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Hydroxyproline-Derived Pseudoenantiomeric [2.2.1] Bicyclic Phosphines: Asymmetric Synthesis of (+)- and (−)-Pyrrolines

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Supporting Information

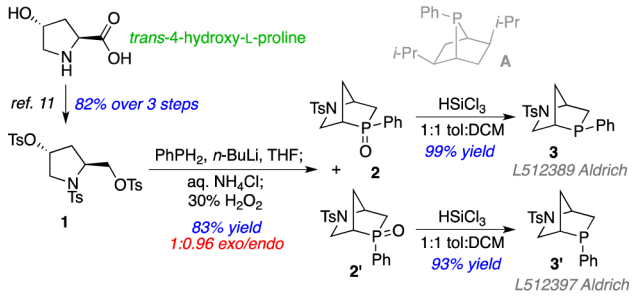
ABSTRACT: We have prepared two new diastereoisomeric 2-aza-5-phosphabicyclo[2.2.1]heptanes from naturally occurring *trans*-4-hydroxy-L-proline in six chemical operations. These syntheses are concise and highly efficient, with straightforward purification. When we used these chiral phosphines as catalysts for reactions of γ-substituted allenoates with imines, we obtained enantiomerically enriched pyrrolines in good yields with excellent enantioselectivities. These two diastereoisomeric phosphines functioned as pseudoenantiomers, providing their chiral pyrrolines with opposite absolute configurations.

Over the past two decades, many novel phosphine-catalyzed ring-forming reactions have been developed in laboratories worldwide.[1] Among them, Lu's [3 + 2] annulations between allenes and alkenes to form cyclopentenes were the first examples of phosphine-catalyzed annulations employing allenes.[2] Shortly after that initial report had appeared, this approach was extended to the syntheses of pyrrolines by conjoining allenes with *N*-sulfonyl imines.[3] The versatility and utility of Lu's strategy have been widely recognized, with subsequent years witnessing the invention of many synthetically valuable phosphine-catalyzed reactions of allenes with various coupling partners to afford a host of small-ring compounds. Not surprisingly, there has been great interest in the development of efficient enantioselective variants of these reactions using chiral phosphine catalysts. Indeed, many successful examples of the syntheses of chiral cyclopentenes have been reported.[4]

Despite the substantial efforts of several research groups, however, efficient asymmetric variants of Lu's pyrroline synthesis remain scarce.[5] Specifically, there exist only two reports—one by Jacobsen and the other by Lu—of asymmetric phosphine-catalyzed syntheses of pyrrolines with ee's of >90%.[6] These two examples are, however, limited in substrate scope. They both employ simple 2,3-butadienoates and *N*-diphenylphosphinoylimines and produce 1,2,3-substituted-2,5-dihydropyrroles. The pyrroline motif available through the allene−imine [3 + 2] annulation is present in many bioactive natural products and intermediates in pharmaceutical synthesis.[7] Some 1,2,3,5-substituted pyrroline derivatives are inhibitors of geranylgeranyltransferase type I (GGTase-I),[8] and others appear in natural products.[9] Therefore, the development of efficient catalytic asymmetric syntheses of these compounds has become a priority. Here, we disclose the design and synthesis of a new class of rigid [2.2.1] bicyclic chiral phosphines and their application as catalysts in highly enantioselective syntheses of 1,2,3,5-substituted pyrrolines.

Another common feature in the two reported enantioselective syntheses of pyrrolines is the use of chiral phosphines containing hydrogen-bond donors.[6] Intrigued by the lack of simple chiral phosphine catalysts that facilitate allene−imine [3 + 2] annulations efficiently, we turned our attention to Zhang's chiral phosphine **A** that was used in the first enantioselective annulation of allenes (Scheme 1).[4a] The key structural feature of the chiral

Scheme 1. Synthesis of the Phosphines 3 and 3′



catalyst **A** is its rigid [2.2.1] bicyclic framework, which eliminates the conformational flexibility associated with other cyclic chiral phosphines (e.g., Duphos, BPE ligands). The reported synthesis of **A**, however, involves eight steps starting from 1,4-diisopropylbenzene, including asymmetric hydroboration using (+)-IpcBH$_2$.[10] Our criteria for catalyst design included a rigid bridged bicyclic framework, a good source of chirality, and convenient methods for synthesis and modification. We realized our objective by employing commercially available *trans*-4-hydroxy-L-proline (Scheme 1).

Following the procedure developed by chemists at Pfizer for the synthesis of danofloxacin, we prepared the tritosylated hydroxyprolinol **1** in 82% overall yield over three steps.[11] Bisalkylation of dilithium phenylphosphide with **1** afforded a 1:0.96 mixture of the exo- and endo-*P*-phenylphosphines **3** (δ_P = −17.5 ppm) and **3′** (δ_P = −16.5 ppm), respectively. Instead of applying borane complexation[12] or tetrafluoroboric acid treatment[13] to the phosphines **3**/**3′**, for purification we opted for an oxidative workup to isolate the corresponding phosphine oxides

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2/**2**′. The H_2O_2-mediated oxidation of the crude alkylation mixture afforded the phosphine oxides **2** (δ_P = +49.3 ppm) and **2**′ (δ_P = +50.5 ppm) in 83% isolated yield, as separable compounds, for the one-pot, two-step sequence.[14] Trichlorosilane reduced the phosphine oxides **2** and **2**′ with retention of stereochemistry to afford the tertiary phosphines **3** and **3**′ in 99 and 93% yields, respectively. As white powders, these free phosphines were sufficiently air-stable to be transferred without elaborate precautions against oxidation, and they were sufficiently pure to be used without further purification. In total, the six-step route (including the oxidation/reduction sequence as a protection/deprotection protocol) provided the phosphines **3** and **3**′ in overall yields >34 and 31%, respectively, from *trans*-4-hydroxy-L-proline.[15]

With the phosphine **3** in hand, we explored its use in enantioselective syntheses of pyrrolines. The initial reaction of ethyl allenoate **4a** with *N*-tosyl benzaldimine **5a** afforded the pyrroline **6a**′ in 91% yield with 53% ee (Table 1, entry 1). Several

Table 1. Enantioselective Allene−Imine [3 + 2] Annulations

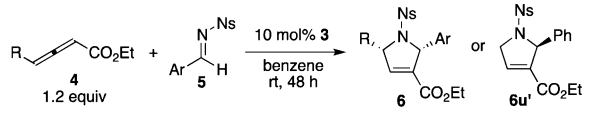
entry	4 (R)	5 (Ar)	yield (%)[a]	ee (%)[b]
1	**4a** (H)	**5a** (*p*-tolyl)	91 (**6a**′)	+53[c]
2	**4b** (Me)	**5a** (*p*-tolyl)	65 (**6b**)	−2
3	**4c** (Et)	**5a** (*p*-tolyl)	83 (**6c**)	−42
4	**4d** (*i*-Pr)	**5a** (*p*-tolyl)	75 (**6d**)	−56
5	**4e** (*t*-Bu)	**5a** (*p*-tolyl)	91 (**6e**)	−72
6	**4e** (*t*-Bu)	**5b** (*p*-anisyl)	99 (**6f**)	−43
7	**4e** (*t*-Bu)	**5c** (Ph)	91 (**6g**)	−54
8	**4e** (*t*-Bu)	**5d** (p-ClC_6H_4)	97 (**6h**)	−90
9	**4e** (*t*-Bu)	**5e** (p-$O_2NC_6H_4$)	97 (**6i**)	−97

[a]Isolated yield after column chromatography. [b]Determined through HPLC using a REGIS (*R*,*R*)-DACH DNB chiral column; see Supporting Information (SI) for details. [c]Selective crystallization provided highly enantioenriched **6a**′ (93% ee).

γ-alkylallenoates afforded 2,5-*cis*-substituted pyrrolines exclusively, with enhanced values of ee upon increasing the size of the γ-substituent (entries 2−5). Interestingly, the products from all the γ-alkylallenoates were the (2*R*)-enantiomers **6b−i**, whereas the product from ethyl allenoate (**4a**) was the (2*S*)-enantiomer **6a**′.[16] We further improved the enantioselectivity by changing the substituents on the *N*-sulfonyl group (entries 6−9), with the highest arising when using imines containing electron-deficient benzenesulfonyl protecting groups (entries 8 and 9). The *p*-nitrobenzenesulfonyl (nosyl, Ns) group provided the highest overall reaction efficiency (97% yield, 97% ee; entry 9). In addition, as a protecting group it is complementary to Jacobsen's diphenylphosphinoyl group and can easily be removed.[17]

The catalyst **3** (10 mol %) facilitated [3 + 2] annulations between ethyl γ-*tert*-butylallenoate and a variety of *N*-nosylimines to produce 2,5-*cis*-substituted pyrrolines in good yields and high ee's (Table 2). Arylimines bearing *o*-, *m*-, and *p*-chlorophenyl rings were suitable substrates (entries 1−3), as were those featuring electron-deficient phenyl rings (entries 4−8). The enantioselectivity diminished when we applied electron-rich benzaldehyde-derived *N*-nosylimines as reaction partners (entries 9−11). Gratifyingly, when employing the *N*-nosylimine **5e** (versus *N*-tosylimine **5a**) in the transformation, the chiral

Table 2. Enantioselective Allene−Imine [3 + 2] Annulations Catalyzed by 3



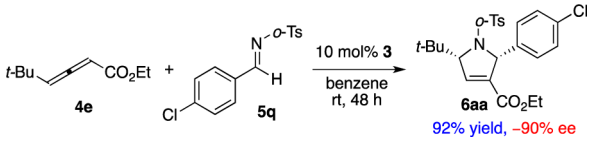
entry	4 (R)	5 (Ar)	yield (%)[a]	ee (%)[b]
1	**4e** (*t*-Bu)	**5f** (o-ClC_6H_4)	80 (**6j**)	>−99
2	**4e** (*t*-Bu)	**5g** (m-ClC_6H_4)	93 (**6k**)	−93[c]
3	**4e** (*t*-Bu)	**5h** (p-ClC_6H_4)	72 (**6l**)	−96
4	**4e** (*t*-Bu)	**5i** (p-BrC_6H_4)	74 (**6m**)	−96
5	**4e** (*t*-Bu)	**5j** (p-FC_6H_4)	78 (**6n**)	−94
6	**4e** (*t*-Bu)	**5k** (p-$CF_3C_6H_4$)	93 (**6o**)	−97
7	**4e** (*t*-Bu)	**5l** (p-NCC_6H_4)	83 (**6p**)	−95
8	**4e** (*t*-Bu)	**5m** (p-$O_2NC_6H_4$)	89 (**6q**)	−93
9	**4e** (*t*-Bu)	**5n** (*p*-tolyl)	75 (**6r**)	−87
10	**4e** (*t*-Bu)	**5o** (*p*-anisyl)	67 (**6s**)	−43
11	**4e** (*t*-Bu)	**5p** (6-Br-3,4-$OCHH_2O$-C_6H_2)	72 (**6t**)	−81[c]
12	**4a** (H)	**5e** (Ph)	69 (**6u**′)	+26
13	**4b** (Me)	**5e** (Ph)	89 (**6v**)	−37
14	**4c** (Et)	**5e** (Ph)	83 (**6w**)	−63
15	**4d** (*i*-Pr)	**5e** (Ph)	88 (**6x**)	−67
16	**4f** (*c*-pent)	**5e** (Ph)	73 (**6y**)	−70
17	**4g** (Cy)	**5e** (Ph)	59 (**6z**)	−65

[a]Isolated yield after column chromatography. [b]Determined through HPLC using a REGIS (*R*,*R*)-DACH DNB chiral column; see SI for details. [c]Determined through HPLC using a Chiral OJ-H column; see SI for details.

catalyst **3** could produce pyrrolines derived from other γ-alkylallenoates with improved ee's (entries 13−17), except for that of the parent allenoate (entry 12 versus entry 1 of Table 1). The trisubstituted pyrroline **6u**′ was again formed with its (2*S*)-isomer as the major enantiomer.

Although *N*-nosylimines provided the best results, imines bearing other nitrogen-protecting groups also produced high ee's. For example, the reaction of **4e** with the *N*-*o*-tosyl benzaldimine **5q** provided **6aa** in 92% yield and 90% ee.[18] This result is particularly significant because the resulting pyrroline is a precursor to a GGTase-I inhibitor that is viable for in vivo anticancer activity.[8c,d]

Scheme 2. Synthesis of the GGTase-I Inhibitor 6aa



The phosphines **3** and **3**′, albeit diastereoisomeric, possess opposite stereochemistry at their P-chiral centers at which the covalent bonds to the allenoates are formed. Therefore, we anticipated that they might produce respective pyrroline antipodes. To our delight, the catalyst **3**′ not only provided the opposite pyrroline enantiomers to those formed using **3** but also with much improved enantioselectivity (Table 3). For instance, when using the endo catalyst **3**′, the reactions between *N*-tosylbenzaldimine (**5a**) and a variety of γ-alkylallenoates furnished (2*S*)-pyrrolines **6**′ in over 90% yield and 90% ee (entries 2−6). We obtained even the trisubstituted pyrroline **6a**′ in 72% ee with the (2*S*)-configuration (entry 1). Not surprisingly, when employing the γ-*tert*-butylallenoate **4e**, all

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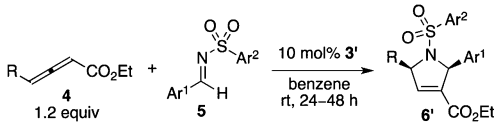
Table 3. Enantioselective Allene−Imine [3 + 2] Annulations Catalyzed by 3′



entry	4[a]	5 (Ar^1, Ar^2)	yield (%)[b]	ee (%)[c]
1	**4a**	**5a** (Ph, *p*-tolyl)	82 (**6a′**)	+72
2	**4b**	**5a** (Ph, *p*-tolyl)	90 (**6b′**)	+97
3	**4c**	**5a** (Ph, *p*-tolyl)	99 (**6c′**)	+98
4	**4d**	**5a** (Ph, *p*-tolyl)	95 (**6d′**)	+98
5	**4e**	**5a** (Ph, *p*-tolyl)	99 (**6e′**)	+99
6	**4e**	**5b** (Ph, *p*-anisyl)	98 (**6f′**)	+98
7	**4e**	**5c** (Ph, Ph)	99 (**6g′**)	>+99
8	**4e**	**5d** (Ph, *p*-ClC_6H_4)	99 (**6h′**)	+99
9	**4e**	**5e** (Ph, *p*-$O_2NC_6H_4$)	99 (**6i′**)	>+99
10	**4e**	**5r** (Ph, *o*-$O_2NC_6H_4$)	88 (**6ab′**)	−99[d]
11	**4a**	**5e** (Ph, *p*-$O_2NC_6H_4$)	78 (**6u′**)	+56
12	**4b**	**5e** (Ph, *p*-$O_2NC_6H_4$)	76 (**6v′**)	+71
13	**4c**	**5e** (Ph, *p*-$O_2NC_6H_4$)	98 (**6w′**)	+92
14	**4d**	**5e** (Ph, *p*-$O_2NC_6H_4$)	97 (**6x′**)	+96
15	**4f**	**5e** (Ph, *p*-$O_2NC_6H_4$)	89 (**6y′**)	+94
16	**4g**	**5e** (Ph, *p*-$O_2NC_6H_4$)	97 (**6z′**)	+96
17	**4e**	**5f** (*o*-ClC_6H_4, *p*-$O_2NC_6H_4$)	81 (**6j′**)	+97
18	**4e**	**5q** (*p*-ClC_6H_4, *o*-tolyl)	99 (**6aa′**)	>+99
19	**4e**	**5s** (*o*-FC_6H_4, *p*-ClC_6H_4)	88 (**6ac′**)	+98
20	**4e**	**5t** (*m*-FC_6H_4, *p*-ClC_6H_4)	99 (**6ad′**)	+99
21	**4e**	**5u** (*p*-FC_6H_4, *p*-ClC_6H_4)	99 (**6ae′**)	+99
22	**4e**	**5v** (*p*-NCC_6H_4, *p*-tolyl)	99 (**6af′**)	+98
23	**4e**	**5w** (*p*-anisyl, *p*-tolyl)	95 (**6ag′**)	>+99
24	**4e**	**5x** (*p*-tolyl, *p*-tolyl)	94 (**6ah′**)	>+99
25	**4e**	**5y** (5-methyl-2-furanyl, *p*-tolyl)	85 (**6ai′**)	+92
26	**4e**	**5z** (1-methyl-2-pyrrolyl, *p*-tolyl)	89 (**6aj′**)	+97
27	**4e**	**5aa** (2-thiophenyl, *p*-tolyl)	89 (**6ak′**)	+98
28	**4h**	**5ab** (*o*-ClC_6H_4, *p*-tolyl)	85 (**6al′**)	+71
29	**4h**	**5ac** (*m*-ClC_6H_4, *p*-tolyl)	89(**6am′**)	+99
30	**4h**	**5ad** (*p*-ClC_6H_4, *p*-tolyl)	82 (**6an′**)	+87

[a]See Tables 1 and 2 for the structures of the allenoates **4a−g**; **4h**: R = Ph. [b]Isolated yield after column chromatography. [c]Determined through HPLC using a REGIS (*R*,*R*)-DACH DNB chiral column; see SI for details. [d]The only (2*S*,5*S*)-pyrroline that exhibited a negative optical rotation; its absolute value (−16°) was much smaller than those of the other compounds, most of which were >100°.

six of the imines **5a−e** and **5r**, containing *N*-sulfonyl substituents of varying electronic and steric properties, produced their corresponding pyrrolines in excellent yields and ee's (entries 5−10). To further compare the performance of **3′** with that of **3**, we reacted *N*-nosylbenzaldimine (**5e**) with allenoates bearing various γ-substituents. Although the catalyst **3′** did indeed furnish the pyrrolines with improved yields and ee's relative to those obtained using **3** (cf. entries 11−16 of Table 3 with entries 12−17 of Table 2), interestingly the ee's were slightly lower than those of the products formed from the *N*-tosylimine **5a** (cf. entries 11−14 with entries 1−4). Catalyst **3′** was also suitable for use with a broad variety of imines (entries 17−24), including heterocyclic imines (entries 25−27). Allenes with various γ-substituents, including γ-phenylallenoate, produced 1,2,3,5-substituted-2,5-dihydropyrroles **6′** in good yields and ee's (entries 28−30).

To gain insight into the factors governing the stereoselection of these reactions, we performed restricted B3LYP/6-31G(d) hybrid density functional theory (DFT) calculations using the G09 suite of programs. We located the transition state structures for the (2*R*)- and (2*S*)-stereofacial imine additions, **TS1** and **TS1′**, respectively, for the reaction between the allenoate **4e** and the imine **5e** (Figure 1). Their $C_\alpha\cdots C_{imine}$ bond forming distances

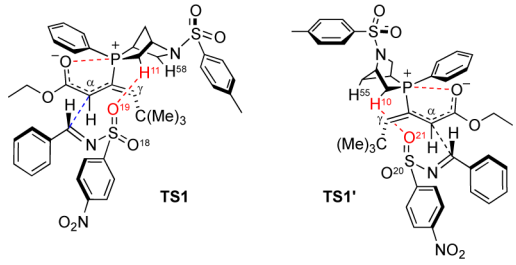


Figure 1. Geometries of **TS1** and **TS1′**.

were similar: 2.19 and 2.22 Å, respectively. Both transition states feature the lowest possible number of unfavorable van der Waals contacts. In the higher-energy transition states, however, it was the bulky *N*-tosyl (of **3**) and *P*-phenyl (of **3′**) groups of the catalysts that experienced the majority of such unfavorable contacts.[19] Two stabilizing factors were common to both transition states for the $C_\alpha\cdots C_{imine}$ bond-forming events during the allene−imine [3 + 2] annulations: (i) a hydrogen bond between the imine *N*-sulfonyl oxygen atom and a hydrogen atom on the bicyclic ring system of the catalyst[20] and (ii) a favorable Coulombic interaction between the allenoate C═O oxygen atom and the phosphorus atom.[21] A notable difference between the two transition states is the relative orientation of the phosphine catalyst, flipped by 180° with respect to the allenoate and imine subassembly. The exophosphine **3** blocked the *Si* face of the phosphonium dienolate, while the endophosphine **3′** blocked the *Re* face, resulting in opposite absolute configurations at the C_{imine} atoms.

Thus, it would appear, based upon these DFT findings, that the relative orientation (i.e., flipped alignment) of the phosphine catalyst, the minimization of unfavorable van der Waals contacts, and the presence of stabilizing interactions within **TS1** and **TS1′** govern the (2*R*)- vs (2*S*)-enantiofacial selectivity of these reactions. These predictive models are consistent with the observed formation of the pyrroline antipodes **6i** and **6i′**.

In summary, we have developed a new class of rigid chiral [2.2.1] bicyclophosphines that are highly effective catalysts for the asymmetric syntheses of 1,2,3,5-substituted pyrrolines. To the best of our knowledge, this paper is the first systematic report on the phosphine-catalyzed asymmetric syntheses of pyrrolines having this type of substitution.[9] The two diastereoisomeric phosphines function as pseudoenantiomers, producing their pyrrolines in opposite enantiomeric forms. To facilitate widespread use of our chiral phosphines, we have already supplied them for sale through Sigma−Aldrich.[15] Our ability to supply these chiral phosphines highlights their simple synthesis. Further exploration of the catalyst structure and application of these catalysts to other transformations are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds (PDF); crystallographic data for compounds **2**, **2d′**, **3**, **6a′**, and **6aa** (CIF). 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) For selected reviews, 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) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (d) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (e) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (f) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. (g) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (h) Wang, S.-X.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, 2766. (i) Fan, Y. C.; Kwon, O. Phosphine Catalysis. In *Science of Synthesis*; List, B., Ed.; Georg Thieme: Stuttgart, 2012; Asymmetric Organocatalysis, Vol *1*, Lewis Base and Acid Catalysts, pp 723−782. (j) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (k) Xu, S.; He, Z. *RSC Adv.* **2013**, *3*, 16885. (l) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588. (m) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927.

(2) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.

(3) (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Zhu, X.-F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276. (d) Zhao, G.-L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975.

(4) For selected examples, see: (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (b) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (c) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (d) Voituriez, A.; Panossian, A.; Fleury-Bregeot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (e) Sampath, M.; Loh, T. P. *Chem. Sci.* **2010**, *1*, 739. (f) Hua, X.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467. (g) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726. (h) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293. (i) Wang, D.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 2764. (j) Steurer, M.; Jensen, K. L.; Worgull, D.; Jorgensen, K. A. *Chem.—Eur. J.* **2012**, *18*, 76. (k) Marco-Martinez, J.; Marcos, V.; Reboredo, S.; Filippone, S.; Martin, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5115.

(5) (a) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141. (b) Scherer, A.; Gladysz, J. A. *Tetrahedron Lett.* **2006**, *47*, 6335. (c) Fleury-Bregeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. *Tetrahedron* **2007**, *63*, 11920. (d) Panossian, A.; Fleury-Bregeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2008**, *22*, 3826. (e) Pinto, N.; Fleury-Bregeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2009**, *23*, 146.

(6) (a) Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660. (b) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767.

(7) (a) Chawla, A. S.; Redha, F. M.; Jackson, A. H. *Phytochemistry* **1985**, *24*, 1821. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (c) Wager, T. T.; Welch, W.; O'Neill, B. T. NK1 Antagonist, WO Patent 2004/110996, December 23, 2004.

(8) (a) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; De Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. (b) Watanabe, M.; Fiji, H. D. G.; Guo, L.; Chan, L.; Kinderman, S. S.; Slamon, D. J.; Kwon, O.; Tamanoi, F. *J. Biol. Chem.* **2008**, *283*, 9571. (c) Lu, J.; Chan, L.; Fiji, H. D. G.; Dahl, R.; Kwon, O.; Tamanoi, F. *Mol. Cancer Ther.* **2009**, *8*, 1218. (d) Zimonjic, D. B.; Chan, L. N.; Tripathi, V.; Lu, J.; Kwon, O.; Popescu, N. C.; Lowy, D. R.; Tamanoi, F. *BMC Cancer* **2013**, *13*, 198.

(9) The chiral phosphine **3′** has been employed previously in a successful asymmetric [3 + 2] annulation between a γ-ethylallenoate and an imine derived from indole-3-carboxaldehyde. This report does not, however, contain any information about the synthesis and characterization of **3′**; see: Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510.

(10) Hydroboration/oxidation of 1,4-diisopropylcyclohexa-1,4-diene using enantiomerically pure isopinocamphenylborane [from (+)-α-pinene] gave a 6:1 mixture of C_2- and C_i-symmetric diols, with an ee for the desired C_2-symmetric diol of ∼83%: Chen, Z.; Eriks, K.; Halterman, R. L. *Organometallics* **1991**, *10*, 3449.

(11) No purification was necessary, except for recrystallization of the final product **1**; the reaction was readily run on a 100-g scale: Braish, T. F.; Fox, D. E. *J. Org. Chem.* **1990**, *55*, 1684.

(12) Imamoto, T. *Pure Appl. Chem.* **1993**, *65*, 655.

(13) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(14) We used X-ray crystallographic analysis to confirm the connectivities and absolute stereochemistries of **2**, **2′** [using endo-*P*-(1-naphthyl)phosphine oxide **2d′** as its proxy], and **3**; see the SI for details.

(15) Ring-closing bisalkylation is a general reaction that can be used to synthesize several chiral phosphines possessing different exocyclic phosphorus substituents. The chiral phosphines **3** and **3′** as well as 10 additional 2-aza-5-phosphabicyclo[2.2.1]heptanes featuring different nitrogen- and phosphorus-based substituents are sold by Sigma−Aldrich; see the SI for their product numbers and structures.

(16) This assignment was substantiated from HPLC traces and optical rotations and established unequivocally by the single-crystal structures of **6a′** and **6aa**; see the SI for details.

(17) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(18) Selective crystallization readily provided highly enantioenriched **6aa** (>99% ee).

(19) In theory, a large number of C_α−C_{imine} bond formations are possible; using our previous findings as a starting point, we were, however, able to generate a total of 32 viable low-energy modes of addition for each entry. For specific details, see the SI and Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643.

(20) Measured distances and natural bond orbital (NBO) interaction energies (E_{NBO}) of these contacts: in **TS1**, $O_{19}\cdots H_{11}$ = 2.33 Å (E_{NBO} = 1.88 kcal/mol) and $O_{18}\cdots H_{58}$ = 2.50 Å (E_{NBO} = 1.46 kcal/mol); in **TS1′**, $O_{21}\cdots H_{10}$ = 2.21 Å (E_{NBO} = 2.28 kcal/mol) and $O_{20}\cdots H_{55}$ = 2.58 Å (E_{NBO} = 1.05 kcal/mol).

(21) Coulombic interactions between the allenoate C═O oxygen atom (−0.578) and the phosphorus atom (0.785) for **TS1** and the corresponding O (−0.565) and P (0.806) atoms for **TS1′** were 2.59 Å (E_{NBO} = 6.04 kcal/mol) and 2.62 Å (E_{NBO} = 5.64 kcal/mol), respectively.