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Enantioselective Fluorescent Recognition of a Soluble "Supported" Chiral Acid: Toward a New Method for Chiral Catalyst Screening

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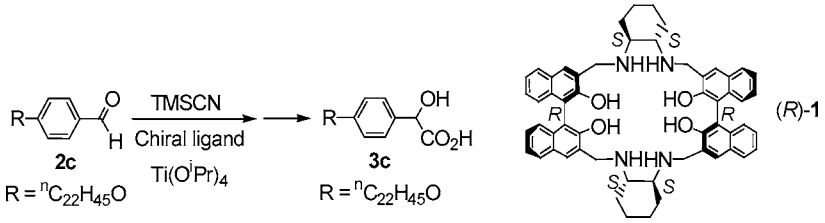
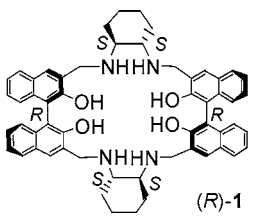
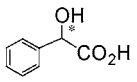
ABSTRACT



The long-chain aliphatic-group-substituted mandelic acid 3c, which is soluble only in THF and insoluble in water and many polar/nonpolar organic solvents, has been synthesized. This unique solubility allows 3c to be easily isolated from reaction mixtures and makes it potentially useful for catalyst screening. The fluorescent sensors (*R*)- and (*S*)-1 can be used to determine the ees of various samples of 3c generated from a series of catalyst screening experiments. The fluorescence measurements correlate well with the conventional HPLC-chiral column analysis. This work demonstrates that the enantioselective fluorescent recognition of organic substrates can lead to a fundamentally new method for chiral catalyst screening.

Development of analytical methods for high-throughput chiral catalyst screening has attracted significant research activity in recent years.[1−6] Among these methods, the use of fluorescence-based enantioselective sensors is particularly interesting because fluorescence can potentially provide both high sensitivity and real-time measurement.[4] Work in this area has led to various fluorescent sensors for the chiral recognition of organic substrates in solution. For example, we have found that the bisbinaphthyl macrocycles (*S*)- and (*R*)-**1** are highly enantioselective fluorescent sensors for mandelic acid in solution.[6]





To conduct a high-throughput catalyst screening experiment, it would be much more convenient to use a supported substrate since this would allow an easy removal of the catalysts and reagents and simplify the analysis of the product. However, if a fluorescent sensor were used to determine the enantiomeric composition of the product, it would require a heterogeneous recognition of the supported product, which is expected to be difficult because of the nonspecific interaction with the surface of the supported material. To apply the enantioselective fluorescent sensors to the chiral catalyst screening, we have proposed to prepare a substrate that would precipitate out of the catalyst screening

(1) Finn, M. G. *Chirality* **2002**, *14*, 534−540.
(2) Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335−1338.
(3) Tsukamoto, M.; Kagan, H. B. *Adv. Synth. Catal.* **2002**, *344*, 453−463.
(4) Pu, L. *Chem. Rev.* **2004**, *104*, 1687−1716.
(5) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2004**, *126*, 14736−14737.
(6) Li, Z.-B.; Lin, J.; Pu, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1690−1693.

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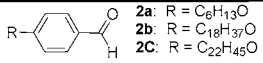
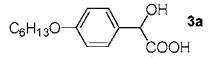
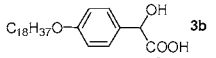
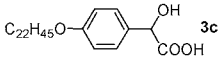
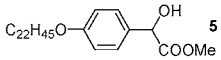
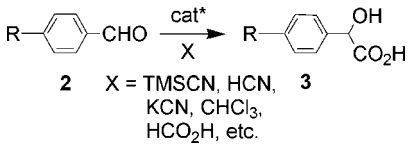
Table 1. Solubility of Compounds **2a**−**c**, **3a**−**c**, and **5** in Various Solvents

compound	methanol	diethyl ether	methylene chloride	ethyl acetate	THF
 **2a**: R = $C_6H_{13}O$ **2b**: R = $C_{18}H_{37}O$ **2C**: R = $C_{22}H_{45}O$	moderate	good	good	good	good
 **3a**	good	good	good	good	good
 **3b**	moderate	moderate	good	good	good
 **3c**	poor (<1 mg/9 mL)	poor	poor (<1 mg/10 mL)	poor	good
 **5**	moderate	good	good	good	good

reaction mixtures to allow simple separation but still be soluble when used to interact with the fluorescent sensors. Herein, we report our finding on the enantioselective fluorescent recognition of a soluble "supported" mandelic acid and its use in enantiomeric excess (ee) determination.

We are interested in developing chiral catalysts for the conversion of the aldehyde **2** to the mandelic acid derivative **3** by various reaction pathways (Scheme 1). The following

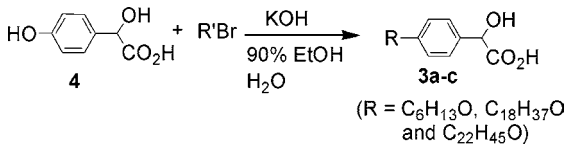
Scheme 1. Asymmetric Conversion of Aldehydes to α-Hydroxy Acids by Various Reaction Pathways



properties are desirable for compounds **2** and **3** when an enantioselective fluorescent sensor is used to determine the ee of **3** produced from the catalyst screening: (1) Compound **2** needs to be soluble in various solvents to allow the conversion to be conducted in a homogeneous environment. (2) After the conversion, **3** can be precipitated out with or without the addition of a poor solvent. (3) Compound **3** should be soluble in a solvent or a mixture of solvents for analysis by using a fluorescent sensor. (4) The fluorescent sensors should show enantioselectivity in the recognition of **3**.

Introduction of a nonpolar aliphatic group to the benzene ring of the highly polar mandelic acid was examined with the expectation that the combination of such distinctively different molecular fragments together should lead to interesting solution properties. As shown in Scheme 2, compound

Scheme 2. Synthesis of Alkylated 4-Hydroxy Mandelic Acid

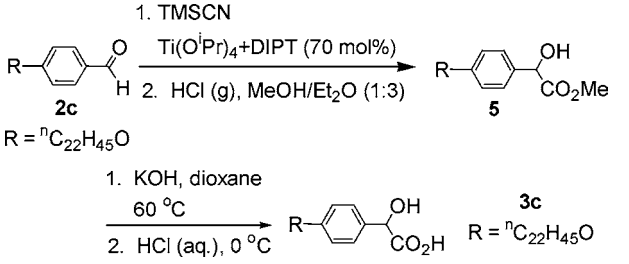


4 was reacted with various linear alkyl bromides in order to introduce alkyl groups to its benzene ring. It was found that in 90% ethanol at reflux, the alkylation of the highly functional **4** in the presence of KOH occurred with remarkably high selectivity at the phenol oxygen to give **3**.

Table 1 summarizes the solubility of the aldehydes **2a**−**c**, the α-hydroxy acids **3a**−**c**, and the ester **5**. As the length of the alkyl chain increases, the solubility of **3** in organic solvents decreases. Compound **3c** containing a 22-carbon chain alkyl group is found to be almost insoluble in most of the organic solvents but still has good solubility in THF. It is also not soluble in water. This compound seems to have all the desired solution properties. The corresponding aldehyde **2c** is soluble in most organic solvents, which would allow its reaction with other reagents to proceed homogeneously, and the product **3c** would be precipitated out in the absence of THF. The good solubility of **3c** in THF will assist its interaction with the fluorescent sensors (*R*)- and (*S*)-**1**, which are soluble in many organic solvents, including THF.

The optically active samples of **3c** were obtained by the asymmetric reaction of **2c** with TMSCN in methylene chloride in the presence of $Ti(O^iPr)_4$ and (+)-/(−)-diisopropyltartrate (DIPT) (70 mol %) at room temperature using a modified literature procedure.[7] The product was then treated with HCl (g) and $MeOH/Et_2O$ (1:3) at room temperature, which gave the methyl ester **5** (Scheme 3).[8] The enantiomeric

Scheme 3. Asymmetric Reaction of **2c** with TMSCN in the Presence of (+)-/(−)-DIPT and $Ti(O^iPr)_4$ to Generate **5** and **3c**



purity of **5** was determined using an HPLC-chiral OD column. The ester (*S*)-**5**, obtained by using (+)-DIPT, was produced with 79.5% ee (that is, 90% (*S*)-enantiomer), and (*R*)-**5**, obtained by using (−)-DIPT, was produced with 72%

ee (that is, 86% (*R*)-enantiomer). Compound **5** was converted to **3c** by treatment with KOH in dioxane at 60 °C, which precipitated out with acidification. To determine if the hydrolysis condition could racemize the chiral center of **3c**, we converted **3c** back to **5** by reaction with HCl (g) and MeOH/Et_2O (1:3). HPLC analysis of **5** showed a slight increase in ee (~3.5%). This demonstrates that no racemization took place during the hydrolysis of **5** to **3c**.

The optically active (*R*)- and (*S*)-**3c** obtained above were allowed to interact with the fluorescent sensors (*S*)- and (*R*)-**1**. We found that in a ternary solvent of THF/hexane/benzene (1:5.5:18.5), the sensors (2.0×10^{-5} M) showed enantioselective fluorescent responses to the chiral acids (2.0×10^{-4} M) (Figure 1). THF was used to dissolve **3c**, and the

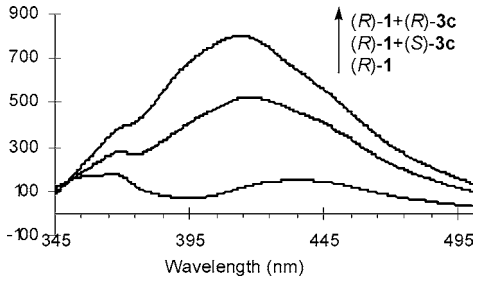


Figure 1. Fluorescence spectra of (*R*)-**1** (2.0×10^{-5} M) with (*R*)- and (*S*)-**3c** (2.0×10^{-4} M) (λ_{exc} = 332 nm, slit = 3.5; 6.5 nm).

combination of benzene and hexane was necessary for the enantioselective fluorescent response. Although the enantioselectivity of the sensor for **3c** is significantly lower than that for the unsubstituted mandelic acid, it is still useful for ee determination (vide infra).[6]

Samples of **3c** (2.0×10^{-4} M) with various enantiomeric compositions were prepared, and their interaction with (*R*)-**1** (2.0×10^{-5} M) in the ternary solvent system was studied. A monotonic relation between the fluorescence intensity and the enantiomeric composition of the acid was obtained (Figure 2). We also studied the interaction of the samples with (*S*)-**1** and observed a mirror image relationship for the fluorescence responses. This confirmed the observed chiral recognition of **3c** by the fluorescent sensor.

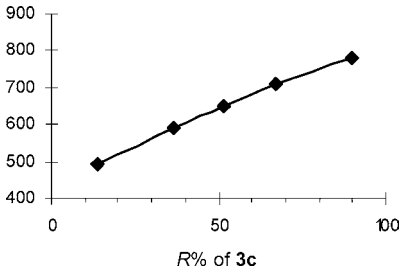


Figure 2. Fluorescence responses of (*R*)-**1** (2.0×10^{-5} M) with **3c** (2.0×10^{-4} M) at various *R* compositions (λ_{exc} = 332 nm, slit = 3.5; 6.5 nm).

On the basis of the interaction of the enantiomeric sensors (*R*)- and (*S*)-**1** with **3c** of various enantiomeric compositions, a linear relationship between the fluorescence intensity difference ΔI [$\Delta I = (I_S/I_{S0}) - (I_R/I_{R0})$; I_S, fluorescence intensity of (*S*)-**1** in the presence of the acid; I_R, fluorescence intensity of (*R*)-**1** in the presence of the acid; I_{S0} and I_{R0}, fluorescence intensity of (*R*)-/(*S*)-**1** without the acid] and the ee of **3c** is established (Figure 3). Thus, using Figure 3, one

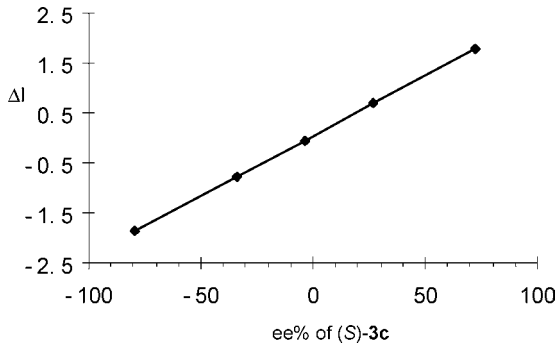


Figure 3. Relationship between ΔI and the enantiomeric composition of mandelic acid.

should be able to determine the enantiomeric composition of a given sample of **3c** from ΔI.

We studied the conversion of **2c** to **3c** by the TMSCN addition in the presence of the chiral ligands (*S*)-/(*R*)-**6**[9] and (+)-/(−)-DIPT in combination with $Ti(O^iPr)_4$ under various conditions as summarized in Table 2. The product **3c** was

Table 2. Asymmetric TMSCN Addition to **2c** and Fluorescent Ee Determination of Product **3c**

entry	solvent	ligand (mol %)	$Ti(O^iPr)_4$ (mol %)	$\Delta I = (I_S/I_{S0} - I_R/I_{R0})$	ee (%)
1	CH_2Cl_2	(+)-DIPT (40)	40	1.92	79
2	CH_2Cl_2	(−)-DIPT (40)	40	−1.81	−77
3	CH_2Cl_2	(*S*)-**6** (10)	8	2.06	84
4	CH_2Cl_2	(*S*)-**6** (10)	10	1.33	54
5	CH_2Cl_2	(*S*)-**6** (10)	12	0.38	14
6	THF	(*S*)-**6** (10)	10	0.99	39
7	ether	(*S*)-**6** (10)	10	0.11	3
8	toluene	(*S*)-**6** (10)	10	0.95	38
9	CH_2Cl_2	(*R*)-**6** (10)	10	−1.26	−54
10	CH_2Cl_2	(*R*)-**6** (10)	2	−1.31	−56

isolated in the range of 60−70% yield simply by centrifugation and filtration because of the insolubility of **3c** in the absence of THF. The 10 samples of **3c** obtained from the above catalyst screening were treated with the fluorescent

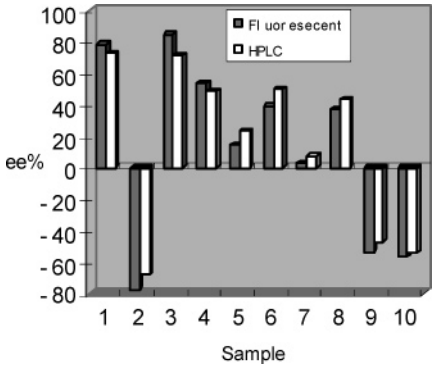
(7) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, *22*, 3135−3140. For the modification, see Supporting Information.
(8) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181−185.
(9) Li, Z.-B.; Rajaram, A. R.; Decharin, N.; Qin, Y.-C.; Pu, L. *Tetrahedron Lett.* **2005**, *46*, 2223−2226.

sensors (*R*)- and (*S*)-**1** under the same conditions as those in Figure 2. The ees of the samples were determined according to Figure 3 by measuring ΔI.

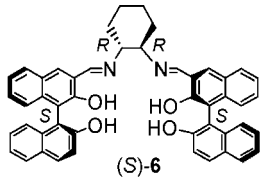
We also used an HPLC-chiral OD column to analyze the ees of the methyl esters **5** obtained from the screening experiments in Table 2. Table 3 compares the HPLC data with those from the fluorescence measurements, and a good correlation is observed.

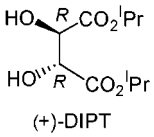
Table 3. Comparison of the Ees from HPLC Analysis with Those from Fluorescence Measurements

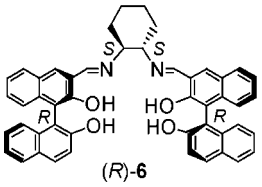
sample	1	2	3	4	5	6	7	8	9	10
FL	79	−77	84	54	14	39	3	38	−54	−56
HPLC	73	−69	72	49	23	50	8	44	−47	−54

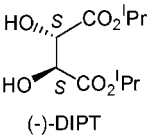


In summary, we have synthesized the long-chain aliphatic-group-substituted mandelic acid **3c**, which is soluble only in THF and insoluble in water and many polar/nonpolar organic solvents. This unique solubility allows **3c** to be easily isolated from a reaction mixture and makes it potentially useful for catalyst screening. We have demonstrated that the fluorescent sensors (*R*)- and (*S*)-**1** can be used to determine the ees of **3c** generated from a series of catalyst screening experiments. The fluorescence measurements correlate well with the conventional HPLC-chiral column analysis. This work demonstrates that the enantioselective fluorescent recognition of organic substrates may open the door to a fundamentally new method for chiral catalyst screening.









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Supporting Information Available: Syntheses and characterizations of the new compounds and details of the fluorescence measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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