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Remote Ester Group Leads to Efficient Kinetic Resolution of Racemic Aliphatic Alcohols via Asymmetric Hydrogenation

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Supporting Information

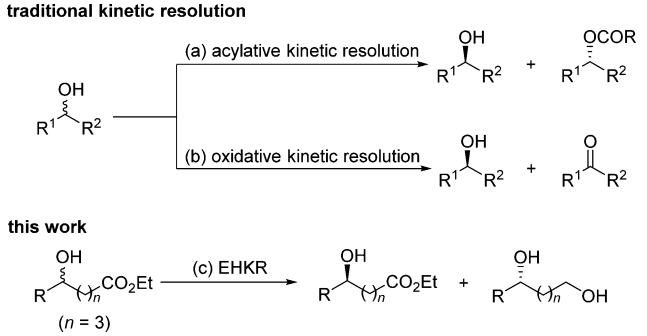
ABSTRACT: A highly efficient method for kinetic resolution of racemic aliphatic alcohols without conversion of the hydroxyl group has been realized; the method involves hydrogenation mediated by a remote ester group and is catalyzed by a chiral iridium complex. This powerful, environmentally friendly method provides chiral δ-alkyl-δ-hydroxy esters and δ-alkyl-1,5-diols in good yields with high enantioselectivities even at extremely low catalyst loading (0.001 mol %).

Optically active aliphatic alcohols are common substructures in natural products and are also useful chiral building blocks for the synthesis of chiral drugs. However, although considerable attention has been devoted to the development of efficient methods for the synthesis of optically active aliphatic alcohols in recent decades, it still remains an open challenge.[1] Catalytic asymmetric hydrogenation of carbonyl compounds is an effective way to obtain chiral alcohols,[2] but this method is limited to the preparation of chiral alcohols with one aryl group or one bulky alkyl group.[3] For this reason, a method for the kinetic resolution of readily available inexpensive racemic aliphatic alcohols would be a valuable alternative for the preparation of optically active aliphatic alcohols.

Kinetic resolution of racemic aliphatic alcohols either enzymatically or by means of artificial chiral catalysts has been extensively studied.[4] However, as far as we know, all of the reported kinetic resolutions of racemic alcohols involve direct conversion of the hydroxyl group of one enantiomer of the substrate into some other functional group and recovery of the unchanged enantiomer with optical activity. For example, the most commonly used method, acylative kinetic resolution, involves the transformation of one enantiomer to an ester,[5] and the well-studied oxidative kinetic resolution method involves an oxidation of one enantiomer to a ketone[6] (Scheme 1a,b). We recently discovered that the hydroxyl groups generated during asymmetric hydrogenation of ketones promote the reduction of ester groups in the substrates.[7] On the basis of these results, we envisioned that introducing a remote ester group into racemic dialkyl carbinol substrates would facilitate their kinetic resolution, leaving the hydroxyl groups unchanged in both enantiomers; we refer to this strategy as ester-hydrogenation-promoted kinetic resolution (EHKR) (Scheme 1c).[8]

We chose racemic δ-alkyl-δ-hydroxy esters as substrates to test the EHKR strategy because optically active δ-alkyl-δ-hydroxy esters and 1,5-diols are versatile building blocks for the synthesis of natural products and pharmaceuticals. For example,

Scheme 1. Kinetic Resolutions of Racemic Alcohols



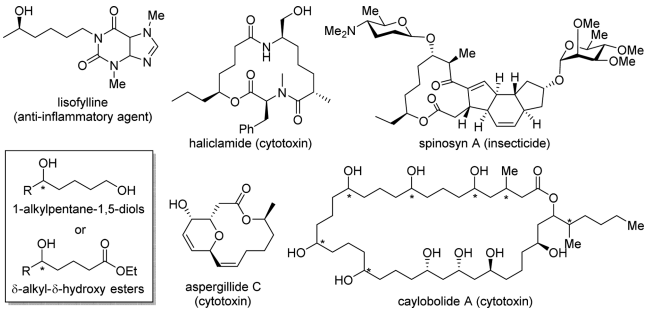
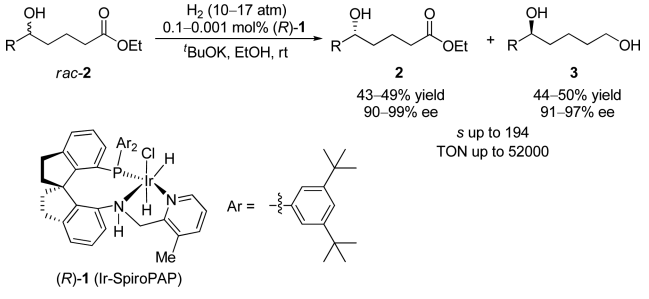


Figure 1. Selected bioactive natural and synthetic compounds prepared from chiral δ-hydroxy esters or 1,5-diols.

Scheme 2. Kinetic Resolution of *rac*-2 via an Ester Hydrogenation Catalyzed by (*R*)-1



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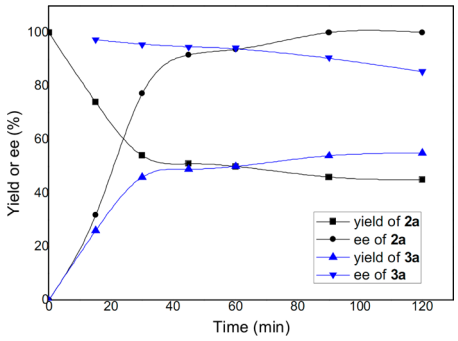


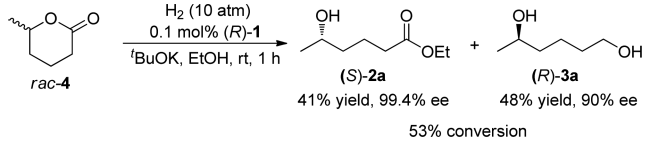
Figure 2. Plots of yields and ee values for the hydrogenation of *rac*-**2a** with (*R*)-**1**.

they have been used for, or are potential key intermediates for, the synthesis of chiral drugs such as lisofylline[9] and bioactive natural products such as aspergillide C,[10] haliclamide,[11] spinosyn A,[12] and caylobolide A[13] (Figure 1), and the reported methods for the synthesis of such functionalized chiral aliphatic alcohols are laborious and lengthy[14] or are limited to enzyme-catalyzed reductions and acylations.[15]

Racemic *δ*-alkyl-*δ*-hydroxy esters *rac*-**2** were hydrogenated in the presence of Ir−(*R*)-SpiroPAP ((*R*)-**1**), a chiral iridium complex that has been shown to efficiently catalyze the asymmetric hydrogenation of simple ketones.[16] The reactions produced chiral *δ*-alkyl-*δ*-hydroxy esters (*S*)-**2** and 1,5-diols (*R*)-**3** with high enantioselectivities (Scheme 2). The EHKR method provides a practical and efficient kinetic resolution of racemic aliphatic alcohols with enantiomeric excess (ee) values of up to 99%, stereoselectivity factor (*s*) values of up to 194,[17] and turnover numbers of up to 52 000.

The hydrogenation of racemic ethyl 5-hydroxyhexanoate (*rac*-**2a**) was initially performed in EtOH under H_2 (10 atm) at room temperature with 0.1 mol % catalyst (*R*)-**1** and 4 mol % ^{t}BuOK. The conversions and yields were determined by ^{1}H NMR analysis and the ee values by chiral HPLC. When the hydrogenation was stopped after 30 min, the hydrogenated product (*R*)-**3a** was obtained in 46% yield with 96% ee, and unchanged alcohol (*S*)-**2a** was recovered in 54% yield with 77% ee. After the reaction was continued for an additional 30 min, the yield of (*R*)-**3a** increased to 50% with a slight decrease in enantioselectivity (94% ee); however, the ee of the recovered (*S*)-**2a** was remarkably increased to 94% with an *s* value of 120. Plots of the temporal dependence of the yield and ee of (*R*)-**3a** showed that most of the (*R*)-**2a** was reduced to (*R*)-**3a** in the first 30 min, after which time the reaction slowed down (Figure 2). The catalytic kinetic resolution method was highly efficient, and the catalyst loading could be reduced to 0.001 mol % without diminishing the yield or ee values of (*R*)-**3a** (46% isolated yield, 52% conversion, turnover number = 52 000, 93% ee) and recovered (*S*)-**2a** (44% isolated yield, 97% ee).

Scheme 3. Hydrogenation of Racemic *δ*-Methyl-*δ*-valerolactone (*rac*-4) with (*R*)-1



Scheme 4. Enantioselective Syntheses of (+)-Civet and (*R*)-Lisofylline

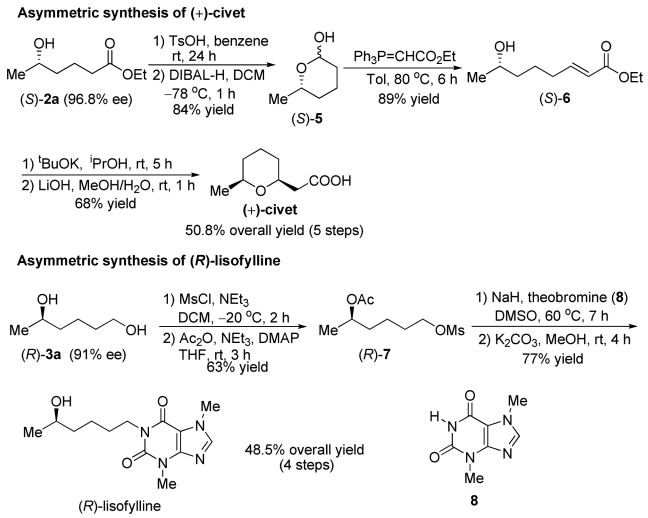
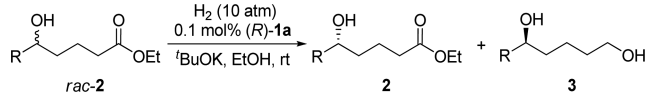


Table 1. EHKR of Racemic 5-Alkyl-5-hydroxypentanoates (*rac*-2) with Catalyst (*R*)-1[a]



				2		3		
entry	R	time (h)	conv (%)[b]	yield (%)[c]	ee (%)[d]	yield (%)[c]	ee (%)[d]	*s*
1	Me (**2a**)	1	50	47	94 (*S*)	46	94 (*R*)	120
2	Et (**2b**)	2	52	44	95 (*S*)	47	94 (*R*)	126
3	^{n}Pr (**2c**)	2	52	43	96 (*S*)	47	96 (*R*)	194
4	^{n}Bu (**2d**)	2	50	45	95 (*S*)	48	96 (*R*)	188
5	^{i}Bu (**2e**)	3	48	49	90 (*R*)	44	96 (*S*)	142
6	^{i}Pr (**2f**)	6	53	43	98 (*R*)	49	97 (*S*)	194
7	Cy (**2g**)	5	54	44	99 (*R*)	50	94 (*S*)	128
8	$MeO(CH_2)_3$ (**2h**)	1	50	45	97 (*R*)	46	91 (*S*)	110
9	$Me_2CHCH(CH_2)_2$ (**2i**)	2	53	44	94 (*R*)	48	93 (*S*)	94
10	Ph (**2j**)	0.5	49	49	94 (*R*)	47	95 (*S*)	139

[a]Reaction conditions: 1.0 mmol scale, [substrate] = 0.5 M, [KO^{t}Bu] = 0.02 M, 0.1 mol % (*R*)-**1**, ethanol (2.0 mL), room temperature (25−30 °C). [b]Determined by ^{1}H NMR analysis. [c]Isolated yields. [d]Determined by HPLC using a chiral column.

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The reactions of racemic δ-alkyl-δ-hydroxy esters *rac*-**2b**−**i** were also evaluated with catalyst (*R*)-**1** (Table 1, entries 2−9). The size of the δ-alkyl group of *rac*-**2** had little effect on the enantioselectivity of the reaction; the ee values of chiral 1,5-diols **3b**−**i** were 91−97% with *s* values ranging from 94 to 194. However, a bulky δ-alkyl group lowered the reaction rate (the required reaction time increased from 1 to 6 h). The ee values of the recovered (*R*)- or (*S*)-**2** were 90−99%, and higher conversion generally led to higher ee values of the recovered (*R*)- or (*S*)-**2**. This method was also efficient for the kinetic resolution of racemic δ-aryl-δ-hydroxy esters. For example, hydrogenation of racemic ethyl 5-phenyl-5-hydroxypentanoate (*rac*-**2j**) for 0.5 h provided diol (*S*)-**3j** in 47% yield with 95% ee and recovered (*R*)-**2j** in 49% yield with 94% ee (*s* = 139; entry 10). It should be noted, however, that hydrogenation of a racemic γ-alkyl-γ-hydroxy ester gave a low yield (22%) and low ee value (<10% ee), and hydrogenation of racemic ε-alkyl-ε-hydroxy esters did not proceed.

Because δ-methyl-δ-valerolactone was detected by ^{1}H NMR spectroscopy as a byproduct (≤2% yield) of the hydrogenation of *rac*-**2a**, we speculated that the kinetic resolution proceeds via hydrogenation of a lactone intermediate. To investigate this possibility, we carried out the hydrogenation of racemic δ-methyl-δ-valerolactone (*rac*-**4**) catalyzed by (*R*)-**1** and obtained diol (*R*)-**3a** in 48% yield with 90% ee; (*S*)-**2a** was recovered in 41% yield with 99.4% ee (Scheme 3). These yields and ee values are comparable to those obtained from the hydrogenation of *rac*-**2a**, which suggests that EHKR of *rac*-**2a** occurred via lactone hydrogenation and also explains why the position of the ester group in the substrate was extremely important for achieving efficient EHKR.

To demonstrate the utility of the method, we synthesized the natural product (+)-civet and the chiral drug (*R*)-lisofylline using EHKR as a key step (Scheme 4). (+)-Civet is an expensive perfume material isolated from the perianal gland secretions of the African civet,[18] and its synthesis has been extensively studied over the past decades.[19] Starting from (*S*)-**2a** (R = Me), we synthesized (+)-civet in 51% overall yield in five steps, including an intramolecular oxa-Michael addition to generate the tetrahydropyran ring. The chiral drug (*R*)-lisofylline, an anti-inflammatory agent and a potent reagent for the treatment of type 1 diabetes,[9] was synthesized conveniently from 1,5-diol (*R*)-**3a** (R = Me) in four steps in 49% overall yield.

In conclusion, we have developed a highly efficient and practical method for kinetic resolution of racemic aliphatic alcohols via catalytic hydrogenation of hydroxyl esters. The EHKR method is a novel approach for the preparation of optically active δ-alkyl-δ-hydroxy esters and δ-alkyl-1,5-diols in high yields with high enantioselectivities. By using EHKR, we achieved the asymmetric syntheses of bioactive natural products and chiral drugs (+)-civet and (*R*)-lisofylline.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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