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An Efficient Homogeneous Catalytic Enantioselective Synthesis of α-Amino Acid Derivatives

Martin J. O'Donnell,*† Francisca Delgado,† Curt Hostettler[1]† and Reinhard Schwesinger‡

†Department of Chemistry, Indiana University-Purdue University at Indianapolis
Indianapolis, IN 46202, USA

‡Chemisches Laboratorium, Institut für Organische Chemie und Biochemie, Universität Freiburg
Albertstraße 21, D-79104 Freiburg, Germany

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Abstract: The catalytic enantioselective alkylation of the benzophenone imine of glycine t-butyl ester is realized by an efficient homogeneous reaction with alkyl halides, the neutral, non-ionic phosphazene base (BEMP or BTPP), and chiral quaternary ammonium salts derived from the *cinchona* alkaloids.

Keywords: Amino acids and derivatives, Alkylation, Enantiocontrol, Phosphazenes.

We have been interested for some time in the application of phase-transfer catalysis (PTC) to the preparation of amino acid derivatives.[2] In 1978 the first general synthesis of racemic amino acids by PTC, based on the alkylation of glycine ester Schiff bases, was reported.[3a] In 1989 chiral, non-racemic catalysts derived from the *cinchona* alkaloids afforded optically active amino acids in up to 66% ee (5:1 ratio of enantiomers for benzylation) in a room-temperature catalytic enantioselective PTC process.[3b,4] A second generation of chiral quaternary ammonium salts, the N,O-dialkylated *cinchona* salts, gave higher selectivities (up to 81% ee, 10:1).[3c,3d] Recently, a third generation of chiral PTC catalysts has been reported independently by the Corey[5] and Lygo groups.[6] Both studies involved the simple, but highly effective change to the N-9-anthracenylmethyl salts either with the O-allylated derivative[5] or by *in-situ* generation of the O-alkylated salts.[6] Benzylations using $CsOH{\bullet}H_2O$ [CH_2Cl_2, -78 °C., 23 h, 87% yield, 94% ee (32:1)][5] or by the more conventional PTC method with 50% aqueous KOH as base [PhMe, RT, 18 h, 68% yield, 91% ee (21:1)],[6] gave impressive enantioselectivites. A variety of different alkyl halides were used (92-99.5% ee[5] and 67-91% ee[6]) and either enantiomer of the product could be prepared by choice of the pseudoenantiomeric cinchonidine[5,6] or cinchonine-derived catalysts.[6]

From a practical standpoint, the need for efficient stirring can be problematic in PTC processes. In the asymmetric PTC synthesis of amino acid derivatives, we[7] and others[6] have noted that, while levels of induction are not affected by stirring rate, in order to obtain rapid reactions, effective stirring is crucial. If the chiral quaternary ammonium catalysts could be used in a homogeneous system while still retaining an important advantage of the PTC process, that is the ability to have *both* the base and the alkyl halide present throughout the alkylation process, it would be possible to avoid the problems associated with stirring of heterogeneous reaction mixtures. We now report that such homogeneous catalytic asymmetric alkylation reactions can be achieved by use of the organic soluble, non-ionic phosphazene (Schwesinger) bases[8-10] in conjunction with chiral quaternary ammonium salts.

A general description of the alkylation reaction involving the Schwesinger bases BEMP (**3**) or BTPP (**4**)[11] in conjunction with the Schiff base substrate **1** and the *cinchona* salt catalysts **5** or **6** is shown below. Since the Schwesinger bases (**3** or **4**) are not readily alkylated,[8] it is possible to have both the base and electrophile present at the start of the reaction. The acidity (pKa in DMSO) of the starting Schiff base ester (**1**, pKa=19.7)[12a] and the conjugate acids of the Schwesinger bases (**3**, pKa=16.2 and **4**, pKa~17.0)[12b] are useful in providing a qualitative rationale for the alkylation reaction. Using either base **3** or **4**, only a small amount of the anion of **1** ($\mathbf{1}^-$) would be formed at equilibrium. This anion could then be "removed" by reaction with the alkyl halide, which, in turn, would serve to drive the formation of further $\mathbf{1}^-$ by reestablishing the acid/base equilibrium.

*Author to whom correspondence should be addressed. E-mail: odonnell@chem.iupui.edu.

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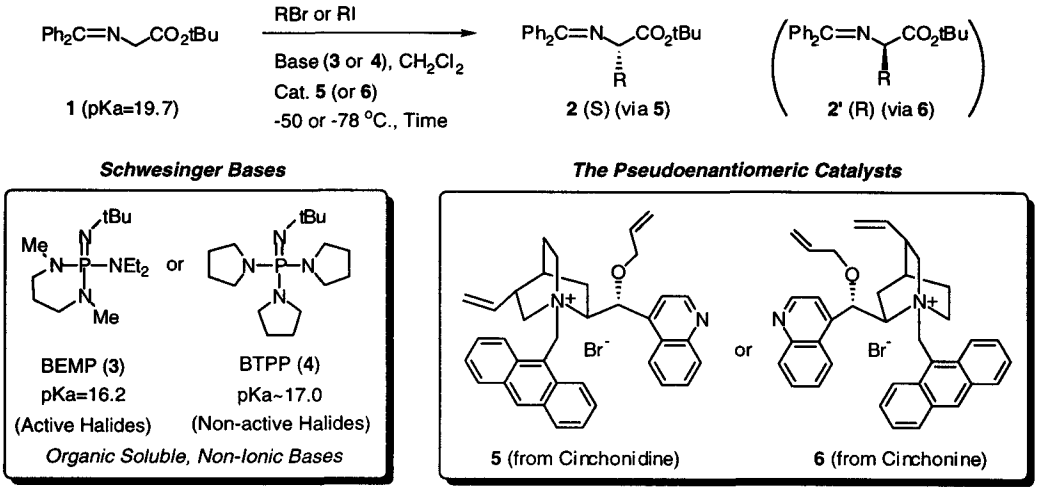
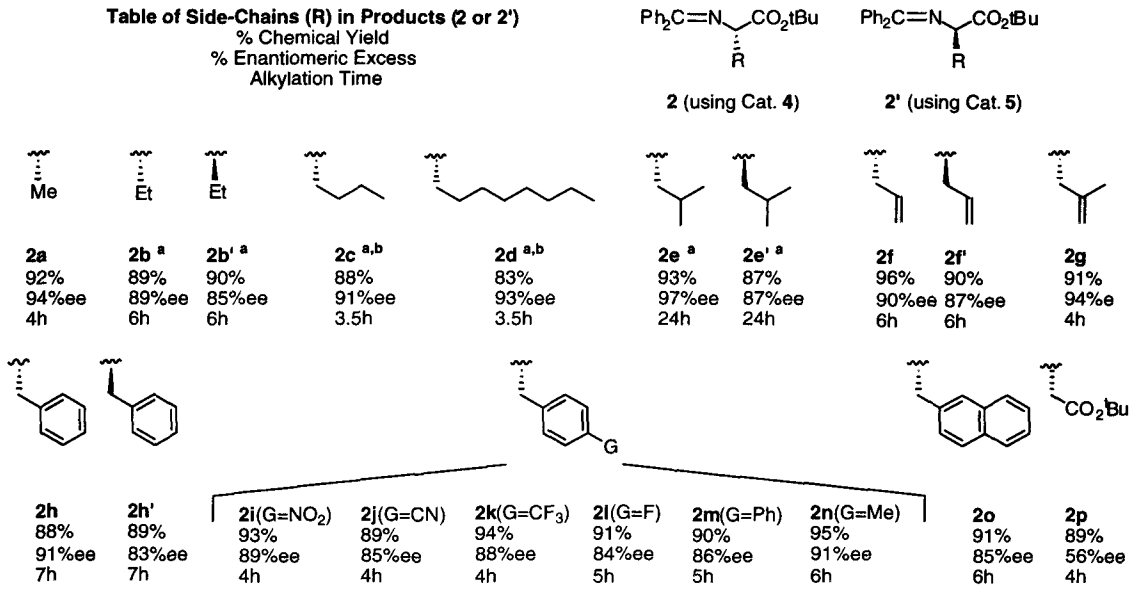


In order for the reaction to be stereoselective, it is necessary for the ion-exchange from the initially formed ion-pair [($\mathbf{1}^-$)($\mathbf{3H}^+$ or $\mathbf{4H}^+$)] to the chiral, non-racemic ion-pair [($\mathbf{1}^-$)($\mathbf{5}^+$ or $\mathbf{6}^+$)] to be fast relative to the rate of alkylation of the initially-formed ion-pair. We reasoned that the interaction of the chiral quaternary ammonium cation ($\mathbf{5}^+$ or $\mathbf{6}^+$) with the Schiff base anion ($\mathbf{1}^-$) should be much stronger than the initial interaction, following deprotonation, of the Schwesinger base cation ($\mathbf{3H}^+$ or $\mathbf{4H}^+$) with $\mathbf{1}^-$ or the interaction of the *cinchona* cation with the halide ion. This assumption was qualitatively confirmed by molecular modeling studies, which showed that cations $\mathbf{3H}^+$ or $\mathbf{4H}^+$ are too small and convex to interact effectively with the expanded and rather flat Schiff base anion ($\mathbf{1}^-$), whereas this substrate anion ($\mathbf{1}^-$) is able to interact strongly with and penetrate the *cinchona* cation (cation of **5** or **6**). We expected that, based on the recent heterogeneous studies,[5,6] this ion-pair exchange could be fast compared to the rate of the alkylation step. Furthermore, since the base is homogeneous in the present study, in contrast to the previously used heterogeneous base systems, the overall rate of reaction might well be faster using the Schwesinger bases **3** or **4**. Finally, the chiral, non-racemic alkylated product (**2** or **2'**) is expected to be considerably less acidic than the starting material **1**[13] and, therefore, product racemization under the mildly basic reaction conditions should not be a problem. This final point is important because the acidity of the chiral, non-racemic product dictates that, in order for the stereoselective alkylation to be successful, a relatively "weak base" must be used. This is accomplished either by the heterogeneous PTC systems[5,6] or by using the weak homogeneous Schwesinger bases.

We were gratified to find that a highly enantioselective alkylation can be achieved under homogeneous conditions by using the Schwesinger bases, BEMP (**3**) or BTPP (**4**), and the chiral quaternary ammonium salt catalysts **5** or **6**. The reaction is easily accomplished by mixing the starting Schiff base (**1**) and the chiral catalyst (**5** or **6**) in methylene chloride under an argon atmosphere, adding the appropriate alkyl halide, cooling the reaction mixture to -78 °C. (for active halides) or -50 °C. (for non-active halides), and then adding BEMP (for active halides) or BTPP (for non-active halides) to the magnetically stirred solution. The reaction is monitored by TLC for disappearance of starting Schiff base and following the reaction a simple workup (the solvent is evaporated and the product is isolated directly by flash chromatography) yields pure product.[14]

The optimal results for the homogeneous catalytic enantioselective alkylation process are summarized in the Table. As expected, either product enantiomer (**2** or **2'**) can be formed by choice of the appropriate pseudoenantiomeric catalyst (**3** or **4**, respectively). Alkylations involving active halides (methyl iodide, allylic bromides and benzylic bromides) are typically conducted using BEMP (**3**) as base at -78 °C., since the reactions are fast at this temperature and reactions at -50 °C., while being faster, give slightly lower levels of selectivity.[15]



[a] Alkylations conducted at -50 °C. with BTPP as base (all other alkylations carried out at -78 °C. with BEMP as base).
[b] 10 equiv. each of RX and base used.

On the other hand, alkylation with less reactive halides (primary straight-chain alkyl iodides and primary alkyl iodides with a β-branch) is accomplished using the stronger base, BTPP (**4**) at -50 °C. At -78 °C. with the non-reactive halides, even though selectivities are slightly better, the reactions are considerably slower.[16-18]

In summary, the catalytic enantioselective alkylation of the Schiff base of glycine t-butyl ester (**1**) has been realized under homogeneous conditions. The procedure, which uses Schwesinger bases (**3** or **4**) in conjunction with chiral quaternary ammonium salts (**5** or **6**) derived from the *cinchona* alkaloids, provides easy access to either enantiomer of a variety of amino acid derivatives in high enantioselectivity.

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11. BEMP = 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; BTPP = tert-butylimino-tri(pyrrolidino)phosphorane.
12. (a) We thank Professor F. G. Bordwell and Dr. X. -M. Zhang for determining the acidity of the benzophenone imine of glycine t-butyl ester (**1**). (b) The pKa of the conjugate acid of BEMP (**3**) in CH_3CN is 27.6 (Ref. 9) while in DMSO it is 16.2 (F. G. Bordwell, unpublished results). The pKa of the conjugate acid of BTPP (**4**) in CH_3CN is 28.4 (Ref. 9) while in DMSO it is estimated to be 17.0.
13. Compare the acidities (pKa, DMSO) of the corresponding Schiff base ethyl ester starting material and alkylated product: $Ph_2C{=}NCH_2CO_2Et$, 18.7 and $Ph_2C{=}NCHMeCO_2Et$, 22.8. See O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozak, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 8520-8525.
14. General reaction procedure: All reactions were conducted under an atmosphere of argon in oven-dried glassware. Alkyl halide (0.43 mmol, 5.0 equiv.) was added to a mixture of tert-butylglycinate benzophenone imine (**1**, 0.05 g, 0.17 mmol, 1.0 eq.) and O-allyl-N-9-anthracenylmethyl cinchonidinium bromide (**5**, 0.1 equiv.) in CH_2Cl_2 (0.5 mL). The reaction mixture was then cooled (-50 or -78 °C), the base was added (1.5 equiv. for active halides, 5.0 equiv. for non-active halides) dropwise over a few seconds, and the reaction mixture was stirred at -50 or -78 °C until starting material **1** had been consumed (TLC, silica gel, hexane/EtOAc, 12:1). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel. (hexane/EtOAc, 12:1). Chiral HPLC (isocratic) was used to determine enantioselectivities using the following (column, mobile phase (ranges used), flow rate (ranges used), detection wavelength, compounds): Baker Bond DNBPG (covalent), hexane-iPrOH (600:1 to 350:1), 0.3 mL/min, 254 nm, **2b**, **2c**, **2d**, **2e**, **2f**, **2h**, **2n**, **2o**); Chiracel OD, hexane:iPrOH (99.5:0.5), 1.0 mL/min, 254 nm, **2a**, **2g**; Whelk-01, hexane:iPrOH (98:2 to 90:10), 1.0 to 0.6 mL/min, 254 nm, **2i**, **2j**, **2k**, **2l**, **2m**, **2p**.
15. A temperature study of the alkylation of an active halide (benzyl bromide) with BEMP (**3**) under normal reaction conditions using catalyst **5** follows (alkylation temperature, time, yield of **2**, %ee): -78 °C., 7h, 88%, 91%ee; -50 °C., 5h, 89%, 83%ee; -20 °C., 88%, 77%ee; RT, 89%, 48%ee.
16. A temperature study of the alkylation of a non-active halide (ethyl iodide) with BTPP (**4**) under normal reaction conditions using catalyst **5** follows (alkylation temperature, time, yield of **2**, %ee): -78 °C., 24h, 84%, 93%ee; -50 °C., 6h, 89%, 89%ee; -20 °C., 89%, 87%ee; RT, 88%, 59%ee.
17. Compared with the optimal conditions (see notes 15 and 16), the stronger base BTPP with an active halide (benzyl bromide) gave a reduced enantioselectivity (-50 °C., 4h, 91%, 81%ee) (-78 °C., 4h, 86%, 88%ee) while the weaker base BEMP with a non-active halide (ethyl iodide) resulted in a much slower reaction (-50 °C., 24h, 78%, 91%ee) (-78 °C., 24h, 63%+starting Schiff base, 93%ee).
18. Reaction with the secondary halide, isopropyl iodide, was not successful. Similarly, reaction with benzhydryl bromide under standard conditions did not yield alkylation product.