam, M. L.; Mahendar, K.; Sreedhar, B.; Choudary, B. M.; Bhargava, S. K.; Priver, S. H. *Tetrahedron* **2010**, *66*, 5042. (e) Ohkura, H.; Handa, M.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2002**, *67*, 2692. (f) Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159. (g) Arroyo, Y.; Meana, Á.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *J. Org. Chem.* **2005**, *70*, 3914.
(9) For selected MCRs via the trapping of oxonium ylides developed by our group, see: (a) Guo, X.; Huang, H.-X.; Yang, L.-P.; Hu, W.-H. *Org. Lett.* **2007**, *9*, 4721. (b) Huang, H.-X.; Guo, X.; Hu, W.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1337. (c) Zhang, X.; Huang, H.-X.; Guo, X.; Guan, X.-Y.; Yang, L.-P.; Hu, W.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6647. (d) Hu, W.-H.; Xu, X.-F.; Zhou, J.; Liu, W.-J.; Huang, H.-X.; Hu, J.; Yang, L.-P.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (e) Zhu, Y.-G.; Zhai, C.-W.; Yang, L.-P.; Hu, W.-H. *Chem. Commun.* **2010**, *46*, 2865. (f) Tang, M.; Xing, D.; Huang, H.-X.; Hu, W.-H. *Chem. Commun.* **2015**, *51*, 10612.
(10) For selected MCRs via the trapping of ammonium ylides developed by our group, see: (a) Jiang, J.; Xu, H.-D.; Xi, J.-B.; Ren, B.-Y.; Lv, F.-P.; Guo, X.; Jiang, L.-Q.; Zhang, Z.-Y.; Hu, W.-H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (b) Jiang, J.; Ma, X.-C.; Liu, S.-Y.; Qian, Y.; Lv, F.-P.; Qiu, L.; Wu, X.; Hu, W.-H. *Chem. Commun.* **2013**, *49*, 4238. (c) Zhu, Y.-G; Zhai, C.-W; Yang, L.; Hu, W.-H. *Eur. J. Org. Chem.* **2011**, *2011*, 1113. (d) Zhu, Y.-G.; Zhai, C.-W.; Yue, Y.-L.; Yang, L.-P.; Hu, W.-H. *Chem. Commun.* **2009**, *11*, 1362. (e) Jing, C.-C.; Xing, D.; Qian, Y.; Shi, T.-D.; Zhao, Y.; Hu, W.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 9289. (f) Ma, X.-C.; Jiang, J.; Lv, S.-Y.; Yao, W.-F.; Yang, Y.; Liu, S.-Y.; Xia, F.; Hu, W.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 13136.
(11) For three-component reactions via electrophilic trapping of ylides developed by others, see: (a) Zhou, C.-Y.; Wang, J.-C.; Wei, J. H.; Xu, Z.-J.; Guo, Z.; Low, K.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11376. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Callejo, R.; Ruiz, M. P.; Torres, M. R. *Eur. J. Org. Chem.* **2012**, *2012*, 2359. (c) Ren, L.; Lian, X.-L.; Gong, L.-Z. *Chem. - Eur. J.* **2013**, *19*, 3315.
(12) (a) Brunner, H.; Wutz, K.; Doyle, M. P. *Monatsh. Chem.* **1990**, *121*, 755. (b) Galardon, E.; Roué, S.; Le Maux, P.; Simonneaux, G. *Tetrahedron Lett.* **1998**, *39*, 2333. (c) Zhang, X.; Ma, M.; Wang, J. *ARKIVOC* **2003**, *2003* (ii), 84. (d) Zhang, Y.-Z.; Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Zhou, Q.-L. *Chem. Commun.* **2009**, *36*, 5362. (e) Xu, B.; Zhu, S.-F.; Zhang, Z.-C.; Yu, Z.-X.; Ma, Y.; Zhou, Q.-L. *Chem. Sci.* **2014**, *5*, 1442.
(13) CCDC 1477619 (*anti*-**4e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(14) For details, see the Supporting Information.
(15) For a similar activation of imine by chiral phosphoric acid and a proposed transition state for stereoselective control, see ref 10a.

DOI: 10.1021/acs.orglett.6b03075
Org. Lett. 2016, 18, 6086−6089