Chiral Pyridines: Optical Resolution of 1-(2-Pyridyl)- and 1-[6-(2,2′-Bipyridyl)]ethanols by Lipase-Catalyzed Enantioselective Acetylation

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The resolution of racemic 1-(2-pyridyl)ethanols **2a**−**n**, including the 2,2′-bipyridyl and isoquinolyl derivatives, by lipase-catalyzed asymmetric acetylation with vinyl acetate is reported. The reactions were carried out in diisopropyl ether at either room temperature or 60 °C using *Candida antarctica* lipase (CAL) to give (*R*)-acetate and unreacted (*S*)-alcohol with excellent enantiomeric purities in good yields. The reaction rate was relatively slow at room temperature for substrates bearing an sp^3-type carbon at the 6-position on the pyridine ring, such as **2c**, **2d**, and **2e**, and for those bearing 1-hydroxypropyl and allyl groups at the 2-position on the pyridine ring, such as **2l** and **2m**. In such cases, a higher temperature was required. Thus, when the reaction was conducted at 60 °C, it was accelerated 3- to 7-fold without losing the high enantiospecificity. However, the reaction of homoallylic alcohol **2n** was not complete, even when the reaction was continued for a longer period of time at 60 °C. This enzymatic resolution can be used practically in a wide range of reaction scales from 10 mg to 10 g or more. This catalyst can be used repeatedly with a 5−10% loss of the initial activity with each use.

Introduction

Over the past decade, a great deal of progress has been made in the area of enantioselective reactions[1] and molecular recognition chemistry,[2] in which chiral ligands play a critical role in stereoselective reactions and molecular recognition processes. Therefore, the synthesis of novel chiral ligands has become increasingly valuable for organic synthesis. In particular, the three-dimensional design of ligand molecules is important to achieve high stereoselective face and site recognition.[3] Pyridine and 2,2′-bipyridine have been widely used as common donor ligands.[4] Although many chiral pyridyl ligands have been reported so far,[5] most have consisted of a nonchiral pyridyl part and another chiral part connected by a carbon−heteroatom bond, and the chiral part is generally obtained from commercial sources. On the other hand, those with a chiral center on the pyridine side have rarely been adopted as chiral ligands.[6] The limited use of chiral pyridyl and 2,2′-bipyridyl ligands may be due to the limited availability of chiral pyridines and 2,2′-bipyridines.[7,8] The introduction of a chiral center directly attached to pyridyl or 2,2′-bipyridyl rings poses a difficult problem. In fact, we initially examined the asymmetric reduction of 2-acylpyridines using modern

(1) *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996.

(2) *Comprehensive Supuramolecular Chemistry*; Lehn, J.-M., Ed. in chief; Elsevier Science Ltd.: New York, 1996.

(3) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995. Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysts, Products and Catalysts*; VCH: Weinhein, 1993; Vol. I. Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysts, Ligands*; VCH: Weinhein, 1993; Vol. II.

(4) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilikinson, Sir G., Ed.; Pergamon Press: London, 1987; Vol. 2; p 73. Constable, E. C. *Metals and Ligand Reactivity*; VCH: Weinheim, 1995.

(5) (a) Brunner, H.; Reiter, B.; Riepl, G. *Chem. Ber.* **1984**, *117*, 1330. (b) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846. (c) Zassinovich, G.; Bettella, R.; Mestroni, G.; Bresciani-Pahor, N.; Geremia, S.; Randaccio, L. *J. Organomet. Chem.* **1989**, *370*, 187. (d) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron: Asymmetry* **1990**, *1*, 843. (e) Wright, M. E.; Svejda, S. A.; Jin, M.-J.; Peterson, M. A. *Organometallics* **1990**, *9*, 136. (f) De Martin, S.; Zassinovich, G.; Mestroni, G. *Inorg. Chim. Acta* **1990**, *174*, 9. (g) Brunner, H.; Brandl, P. *Tetrahedron: Asymmetry* **1991**, *2*, 919. (h) Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1235. (i) Ishida, H.; Hamada, T.; Fujishita, Y.; Saito, Y.; Ohkubo, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 714. (j) Kandzia, C.; Steckhan, E.; Knoch, F. *Tetrahedron: Asymmetry* **1993**, *4*, 39. (k) Scrimin, P.; Tecilla, P.; Tonellato, U. *J. Org. Chem.* **1994**, *59*, 4194. (l) Brunner, H.; Altmann, S. *Chem. Ber.* **1994**, *127*, 2285.

(6) Chiral pyridine and bipyridine ligands. Pioneering work was made by the Italian group; see: (a) Botteghi, C.; Caccia, G.; Chelucci, G.; Soccolini, F. *J. Org. Chem.* **1984**, *49*, 4290. (b) Botteghi, C.; Chelucci, G.; Chessa, G.; Delogu, G.; Gladiali, S.; Soccolini, F. *J. Organomet. Chem.* **1986**, *304*, 217. (c) Chelucci, G. *Tetrahedron: Asymmetry* **1995**, *6*, 811. For recent excellent pyridyl and 2,2′-bipyridyl ligands, see: (d) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011. (e) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, 125, 1191.

(7) For the construction of pyridine and 2,2′-bipyridine ring from chiral cyanides, see: (a) Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymmetry* **1990**, *1*, 635. (b) Hayoz, P.; von Zelewsky, A. *Tetrahedron Lett.* **1992**, *33*, 5165. (c) Falorni, M.; Chelucci, G.; Conti, S.; Giacomelli, G. *Synthesis* **1992**, 972. (d) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1992**, *48*, 3653. (e) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Marchetti, M. *Tetrahedron: Asymmetry*, **1994**, *5*, 299.

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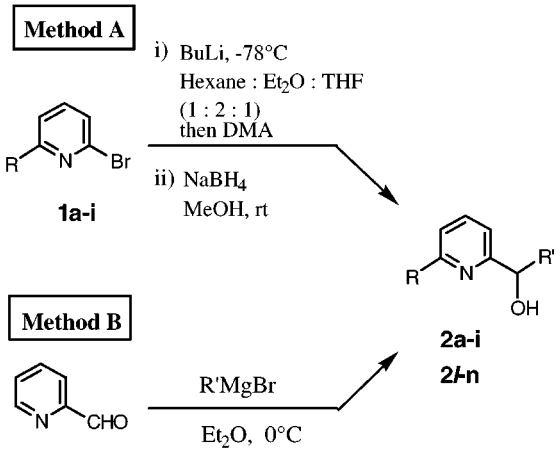
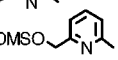
chiral metal hydrides,[9] such as under Corey−Itsuno conditions.[10] Although the chemical yields were excellent (80−98%), the enantiomeric excess values ranged from 35 to 96%. The face selectivities greatly depended on the substrate and the reaction conditions. In particular, they were influenced by a small quantity of moisture, and the resulting ee values varied greatly, at least in our hands. Soai reported an asymmetric reduction of aryl methyl ketones with excellent enantiomeric purities, but with a lower ee value in the case of 2-acetylpyridine.[11] Exceptionally good results of up to 92% ee in some pyridyl ketones were reported by Bolm using optically pure $(Ipc)_2BCl$ as the chiral reducing reagent.[12] In principle, the enantioselectivity in the metal hydride reduction of the carbonyl group is dependent on the steric course of hydrogen delivery onto the carbonyl face, which can be controlled by the three-dimensional structure of the metal hydride−carbonyl complex. When strong coordinating groups such pyridine and nitrogen heterocycles are next to the carbonyl, the inherent face and site selectivity of the chiral reducing reagent must generally decrease due to the coordination effect of the heteroatom. As long as a chiral metal-reducing reagent is used for the carbonyl group, substrates bearing a nitrogen atom located near the carbonyl center are not appropriate. In such cases, the presence of a small amount of moisture may influence the delicate selectivity. Recently, Corey resolved this problem and succeeded in the asymmetric reduction of 2-pyridyl ketone.[13] He masked the lone pair of the pyridyl nitrogen atom through the formation of an *N*-allylpyridinium salt before asymmetric reduction, which resulted in satisfactory enantioselectivities and excellent yields of the corresponding pyridyl alcohols. Nonetheless, it is still necessary to find a new, general, and reliable method for producing chiral pyridyl alcohols. Since biocatalysts have become popular and powerful in organic synthesis,[14] enzymatic acetylation can sometimes be very useful if it works well for individual alcohols. In 1994, we reported the lipase-catalyzed asymmetric acetylation of 1-(2-pyridyl)ethanols,[15] in which (*R*)-acetate and unreacted (*S*)-alcohol were obtained with excellent enantiomeric purity in good total yields. At that stage, the reaction was limited to some 1-(2-pyridyl)ethanols. 2-Pyridyl alcohols with an additional functional groups

Scheme 1



a ;	R=H	R'=Me
b ;	R=Br	R'=Me
c ;	R=Me	R'=Me
d ;	R=TBDMSOCH$_2$	R'=Me
e ;	R=TrOCH$_2$	R'=Me
f ;	R=Ph	R'=Me
g ;	R=2-Py	R'=Me
h ;	R= 	R'=Me
i ;	R= 	R'=Me
l ;	R=H	R'=Et
m;	R=H	R'=vinyl
n ;	R=H	R'=allyl

substituted at the 6-position on the pyridine ring or other alcohols are desirable as the substrate. In particular, functional groups, such as hydroxymethyl, vinyl, and allyl functionalities that can extend the carbon chain after appropriate functionalization, are most likely to be introduced. In this paper, we report the preparation of optically pure 2-pyridyl, 2,2′-bipyridyl, and 1- and 3-isoquinolyl alcohols (*S*)-**2a**−**n** and their acetates (*R*)-**3a**−**n** by lipase-catalyzed asymmetric acetylation reactions.

Results and Discussion

Preparation of 1-(2-Pyridyl)- and 6-(2,2′-Bipyridyl)ethanols 2a−n. 1-(2-Pyridyl)ethanols **2b**−**d,f** and 6-(2,2′-bipyridyl)ethanols **2g**−**i** were synthesized in two steps from 2-bromopyridines **1b**−**d,f,g,i** (Method A). Thus, 2-pyridyllithium, generated from 2-bromopyridine with BuLi as previously reported,[16] reacted with an excess of DMA (*N*,*N*-dimethylacetamide) to afford 2-acetylpyridine. The crude extract was directly reduced by $NaBH_4$ to give the corresponding 1-(2-pyridyl)ethanol. The reaction is shown in Scheme 1. The two-step yields were moderate (45−73%) and are listed in Table 1. On the other hand, compounds **2a,l,m,n** were prepared in yields of 92, 52, 87, and 88%, respectively, by the simple addition of Grignard reagents with 2-pyridinecarboxal-

(8) For the separation of diastereomers of pyridine and 2,2′-bipyridines, see: (a) Ito, K.; Katsuki, T. *Tetrahedron Lett.* **1993**, *34*, 2661. (b) Macedo, E.; Moberg, C. *Tetrahedron: Asymmetry*, **1995**, *6*, 549. (c) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002. (d) Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411.

(9) For reviews of the asymmetric reduction of the carbonyl group: *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. 7.

(10) Reviews for the Corey−Itsuno reduction using oxazaborolidines: (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.

(11) Soai, K.; Niwa, S.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 801.

(12) (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205. (b) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.

(13) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675.

(14) Reviews: (a) Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, 1992. (b) Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63. (c) Chen. C.-S.; Sih, C. *J. Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (d) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (e) Ward, S. C. *Chem. Rev.* **1990**, *90*, 1. (f) *Enzyme Catalsis in Organic Synthesis*; Drauz, K., Waldmann, H., Eds.; VCH: New York, 1995. (g) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071.

(15) Uenishi, J.; Nishiwaki, K.; Hata, S.; Nakamura, K. *Tetrahedron Lett.* **1994**, *35*, 7973.

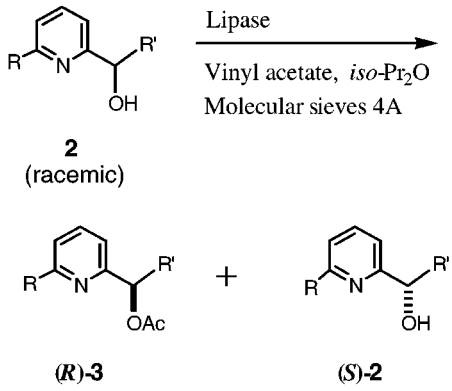
(16) (a) Uenishi, J.; Tanaka, T.; Nishiwaki, K.; Wakabayashi, S.; Oae, S.; Tsukube, H. *J. Org. Chem.* **1993**, *58*, 4382. (b) Tsukube, H.; Uenishi, J.; Higaki, H.; Kikkawa, K.; Tanaka, T.; Wakabayashi, S.; Oae, S. *J. Org. Chem.* **1993**, *58*, 4389.

Table 1. Enantioselective Acetylation of Racemic Pyridylalcohols 2a−i,l,m and Isoquinolylethanols 2j,k

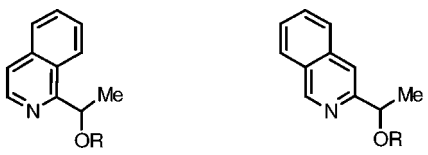
	preparation of substrates			enantioselective acetylation								
entry	substrate	method	yield (%)	time (h)	*T* (°C)	acetate[a] **3**	yield[b] (%)	ee (%)	recovered alcohol[a] **2**	yield[b] (%)	ee (%)	*E* value[c]
1	**2a**[19]	B	92	4	rt	**(*R*)-3a**[19]	47	99[d]	**(*S*)-2a**[19]	46	97[e]	>500
2	**2b**[12b]	A	73	6	rt	**(*R*)-3b**	46	97[d]	**(*S*)-2b**[12b]	49	93[e]	225
3	**2c**[25]	A	58	46	rt	**(*R*)-3c**	47	97[d]	**(*S*)-2c**	45	97[e]	278
4	**2c**			7	60	**(*R*)-3c**	47	99[d]	**(*S*)-2c**	47	99[e]	>500
5	**2d**	A	70	60	rt	**(*R*)-3d**	48	99[f]	**(*S*)-2d**	46	99[f]	>500
6	**2d**			12	60	**(*R*)-3d**	48	97[f]	**(*S*)-2d**	49	97[f]	278
7	**2e**	*g*		78	rt	**(*R*)-3e**	12	99[f]	**(*S*)-2e**	74	21[f]	244
8	**2e**			60	60	**(*R*)-3e**	44	99[f]	**(*S*)-2e**	46	98[f]	>500
9	**2f**[12b]	A	45	7	rt	**(*R*)-3f**	45	98[h]	**(*S*)-2f**[12b]	45	99[i]	>500
10	**2g**	A	56	7	rt	**(*R*)-3g**	49	97[d]	**(*S*)-2g**	47	98[e]	303
11	**2h**	*j*		11	rt	**(*R*)-3h**	49	99[d]	**(*S*)-2h**	49	98[e]	>500
12	**2i**	A	51	13	rt	**(*R*)-3i**	46	99[h]	**(*S*)-2i**	48	99[i]	>500
13	**2j**[17]	ref 17		14	rt	**(*R*)-3j**	49	99[i]	**(*S*)-2j**	46	98[k]	>500
14	**2k**[18]	ref 18		10	rt	**(*R*)-3k**	45	99[i]	**(*S*)-2k**	49	99[k]	>500
15	**2l**[26]	B	52[l]	40	rt	**(*R*)-3l**	45	99[d]	**(*S*)-2l**[26]	43	98[d]	>500
16	**2l**			12	60	**(*R*)-3l**	46	97[i]	**(*S*)-2l**	49	93[k]	225
17	**2m**	B	87	20	60	**(*R*)-3m**	49	99[i]	**(*S*)-2m**	46	95[k]	>500
18	**2n**[22]	B	88	72	60	**(*R*)-3n**	31	92[d]	**(*S*)-2n**[22]	58	78[l]	56

[a] The $[\alpha]_D$ values were described in the Experimental Section. [b] Isolated yields. [c] See ref 24. [d] Ee value was determined by the Mosher analysis after hydrolysis of the acetate, leading to the MTPA ester. [e] Ee value was determined by the Mosher analysis after conversion to the MTPA ester. [f] Ee value was determined by HPLC using chiral column (Dicel OJ) after conversion to 2-(1-acetoxyethyl)-6-(hydroxymethyl)pyridine. [g] Trityl derivative **2e** was derived from **2d** in two steps; see the Experimental Section. [h] Ee value was determined by HPLC using chiral column (Dicel OJ) after hydrolysis of the acetate. [i] Ee value was determined by HPLC using chiral column (Dicel OJ). [j] TBDMS ether **2h** was prepared from **1i** in three steps; see the Experimental Section. [k] Ee value was determined by HPLC using chiral column (Dicel OJ) after conversion to the acetate. [l] 2-Pyridylmethanol was obtained in 40% yield as a side product.

Scheme 2



dehyde (Method B). The yields are shown in Table 1. The trityl derivative **2e** was prepared in 77% yield from **2d** by replacing the silyl ether of **2d** with trityl ether in two steps: desilylation with Bu_4NF followed by tritylation with trityl chloride. 6′-Bromo-2,2′-bipyridyl derivative **2h** was obtained from **1i** in 61% yield in three steps: (i) desilylation of the silyl ether, (ii) Swern oxidation of the alcohol to an aldehyde, and (iii) addition of methylmagnesium bromide to the aldehyde. Isoquinolyl substrates **2j,k** were prepared as reported in the literature.[17,18]



2j : R = H **2k** : R = H

3j : R = Ac **3k** : R = Ac

Enantioselective Acetylation of Pyridylethanols by Lipase. Pyridylethanol **2d** and bipyridylethanol **2i** were chosen as substrates for the primary examination of lipases. An enzymatic acetylation was carried out in diisopropyl ether with vinyl acetate in the presence of powdered molecular sieves 4A and lipase at room temperature. We tested several lipases, including lipozyme (*Mucor miehei*), AK (*Pseudomonas sp.*), PS (*Pseudomonas cepacia*), and CAL (*Candida antarctica* lipase). All of the lipases gave (+)-acetates **3d** and **3i** with an (*R*)-chiral center and the recovery of (*S*)-alcohols (−)-**2d** and (+)-**2i**, respectively. Among the lipases, CAL gave the best enantioselectivities and chemical yields for both the acetate and alcohol, while other lipases did not give satisfactory results. These absolute configurations were confirmed by comparing their CD spectra with those of established 2-pyridyl and 2,2′-bipyridylethanols (*S*)-**2a**[19] and (*S*)-**2g**.[20] The CD spectra of (−)-**2d** and (+)-**2i** together with those of (*S*)-**2a** and (*S*)-**2g** are shown in Figure 1. Pyridylethanols (*S*)-**2a** and (−)-**2d** gave similar curves for the (+)-Cotton effect, which suggested that (−)-**2d** possessed an *S*-chiral center. (+)-Cotton curves were also observed in the CD spectra of (*S*)-**2g** and (+)-**2i**, indicating an (*S*)-configuration for (+)-**2i**.

Next, 14 pyridylethanols **2a**−**n** were examined under the above conditions, and the results are described in Table 1. The enantiomeric excess values of the alcohols were determined by either HPLC with a chiral column or Mosher analysis. The values of the acetates were also determined by HPLC or Mosher analysis after hydrolysis of the acetate. The absolute configurations were determined by comparison with the reported polarities for **2a**,[19] **2b**,[12b] and **2f**.[12b,21] The other alcohols were confirmed to possess an (*S*)-configuration by comparison of their CD

(17) Racemic **2j**: Wefer, J. M.; Popp, F. D. *J. Org. Chem.* **1967**, *32*, 1999.

(18) Racemic **2k**: Glyde, E.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1783.

(19) Seemayer, R.; Schneider, M. P. *Tetrahedron: Asymmetry* **1992**, *3*, 827.

(20) The authentic material (*S*)-**2g** was prepared according to Bolm's procedure described in ref 12b.

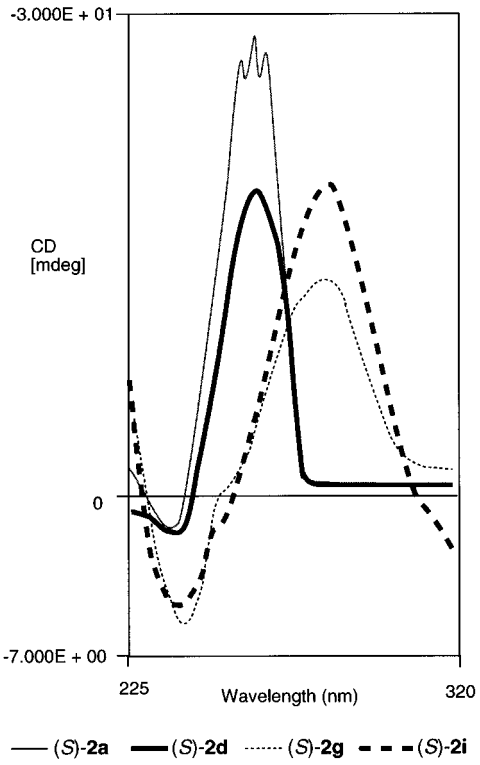


Figure 1. CD Spectra of (*S*)-**2a**, (*S*)-**2d**, (*S*)-**2g**, and (*S*)-**2i**.

spectra with those of the (*S*)-alcohols described in Figure 1. Therefore, the acetates were assigned an (*R*)-configuration. In fact, after the acetate was hydrolyzed, the resulting alcohols showed a sign opposite to that of the (*S*)-alcohols.

The acetylation of pyridylethanol **2a** and pyridylethanols bearing bromo, phenyl, 2-pyridyl, 2-(6-bromopyridyl), and 2-[6-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyridyl] groups at the 6-position on the pyridine ring, **2b,f**−**i** gave almost perfect selectivities with excellent yields (Table 1, entries 1, 2, 9, 10, 11, and 12). The reaction of 1- and 3-isoquinolylethanols **2j** and **2k** also proceeded quite well to give (*R*)-acetates and recovery of (*S*)-alcohols, respectively (Table 1, entries 13 and 14). In most cases, the acetylation of (*R*)-alcohol was complete within half a day, and the reaction rate of (*S*)-alcohol was considerably slower than that of (*R*)-alcohol. Even when the reaction of **2b** was allowed to continue for 1 week, (*S*)-**3b** was not obtained, and the chemical yield and enantiomeric purity of (*R*)-**3b** and (*S*)-**2b** did not change from those indicated in entry 2 (Table 1). In this case, it is assumed that the rate of the reaction of the (*S*)-alcohol would be at least 10^2 times slower than that of the (*R*)-alcohol.

On the other hand, the reactions for **2c** and **2d**, which have methyl and [(*tert*-butyldimethylsilyl)oxy]methyl groups at the 6-position on the pyridine ring, took a much longer time (Table 1, entries 3 and 5). In the case of trityl ether **2e** (Table 1, entry 7), the yield was only 12% even after 3 days, although the ee value of the acetate was excellent. In these cases, the sp^3 character of the carbon may contribute to the slow reaction rate. Although **2c** and **2d** are still acceptable, the reaction of **2e** was not complete at room temperature after 1 week, and the reaction finally became slightly sluggish. The same

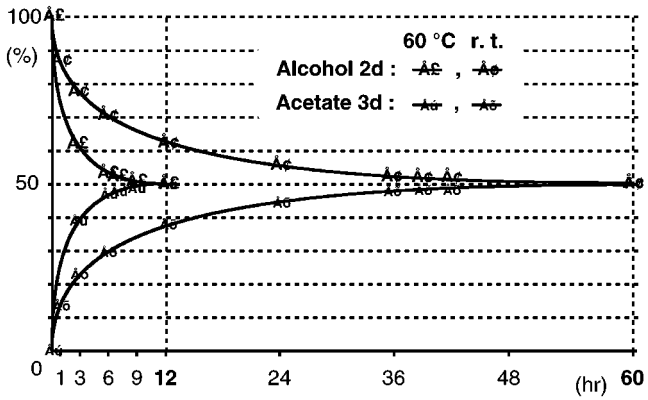


Figure 2. CAL-catalyzed acetylation of racemic **2d**.

problem occurred when 1-(2-pyridyl)-1-propanol (**2l**) was used for the substrate (Table 1, entry 15). Therefore, the reaction rate must be enhanced in such cases. Fortunately, when the reaction was carried out at a higher temperature, the reaction was accelerated. Figure 2 shows the progress of the reactions for **2d** monitored by ^{1}H NMR. The reactions at room temperature and at 60 °C were compared. Formation of the acetate **3d** and consumption of the alcohol **2d** were observed against time. The reaction rate at 60 °C was 5-fold faster than that at room temperature. However, when the temperature was raised to 90 °C, the reaction time to 50% conversion did not change much. It is very important to note that the reaction proceeded without losing the excellent selectivity even at the higher temperatures. The results of the reactions conducted at 60 °C for **2c**−**e,l**−**n** are indicated in Table 1. The reactions of **2c** and **2d** were complete within a shorter time at 60 °C (Table 1, entries 4 and 6), and the acetylation of **2e** was complete to give excellent yields of both the acetate and alcohol with a good enantiomeric excess ratio (Table 1, entry 8). The reaction of **2l** took 40 h at room temperature but only 12 h at 60 °C (Table 1, entries 15 and 16). Allylic alcohol **2m** became a good substrate at 60 °C to give an excellent *E* value (Table 1, entry 17). However, in the case of homoallyl alcohol **2n**[22] (Table 1, entry 18), the acetate was obtained in 31% yield with 92% ee, and the reaction gave 58% recovery of the alcohol with a poor ee. This result indicates that three carbons are the maximum effective length for the alcohol part in this lipase-catalyzed acetylation reaction.

Although all of these results were carried out on a 100-mg scale, this reaction can be used on scales from 10 mg to greater than 10 g. When the reaction of **2b** was carried out on a 10-g scale, the chemical yields fell slightly to 43−46% for both (*R*)-**3b** and (*S*)-**2b**. However, the selectivity did not change, and the acetate was obtained in 97% ee. In a large-scale reaction, the lipase and molecular sieves could be reused for the next reaction after a decantation of the solvent.[23]

Conclusion

The acetylation of a wide range of pyridyl and bipyridylethanols catalyzed by CAL was achieved with a good

(21) Chelucci, G.; Cabras, M. A.; Saba, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1973.

(22) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614.

(23) An appropriate amount of molecular sieves 4A and vinyl acetate should be added for the next batch of the reaction.

yield and an excellent enantiomeric excess. This reaction provides an (*R*)-acetate and the recovery of an (*S*)-alcohol. This method offers several advantages: (i) a simple and very convenient recipe, (ii) a clean reaction even at a large scale, (iii) excellent enantioselectivity and a high chemical yield, (iv) both (*R*)- and (*S*)-isomers are available in one reaction, and (v) the lipase can be used repeatedly. The obtained optically pure pyridines and 2,2′-bipyridines may be important building blocks for the construction of chiral ligand molecules, which should be useful in asymmetric reactions and molecular recognition chemistry.

Experimental Section

General Procedures. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under Ar atmosphere. Solvents were distilled freshly over sodium/benzophenone ketyl for THF, ether, and benzene, over P_2O_5 for CH_2Cl_2, and over CaH_2 for hexane, toluene, DMSO, and DMF under nitrogen atmosphere. Thin-layer chromatography (TLC) was performed with Merck $60F_{254}$ precoated silica gel plates. Column chromatography was carried out using Merck silica gel 60 (70−230 mesh) for gravity column and Wako neutral alumina (200 mesh). CAL (Novozym 435) was purchased from Novo Nordisk Bioindustry.

Preparation of Pyridylethanol (Method A). To a stirred solution of bromopyridine (3.3 mmol) in a mixture of ether, hexane, and THF (2:1:1, 66 mL) was added *n*-BuLi (3.3 mmol, 1.56 M in hexane solution) dropwise at −78 °C during 5−10 min. To the resulting dark brown solution was dropped anhydrous DMA (5 mmol) at the same temperature. The reaction mixture was stirred for 5−30 min and then quenched with water (5 mL) and extracted with EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent gave the crude ketone. To a methanol solution (5 mL) of the crude ketone was added an excess of $NaBH_4$ (150 mg, 4 mmol) at room temperature. After being stirred for 1 h, the mixture was poured into ice−water and extracted with EtOAc. A purification by column chromatography on silica gel gave the corresponding pyridylethanol. The chemical yields are shown in Table 1. Spectroscopic and analytical data for **2b**−**d,f,g,i** were described as follows:

1-[2-(6-Bromopyridyl)]ethanol (2b):[12b] oil; R_f = 0.40 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, t, J = 7.7 Hz), 7.39 (1H, d, J = 7.7 Hz), 7.28 (1H, d, J = 7.7 Hz), 4.88 (1H, q, J = 6.5), 3.40 (1H, br s), 1.51 (3H, d, J = 6.5 Hz).

1-[2-(6-Methylpyridyl)]ethanol (2c):[25] oil; R_f = 0.29 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, t, J = 7.7 Hz), 7.07 (1H, d, J = 7.7 Hz), 7.04 (1H, d, J = 7.7 Hz), 4.91 (1H, br s), 4.85 (1H, q, J = 6.6 Hz), 2.54 (3H, s), 1.49 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 156.8, 137.1, 121.6, 116.6, 68.4, 24.1, 24.1; IR (film) 3370 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 137 (M^+, 17); HRMS calcd for $C_8H_{11}NO$ M^+, 137.0841 (M^+), found *m*/*z* 137.0868.

1-[2-[6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]pyridyl]-ethanol (2d): oil; R_f = 0.28 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, t, J = 7.7 Hz), 7.40 (1H, d, J = 7.7 Hz), 7.11 (1H, d, J = 7.7 Hz), 4.84 (1H, q, J = 6.6 Hz), 4.83 (2H, s), 4.45 (1H, br s), 1.48 (3H, d, J = 6.6 Hz), 0.96 (9H, s), 0.13 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 159.8, 137.4, 118.3, 117.7, 68.5, 65.8, 25.8, 24.2, 18.3, −5.4; IR (film) 3400 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 210 (M^+ − 57, base), 195 (17), 194 (62), 118 (24); HRMS (FAB) calcd for $C_{14}H_{26}NO_2Si$ MH^+, 268.1733, found *m*/*z* 268.1742.

1-[2-(6-Phenylpyridyl)]ethanol (2f):[12b] oil; R_f = 0.29 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, dm, J = 7.2 Hz), 7.70 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.45 (2H, tm, J = 7.2 Hz), 7.39 (1H, tm, J = 7.2 Hz), 7.17 (1H, d, J = 7.8 Hz), 4.92 (1H, q, J = 6.6 Hz), 4.77 (1H, br s), 1.53 (3H, d, J = 6.6 Hz).

1-[6-(2,2′-Bipyridyl)]ethanol (2g): oil; R_f = 0.52 (60% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (1H, dm, J = 4.9 Hz), 8.44 (1H, dm, J = 7.8 Hz), 8.34 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J = 7.8, 1.2 Hz), 7.84 (1H, t, J = 7.8 Hz), 7.34 (1H, ddd, J = 7.8, 4.9, 1.2 Hz), 7.29 (1H, d, J = 7.8 Hz), 4.97 (1H, m), 4.60 (1H, d, J = 4.7 Hz), 1.57 (3H, d, J = 6.6 Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 155.4, 154.2, 148.9, 137.6, 136.7, 123.6, 120.9, 119.7, 119.3, 68.7, 24.1; IR (KBr) 3390 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 200 (M^+, 28), 199 (19), 185 (base), 183 (36); HRMS calcd for $C_{12}H_{12}N_2O$ M^+, 200.0950, found *m*/*z* 200.0950.

1-[6-[6′-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,2′-bipyridyl]]ethanol (2i): oil; R_f = 0.56 (60% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, d, J = 7.8 Hz), 8.27 (1H, d, J = 7.7 Hz), 7.85 (1H, t, J = 7.8 Hz), 7.81 (1H, t, J = 7.7 Hz), 7.54 (1H, dd, J = 7.8, 1.1 Hz), 7.26 (1H, d, J = 7.7 Hz), 4.96 (1H, q, J = 6.6 Hz), 4.92 (2H, s), 4.68 (1H, br s), 1.56 (3H, d, J = 6.6 Hz), 0.98 (9H, s), 0.15 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 160.9, 154.5, 154.4, 137.6, 137.3, 120.1, 119.6, 119.5, 119.0, 68.6, 66.2, 25.9, 24.2, 18.3, −5.4; IR (film) 3420 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 345 (MH^+, base), 329 (18), 288 (15), 287 (56), 195 (60). Anal. Calcd for $C_{19}H_{28}N_2O_2Si$: C, 66.24; H, 8.19; N, 8.13. Found: C, 66.48; H, 8.30; N, 8.06.

Preparation of 1-[2-[6-[(Trityloxy)methyl]pyridyl]]ethanol (2e). To a THF solution (9 mL) of **2d** (470 mg, 1.77 mmol) was added Bu_4NF (2.64 mL of a 1 M solution in THF, 2.64 mmol), and the mixture was stirred for 1.5 h at room temperature. The mixture was diluted with CH_2Cl_2 (200 mL) and washed with water and brine. After drying over $MgSO_4$, the solvent was removed and the residual oil was purified by silica gel column chromatography eluted with EtOAc to give 1-[2-[6-(hydroxymethyl)pyridyl]]ethanol (231 mg) in 85% yield. **1-[2-[6-(Hydroxymethyl)pyridyl]]ethanol**: oil, R_f = 0.13 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, J = 7.7 Hz), 7.20 (1H, d, J = 7.7 Hz), 7.17 (1H, t, J = 7.7 Hz), 4.88 (1H, q, J = 6.6 Hz), 4.73 (2H, s), 4.23 (1H, br s), 1.49 (3H, d, J = 6.6 Hz), 4.34 (2H, s), 4.31 (1H, d, J = 4.4 Hz), 1.45 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 158.1, 137.6, 119.1, 118.4, 69.1, 64.3, 24.0; MS (EI) *m*/*z* (rel intensity) 153 (M^+, 9), 138 (base), 136 (64), 120 (74). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.65; H, 7.37; N, 8.94. A mixture of the above alcohol (231 mg, 1.51 mmol), trityl chloride (482 mg, 1.73 mmol), and Et_3N (487 μL, 3.5 mmol) in a mixture of THF (0.7 mL) and CH_2Cl_2 (6.3 mL) was stirred at room temperature for 8 h. Then the mixture was diluted with CH_2Cl_2 (50 mL) and washed with water and brine. The extract was dried over $MgSO_4$ and condensed. The residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give **2e** (536 mg) in 90% yield: colorless crystals; mp 33−34 °C (hexane); R_f = 0.31 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, t, J = 7.7 Hz), 7.65 (1H, d, J = 7.7 Hz), 7.52 (6H, d, J = 7.5 Hz), 7.32 (6H, t, J = 7.5 Hz), 7.23 (3H, t, J = 7.5 Hz), 7.12 (1H, d, J = 7.7 Hz), 4.81 (1H, m), 4.34 (2H, s), 4.31 (1H, d, J = 4.4 Hz), 1.45 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 157.8, 143.8, 137.4, 128.6, 127.9, 127.1, 119.2, 117.9, 87.2, 68.4, 66.8, 24.2; IR (KBr) 3420 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 395 (M^+, 2), 362 (11), 318 (19), 300 (20), 279 (35), 243 (base). Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.92; H, 6.37; N, 3.59.

Preparation of 1-[6-(6′-Bromo-2,2′-bipyridyl)]ethanol (2h). To a solution of **1i** (965 mg, 2.54 mmol) in THF (12 mL) was added Bu_4NF (3.82 mL, 1 M in THF solution) at room temperature. The mixture was stirred for 10 min and diluted with EtOAc (100 mL). Then, it was washed with water and brine and dried over $MgSO_4$. The organic layer was condensed, and the residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give alcohol (571 mg) in 85% yield. **6-Bromo-6′-(hydroxymethyl)-2,2′-bipyridine**: colorless crystals; mp 154−155 °C (ether/hexane = 1:9); R_f = 0.42 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (1H, d, J = 7.7 Hz), 8.34 (1H, d, J = 7.7 Hz), 7.83 (1H,

(24) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

(25) Amin, H. B.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 624.

t, J = 7.7 Hz), 7.68 (1H, t, J = 7.7 Hz), 7.50 (1H, d, J = 7.7 Hz), 7.27 (1H, d, J = 7.7 Hz), 4.83 (2H, s), 3.80 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.8, 153.2, 141.6, 139.2, 137.7, 128.1, 121.0, 120.2, 119.6, 64.0; IR (KBr) 3420 cm^{-1}; MS (EI) *m/z* (rel intensity) 265 and 263 (M^+, base and 93), 237 and 235 (26 and 39), 210 and 208 (4 and 4), 183 (11), 155 (51). Anal. Calcd for $C_{11}H_9N_2OBr$: C, 49.84; H,3.42; N, 10.57. Found: C, 49.76; H, 3.38; N, 10.50. The above alcohol (563 mg, 2.12 mmol) was subjected to the standard Swern oxidation to give the corresponding aldehyde, which was dissolved in a mixture of dichloromethnane and ether (15 mL, 2:1). A ethereal solution of methylmagnesium bromide (2.76 mL, 0.9 M solution in ether) was added to the aldehyde at 0 °C. The mixture was stirred for 10 min at the same temperature and quenched with water (5 mL). The reaction mixture was extracted with EtOAc (50 mL), washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by silica gel column chromatography eluted with 50% EtOAc to give **2h** (417 mg) in 72% yield: colorless crystals; mp 76−77 °C (hexane), R_f = 0.58 (50% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (1H, dd, J = 7.7, 0.7 Hz), 8.31 (1H, d, J = 7.9 Hz), 7.81 (1H, t, J = 7.7 Hz), 7.66 (1H, t, J = 7.7 Hz), 7.48 (1H, dd, J = 7.7, 0.7 Hz), 7.30 (1H, d, J = 7.7 Hz), 4.94 (1H, q, J = 6.6 Hz), 4.38 (1H, br s), 1.54 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 156.7, 152.8, 141.6, 139.1, 137.9, 128.1, 120.5, 120.0, 119.6, 68.7, 24.2; IR (KBr) 3240 cm^{-1}; MS (EI) *m/z* (rel intensity) 280 and 278 (M^+, 19 and 19), 265 and 263 (82 and base), 155 (25). Anal. Calcd for $C_{12}H_{11}N_2OBr$: C, 51.64; H,3.97; N, 10.04. Found: C, 51.74; H, 3.97; N, 10.04.

Preparation of Pyridyl Alcohol (Method B). To an ethereal solution (186 mL) of 2-pyridinecarboxaldehyde (2 g, 18.7 mmol) was added methyl-, ethyl-, vinyl-, or allylmagnesium bromide in ether or THF (24.27 mmol) at 0 °C. The mixture was stirred for 2 h, quenched with ice−water (5 mL), and extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel eluted with 100%, 50%, 50%, and 40% EtOAc in hexane, respectively, for **2a**,[19] **2l**, **2m**, and **2n**. The physical and spectroscopic data for **2l**, **2m**, and **2n** are described as follows:

1-(2-Pyridyl)propanol (2l).[26] oil; R_f = 0.27 (70% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, dm, J = 4.8 Hz), 7.66 (1H, td, J = 7.7, 1.7 Hz), 7.24 (1H, d, J = 7.7 Hz), 7.18 (1H, ddm, J = 7.7, 4.8 Hz), 4.68 (1H, dd, J = 7.4, 4.7 Hz), 4.25 (1H, br s), 1.87 (1H, m), 1.71 (1H, dq, J = 14.1, 7.4 Hz), 0.93 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 148.1, 136.6, 122.2, 120.4, 73.7, 31.3, 9.4; IR (film) 3400 cm^{-1}; MS (FAB) *m/z* 138 (MH^+); HRMS calcd for $C_8H_{12}NO$ MH^+, 138.0919, found *m/z* 138.0915.

1-(2-Pyridyl)-2-propen-1-ol (2m): oil; R_f = 0.30 (60% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, dm, J = 4.8 Hz), 7.70 (1H, td, J = 7.7, 1.6 Hz), 7.30 (1H, d, J = 7.7 Hz), 7.22 (1H, ddm, J = 7.7, 4.8 Hz), 5.97 (1H, ddd, J = 17.0, 10.2, 6.7 Hz), 5.46 (1H, dm, J = 17.0 Hz), 5.25 (1H, dm, J = 10.2 Hz), 5.19 (1H, d, J = 6.7 Hz), 4.75 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 148.1, 139.4, 136.8, 122.5, 120.9, 116.5, 74.2; IR (film) 3320 cm^{-1}; MS (FAB) *m/z* 136 (MH^+); HRMS calcd for $C_8H_{10}NO$ MH^+, 136.0762, found *m/z* 136.0741.

1-(2-Pyridyl)-3-buten-1-ol (2n):[22] oil; R_f = 0.27 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, dm, J = 4.7 Hz), 7.68 (1H, td, J = 7.7, 1.7 Hz), 7.31 (1H, d, J = 7.7 Hz), 7.19 (1H, ddm, J = 7.7, 4.7 Hz), 5.83 (1H, m), 5.13−5.08 (2H, m), 4.81 (1H, dd, J = 7.1, 4.9 Hz), 4.26 (1H, br s), 2.63 (1H, m), 2.49 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 148.2, 136.6, 134.1, 122.3, 120.4, 117.9, 72.3, 42.8; IR (film) 3360 cm^{-1}; MS (FAB) *m/z* 150 (MH^+); HRMS calcd for $C_9H_{12}NO$ MH^+, 150.0919, found *m/z* 150.0933.

Asymmetric Acetylation of Pyridyl Alcohols 2a−n (General Procedure). A mixture of secondary alcohol (100 mg), lipase (30 mg), and vinyl acetate (0.2 mL) in dry diisopropyl ether (20 mL) was stirred vigorously in the presence of molecular sieves 4A (100 mg). The reaction time, temperature, and yield are indicated in Table 1. After the reaction was complete, in which half of the alcohol was converted to the acetate, the reaction mixture was filtered through a Celite pad or filtering paper. The filtrate was condensed, and the residue was purified by column chromatography on silica gel to give the (*R*)-acetate and a recovery of the (*S*)-alcohol. Each enantiomeric purity was determined by HPLC connected with a chiral column directly or a transformation to the appropriate derivatives, or alternatively by Mosher analysis. Physical properties including specific rotation values and spectroscopic data for the (*R*)-acetates and physical data and specific rotation values for the recovered (*S*)-alcohols are described as follows:

(*R*)-3a: oil; $[\alpha]^{28}_D$ +97.4° (*c* 2.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (1H, dm, J = 4.9 Hz), 7.69 (1H, td, J = 7.7, 1.8 Hz), 7.33 (1H, d, J = 7.7 Hz), 7.23 (1H, ddm, J = 7.7, 4.9 Hz), 5.91 (1H, q, J = 6.7 Hz), 2.13 (3H, s), 1.60 (3H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 160.1, 149.1, 136.6, 122.5, 120.3, 72.9, 21.1, 20.6; IR (film) 1730 cm^{-1}; MS (FAB) *m/z* 166 (MH^+); HRMS calcd for $C_9H_{12}NO_2$ MH^+, 166.0868, found *m/z* 166.0843. **(*S*)-2a**:[19] colorless crystals; mp 28−29 °C (hexane); $[\alpha]^{29}_D$ −28.1° (*c* 2.23, $CHCl_3$).

(*R*)-3b: oil; $[\alpha]^{25}_D$ +72.1° (*c* 2.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, t, J = 7.7 Hz), 7.43 (1H, d, J = 7.7 Hz), 7.29 (1H, d, J = 7.7 Hz), 5.86 (1H, q, J = 6.7 Hz), 2.13 (1H, s), 1.51 (3H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 161.8, 141.5, 139.0, 127.0, 118.9, 72.3, 21.1, 20.6; IR (film) 1740 cm^{-1}; MS (FAB) *m/z* 244 and 246 (MH^+) HRMS calcd for $C_9H_{11}BrNO_2$ MH^+, 243.9973 and 245.9953, found *m/z* 243.9981 and 245.9935. **(*S*)-2b**:[12b] oil; $[\alpha]^{25}_D$ −11.0° (*c* 2.15, $CHCl_3$).

(*R*)-3c: oil; $[\alpha]^{25}_D$ +104° (*c* 2.0, $CHCl_3$); R_f = 0.63 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, t, J = 7.7 Hz), 7.12 (1H, d, J = 7.7 Hz), 7.05 (1H, d, J = 7.7 Hz), 5.87 (1H, q, J = 6.7 Hz), 2.55 (3H, s), 2.12 (3H, s), 1.58 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.8, 157.9, 136.8, 122.2, 116.9, 73.3, 24.4, 21.2, 20.9; IR (film) 1730 cm^{-1}; MS (EI) *m/z* (rel intensity) 179 (M^+, 6); HRMS calcd for $C_{10}H_{14}NO_2$ MH^+, 180.1025, found *m/z* 180.1017. **(*S*)-2c**: colorless crystals; mp 43−44 °C (hexane); $[\alpha]^{25}_D$ −10.1° (*c* 1.51, $CHCl_3$).

(*R*)-3d: oil; $[\alpha]^{25}_D$ +58° (*c* 0.40, $CHCl_3$); R_f = 0.50 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (1H, t, J = 7.7 Hz), 7.42 (1H, d, J = 7.7 Hz), 7.18 (1H, d, J = 7.7 Hz), 5.86 (1H, q, J = 6.7 Hz), 4.83 (2H, s), 2.11 (3H, s), 1.56 (3H, d, J = 6.7 Hz), 0.95 (9H, s), 0.12 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 160.9, 159.2, 137.1, 118.7, 118.1, 73.0, 66.0, 25.8, 21.1, 20.7, 18.2, −5.5; IR (film) 1738 cm^{-1}; MS (FAB) *m/z* 310 (MH^+, 59); HRMS calcd for $C_{16}H_{28}NO_3Si$ MH^+, 310.1839, found *m/z* 310.1858. **(*S*)-2d**: oil; $[\alpha]^{25}_D$ −2.9° (*c* 1.97, $CHCl_3$).

(*R*)-3e: oil; $[\alpha]^{25}_D$ +67° (*c* 0.73, $CHCl_3$); R_f = 0.38 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, t, J = 7.6 Hz), 7.69 (1H, d, J = 7.6 Hz), 7.50 (6H, d, J = 7.7 Hz), 7.30 (6H, t, J = 7.7 Hz), 7.23 (3H, tm, J = 7.7 Hz), 7.19 (1H, d, J = 7.6 Hz), 5.82 (1H, q, J = 6.6 Hz), 4.38 (1H, d, J = 14.0 Hz), 4.33 (1H, d, J = 14.0 Hz), 2.08 (3H, s), 1.51 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.4, 159.1, 143.9, 137.3, 128.7, 127.9, 127.1, 119.6, 118.4, 87.2, 73.1, 66.9, 21.2, 20.8; IR (film) 1780 cm^{-1}; MS (EI) *m/z* (rel intensity) 194 (M^+ − 243, 17), 407 (4), 360 (19), 243 (base). Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.61; H, 6.22; N, 3.20. Found: C, 79.55; H, 6.32; N, 3.08. **(*S*)-2e**: colorless crystals; mp 36−37 °C (hexane); $[\alpha]^{25}_D$ +0.2° (*c* 1.83, $CHCl_3$).

(*R*)-3f: oil; $[\alpha]^{25}_D$ +86° (*c* 1.00, $CHCl_3$); R_f = 0.27 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2H, dm, J = 7.5 Hz), 7.70 (1H, t, J = 7.6 Hz), 7.60 (1H, d, J = 7.6 Hz), 7.44 (2H, tm, J = 7.5 Hz), 7.38 (1H, tm, J = 7.5 Hz), 7.25 (1H, d, J = 7.6 Hz), 6.01 (1H, q, J = 6.6 Hz), 2.15 (3H, s), 1.66 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 160.1, 156.5, 139.1, 137.3, 128.9, 128.6, 126.9, 119.0, 118.3, 73.2, 21.2, 20.6; IR (film) 1740 cm^{-1}; MS (EI) *m/z* (rel intensity) 241 (M^+, 14), 198 (89), 182 (base), 155 (34), 154 (57); HRMS calcd for

(26) Brown, H. C.; Vara Prasad, J. V. N.; Zee, S.-H. *J. Org. Chem.* **1986**, *51*, 439. Ohno, A.; Nakai, J.; Nakamura, K.; Goto, T.; Oka, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3482.

$C_{15}H_{15}NO_2$ M^+, 241.1103, found *m*/*z* 241.1089. **(*S*)-2f**:[12b] oil; $[\alpha]^{25}_D$ +28° (*c* 1.00, $CHCl_3$).

(*R*)-3g: oil; $[\alpha]^{25}_D$ +85° (*c* 1.87, $CHCl_3$); R_f = 0.44 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (1H, dm, *J* = 4.2 Hz), 8.47 (1H, d, *J* = 7.8 Hz), 8.31 (1H, d, *J* = 7.8 Hz), 7.80 (1H, dt, *J* = 7.8 Hz), 7.80 (1H, t, *J* = 7.8 Hz), 7.35 (1H, d, *J* = 7.8 Hz), 7.29 (1H, ddd, *J* = 7.8, 4.8, 1.0 Hz), 6.03 (1H, q, *J* = 6.6 Hz), 2.15 (3H, s), 1.67 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.6, 156.0, 155.3, 148.9, 137.5, 136.8, 123.7, 121.3, 120.1, 119.7, 73.1, 21.2, 20.5; IR (film) 1735 cm^{-1}; MS (FAB) *m*/*z* 243 (MH^+); HRMS calcd for $C_{14}H_{15}N_2O_2$ MH^+, 243.1134, found *m*/*z* 243.1105. **(*S*)-2g**: oil; $[\alpha]^{25}_D$ +26° (*c* 1.62, $CHCl_3$).

(*R*)-3h: colorless crystals; mp 40−41 °C (hexane); $[\alpha]^{25}_D$ +72° (*c* 1.90, $CHCl_3$); R_f = 0.54 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (1H, dd, *J* = 7.8, 1.1 Hz), 8.32 (1H, d, *J* = 7.8 Hz), 7.81 (1H, t, *J* = 7.8 Hz), 7.66 (1H, t, *J* = 7.8 Hz), 7.48 (1H, dd, *J* = 7.8, 1.1 Hz), 7.37 (1H, d, *J* = 7.8 Hz), 6.00 (1H, q, *J* = 6.6 Hz), 2.15 (3H, s), 1.65 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 159.8, 157.2, 153.7, 141.4, 139.1, 137.7, 127.9, 120.7, 120.2, 119.9, 73.1, 21.3, 20.6; IR (KBr) 1730 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 322 and 320 (M^+, 18 and 18), 279 and 277 (92 and 89), 263 and 261 (53 and 55), 43 (base). Anal. Calcd for $C_{14}H_{13}N_2O_2Br$: C, 52.36; H,4.08; N, 8.72. Found: C, 52.55; H, 4.23; N, 8.52. **(*S*)-2h**: colorless crystals; mp 82−83 °C (hexane); $[\alpha]^{25}_D$ +11.9 (*c* 1.53, $CHCl_3$).

(*R*)-3i: oil; $[\alpha]^{25}_D$ +78° (*c* 2.13, $CHCl_3$); R_f = 0.67 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (1H, d, *J* = 7.7 Hz), 8.30 (1H, d, *J* = 7.7 Hz), 7.82 (1H, t, *J* = 7.7 Hz), 7.78 (1H, t, *J* = 7.7 Hz), 7.52 (1H, d, *J* = 7.7 Hz), 7.33 (1H, d, *J* = 7.7 Hz), 6.02 (1H, q, *J* = 6.6 Hz), 4.91 (2H, s), 2.15 (3H, s), 1.66 (3H, d, *J* = 6.6 Hz), 0.98 (9H, s), 0.15 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 160.7, 159.6, 155.6, 155.0, 137.4, 137.3, 120.0, 120.0, 119.8, 119.4, 73.2, 66.3, 25.9, 21.3, 20.6, 18.4, −5.3; IR (film) 1740 cm^{-1}, MS (EI) *m*/*z* (rel intensity) 329 (M^+, base), 269 (92), 243 (5), 195 (11); HRMS calcd for $C_{21}H_{30}N_2O_2Si$ M^+, 386.2026, found *m*/*z* 386.2036. **(*S*)-2i**: colorless crystals; mp 32−33 (hexane); $[\alpha]^{25}_D$ +12.6° (*c* 3.07, $CHCl_3$).

(*R*)-3j: colorless crystals; mp 102−104 °C (hexane); R_f = 0.53° (50% EtOAc in hexane); $[\alpha]^{24}_D$ +32.8° (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ 8.53 (1H, d, *J* = 5.5 Hz), 8.24 (1H, d, *J* = 8.4 Hz), 7.85 (1H, d, *J* = 8.1 Hz), 7.70 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz), 7.65−7.61 (2H, m), 6.73 (1H, q, *J* = 6.6 Hz), 2.13 (3H, s), 1.76 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.3, 141.8, 136.5, 129.9, 127.5, 127.4, 125.7, 124.2, 120.8, 69.7, 21.1, 19.7; IR (KBr) 1730 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 215 (M^+, 20); HRMS calcd for $C_{13}H_{13}NO_2$ M^+, 215.0946, found *m*/*z* 215.0935. **(*S*)-1-(1-Isoquinolyl)ethanol (2j)**: oil; $[\alpha]^{25}_D$ −88° (*c* 0.50, $CHCl_3$); R_f = 0.31 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (1H, d, *J* = 5.9 Hz), 8.05 (1H, dd, *J* = 8.4, 1.5 Hz), 7.87 (1H, dd, *J* = 8.4, 1.5 Hz), 7.71 (1H, ddd, *J* = 8.4, 7.0, 1.5 Hz), 7.63 (1H, ddd, *J* = 8.4, 7.0 and 1.5 Hz), 7.60 (1H, d, *J* = 5.9 Hz), 5.59 (1H, q, *J* = 6.6 Hz), 5.30 (1H, br s), 1.60 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 140.2, 136.2, 130.0, 127.3, 127.1, 124.4, 123.9, 120.2, 65.8, 25.1; IR (KBr) 3400 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 173 (M^+, 33), 158 (base), 130 (51); HRMS calcd for $C_{11}H_{11}NO$ M^+, 173.0841, found *m*/*z* 173.0865.

(*R*)-3k: oil; $[\alpha]^{25}_D$ +91° (*c* 0.50, $CHCl_3$); R_f = 0.70 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (1H, s), 7.97 (1H, dd, *J* = 8.1, 1.1 Hz), 7.83 (1H, dd, *J* = 8.4, 1.1 Hz), 7.70 (1H, ddd, *J* = 8.4, 7.0, 1.1 Hz), 7.68 (1H, s), 7.60 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz), 6.09 (1H, q, *J* = 6.6 Hz), 2.15 (3H, s), 1.96 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 153.5, 152.3, 136.1, 130.4, 128.0, 127.4, 127.2, 126.6, 116.8, 73.0, 21.2, 20.7; IR (film) 1720 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 215 (M^+, 15); HRMS calcd for $C_{13}H_{13}NO_2$ M^+, 215.0946, found *m*/*z* 215.0966. **(*S*)-1-(3-Isoquinolyl)ethanol (2k)**: colorless crystals; mp 88−90 °C (hexane); $[\alpha]^{25}_D$ −34° (*c* 0.50, $CHCl_3$); R_f = 0.38 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (1H, s), 7.97 (1H, dd, *J* = 8.1, 1.1 Hz), 7.82 (1H, dd, *J* = 8.1, 1.1 Hz), 7.69 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz), 7.65 (1H, s), 7.58 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz), 5.07 (1H, q, *J* = 6.6 Hz), 3.78 (1H, br s), 1.62 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 151.6, 136.5, 130.6, 127.9, 127.6, 127.0, 126.6, 115.5, 69.5, 24.2; IR (KBr) 3300 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 173 (M^+, 45), 158 (base), 130 (59); HRMS calcd for $C_{11}H_{11}NO$ M^+, 173.0841, found *m*/*z* 173.0864.

(*R*)-3l: oil; $[\alpha]^{25}_D$ +101° (*c* 1.74, $CHCl_3$); R_f = 0.54 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (1H, dd, *J* = 4.3, 0.9 Hz), 7.62 (1H, td, *J* = 7.7, 1.6 Hz), 7.25 (1H, dm, *J* = 7.7 Hz), 7.14 (1H, ddd, *J* = 7.7, 4.3, 0.9 Hz), 5.68 (1H, t, *J* = 6.6 Hz), 2.09 (3H, s), 1.97−1.90 (2H, m), 0.87 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.3, 149.2, 136.4, 122.5, 121.0, 77.7, 27.8, 21.0, 9.5; IR (film) 1730 cm^{-1}; MS (FAB) *m*/*z* 180 (MH^+); HRMS calcd for $C_{10}H_{14}NO_2$ MH^+, 180.1025, found *m*/*z* 180.1007. **(*S*)-2l**:[26] oil; $[\alpha]^{27}_D$ −33.8° (*c* 1.81, $CHCl_3$).

(*R*)-3m: oil; $[\alpha]^{25}_D$ +49° (*c* 1.84, CHC_{l3}); R_f = 0.50 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (1H, dd, *J* = 4.3, 0.9 Hz), 7.70 (1H, td, *J* = 7.8, 1.7 Hz), 7.36 (1H, dm, *J* = 7.8 Hz), 7.22 (1H, ddd, *J* = 7.8, 4.3, 0.9 Hz), 6.30 (1H, t, *J* = 6.3 Hz), 6.11 (1H, ddd, *J* = 17.2, 10.5, 6.3 Hz), 5.39 (1H, dm, *J* = 17.2 Hz), 5.30 (1H, dm, *J* = 10.5 Hz), 2.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 158.1, 149.5, 136.8, 135.0, 122.9, 121.3, 117.8, 21.1; IR (film) 1740 cm^{-1}; MS (FAB) *m*/*z* 178 (MH^+); HRMS *m*/*z* calcd for $C_{10}H_{12}NO_2$ M^+, 178.0868, found *m*/*z* 178.0861. **(*S*)-2m**: oil; $[\alpha]^{25}_D$ +70° (*c* 1.80, $CHCl_3$).

(*R*)-3n: oil; $[\alpha]^{25}_D$ +75° (*c* 2.01, $CHCl_3$); R_f = 0.43 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, dd, *J* = 5.0, 0.9 Hz), 7.64 (1H, td, *J* = 7.7, 1.8 Hz), 7.27 (1H, dm, *J* = 7.7 Hz), 7.17 (1H, ddd, *J* = 7.7, 5.0, 0.9 Hz), 5.83 (1H, dd, *J* = 7.4, 5.8 Hz), 5.70 (1H, m), 5.04 (1H, dd, *J* = 17.8, 1.7 Hz), 5.01 (1H, dm, *J* = 10.2 Hz), 2.72−2.65 (2H, m), 2.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 158.7, 149.3, 136.5, 133.0, 122.7, 121.1, 118.1, 75.6, 39.0, 21.0; IR (film) 1740 cm^{-1}; MS (FAB) *m*/*z* 92 (MH^+); HRMS calcd for $C_{11}H_{14}NO_2$ MH^+, 192.1025, found *m*/*z* 192.1013. **(*S*)-2n**:[22] oil; $[\alpha]^{25}_D$ −38° (*c* 1.85, $CHCl_3$).

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Supporting Information Available: Copies of ^{1}H and/or ^{13}C NMR spectra for 38 new and known compounds. Experimental procedures for **1f** and **1i** and physical and spectroscopic data for the 2-acetyl intermediates **2b−d,f,g,i** (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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