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Biphasic enantioselective partitioning studies using small-molecule chiral selectors

Seth E. Snyder,* James R. Carey and William H. Pirkle

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

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Abstract—Enantioselective partitioning of racemic *N*-3,5-(dinitrobenzoyl)leucine or racemic naproxen was studied using a two-component chiral phase transfer approach. A combination of an achiral ion-pairing reagent and a chiral complexing agent (selector) is necessary to effect enantioselective partitioning between an aqueous bicarbonate solution and a nonpolar organic solvent. In these biphasic resolutions, the interplay between the ion-pairing reagent and the selector is essential for maximizing enantioselectivities. Furthermore, the lipophilicity of the ion-pairing reagent, the concentration of the ion-pairing reagent and selector, and the polarity of the organic solvent all exert a considerable influence on the biphasic process. In this manuscript, we conduct optimization studies through analysis of solvent, concentration and ion-pairing effects. Conclusions concerning the mechanistic rationale behind enantioselective partitioning are given.

1. Introduction

Owing to the dramatic increase in sales of single enantiomer drugs over the past decade, the development of new chiral technologies continues to be a very active area of research in the pharmaceutical and specialty chemicals industries. Strategies aimed at the preparative resolution of racemic compounds are amongst the most important means of producing drugs in single enantiomer form.[1] Traditional methods employ crystallization[2] and preparative chromatographic separations.[3] Despite their widespread usage in industrial scale-up processes, these techniques are limited to batch or sequential processes.[4] From an economic standpoint, a continuous separation process is ideal. Indeed, simulated counter-current processes have found growing application in enantioselective separation processes. In particular, simulated moving-bed (SMB) technology has become an important means of performing preparative chiral separations.[5] Nonetheless, SMB often requires extremely thorough optimization procedures and can be quite costly.

An alternative approach to continuous enantioselective separation processes involves using membrane devices.[6] Many of the drawbacks associated with conventional separation strategies such as low substrate throughput and solvent conservation can be circumvented with enantioselective membrane-based separations. Several examples have been demonstrated using chiral selectors that are soluble in one of two liquid phases separated by a semipermeable membrane. The chiral selector mediates transfer of a racemic compound across the membrane by associating with each enantiomer of the racemate, generating diastereomeric complexes. Owing to the nature and directionality of the intermolecular interactions involved, these complexes may be energetically nondegenerate. As a result, the selector is capable of influencing the position of equilibrium of each enantiomer between the respective phases. In general, the more highly complexed enantiomer is preferentially extracted into the phase containing the selector. A variety of chiral selectors have been employed in enantioselective membrane separations including tartaric acid derivatives,[7] chiral amine hydrochlorides,[8] chiral ionophores,[9] chiral crown ethers,[10] polyamino acid derivatives,[11] cyclodextrins,[12] quinine-based compounds[13] and hydroxyproline derived compounds.[14]

Chiral selectors synthesized from small organic molecules developed in our laboratories are capable of separating a variety of enantiomers when used as chromatographic chiral stationary phases (CSPs).[15] These selectors have been designed using first principles through consideration of the minimum requirements that necessitate strong chiral recognition. The majority of selectors incorporate a combination of hydrogen bonding and π–π interactions. Acting in conjunction, these intermolecular forces can exert a significant level of stereochemical control. Many designed

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* Corresponding author. Tel.: +1 217 3332819; fax: +1 217 3332685; e-mail: sesnyder@mail.med.upenn.edu

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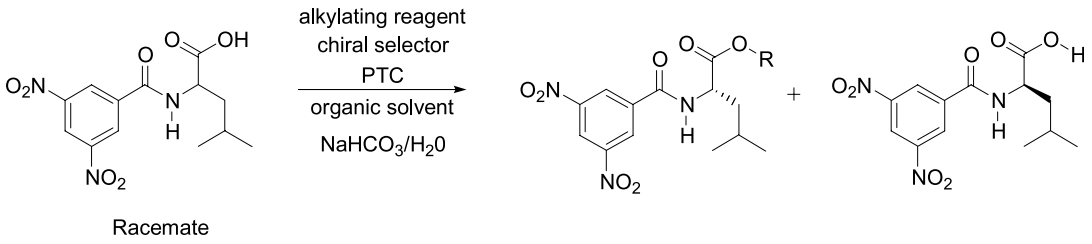
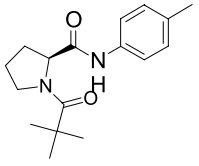


Scheme 1.

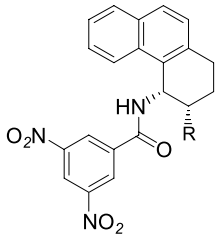
chiral selectors show high levels of enantiodiscrimination for pharmaceutically important compounds and are thus amenable to preparative chromatographic and membrane-based separation processes. For instance, a chiral selector has been used in a hollow fiber membrane system (Sepracor) to separate the enantiomers of *N*-protected amino acids.[16] The approach relies on using the chiral selector in combination with an achiral phase transfer catalyst (PTC) to achieve appreciable rates of extraction across the membrane. Recently, we have extended the methodology to performing biphasic kinetic resolutions by coupling the enantioselective transport to a subsequent chemical reaction, a process referred to as two-component chiral phase transfer catalysis (Scheme 1).[17] Although these kinetic resolutions are performed as batch processes, they are potentially extendable to membrane type reactors. Herein, we report on the various factors that contribute to enantiodiscrimination in two-component chiral phase transfer catalysis, the ultimate goal being optimization for potential enantioselective membrane extraction systems, membrane reactors, and process-scale chiral organocatalytic reactions.

2. Results and discussion

Success of the kinetic resolutions in two-component chiral phase transfer catalysis stems primarily from the enantioselective partitioning step, although secondary effects such as differences in reaction rates between the complexed and uncomplexed enantiomer contribute slightly.[17] Therefore, our primary focus involved optimizing the enantioselective extraction step. To this end, a chiral selector ((*S*)-**1**, (*S*)-**2a** or (3*S*,4*S*)-**2b**) was dissolved in an organic solvent and mixed with an aqueous sodium bicarbonate solution containing either racemic *N*-(3,5-dinitrobenzoyl)leucine, (±)-**3**, or racemic naproxen, (±)-**4**, in the presence of a suitable achiral ion-pairing reagent. Three symmetrical ion-pairing reagents were employed in this study, namely tetrahexylammonium chloride (THAC) tetrahexylammonium bromide (THAB) and tetrabutylammonium chloride (TBAC). The simple partitioning studies were designed to study the effects of selector concentration, racemate

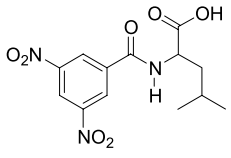


(*S*)-**1**

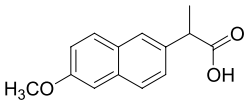


(*S*)-**2a**: R = H

(*3S, 4S*)-**2b**: R = allyl



(±)-**3**



(±)-**4**

Table 1. Biphasic Enantioselective Partitioning of (±)-**3** in the Presence of (*S*)-**1**[a]

EntrySolvent	Solvent	(*S*)-**1** (equiv)	[(*S*)-**1**] (M)	$N^+(alkyl)_4X^-$	$N^+(alkyl)_4X^-$ (mol%)	% Extracted[b]	%ee (*S*)[c]
1	CH_2Cl_2	1.0	0.008	$N^+(hexyl)_4Cl^-$	20	20.2	27
2	CH_2Cl_2	1.0	0.025	$N^+(hexyl)_4Cl^-$	20	19.6	50
3	CH_2Cl_2	1.0	0.10	$N^+(hexyl)_4Cl^-$	20	19.5	70
4	CH_2Cl_2	1.0	0.30	$N^+(hexyl)_4Cl^-$	20	21.0	84
5	CCl_4	1.0	0.008	$N^+(hexyl)_4Cl^-$	20	19.5	76
6	CCl_4	1.0	0.025	$N^+(hexyl)_4Cl^-$	20	19.7	93
7	CCl_4	1.0	0.10	$N^+(hexyl)_4Cl^-$	20	21.0	96
8	CCl_4	0.25	0.002	$N^+(hexyl)_4Cl^-$	20	19.4	50
9	CCl_4	0.25	0.006	$N^+(hexyl)_4Cl^-$	20	20.0	57
10	CCl_4	0.25	0.025	$N^+(hexyl)_4Cl^-$	20	19.5	67
11	CCl_4	1.0	0.025	$N^+(hexyl)_4Cl^-$	40	38.0	73
12	CCl_4	1.0	0.025	$N^+(hexyl)_4Br^-$	40	37.5	74
13	CCl_4	1.0	0.025	$N^+(butyl)_4Cl^-$	40	17.0	91
14	Hexane	1.0	0.025	$N^+(hexyl)_4Cl^-$	40	19.5	90

[a] Standard conditions entailed vigorously mixing 0.10 mmol (1.0 M equiv) of (±)-**3** in 4.0 mL of saturated $NaHCO_3$ with an organic solution containing selector (*S*)-**1** and the indicated ion-pairing reagent at room temperature. Layers were separated and **3** was derivatized with excess phenacyl bromide.
[b] Determined by HPLC internal standard analysis (see Section 4).
[c] Refers to %ee of the compound extracted into the organic layer. Determined by chiral HPLC (see Section 4).

concentration, solvent and ion-pairing reagent on enantioselective partitioning.

Results of enantioselective partitioning of (±)-**3** in the presence of chiral selector (*S*)-**1** are displayed in Table 1. A general schematic of the equilibrium process is shown in Figure 1. In all cases, 1 M equiv of (±)-**3** was dissolved in an aqueous bicarbonate solution and mixed with an organic solvent containing the selector and a tetraalkylammonium halide. Mixtures were shaken vigorously and allowed to equilibrate. The layers were separated and analyzed. Equilibration occurs rapidly once the layers are mixed and results are independent of the contact time between layers. The concentration of (±)-**3** in the aqueous layer was kept constant at 0.025 M for all enantioselective extractions shown in Table 1. The natures of the organic solvent and tetraalkylammonium salt as well as the concentration of selector (*S*)-**1** were varied from one run to the next.

In entries 1–4 of Table 1, methylene chloride (CH_2Cl_2) was used as the extraction solvent. In each case, 1 M equiv of the chiral selector (*S*)-**1** and 20 mol% THAC are present in the organic layer. Changing the effective concentration of selector (and THAC) in the organic layer was accomplished by diluting with methylene chloride. The results from these partitioning studies reveal that the quantity of **3** extracted into CH_2Cl_2 is generally equivalent to the mole% of THAC in the solution. The selector by itself is incapable of effecting transfer between layers. The enantiomeric excess of the extracted **3** is highly dependent on the concentration of selector in the CH_2Cl_2. A threefold increase in enantioselectivity is observed as selector concentration is increased from 0.008 to 0.30 M.

The same general trends are observed with carbon tetrachloride (CCl_4) as the extraction solvent. However, the polarity of the organic solvent also has a considerable influence on enantioselective bias. Association constants for selector/substrate complexes are maximum in nonpolar solvents where there is less competitive solvation from the

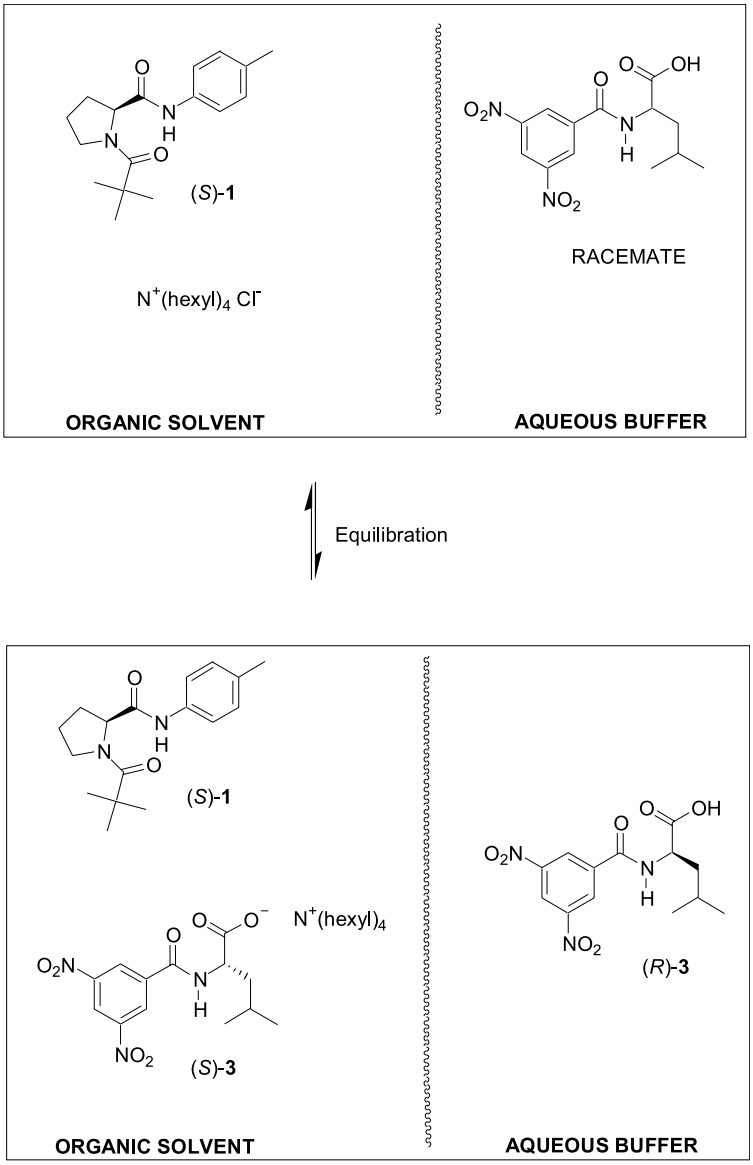


Figure 1. Schematic of the two-component enantioselective partitioning process.

medium. Hence, extractions performed in CH_2Cl_2 are far less selective than those performed in CCl_4. For instance, comparing entry 2 with entry 6 in Table 1, an increase from 50%ee (19.6% extracted) to 93%ee (19.7% extracted) is observed when the extraction solvent is changed from CH_2Cl_2 to CCl_4 under otherwise identical conditions. The ratio of racemate/selector in the biphasic solution also has a significant influence on enantioselective partitioning. As seen in entries 6 and 10 in Table 1, decreasing the number of molar equivalents of selector (*S*)-**1** from 1.0 to 0.25 while keeping the selector concentration constant (by adjusting the amount of CCl_4) gives significantly lower enantioselectivities of extraction. Presumably, in the later case, an increased amount of achiral extraction ensues as the selector is effectively 'tied-up' through its strong association with a single enantiomer of the racemate. Changing the counterion of the achiral ion-pairing reagent from chloride to bromide has little influence on the enantioselective partitioning process, as seen in entries 11 and 12 of Table 1.

To analyze the influence of changing the mol% of achiral ion-pairing reagent, it is necessary to define the stereoselectivity factor (*s*) of enantioselective partitioning. In a kinetic resolution, the *s* factor represents the ratio of rate constants between the enantiomers and is given by the following equation:

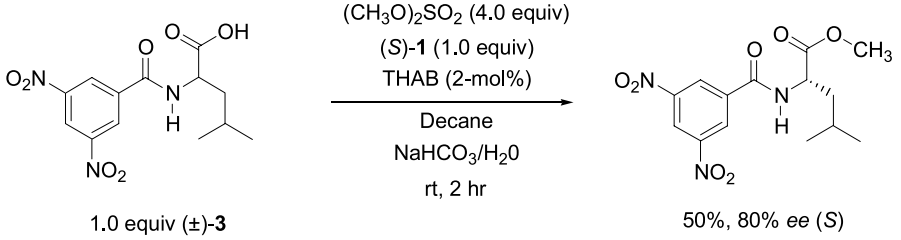
$$s = \ln[1 - C(1 + \mathrm{ee}\prime)]/\ln[1 - C(1 - \mathrm{ee}\prime)]$$

where ee′ is the enantiomeric excess of product at conversion C.[18] The *s* factor is expected to remain constant throughout the course of a kinetic resolution unless secondary effects (e.g., product inhibition) contribute to the selectivity of the process. In the present case, the *s* factor for enantioselective partitioning may be defined as the relative ratio of partitioning coefficients of the enantiomers between the respective layers. The above equation still applies, accept that the term *C* corresponds to the total amount extracted into the organic layer. As displayed in Table 1, increasing the mol% of THAC from 20% (entry 6) to 40% (entry 11), the total quantity of **3** extracted increases from 19.7 to 38% and the ee decreases from 93 to 73%, corresponding to an *s* factor of 35 and 10, respectively. The decrease in *s* factor most likely results from a greater degree of achiral partitioning with increased amounts of THAC, although the influence of ion-pair aggregation may also be a factor.

To mitigate the effects of achiral background partitioning, one may adjust the lipophilicity of the ion-pairing reagent such that the selector is necessary to effect transfer between the aqueous and organic layers. Under standard partitioning conditions (Table 1) but in the absence of a chiral selector, enantiomeric ion-pairs formed between TBAC and (±)-**3** partition almost exclusively into the aqueous layer. On the other hand, in the presence of selector (*S*)-**1**, a significant quantity of **3** is extracted into the CCl_4 (e.g., entry 13 in Table 1). This result indicates that the association constant between selector (*S*)-**1** and (*S*)-**3** is sufficiently large as to perturb the partitioning equilibrium that exists without selector present. The diastereomeric associates likely form at the biphasic interface as two polar groups of (*S*)-**3** lose their hydrophilicity owing to strong hydrogen bonding interactions with the selector. Furthermore, a multipoint π–π interaction provides the essential third point of contact and ensures strong complexation necessary for extraction into the organic layer.

Background extraction is also reduced significantly by using hydrocarbon solvents such as hexane (entry 14 of Table 1) or decane, although symmetrical ion-pairing reagents used in this study have limited solubility in both hydrocarbon and aqueous solutions. From an environmental standpoint, hydrocarbon solvents are far more ideal than halogenated solvents such as CCl_4.As a result, we explored the use of decane as a solvent in the two-component chiral phase transfer catalysis (Scheme 1). With phenacyl halides as alkylating reagents, reactions proceed very slowly unless significant quantities of ion-pairing reagent are added. Simple methyl or ethyl esters of 3 can be prepared by the two-component chiral phase transfer methodology. Although methyl halides are not reactive in the two-component systems, dimethyl sulfate ($(CH_3O)_2SO_2$)) is a highly reactive methylating reagent capable of converting **3** into its corresponding ester quite rapidly with significant enantioselectivity (Scheme 2). Notably, the reaction is accomplished in a hydrocarbon solvent (decane) using a catalytic amount of THAB. However, competitive hydrolysis of dimethyl sulfate restricts one to use greater than stoichiometric quantities of this electrophile. As shown in Scheme 2, four equivalents of dimethyl sulfate are required for 50% of **3** to be esterified.

Chromatographic separation of underivatized naproxen, (±)-**4**, may be accomplished through using a CSP derived from (*S*)-**2a** or (3*S*,4*S*)-**2b**. Separation factors are modest, ranging from 2.25 to 2.95 depending on the means by which the selector is tethered to the silica support.[19] Enantiomers of naproxen may also be separated by the selector mediated partitioning process described above. Data for the biphasic enantioselective partitioning of 0.10 mmol (1.0 M equiv) of (±)-**4** in the presence of 0.10 mmol of selector (*S*)-**2a** or (3*S*,4*S*)-**2b** and 20-mol% THAC is given in Table 2. Unlike biphasic extractions of **3** discussed above, the quantity of **4** extracted into the organic layer not only depends on the



Scheme 2.

Table 2. Biphasic enantioselective partitioning of (±)-**4** with 20-mol% THAC[a]

Entry	Solvent	Selector	[Selector] (M)	[(±)-**4**] (M)	% Extracted[b]	%ee (*S*)[c]	*s*[d]
1	CH_2Cl_2	(*S*)-**2a**	0.025	0.025	20.8	18	1.5
2	CH_2Cl_2	(*S*)-**2a**	0.10	0.025	11.6	33	2.2
3	CH_2Cl_2	(3*S*,4*S*)-**2b**	0.025	0.025	20.1	33	2.1
4	CH_2Cl_2	(3*S*,4*S*)-**2b**	0.10	0.025	13.5	51	3.4
5	CCl_2/CH_2Cl_2[e]	(3*S*,4*S*)-**2b**	0.025	0.025	16.8	50	3.3
6	CH_2Cl_2	(3*S*,4*S*)-**2b**	0.10	0.10	18.0	45	2.9
7	CCl_2/CH_2Cl_2[e]	(3*S*,4*S*)-**2b**	0.025	0.10	17.0	50	3.3

[a] Standard conditions entailed vigorously mixing 0.10 mmol (1.0 M equiv) of (±)-**4** in 4 mL of saturated $NaHCO_3$ with an organic solvent containing the indicated chiral selector and 20 mol% THAC at room temperature. Layers were separated and **4** was derivatized with excess dimethyl sulfate.
[b] Determined by HPLC internal standard analysis (see Section 4).
[c] Determined by chiral HPLC (see Section 4).
[d] Stereoselectivity factor.
[e] Used a 3:1 ratio of CCl_4/CH_2Cl_2.

mol% of THAC in solution but also the amount of solvent in the respective layers. Generally, the quantity extracted is equal to or less than 20%. Dilution of the organic layer or concentration of the aqueous layer results in a larger quantity of naproxen ion-pairs extracted. For comparative purposes, the stereoselectivity factor (*s*) for each experiment was calculated. Comparing entry 1 to entry 2 or entry 3 to entry 4 of Table 2, one observes that more concentrated solutions of the selector result in less total naproxen extracted but with higher *s* factors. The *cis*-**3** substituted selector (3*S*,4*S*)-**2b** gives higher *s* factors than (*S*)-**2a** for these partitioning studies, a result consistent with chromatographic studies (table 2; entry 1,2 vs 3,4).[20] Ideally, one should develop a more soluble analogue of (3*S*,4*S*)-**2b** by increasing the bulk on the second stereocenter of the cyclohexane ring, hence making it possible to perform these enantioselective partitionings in more nonpolar or concentrated solvent systems.

3. Conclusions

The biphasic enantioselective partitioning studies and kinetic resolutions described in this paper may have a significant practical value. The method provides a simple and convenient way to resolve a variety of enantiomers, provided that a suitable chiral complexing agent is available. Two such examples were demonstrated, resolution of *N*-(3,5-dinitrobenzoyl)leucine and resolution of naproxen. In the former case, high levels of enantiodiscrimination were achieved both for enantioselective partitioning and kinetic resolutions, even for the simple batch experiments described. Furthermore, results for separation of naproxen by a single-stage batch extraction process are encouraging although enantioselectivities are far below that needed for practical separation of enantiomers. The same will likely be true of many racemate/selector combinations. Hence, a continuous process involving multiple membrane units (staging) will be needed for such cases. Indeed, Ding and co-workers have developed an enantioselective hollow-fiber membrane approach using countercurrent flow of the two phases leading to complete separation of enantiomers, even for a selector with an undesirably low enantioselectivity.[14] This type of enantioselective membrane approach can clearly be applied to two-component chiral phase transfer separations and reactions. Furthermore, this methodology provides a simple means of assessing models of chiral recognition. This should greatly facilitate the production of future CSPs and chiral organocatalysts.

4. Experimental

The racemates and chiral selectors used in this study were prepared in a manner described by the original workers.[19,21] Selector (3*S*,4*S*)-**2b** was obtained from Merck. All ion-pairing reagents, phenacyl bromide and dimethyl sulfate were purchased from Aldrich. Carbon tetrachloride was purchased from Fisher. HPLC was conducted using the following equipment: injectors (Beckman, Rheodyne), pumps (Rainin Rabbit-HPX, Beckman 100B, Alcott 760), variable wavelength (λ) UV-detector (Linear UVIS 200), recorder/integrator (HP 3390A). Chromatographic runs were recorded at ambient temperature with the flow rate 2 mL/min. Dimensions of all analytical HPLC columns were 24 cm×4.6 mm.

4.1. Typical procedure for enantioselective partitioning

A solution containing (±)-**3** (0.10 mmol, 32.5 mg) in 4 mL saturated $NaHCO_3$ was added to 4 mL CH_2Cl_2 containing (*S*)-**1** (0.10 mmol, 28.8 mg) and THAC (0.02 mmol, 7.8 mg). The solution was added to a screw-capped scintillation vial, shaken vigorously for 1 min and allowed to settle for an additional 3 min. The contents were placed in a separatory funnel and the layers were separated. The organic layer was dried over magnesium sulfate. The extracted ion-pairs of **3** were converted to their phenacyl ester derivatives by the addition of excess phenacyl bromide (0.12 mmol, 23.9 mg). Enantioselective partitioning of (±)-**4** were carried out in similar fashion except that enantioenriched extracted ion-pairs of **4** were converted to their methyl ester derivatives by the addition of excess dimethyl sulfate. Residual dimethyl sulfate was hydrolyzed with a saturated solution of $NaHCO_3$.

4.2. HPLC analysis

Enantiomeric excess was determined by chiral HPLC by analyzing the ester derivatives of the extracted ion-pairs of **3** and **4**. In the former case the enantiomers of the phenacyl ester of **3** were separated using (D)-Leucine CSP (mobile phase 15% 2-propanol in hexane, λ=270 nm) available from Regis Technologies. Enantiomers of methyl esters of **4** were separated using an (*R*,*R*)-Whelk-O1 CSP (mobile

phase 10% 2-propanol in hexane, $\lambda = 283$ nm) available from Regis Technologies. In all cases, absolute configurations were assigned by comparison with authentic samples.

Quantities extracted were determined by HPLC using internal standard analysis. The chiral selector was used as an internal standard. Calibration curves for each study were generated by preparing stock solutions of the chiral selector with the appropriate racemic ester derivative of the compound being studied (i.e., the phenacyl ester derivative of **3** or the methyl ester derivative of **4**) at various concentrations. Linear plots were obtained in all cases. To determine the amounts extracted, aliquots from the worked-up organic layer were injected and compared to the calibration data.

4.3. Procedure for biphasic reaction between (±)-3 and dimethyl sulfate in the presence of selector (*S*)-1 (Scheme 2)

To a 10 mL round bottom flask equipped with magnetic stir bar was added 1.0 mol equiv of (±)-**3** (0.10 mmol, 32.5 mg) dissolved in saturated $NaHCO_3$. To this solution was added 3.0 mL of decane containing 1.0 mol equiv (*S*)-**1** (0.10 mmol, 28.8 mg) and 0.1 mL of CH_2Cl_2 containing 2-mol% THAB (0.002 mmol, 0.87 mg). The biphasic mixture was stirred magnetically and 0.1 mL of CH_2Cl_2 containing 4.0 mol equiv dimethyl sulfate (0.40 mmol 50.5 mg) was added drop wise. Aliquots were assayed periodically by chiral HPLC using a (*R*, *R*)-Whelk-O1 column (12% 2-propanol in hexane, $\lambda = 283$ nm) available from Regis Technologies. Conversion was measured by internal standard analysis (see above). Production of ester stopped after approximately 2 h. At this point, close to 50% conversion had been reached. Addition of more dimethyl sulfate leads to additional conversion. Workup was carried out as follows: the organic layer was diluted with CH_2Cl_2, and the aqueous layer was diluted by adding H_2O. The layers were separated and the organic layer was washed sequentially with 1 M HCl, saturated NaCl and water. The solution was dried over sodium sulfate and concentrated under reduced pressure to yield a mixture of product ester, THAB and (*S*)-**3**. Separation of the mixture was accomplished by flash column chromatography (SiO_2, hexane/ethyl acetate).

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