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# Asymmetric Synthesis of β-Hydroxy Amino Acids via Aldol Reactions Catalyzed by Chiral Ammonium Salts

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**Abstract:** The *Cinchona* alkaloid derived chiral ammonium salt developed by Park and Jew functions as an effective catalyst for the synthesis of β-hydroxy α-amino acids via asymmetric aldol reactions under homogeneous conditions. The *syn* diastereomers are obtained in good ee, and aryl-substituted aliphatic aldehydes are the best substrates for the reaction. These results represent the highest ee's obtained to date in direct aldol reactions of glycine equivalents catalyzed by inexpensive, readily prepared chiral ammonium salts.

β-Hydroxy α-amino acids are constituents of several complex bioactive peptide natural products.[1] In addition, they are useful chiral intermediates due to their ability to undergo a variety of transformations.[2] Accordingly, several methods have been devised for their synthesis, many of which require a stoichiometric amount of a chiral auxiliary.[3,4] A particularly attractive approach involves the direct aldol reaction of a glycine equivalent with an aldehyde mediated by a chiral catalyst. In fact, Miller has reported such a process, albeit with low ee values (3−12%), that employs O'Donnell's *Cinchona* alkaloid derived phase-transfer catalyst.[5] Furthermore, the asymmetric synthesis of β-hydroxy amino acids via enzyme-catalyzed aldol reactions has been disclosed; however, these protocols suffer from limited substrate scope, modest yields, and low diastereoselectivities in some cases.[6] Recently, Maruoka[7] and Shibasaki[8] have prepared novel catalysts for direct aldol reactions of glycinate Schiff bases with a variety of aliphatic aldehydes. Although the Maruoka catalyst is particularly effective, providing *anti*-β-hydroxy-α-amino acid derivatives in high ee (≥90%), we were intrigued with the idea of employing *Cinchona* alkaloid based catalysts in these reactions due to their low cost and ease of synthesis.[9] Despite the fact that Miller previously obtained poor enantioselectivities with such a catalyst, we felt that the advent of newer, more active catalysts of this type[10] merited a reexamination of this process. We now report that the trifluorobenzyl-substituted *Cinchona* alkaloid derived catalyst reported by Park and Jew (**5**, Figure 1)[10b] effectively catalyzes the aldol reaction between a glycinate Schiff base and aliphatic aldehydes under *homogeneous* conditions. Although the diastereoselectivity is negligible, useful levels of enantioselectivity (up to 83% ee) can be obtained for the *syn* aldol product.

We selected hydrocinnamaldehyde (**6a**, Table 1) and *tert*-butyl glycinate benzophenone imine (**7**) as the substrates for testing the efficacy of catalysts **1**−**5** in the asymmetric aldol reaction. In our hands, the reaction was extremely sluggish under the biphasic conditions employed by Maruoka in the identical reaction catalyzed by chiral ammonium salts derived from BINOL.[7] Trace amounts of aldol products were detected along with several byproducts presumably formed by aldehyde self-condensation.[11] In contrast, use of the phosphazene base *tert*-butyliminotri(pyrrolidino)phosphorane (BTTP) under

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(3) Recent chiral auxiliary or reagent-based syntheses: (a) MacMillan, J. B.; Molinski, T. F. *Org. Lett.* **2002**, *4*, 1883. (b) Belokon, Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Strelkova, T. V.; Harutyunyan, S. R.; Saghiyan, A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 481. (c) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron Lett.* **2000**, *41*, 5963. (d) Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663. (e) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195. (f) Di Felice, P.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2191. (g) Hutton, C. A. *Org. Lett.* **1999**, *1*, 295. (h) Alker, D.; Hamblett, G.; Harwood: L. M.; Robertson, S. M.; Watkin, D. J.; Williams, C. E. *Tetrahedron* **1998**, *54*, 6089. (i) Iwanowicz, E. J.; Blomgren, P.; Cheng, P. T. W.; Smith, K.; Lau, W. F.; Pan, Y. Y.; Gu, H. H.; Malley, M. F.; Gougoutas, J. Z. *Synlett* **1998**, 664.

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(8) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 8289.

(9) (−)-Cinchonidine can be purchased for $0.61/g (Aldrich); in contrast, (*S*)-BINOL, the chiral component of the Maruoka and Shibasaki, catalysts, costs $36/g (Aldrich). The catalysts used in this study were synthesized from (−)-cinchonidine in two to three steps, whereas Maruoka's catalyst requires a longest linear sequence of 11 steps (see: Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139).

(10) (a) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497. (b) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I.-Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245. (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036. (d) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (e) For a review on the use of phase-transfer catalysts in amino acid synthesis, see: Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

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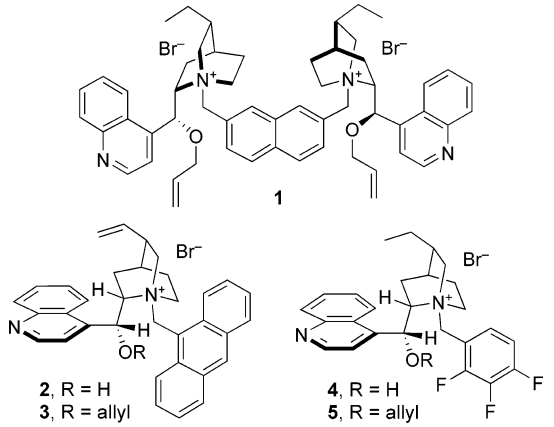
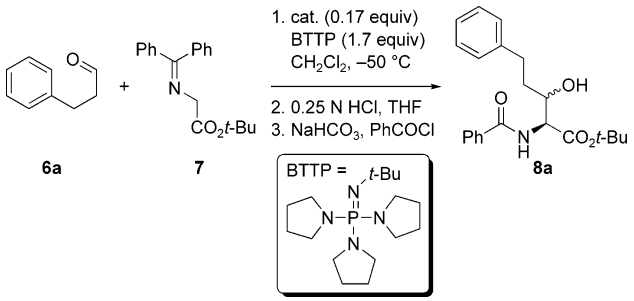



**FIGURE 1.** Catalysts surveyed in this study.

**TABLE 1. Asymmetric Aldol Reaction of 6a with 7[a]**




| catalyst | yield (%) | *anti*/*syn* | *anti* ee[b] (%) | *syn* ee[b] (%) |
|---|---|---|---|---|
| **1** | 63 | 1.4:1 | 9 | 21 |
| **2** | 18 | 1.8:1 | 0 | 2 |
| **3** | 54 | 2:1 | 41 | 47 |
| **4** | 54 | 1.2:1 | 0 | 2 |
| **5** | 40 | 1:1.9 | 13 | 66 |

[a] 4.0 equiv of aldehyde was used in each reaction. [b] Measured by HPLC (Chiralcel OD-H, 97:3 hexanes/*i*-PrOH, 1 mL/min).

*homogeneous* conditions described by O'Donnell and Schwesinger for alkylations of **7**[12] resulted in a facile reaction. The aldol adducts were not isolable due to instability presumably derived from retro aldol reactions during chromatography. Thus, the crude products were subjected to a sequence of imine hydrolysis and acylation to afford the stable, isolable benzoate **8a** as a mixture of diastereomers (Table 1).

The data summarized in Table 1 show that the trifluorobenzyl-substituted catalyst **5** of Park and Jew[10b] exhibited the highest levels of enantioselectivity for the *syn* aldol product. Corey's catalyst **3**[10d] provided both *syn*- and *anti*-**8a** in moderate ee, whereas none of the other catalysts examined afforded either diastereomer with useful levels of enantioselectivity. Notably, the complete lack of selectivity in reactions catalyzed by free alcohols **2** and **4** indicates that alkylation of the (−)-cinchonidine alcohol is necessary in order to obtain active catalysts for this homogeneous aldol reaction. Finally, all of the catalysts examined delivered **8a** with low diastereoselectivity, although the Park−Jew catalyst **5** was alone in displaying selectivity for the *syn* isomer. Accordingly, we employed **5** in our attempts to optimize the reaction conditions (Table 2).

**TABLE 2. Optimization of Aldol Reactions Catalyzed by 5[a]**

| solvent | equiv of BTTP | equiv **5** | yield of **8a** (%) | *anti*/*syn* | *anti* ee (%) | *syn* ee (%) |
|---|---|---|---|---|---|---|
| THF | 1.7 | 0.17 | 85 | 1.1:1 | 12 | 18 |
| tol/$CHCl_3$[b] | 1.7 | 0.17 | 26 | 1:1.3 | 48 | 89 |
| tol/$CHCl_3$[b] | 1.0 | 0.17 | 35 | 1.1:1 | 36 | 78 |
| tol/$CHCl_3$[b] | 2.5 | 0.17 | 64 | 1:1.3 | 33 | 80 |
| tol/$CHCl_3$[b] | 2.5 | 0.085 | 10 | 1:1 | 34 | 81 |

[a] All aldol reactions were run with 4.0 equiv of aldehyde **6a** at −50 °C for 1 h. [b] Toluene−$CHCl_3$ 7:3

Changing the solvent from $CH_2Cl_2$ to THF resulted in a high yield of **8a**; however, the ee was negligible for both diastereomers. Fortunately, *syn*-**8a** was delivered in 89% ee when toluene-$CHCl_3$ 7:3[13] was used as the solvent. The yield could be raised to acceptable levels by increasing the amount of base from 1.7 equiv to 2.5 equiv, albeit with a small drop in ee. Halving the catalyst loading did not affect the enantioselectivity of the reaction, but the yield dropped precipitously from 64% to 10%. Although not investigated in detail, this result suggests that the initially formed achiral enolate of **7** is consumed via undesired competitive pathways when the catalyst is employed at less than optimal levels.[14] Additionally, the lack of erosion in enantioselectivity indicates that the achiral enolate is not reacting with aldehyde **6a** at an appreciable rate under these conditions. Unfortunately, all of the conditions examined to date have provided **8a** in negligible diastereoselectivity.

Based on these studies, we selected 2.5 equiv of BTTP and 0.17 equiv of catalyst **5** in toluene-$CHCl_3$ 7:3 as our optimized reaction conditions and investigated the scope of the aldol reaction with respect to the aldehyde structure (Table 3). Aliphatic aldehydes containing phenyl groups, such as hydrocinnamaldehyde (**6a**) and benzyloxyacetaldehyde (**6b**), afforded adducts **8a** and **8b** in good yields and *syn* ee's of ≥80%. Interestingly, reactions employing *p*-nitrohydrocinnamaldehyde (**6c**)[15] delivered the highest *anti* ee's (60%) observed in this study; however, *syn*-**8c** was obtained in slightly lower ee than were *syn*-**8a** and *syn*-**8b**. Although adducts **8d** were obtained in good yield from *p*-methoxyhydrocinnamal-

(11) In a footnote contained in ref 7, it is reported that reaction of **6** with **7** catalyzed by **3** under biphasic conditions yields aldol products in 60% yield with a *syn*/*anti* ratio of 5.3:1 and 25% ee for the *syn* diastereomer. In our hands, this reaction has been too sluggish to provide any isolable aldol products. Maruoka has recently disclosed new biphasic conditions for direct asymmetric aldol reactions of **7**: Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685.

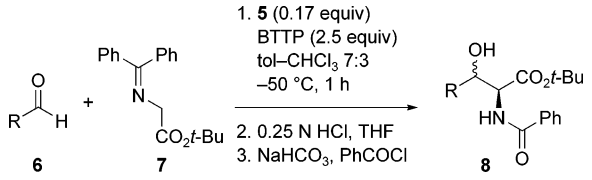
(12) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775. The phosphazene base 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) was equally effective in the aldol reaction; however, BTTP was typically employed due to its lower cost.

(13) This solvent mixture was employed by Park and Jew as the organic phase in phase-transfer-catalyzed alkylations of **7** with **1** or **5** as the catalyst: see ref 10b,c.

(14) Since all reactions in Table 2 were run for the same amount of time (1 h), halving the catalyst loading should result in a decrease in yield of no more than half if the rate is limited by catalyst turnover. Since we observed a more dramatic decrease in yield, we believe that the slower rate of chiral ammonium enolate formation with half of the normal catalyst loading results in consumption of the initially formed achiral enolate of **7** via undesired pathways.

(15) Griesgraber, G.; Kramer, M. J.; Elliott, R. L.; Nilius, A. M.; Ewing, P. J.; Raney, P. M.; Bui, M.-H.; Flamm. R. K.; Chu, D. T. W.; Plattner, J. J.; Or, Y. S. *J. Med. Chem.* **1998**, *41*, 1660.

**TABLE 3. Aldol Reactions of 7 with Selected Aldehydes**[a]




| R | yield (%) | *anti*/*syn* | *anti* ee[b] (%) | *syn* ee[b] (%) |
|---|---|---|---|---|
| $PhCH_2CH_2$ (**a**) | 64 | 1:1.3 | 33 | 80 |
| $BnOCH_2$ (**b**) | 70 | 1:1 | 45 | 83 |
| *p*-$NO_2PhCH_2CH_2$ (**c**) | 74 | 1:1.3 | 60 | 75 |
| *p*-$OMePhCH_2CH_2$ (**d**) | 78 | 1:1.2 | 10 | 50 |
| $CH_2{=}CHCH_2CH_2$ (**e**) | 46 | 1:1.2 | 19 | 60 |
| $CH_3(CH_2)_4CH_2$ (**f**) | 34 | 1:1.2 | 6.5 | 52 |

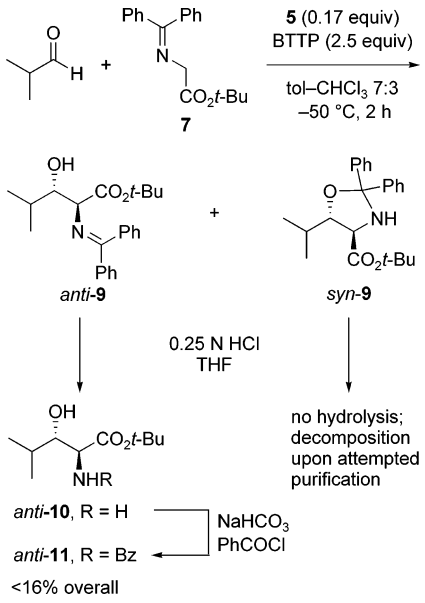
[a] Data are the average of two runs. 4.0 equiv of aldehyde was used in each reaction. [b] Measured by HPLC (Chiralcel OD-H, 90:10 (**8c**), 96:4 (**8d**), 97:3 (**8a**, **8e**,**f**) or 98:2 hexanes/*i*-PrOH (**8b**), 1 mL/min).

dehyde (**6d**),[16] their ee's were significantly lower than those of **8a**−**c**. The use of 4-pentenal (**6e**) and heptanal (**6f**) also resulted in modest ee's; additionally, the yields of **8e** and **8f** were relatively poor. Finally, each adduct except for **8b** was obtained with a very slight preference for the *syn* isomer.

Analysis of the data in Table 3 reveals that aldehydes containing aromatic groups give the best yields in this aldol reaction, followed by alkene-containing aldehydes and saturated aldehydes, respectively. It is more difficult to identify a trend in the ee's with respect to aldehyde structure, although it is clear that aldehydes possessing either electronically neutral or electron-poor aromatic rings give the best ee's. Since the possibility exists for multiple types of $\pi-\pi$ interactions between aldehydes **6a**−**e**, catalyst **5**, and benzophenone imine **7**, analysis of potential transition states is a complex issue deserving of further study. Although the observed ee's are not as high as those reported by Maruoka,[7] they nevertheless represent the highest ee's obtained to date with readily available *Cinchona* alkaloid derived catalysts in direct aldol reactions.[17]

To probe the steric requirements of the aldehyde, we performed the aldol reaction between **7** and isobutyraldehyde (Scheme 1). This reaction was more sluggish than those of unbranched aldehydes and required 2 h for complete consumption of **7**. However, the aldol adduct *syn*-**9** did not undergo hydrolysis; prolonged reaction times only led to decomposition. Surprisingly, retro aldol scission also took place under the hydrolysis conditions as evidenced by the generation of *tert*-butyl glycinate.[18] Attempted separation of *syn*-**9** and amino alcohol *anti*-

**SCHEME 1. Asymmetric Aldol Reactions with Isobutyraldehyde**




**10** met with failure, as *syn*-**9** was unstable to chromatography. In the end, we were able to obtain crude benzoate *anti*-**11** in poor yield (<16%) and enantiomeric excess (12%).[19] The low *anti* ee is consistent with the ee's obtained from aldehydes **6d**−**f**. Thus, extension of this method to α-branched aldehydes will require the development of improved hydrolysis conditions.

In an attempt to prepare $\beta$-hydroxyphenylalanine derivatives such as those present in vancomycin and related glycopeptide antibiotics,[1a,b] we examined the use of benzaldehyde in this asymmetric aldol reaction. Although we were able to observe the aldol adducts by comparison of $^1$H NMR spectra of crude reaction mixtures to published data,[3a] all attempts to purify or subject them to further transformations resulted in rapid decomposition.[20] We attribute the instability of the aldol products to an extremely facile retro-aldol process, as copious quantities of benzaldehyde were observed in the course of purification attempts.[21] Consequently, studies aimed at derivatizing the free alcohol without promoting this destructive pathway are in progress.

(16) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888.

(17) Corey[4e] has observed higher ee's in Mukaiyama aldol reactions employing a *Cinchona* alkaloid derived catalyst; however, this method is limited by the fact that the silyl ketene acetal derived from **7** is only stable in dry $CH_2Cl_2$ solutions at temperatures under −20 °C. Kobayashi has recently utilized a more stable silyl ketene acetal glycine equivalent in Mukaiyama aldol reactions: Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192.

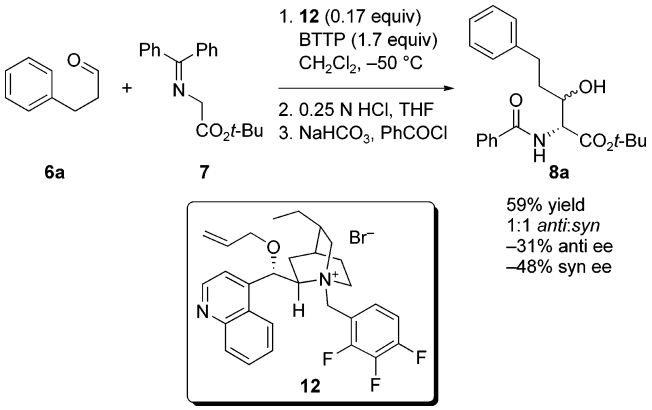
(18) Since **7** was completely consumed in the aldol reaction with isobutyraldehyde, the *tert*-butyl glycinate must be formed via retro aldol cleavage of **9** to return isobutyraldehyde and **7** followed by hydrolysis of **7**.

(19) We were unable to isolate *anti*-**11** from the byproducts of hydrolysis and the competing retro aldol reaction. Thus, the 16% yield represents an upper limit. However, our sample was of sufficient purity to determine the ee using chiral HPLC (Chiralcel OD-H, 98:2 hexanes/*i*-PrOH, 1 mL/min).

(20) Our observations are consistent with those of Miller,[5a] who reported an estimated crude yield for the aldol reaction of **7** and benzaldehyde yet did not report the isolation or further derivatization of the product. However, our observations contrast with those of Molinski,[3a] who has reported isolation of the same aldol adduct from a reaction mediated by *n*-BuLi and (−)-sparteine. Additionally, Molinski has reported the isolation of *anti*-**9** and *syn*-**9** via $SiO_2$ chromatography; as detailed above, we were unable to perform this separation in our system. For a discussion of the possible source of these discrepancies, please see footnote 21.

(21) We speculate that the presence of the phosphazene base in the crude reaction mixture may be initiating the retro aldol reaction on silica gel. In the aldol reactions reported by Molinski,[3a] base is presumably not present in the mixture at the time of chromatography and therefore is unable to promote a retro aldol reaction. Thus, we are currently examining the use of other bases that can be removed prior to chromatography in order to extend the substrate scope to aryl aldehydes.

**SCHEME 2. Use of Cinchonine-Derived Catalyst**




We were curious to see how the pseudoenantiomeric catalyst derived from (+)-cinchonine would behave in this aldol reaction. Accordingly, we prepared chiral ammonium salt **12** via a slight modification of the procedure used by Park and Jew to synthesize **5**.[10b] As expected, catalysis by **12** of the aldol reaction between **6a** and **7** resulted in opposite enantioselectivities relative to reactions mediated by **5** (Scheme 2). The magnitude of the *anti* ee was similar to that afforded by the cinchonidine-derived catalyst; unfortunately, the *syn* ee dropped significantly. O′Donnell has previously noted higher enantioselectivities in alkylations of **7** that employ cinchonidine-based catalysts versus the psuedoenantiomeric cinchonine derivatives.[12] However, the differences in ee were more modest (3−10%) than the differences we observed for *syn*-**8a**.

In conclusion, we have found that glycinate Schiff base **7** undergoes asymmetric aldol reactions catalyzed by *Cinchona* alkaloid derived ammonium salts under homogeneous conditions. The reaction is most useful for aliphatic aldehydes containing either phenyl groups or electron-poor aromatic rings. Studies to increase the diastereoselectivity, enantioselectivity, and substrate scope of the reaction are underway. Avenues under exploration include the use of different bases, the development of new hydrolysis conditions, and the preparation of novel, potentially more active catalysts based on cinchonidine. Despite the current limitations, this process affords the highest enantioselectivities recorded to date in a direct asymmetric aldol reaction catalyzed by an inexpensive, easily synthesized *Cinchona* alkaloid derived salt. Moreover, we note that this is the second asymmetric reaction we have studied in which **5** is clearly superior to closely related catalysts.[22] Furthermore, Andrus has recently disclosed the unique efficacy of **5** in asymmetric glycolate alkylations.[23] Together, these reports suggest that **5** may be a useful catalyst in a wide range of reactions and that efforts to design new and improved chiral ammonium salt catalysts should make use of the 2,3,4-trifluorobenzyl moiety.

## Experimental Section

**General Procedure for Aldol Reaction, Hydrolysis, and Benzoate Formation.** To a solution of *tert*-butyl glycinate benzophenone imine (**7**, 25 mg, 0.085 mmol) and chiral ammonium salt **5** (8.0 mg, 0.014 mmol) in anhydrous toluene−$CHCl_3$ (7:3, 0.35 mL) at −50 °C was added *tert*-butyliminotri(pyrrolidino)phosphorane (64 $\mu$L, 65 mg, 0.21 mmol) dropwise over 5 min. A solution of aldehyde (0.34 mmol) in anhydrous toluene−$CHCl_3$ (7:3, 0.10 mL) was then added via syringe pump over 30 min. The resulting mixture was stirred at −50 °C under $N_2$ for 1 h, diluted with $CH_2Cl_2$ (1 mL), and treated with satd aq $NaHCO_3$ (0.5 mL) and $H_2O$ (1 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 3 mL), and the combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The crude aldol product was then dissolved in THF (2 mL), cooled to 0 °C, and treated with 0.25 N HCl (0.35 mL, 0.088 mmol). The resulting mixture was stirred at 0 °C for 1 h, treated with satd aq $NaHCO_3$ (0.5 mL), and extracted with EtOAc (2 × 3 mL). The combined organic layers were washed with brine (2 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The crude amine was dissolved in dioxane−$H_2O$ (10:1, 1.5 mL) and treated with $NaHCO_3$ (16 mg, 0.19 mmol) followed by benzoyl chloride (24 $\mu$L, 29 mg, 0.21 mmol). The resulting mixture was stirred at rt for 1 h, diluted with $H_2O$ (0.5 mL), and extracted with $CH_2Cl_2$ (2 × 5 mL). The organic layer was dried ($Na_2SO_4$) and concentrated in vacuo. Flash chromatography ($SiO_2$, 2 × 10 cm, 5−10% acetone in hexanes gradient elution) afforded the benzoates **8** as colorless oils that were mixtures of diastereomers.

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**Supporting Information Available:** General experimental details, spectral data for **8a**−**f**, synthetic procedure and spectral data for **12**, and $^1H$ and $^{13}C$ NMR spectra for **8a**−**f** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611.
(23) Andrus, M. B.; Hicken, E. J.; Stephens, J. C. *Org. Lett.* **2004**, *6*, 2289.