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Enantiomeric resolution of fluorous mixture by chiral CD columns: asymmetric reduction of a mixture of fluorous ketones

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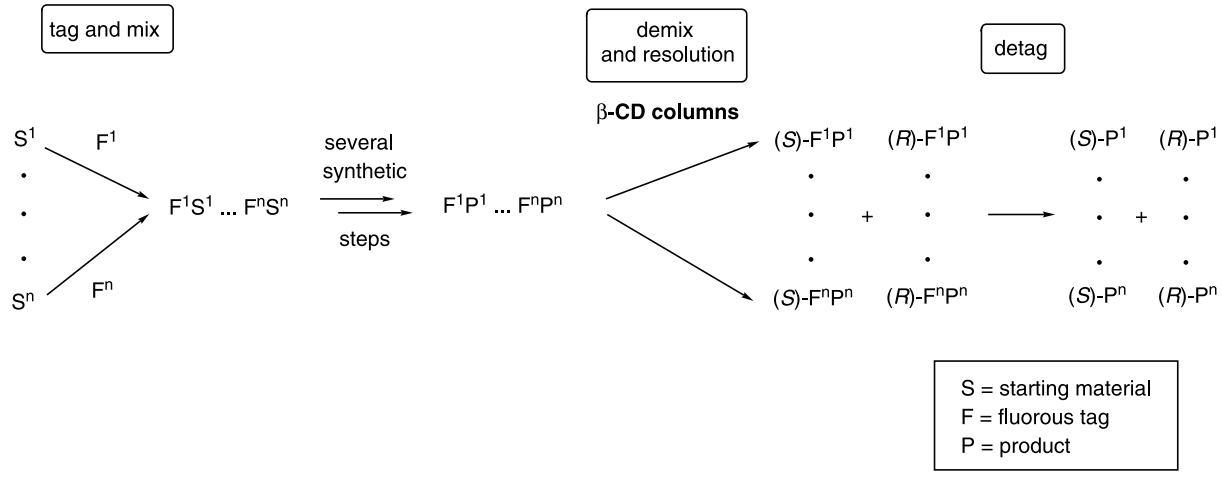
Abstract—Asymmetric reduction of a mixture of four fluorous ketone analogues was carried out with (*R*)-oxazaborolidine as a catalyst. The fluorous mixture products were resolved by a reverse phase HPLC with chiral β-cyclodextrin column to result in good separation of the enantiomers.

Curran and co-workers made an epoch-making discovery in 1999 that a fluorocarbon bonded silica gel HPLC column (silica-$OSi(CH_3)_2(CH_2)_2C_nF_{2n+1}$), Fluofix® 120E, was able to separate molecules that had fluorous tags of $CH_2CH_2C_nF_{2n+1}$ ($n=3$–10) in a very regular way depending upon their fluorine contents; the more fluorines a molecule possesses, the slower it moves in a 'reverse-phase' mode.[1] Based upon this discovery they created a new strategic technique of combinatorial chemistry, 'Fluorous Mixture Synthesis'.[2] Seven fluorous tags, $CH_2CH_2C_nF_{2n+1}$ ($n=3$, 4, 6–10), enabled a synthesis of a library including 560 mappicine analogues in miligram order of isolated samples via several steps of mixture (internal parallel) and split-parallel (double parallel) reactions, 'demixing' the products and finally removing the fluorous tags. On the other hand, Mikami and co-workers have recently discovered a high separating ability of β-cyclodextrin (β-CD) HPLC columns (SUMICHIRAL® OA-7000 series) for fluorous compounds such as benzoic acid and benzenesulfonic acid fluoroalkyl esters.[3] The chiral CD columns demonstrated more efficient separation of the com-



Scheme 1. Enantiomeric resolution of fluorous mixture by chiral β-CD columns.

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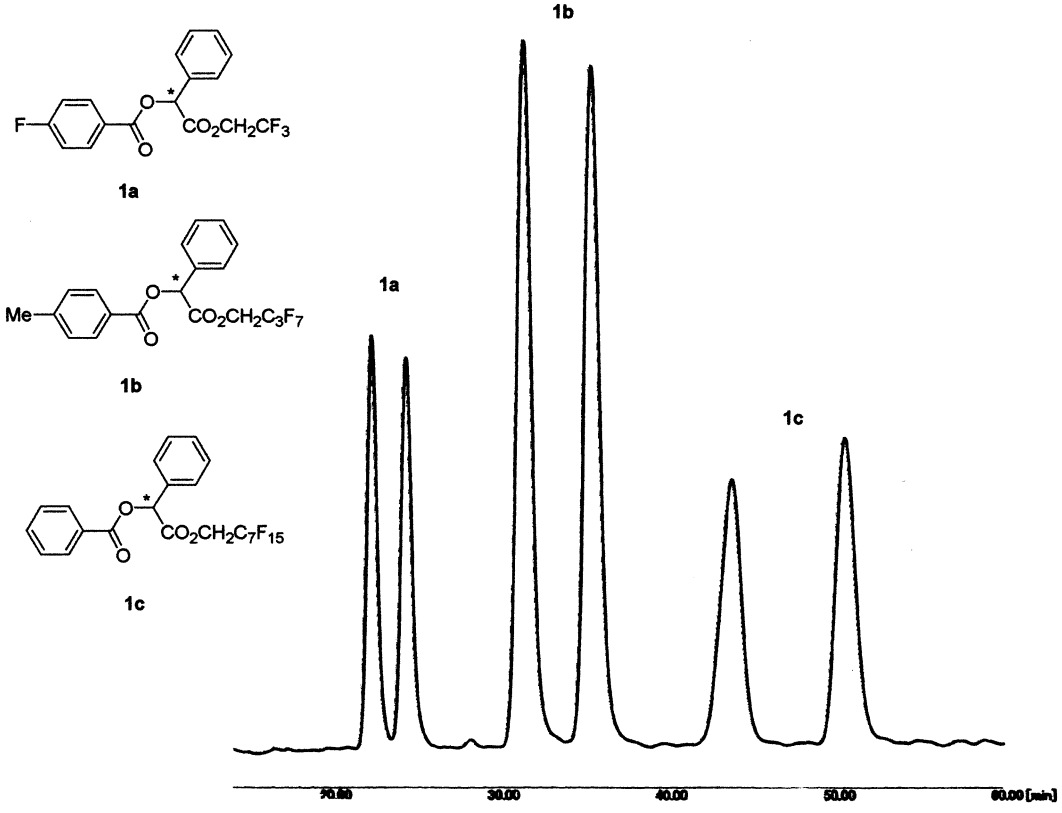
pounds bearing short (CF_3) to long (C_9F_{19}) tags as compared to Fluofix 120E.

Takeuchi and co-workers have reported a different kind of mixture reaction, an asymmetric addition of $ZnEt_2$ to aromatic aldehydes using a fluorous chiral BINOL-Ti complexes as catalysts.[4] Five kinds of aromatic aldehydes were reacted with $ZnEt_2$ in one-pot and the product mixture was separated from the catalyst by a fluorous reverse phase silica gel and then analyzed by gas chromatography with chiral column. The products and their enantiomers were well separated to lead to a simultaneous evaluation of yields and % ee for each product. In contrast to the results, however, attempts to separate the products and their enantiomers simultaneously by HPLC with chiral columns were unsuccessful. Therefore, this approach is useful for analysis of a mixture of products but not suitable for resolution thereof. Curran group's new strategy of 'Fluorous Mixture Synthesis' in combination with Mikami's strategy of discrimination of fluorous chains by chiral CD column prompted us to undertake an asymmetric fluorous mixture resolution because it will provide us a useful method not only for analysis of enantioselectivities of the products but also for isolation of the pure enantiomers (Scheme 1).

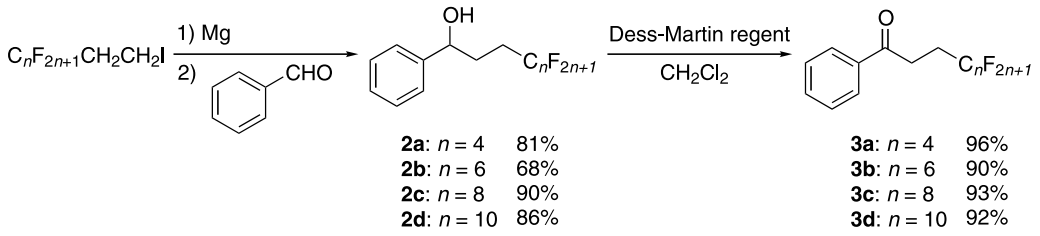
First, we checked efficiency in resolution of a racemic mixture of substrates with different length of fluorous tags with β-CD columns (Scheme 2). Three *O*-benzoylmandelate derivatives bearing different length of fluorous tags were synthesized individually, and these esters were mixed and then resolved. It was found that the mixture of racemic *O*-benzoylmandelate derivatives was resolved using OA-7500 as a β-CD column. In this case, esters were eluted first from *O*-(*p*-fluorobenzoyl)mandelate **1a** bearing C1 tag. *O*-Benzoylmandelate **1c** bearing C7 tag showed the best resolution (Rs) amongst all the esters.

Keeping it in our mind, we next examined the Corey–Itsuno asymmetric borane reduction for fluorous ketonic substrates using (*R*)-oxazaborolidine as a catalyst (Scheme 3). The fluorous groups are skeletal parts of the molecules and are unable to be removed after the reaction. Thus the substrates just seem to have a role to test our idea for the time being but these kinds of chiral compounds will become useful for fluorous chemistry in the long run.

The fluorous ketones **3a**–**d** were prepared in good yields via two steps. At the outset, each substrate underwent independently the asymmetric reduction at 25°C in THF for 15 min under argon.[5] The products **2a**–**d** were analyzed by HPLC with DAICEL CHIRALCEL OD-H under normal phase separation conditions to get enantioselectivity of each product and then analyzed by HPLC with Fluofix 120E under the reverse phase separation conditions by both CD and UV detectors to obtain g value (the ratio of absorption coefficient of CD to that of UV) of each product for super high-throughput screening (SHTS).[6] From the enantioselec-



Scheme 2. Resolution of *O*-benzoylmandelate derivatives **1a**–**c** with β-CD column. Column: OA-7500: mobile phase, methanol–water (0 to 60 min, 75/25 up to 85/15, v/v); flow rate, 0.5 mL/min; detector, absorption at 254 nm; column temperature, 20°C.



Scheme 3.

tivity and the g value of each product, g values for enantiomerically pure products (entry 1 in Table 1) were calculated. The four products were clearly separated by HPLC with Fluofix 120E under the conditions shown in Figure 1. The measurement of CD and UV absorption coefficient for each product mentioned above was carried out under the same separating conditions as those in Figure 1. Next we examined the reaction of a mixture of the four substrates **3a–d** and the product mixture was analyzed by HPLC with Fluofix 120E to get g value for each product (Fig. 1). The enantiomeric excesses were evaluated by the g values obtained above for enantiomerically pure products. The enantioselectivities were almost the same as those obtained by the independent reactions as shown in Table 1 (entry 2).

As seen above, when we take the procedure, that is, determination of the products' enantiomeric excesses by HPLC or GC analysis independently and then correlate the % ees to the g values of the products in advance, we will be able to assess the enantioselectivity of each product in the mixture product and to get enantiomerically enriched sample of each product as long as each product can be separated clearly by HPLC with an effective column such as Fluofix 120E. This technique must be very useful for finding the most efficient reaction and optimal conditions to provide isolated products of the highest enantioselectivities.

Finally we tried to separate the products and their enantiomers simultaneously by using HPLC with CD chiral columns. Each enantiomer pair of the four racemic fluorous alcohols was separated by SUMICHIRAL OA-7500 column although the separation was not perfect, and was not separable at all by OA-7000 and OA-7100 columns (Fig. 2). When the product mixture was analyzed by the chiral column, somewhat lower values of enantioselectivity were obtained as compared to those evaluated by g values, probably because of incomplete separation of the enantiomer pairs (entry 3 in Table 1).

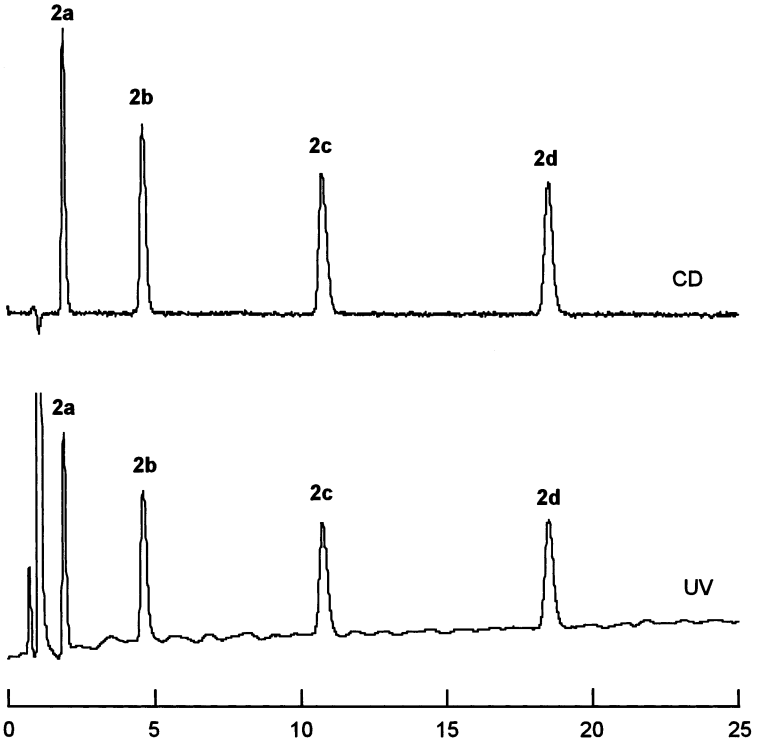
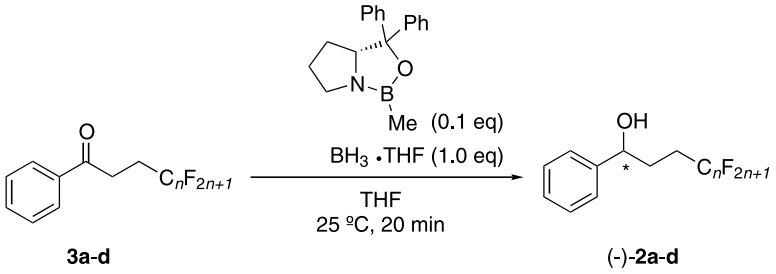


Figure 1. HPLC chromatograms of alcohols **2a–d**. Column: Fluofix 120E; mobile phase: CH_3OH–H_2O (0 to 30 min, 80/20 up to 100/0 v/v); flow rate: 1.0 mL/min; detector: 268 nm CD and UV.

Table 1. Enantioselective borane reduction of perfluoroalkyl ketones **3a–d** catalyzed by chiral oxazaborolidine



3a-d (-)-**2a-d**

Entry	Yield (%)				% ee			
	2a	**2b**	**2c**	**2d**	**2a**	**2b**	**2c**	**2d**
1[a]	98	97	97	95	88	85	87	84
2[b]	99	99	100	99	85	85	83	87
3[c]	N.D.	N.D.	N.D.	N.D.	82	75	77	71

[a] The reactions were carried out independently. The yields were isolated yields. The ees were determined by HPLC analysis using DAICEL CHIRALCEL OD-H (hexane/2-propanol = 99/5, 1.0 mL/min, 254 nm UV).

[b] The yields and ees were determined by HPLC analysis with Fluofix 120E by using BTF as an internal standard (80% MeOH/H_2O to 100% MeOH for 30 min, 1.0 mL/min, 268 nm UV and CD). Ee was calculated based on the dissymmetric factor (g).

[c] Determined by HPLC analysis using SUMICHIRAL OA-7500.

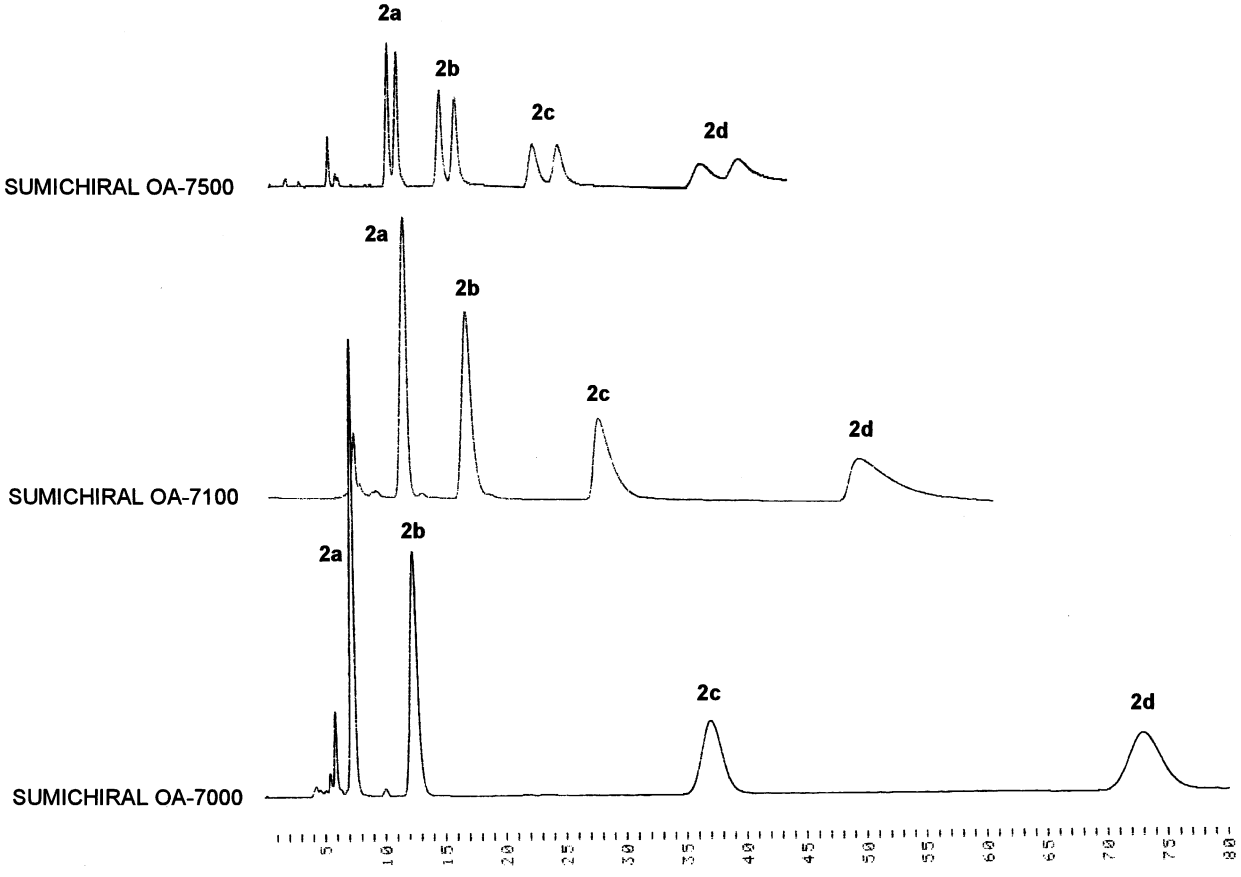


Figure 2. HPLC chromatograms of recemic alcohols **2a–d**. Top: $CH_3CN/H_2O = 55/45$, 0.5 mL/min, 254 nm UV. Middle and bottom: 0 to 60 min, $CH_3CN/H_2O = 60/40$ up to $CH_3CN/H_2O = 80/20$; 60 to 80 min. $CH_3CN/H_2O = 80/20$, 0.5 mL/min, 254 nm UV.

As seen from the HPLC chart, it is expected that enantiomer pairs of another series of the fluorous alcohol **2e**–**h** ($n=3$, 5, 7, 9, respectively) will be separable by the chiral column and their peaks will appear before and between the peaks of **2a**–**d** without any serious overlap. We are now preparing many kinds of such fluorous substrates and testing separation of the products and their enantiomers by using reverse phase HPLC chiral columns including CD ones in order to find more efficient chiral columns and/or analytical conditions for complete separation.

Acknowledgements

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5. A typical procedure for entry 1 in Table 1: To a solution of ketone **3a** (176 mg, 0.5 mmol) and (*R*)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 0.05 mL, 0.05 mmol) in THF (2 mL) was added borane–THF (1.0 M in THF, 0.5 mL, 0.5 mmol) at 25°C under argon. After stirring at that temperature for 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and then extracted with ether (3×10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and then concentrated in vacuo. The residue was purified on a silica gel column with hexane/ether (10/1) to afford alcohol (−)-**2a** (173 mg, 98% yield) in 88% ee as a colorless solid.
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