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SYNTHESIS OF β-HYDROXY-α-AMINO ACIDS BY ALDOL CONDENSATION USING A CHIRAL PHASE TRANSFER CATALYST

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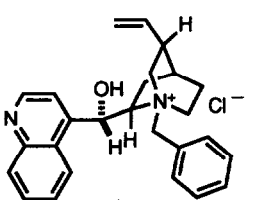
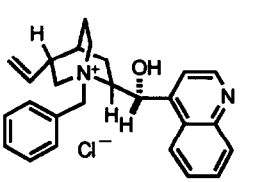
Abstract: Efficient, nearly racemic syntheses of β-hydroxy-α-amino acids by aldol condensations between *t*-butyl (diphenylmethylene)glycinate **2** and aldehydes under phase transfer catalytic conditions in the presence of the chiral catalyst N benzylcinchoninium chloride are described.

INTRODUCTION

Chiral phase transfer catalysts have been employed to effect stereoselective transformations under phase transfer conditions. For example, derivatives of the cinchona alkaloid family have been used to catalyze epoxidations,[1a-d] Darzens' condensations,[1d,e] Michael reactions,[1f] Robinson annulations,[1g] reductions,[1h] and alkylations.[1h-j] Enantioselectivity in these reactions ranged over 5-92% ee (enantiomeric excess). One of the more stereoselective alkylations reported was the monoalkylation of a glycine derivative.[1i] Using N-benzyl-cinchoninium chloride (**1a**) as a chiral catalyst (or the diastereomer **1b**), O'Donnell *et al.*, reacted an N-(diphenylmethylene)glycinate ester with various alkyl halides under phase transfer catalytic (PTC) conditions (eq. 1). The resulting protected α-amino acids were obtained in 60-85% yield with enantiomeric excesses of 42-66% ee (with the opposite major enantiomer obtained with catalyst **1b**). Furthermore, a single recrystallization gave as high as >99% ee in several cases. Although the role of the catalyst was not fully determined, it apparently selectively bound one face of the intermediate glycine enolate, thereby blocking alkylation on this side.



1a



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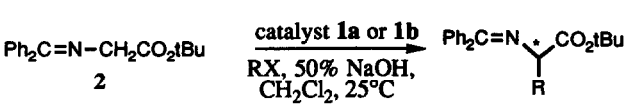


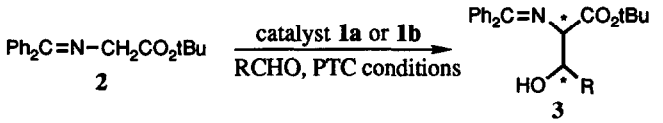
(1)

Based on this precedent, we saw the potential for stereoselective aldol reaction between the imine protected glycine ester and an aldehyde in the presence of the cinchoninium catalyst.[2] To our knowledge, no previous report of an aldol condensation between a glycine equivalent and an aldehyde effected with a chiral phase transfer catalyst is in the literature.[3] Not only is such a proposal a logical extension of O'Donnell's work as an exploration of a method's scope, but the resulting protected β-hydroxy-α-amino acids are important as chemical synthons and as essential components of many biologically active compounds.[4]

For the PTC aldol condensation to be completely stereoselective, enantioselectivity as well as diastereoselectivity must be controlled. The results of O'Donnell implied stereoselective formation of a catalyst–enolate complex. The assumption that the significant catalyst–substrate interactions would remain the same in both aldol and alkylation reactions suggested that the stereochemistry at the α carbon in the protected β-hydroxy-α-amino acid would be set. We were concerned, however, about the degree of selectivity at the second stereocenter, the β position, during the aldol condensation. Orientation of the reacting aldehyde with the catalyst–enolate complex in a stereoselective manner would be essential. In asymmetric *anhydrous* aldol reactions, metal chelation with each of the substrates controlled the stereochemical outcome.[5] In our case, the cinchoninium catalyst was solely responsible for mimicking the appropriate "chelation" to induce relative diastereoselectivity. One would expect that the degree of this chiral interaction would be dependent upon aldehyde structure. We have investigated the effect of varying substrate structure as well as specific reaction conditions on yield and stereochemical outcome of this proposed aldol synthesis. The results are presented here.

RESULTS AND DISCUSSION

The conditions used in the precedent alkylations (eq.1) were too harsh for our desired aldol reaction. Although the starting imine **2** was partially recovered, the highly basic conditions apparently promoted undesired aldehyde self-condensation and subsequent transformations. After some initial studies, acceptable yields were obtained with 10 mol% of catalyst, 0.1 M imine **2** in CH_2Cl_2, 500 mol% of aldehyde, and 200 mol% of base as 5% w/v (weight/volume) sodium hydroxide (eq. 2). Usually both major and minor diastereomeric aldol products were obtained in a ratio determined by integration of the C-2 (α carbon) proton doublets observed by ^1H NMR. Since the product mixture seemed to partially cyclize to the corresponding oxazolidine forms (**3c**)[3,6] over time and during chromatographic purification, additional characterization was done on the reduced imine (**4**) or on the completely deprotected amino acid (**5**) (Scheme 1).



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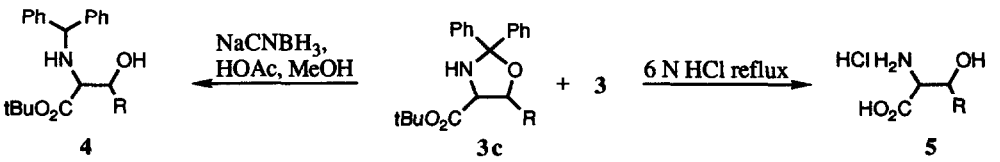


Scheme 1

The aldol condensation between imine **2** and heptanal under the specified conditions was used as a standard by which the effect of the variations shown in Table I were measured with respect to chemical yield and diastereoselectivity. These two parameters alone were chosen because they were easily obtained from the ^{1}H NMR of the crude product, thus allowing a rapid appraisal of many variations. The effect on enantioselectivity, measurement of which required diastereomeric separation and derivatization, was not determined at this point in our survey, but will be addressed later in this paper. Several trends are worth noting. First, the general cinchona alkaloid structure of the β-hydroxylammonium catalyst appeared to be important for efficient enolate formation and subsequent aldehyde attack (entries 1-6, Table I). Substitution of either catalyst isomer **1a** or **1b** resulted in essentially the same yield as well as diastereoselectivity. This stereochemical measurement was not wholly unexpected since the enantioselectivity may be the only stereoparameter dependent upon which catalyst isomer was employed. The lack of reaction with tetra-n-butylammonium chloride, benzyltriethylammonium chloride, and choline chloride (an achiral β-hydroxylammonium catalyst)[7] was additional evidence that a structure simpler than the cinchona compounds could not be effectively substituted in the phase transfer reaction.[3] Second, the strength of the base affected overall yield, but the size of the counter ion appeared to have little effect (entries 7 and 8). Moreover, only a catalytic amount of base was required for aldol formation (entry 9). Most previous phase transfer reactions catalyzed by cinchona alkaloid derivatives were performed with an excess of base usually present in high concentration.[1] Although the yield for the aldol reaction was decreased, less aldehyde self-condensation occurred in this case (entry 9) as compared to the standard conditions. Furthermore, the ionic strength of the aqueous phase altered diastereoselectivity. Use of either 50% sodium hydroxide or 5% sodium hydroxide in 50% sodium fluoride increased diastereomeric excess by over 10% de compared to that obtained in just 5% base (compare entries 12 and 13 with entry 1).[8] Too little water in the phase transfer reaction, however, appeared to drastically suppress aldol formation (entries 10 and 11). Finally, substitution of toluene for methylene chloride as solvent gave a slightly lower yield and decreased the diastereomeric excess by 13% (entry 14).[9]

The structure of the aldehyde also affected the reaction outcome (Table II). For example, an increase in chain length from acetaldehyde to butanal, 4-pentenal, heptanal, and then 4-*cis*-decenal (entries 1-5) resulted in an increase in diastereomeric excess (from 14 to 56%) as well as some improvement in yield (from 46% to as high as 78%). This observation could be due to the decreased water solubility of the long chain aldehyde, thereby making it more predominant in the organic phase and perhaps more strictly oriented with respect to enolate–catalyst interactions. Aldehydes containing aromatic functionality were reacted as well (entries 7-12). Benzaldehyde (entry 7), although giving the protected β-phenylserine in good yield, showed poor diastereoselectivity. The longer chain hydrocinnamaldehyde and 3-(p-methoxyphenyl)propanal (entries 10 and 11, respectively) produced aldol products with diastereomeric excesses comparable to those obtained with the mid-sized alkyl aldehydes (entries 2-4). Note that attempts at aldol condensations with several aromatic esters of succinic semialdehyde (entry 6) led instead to ester hydrolysis under the phase transfer conditions, even for the bulky 9-fluorenyl ester. Thus, hydrophobic aryl or alkyl aldehydes seemed to react most favorably.[10]

It is interesting to compare the aldol condensation between imine **2** and heptanal under typical anhydrous conditions and chiral phase transfer catalytic conditions. In the former, the lithium enolate was formed with lithium hexamethyldisilazide at -78°C in tetrahydrofuran followed by addition of heptanal (1000 mol%), stirring for 1.5 hours, and quenching at this temperature. Comparison of the ^{1}H NMR spectrum for this crude product with that for the corresponding aldol obtained under phase transfer conditions (Table II, entry 3) showed that the anhydrous method *gave opposite and attenuated diastereoselectivity (10% de).* Moreover, although no aldehyde self-condensation was observed, the anhydrous reaction *was not as clean* overall compared to the phase transfer reaction.[11]

Table I. Variations on Conditions for PTC Aldol Reaction of Imine 2 and Heptanal.

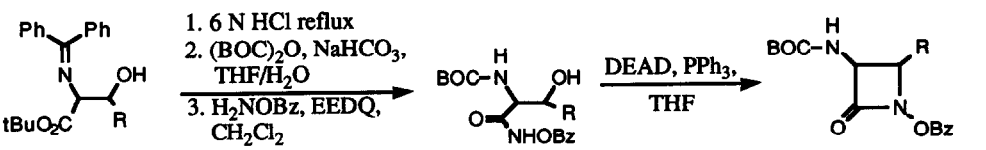
ENTRY	CONDITIONS[a]	%YIELD[b]	%de[c]
1	usual	81	39
2	no catalyst	0	--
3	N-benzylcinchonidinium chloride (**1b**) as catalyst	86	43
4	$nBu_4N^+Cl^-$ as catalyst	<25	nd[d]
5	$(PhCH_2)(Et)_3N^+Cl^-$ as catalyst	0	--
6	choline chloride as catalyst	0	--
7	Na_2CO_3 as base	25	43
8	LiOH as base	89	40
9	20 mol% of 5% NaOH	50	43
10	catalytic 50% NaOH	0	--
11	catalytic solid NaOH	<5	--
12	210 mol% of 50% NaOH	52	56
13	200 mol% of 5% NaOH in 50% NaF	29	52
14	toluene as solvent	75	26

[a]Unless specifically changed, conditions include: 0.1 M imine **2** in methylene chloride (25-50mg scale), 10 mol% N-benzylcinchoninium chloride **1a**, 500 mol% heptanal, 200 mol% of NaOH (5% w/v). [b]crude yield estimated from ^1H NMR integration. [c]Determined from ^1H NMR integration on crude product. [d]Not determined.

Table II. Reaction of Various Aldehydes and Imine 2–Yield, Diastereoselectivity.[a]

ENTRY	RCHO, R=	%YIELD	%de[b]
1	CH_3	46[c]	14
2	$CH_2CH_2CH_3$	54[d]	43
3	$(CH_2)_5CH_3$	81[c]	39
4	$(CH_2)_2CH{=}CH_2$	74[c]	40
5	*cis* $(CH_2)_2CH{=}CH(CH_2)_4CH_3$	74[c]	56
6	$CH_2CH_2CO_2R'$ R'=isopropyl, benzyl, p-nitrobenzyl, 9-fluorenyl	0	--
7	Ph	92[c]	0
8	CH_2CH_2(2-furyl)	e	--
9	*trans* CH=CH(2-furyl)	e	--
10	CH_2CH_2Ph	76[c]	33
11	CH_2CH_2(Ph-4-OCH_3)	85[c]	40
12	*trans* CH=CHPh	e	--

[a]Conditions include: 0.1 M imine **2** in methylene chloride (25-50mg scale), 10 mol% N-benzylcinchoninium chloride **1a**, 500 mol% aldehyde, 200 mol% of NaOH (5% w/v). [b]Determined from ^1H NMR integration of crude product unless diagnostic resonances were obscured. [c]Crude yield estimated from ^1H NMR integration. [d]Determined on purified mixture of diastereomeric products. [e]Several products were formed and were not further identified.



3a R=$(CH_2)_5CH_3$
3b R=$(CH_2)_2Ph$

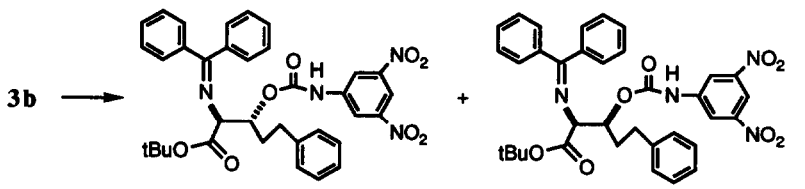
6a R=$(CH_2)_5CH_3$
6b R=$(CH_2)_2Ph$

$(BOC)_2O$ = *t*-butoxycarbonylanhydride
EEDQ = 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
DEAD = diethylazodicarboxylate

Scheme 2

Relative stereochemistry as well as enantiomeric excess were determined for the aldol products of two structurally representative aldehydes—heptanal and hydrocinnamaldehyde. In order to determine the relative configuration at the stereoisomeric centers for each case, the crude aldol product (consisting of both diastereomers in a known ratio) was merely converted to the corresponding mixture of diastereomeric β-lactams by a series of proven protection, coupling, and cyclization steps used routinely in our lab as well as in others.[4e] Analysis of the coupling constants in the ^{1}H NMR confirmed that the major β-lactam was the *trans* form in each case, which suggested that the original aldol product consisted predominantly of the *threo* (syn) isomer (Scheme 2).

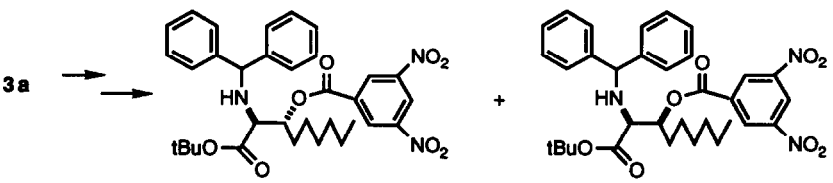
The degree of enantioselectivity was determined by chiral chromatography and ^{1}H NMR analysis with a chiral shift reagent. In the case of hydrocinnamaldehyde, the aldol mixture was derivatized as the 3,5-dinitrophenyl carbamate,[12] and the individual aldol diastereomers were analyzed for enantiomeric excess after chromatographic separation (eq. 3). Each showed less than 10% ee.[13] In order to eliminate complications due to partial cyclization, the heptanal aldol diastereomers were derivatized as the 3,5-dinitrobenzoyl esters of the reduced imines (eq. 4).[12] Again, the diastereomers were separated chromatographically and then each was subjected to chiral chromatography. A 12% ee was obtained for the major (*threo*) diastereomeric ester. The enantiomers of the minor (*erythro*) diastereomeric ester, however, apparently did not resolve chromatographically. The enantiomeric excess was determined instead by using the chiral shift reagent Eu(hfc)$_3$. Complete separation of the stereoisomeric benzhydryl proton signals resulted, with the resonances integrating to 7% ee.[14]



(3)

7b major (*threo*) derivative 3-6% ee

8b minor (*erythro*) derivative 6% ee



(4)

7a major (*threo*) diastereomer 12% ee

8a minor (*erythro*) diastereomer 7% ee

The data summarized in Table I (entries 1-5) suggested that the cinchoninium structure of the catalyst was important in effecting the aldol reaction between the Schiff base and the aldehyde. However, in contrast to the monoalkylation results,[1i] the necessary interaction among catalyst, enolate, and aldehyde must not be intimate enough to induce high enantioselectivity under the conditions investigated here.[15] On the other hand, some diastereoselectivity, the degree of which was dependent on several factors in the reaction, was observed. O'Donnell has shown for alkylation[1i] and we have shown for aldol formation that variation in

reaction conditions—such as strength and concentration of base, identity of solvent, and ionic strength of the aqueous phase—can alter stereoselectivity. Although further optimization may enhance the usefulness of this chemistry, the process provided cleaner product and opposite diastereoselectivity compared to the anhydrously generated amino acid.[11] Since this procedure required no scrupulously anhydrous conditions or extreme temperatures, and the starting materials were easily accessible, the method made synthesis of several nearly racemic β-hydroxy-α-amino acids (especially those containing long alkyl or aryl side chains) possible in an efficient two-step process.

EXPERIMENTAL SECTION

General Methods. NMR spectroscopy utilized a General Electric GN-300 instrument. All ^1H spectra were taken at 300 MHz in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as reference and ^{13}C spectra at 75 MHz with $CDCl_3$ as solvent and reference. Characterization of the aldol products or derivatives was usually done on the mixture of diastereomers since separation was either difficult or unnecessary. In these cases, ^1H NMR resonances were assigned, and integration was referenced according to the major diasteromer, with the minor diastereomeric signals reported as fractional values. NMR integration values were reported as measured without correction and were within 10-15% integration capabilities unless stated otherwise. Infrared data were obtained with a Perkin-Elmer Model 1420 spectrophotometer referenced to polystyrene either neat, as films evaporated from CH_2Cl_2 or $CHCl_3$ solutions, or as KBr pellets. Solvents and reagents were obtained from reputable sources and were purified by standard methods before use as necessary. Normal phase chromatography was done using Silica Gel 60 PF_{254} (EM Science). Unless stated otherwise, chromatography was performed with a Harrison Research Chromatotron Model 7924. TLC work employed aluminum backed plates of 0.2 mm thickness. Most HPLC analyses were accomplished with a Beckmann Model 332 Liquid Chromatography System using Alltech Econosil columns (5 μ silica, 25 cm x 4.6 mm i. d.–internal diameter–for analytical work and 10 μ silica, 25 cm x 10 mm i. d. for preparatory work) or a Regis Pirkle Cov D-Naphthylalanine column (5 μ, 25 cm x 4.6 mm i. d.) at 254 nm detection. Reverse phase HPLC employed Alltech C-8 columns (10 μ, 25 cm x 4.6 mm i. d.) integrated with an ISCO HPLC system consisting of pump (Model 2350), gradient programmer (Model 2360), and fluorescence detector (model FL-2) connected to a Hewlett Packard SP 4290 integrator. Mass spectral data were obtained on a Finnagan MAT Model 8430 spectrometer by electron impact (EI) at 70 eV or by chemical ionization (CI) with isobutane.

General Procedure for Phase Transfer Catalyzed Aldol Reaction (3). To a suspension of *tert*-butyl N-(diphenylmethylene)glycinate (**2**, 50 mg, 0.17 mmol)[16] and N-benzylcinchoninium chloride (**1a**, 7.1 mg, 0.017 mmol, 10 mol%) in 1.7 mL of CH_2Cl_2 under argon were added 270 μL of 5% w/v sodium hydroxide (0.34 mmol, 200 mol%) and the aldehyde (neat, 0.85 mmol, 500 mol%). The reaction mixture was magnetically stirred vigorously at room temperature for 3-4 h (until no change was observed by TLC). Workup was accomplished by first diluting with 10 mL each of H_2O and CH_2Cl_2. The organic layer was then evaporated; the residue was dissolved in ether or EtOAc (ethyl acetate) and washed with H_2O and saturated NaCl. After drying with $MgSO_4$ and subsequently filtering, the solvent was evaporated to yield a crude mixture of aldol diastereomers, starting materials, and the aldehyde self-condensation side product. Purification could be accomplished by silica chromatography using hexanes, CH_2Cl_2, and EtOAc as solvents, although significant degradation was observed in some instances. The presence of the desired aldol diastereomers was confirmed by ^1H NMR and high resolution mass spectrometry in nearly all cases, but additional characterization was obtained on the products in a more stable form. Evidence for the oxazolidine form of the aldol diastereomers was not conclusive in the ^1H NMR spectra, but was suggested by the

complicated nature of the ^{13}C NMR spectra (data not reported): Resonances representing the C-2 of the 1,3-oxazolidine ring were observed in the expected region (near 100 ppm).[6] The aldol reaction has been scaled up to 500 mg of Schiff base (0.85 mmol) with improvement in yield. Listed below are the characterization data for the two representative aldol products **3a** and **3b**.

***tert*-Butyl 2-[(diphenylmethylene)amino]-3-hydroxynonanoate (3a):** A 74% yield of a mixture of the two diastereomers in a ratio of 0.3 to 1.0 was obtained after chromatography (the oxazolidine form of the aldol product appeared to be present as well in a ratio of 0.1 to 1.0 compared to the major diastereomer); oil; ^1H NMR δ 7.90-7.15 (m, 16.0 H of the expected 14.0 H), 3.95 (m, 1.4 H, H-3, all isomers), 3.86 (d, *J*=3.0 Hz, 0.1 H, presumed to be H-2 of oxazolidine form), 3.79 (m or apparent d, *J*=8.1 Hz, 0.3 H, H-2 minor), 3.47 (d, *J*=7.8 Hz, 1.0 H, H-2 major), 3.23 (broad s, H-heteroatom), 1.46 and 1.45 and 1.27 (s, s, m, respectively, total 28.7 H of the expected 26.6 H, *t*-butyl minor and major, side chain, respectively), 0.88 (t, *J*=7 Hz, 4.7 H of the expected 4.2 H, side chain methyls); IR (neat) 3700-3100, 1730 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{35}NO_3$ 409.2616, found 409.2615.

***tert*-Butyl 2-[(diphenylmethylene)amino]-3-hydroxy-5-phenylpentanoate (3b):** A 76% yield of a crude product mixture was obtained (ratio of 0.3 to 1.0 for diastereomers), 27% yield of the two diastereomers after chromatography; oil; ^1H NMR δ 7.9-7.0 (m, 17.4 H of the expected 19.5 H), 3.96 (m, 1.3 H, H-3 major and minor), 3.80 (m or apparent d, *J*=8.7 Hz, 0.3 H, H-2 minor), 3.53 (d, *J*=7.8 Hz, 1.0 H, H-2 major), 3.23 (broad s, H-heteroatom), 2.7-3.1 (m, 2.3 H of the expected 2.6 H, H-5), 1.5-1.9 (m, 2.3H of the expected 2.6 H, H-4), 1.42 and 1.39 (s, s, total 10.0 H of the expected 11.7 H, minor and major *t*-butyl, respectively); IR (neat) 3700-3200, 1731 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{31}NO_3$ 429.2293, found 429.2303.

General Procedure for Anhydrous Aldol Reaction (3a). All glassware was oven- or flame-dried and all manipulations were done under argon. A solution of lithium hexamethyldisilazide was made by adding N-butyl lithium in THF (196 μL, 0.373 mmol, 110 mol%) to hexamethyldisilazane (93 μL, 0.441 mmol, 130 mol%) at ~4°C and stirring 0.5 h. The colorless solution was cooled to -78°C and *tert*-butyl N-(diphenyl-methylene)glycinate **2** (100 mg, 0.339 mmol, 100 mol%)[16] was added as a solution in 1.2 mL of THF over 10 min; the resulting bright yellow solution was stirred for 35 min at -78°C. Heptanal (478 μL, 387 mg, 3.39 mmol, 1000 mol%) in 400 μL of THF was added dropwise over 10 min followed by 100 μL of additional solvent as a rinse. The solution was stirred at -78°C for ~1.5 h, after which time the starting material **2** was consumed as determined by TLC. Quenching at -78°C was accomplished by addition of 6-8 mL of 100 mM aqueous potassium phosphate, pH 7.5. An equal volume of EtOAc was added and the layers were separated. The aqueous phase was extracted six times with fresh organic solvent, and the combined organic layers were concentrated to 30 mL and washed with saturated $NaHSO_3$,[17] H_2O, and saturated NaCl. After drying over $MgSO_4$ and filtering, the solvent was removed *in vacuo* to leave 265 mg of crude product. ^1H NMR suggested a 10% de with the *erythro* diastereomer being the major product. No starting material resonances were observed, but the presence of unidentified side products made calculation of yield impossible. The crude material was not further purified or characterized.

Reduction of the aldol diastereomers to the tert-butyl 2-benzhydrylamino-3-hydroxy esters (4). The aldol product, in crude or purified form, was dissolved in MeOH (0.2 M) under argon. $NaCNBH_3$ (300-500 mol%) was added followed by an excess of HOAc (2000-3000 mol%), and the solution was stirred at room temperature. After starting material was consumed as determined by TLC (about 30 min), the solvent was evaporated and the residue was dissolved in CH_2Cl_2/H_2O (ratio 1:1, about 20 mL total solvent for 0.5 to 1.0 mmol of material). The aqueous phase was extracted with fresh CH_2Cl_2 and the combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and filtered. The solvent was removed to leave the

crude product, which could be purified to a mixture of diastereomers or, less frequently, to the individual separated diastereomers by chromatography using hexanes, CH_2Cl_2, and EtOAc as eluents. Listed below are the characterization data for the two representative reduced aldol products **4a** and **4b**.

***tert*-Butyl 2-(benzhydrylamino)-3-hydroxynonanoate (4a, R=$(CH_2)_5CH_3$):** A 66% yield of diastereomers was obtained after chromatography (reaction performed on a 0.52 mmol scale on crude aldol product), the major diastereomer of which was completely separated and fully and separately characterized (the minor diastereomer was characterized as the mixture of diastereomers, the data of which are not reported here): oil; ^{1}H NMR δ 7.4-7.2 (m, 11 H of the expected 10 H), 4.83 (s, 1 H), 3.62 (m, 1 H), 3.21 (broad s, 1 H), 2.98 (d, J=6.3 Hz, 1 H), 2.46 (broad s, 1 H), 1.47 and 1.26 (s, m, respectively, 19 H), 0.870 (t, J=6.6 Hz, 3 H); ^{13}C NMR δ 173.16, 143.79, 142.08, 128.53, 128.50, 127.61, 127.26, 127.18, 81.72, 72.25, 65.58, 64.29, 33.61, 31.69, 29.20, 28.07, 25.34, 22.54, 14.02; IR (neat) 3650-3300, 1720 cm^{-1}; HRMS (CI) $C_{26}H_{37}NO_3$ calcd MH^+ 412.2851, found 412.2839.

***tert*-Butyl 2-(benzhydrylamino)-3-hydroxy-5-phenylpentanoate (4b, R=CH_2CH_2Ph):** An 80% yield was obtained from a purified mixture of aldol diastereomers in a ratio of 0.50 to 1.0 (0.038 mmol scale); oil; ^{1}H NMR δ 7.45-7.1 (m, 22.7 H of the expected 22.5 H), 4.85 and 4.83 (s, s, total 1.3 H of the expected 1.5 H, minor, major benzhydryl H, respectively), 3.75 (m, 0.5 H, H-3 minor), 3.62 (m, 1.0 H, H-3 major), 3.27 (d, J=4.8 Hz, 0.5 H, H-2 minor), 3.02 (d, J=6.3 Hz, 1.0 H, H-2 major), 2.78-2.65 (m, 5.0 H of the expected 4.5 H, H-5 and H-heteroatom), 1.83-1.65 (m, 3.3 H of the expected 3.0 H, H-4). 1.423 and 1.393 (s, s, total 12.0 H of the expected 13.5 H, major, minor *t*-butyl, respectively); ^{13}C NMR δ 172.84, 172.32, 143.71, 143.64, 142.06, 141.96, 141.83, 141.67, 128.49, 128.43, 128.34, 128.23, 127.63, 127.58, 127.28, 127.25, 127.18, 127.12, 125.66, 81.76, 71.32, 70.76, 65.55, 64.14, 63.55, 35.26, 34.72, 31.84, 31.56, 27.99; IR (neat) 3600-3200, 1721 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{33}NO_3$ 431.2460, found 431.2444.

Complete deprotection of aldol diastereomers to β-hydroxy-α-amino acid hydrochloride salts (5). The crude aldol products were heated to reflux in 6 N HCl (final substrate concentration approximately 0.1 N) under argon for 3 h. After cooling, the aqueous phase was washed three times with CH_2Cl_2 and then lyophilized. Yields ranged from 80% to near quantitative. In the case of β-phenylserine and β-hydroxynorleucine, the identity of the deprotected amino acid was confirmed by reverse phase HPLC by coinjection of the *o*-phthalaldehyde derivative[18] with that of authentic material synthesized by a different procedure.[19] The de for β-hydroxy-α-amino acid hydrochloride salts from heptanal (**5a**, R=$(CH_2)_5CH_3$) and hydrocinnamaldehyde (**5b**, R=CH_2CH_2Ph) were determined by *o*-phthalaldehyde derivatization and reverse phase HPLC[18] and were carried through the β-lactam formation procedure below.

Synthesis of β-lactam derivatives of the aldol diastereomers for determination of relative stereochemistry (6).[4e] The amino group of the deprotected β-hydroxy-α-amino acid hydrochloride salts **5a** or **5b** (diastereomeric mixture of known ratio) was protected (1.7 mmol scale) with *t*-butoxycarbonylanhydride (200 mol%) in the presence of $NaHCO_3$ (300 mol%) in THF/H_2O (4:3, 45-50 mL total volume). The crude product was coupled to O-benzylhydroxylamine (100 mol%) with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ, 100 mol%) in anhydrous CH_2Cl_2 (10-15 mL). After chromatography to remove byproducts, ring closure was effected under Mitsunobu conditions (120 mol% triphenylphosphine, 100 mol% diethylazodicarboxylate in 10 mL THF).[20] Another chromatographic step removed byproducts, but the two β-lactam diastereomers were inseparable. Relative stereochemistry of the C-3/C-4 ring positions for each diastereomer in the mixture was determined by analysis of the coupling constants in ^{1}H NMR spectrum. Note that care was taken to ensure the initial ratio of aldol diastereomers remained nearly constant throughout

these steps, and the final β-lactam derivative was characterized as the unaltered diastereomeric mixture (except for determination of mp, in which case the mixture was recrystallized from ether/hexanes).

Derivative from the heptanal aldol product (6a): A white solid in 33% overall yield was obtained (0.4 to 1.0 diastereomeric ratio), which could be enriched in the major diastereomer by recrystallization (mp=105-106°C); ^{1}H NMR δ 7.39 (m, 7.3 H of the expected 7.0 H), 5.09 (broad d, major and minor NH), 4.98 and 4.97 (m, m, 2.8 H total, major and minor benzylic H), 4.73 (dd, *J*=4.8 Hz, 8.4 Hz, 0.4 H, minor ring H-3), 4.16 (d, *J*=6.3-6.9 Hz, 1.0 H, major ring H-3), 3.54 (m, 0.4 H, minor ring H-4), 3.41 (m, 1.1 H of the expected 1.0 H, major ring H-4), 1.7-1.15 (several overlapping signals of C-4 alkyl chain and *t*-butyl, total 29 H of the expected 26.6 H), 0.88 (t, *J*=6.8 Hz, 4.3 H, C-4 alkyl methyl); ^{13}C NMR δ 162.545, 154.99, 154.73, 134.89, 134.74, 129.36, 129.22, 129.14, 129.02, 128.64, 128.55, 80.44, 80.37, 78.21, 78.02, 67.73, 64.37, 58.70, 55.79, 31.49, 30.91, 29.13, 29.03, 28.19, 25.57, 25.10, 22.44, 13.97; IR (film) 1770, 1710 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{32}N_2O_4$ 377.2440, found 377.2445.

Derivative of the hydrocinnamaldehyde aldol product (6b): A white solid in 37% overall yield was obtained (0.6 to 1.0 diastereomeric ratio), which could be enriched in the minor diastereomer by recrystallization (mp=139-140°C); ^{1}H NMR δ 7.4-7.1 (m, 18.0 H of the expected 16.0 H), 5.25 (d, *J*=8.1 Hz, minor NH), 5.13 (d, *J*=6.6 Hz, major NH), 4.96 (m, 3.6 H of the expected 3.2 H, major and minor benzylic H), 4.76 (dd, *J*=4.8, 8.1 Hz, 0.6 H, minor ring H-3), 4.18 (dd, *J*=6.6, 0.6 Hz, 1.0 H, major ring H-3), 3.59 (m, 0.6 H, minor ring H-4), 3.42 (m, 1.1 H of the expected 1.0 H, major ring H-4), 2.70 and 2.55 (m, m, total 3.3 H of the expected 3.2 H, major and minor H-6), 2.0-1.7 (m, 3.6 H of the expected 3.2 H, major and minor H-5), 1.45 and 1.42 (*s*, s, total 16.7 H of the expected 14.4 H, major, minor *t*-butyl, respectively); ^{13}C NMR δ 162.48, 155.09, 154.74, 140.76, 140.61, 134.78, 134.59, 129.28, 129.10, 128.97, 128.59, 128.50, 128.34, 128.23, 126.01, 80.46, 80.27, 78.28, 78.04, 66.80, 63.56, 58.93, 55.82, 32.34, 31.68, 31.26, 30.02, 28.13, 28.17; IR (film) 1775, 1710 cm^{-1}. Analysis calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 70.08, H, 7.20; N, 7.10.

*3,5-Dinitrophenyl carbamate derivatization of the crude aldol product from hydrocinnamaldehyde (**7b** and **8b**).* The aldol reaction was performed as described above on 0.17-1.0 mmol of Schiff base **2**. Immediately after workup the crude product **3b** was derivatized with 3,5-dinitrobenzoyl azide according to the procedure of Pirkle.[12] After chromatography using hexanes/ethyl acetate solvent systems to remove side products, the derivatized diastereomers (67% yield from starting Schiff base **2**) could be separated analytically by normal phase HPLC (2 ml/min flow rate, 0.25% isopropyl alcohol–IPA–in hexanes, retention times 10.3 and 15.0 min, major and minor diastereomers, respectively) for enantioselectivity determination. Chiral HPLC analysis (2.0 mL/min flow rate, 0.75% IPA in hexanes) gave 6.5% ee for major (**7b**, *threo*) derivative and 8.7% ee for minor (**8b**, *erythro*) derivative.The major and minor diastereomers could be crystallized from benzene and methanol, respectively, for characterization.

Major diastereomer derivative (*threo*, 7b): mp=174-176°C; ^{1}H NMR δ 8.67 (broad s, 1 H), 8.56 (m, total 2 H), 7.60-7.20 (m, 16 H of the expected 15 H), 5.44 (m, 1 H), 4.35 (d, *J*=5.1 Hz, 1 H), 2.72 (t, *J*=7.8 Hz, 2 H), 2.28 (m, 1 H), 2.18 (m, 1 H), 1.40 (s, 9 H); ^{13}C NMR δ 172.39, 168.76, 152.39, 148.66, 141.13, 140.65, 139.03, 135.88, 130.63, 128.94, 128.77, 128.47, 127.97, 127.64, 126.04, 118.18, 112.54, 82.41, 78.37, 68.12, 32.17, 31.85, 27.89; IR (film) 3400-3220, 1735, 1710, 1540, 1340 cm^{-1}; HRMS (EI) calcd for $C_{35}H_{34}N_4O_8$ 638.2376, found 638.2370.

Minor diastereomer derivative (*erythro*, 8b): mp=110-113°C; ^{1}H NMR δ 9.01, 8.61, 8.52 (overlapping broad s, total 3 H), 7.46-7.10 (m, 17 H of the expected 15 H), 5.58 (m, 1 H), 4.26 (d, *J*=2.7 Hz, 1 H), 2.65 and 2.54 (m, m, total 2 H), 2.22 (m, 1 H), 1.97 (m, 1 H), 1.48 (s, 10 H of the expected 9 H); ^{13}C NMR δ 174.01, 170.42, 153.29, 148.30, 141.20, 140.74, 138.64, 135.47, 130.82, 129.46, 128.74, 128.58, 128.51, 128.06, 127.77, 127.61, 126.06, 118.37, 111.94, 83.04, 75.73, 68.12, 33.11,

31.45, 27.82; IR (film) 3350-3220, 1745-1700, 1540, 1340 cm^{-1}; HRMS calcd for $C_{35}H_{34}N_4O_8$ 638.2376, found 638.2370. Analysis calcd for $C_{35}H_{34}N_4O_8$: C, 65.82; H, 5.37; N, 8.77. Found: C, 66.00; H, 5.50; N, 8.90.

3,5-Dinitrobenzoyl derivatization of the tert-butyl 2-(benzhydrylamino)-3-hydroxynonanoate (7a and 8a). The aldol reaction and subsequent reduction were performed as described above on a 0.85 mmol Schiff base **2** scale. The crude product **4a** was derivatized with 3,5-dinitrobenzoyl chloride in the presence of triethylamine (110 mol%) in 10 mL CH_2Cl_2[12] also with a catalytic amount of 4-dimethylaminopyridine (5 mol%). The resulting crude product was partially purified by preparatory thin layer chromatography (95:5 hexanes/ acetone) in 25% overall yield. This material was separated into its major and minor diastereomers by preparatory HPLC (1 mL/min flow rate, 1% THF in hexanes). The corresponding conditions on an analytical sized column showed that the samples were homogeneous, with retention times of 36 and 47 min, for the major and minor diastereomers, respectively. Chiral HPLC analysis (0.5 mL/min flow rate, 0.25% IPA in hexanes) gave 12% ee for the major (**7a**, *threo*) derivative and no apparent enantiomeric separation for the minor derivative (**8a**, *erythro*). Analysis of enantiomeric purity by use of the chiral shift reagent tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III), [Eu(hfc)$_3$] gave 3.6% ee (major–*threo*–derivative) and 7.0% ee (minor–*erythro*–derivative) by integration of the separated benzhydryl signals upon addition of 10-15 mol% of chiral shift reagent.

Major derivative (*threo*, 7a): oil; ^{1}H NMR δ 9.23 (t, *J*=2.1 Hz, 1 H), 9.11 (d, *J*=2.1 Hz, 2 H), 7.45-7.15 (m, 11 H of the expected 10 H), 5.45 (m, 1 H), 4.82 (s, 1 H), 3.29 (d, *J*=3.9 Hz, 1 H), 2.26 (broad s, H-heteroatom), 1.89 (m, 2 H), 1.44 (s, 9 H), 1.26 (m, 8 H), 0.88 (t, *J*=6.6 Hz, 3 H); ^{13}C NMR δ 171.17, 161.98, 148.64, 143.77, 142.03, 133.94, 129.39, 128.63, 128.50, 128.53, 127.83, 127.05, 127.50, 127.31, 127.05, 122.37, 82.37, 77.56, 65.43, 61.96, 31.58, 31.05, 28.94, 27.98, 25.32, 22.50, 14.00; IR(neat): 1735, 1550 cm^{-1}; HRMS (CI) calcd for $C_{33}H_{40}N_3O_8$ 606.2815, found 606.2793.

Minor derivative (*erythro*, 8a): oil; ^{1}H NMR δ 9.23 (t, *J*=2.1 Hz, 1 H), 9.12 (d, *J*=2.1 Hz, 2 H), 7. 1-7.5 (m, 10 H), 5.39 (m, 1 H), 4.81 (s, 1 H), 3.44 (d, *J*=5.1 Hz, 1 H), 2.4 (broad s, 1 H), 1.9 (m, 2 H), 1.480 (s, 9 H), 1.22 (m, 11 H of the expected 8 H), 0.867 (t, *J*=6.6 Hz, 4 H of the expected 3 H), note that integration of the alkyl region δ 1.3-0.7 integrates slightly higher than the 10-15% deviation from the expected value; ^{13}C NMR δ 171.33, 161.79, 148.67, 143.72, 142.26, 133.58, 129.43, 128.62, 128.47, 127.76, 127.37, 127.17, 122.37, 83.31, 78.13, 65.74, 62.06, 31.58, 30.79, 28.96, 28.14, 25.16, 22.51, 14.00; IR(neat): 1735, 1550 cm^{-1}; HRMS (CI) calcd for $C_{33}H_{40}N_3O_8$ 606.2815, found 606.2799.

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2. Further precedent can be found in the enzymatically catalyzed aldol reaction with an enzyme-bound glycine–pyridoxal phosphate imine, which occurred with high stereoselectivity. Lotz, B. T.; Gasparski, C. M.; Peterson, K.; Miller, M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1107.
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8. In the case of 50% NaOH, the drop in yield of desired aldol product can be explained by the more facile formation of aldehyde self-condensation side product under these conditions. NaF was chosen as salt because the equilibrium constant for exchange of various counter ions for F^- with a quaternary salt is generally quite low. See reference 7, pp. 24, 27. Thus, minimal perturbation by F^- on the action of the catalyst was expected, although the low yield in this case could be due to some cinchoninium-fluoride interactions. Note, however, that the same trend toward better diastereoselectivity with higher ionic strength in aqueous solution was not observed for the aldol reaction with 4-*cis*-decenal: The de was decreased from 56% to 32% with a change of 5% w/v to 50% w/w (weight/weight) NaOH.
9. A change from toluene to CH_2Cl_2 improved enantioselectivity in O'Donnell's alkylations, but several examples exist in which a cinchoninium salt was used as a chiral phase transfer catalyst with toluene as the organic solvent. See references 1b, g, j.
10. Some evidence was obtained which suggested that the imine structure **2** also affected stereochemical outcome. For example, we expected that the change from a *t*-butyl to the aromatic tricyclic planar

ester 9-fluorenyl might allow tighter binding or different orientation of the enolate with the catalyst. Phase transfer catalyzed aldol with this substrate and heptanal yielded 78% product in 47% de (compare to Table II, entry 3).

11. In a personal communication, O'Donnell has reported 91:9 mixture of erythro:threo diastereomers of the aldol product from N-(diphenylmethylene)glycinate ethyl ester and acetaldehyde obtained under anhydrous conditions in 72% yield.
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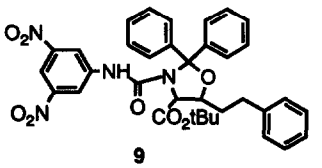
13. During this derivatization process for aldol product **3b**, a third minor product was isolated which was formed in significant amounts only when the aldol diastereomers were initially chromatographed before derivatization. The fact that mass spectrometry data was shown to have the same mass as the two derivatized aldol diastereomers suggested that this third product was the 3,5-dinitrobenzoylurea of the oxazolidine form of the aldol adduct (**9**).



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14. It was also shown for the major (*threo*) diastereomer of the heptanal aldol product that [Eu(hfc)$_3$] effected separation of the enantiomeric t-butyl resonances of the *underivatized form* of reduced imine **4a** (R=$(CH_2)_5CH_3$). Enantiomeric excess determined in this manner, 5-8% ee, corresponded well with that obtained for the derivatized form, thus confirming the fact that the ester derivatization process did not alter stereochemical outcome.
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