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# Enantioselective Hydrolysis of N-Acylated α-Amino Esters at a Biphasic Interface: Tandem Reaction Kinetic Resolution Using a Chiral Complexing Agent

**Seth E. Snyder* and William H. Pirkle***

*School of Chemical Sciences, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801*

*sesnyder@uiuc.edu*

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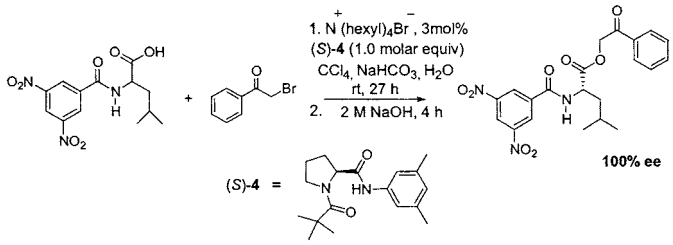
## ABSTRACT




**Highly enantioselective hydrolytic kinetic resolutions of esters derived from *N*-acylated α-amino acids proceed rapidly at hydrocarbon/water interfaces in the presence of a proline-derived chiral selector. When performed in tandem with an enantioselective biphasic esterification reaction, esters of 100% enantiomeric excess are obtained**

The design of metal-free organocatalysts that effect enantioselective reactions has been an active area of research in recent years.[1] One such approach involves the kinetic resolution of racemic substrates.[2] By using low molecular weight organic catalysts such as peptides,[3] cinchona alkaloids,[4] proline-derived catalysts,[5] and template-imprinted polymers,[6] a variety of highly enantioselective kinetic resolutions have been developed for different types of organic transformations. In these systems, most of which are homogeneous, assorted noncovalent interactions contribute to the observed chiral recognition. Interestingly, rather scant attention has been paid to nonenzymatic kinetic resolutions conducted in biphasic liquid systems.[7,8] We herein report the kinetic resolution of *N*-acylated α-amino acids and their esters using a biphasic solvent system containing a chiral complexing agent that differentially affects the reactivities of the enantiomers.

The use of a chiral selector initially developed for the chromatographic separation of enantiomers was recently reported to be efficacious as one component of a two-

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(2) For pertinent reviews on kinetic resolution, see: (a) Keith J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. (b) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(3) Miller, S. J.; Copeland, G. T.; Papaioaaou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629−1630.

(4) Chen, Y.; Tian, S.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542−9543.

(5) (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543−8546. (b) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265−266.

(6) Sellergren, B.; Shea, K. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1403−1406.

(7) For relevant articles dealing with enantioselective ester hydrolysis at a micellar interface, see: (a) Scrimin, P.; Tecilla, P.; Tonellato, U. *J. Org. Chem.* **1994**, *59*, 4194−4201. (b) Cleij, M. C.; Scrimin, P.; Tecilla, P.; Tonellato, U. *Langmuir* **1996**, *12*, 2596−2560. (c) Cleij, M. C.; Drenth, W.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3883−3891.

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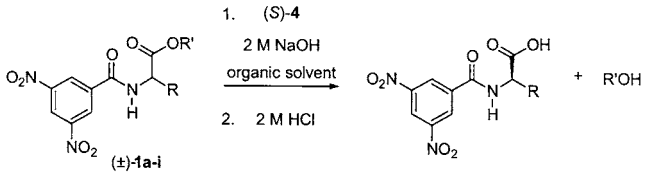
component chiral phase transfer catalyst employed for the biphasic kinetic resolution of a racemic *N*-acylated α-amino acid.[9] In particular, a combination of an (*S*)-proline-derived selector and an achiral phase transfer catalyst such as tetrahexylammonium bromide (TBAB) suffices to preferentially transport one enantiomer of a racemic *N*-3,5-dinitrobenzoyl amino acid (such as leucine) from an aqueous carbonate or bicarbonate solution into an immiscible organic phase containing an alkylating agent. After reaction with 0.5 molar equiv of the alkylating agent, the organic phase contains enantioenriched ester, the aqueous phase contains enantiodepleated *N*-acyl amino acid. Nonpolar solvents (e.g., hexane, decane) afford the greatest enantioselectivity. Serendipitously, it was noted that prolonged stirring of the reaction mixture, long past consumption of the alkylating agent, causes gradual loss of the ester from the organic layer with a concomitant increase in its enantiomeric purity. It was suspected that enantioselective hydrolysis was occurring, and if so, this could be used to increase the enantiomeric purity of the product ester.

That enantioselective hydrolysis is occurring was tested by stirring a variety of racemic esters in nonpolar organic solvents with 2 M sodium hydroxide in the presence of a water-immiscible solution of the chiral selector. We presently restrict ourselves to the hydrolysis of *N*-3,5-dinitrobenzoyl esters of racemic carboxylate acids (**1a**−**i**) and α-aminophosphonic acids (**2**), as well as an *N*-3,5-dinitrobenzoyl derivative of a racemic α-aminolactam (**3**).[10] Selector (*S*)-**4** was used as a chiral complexing agent.[11] Table 1 provides several examples of the effects of selector concentration, temperature, and organic solvent on the apparent stereoselectivity factor, *s*, of hydrolysis of carboxylate esters **1a**−**i**. The enantioselectivities in Table 1 are reported for hydrolysis of 50% of the ester initially present, the required times varying between 30 min and 6 h.[12] Preferential hydrolysis of the less complexed enantiomer is observed in all cases, reaction rate increasing markedly with stirring speed (although stirring rate has no influence on enantioselectivity).

**Table 1.** Enantioselective Biphasic Hydrolysis of Esters of *N*-Acylated α-Amino Acids[a]




| entry | ester | (*S*)-**4** (equiv) | *T* (°C) | solvent | % ee[e] | s[f] |
|---|---|---|---|---|---|---|
| 1 | **1a** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 65 | 9.0 |
| 2 | **1a** | 2.0 | 0 | $CCl_4/CH_2Cl_2$[b] | 84 | 30.3 |
| 3 | **1b** | 2.0 | rt | $Hex/CH_2Cl_2$[c] | 83 | 27.8 |
| 4 | **1b** | 2.0 | 0 | $Hex/CH_2Cl_2$[c] | 92 | 80.4 |
| 5 | **1b** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 79 | 20.3 |
| 6 | **1b** | 0.5 | rt | $Hex/CH_2Cl_2$[c] | 59 | 6.9 |
| 7 | **1b** | 0.5 | 0 | $Hex/CH_2Cl_2$[c] | 67 | 10.0 |
| 8 | **1c** | 2.0 | rt | $Hex/CH_2Cl_2$[c] | 86 | 36.7 |
| 9 | **1c** | 2.0 | 0 | $Hex/CH_2Cl_2$[c] | 92 | 80.4 |
| 10 | **1d** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 65 | 9.0 |
| 11 | **1e** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 70 | 11.7 |
| 12 | **1e** | 2.0 | rt | $Hex/CH_2Cl_2$[d] | 79 | 20.3 |
| 13 | **1f** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 61 | 7.5 |
| 14 | **1f** | 2.0 | 0 | $CCl_4/CH_2Cl_2$[b] | 75 | 15.5 |
| 15 | **1g** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 41 | 3.5 |
| 16 | **1g** | 2.0 | 0 | $CCl_4/CH_2Cl_2$[b] | 62 | 7.9 |
| 17 | **1h** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 57 | 6.3 |
| 18 | **1h** | 2.0 | 0 | $CCl_4/CH_2Cl_2$[b] | 74 | 14.6 |
| 19 | **1i** | 2.0 | rt | $CCl_4/CH_2Cl_2$[b] | 20 | 1.8 |
| 20 | **1i** | 2.0 | 0 | $CCl_4/CH_2Cl_2$[b] | 31 | 2.5 |

[a] Standard conditions entailed use of 0.023 mmol (1 molar equiv) of racemic ester and the indicated number of molar equiv of (*S*)-**4** in the indicated organic solvent and 3.0 mL of 2 M sodium hydroxide. The reaction was rapidly stirred magnetically. Aliquots were assayed periodically by chiral HPLC. [b] Racemic ester and (*S*)-**4** dissolved in 2.5 mL of $CCl_4$ and 0.5 mL of $CH_2Cl_2$. [c] Racemic ester and (*S*)-**4** dissolved in 2.9 mL of hexane and 0.15 mL of $CH_2Cl_2$. [d] Racemic ester and (*S*)-**4** dissolved in 2.5 mL of hexane and 0.5 mL of $CH_2Cl_2$. [e] % ee of both the residual ester (enriched in (*S*) enantiomer) and the product DNB amino acids (enriched in the (*R*) enantiomer) at 50% conversion determined by using a chiral stationary phase (**1a**, **1h**, and **1i**, *N*-(10-undecenoyl)-(*S*)-proline-3,5-dimethylanilide column (30% $^i$PrOH in hexane) developed in these laboratories;[11] **1b**, **1f**, **1g**, and **1d**, (*R*,*R*)-Whelk O1 (13% $^i$PrOH in hexane) available from Regis Technologies; **1c** and **1e**, (D)-leucine (10% $^i$PrOH in hexane) available from Regis Technologies). Absolute configurations were assigned by comparison with authentic samples. [f] Stereoselectivity factor.

Clearly, reaction occurs at the interface since reaction rate increases with increased interfacial surface area. Hydrolysis occurs more rapidly in the absence of the selector, demonstrating that complexation inhibits hydrolysis. Increasing the concentration of the selector slows hydrolysis but increases enantioselectivity. The presence of a phase transfer catalyst is not essential to the hydrolysis but does influence rate, presumably by increasing the concentration of the anionic nucleophile on the aqueous side of the interface. Once hydrolysis has proceeded to the desired extent, isolation and acidification of the aqueous layer liberates the enantioenriched carboxylic acid. The chiral selector and the enantioenriched ester remain in the organic layer and can be recovered either by chromatography on silica or by hydrolysis of the ester and extraction of the enantioenriched acid.

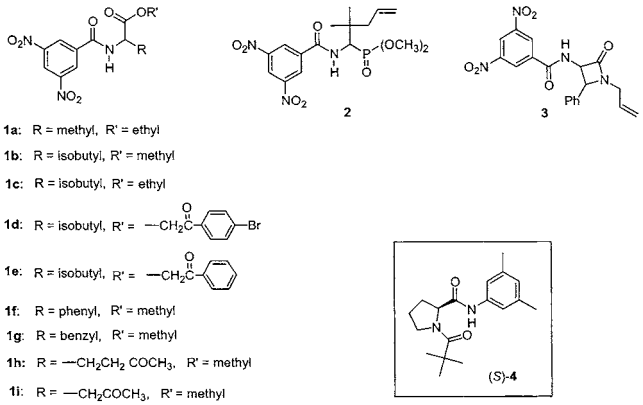
(8) For the biphasic kinetic resolution of racemic aldols using aldolase antibodies, see: Turner, J. M.; Bui, T.; Lerner, R. A.; Barbas, C. F., III; List, B. *Chem. Eur. J.* **2000**, *6*, 2772−2774.

(9) Pirkle, W. H.; Snyder, S. E. *Org. Lett.* **2001**, *3*, 1821−1823.

(10) For preparation of racemates used in this study, see: (a) Pirkle, W. H.; Hyun, M. H.; Bank, B. *J. Chromatogr.* **1984**, *316*, 585−604. (b) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Field, R. M. *J. Chromatogr.* **1985**, *348*, 89−96. (c) Pirkle, W. H.; Burke, J. A., III. *J. Chromatogr.* **1991**, *557*, 173−185.

(11) For preparation of (*S*)-**4**, see: Pirkle, W. H.; Koscho, M. E. *J. Chromatogr. A* **1999**, *840*, 151−158.

(12) **Typical Procedure for Biphasic Hydrolysis.** Racemic **1** (0.023 mmol) and (*S*)-**4** (0.046 mmol) were dissolved in 2.9 mL of hexane and 0.15 mL of $CH_2Cl_2$. The solution was stirred rapidly at room temperature, and 3.0 mL of 2 M sodium hydroxide was added. Reaction progress was monitored periodically by HPLC using a (DL)-phenylglycine column or a Whelk O1 column available from Regis Technologies (the selector, (*S*)-**4**, was used as an internal standard.) The reaction was stirred for 1 h, at which point HPLC indicated approximately 50% conversion. The layers were separated, and the aqueous layer was extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Separation of **1** and (*S*)-**4** was done by flash column chromatography ($SiO_2$, hexane/ethyl acetate). The original aqueous layer was acidified with 2 M HCl and extracted three times into ethyl acetate. Following methylation of the N-protected amino acids, enantiomeric excess was determined by using a chiral stationary phase ((*R*,*R*)-Whelk O1, (10% $^i$PrOH in hexane)).



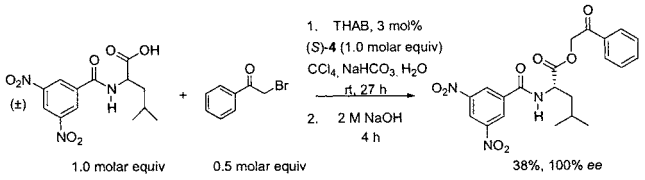

In the absence of a phase transfer catalyst, hydrolysis of these esters is at least 20 times faster in hexane than in methylene chloride and the enantioselectivity is greater as well. This rate enhancement is presumed to stem from the poorer solvating ability of hexane leading to increased adsorption of the ester onto the aqueous interface where hydrolysis occurs. It should be pointed out that both the relative and absolute rates of reaction of two compounds may be quite different depending on whether the reaction occurs in homogeneous solution or while the compounds are adsorbed onto a liquid interface, especially with the incoming reagent being contained in but one of the two liquid phases.[13]

Owing to the dynamic complexity of these systems, the *s* factors depend on the concentration of the selector but remain essentially constant (under the described conditions) throughout the reaction once a 2-fold excess of selector is present. At lower concentrations of selector, the calculated *s* factors increase throughout the reaction. Although a variety of factors may contribute to the observed enantioselectivities, the extent of differential complexation between (*S*)-**4** and with the enantiomers of **1a**−**i** appears to be an important factor. Indeed, esters showing higher chromatographic separation factors on a chiral stationary phase derived from (*S*)-**4** also give higher *s* factors for hydrolysis. Notably, dimethyl esters of glutamic acid (**1h**) give substantially higher *s* factors than the corresponding esters of aspartic acid (**1i**), a result consistent with chromatographic data.[14] In the later case, the remote carbonyl group presumably reduces chiral recognition by providing an alternative hydrogen-bonding site close to the stereocenter for the otherwise less strongly complexed enantiomer. For the less strongly complexed enantiomer of an ester of glutamic acid, this alternative potential interaction site is even more remote and consequently interferes less with the chiral recognition process.

Biphasic enantioselective hydrolysis reactions are possible with other hydrolytically labile compounds such as racemic phosphonate esters (**2**) and racemic lactams (**3**), albeit with substantially reduced rates. Hydrolysis of **2** under the standard reaction conditions using 2 molar equiv of (*S*)-**4** gives *s* factors between 10 and 15, 50% conversion being achieved after 2 days of rapid stirring at room temperature. Hydrolysis of racemic **3** under standard conditions gives *s* factors between 2 and 3, 50% conversion being achieved in approximately 1 week.

Because the biphasic alkylation reaction preferentially esterifies the acid enantiomer most strongly associated with the chiral selector whereas it is the less strongly associated ester enantiomer that is preferentially hydrolyzed, the hydrolysis reaction can be used to scavenge the minor enantiomer produced during esterification. Thus, it is possible to run these reactions sequentially in the presence of a phase transfer catalyst to obtain each enantiomer in substantially enriched form, one as the acid, the other as the ester (Scheme 1). Sodium bicarbonate is employed for the esterification

**Scheme 1**




reaction to minimize competitive hydrolysis of the alkylating agent. Since the hydrolysis is relatively slow, increasing the pH of the aqueous solution (by addition of 2 M NaOH) once the esterification reaction is complete facilitates the overall process.[15] The interplay between concentration of the various components, reaction times, yields, and enantiomeric purities is complex. Under typical conditions, with 0.5 molar equiv of phenacyl bromide for each equivalent of racemic *N*-3,5-dinitrobenzoyl leucine, 38% of enantiomerically pure ester was obtained after workup (maximum possible conversion being 50%).[16] Higher conversions of enantiomerically pure ester can be achieved by increasing the quantity of phenacyl bromide; the optimum amount will need to be determined by experiment for each amino acid and each alkylating agent. Dimethyl sulfate, diethyl sulfate, and various phenacyl halides have been employed successfully as alkylating agents.

In summary, we have demonstrated a method of performing enantioselective hydrolysis reactions occurring at the aqueous/organic interface. Furthermore, we have described a one-pot enantioselective esterification/hydrolysis approach. In one sense, this simple biphasic-chiral selector combination emulates the kind of chemistry afforded by esterases but with

(13) For a recent article dealing with control over regioselectivity by orientation at interfaces, see: Buijnsters P. J. J. A.; Feiters, M. C.; Nolte, R. J. M.; Sommerdijk, N. A. J. M.; Zwanenburg, B. *Chem. Commun.* **2001**, 269−270.

(14) Isolation of products from the hydrolysis of the dimethyl esters of glutamic and aspartic acid reveals that both methyl groups are cleaved.

(15) **Typical Procedure for Tandem Esterification/Hydrolysis Reaction.** A solution of phenacyl bromide (0.05 mmol), (*S*)-**4** (0.10 mmol), and tetrahexylammonium bromide (0.003 mmol) in 2.75 mL of carbon tetrachloride and 0.10 mL of methylyne chloride was stirred with a solution of *N*-3,5-dinitrobenzoyl leucine (0.10 mmol) in 1.25 mL of saturated sodium bicarbonate for 27 h. At this point, 1.25 mL of 2 M NaOH was added, and the reaction mixture was stirred for an additional 4 h. The layers were separated and worked up as described in ref 12.

(16) Immediately following the addition of 2 M sodium hydroxide, the organic layer turns dark purple. The color disappears following acidic workup. The effect is attributed to the formation of a transient Meisenheimer complex stabilized by the quaternary ammonium cation. This secondary process is currently under investigation.

some important differences. For example, unlike the tandem reaction herein described, an esterase preferentially promotes both the forward and reverse reaction for the same enantiomer (microscopic reversibility). While resolution of the compounds described herein is of but minor practical consequence, we have demonstrated that chiral complexing agents can alter the reactivity of a complexed enantiomer to the point that highly enantioselective reactions can be performed. Potentially, this methodology might be applied to a variety of hydrolytically labile organic compounds, provided that a suitable chiral complexing agent is present. Furthermore, the method can be used to identify the ideal chiral agent for a specific substrate through simple chromatographic screening. We are now in the process of unraveling the mechanistic details governing chiral discrimination with the hope of designing a broader base of chiral selectors that influence the stereochemistry of specific organic reactions.

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