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# Dynamic Kinetic Resolution of Diarylmethanols with an Activated Lipoprotein Lipase

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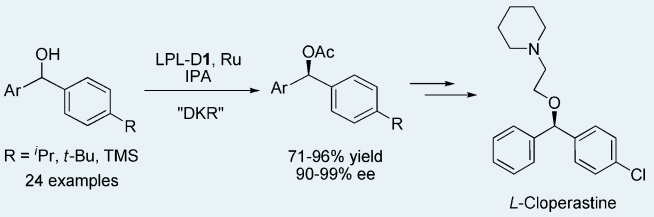
Supporting Information

**ABSTRACT:** We explored the kinetic resolution of 31 different diarylmethanols with an activated lipoprotein lipase (LPL-D**1**) which was about 3000-fold more active than its native counterpart in organic solvent. Most of the substrates tested were accepted by LPL-D**1** with good to high enantioselectivity in the kinetic resolution. Next, we explored the dynamic kinetic resolutions (DKRs) of these substrates (24 out of 31) using LPL-D**1** and a ruthenium-based racemization catalyst in combination, which provided satisfactory yields (71−96%) and high enantiopurities (90−99% ee). As an illustrative example for the synthetic applications of the DKR procedure, we synthesized *L*-cloperastine, an antitussive drug, from phenyl-(*p*-trimethylsilylphenyl)methanol via DKR.



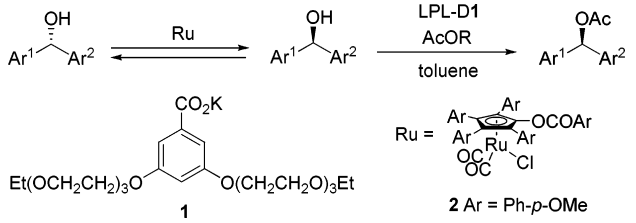

**KEYWORDS:** *diarylmethanol, dynamic kinetic resolution, lipase, ruthenium, catalysis*

## INTRODUCTION

Dynamic kinetic resolution (DKR) provides a powerful methodology for the complete transformations of racemates to single enantiomers.[1] Over the past decade, the procedures employing an enzyme as the resolution catalyst and a metal (complex) as the racemization catalyst have been intensively explored for the efficient DKR.[2−6] Several useful procedures are now available for the DKR of alcohols,[7−22] amines,[23−33] and amino acids.[34−38] The wider applications of the DKR procedures, however, are limited by the low activity, narrow substrate specificity, or modest enantioselectivity of enzyme employed. For example, *Candida antarctica* lipase B (CALB; brand name, Novozym 435), which has been most frequently employed in the DKR of alcohols, has good activity in organic solvent but does not accept sterically demanding substrates such as diarylmethanols.[39] Recently, we reported that an ionic-surfactant-coated *Burkholderia cepacia* lipase (ISCBCL) was highly active in organic solvent[40] and accepted a wider range of secondary alcohols in the DKR.[41] Unfortunately, the DKR of diarylmethanols with this enzyme was not satisfactory. Later, we communicated that a lipoprotein lipase[42] (LPL) from *Burkholderia species* was also highly active in organic solvent if it was coated with both dextrin (D) and ionic surfactant (**1**) via lyophilization.[43] We now wish to report a successful application of this LPL preparation (LPL-D**1**) to the DKR of diarylmethanols including aryl heteroarylmethanols (Scheme 1).

Enantiomerically enriched diarylmethanols are useful as the precursors or building blocks for the synthesis of pharmaceutically important compounds such as antihistaminic, antiarrhythmic, and anticholinergic agents.[44] Several chemical procedures have been explored to provide the routes to them. Two common approaches include the enantioselective additions of aryl nucleophiles to aromatic aldehydes[45,46] and the asymmetric hydrogenations of diaryl ketones.[47−49] The enzymatic methods are available as well. They include the asymmetric reduction of ketones employing ketoreductases[50,51] and the lipase-catalyzed kinetic resolution of racemic alcohols.[39] All of these chemical and enzymatic methods have advantages and disadvantages. In particular, the enzymatic kinetic resolution has a serious limitation that the theoretical maximum yield is 50% for the wanted enantiomer. The DKR procedure described in this manuscript provides higher yields.

**Scheme 1. DKR of Diarylmethanols with LPL-D1 and a Ru Complex**




## RESULTS AND DISCUSSION

**Activity of LPL-D1.** LPL-D**1** was prepared by freeze-drying a solution containing LPL (52% protein),[52] dextrin (D), and **1** at a 1:2:1 weight ratio in 1:1 (v/v) water−dioxane. The activities of LPL-D**1** were measured for the hydrolysis and

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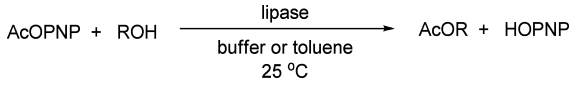
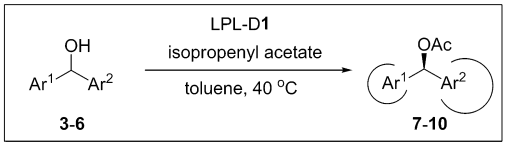
**Table 1. Kinetic Parameters of LPL and LPL-D1 for the Hydrolysis and Alcoholysis of *p*-Nitrophenyl Acetate**

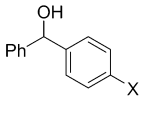



| entry | lipase | ROH | $k_{cat}$ ($s^{-1}$)[a] | $K_m$ (M)[a] | $k_{cat}/K_m$ ($s^{-1}$/M) |
|---|---|---|---|---|---|
| 1 | LPL | $H_2O$ | $2.8 \times 10^{2}$ | $4.8 \times 10^{-4}$ | $5.7 \times 10^{5}$ |
| 2 | LPL | $PhCH_2OH$ | $6.4 \times 10^{-2}$ | $2.5 \times 10^{-1}$ | $2.6 \times 10^{-1}$ |
| 3 | LPL | $PhCH(CH_3)OH$ | $1.7 \times 10^{-2}$ | $8.7 \times 10^{-2}$ | $2.0 \times 10^{-1}$ |
| 4 | LPL-D**1** | $H_2O$ | $3.0 \times 10^{2}$ | $4.7 \times 10^{-4}$ | $6.3 \times 10^{5}$ |
| 5 | LPL-D**1** | $PhCH_2OH$ | $5.7 \times 10^{2}$ | $6.4 \times 10^{-1}$ | $8.8 \times 10^{2}$ |
| 6 | LPL-D**1** | $PhCH(CH_3)OH$ | $5.5 \times 10$ | $1.0 \times 10^{-1}$ | $5.5 \times 10^{2}$ |

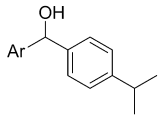
[a]The $V_{max}$ and $K_m$ values were obtained using the nonlinear curve fitting of average rates per 1 mg of LPL (52% protein) measured in duplicate. Each $k_{cat}$ was then calculated using the equation $V_{max} = k_{cat}[E]_0$, where $[E]_0$ is total concentration of enzyme (MW 33 000).

**Chart 1. Enantioselectivity of LPL-D1 in the Kinetic Resolution of Diarylmethanols[a]**

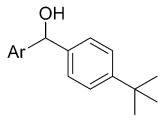


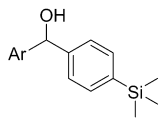

**3a** X = Cl: *E* = 2
**3b** X = Br: *E* = 2




**4a** Ar = Ph: *E* = 45
**4b** Ar = Ph-*m*-F: *E* = 40
**4c** Ar = Ph-*m*-Me: *E* = 23
**4d** Ar = Ph-*p*-F: *E* = 28
**4e** Ar = Ph-*p*-Cl: *E* = 14
**4f** Ar = Ph-*p*-OMe: *E* = 13
**4g** Ar = Ph-*p*-$NO_2$: *E* = 11
**4h** Ar = 2-furyl: *E* = 93
**4i** Ar = 3-furyl: *E* = 78
**4j** Ar = 2-thiophenyl: *E* = 81
**4k** Ar = 3-thiophenyl: *E* = 39
**4l** Ar = 3-pyridyl: *E* = 79
**4m** Ar = 4-pyridyl: *E* = 57




**5a** Ar = Ph: *E* = 114
**5b** Ar = Ph-*m*-F: *E* = 76
**5c** Ar = Ph-*m*-Me: *E* = 55
**5d** Ar = Ph-*p*-F: *E* = 81
**5e** Ar = Ph-*p*-Cl: *E* = 33
**5f** Ar = Ph-*p*-OMe: *E* = 24
**5g** Ar = Ph-*p*-$NO_2$: *E* = 21
**5h** Ar = 2-furyl: *E* = 145
**5i** Ar = 3-furyl: *E* = 146
**5j** Ar = 2-thiophenyl: *E* = 141
**5k** Ar = 3-thiophenyl: *E* = 65
**5l** Ar = 3-pyridyl: *E* = >200
**5m** Ar = 4-pyridyl: *E* = >200




**6a** Ar = Ph: *E* = 30
**6b** Ar = 2-thiophenyl: *E* = 49
**6c** Ar = 3-pyridyl: *E* = 43

[a]The *E* value on the right side of each substrate number indicates the enantioselectivity.

alcoholysis of *p*-nitrophenyl acetate (AcOPNP) to compare with those of its native counterpart in water and organic solvent. The data ($k_{cat}/K_m$) from Table 1 indicate that LPL-D**1** was as active as its native counterpart in water (compare the entries 1 and 4) but about 3000-fold more active than the latter in organic solvent (compare the entries 2 and 5 or the entries 3 and 6). It is particularly noteworthy that, in the reaction of AcOPNP with benzyl alcohol in toluene, the turnover frequency (TOF, $k_{cat}$) of LPL-D**1** reached the aqueous-level (entry 5). To the best of our knowledge, LPL-D**1** is the first lipase preparation that has displayed the aqueous-level TOF in anhydrous organic solvent. We guess that dextrin and **1** induced such a dramatic activation in organic solvent by providing both water-mimicking and oil-like microenvironments around the enzyme. Despite the aqueous-level TOF, the overall catalytic efficiency ($k_{cat}/K_m$) in organic solvent was still below the aqueous level owing to the relatively large $K_m$ (compare the entries 4 and 5). So, further improvements in the $K_m$ are needed to realize the aqueous-level catalytic efficiency in organic solvent.

**Enantioselectivity of LPL-D1 in the Kinetic Resolution of Diarylmethanols.** A total of 31 different diaryl and aryl heteroarylmethanols were chosen as the substrates of LPL-D**1** to examine the enantioselectivity in the kinetic resolution (Chart 1). The enantioselectivity of LPL-D**1** for each substrate was determined by performing the transesterification of each substrate in the presence of isopropenyl acetate (IPA) as the acyl donor in toluene at 40 °C. It is noted that the elevated temperature was chosen because most DKR reactions were performed at this temperature. The reaction of each substrate was carried out with a solution containing substrate (0.1 mmol), LPL-D**1** (20 mg/mmol of substrate; enzyme content: ca. 13%, w/w), and IPA (1.5 equiv) in toluene. The enantioselectivity in each reaction was determined as the *E* value, $E = \ln [1 - c\,(1 + ee_p)]/\ln [1 - c\,(1 - ee_p)]$ where $c = ee_s/(ee_s + ee_p)$,[53] by analyzing the enantiomeric excesses ($ee_s$, $ee_p$) of acetylated product and remaining substrate when the reaction approached near 50% conversion ($c$). The *E* value for each substrate is described on the right side of each substrate number in Chart 1.

The *E* values from Chart 1 indicate that, in general, the enantioselectivity of LPL-D**1** increased with increasing the difference in size between two aryl groups at the hydroxymethine center of substrate. The enantioselectivity was low for monohalogenated **3** but increased significantly in the case that the halogen was substituted by a bulkier substituent such as $^{i}$Pr, *t*-Bu or trimethylsilyl (TMS) (compare **3a**, **4a**, **5a**, and **6a**): here, the order of increasing the enantioselectivity was X < TMS < $^{i}$Pr < *t*-Bu. It was rather surprising that the steric effect of a TMS group was less significant than that of an isopropyl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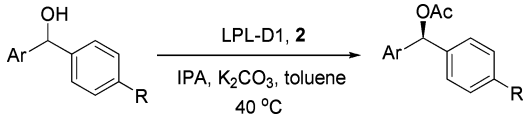
group in enhancing the enantioselectivity. The presence of a second substituent on the other aromatic ring reduced the enantioselectivity. In this case, the enantioselectivity decreased as the size of second substituent increased ($E$ = H > F > Cl > OMe > $NO_2$; compare **4a**−**g** or **5a**−**g**). As expected, the replacement of a phenyl ring by a smaller heteroaromatic ring increased the enantioselectivity (compare **4a**,**h**,**i** or **5a**,**h**,**i** or **6a**,**b**). Interestingly, the change of a phenyl ring to a similar size of pyridyl ring also increased the enantioselectivity (compare between **4a** and **4l**,**m** or **5a** and **5l**,**m** or **6a**,**c**), suggesting that the basic pyridine ring seems to bind to the active site of enzyme more favorably. The enantioselectivity for aryl heteroarylmethanols was also dependent on the nature of a substituent on the aryl ring: it increased in an order of TMS < $^i$Pr < *t*-Bu as observed for diarylmethanols (compare between **4j**, **5j**, and **6b** or between **4l**, **5l**, and **6c**). On the basis of this similarity, we think that, for all the substrates tested, LPL-D**1** should have the same stereopreference, which is controlled largely by the steric difference between two aromatic rings of substrate (see the scheme in Chart 1). Overall, most of the substrates tested (26 out of 31) were accepted by LPL-D**1** with synthetically useful enantioselectivity ($E$ = >20) and six of them with high enantioselectivity ($E$ = >100). These results thus encouraged us to explore the DKR of diarylmethanols with LPL-D**1**.

**Dynamic Kinetic Resolution of Diarylmethanols with LPL-D1.** We explored the DKR of 24 diarylmethanols which were accepted by LPL-D**1** with good to high enantioselectivity. The DKR reactions were carried out under the optimized conditions: substrate (0.1 mmol), LPL-D**1** (30−50 mg/mmol of substrate), ruthenium complex **2**[54] (5 mol %), isopropenyl acetate (1.5 equiv), and $K_2CO_3$ (1 equiv) in toluene at 40 °C. It is noted that the ruthenium complex **2** as the racemization catalyst was chosen because it had displayed a good performance in the previous DKR.[41] The DKR reactions of **4a** and its *p*-F-substituted analog **4d** were complete in 48 h and provided good enantiopurities (91−94% ee) and satisfactory yields (88−91%) (entries 1 and 4, Table 2). Those of *m*-substituted derivatives **4b**,**c** needed a longer time due to lower enzymatic activity and provided lower yields (entries 2 and 3). The DKR reactions of furyl or thiophenyl-containing substrates **4h**−**k** proceeded more rapidly. These reactions were complete in 24−36 h to afford better enantiopurities (95−97% ee) (entries 5−8). To the contrary, those of pyridyl-containing substrates **4l**,**m** were sluggish due to slower racemization so that they were performed at higher temperature (60 °C) for longer time (72 h). The yields and enantiopurities were satisfactory (entries 9 and 10). The DKR reactions of **5** (carrying a *t*-butyl substituent), in general, took longer times (48−96 h) compared to those of **4** (carrying an isopropyl substituent) but provided higher enantiopurities (94−99% ee) as expected. The yields ranged from 74 to 92% (entries 11−21). The DKR reactions of **6** (carrying a TMS substituent) also required rather long times (60−72 h) to provide high enantiopurities (94−96% ee) with satisfactory yields (82−92%) (entries 22−24). Overall, all the DKR reactions were successful and provided high enantiomeric excesses with satisfactory yields. It is noted that the lower yields (71−79%) in some cases were partly due to the oxidation of substrates to the corresponding ketones.

**Synthesis of *L*-Cloperastine.** To show a synthetic application of our DKR procedure, we synthesized *L*-cloperastine (**11**), an antitussive drug, from (*R*)-**10a** (96% ee) which had been obtained from the DKR of **6a**. In the first step, (*R*)-**10a** was deacetylated by the treatment with $K_2CO_3$ in MeOH-$H_2O$ to yield (*R*)-**6a**, which in turn was subject to chlorodesilylation with KCl and *N*-chlorosuccinimide (NCS) to obtain (*R*)-**3a**. Finally, the reaction of (*R*)-**3a** with 1-(2-chloroethyl)piperidine gave **11**. All the reactions from (*R*)-**10a** proceeded without loss in the enantiopurity, and the overall yield was 57% from **6a** (Scheme 2).

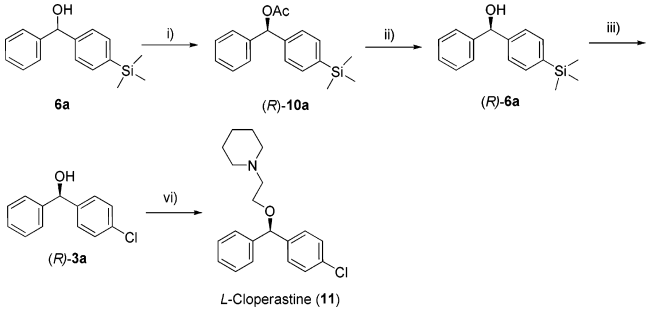
**Table 2. DKR of Diarylmethanols with LPL-D1 and Ruthenium Catalyst 2**




| entry | substrate | product | time (h) | yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **4a** | **8a** | 48 | 88 | 94 |
| 2 | **4b** | **8b** | 72 | 79 | 90 |
| 3 | **4c** | **8c** | 72 | 71 | 91 |
| 4 | **4d** | **8d** | 48 | 91 | 91 |
| 5 | **4h** | **8h** | 24 | 96 | 96 |
| 6 | **4i** | **8i** | 30 | 89 | 95 |
| 7 | **4j** | **8j** | 24 | 80 | 97 |
| 8 | **4k** | **8k** | 36 | 72 | 97 |
| 9 | **4l** | **8l** | 72[c] | 89 | 95 |
| 10 | **4m** | **8m** | 72[c] | 76 | 92 |
| 11 | **5a** | **9a** | 60 | 92 | 98 |
| 12 | **5b** | **9b** | 72 | 88 | 97 |
| 13 | **5c** | **9c** | 72 | 90 | 97 |
| 14 | **5d** | **9d** | 72 | 92 | 96 |
| 15 | **5e** | **9e** | 72 | 84 | 95 |
| 16 | **5h** | **9h** | 48 | 91 | 97 |
| 17 | **5i** | **9i** | 48 | 85 | 98 |
| 18 | **5i** | **9j** | 48 | 81 | 98 |
| 19 | **5k** | **9k** | 48 | 74 | 96 |
| 20 | **5l** | **9l** | 96[c] | 76 | 94 |
| 21 | **5m** | **9m** | 96[c] | 75 | >99 |
| 22 | **6a** | **10a** | 72 | 82 | 96 |
| 23 | **6b** | **10b** | 60 | 82 | 96 |
| 24 | **6c** | **10c** | 60 | 92 | 94 |

[a]Isolated yield. [b]Determined by HPLC. [c]60 °C.

**Scheme 2. Synthesis of *L*-Cloperastine[a]**




[a]Reagents and conditions: (i) **2** (5 mol %), LPL-D**1** (2 mg), isopropenyl acetate (1.5 equiv), $K_2CO_3$ (1 equiv), toluene 0.3 M, 40 °C, 72 h, 82%, 96% ee. (ii) $K_2CO_3$ (3 equiv), MeOH-$H_2O$, r.t., 2 h, 92%, 96% ee. (iii) KCl (1.2 equiv), *N*-chlorosuccinimide (1.2 equiv), MeOH, 60 °C, 2 h, 81%, 96% ee. (vi) 1-(2-chloroethyl)piperidine hydrochloride (1.5 equiv), NaOH (3 equiv), $CH_2Cl_2$, r.t., overnight, 94%, 96% ee.



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## CONCLUSION

We have demonstrated that LPL displayed about 3000-fold enhanced activity in organic solvent, if it was formulated with dextrin (D) and ionic surfactant (**1**), and its TOF in organic solvent reached the aqueous-level. The activated LPL (LPL-D**1**) accepted a wider range of diarylmethanols with useful to high enantioselectivity in the kinetic resolution. The DKR reactions of these substrates with the LPL-D**1** were successful and provided high enantiopurities and satisfactory yields. We thus have developed a useful protocol for the DKR of diarylmethanols which was difficult to achieve with other enzymes. In addition, we synthesized *L*-cloperastine, a chiral drug for the treatment of cough, from a racemic diarylmethanol via the DKR.

## EXPERIMENTAL SECTION

**Determination of Enzymatic Activity.** The kinetic parameters ($V_{max}$ and $K_m$) of LPL and LPL-D**1** for the alcoholysis of AcOPNP with 1-phenylethanol were obtained through two sets of experiments to determine $V_{max}$ and $V_{max}/K_m$ separately. The $V_{max}$ value of LPL was determined with solutions containing AcOPNP (0.075−0.25 M), lipase (10 mg), and 1-phenylethanol (2 equiv) in toluene (1 mL) at 25 °C. The $V_{max}/K_m$ value of LPL was determined with solutions containing AcOPNP (0.075−0.25 M), lipase (10 mg), and 1-phenylethanol (0.5 M) in toluene (1 mL) at 25 °C. The $V_{max}$ of LPL-D**1** was determined with solutions containing AcOPNP (0.11−0.75 M), LPL-D**1** (1 mg), and 1-phenylethanol (0.67 equiv) in toluene (1 mL). The $V_{max}/K_m$ value of LPL-D**1** was determined with solutions containing AcOPNP (0.3−0.75 M), LPL-D**1** (1 mg), and 1-phenylethanol (0.5 M) in toluene (1 mL) at 25 °C. The rate measurement at each substrate concentration was performed twice as follows. The solution was shaken at 250 rpm. An aliquot was sampled periodically, filtered through a short silica gel-pad, and analyzed by HPLC to determine the conversion % against time. The $k_{cat}$ and $K_m$ values were then obtained using the nonlinear curve fitting for the average rates.

**Determination of the Enantioselectivity of LPL-D1.** According to the procedure reported previously,[43] LPL-D**1** was prepared by freeze-drying a solution containing LPL (52% protein), dextrin (D), and **1** at a 1:2:1 weight ratio in 1:1 (v/v) water-dioxane. The enantioselectivity of LPL-D**1** for each substrate was determined by performing the transesterification of each substrate in the presence of isopropenyl acetate (IPA) as the acyl donor in toluene at 40 °C. In a typical procedure, IPA (1.5 equiv) was added to a 4 mL-vial containing LPL-D**1** (30 mg/mmol), substrate (0.1 mmol), and anhydrous toluene (0.3 M, 330 μL). The resulting solution was then shaken at 40 °C until the reaction reached near 50% conversion (*c*). After being diluted with methylene chloride, the reaction mixture was filtered through a silica gel-pad, concentrated, and then analyzed by HPLC to determine the enantiomeric excesses of remaining substrate ($ee_s$) and acetylated product ($ee_p$). The enantioselectivity (*E*) of LPL-D**1** was then calculated using the equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$ where $c = ee_s/(ee_s + ee_p)$.[53]

**Dynamic Kinetic Resolution of Diarylmethanols.** As the representative procedure, the DKR of **4a** is described. Freshly dried and degassed toluene (0.3 M, 330 μL) was added to a pear-shaped Schlenk flask containing the ruthenium catalyst **2** (4 mg, 5 mol %), LPL-D**1** (30 mg/mmol), $K_2CO_3$ (13.82 mg, 0.1 mmol), alcohol (0.1 mmol) under argon. The resulting solution was stirred for 30 min at 60 °C. After stirred for 30 min, isopropenyl acetate (16 μL, 0.15 mmol) was added into the flask and the solution was stirred at 40 °C for 48 h. The solution was diluted with methylene chloride and filtered through a Celite pad. The filtrate was concentrated and purified by silica gel chromatography to give product.

*(R)-(4-Isopropylphenyl)(phenyl)methyl Acetate (**8a**).* 88% yield, 94% ee; analytical data were in good agreement with the literature values.[41]

*(R)-(3-Fluorophenyl)(4-isopropylphenyl)methyl Acetate (**8b**).* 79% yield, 90% ee; $[\alpha]_D^{25}$ +26.5 (*c* = 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): δ 7.30−7.18 (m, 4H), 7.12−7.07 (m, 2H), 6.96−6.92 (m, 2H), 6.82 (s, 1H), 2.93−2.84 (m, 1H), 2.16 (s, 3H), 1.24−1.21 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.9, 164.4, 161.2, 148.9, 142.9, 136.9, 130.0, 127.2, 126.6, 122.5, 114.8, 114.5, 113.9, 113.6, 76.1, 33.8, 23.8, 21.2; HPLC conditions (hydrolysis product: *alcohol-form*): Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.7 min *(R)*, 8.4 min *(S)*; TOF-MS (ESI+) calcd for $[C_{18}H_{19}FO_2-OAc]^+$, 227.12360; found, 227.12167.

*(R)-(4-Isopropylphenyl)(m-tolyl)methyl Acetate (**8c**).* 71% yield, 91% ee; $[\alpha]_D^{25}$ +15.5 (*c* = 0.9, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): δ 7.26−7.05 (m, 8H), 6.81 (s, 1H), 2.92−2.83 (m, 1H), 2.33 (s, 3H), 2.15 (s, 3H), 1.23−1.21 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 170.1, 148.5, 140.2, 138.1, 137.6, 128.5, 128.3, 127.6, 127.1, 126.5, 124.0, 76.5, 33.7, 23.9, 21.4, 21.3; HPLC conditions (hydrolysis product: *alcohol-form*): Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 7.9 min *(R)*, 9.0 min *(S)*; TOF-MS (ESI+) calcd for $[C_{19}H_{22}O_2-OAc]^+$, 223.14868; found, 223.14671.

*(R)-(4-Fluorophenyl)(4-isopropylphenyl)methyl Acetate (**8d**).* 91% yield, 91% ee; analytical data were in good agreement with the literature values.[41]

*(S)-Furan-2-yl(4-isopropylphenyl)methyl Acetate (**8h**).* 96% yield, 96% ee; $[\alpha]_D^{25}$ −36.8 (*c* = 1.25, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): δ 7.37−7.34 (m, 3H), 7.23−7.20 (d, *J* = 8.05 Hz, 2H), 6.86 (s, 1H), 6.30−6.28 (m, 1H), 6.18−6.17 (m, 1H), 2.96−2.83 (m, 1H), 2.10 (s, 3H), 1.24−1.22 (d, *J* = 6.86 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.9, 152.6, 149.1, 143.0, 134.7, 127.3, 126.6, 110.2, 109.4, 70.4, 33.8, 23.9, 21.1; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.6 min *(R)*, 8.9 min *(S)*; TOF-MS (ESI+) calcd for $[C_{16}H_{18}O_3-OAc]^+$, 199.11229; found, 199.11009.

*(S)-Furan-3-yl(4-isopropylphenyl)methyl Acetate (**8i**).* 89% yield, 95% ee; $[\alpha]_D^{25}$ +10.8 (*c* = 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): δ 7.36−7.28 (m, 4H), 7.23−7.19 (m, 2H), 6.80 (s, 1H), 6.33−6.32 (m, 1H), 2.94−2.85 (m, 1H), 2.11 (s, 3H), 1.25−1.22 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 170.1, 148.9, 143.3, 140.7, 136.6, 127.0, 126.5, 125.6, 109.6, 70.3, 33.8, 23.9, 21.2; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.2 min *(R)*, 7.9 min *(S)*; TOF-MS (ESI+) calcd for $[C_{16}H_{18}O_3-OAc]^+$, 199.11229; found, 199.11089.

*(S)-(4-Isopropylphenyl)(thiophen-2-yl)methyl Acetate (**8j**).* 80% yield, 97% ee; $[\alpha]_D^{25}$ −32.7 (*c* = 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): δ 7.36−7.33 (m, 2H), 7.28−7.25 (m, 3H), 7.06 (s, 1H), 6.95−6.92 (m, 2H), 2.97−2.83 (m, 1H), 2.13 (s, 3H), 1.25−1.23 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (75



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MHz, $CDCl_3$, ppm): 169.9, 149.0, 143.8, 136.9, 126.8, 126.5, 126.4, 125.9, 72.7, 33.8, 23.9, 21.2; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.4 min (*R*), 7.9 min (*S*); TOF-MS (ESI+) calcd for $[C_{16}H_{18}O_2S-OAc]^+$, 215.08945; found, 215.09132.

*(S)-(4-Isopropylphenyl)(thiophen-3-yl)methyl Acetate (**8k**).* 72% yield, 97% ee; $[\alpha]_D^{25}$ +3.5 (*c* = 0.75, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.30−7.15 (m, 6H), 7.0−6.98 (m, 1H), 6.92 (s, 1H), 2.92−2.87 (m, 1H), 2.13 (s, 3H), 1.24−1.22 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 170.1, 148.7, 141.4, 137.0, 127.1, 126.7, 126.5, 126.0, 122.8, 73.3, 33.8, 23.9, 21.3; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 7.3 min (*R*), 8.8 min (*S*); TOF-MS (ESI+) calcd for $[C_{16}H_{18}O_2S-OAc]^+$, 215.08945; found, 215.09327.

*(S)-(4-Isopropylphenyl)(pyridin-3-yl)methyl Acetate (**8l**).* 89% yield, 95% ee; $[\alpha]_D^{25}$ +24.8 (*c* = 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 8.63−8.62 (d, *J* = 2.2 Hz, 1H), 8.54−8.52 (m, 1H), 7.65−7.61(m, 1H), 7.28−7.19 (m, 5H), 6.87 (s, 1H), 2.96−2.82 (m, 1H), 2.16 (s, 3H), 1.24−1.22 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.9, 149.2, 149.1, 148.6, 136.4, 136.0, 134.6, 127.1, 126.8, 123.3, 74.8, 33.8, 23.9, 21.2; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV = 217 nm, retention times 25.4 min (*R*), 28.3 min (*S*); TOF-MS (ESI+) calcd for $[C_{17}H_{19}NO_2-OAc]^+$, 210.12827; found, 210.12573.

*(S)-(4-Isopropylphenyl)(pyridin-4-yl)methyl Acetate (**8m**).* 76% yield, 92% ee; $[\alpha]_D^{25}$ +58.6 (*c* = 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 8.58−8.56 (m, 2H), 7.26−7.21 (m, 7H), 6.79 (s, 1H), 2.93−2.82 (m, 1H), 2.17 (s, 3H), 1.24−1.21 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.8, 150.0, 149.4, 149.0, 136.0, 127.5, 126.8, 121.3, 75.5, 33.8, 23.8, 21.1; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 54.2 min (*R*), 57.6 min (*S*); TOF-MS (ESI+) calcd for $[C_{17}H_{19}NO_2-OAc]^+$, 210.12827; found, 210.12929.

*(R)-(4-tert-Butylphenyl)(phenyl)methyl Acetate (**9a**).* 92% yield, 98% ee; analytical data were in good agreement with the literature values.[41]

*(R)-(4-tert-Butylphenyl)(3-fluorophenyl)methyl Acetate (**9b**).* 88% yield, 97% ee; $[\alpha]_D^{25}$ +28.3 (*c* = 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.42−7.26 (m, 5H), 7.13−7.07 (m, 2H), 7.04−6.96 (m, 1H), 6.82 (s, 1H), 2.16 (s, 3H), 1.29 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.9, 164.4, 161.2, 151.2, 142.9, 136.5, 130.0, 126.9, 125.5, 122.5, 114.8, 114.5, 114.0, 113.7, 76.0, 34.5, 31.2, 21.2; HPLC conditions (hydrolysis product: *alcohol-form*): Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.6 min (*R*), 8.7 min (*S*); TOF-MS (ESI+) calcd for $[C_{19}H_{21}FO_2-OAc]^+$, 241.13925; found, 241.13765.

*(R)-4-tert-Butylphenyl)(m-tolyl)methyl Acetate (**9c**).* 90% yield, 97% ee; $[\alpha]_D^{25}$ +14.5 (*c* = 0.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.36−7.07 (m, 8H), 6.82 (s, 1H), 2.33 (s, 3H), 2.15 (s, 3H), 1.29 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 170.0, 150.7, 140.2, 138.1, 137.2, 128.5, 128.3, 127.6, 126.8, 125.4, 124.0, 76.5, 34.5, 31.3, 21.4, 21.3; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 7.5 min (*R*), 10.8 min (*S*); TOF-MS (ESI+) calcd for $[C_{20}H_{24}O_2-OAc]^+$, 237.16433; found, 237.16287.

*(R)-(4-tert-Butylphenyl)(4-fluorophenyl)methyl Acetate (**9d**).* 92% yield, 96% ee; analytical data were in good agreement with the literature values.[41]

*(R)-(4-tert-Butylphenyl)(4-chlorophenyl)methyl Acetate (**9e**).* 84% yield, 95% ee; $[\alpha]_D^{25}$ +14.7 (*c* = 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.36−7.21 (m, 8H), 6.81 (s, 1H), 2.14 (s, 3H), 1.29 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.9, 151.1, 138.9, 136.6, 133.6, 128.6, 128.4, 126.8, 125.5, 76.0, 34.5, 31.2, 21.2; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.8 min (*R*), 9.3 min (*S*); TOF-MS (ESI+) calcd for $[C_{19}H_{21}ClO_2-OAc]^+$, 257.10970; found, 257.10836.

*(S)-(4-(tert-Butyl)phenyl)(furan-2-yl)methyl Acetate (**9h**).* 91% yield, 97% ee; $[\alpha]_D^{25}$ −34.7 (*c* = 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.40−7.34 (m, 5H), 6.87 (s, 1H), 6.32−6.30 (m, 1H), 6.20−6.19 (m, 1H), 2.12 (s, 3H), 1.31 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.9, 152.5, 151.3, 143.0, 134.2, 126.9, 125.4, 110.2, 109.4, 70.3, 34.6, 31.2, 21.1; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.2 min (*R*), 7.7 min (*S*); TOF-MS (ESI+) calcd for $[C_{17}H_{20}O_3-OAc]^+$, 213.12794; found, 213.12393.

*(S)-(4-(tert-Butyl)phenyl)(furan-3-yl)methyl Acetate (**9i**).* 85% yield, 98% ee; $[\alpha]_D^{25}$ +10.3 (*c* = 0.65, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.39−7.22 (m, 5H), 6.81 (s, 1H), 6.34−6.33 (m, 1H), 2.11 (s, 3H), 1.31 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 170.1, 151.1, 143.3, 140.7, 136.2, 126.7, 125.5, 125.4, 109.6, 70.2, 34.5, 31.3, 21.3; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.1 min (*R*), 7.3 min (*S*); TOF-MS (ESI+) calcd for $[C_{17}H_{20}O_3-OAc]^+$, 213.12794; found, 213.12358.

*(S)-(4-(tert-Butyl)phenyl)(thiophene-2-yl)methyl Acetate (**9j**).* 81% yield, 98% ee; $[\alpha]_D^{25}$ −26.2 (*c* = 0.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.40−7.33 (m, 4H), 7.25−7.23 (m, 1H), 7.07 (s, 1H), 6.92−6.90 (m, 2H), 2.11 (s, 3H), 1.30 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.8, 151.2, 143.7, 136.5, 126.5, 126.4, 125.9, 125.4, 72.6, 34.5, 31.2, 21.2; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 7.8 min (*R*), 9.3 min (*S*); TOF-MS (ESI+) calcd for $[C_{17}H_{20}O_2S$-$OAc]^+$, 229.10510; found, 229.10368.

*(S)-(4-(tert-Butyl)phenyl)(thiophen-3-yl)methyl Acetate (**9k**).* 74% yield, 96% ee; $[\alpha]_D^{25}$ +1.5 (*c* = 0.45, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.38−7.35 (m, 2H), 7.30−7.25 (m, 2H), 7.16−7.15 (m, 1H), 7.01−6.99 (m, 1H), 6.92 (s, 1H), 2.13 (s, 3H), 1.30 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 170.1, 151.0, 141.4, 136.7, 126.8, 126.7, 126.0, 125.4, 122.8, 73.2, 34.5, 31.3, 21.3; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 7.2 min (*R*), 8.1 min (*S*); TOF-MS (ESI+) calcd for $[C_{17}H_{20}O_2S$-$OAc]^+$, 229.10510; found, 229.10378.

*(S)-(4-(tert-Butyl)phenyl)(pyridin-3-yl)methyl Acetate (**9l**).* 76% yield, 94% ee; $[\alpha]_D^{25}$ +18.2 (*c* = 0.7, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 8.63−8.62 (m, 1H), 8.54−8.52 (m, 1H), 7.65−7.61 (m, 1H), 7.38−7.36 (m, 2H), 7.28−7.24 (m, 3H), 6.88 (s, 1H), 2.16 (s, 3H), 1.30 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.9, 151.3, 149.1, 148.6, 136.0, 135.9, 134.6, 126.8, 125.6, 123.3, 74.7, 34.5, 31.2, 21.2; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 62.9 min (*R*), 67.4 min (*S*); TOF-MS (ESI+) calcd for $[C_{18}H_{21}NO_2-OAc]^+$, 224.14392; found, 224.14281.



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*(S)-(4-(tert-Butyl)phenyl)(pyridin-4-yl)methyl Acetate (**9m**).* 75% yield, >99% ee; $[\alpha]_D^{25}$ +70.3 ($c$ = 0.4, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 8.58−8.56 (m, 2H), 7.39−7.35 (m, 2H), 7.26−7.22 (m, 4H), 6.79 (s, 1H), 2.18 (s, 3H), 1.29 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 169.8, 151.6, 150.0, 149.0, 135.6, 127.2, 125.7, 121.3, 75.4, 34.6, 31.2, 21.1; HPLC conditions (hydrolysis product: *alcohol-form*): Whelk-O1, *n*-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV = 217 nm, retention times 39.1 min (*R*), 46.1 min (*S*); TOF-MS (ESI+) calcd for $[C_{18}H_{21}NO_2-OAc]^+$, 224.14392; found, 224.14029.

*(R)-Phenyl(4-(trimethylsilyl)phenyl)methyl Acetate (**10a**).* 82% yield, 96% ee; $[\alpha]_D^{25}$ +17.1 ($c$ = 0.9, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.50−7.47 (m, 2H), 7.34−7.26 (m, 7H), 6.86 (s, 1H), 2.14 (s, 3H), 0.24 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 171.1, 141.8, 141.3, 134.6, 129.6, 129.0, 128.2, 127.5, 78.0, 22.4, 0.0; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 7.3 min (*R*), 8.2 min (*S*); TOF-MS (ESI+) calcd for $[C_{18}H_{22}O_2Si-OAc]^+$, 239.12560; found, 239.12369.

*(S)-Thiophen-2-yl(4-(trimethylsilyl)phenyl)methyl Acetate (**10b**).* 82% yield, 96% ee; $[\alpha]_D^{25}$ −18.3 ($c$ = 1.3, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.52 (d, $J$ = 8.1 Hz, 2H), 7.40 (d, $J$ = 8.1 Hz, 2H), 7.27−7.24 (m, 1H), 7.07 (s, 1H), 6.95−6.91 (m, 1H), 2.14 (s, 3H), 0.26 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm) 171.0, 144.7, 141.8, 141.2, 134.7, 129.7, 127.7, 127.2, 73.9, 22.3, 0.0; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 96/4, flow rate = 1.0 mL/min, UV = 217 nm, retention times 5.5 min (*R*), 6.4 min (*S*); TOF-MS (ESI+) calcd for $[C_{16}H_{20}O_2SSi-OAc]^+$, 245.08202; found, 245.07877.

*(S)-Pyridin-3-yl(4-(trimethylsilyl)phenyl)methyl Acetate (**10c**).* 92% yield, 94% ee; $[\alpha]_D^{25}$ +19.4 ($c$ = 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 8.63 (d, $J$ = 2.1 Hz, 1H), 8.54−8.52 (m, 1H), 7.64−7.61 (m, 1H), 7.51 (d, $J$ = 8.1 Hz, 2H), 7.31 (d, $J$ = 8.1 Hz, 2H), 7.27−7.23 (m, 1H), 6.88 (s, 1H), 2.16 (s, 3H), 0.25 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 171.0, 150.5, 149.9, 142.1, 140.7, 137.0, 135.9, 134.9, 127.5, 124.5, 76.1, 22.3, 0.0; HPLC conditions: Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 21.4 min (*R*), 24.1 min (*S*); TOF-MS (ESI+) calcd for $[C_{17}H_{21}NO_2Si-OAc]^+$, 240.12085; found, 240.11560.

**Synthesis of *L*-Cloperastine (11).** To a solution containing (*R*)-**10a** (0.5 mmol, 96% ee) in MeOH-$H_2O$ (5 mL, 0.1 M) was added $K_2CO_3$ (240 mg, 1.5 mmol). The resulting solution was stirred at room temperature for 2 h and then concentrated by removing solvent under reduced pressure. The residue was purified through a silica gel column chromatography to provide ***(R)*-6a** (0.46 mmol, 92% yield, 96% ee); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.52−7.45 (m, 2H), 7.39−7.20 (m, 7H), 5.88−5.82 (m, 1H), 2.22−2.18 (m, 1H), 0.24 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 145.4, 144.8, 140.9, 134.7, 129.6, 128.7, 127.6, 126.9, 77.3. 0.0; HPLC condition: Whelk-O1, *n*-hexane/2-propanol = 96/4, flow rate = 1.0 mL/min, UV = 217 nm; retention times 7.2 min (*R*), 8.3 min (*S*); TOF-MS (ESI+) calcd for $[C_{16}H_{20}OSi-OH]^+$, 239.12560; found, 239.12656.

To a solution containing (*R*)-**6a** (0.5 mmol, 96% ee) in MeOH (5 mL, 0.1 M) was added KCl (0.6 mmol, 45 mg) and NCS (0.6 mmol, 83 mg). The resulting solution was stirred at 60 °C for 2 h, then quenched with $H_2O$, and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (*R*)-**3a** (0.41 mmol, 81% yield, 96% ee): $[\alpha]_D^{25}$ −18.1 ($c$ = 0.6, $CHCl_3$) (lit.[55] $[\alpha]_D^{25}$ = −20 ($c$ = 1.0, AcOEt, 90% ee)); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.38−7.23 (m, 9H), 5.80−5.83 (m, 1H), 2.25−2.22 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 143.4, 142.2, 133.2, 128.6, 127.8, 126.5, 75.6; HPLC conditions: Chiralcel-OD, *n*-hexane/2-propanol = 98/2, flow rate = 1.0 mL/min, UV = 217 nm, retention times 56.8 min (*S*), 63.0 min (*R*); TOF-MS (ESI+) calcd for $[C_{13}H_{11}ClO-OH]^+$, 201.04710; found, 201.04921.

To a solution containing (*R*)-**3a** (0.4 mmol, 96% ee) in $CH_2Cl_2$ (4 mL, 0.1 M) was added 1-(2-chloroethyl)piperidine hydrochloride (120 mg, 0.6 mmol). The resulting solution was cooled at 0 °C followed by the addition of NaOH (48 mg, 1.2 mmol). After the mixture had been stirred for 20 min at 0 °C and then overnight at room temperature, it was quenched with $H_2O$ and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **11** (0.38 mmol, 94% yield, 96% ee): $[\alpha]_D^{25}$ −6.29 ($c$ = 1.0, $CHCl_3$) (lit.[56] $[\alpha]_D$ −6 ∼ −6.5); $^1H$ NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.35−7.21 (m, 9H), 5.34 (s, 1H), 3.57 (t, $J$ = 6.27 Hz, 2H), 2.63 (t, $J$ = 6.27 Hz, 2H), 2.47−2.40 (m, 4H), 1.59−1.52 (m, 4H), 1.51−1.32 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$, ppm): 141.8, 140.9, 133.0, 128.4, 128.3, 127.6, 126.9, 83.2, 67.1, 58.6, 55.0, 26.0, 24.2; HPLC condition: Chiralcel OD-H, *n*-hexane/2-propanol = 80/20, flow rate = 0.5 mL/min, UV = 254 nm; retention times 7.44 min (*S*), 7.74 min (*R*); TOF-MS (ESI+) calcd for $[C_{20}H_{24}ClNO-C_7H_{14}NO]^+$, 201.04710; found, 201.04303.

## ■ ASSOCIATED CONTENT

### Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501629m.

NMR spectra and HPLC chromatograms of products (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Pellissier, H. *Chirality from dynamic kinetic resolution*; Royal Society of Chemistry: Cambridge, 2011.
(2) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 7623−7626.
(3) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Biol.* **2007**, *11*, 226−232.
(4) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999−1015.
(5) Kim, Y.; Park, J.; Kim, M.-J. *ChemCatChem* **2011**, *3*, 271−277.
(6) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769−3802.




DOI: 10.1021/cs501629m
*ACS Catal.* 2015, 5, 683−689

(7) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645−1650.
(8) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373−2376.
(9) Kim, M.-J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494−11495.
(10) Martín-Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535−6539.
(11) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972−1977.
(12) Martín-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817−8825.
(13) Berkessel, A.; Sebastian-Ibarz, M. L.; Müller, T. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6567−6570.
(14) Hoyos, P.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. *J. Org. Chem.* **2006**, *71*, 7632−7637.
(15) Akai, S.; Tanimoto, K.; Kanao, Y.; Egi, M.; Yamamoto, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 2592−2595.
(16) Kim, M.-J.; Choi, Y. K.; Kim, S.; Kim, D.; Han, K.; Ko, S.-B.; Park, J. *Org. Lett.* **2008**, *10*, 1295−1298.
(17) Haak, R. M.; Berthiol, F.; Jerphagnon, T.; Gayet, J. A.; Tababiono, C.; Postema, C. P.; Ritleng, V.; Pfeffer, M.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L.; De Vries, J. G. *J. Am. Chem. Soc.* **2008**, *130*, 13508−13509.
(18) Thalen, L. K.; Sumic, A.; Bogar, K.; Norinder, J.; Persson, A. K. A.; Bäckvall, J.-E. *J. Org. Chem.* **2010**, *75*, 6842−6847.
(19) Ema, T.; Nakano, Y.; Yoshida, D.; Kamata, S.; Sakai, T. *Org. Biomol. Chem.* **2012**, *10*, 6299−6308.
(20) Egi, M.; Sugiyama, K.; Saneto, M.; Hanada, R.; Kato, K.; Akai, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3654−3658.
(21) Agrawal, S.; Martínez-Castro, E.; Marcos, R.; Martín-Matute, B. *Org. Lett.* **2014**, *16*, 2256−2259.
(22) Nieguth, R.; ten Dam, J.; Petrenz, A.; Ramanathan, A.; Hanefeld, U.; Ansorge-Schumacher, B. *RSC Adv.* **2014**, *4*, 45495−45503.
(23) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 4099−4101.
(24) Paetzold, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 17620−17621.
(25) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247−1250.
(26) Veld, M. A. J.; Hult, K.; Palmans, A. R. A.; Meijer, E. W. *Eur. J. Org. Chem.* **2007**, 5416−5421.
(27) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem.—Eur. J.* **2007**, *13*, 2034−2043.
(28) Kim, M.-J.; Kim, W.-H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157−1159.
(29) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Adv. Synth. Catal.* **2008**, *350*, 113−121.
(30) Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2008**, *73*, 4302−4304.
(31) Andrade, L. H.; Silva, A. V.; Pderozo, E. C. *Tetrahedron Lett.* **2009**, *50*, 4331−4334.
(32) Kim, Y.; Park, J.; Kim, M.-J. *Tetrahedron Lett.* **2010**, *51*, 5581−5584.
(33) Engström, K.; Johnston, E. V.; Verho, O.; Gustafson, K. P. J.; Sakeǹ, M.; Tai, C.-W.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2013**, *52*, 14006−14010.
(34) Zimmermann, V.; Beller, M.; Kragl, U. *Org. Process Res. Dev.* **2006**, *10*, 622−627.
(35) Choi, Y. K.; Kim, Y.; Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2009**, *74*, 9543−9545.
(36) Shakeri, M.; Engström, K.; Sandström, A. G.; Bäckvall, J.-E. *ChemCatChem* **2010**, *2*, 534−538.
(37) Engström, K.; Shakeri, M.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **2011**, 1827−1830.
(38) Choi, E.; Kim, Y.; Ahn, Y.; Park, J.; Kim, M.-J. *Tetrahedron: Asymmetry* **2013**, *24*, 1449−1452.
(39) It was recently reported that a mutant of CALB accepted diarylmethanols. See: Engström, K.; Vallin, M.; Hult, K.; Bäckvall, J.-E. *Tetrahedron* **2012**, *68*, 7613−7618.
(40) Kim, H.; Choi, Y. K.; Lee, J.; Lee, E.; Park, J.; Kim, M.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10944−10948.
(41) Kim, C.; Lee, J.; Cho, J.; Oh, Y.; Choi, Y. K.; Choi, E.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2013**, *78*, 2571−2578.
(42) Mead, J. R.; Irvin, S. A.; Ramji, D. P. *J. Mol. Med.* **2002**, *80*, 753−769.
(43) Lee, E.; Oh, Y.; Choi, Y. K.; Kim, M.-J. *ACS Catal.* **2014**, *4*, 3590−3592.
(44) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454−470.
(45) Salvi, L.; Kim, J. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 12483−12493.
(46) Uenishi, A.; Nakagawa, Y.; Osumi, H.; Harada, T. *Chem.—Eur. J.* **2013**, *19*, 4896−4905.
(47) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659−662.
(48) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749−1751.
(49) Chen, C.-Y.; Reamar, R. A.; Chilenski, J. R.; McWilliams, C. J. *Org. Lett.* **2003**, *5*, 5039−5042.
(50) Truppe, M. D.; Pollard, D.; Devine, P. *Org, Lett.* **2007**, *9*, 335−338.
(51) Magnus, N. A.; Coffey, D. S.; DeBaillie, A. C.; Jones, C. D.; Kaluzna, I. A.; Kambourakis, S.; Pu, Y. J.; Wepsiec, J. P. *Org. Process Res. Dev.* **2011**, *15*, 1377−1381.
(52) Commercially available as lipoprotein lipase-3 for diagnostic use from Amano.
(53) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299.
(54) Lee, J. H.; Kim, N.; Kim, M.-J.; Park, J. *ChemCatChem* **2011**, *3*, 354−359.
(55) Soares, L. C.; Alberto, E. E.; Schwab, R. S.; Taube, P. S.; Nascimento, V.; Rodriguesa, O. E. D.; Brag, A. L. *Org. Biomol. Chem.* **2012**, *10*, 6595−6599.
(56) Puricelli, L. EP 0385491 A1, 1990.


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*ACS Catal.* 2015, 5, 683−689