

Brønsted Acid Catalyzed Phosphoramidic Acid Additions to Alkenes: Diastereo- and Enantioselective Halogenative Cyclizations for the Synthesis of C- and P-Chiral Phosphoramidates

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S Supporting Information

ABSTRACT: The first highly diastereo- and enantioselective additions of a halogen and phosphoramidic acid to unactivated alkenes have been developed, catalyzed by a chiral Brønsted acid. A unique feature of these additions is the opportunity for stereocontrol at two noncontiguous chiral centers, carbon and phosphorus, leading to cyclic P-chiral phosphoramidates. In addition to their inherent value, the phosphoramidates are precursors to enantioenriched epoxy allylamines.

Phosphoramidates and their derivatives are organophosphorous(V) compounds featuring a P–N bond and are used as pesticides in agriculture and prodrugs in therapeutic development, among other synthetic applications.¹ The central chirality of the phosphorus group of a phosphoramidate has a strong impact on the biological activity of the drug;^{2,3} therefore, methods to stereoselectively construct phosphorus (P-) chiral centers are essential tools. The diastereoselective synthesis of phosphoramidate prodrugs was recently reported by using phosphoryl chloride with a chiral auxiliary, where the phosphorus group plays a role as the electrophilic reagent.^{3b} The preparation of P-stereogenic compounds is still challenging,^{4,5} and to the best of our knowledge, there are no examples of enantioselective reactions in which the phosphoramidate configuration is governed by a chiral catalyst. In contrast to the use of phosphorus electrophiles, we reasoned that phosphoramidic acids might add as nucleophiles to a halogen-activated alkene. The halogen, in turn, could be activated by a hydrogen bond catalyst.⁶ This design raised the interesting challenge of not only controlling diastereotopic oxygen–carbon bond formation but also using a chiral Brønsted acid reagent as the master stereocontrol element since phosphoric acids and their derivatives are effective catalysts.⁷ We reasoned that the use of a polar ionic hydrogen-bond catalyst might offer the ion pairing necessary to achieve reagent-controlled stereoselection, and ultimately an innovative entry to P-chiral small molecules (Figure 1). Phosphoramidic acids have Brønsted acidic (O–H) and Brønsted basic (O) sites which offer potential interactions with a bifunctional Brønsted acid/base catalyst.

Since 2010, enantioselective alkene functionalizations using an electrophilic halogen source by organocatalysis have

- electrophilic functionalization of alkenes by a halonium ion -

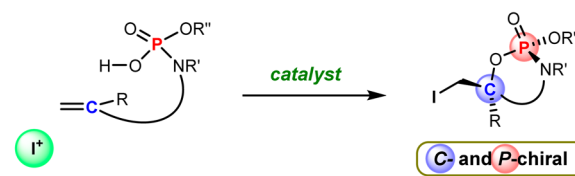


Figure 1. Addition of phosphoramidic acids to alkenes using an electrophilic halogen source for the construction of carbon and phosphorus chiral centers.

emerged as an attractive method in asymmetric synthesis.^{8–10} Considerable efforts have been devoted to this area, especially to the development of enantioselective halolactonizations.^{9c} We reported an enantioselective iodolactonization catalyzed by a chiral Brønsted acid, StilbPBAM·HNTf₂ (1·HNTf₂), which is composed of an uncharged chiral Brønsted base backbone with an achiral Brønsted acid.⁶ A variety of nucleophilic donors, e.g., carboxylic acids, amides, alcohols, and N-protected amines, have been employed for this class of reactions.^{9i,10} Organophosphorus acid derivatives are conspicuously absent from either chiral Brønsted acid or transition-metal-catalyzed alkene halo-oxygenation reactions, presumably due to the lower nucleophilicity of these acids relative to carboxylic acids.¹¹ Conversely, this character may be responsible for their extensive success in catalysis, engaging substrates only transiently and in a noncovalent manner.^{7,12} Herein, we report the chiral Brønsted acid catalyzed diastereo- and enantioselective iodocyclizations of phosphoramidic acid 3 for the synthesis of C- and P-chiral cyclic phosphoramidates 4.¹³ Two noncontiguous chiral centers are constructed during the formation of 4, with high levels of absolute and relative stereocontrol.

At the outset of these studies, a control experiment was performed using phosphoramidic acid 3aa, 1.5 equiv of N-iodosuccinimide (NIS), and molecular sieves (MS) 4A in toluene at –20 °C for 48 h (Table 1, entry 1). NIS cleanly afforded product 4aa in good yield (82%) but with low diastereoselection (2:1 dr). Insofar as the substrate is a Brønsted acid itself, capable of catalyzing the transformation,

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Table 1. Iodocyclization Catalyzed by a Chiral Brønsted Acid: Initial Study^a

entry	catalyst	yield ^b	dr ^c	ee ^d
1	none	82	2:1	—
2	1	86	>20:1	83
3	1 ·HNTf ₂	85	>20:1	96
4	1 ·(HNTf ₂) ₂	85	>20:1	94
5	1 ·(HNTf ₂) ₃	70	3:1	15
6	2	62	4:1	32
7	2 ·HNTf ₂	70	4:1	46
8	2 ·(HNTf ₂) ₂	76	3:1	10
9 ^e	1 ·HNTf ₂	33	7:1	45

^aUnless otherwise noted, all reactions were carried out at 0.10 mmol scale using 1 equiv of phosphoramidic acid **3aa**, 10 mol % catalyst, and 1.5 equiv of NIS in toluene (0.08 M) at $-20\text{ }^{\circ}\text{C}$ for 48 h. The relative and absolute configurations of **4aa** have been determined by X-ray crystal structure analysis of **4ad**; see Supporting Information for details. ^bIsolated yield of a mixture of diastereomers. ^cDetermined by ¹H NMR. ^dDetermined by HPLC with a chiral stationary phase for the major diastereomer. ^eI₂ was used instead of NIS.

a series of experiments directed at formation of a chiral proton complex with a Bis(AMidine) ligand was performed; use of the chiral free base alone could form a phosphoramidic acid salt, whereas a separate strong Brønsted acid might favor a distinct chiral proton complex. This was investigated by probing the effect of the protonation state of StilbPBAM (**1**) on selectivity. Brønsted base **1** catalyzed the iodocyclization efficiently, affording **4aa** in good yield with high diastereoselectivity and moderate enantioselectivity in spite of the background reaction proceeding under the same conditions (Table 1, entry 2). A higher level of enantioselection was observed with the preformed triflimidic acid complex (**1**·HNTf₂) (Table 1, entry 3), and interestingly, a 1:2 mixture of free base (**1**) and HNTf₂ gave the product in 94% ee (Table 1, entry 4). However, a 1:3 ratio of the **1**/HNTf₂ decreased the diastereo- and enantioselectivity (Table 1, entry 5) and illustrated the potential to inhibit the reaction relative to the catalyst-free case (Table 1, entry 1). In order to probe the importance of the bifunctional chiral acid's basicity,¹⁴ we employed chiral base **2**, having no pyrrolidine substituents, in an otherwise identical reaction. The reaction of **2** led to a considerable reduction in the stereoselectivity (Table 1, entry 6). In addition, both **2**·HNTf₂ and **2**·(HNTf₂)₂ gave lower levels of diastereo- and enantioselection than those of **1** (Table 1, entries 7 and 8). These results indicate that the pyrrolidine unit is critical to achieve high levels of selectivity. Furthermore, iodine (I₂) was tested as another halogen source, but both the chemical yield

Table 2. Substrate Scope of the Chiral Brønsted Acid Catalyzed Diastereo- and Enantioselective Iodocyclization^a

entry	3	R ¹ , R ²	yield ^b	dr ^c	ee ^d
1	ab	4-MeOC ₆ H ₄ , H	83	18:1	94
2	ac	3-MeOC ₆ H ₄ , H	71	18:1	93
3	ad	4-ClC ₆ H ₄ , H	74	>20:1	97
4	ae	2-FC ₆ H ₄ , H	80	>20:1	96
5	af	Cy, H	95	>20:1	95
6	ag	3-butenyl, H	92	>20:1	98
7	ah	Me, H	91	8:1	91
8	ai	H, H	69	1:1	68/75 ^e
9	aj	Me, Me	92 ^f	6:1	93
10	ba	Ph, H	85	>20:1	93

^aUnless otherwise noted, all reactions were carried out at 0.10–0.20 mmol scale using 1 equiv of the phosphoramidic acid, 10 mol % of **1**·HNTf₂, and 1.5 equiv of NIS in toluene (0.08 M) at $-20\text{ }^{\circ}\text{C}$ for 48 h.

^bIsolated yield of a mixture of diastereomers. ^cDetermined by ¹H NMR and/or HPLC. ^dDetermined by HPLC with a chiral stationary phase for the major diastereomers. ^eEe for each diastereomer. ^fCombined yield of 5-*exo* and 6-*endo* product.

and stereoselectivity of **4aa** dramatically dropped (Table 1, entry 9).¹⁵

The initial scope is summarized in Table 2. The investigation of substituents on the aromatic ring showed that both electron-donating groups¹⁶ and electron-withdrawing groups were tolerated to give the products in good yields with high levels of stereoselection (Table 2, entries 1–4). Secondary and primary alkyl groups also underwent the iodocyclization well, while lower diastereoselectivity (8:1 dr) was observed in the case of a sterically less hindered methyl group (Table 2, entries 5–7). Allylamine derivative **3ai** was most challenging (Table 2, entry 8), and although the enantioselectivity for this case was promising at the 68/75% ee level, the transformation was not diastereoselective; overall, a substituent at the internal position of the alkene appears essential for relative stereocontrol. To expand the substrate scope and further challenge the catalyst, a trisubstituted alkene was examined. The reaction of **4aj** having a dimethyl *cis*-substituted alkene afforded only two diastereomers with 6:1 dr and 93% ee, the same level of enantioselection as that for disubstituted alkenes (Table 2, entry 9). It should be noted that a trace amount of 6-*endo*-cyclized product was observed in the reaction using trisubstituted alkene **3aj**. Phosphoramidic acid **3ba**, bearing an *N*-4-methoxybenzyl (PMB) group, behaves similarly to **3aa** (cf. Table 2, entry 10 and Table 1, entry 3). The relative and absolute configurations of phosphoramidate **4ad** (R¹ = 4-ClC₆H₄, R² = H; Table 2, entry 3) was determined by X-ray crystallographic analysis (Figure 2). Intriguingly, a methoxy group on the phosphorus (P2) and a phenyl group on the quaternary carbon (C5) are located in the pseudo axial position of cyclic phosphoramidate **4ad**.

The regioisomer and minor diastereomer could be removed by column chromatography, and as a result, **4aj** was obtained in 63% yield (over 2 steps, from dimethyl phosphoramidate **5**) with 92% ee (Scheme 1). Taking into account the electrophilic

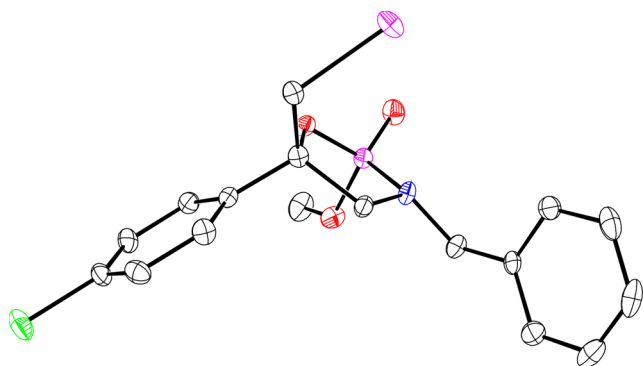
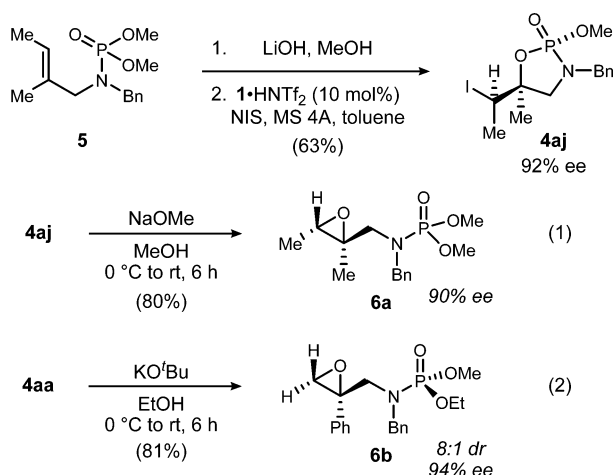


Figure 2. ORTEP drawing of cyclic phosphoramidate (2*R*,5*S*)-4ad.

Scheme 1. Formal Asymmetric Epoxidation of Allylamine Derivatives via the Chiral Brønsted Acid Catalyzed Diastereo- and Enantioselective Iodocyclization Sequence



feature of cyclic organophosphorous compounds,^{11a} iodophosphoramidate **4aj** was treated with sodium methoxide to afford the corresponding *cis*-dimethyl-epoxide **6a**. The present method could be regarded as a formal asymmetric epoxidation of allylamine derivatives, where only one example of an enantioselective epoxidation of allylamine derivatives has been reported.¹⁷ The protocol is also applicable to the synthesis of *gem*-disubstituted epoxy allylamines. Although partial epimerization at the *P*-chiral center was observed, cyclic phosphoramidate **4aa** (>20:1 dr, 96% ee) was converted to enantioenriched epoxide **6b**¹⁸ as an acyclic chiral phosphoramidate in good yield with high enantioselectivity.^{1c,d,3b}

In conclusion, the functionalization of unactivated alkenes with the use of NIS and phosphoramidic acids has been developed, leading to cyclic phosphoramidates in which both carbon and phosphorus configurations are forged with a high degree of absolute stereocontrol. Importantly, the present reaction enables a catalytic formation of *P*-chiral phosphoramidates using a tactic that could be applied more broadly to organophosphorous compounds. While stereodefined phosphoramidates are valuable in their own right, their treatment with a base leads to an epoxide and, vis-a-vis, epoxy allylamines in high enantiomeric excess. Noteworthy is the use of a (chiral) polar ionic bond to promote the enantioselective cyclization involving a polar covalent hydrogen bond. Efforts to identify new synergistic transformations using these two types of hydrogen bonds will be reported in due course.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures and spectroscopic data for all new compounds, and X-ray data (cif) for **4ad**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Eto, M. *Organophosphorous Pesticides: Organic and Biological Chemistry*; CRC: Cleveland, OH, 1974. (b) Fest, C.; Schmidt, K. J. *The Chemistry of Organophosphorous Pesticides*; Springer: Berlin, Heidelberg, NY, 1982. (c) Mehellou, Y.; Balzarini, J.; McGuigan, C. *ChemMedChem* **2009**, *4*, 1779–1791. (d) Sofia, M. J.; Chang, W.; Furman, P. A.; Mosley, R. T.; Ross, B. S. *J. Med. Chem.* **2012**, *55*, 2481–2531. (e) Molt, O.; Schrader, T. *Synthesis* **2002**, 2633–2670.
- (2) (a) Lin, K.; Zhou, S.; Xu, C.; Liu, W. *J. Agric. Food Chem.* **2006**, *54*, 8134–8138. (b) Wang, C.; Zhang, N.; Li, L.; Zhang, Q.; Zhao, M.; Liu, W. *Chirality* **2010**, *22*, 612–617.
- (3) (a) Morales, E. H. R.; Balzarini, J.; Meier, C. *Chem.—Eur. J.* **2011**, *17*, 1649–1659. (b) Román, C. A.; Wasserthal, P.; Balzarini, J.; Meier, C. *Eur. J. Org. Chem.* **2011**, 4899–4909. Related work, see: (c) Wu, S.-Y.; Hirashima, A.; Eto, M.; Yanagi, K.; Nishioka, E.; Moriguchi, K. *Agric. Biol. Chem.* **1989**, *53*, 157–163.
- (4) For selected reviews on *P*-stereogenic compounds, see: (a) Wozniak, L. A.; Okruszek, A. *Chem. Soc. Rev.* **2003**, *32*, 158–169. (b) Glueck, D. S. *Synlett* **2007**, 2627–2634. (c) Grabulosa, A.; Granel, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25–90. (d) Harvey, J. S.; Gouverneur, V. *Chem. Commun.* **2010**, *46*, 7477–7485. (e) Kolodiazny, O. I. *Tetrahedron: Asymmetry* **2012**, *23*, 1–46.
- (5) Recent reports: (a) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. J.; Wang, G.; Senanayake, C. H. *J. Am. Chem. Soc.* **2013**, *135*, 2474–2477. (b) Ding, B.; Zhang, Z.; Xu, Y.; Liu, Y.; Sugiya, M.; Imamoto, T.; Zhang, W. *Org. Lett.* **2013**, *15*, 5476–5479. (c) Nikitin, K.; Rajendran, K. V.; Müller-Bunz, H.; Gilheany, D. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1906–1909. (d) Huang, Y.; Li, Y.; Leung, P.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2014**, *136*, 4865–4868.
- (6) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068–6071.
- (7) For seminal studies on phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Uruguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. For selected reviews, see: (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (d) Terada, M. *Synthesis* **2010**, 1929–1982. (e) Rueping, M.; Kuenkel, A.; Atodiressei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539–4549. See also: (f) Vellalath, S.; Čorić, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749–9752. (g) Čorić, I.; List, B. *Nature* **2012**, *483*, 315–319.
- (8) Selected reports: (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300. (b) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665. (c) Cai, Y.; Liu, X.; Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160–6164. (d) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung,

Y.-Y. J. *Am. Chem. Soc.* **2010**, *132*, 15474–15476. (e) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332–7335. (f) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174–9177. (g) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128–11131. See also: (h) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874–2876.

(9) For reviews, see: (a) Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306–8308. (b) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**, 1335–1339. (c) Castellanos, A.; Fletcher, S. P. *Chem.—Eur. J.* **2011**, *17*, 5766–5776. (d) Hennecke, U. *Chem.—Asian J.* **2012**, *7*, 456–465. (e) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938–10953. (f) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, 49, 7985–7996. (g) Murai, H.; Fujioka, H. *Heterocycles* **2013**, *87*, 763–805. (h) Nolsøe, J. M. J.; Hansen, T. V. *Eur. J. Org. Chem.* **2014**, 3051–3065. (i) Tripathi, C. B.; Mukherjee, S. *Synlett* **2014**, 25, 163–169.

(10) (a) Zhang, Y.; Xing, H.; Xie, W.; Wan, X.; Lai, Y.; Ma, D. *Adv. Synth. Catal.* **2013**, *355*, 68–72. (b) Brindle, C. S.; Yeung, C. S.; Jacobsen, E. N. *Chem. Sci.* **2013**, *4*, 2100–2104. (c) Tripathi, C. B.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8450–8453. For other alkene halogenations, see: (d) Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251–1255. (e) Chen, Z.-M.; Zhang, Q.-W.; Chen, Z.-H.; Li, H.; Tu, Y.-Q.; Zhang, F.-M.; Tian, J.-M. *J. Am. Chem. Soc.* **2011**, *133*, 8818–8821. (f) Li, H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Q.-W.; Chen, Z.-M.; Chen, Z.-H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839–1841.

(11) For selected examples of the synthesis of racemic cyclic organophosphorus compounds via iodocyclization, see: (a) Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829–4830. (b) Zhao, Y.-F.; Yan, S.-J.; Zhai, C. *J. Org. Chem.* **1985**, *50*, 2136–2140. (c) Ye, M.-C.; Chai, W.-G.; Li, L.-P.; Zhao, Y.-F. *Tetrahedron Lett.* **1987**, *28*, 2615–2618. (d) Yokomatsu, T.; Shioya, Y.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1997**, *46*, 463–472. (e) André, V.; Lahrache, H.; Robin, S.; Rousseau, G. *Tetrahedron* **2007**, *63*, 10059–10066. See also: (f) Hatano, M.; Horibe, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4549–4553.

(12) For asymmetric additions of a dithiophosphoric acid, see: Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245–249.

(13) Kumar, A.; Coe, P. L.; Jones, A. S.; Walker, R. T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1990**, *33*, 2368–2375.

(14) Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880–2882.

(15) NBS afforded the corresponding product in good yield and with modest enantioselection. It is significant that these reactions provided moderate diastereo- and enantioselectivity, even with a different halogen donor. To-date, a single system is equally effective with two types of halogen sources; see: Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928–12931.

(16) Product **4ab** ($R^1 = 4\text{-MeOC}_6\text{H}_4$, $R^2 = \text{H}$) racemizes at room temperature (1:1 dr, 45% ee after 3 days). The enantioenriched product could be obtained by a quick workup after the reaction; see Supporting Information for details.

(17) Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 5440–5443.

(18) The *P*-stereochemistry of **6b** is postulated by an inversion mechanism, in accord with prior studies (see ref 4a and 4c).