A Rational Approach to Catalytic Enantioselective Enolate Alkylation Using a Structurally Rigidified and Defined Chiral Quaternary Ammonium Salt under Phase Transfer Conditions

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Ion-pair-mediated reactions under phase transfer conditions (phase transfer catalysis, PTC) have been increasingly useful in organic synthesis since their introduction.[1] However, there have been no successful applications to catalytic asymmetric synthesis,[1d] except for a few involving the use of cinchona-alkaloid-derived quaternary ammonium salts. The most outstanding of these is the methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone using *N*-(*p*-trifluoromethyl)benzylcinchoninium bromide sodium hydroxide complex under PTC to form (*S*)-α-methylated indanone in 92% enantiomeric excess (ee).[2] Noteworthy, but more modest enantioselectivities have been reported for the alkylation of *tert*-butyl glycinate−benzophenone Schiff base (range of 5:1−2.5:1) using the *N*-benzylcinchoninium ion−sodium hydroxide PTC system.[3] The reasons for the enantioselective bias in these cases have been unclear. In this paper, we present the initial results of a research program aimed at the determination of the mechanistic and geometrical factors responsible for enantioselectivity in PTC and the rational design of highly effective new phase transfer catalysts based on the cinchona alkaloid system. We have focused on the development of catalytic asymmetric alkylation at carbon because this is one of the most urgently needed synthetic methods.

Our approach may be summarized simply. If the bridgehead nitrogen of a cinchona alkaloid quaternary salt is taken to be at the center of a tetrahedron, the phase transfer catalyst should be structured so as to provide steric screening which prevents close approach of the counterion to three of the faces of this tetrahedron, while the fourth face should be sufficiently open to allow close contact between the substrate counterion and N^+. There should also be a nearby binding surface for attractive van der Waals interaction. Quaternary ammonium salts of cinchona alkaloids are ideal because one of the tetrahedron faces about the charged bridged nitrogen is totally blocked by the ring system itself. In addition, recent studies[4] have elucidated the fundamental reasons for enantioselectivity in the bis-cinchona-alkaloid-catalyzed dihydroxylation of olefins by OsO_4. Especially relevant was the finding that the attachment of the 9-anthracenylmethyl (anth) group to a bridgehead nitrogen leads to a quaternary ammonium structure of well-defined geometry in which a second tetrahedral face about N^+ is blocked by the 9-anthracenyl subunit, whose spatial position is fixed for steric reasons.[4f] Further, it was apparent that a third tetrahedral face about N^+ could be effectively screened simply by the attachment of an allyl or benzyl group to the secondary hydroxyl group; indeed, such ethers had already been studied in PTC reactions.[3b]

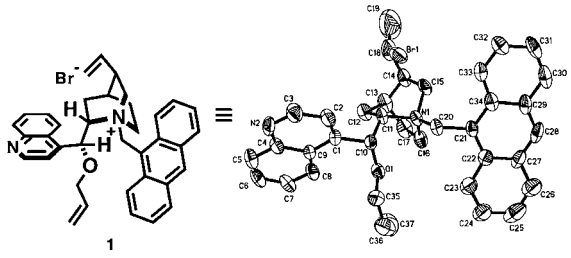

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Figure 1. ORTEP structure of *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide (**1**) (left).

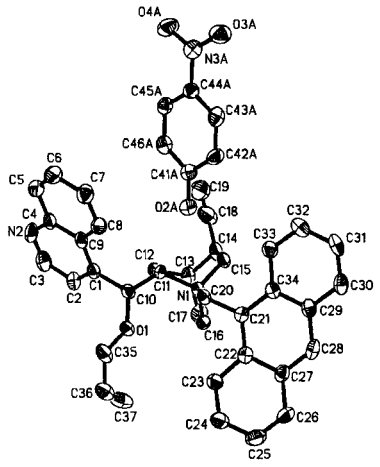

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Figure 2. ORTEP structure of *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium *p*-nitrophenoxide (**2**).

O(9)-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**1**) was prepared in two steps from cinchonidine and subjected to single-crystal X-ray diffraction analysis which revealed the structure shown in Figure 1.[6] As expected,[4f] the substituents about the N^+-CH_2 anth bond were staggered with the 9-anth carbon (C(21) in Figure 1) antiperiplanar to C(11), and the Br^- counterion was positioned in close contact with N(1) at the open tetrahedral face (backside to C(16)) with a Br−N(1) distance of 4.06 Å. Essentially the same structural arrangement was determined for the chloride corresponding to **1** by X-ray diffraction. Crystals of *O*(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium *p*-nitrophenoxide (**2**) were also prepared and subjected to X-ray crystallographic analysis, which revealed the analogous structure shown in Figure 2.[7] In this case the negative oxygen of the aryloxide counterion is also in close contact (3.46

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(2) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745.

(3) (a) O'Donnell, M. J.; Benett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (c) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181. (d) O'Donnell, M. J. et al. U.S. Patent 5,554, 753, September 10, 1996. (e) O'Donnell, M. J.; Esikova, I. A.; Mi. A.; Shullenberger, D. F.; Wu, S. In *Phase-Transfer Catalysis*; Halpern, M. E., Ed.; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; Chapter 10.

(4) (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038. (b) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579. (c) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861. (d) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319. (e) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828. (f) Corey, E. J.; Noe, M. C.; Ting, A. *Tetrahedron Lett.* **1996**, *37*, 1735.

(5) Quaternary bromide **1** was prepared in 94% yield by the following sequence: (1) reaction of cinchonidine with 9-(chloromethyl)anthracene in toluene at reflux for 2 h and (2) *O*-allylation of the resulting quaternary salt with allyl bromide in a CH_2Cl_2−50% aqueous KOH mixture at 23 °C for 4 h to form **1**, mp 194−196 °C, $[\alpha]^{23}_D$ −320 (*c* 0.45, $CHCl_3$).

(6) (a) Crystal structure data for **1**: $C_{39}H_{48}BrN_2O_2$, orthorhombic, $P2_12_12_1$, a = 12.0138(3) Å, b = 14.8225(2) Å; c = 20.0482(4) Å; $\alpha = \beta = \gamma = 90°$, $Z = 4$, $R_1(I > 2\sigma I) = 0.0668$. (b) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(7) Salt **2** was prepared by reaction of **1** with potassium *p*-nitrophenoxide in CH_3OH and recrystallized from CH_2Cl_2−hexane (vapor diffusion). Crystal structure data for **2**·$2CH_2Cl_2$: $C_{45}H_{45}Cl_4N_3O_4$, orthorhombic, $P2_12_12_1$, a = 9.2400(6) Å, b = 18.987(1) Å; c = 23.257(2) Å; $\alpha = \beta = \gamma = 90°$, Z = 4, $R_1(I > 2\sigma I) = 0.0540$.

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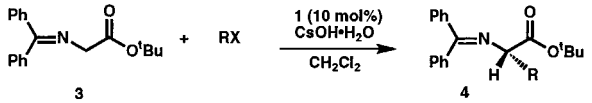
Table 1. Enantioselective Catalytic Phase Transfer Alkylation



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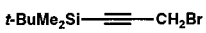
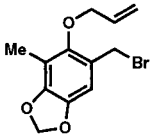
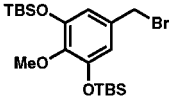
Entry	RX[a]	Temp, Time	ee%[b,c]	Yield (%)[d]
1.	CH_3I	-60 °C, 28 h	97	71
2.	CH_3CH_2I	-60 °C, 30 h	98	82
3.	$CH_3(CH_2)_4CH_2I$	-60 °C, 32 h	99.5	79
4.		- 60 °C, 36 h	99	75
5.		-78 °C, 22 h	97	89
6.		-78 °C, 20 h	92	91
7.		-78 °C, 18 h	95	68
8.	$PhCH_2Br$	-78 °C, 23 h	94	87
9.	Ph_2CHBr	-78 °C, 22 h	99.5	73
10.		-78 °C, 24 h	96	81
11.		-78 °C, 24 h	97	67

[a]An excess of RX was employed, *ca.* 5 equiv for entries 1-9 and 1.5 equiv for entries 10 and 11. [b]The (*S*) absolute configuration was established experimentally for the entries 1,2,5,8 and 11 by conversion of **4** to the corresponding α-amino acid or ester and comparison with an authentic sample. [c]Enantiopurity of **4** was determined by HPLC analysis of the alkylated imine using a chiral column (Chiral Technologies Chiracel OD column for entries 1-3 and 8 or a Regis Whelk-O1 column for entries 4-7 and 9-11 with hexane-2-propanol as solvent; in each case it was established by analysis of racemic **4** that the enantiomers were fully resolved. [d]Yields refer to chromatographically pure, isolated product **4**.

Å) with that same tetrahedral face of N(1) (backside to C(16)). These X-ray structures provide experimental evidence that the tetrahedral face of N^+ in these salts which is least subject to steric shielding is the one that contacts the counteranion; this face is backside to the unsubstituted two-carbon (CH_2-CH_2) bridge of the quinuclidinium subunit of **1**. If enolate ions pair selectively and intimately with the cation **1** in the same way as *p*-nitrophenoxide, this preferred arrangement coupled with the expected rigidity of the cation and the effects of van der Waals contacts could lead to enantioselective alkylation by a carbon electrophile. This prediction has been confirmed in gratifying fashion by the results which are summarized below.

We chose for initial investigations the alkylation of the enolate derived from *tert*-butyl glycinate−benzophenone Schiff base (**3**) since this substrate had been thoroughly studied in the pioneering research of O'Donnell et al.,[3] which demonstrated an enantioselectivity base line of 5:1 to 2.5:1. We used solid cesium hydroxide monohydrate as the basic phase in order to minimize the possibility of water in the organic phase (CH_2Cl_2) and to allow the use of lower temperatures (−60 to −78 °C) than are possible with 50% aqueous KOH or NaOH.[2,3] Table 1 summarizes the results obtained for the alkylation of **3** with a wide variety of carbon halides (RBr or RI) using 10 mol % of catalyst **1** and $CsOH\cdot H_2O$ as base in CH_2Cl_2 at −60 to −78 °C. Extremely high enantioselectivities, as high as 400:1 and averaging 65:1, were observed for the products (**4**), an indication that catalyst **1** is indeed very effective and that these reactions

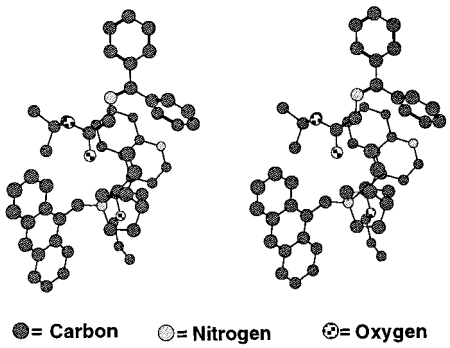


Figure 3. Stereopair representation of the preferred three-dimensional arrangement of the ion pair from **1** and the enolate **3**. Alkylation of the enolate occurs by attack of the electrophile at *si* (front) face of the enolate for steric reasons, leading to the enantiomeric products shown in Table 1.

proceed via a highly organized transition state.[8] This process is very practical (especially for nonnatural amino acids)[9] since the chiral PTC catalyst is efficently extracted from aqueous solution for reuse.[10]

Taking into account all of the above results, including the X-ray crystal data for **1** and **2**, the transition-state assembly shown in Figure 3 follows as most likely (the electrophile has been omitted for clarity). We regard these exothermic alkylations as proceeding via an early transition state with the major reaction channel being through the most stable geometry of the tight ion pair of cation **1** and enolate **3**, as shown in Figure 3, and with approach of the electrophile to the *si* (front) face of the ion-paired enolate. The reasons why the three-dimensional arrangement of the ion pair shown in Figure 3 is favored include the following: (1) the fixed orientation of the bulky *N*-9-anthracenylmethyl substituent in **1** provides steric screening and also rigidifies the cation so that there is a minimum entropic cost in forming the intimate, highly structured ion pair shown in Figure 3; (2) as indicated in the Introduction, direction-specific ion pairing occurs so as to bring into proximity the enolate oxygen with the sterically least encumbered face of the bridgehead N^+; and (3) complementary surfaces of the gegenions are brought together for maximum van der Waals attraction. Extensive search for alternative ion-pairing geometries, with the same arrangement of O^- and N^+ as shown in Figure 3, that would lead to the enantiomeric (*R*) alkylation products has revealed no structures with van der Waals contacts comparable to those shown in Figure 3.

We believe that the ideas expressed herein provide a useful new paradigm for enantioselective catalysis using ordered contact ion pairing. They are easily testable and provide clear guidance for the design of still more effective catalysts.

Acknowledgment. This paper is dedicated to the memory of Wolfgang von Oppolzer. We are grateful to the National Institutes of Health and the National Science Foundation for financial support and to Dr. Florian Kühnle for the X-ray crystallographic data.

Supporting Information Available: Experimental procedures, spectroscopic data for synthetic intermediates, and detailed X-ray crystallographic data for **1** and **2** (25 pages). See any current masthead page for ordering and Internet access information.

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(8) Somewhat lower enantioselectivities (average 20:1) were observed using 50% aqueous KOH at −20 °C instead of the $CsOH\cdot H_2O$ system as in Table 1. Also, lower enantioselectivities resulted when the methyl or ethyl ester of the glycine−benzophenone Schiff base was used as the substrate for alkylation.

(9) The amino acid derivatives produced from entries 10 and 11 in Table 1 are valuable building blocks for the synthesis of the potent antitumor agent ecteinascidin 743, see: Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202.

(10) Extensions of this research to highly enantioselective Michael addition and ring-forming double-alkylation reactions will be described in a separate publication.