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Two-Component Chiral Phase Transfer Catalysts: Enantioselective Esterification of an N-Acylated Amino Acid

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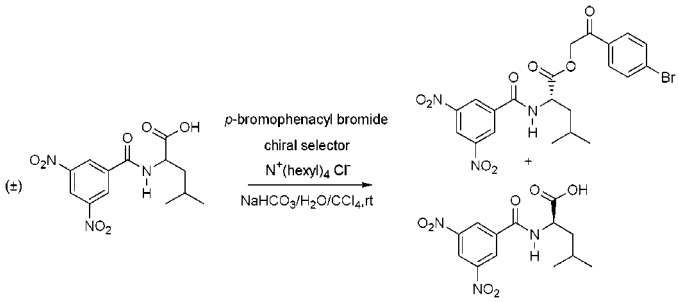
ABSTRACT



The first example of a two-component chiral phase transfer catalyst is described which, operating in a biphasic solvent system, preferentially esterifies one enantiomer of a racemic N-acylated amino acid. The two-component catalyst is comprised of an achiral quaternary ammonium ion and a proline-derived chiral selector initially developed for the liquid chromatographic separation of enantiomers.

The development of simple sturdy chiral catalytic systems for asymmetric induction is being actively pursued by many research groups. Several examples of rather successful chiral phase transfer catalysts (CPTC) have been described,[1] these being one-component entities typically derived from cinchona alkaloids.[2] That one might someday parlay the design of effective chromatographic chiral selectors into CPTC has been anticipated for some time. For example, several proline-derived selectors, when immobilized, have shown high levels of chromatographic enantioselectivity toward *N*-3,5-(dinitrobenzoyl) amino acid derivatives and related compounds.[3] Since similar systems have been demonstrated to selectively transport one enantiomer of a racemate from one immiscible liquid phase into another,[4] coupling the transport with a subsequent chemical reaction seemed a logical approach for kinetic resolution of these amino acid derivatives.[5]

In the examples of kinetic resolution described, racemic *N*-(3,5-dinitrobenzoyl) leucine (DNBleu), **1a**, dissolved in dilute aqueous sodium bicarbonate, is exposed to *p*-bromophenacyl bromide (BPB), tetra *n*-hexylammonium chloride (THAC), and an N-acylated L-proline anilide, (*S*)-**2**, all dissolved in a nonpolar water immiscible solvent such as carbon tetrachloride. Acting in conjunction, the latter two reagents selectively transport one enantiomer of the leucine derivative from the aqueous phase into the organic phase where it is alkylated by the *p*-bromophenacyl bromide to afford enantioenriched *p*-bromophenacyl ester (**1b**). Thus,

(1) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: New York, 1993; pp 727−756.

(2) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (b) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446−447. (c) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenwaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745−4752.

(3) (a) Pirkle, W. H.; Murray, P. J. *J. Chromatogr.* **1993**, *641*, 11−19. (b) Pirkle, W. H.; Koscho, M. E. *J. Chromatogr. A.* **1999**, *840*, 151−158.

(4) (a) Kellner, K.-H.; Blasch, A.; Chmiel, H.; Lämmerhofer, M.; Lindner, W. *Chirality* **1997**, *9*, 268−273. (b) Pirkle, W. H.; Bowen, W. E. *Tetrahedron: Asymmetry* **1994**, *5*, 773−776.

(5) A preliminary account of this research was presented at the International Symposium on Chiral Discrimination, 1998; Vienna, Austria.

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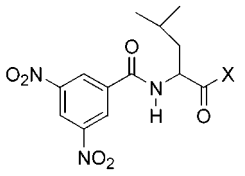
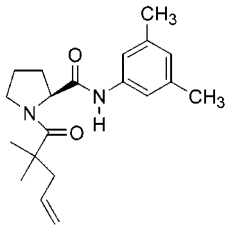
one has a two-component CPTC. At present, few one-component chiral phase transfer catalysts are known which



1a X=OH

1b X=$CH_2CO(4\text{-}BrC_6H_4)$



(*S*)-**2**

are effective in converting racemic acids into enantioenriched esters, something normally considered to be the province of selected enzymes.

Using a standard reaction protocol, it was found that in a stirred biphasic solvent system of aqueous sodium bicarbonate and carbon tetrachloride containing 1.0 mol equiv each of racemic DNBleu, **1a**, and 0.5 mol equiv of BPB, little or no esterification occurs at room temperature. Addition of 1.0 mol equiv of the L-proline-derived selector, (*S*)-**2**, does not alter this situation. However, addition of a small amount of the achiral THAC leads to production of ester **1b**. Enantiomerically enriched ester is produced when selector (*S*)-**2** is present; racemic ester is produced when it is not. This latter observation demonstrates that THAC is sufficiently lipophilic to transport the carboxylate anion into the carbon tetrachloride in the absence of selector (*S*)-**2**, which, by itself however, is incapable of effecting transport of the strongly solvated sodium carboxylate to any significant extent.

Simple partitioning experiments demonstrate that the enantiomeric purity and the amount of transported DNBleu depends on both the amount of THAC and selector (*S*)-**2** present. When the carbon tetrachloride layer was isolated after equilibration with the sodium bicarbonate, racemic **1a**, selector (*S*)-**2**, and THAC mixture, and BPB is then added, subsequent HPLC assay on an (*R,R*)-Whelk-O column shows that the amount of ester produced corresponds to the amount of THAC added (Table 1). Furthermore, as the amount of selector is decreased, one observes a corresponding decrease in the enantiomeric purity of the transported ion pair.

Table 1. Extraction of (±) **1a** from Saturated Sodium Bicarbonate into Carbon Tetrachloride with THAC (0.19 equiv) and Varying Amounts of Selector (*S*)-**2**[a]

(±) **1a** (equiv)	(*S*)-**2** (equiv)	THAC (equiv)	%extracted[b]	%ee[c]
1.0	2.00	0.19	19	86
1.0	1.00	0.19	19	77
1.0	0.50	0.19	19	59
1.0	0.25	0.19	19	46

[a] Standard conditions entailed use of 0.037 mmol (1 mol equiv) of (±)-**1** and the indicated number of mol equiv of the other reagents in 2.6 mL of saturated sodium bicarbonate and 2.6 mL of CCl_4. The layers were equilibrated by rapid stirring at room temperature for 15 min. Layers were separated, and the CCl_4 was washed with water and dried over magnesium sulfate. Excess BPB was added to the CCl_4, and aliquots were assayed periodically on racemic (%extracted) and (*R,R*)-Whelko (%ee) HPLC columns. The selector was utilized as the internal standard. [b] Represents percentage of DNBleu carboxylate ion extracted into organic layer. [c] Enantiomeric excess of the *p*-bromophenacyl bromide ester.

In biphasic reactions containing all the aforementioned components, with BPB present initially, the enantiomeric purity of the ester again increases as the concentration of selector (*S*)-**2** is increased and as the concentration of THAC is decreased (Table 2). Ideally, one should adjust the lipophilicity of the achiral PTC so that, by itself, it cannot effect transport of the carboxylate anions unless the lipophilic chiral selector is also involved. This would suppress the background production of racemic ester, arising from transport occurring independent of the chiral selector. However, this background reaction can be lessened through use of an excess of the chiral selector even if the achiral PTC is capable of unassisted transport.

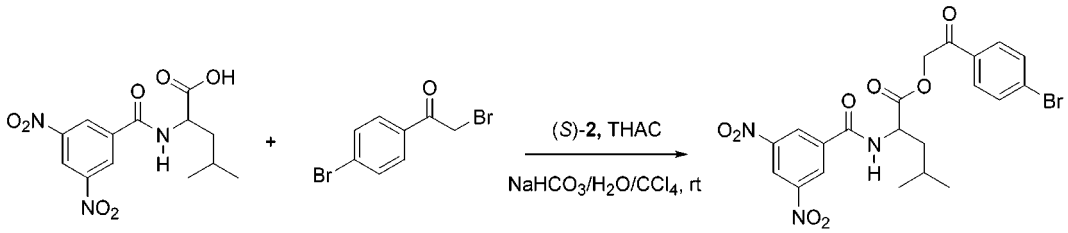
Dilution reduces reaction rate and enantioselectivity. As expected for a kinetic resolution, the enantiomeric purity of ester **1b** decreases somewhat as the extent of conversion increases, owing to depletion of the bicarbonate solution of the more rapidly esterified (*S*)-enantiomer of DNBleu.

Conversely, the enantiomeric purity of the residual (*R*)-DNBleu increases as the extent of esterification increases. Reaction at 4 °C increases the enantioselectivity of the esterification but slows the process. Because ester can be produced by an achiral pathway as well as by the process involving selector (*S*)-**2**, the extent to which each process contributes affects the enantiomeric composition of the ester produced. Consequently, the stereoselectivity factor (**s**) is influenced by the concentrations of the various species. In one of the examples shown in Table 2, the *s* factor was 25.8, a minimum value for the stereoselectivity of the unadulterated chiral process.

The success of this particular kinetic resolution process stems from the enantioselective transport process, which largely masks secondary processes. For example, while the more stable homochiral complex of (*S*)-**2** and ion pair formed from (*S*)-DNBleu and THAC is present in the carbon tetrachloride to a far greater extent than its heterochiral counterpart, they may, and do, have different reactivities toward BPB. Addition of BPB to a carbon tetrachloride solution containing (*S*)-**2** and the racemic ion pair shows that, initially, the (*R*)-ester is formed somewhat (ca. 1.5 times) more rapidly. Thus, either the less stable diastereomeric ion pair complex is more reactive than its more stable homochiral counterpart or it is relatively more dissociated and the noncomplexed ion pair is more reactive toward BPB than either of the diastereomeric complexes.

Although good kinetic data are hard to obtain in biphasic reactions owing to the dependence of reaction rates on mixing rates, one can certainly envision the occurrence of a type of "product inhibition" arising from the ability of the major product, the *(S)*-ester, to associate with selector *(S)*-**2**, thus lowering its effective concentration, something which could affect both reaction rates and enantioselectivities. Regardless of these complexities, the details of which remain to be unraveled, it is clear that two-component CPTCs can offer a practical means of kinetic resolution. The system described here is not optimized and is considered more a "proof of

Table 2. Enantioselective Biphasic Esterification Reactions[a]



(±) **1a** **3** **1b**

(±) **1a** (equiv)	**3** (equiv)	(*S*)-**2** (equiv)	THAC (equiv)	%ee (*S*)-**1b**	**S**[b]
1.0	0.50	2.00	0.035	87	25.8
1.0	0.50	1.00	0.035	76	12.2
1.0	0.50	0.50	0.035	63	6.60
1.0	0.50	0.25	0.035	44	3.39
1.0	0.50	2.00	0.085	74	10.9
1.0	0.50	1.00	0.085	62	6.33

[a] Standard conditions entailed use of 0.11 mmol (1 mol equiv) of (±)-**1** and the indicated number of mol equiv of the other reagents in 2.2 mL of saturated sodium bicarbonate and 2.2 mL of CCl_4. The reaction was rapidly stirred magnetically at room temperature. Aliquots were assayed periodically on racemic (extent of conversion) and (*R*,*R*)-Whelko (%ee) HPLC columns. The selector was utilized as the internal standard. Enantiomeric excess values are reported at the point where 40% of the initially racemic **1a** had been converted to ester (i.e., 80% of the theoretical yield). [b] Stereoselectivity factor.

principle" than as utilitarian example. Even so, from chromatographic data obtained using chiral columns containing immobilized selectors very similar to (*S*)-**2**, it is clear that *N*-(3,5-dinitrobenzoyl) amino acids other than leucine could be similarly resolved. Indeed, the *N*-(3,5-dinitrobenzoyl) derivatives of some synthetic amino acids prepared as the racemates do, once resolved, find usage as selectors in chiral chromatography columns capable of separating the enantiomers of many other compounds.

It is evident that other alkylating agents, chiral selectors, and achiral quaternary ammonium ions can be utilized in a fashion similar to that just described.[6] Very likely, chiral quaternary ammonium ions might be utilized in conjunction with the chiral selector in a "double asymmetric induction" fashion to further enhance enantioselectivity. Indeed, incorporation of a quaternary ammonium site into a chiral selector is clearly possible although where this site is located with respect to the essential recognition sites in the selector is expected to be rather critical. Having the quaternary site free to "float spatially" is advantageous in the sense that the stronger electrostatic ion pair interaction does not interfere with the simultaneous occurrence of the interactions responsible for the enantioselectivity of the selector.

(6) Use of stronger bases lead to subsequent enantioselective ester hydrolysis. This aspect of two-component chiral phase transfer catalysis is being actively pursued and will be reported shortly.

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