Organic LETTERS

Letter

pubs.acs.org/OrgLett

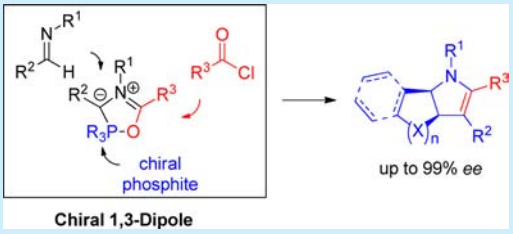
Chiral Phosphorus-Based 1,3-Dipoles: A Modular Approach to Enantioselective 1,3-Dipolar Cycloaddition and Polycyclic 2-Pyrroline Synthesis

Marie S. T. Morin and Bruce A. Arndtsen*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montréal, QC, H3A 0B8, Canada

Supporting Information

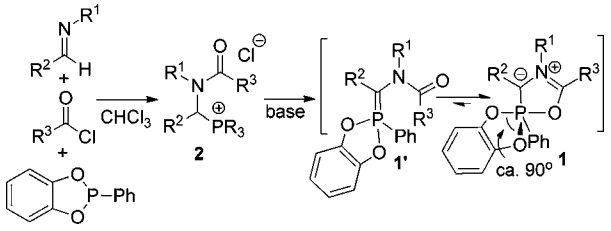
ABSTRACT: The design of a new class of chiral 1,3-dipoles for enantioselective cycloaddition reactions is reported. These phosphorus-based dipoles are easily formed (from imines, acid chlorides, and chiral phosphites), rigidly chiral, and undergo intramolecular alkene cycloaddition with high enantioselectivity. Overall, this provides a straightforward and modular approach to synthesize chiral 2-pyrrolines and pyrrolidines in up to 99% ee.



Enantioselective 1,3-dipolar cycloaddition reactions provide an efficient method to construct chiral heterocycles. A challenge with a number of 1,3-dipoles, however, is the design of reliable methods to control enantioselectivity. An example is the cycloaddition of 1,3-oxazolium 5-oxides (i.e., münchnones) with alkenes. This transformation was first reported by Huisgen in 1964[1] and has since been employed in the synthesis of numerous pyrrolines and the fully reduced pyrrolidines,[2] motifs found in a wide range of natural products,[3] pharmaceutical cores,[4] and related biologically relevant compounds.[5] Despite the utility of these products, a challenge with münchnones is the design of reliable methods to control enantioselectivity. Only a few examples of asymmetric 1,3-dipolar cycloaddition reactions with münchnones have been reported, and most with only moderate enantioselectivity. These use either chiral substituents or catalysts.[6,7] Chiral substituents, while reliable, often require multiple synthetic steps to introduce and then remove and have not been shown to lead to high enantioselectivity with münchnones, presumably due to their positioning at remote sites.[6] Alternatively, chiral gold catalysts have been found by Toste and others to mediate enantioselective cycloadditions with certain presynthesized *N*-unsubstituted münchnones to form 1-pyrrolines.[7] In general, however, a route to asymmetric alkene 1,3-dipolar cycloaddition with münchnone derivatives with broad generality, high selectivity, and synthetic accessibility, especially with highly substituted dipoles, has remained elusive.

We have recently reported a new 1,3-dipole **1** that suggests an alternative to these methods (Scheme 1).[8] The phosphorus-containing **1** can be generated in one step from imines, acid chlorides, and phosphonites and undergoes dipolar cycloaddition with alkynes, or intramolecular cycloaddition with alkenes,[9] in analogy to münchnones. In addition to its modularity, the presence of a phosphine in **1**, rather than the planar carbonyl in münchnones, offers another potential: enantioselectivity. Chiral phosphorus reagents are readily

Scheme 1. Multicomponent Generation of 1,3-Dipole 1



available, and their incorporation into **1** would generate a 1,3-dipole that is (i) chiral, (ii) modular, and (iii) easily prepared (Figure 1). In addition, the chiral unit would require no

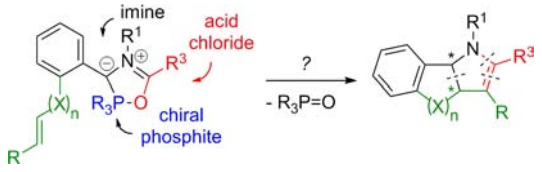


Figure 1. Modular and chiral 1,3-dipole for enantioselective cycloaddition.

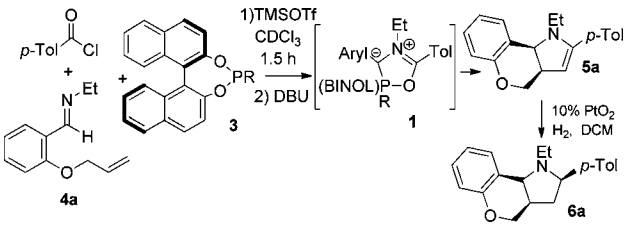
additional steps to introduce or remove yet is rigidly associated into **1**, suggesting relatively simple chiral units may lead to high selectivity. We describe our efforts toward the design of these chiral 1,3-dipoles below. This has resulted in a straightforward new approach to perform asymmetric 1,3-dipolar cycloaddition reactions and construct 2-pyrrolines in a modular fashion in up to 99% enantioselectivity.

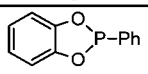
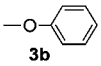
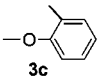
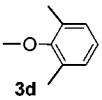
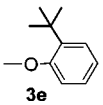
Catechol-based phosphonites of the form PhP(2-catechyl) have been shown to be effective in generating the phosphorus

Received: December 8, 2013
Published: February 6, 2014

dx.doi.org/10.1021/ol4035512 | *Org. Lett.* 2014, 16, 1056–1059

Table 1. Chiral Phosphites in Enantioselective 1,3-Dipolar Cycloaddition[a]



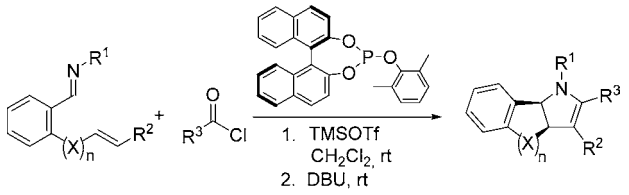
entry	3	temp	time	yield 5a[b]	ee[c] (O.R.)
1		rt	10 min	85%	/
2	R=  3a	70 °C	11 h	67%	60% (-)
3	R= $-OCH_2CF_3$	rt	4 h	<10%	-
4	R=  3b	rt	8 h	89%	86% (-)
5	R=  3c	rt	24 h	89%	2% (+)
6	R=  3d	rt	30 h	84% (80%)[d]	97% (+)
7	R=  3e	rt	30 h	82%	98% (+)

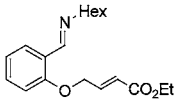
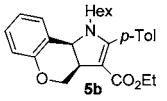
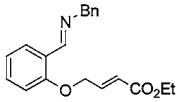
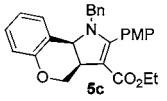
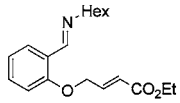
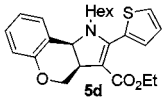
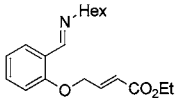
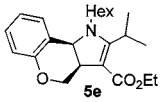
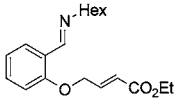
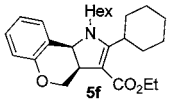
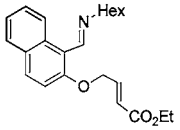
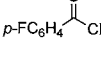
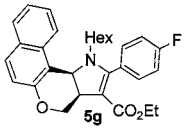
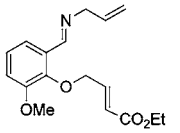
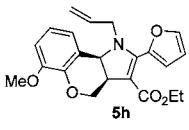
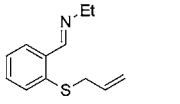
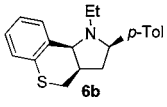
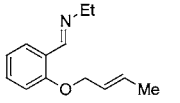
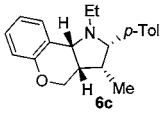
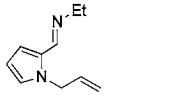
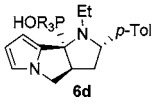
[a]**4a** (38 mg, 0.2 mmol), *p*-toluoyl chloride (34 mg, 0.22 mmol), 0.5 mL of $CDCl_3$, 30 min; PR_3 (0.22 mmol), TMSOTf (46.7 mg, 0.21 mmol), 90 min; DBU (76 mg, 0.5 mmol). [b]NMR yield. [c]**5a** reduced to **6a** for HPLC analysis. O.R. = optical rotation. [d]Isolated yield of **6a**.

dipole **1**.[8] These phosphonites provide a useful balance of nucleophilicity to generate **2** (Scheme 1) while retaining the phosphorus electrophilicity required to favor cyclization of the amide-substituted Wittig ylide **1′** to its dipole form. We postulated that BINOL-based phosphonites might provide a similar electronic balance. The (*R*)-BINOL-derived phosphonite **3a** (Table 1) can be prepared by reaction of $PhPCl_2$ with the commercially available diol.[10] As shown in Table 1, **3a** can be incorporated in the phospha-münchnone structure by reaction with imine **4a**, *p*-toluoyl chloride, and base and mediates cycloaddition in a similar fashion to PhP(2-catechyl), although it requires heating to 70 °C (entry 2).[11,12] Pyrroline **5a** partially decomposes on chromatography, but HPLC analysis of the more stable pyrrolidine **6a**, generated by hydrogenation of **5a** on PtO_2, shows this product is formed in 60% ee.

In considering methods to increase selectivity, we noted the elevated temperature needed to induce cycloaddition with **3a**, which contrasts with the rapid reaction with PhP(2-catechyl). The lower reactivity with **3a** presumably results from the loss of angle strain in BINOL and disfavored cyclization of **1′** to generate the trigonal bipyramidal 1,3-dipole (with a ca. 90° O–P–O bond angle).[8c,13,14] To help favor amide chelation, we turned to more electron-poor phosphites. Alkyl-substituted phosphites are not reactive (entry 3), but aryl phosphite **3b** allows the formation of pyrroline **5a** at now ambient temperature and in significantly improved 86% ee (entry 4). As substituted phenols are readily available, it was easy to further tune the phosphite without resorting to synthetic BINOL derivatives (entries 4–7). Interestingly, the *o*-tolyl-substituted **3c** led to a complete loss in selectivity (vide infra). However, further increasing steric bulk with **3d** or **3e** resulted in a dramatic enhancement of enantioselectivity, forming **5a** in 98% ee.

Table 2. Generality of Enantioselective Cycloaddition[a]



entry	imine	acid chloride	product	yield (%)	ee (%)
1			 5b	77	95
2			 5c	85	95
3[b]			 5d	73	96
4			 5e	64	87
5[b,c]			 5f	85	87
6[c,d]			 5g	61	99
7[c]			 5h	83	97
8[e]			 6b	71	90
9[f,g]			 6c	65	-89
10[g]			 6d	83[h]	>95

[a]Table 1, entry 6, conditions. [b]With **3e**. [c]12 h before DBU added. [d]1.5 d cycloaddition. [e]5 d, 45 °C; H_2, 10% PtO_2, DCM, 18 h. [f]With **3b**, AgOTf instead of TMSOTf, 2 h; LiHMDS as base at −78 °C; 2 d, 50 °C. [g]3 d. [h]$NaBH(OAc)_3$, 1 M HCl/ether reduction.

Since the 1,3-dipoles are formed in a modular fashion, in addition to generating pyrroline **5a**, this can provide a general approach to enantioselective polycyclic 2-pyrroline synthesis. Examples of these are shown in Table 2. A range of aryl-, functionalized aryl-, heteroaryl-, and alkyl-substituted acid

dx.doi.org/10.1021/ol4035512 | Org. Lett. 2014, 16, 1056–1059

chlorides can be used in this reaction (entries 1−7). Despite their varying steric profile, these each undergo cycloaddition to yield pyrrolines with high enantioselectivity (up to 99% ee). The ester substituted pyrrolines **5b−h** are more stable than **5a** and can be isolated and analyzed in their unreduced form. Both terminal and internal alkenes can be employed as dipolarophiles, including internal unactivated alkenes (entry 9), which upon heating with the less sterically encumbered phosphite **3b**, lead to product in 89% ee. Similar to that observed in Table 1, this pyrroline was generated as the opposite enantiomer to those from the more bulky **3d** (vide infra).[15] A number of aromatic and even heteroaromatic spacers are also viable (entries 6, 7, and 10), as are 5,5-fused ring products (entry 10). In this latter case, the phosphite unit does not eliminate upon cycloaddition, potentially due to the greater ring strain in this product. This generates the quaternary product **6d** with high enantioselectivity.

In addition to generating 2-pyrrolines, this cycloaddition reaction can be coupled with in situ reduction. As shown in entries 8−10, this allows the build-up of polycyclic pyrrolidines in one pot with control of three or four different stereogenic centers and as a single observable diastereomer.[16]

In general, despite the varying nature of the alkene, imine, and acid chloride units, all of the cycloadditions attempted with this system proceed with high enantioselectivity. This selectivity is presumably related to the rigid chiral environment created by BINOL in **1**. However, the phosphine screening in Table 1 clearly showed that the achiral phosphorus substituent also has a significant effect on the reaction (e.g., entries 4−6). To probe the origin of these influences, we prepared the model dipole **1d**, which lacks the tethered alkene for cycloaddition. The results of X-ray crystallographic are shown in Figure 2. The phosphorus

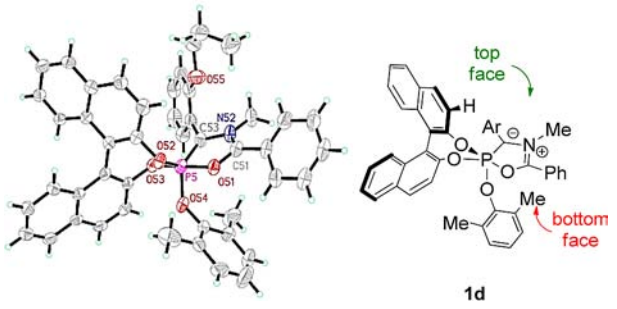
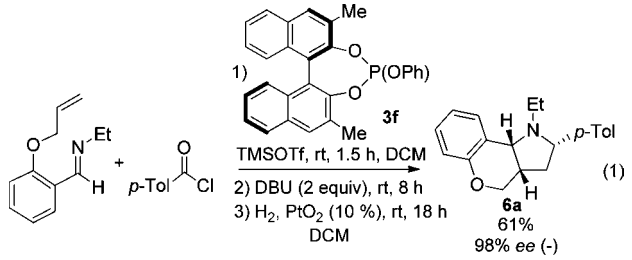


Figure 2. X-ray crystal structure of **1d** (ORTEP view). Ar = 2-$C_6H_4(OCH_2CH_2CH_3)$. The asymmetric unit contains two molecules which differ by the structural arrangement of the *O*-propyl chain (see the Supporting Information). Selected bond lengths (Å) and angles (deg): P(5)−O(51), 1.800(3); P(5)−O(52), 1.646(3); P(5)−O(53), 1.667(3); P(5)−O(54), 1.621(4); P(5)−C(53), 1.702(5); O(51)−C(51), 1.313(6); C(51)−N(52), 1,303(6); N(52)−C(53), 1.426(6); O(54)−P(5)−O(53), 90.92(16); O(52)−P(5)−O(53), 94.00(16); O(54)−P(5)−C(53), 128.1(2); O(52)−P(5)−C(53), 128.7(2); O(53)−P(5)−O(51), 179.24(18); C(53)−P(5)−O(51), 86.48(19).

in **1d** adopts a trigonal bipyramidal geometry, with the (*R*)-BINOL unit in an axial−equatorial orientation (O(52)−P(5)−O(53) = 94.00(16)°) and the amide oxygen in the other axial site.[8c] The phosphorus in **1d** is itself a stereogenic center. Thus, the major stereochemical influence of the chiral BINOL appears to be to form **1d** as a single diastereomer, with the biphenyl on the axial oxygen directed away from the aryl on C(53) [O(53)−P(5)−C(53), 92.86(19)°]. In this configuration, the large 2,6-dimethylphenol effectively blocks the bottom approach to the dipole and would be expected to result in cycloaddition syn to the BINOL unit, regardless of the alkene or dipole substituents. This is supported by X-ray structural analysis of the pyrrolidine product **6a**, which shows it to be formed as the (*R,R,S*)-enantiomer (see the Supporting Information for the structure).

The model in Figure 2 suggests that minimizing the steric profile of the phenol should favor the opposite pyrroline enantiomer. This is borne out in the screening Table 1: simple phenol-derived **3b** provides pyrroline with good enantioselectivity (entry 3) but as the opposite enantiomer to that with larger phenols (−86% ee).[17] 2-Methylphenol appears to balance these factors and leads to **5a** in nearly racemic form. These data imply that increasing the steric profile of the BINOL unit should further favor the other enantiomer of **5a**. Indeed, as illustrated in eq 1, the (*R*)-3,3′-dimethyl-BINOL-



derived **3f** leads to **6a** with high enantioselectivity, yet as the (*S,S,R*)-enantiomer. This enantiomer change is obtained without modifying the chirality of the BINOL unit. These features in **1** create a highly controllable (and predictable) chiral environment for 1,3-dipolar cycloaddition reactions.

In conclusion, we have reported a new class of chiral 1,3-dipole. The phosphorus-based **1** offers several features: it is easily generated in a multicomponent fashion, has chirality rigidly incorporated into the backbone for high enantioselectivity, and employs an available chiral unit (BINOL) that is liberated from the product upon cycloaddition. As far as we are aware, this represents a new way of performing enantioselective cycloadditions to form chiral 2-pyrrolines in a general fashion. Experiments directed toward the application of this method to create other chiral heterocycles are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*bruce.arndtsen@mcgill.ca

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSERC, CFI, and the FQRNT supported Centre for Green Chemistry and Catalysis for their financial support and Françine Bélanger and Michel Simard (Universite de Montreal) for X-ray structure analyses.

REFERENCES

(1) Gotthardt, H.; Huisgen, R.; Schaefer, F. C. *Tetrahedron Lett.* **1964**, *5*, 487.

(2) (a) Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1970**, *103*, 2625. (b) Maryanoff, C. A.; Karash, C. B.; Turchi, I. J.; Corey, E. R.; Maryanoff, B. E. *J. Org. Chem.* **1989**, *54*, 3790. (c) Bélanger, G.; April, M.; Dauphin, É.; Roy, S. *J. Org. Chem.* **2007**, *72*, 1104. (d) Myers, J. A.; Wilkerson, W. W.; Council, S. L. *J. Org. Chem.* **1975**, *40*, 2875. (e) Padwa, A.; Gingrich, H. L.; Lim, R. J. *Org. Chem.* **1982**, *47*, 2447. For reviews, see: (f) Gribble, G. W. In *The Chemistry of Heterocyclic Compounds: Oxazole: Synthesis, Reactivity and Spectroscopy*; Palmer, D., Ed.; Wiley: New York, 2003; Vol. *60*, p 473. (g) Gingrich, H. L.; Baum, J. S. *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; p 731.

(3) For examples, see: (a) Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (c) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581. (d) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (e) Vanhoof, G.; Goossens, F.; De Meester, I.; Hendriks, D.; Scharpé, S. *FASEB* **1995**, *9*, 736.

(4) For examples, see: (a) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1. (b) Cushman, D. W.; Ondetti, M. A. *Nat. Med.* **1999**, *5*, 1110. (c) Cocito, C. *Microbiol. Rev.* **1979**, 145.

(5) (a) Maclean, D.; Schullek, J. R.; Murphy, M. M.; Ni, Z.-J.; Gordon, E. M.; Gallop, M. A. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2805. (b) Efimov, V.; Aralov, A.; Chakhmakhcheva, O. *Russ. J. Bioorg. Chem.* **2010**, *36*, 663. (c) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Baker, A.; Earnshaw, D. L.; Hofmann, G. A.; Keenan, R. M.; Dhanak, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1553. (d) Borthwick, A. D. *Med. Res. Rev.* **2005**, *25*, 427.

(6) (a) Pinho e Melo, T. M. V. D.; Gomes, C. S. B.; Rocha Gonsalves, A. M. d. A.; Paixão, J. A.; Beja, A. M.; Ramos Silva, M.; Alte da Veiga, L. *Tetrahedron* **2002**, *58*, 5093. (b) Arévalo, M. a. J.; Avalos, M. n.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron: Asymmetry* **2002**, *13*, 223. (c) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2001**, *66*, 5139. (d) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Dianez, M. J.; Estrada, M. D.; Jimenez, J. L.; Lopez-Castro, A.; Palacios, J. C.; Garrido, S. P. *J. Chem. Soc., Chem. Commun.* **1995**, 2213.

(7) (a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638. (b) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 3517. (c) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M. *Synlett* **2012**, *2012*, 62.

(8) (a) St. Cyr, D. J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366. (b) Krenske, E. H.; Houk, K. N.; Arndtsen, B. A.; St. Cyr, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10052. (c) St-Cyr, D. J.; Morin, M. S. T.; Bélanger-Gariépy, F.; Arndtsen, B. A.; Krenske, E. H.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 4261. (d) Morin, M. S. T.; St-Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2010**, *12*, 4916. (e) Lu, Y.; Arndtsen, B. A. *Org. Lett.* **2009**, *11*, 1369. (f) Morin, M. S. T.; St-Cyr, D. J.; Arndtsen, B. A.; Krenske, E. H.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 17349.

(9) Morin, M. S. T.; Aly, S.; Arndtsen, B. A. *Chem. Commun.* **2013**, *49*, 883.

(10) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333.

(11) Attempts to employ **1** in intermolecular alkene cycloadditon led to mixtures pyrroline and bicyclic products via double-alkene addition.

(12) TMSOTf forms a more reactive *N*-acyliminium salt^{+} OTf^{-} salt for the addition of the less nucleophilic BINOL-substituted **3** to form **2**.

(13) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

(14) In situ ^{31}P NMR analysis is consistent with this analysis, showing a downfield ^{31}P NMR resonance (+76.0 ppm) in the region of a Wittig-type **1a**′ rather than a 5-coordinate phosphorus (+10 to −90 ppm). Tebby, J. C. *Handbook of Phosphorus-31 NMR Data*; CRC Press: Boston, 1991.

(15) A stronger base (LiHMDS) and triflating agent (AgOTf) were also used to facilitate the formation of **1**. These reagents were tested in the reaction of Table 1 and do not influence enantioselectivity.

(16) The reaction in Table 2, entry 1, can also be scaled to at least 0.5 mmol with no appreciable loss in yield.

(17) The small phenol may also favor the generation of the opposite diastereomer of the dipole **1b**. We at present cannot distinguish between these possibilities and thank the reviewer for this suggestion.

dx.doi.org/10.1021/ol4035512 | *Org. Lett.* 2014, 16, 1056−1059