JOC The Journal of Organic Chemistry

Article

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Kinetic and Dynamic Kinetic Resolution of Secondary Alcohols with Ionic-Surfactant-Coated *Burkholderia cepacia* Lipase: Substrate Scope and Enantioselectivity

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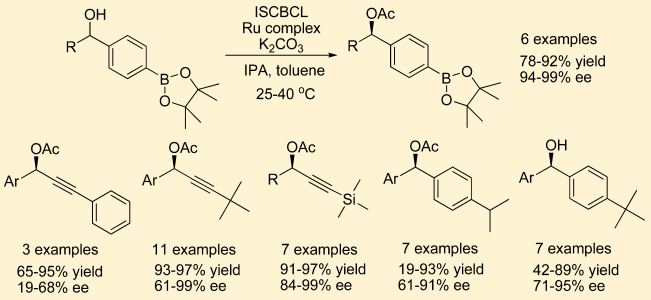
Supporting Information

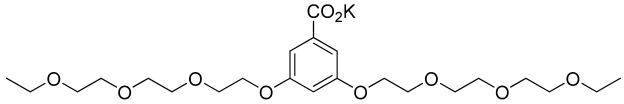
ABSTRACT: Forty-four different secondary alcohols, which can be classified into several types (II-IX), were tested as the substrates of ionic surfactant-coated *Burkholderia cepacia* lipase (ISCBCL) to see its substrate scope and enantioselectivity in kinetic and dynamic kinetic resolution (KR and DKR). They include 6 boron-containing alcohols, 24 chiral propargyl alcohols, and 14 diarylmethanols. The results from the studies on KR indicate that ISCBCL accepted most of them with high enantioselectivity at ambient temperature and with useful to high enantioselectivity at elevated temperatures. In particular, ISCBCL displayed high enantioselectivity toward sterically demanding secondary alcohols (types VIII and IX) which have two bulky substituents at the hydroxymethine center. DKR reactions were performed by the combination of ISCBCL with a ruthenium-based racemization catalyst at 25−60 °C. Forty-one secondary alcohols were tested for DKR. About half of them were transformed into their acetates of high enantiopurity (>90% ee) with good yields (>80%). It is concluded that ISCBCL appears to be a superb enzyme for the KR and DKR of secondary alcohols.



INTRODUCTION

Enantioselective transformations by lipases provide convenient routes to a wide range of nonracemic compounds, particularly optically active alcohols, carboxylic acids, amines, amino acids, and their derivatives.[1] Most of them employ racemic substrates and usually provide a pair of separated enantiomers via kinetic resolution (KR). These processes thus suffer from a serious limitation that the theoretical maximum yield for a wanted enantiomer is 50%. Over the past decade, several groups including ours have developed more practical processes employing a lipase and a ruthenium-based racemization catalyst in combination for dynamic kinetic resolution (DKR)[2−5] to overcome the limitations of classical enzymatic KR. The scope of chemoenzymatic DKR is determined largely by the substrate specificity and enantioselectivity of enzyme employed. Accordingly, enzymes with both broad substrate specificity and high enantioselectivity are needed for the wide applications of chemoenzymatic DKR. Lately, we communicated that ionic-surfactant-coated *Burkholderia cepacia* lipase (ISCBCL), which was prepared by coating an aqueous extract of a commercial lipase (lipase PS) with an ionic surfactant (**1**), had great potential as such an enzyme.[6] We now wish to report a full account on the substrate scope and enantioselectivity of ISCBCL examined with a wider range of new substrates.

We could classify secondary alcohols into nine types (I−IX, Figure 1) according to the nature of two substituents at the hydroxymethine center to show the substrate specificity of a lipase. Among commercially available lipases, few accept all nine types of substrates with good activity and high enantioselectivity. The most popular *Candida antarctica* lipase B (CALB; brand name Novozym 435) has been known to accept only three types (I, II, and V) of secondary alcohols and carries a small and a relatively large substituent at the hydroxymethine center, with good to high enantioselectivity at synthetically useful rates.[7] Recent studies, however, revealed that CALB could be engineered by site-directed mutagenesis to accept sterically more demanding types. A mutant of CALB accepted the substrates of type VI, VII,[8a] and IX[8b] with useful enantioselectivity. In our previous communication,[6] we demonstrated that ISCBCL accepted the substrates of three types (VI−VIII) in DKR with good results. The results encouraged us to explore further the substrate scope and enantioselectivity of ISCBCL. It was found that ISCBCL could



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Received: December 21, 2012
Published: February 13, 2013

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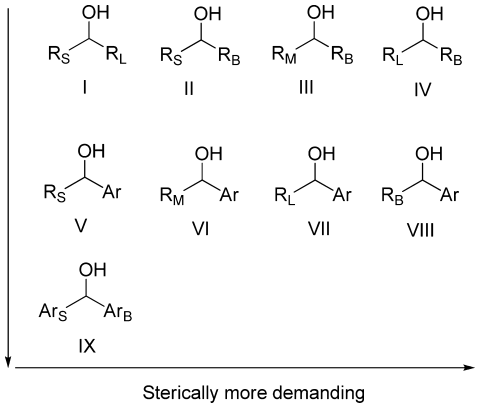


Figure 1. Types of secondary alcohols as the substrates of lipases: R_S, small aliphatic; R_M, medium-sized aliphatic; R_L, long aliphatic; R_B, branched and bulky aliphatic; Ar, aromatic; Ar_S, small or simple aromatic; Ar_B, branched and bulky aromatic.

accept all eight types (II–IX) of secondary alcohols with useful to high enantioselectivity.

BCL may be coated with commercially available surfactants (such as PEG and AOT) or ionic liquids for enhancing its activity in organic solvent. We observed that commercial surfactants were weakly activating. The coating of BCL with **1**, however, enhanced its activity in organic solvent by 1000-fold relative to its commercial precursor.[6] ISCBCL thus was more active than Novozym 435 and displayed an excellent performance in the DKR of substrates of type VI–VIII. Recently, Itoh et al. reported that some synthetic ionic liquids enhanced the activity of BCL by orders of magnitude,[9] but the application of ionic-liquid-coated BCL to DKR has not been reported yet.

RESULTS AND DISCUSSION

Types of Secondary Alcohols Tested As the Substrates of ISCBCL. The 44 secondary alcohols tested as the substrates of ISCBCL are described in Figure 2. Seven TMS-protected propargyl alcohols **2a–g** have an alkyl (C1∼C6) and a TMS-ethynyl substituent at the hydroxymethine center, thus representing three types (II–IV) of substrates. Six boron-containing secondary alcohols **3a–f** with an alkyl (C1–C6) and an aryl substituent at the hydroxymethine center can be considered as another three types, V–VII. Seventeen disubstituted propargyl alcohols **4a–q** carrying an aryl and a phenyl- or *tert*-butylethynyl substituent at the stereocenter belong to the type VIII. Fourteen diarylmethanols **5a–n** are the type IX substrates. To the best of our knowledge, none of them (**2a–5n**) has been tested before as the substrates of lipase for DKR. It is noted that the CALB mutant has been used in the DKR of substrates of types VI and VII with good results.[8a] In this case, however, the substrates were 1-phenylalkanols (RCH(OH)Ph, R = butyl and hexyl).

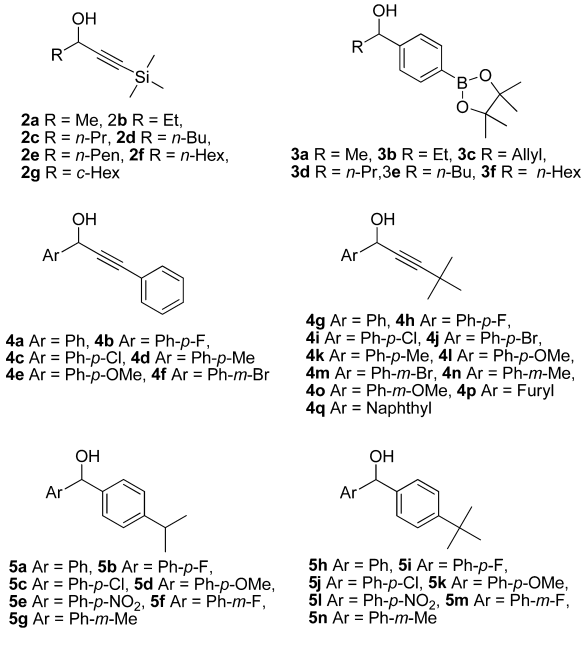


Figure 2. Secondary alcohols tested as the substrates of ISCBCL.

Active-Site Model and Enantioselectivity of ISCBCL. It is possible to predict the enantioselectivity of ISCBCL using the active-site model based on the X-ray structure of BCL[10] (Figure 3). BCL has three binding pockets (HA, HB, and HH) at its active site for anchoring three substituents at the stereocenter of substrate. Among them, the HH binding pocket appears to play an essential role in determining the substrate specificity and enantioselectivity. It has two rooms, a hydrophilic trench and its entrance (a space of 4.5 Å in diameter), which are separated by a contraction.[10a] It can accept small, medium, or long aliphatic groups. It can also accommodate flat aromatic rings. However, branched and bulky aliphatic and aromatic groups are difficult to fit into the pocket owing to severe steric repulsion around the contraction of the pocket. Therefore, the enantiomers shown in Figure 3 should bind more favorably and thus react more rapidly than their antipodes[11] (Figure 3). And it is also expected that the enantioselectivity should be high.

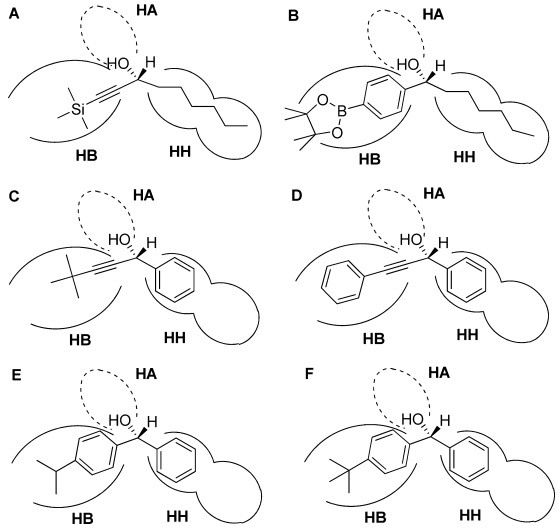
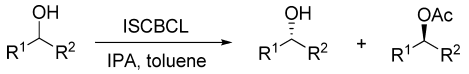


Figure 3. Active-site model of ISCBCL showing the binding of more reactive enantiomers.

Enantioselectivity of ISCBCL in Kinetic Resolution. The enantioselectivity of ISCBCL for each of the secondary alcohols was examined with the ISCBCL-catalyzed transesterification. In typical procedures, the reactions were performed with solutions containing a substrate (0.1 mmol), ISCBCL[6] (10–30 mg/mmol), and isopropenyl acetate (IPA, 1.5 equiv) in toluene at 25–60 °C. The reactions at elevated temperatures (40–60 °C) were done for the applications to the higher temperature DKR. After the reactions reached near 50% completion, the acylated

dx.doi.org/10.1021/jo3027627 | J. Org. Chem. 2013, 78, 2571–2578

Table 1. Enantioselectivity of ISCBCL in Transesterification



entry	substrate	T (°C)	E^a	entry	substrate	T (°C)	E^a	entry	substrate	T (°C)	E^a
1	**2b**	25	>200	14	**4f**	25	65	27	**5b**	60	29
2	**2g**	25	>200	15	**4g**	25	>200	28	**5c**	60	17
3	**3a**	25	>200	16	**4h**	60	>200	29	**5d**	60	18
4	**3b**	25	>200	17	**4i**	60	>200	30	**5e**	60	22
5	**3c**	40	118	18	**4j**	60	>200	31	**5f**	60	19
6	**3d**	40	58	19	**4k**	60	>200	32	**5g**	60	23
7	**3e**	40	50	20	**4l**	60	65	33	**5h**	60	103
8	**3f**	40	50	21	**4m**	60	60	34	**5i**	60	94
9	**4a**	25	>200	22	**4n**	60	51	35	**5j**	60	44
10	**4b**	25	>200	23	**4o**	60	43	36	**5k**	60	43
11	**4c**	25	>200	24	**4p**	60	>200	37	**5l**	60	70
12	**4d**	25	>200	25	**4q**	60	20	38	**5m**	60	69
13	**4e**	25	>200	26	**5a**	25	>200	39	**5n**	60	37

[a]The enantioselectivity was calculated using the equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$ where $c = ee_s/(ee_s + ee_p)$.

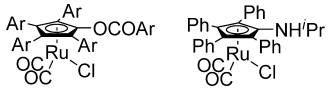
products and remaining substrates were isolated and analyzed by HPLC or GC for determining their enantiomeric excesses. The enantioselectivity (E) of ISCBCL for each substrate was then calculated using the equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$ where $c = ee_s/(ee_s + ee_p)$. The results are described in Table 1.

The enantioselectivity of ISCBCL toward TMS-protected propargyl alcohols[12] was examined for two substrates (**2b** and **2g**) at 25 °C. Both of them were accepted with high enantioselectivity (E = >200) (entries 1 and 2). The high enantioselectivity for **2g** is particularly noteworthy because it has two bulky substituents at the stereocenter. These results thus indicate that ISCBCL can accept the three types of substrates (II–IV) with high enantioselectivity. The enantioselectivity of ISCBCL toward the boron-containing substrates[13] (**3a–f**) was high at 25 °C (entries 3 and 4) and good at 40 °C (entries 5–8). These results prove that the three types of substrates (V–VII) are accepted by ISCBCL enantioselectively. The enantioselectivity of ISCBCL toward α-arylpropargyl alcohols (**4a–q**) was generally good to high but dependent on the substitution pattern of α-aromatic ring. It was high (E = >200) for those having no substituent (entries 9 and 15) or a *para*-substituent on the α-aromatic ring (entries 10–13 and 16–19) but lower (E = 43–60) for those having a *meta*-substitutent on the α-aromatic ring (entries 14, 21–23). It is notable that the enantioselectivities for some substrates were high even at 60 °C (entries 16–19). The size of the α-aromatic ring also affected the enantioselectivity. It was high (E = >200) if the α-aromatic ring was furyl but modest (E = 20) if the α-aromatic ring was naphthyl (entries 24 and 25).

The enantioselectivity of ISCBCL toward diarylmethanols was surprisingly high (E = >200) at 25 °C (entry 26). The enantioselectivity at 60 °C was significantly lower but increased if *p*-isopropylphenyl was replaced by *p*-*tert*-butylphenyl (compare entries 27–32 with entries 34–39). The results indicate that diarylmethanols can be accepted by ISCBCL with good to high enantioselectivity if they have a simple and a bulky aromatic substituent.

Overall, ISCBCL displayed high enantioselectivity (E = >200) toward all the substrates except one tested at 25 °C and some substrates tested at elevated temperatures. The lower enantioselectivities at elevated temperatures are still synthetically acceptable in most cases. In general, the enantioselectivity of ISCBCL is in good agreement with our prediction based on the active-site model of ISCBCL.

Dynamic Kinetic Resolution with ISCBCL. The secondary alcohols described in Figure 2 were subjected to the ISCBCL-catalyzed DKR in toluene. The DKR reactions were performed at three different temperatures (rt, 40, and 60 °C) depending on the reactivity of substrate. In all the DKR reactions, isopropenyl acetate (IPA) was employed as the acyl donor, and in most of them, ruthenium complex **6**[14b] was employed as the racemization catalyst.



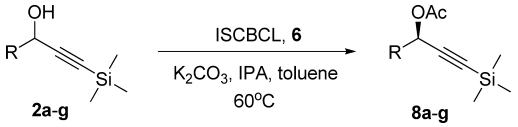
6 Ar = Ph-*p*-OMe **7**

The DKR reactions of TMS-propargyl alcohols **2a–g** were performed with solutions containing substrate (0.3 mmol), ISCBCL (3 mg), **6** (5 mol %), K_2CO_3 (0.3 mmol), and IPA (1.5 equiv) in toluene at 60 °C. Here, the elevated temperature was needed to promote the ruthenium-catalyzed racemization of substrate. The DKR reactions of **2a–c** were complete in 24 h to give good yields and excellent enantiomeric excesses (Table 2). Those of **2d–f** required a longer reaction time (36 h) for the completion and provided good yields but slightly reduced enantiopurities. The DKR reaction of **2g** was rather sluggish due to the increased bulkiness of α-substituent (*c*-Hex) and thus needed a much longer reaction time (72 h). In this case, the enantiopurity was relatively lower probably due to the slow racemization. Overall, the results indicate that the DKR of α-alkyl-TMS-propargyl alcohols was successful. This DKR complements the DKR of α-aryl-TMS-propargyl alcohols reported in the previous communication.[6]

It is noted that the acylated products from these DKRs can be readily converted to TMS-free acetates or alcohols by treatment with TBAF or K_2CO_3, respectively, without any loss in enantiopurity (Scheme 1).[6,12b] Accordingly, the DKR of TMS-protected α-chiral propargyl alcohols provides a practical route to enantioenriched α-chiral propargyl alcohols and acetates which are useful building blocks in asymmetric synthesis.[15] Recently, Ariza et al. reported that enantiopure α-

dx.doi.org/10.1021/jo3027627 | J. Org. Chem. 2013, 78, 2571–2578

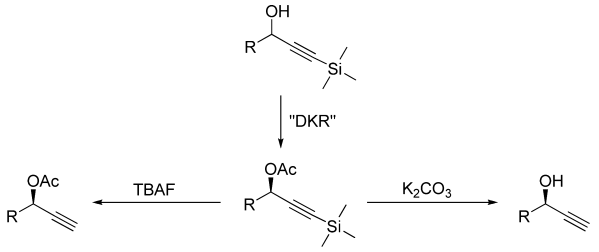
Table 2. DKR of TMS-propargyl Alcohols with ISCBCL



entry	substrate	product	time (h)	yield[a] (%)	ee (%)
1	**2a**	**8a**[b]	24	92	99
2	**2b**	**8b**[b]	24	92	99
3	**2c**	**8c**	24	93	98[c]
4	**2d**	**8d**	36	94	97[c]
5	**2e**	**8e**	36	97	92[c]
6	**2f**	**8f**	36	97	92[c]
7	**2g**	**8g**	72	91	84[d]

[a]Isolated yield. [b]Absolute configurations were confirmed by comparing their optical rotations with the literature data (see the Experimental Section). [c]Determined after TMS was removed. [d]Determined after TMS and acyl were removed.

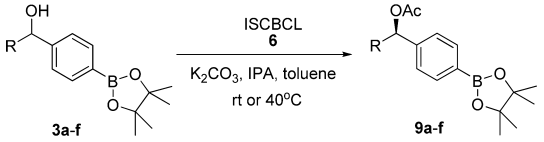
Scheme 1. Deprotection of TMS-propargyl Acetates



chiral propargyl acetate was particularly useful as the building block for the stereoselective construction of polyhydroxylated chains.[16]

The DKR reactions of boron-containing substrates **3a,b** were carried out with solutions containing substrate (0.1 mmol), ISCBCL (1 mg), ruthenium complex **6** (4 mol %), K_2CO_3 (0.1 mmol), and IPA (1.5 equiv) in toluene at room temperature to give the products with good yields and high enantiomeric excesses (entries 1 and 2, Table 3). The DKR of less reactive **3c–f** was done with a larger amount (2 mg) of enzyme at 40 °C to obtain good yields and good enantiomeric excesses (entries 3–6). In the case of **3c** (entry 3), ruthenium complex **7** was used instead of **6** as the racemization catalyst because **6** catalyzed the isomerization of substrate to the corresponding ketone via dehydrogenation of hydroxy group and hydrogenation of allylic group. In the case of **3f**, the DKR reaction was sluggish and thus required a long reaction time. Overall, the results indicate that the DKR of boron-containing alcohols was successfully achieved. It is noted that the DKR products can be utilized as chiral building blocks for the enantioselective synthesis of more complex compounds via the well-known Suzuki cross coupling reaction.[17]

Table 3. DKR of Boron-Containing Alcohols with ISCBCL[a]

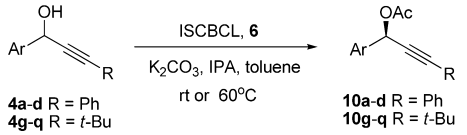


entry	substrate	product	time (h)	yield[b] (%)	ee (%)
1	**3a**	**9a**[c]	24	89	98
2	**3b**	**9b**	24	92	99
3[d]	**3c**	**9c**	72	78	94
4	**3d**	**9d**	60	85	94
5	**3e**	**9e**	60	87	94
6	**3f**	**9f**	108	88	94

[a]The reactions of **3a,b** were performed at 25 °C and those of the rest at 40 °C. [b]Isolated yield. [c]Absolute configuration was confirmed by comparing its optical rotation with the literature value (see the Experimental Section). [d]Compound **7** was employed as the racemization catalyst instead of **6**.

The DKR reactions of α-arylpropargyl alcohols **4a–q** were carried out with solutions containing substrate (0.1 mmol), ISCBCL (1–3 mg), **6** (4 mol %), K_2CO_3 (0.1 mmol), and IPA (1.5 equiv) in toluene. The DKR reaction of **4a** at room temperature was sluggish and provided modest enantiopurity (entry 1, Table 4). The reactions of **4b** and **4d** performed at 60 °C gave disappointedly low enantiopurity (entries 2 and 3, Table 4). It was found that spontaneous chemical acylation took place significantly in these cases. These results indicate that the DKR of diarylpropargyl alcohols is less than satisfactory and thus needs more efforts for improvement. In contrast to this, the DKR of α-aryl-*tert*-butylpropargyl alcohols **4g–q** at 60 °C provided better results. The high enantiopurities with good yields were obtained for the DKR of **4g–k** (entries 4–8, Table 4). In case of **4l–q**, the enantiopurity was substantially lowered due to minor chemical acylation (entries 9–14). These results indicate that the enantioselectivity was apparently dependent on the nature of α-aryl ring. In general, the *para*-substituted α-aryl rings led to good enantioselectivity relative to their *meta*-substituted counterparts.

Table 4. DKR of α-Arylpropargyl Alcohols with ISCBCL[a]



entry	substrate	product	time (h)	yield[b] (%)	ee (%)
1	**4a**	**10a**[c]	72	65	68
2	**4b**	**10b**	24	90	19
3	**4d**	**10d**	24	95	24
4	**4g**	**10g**[c]	24	97	99
5	**4h**	**10h**	48	97	95
6	**4i**	**10i**	48	96	95
7	**4j**	**10j**	48	97	92
8	**4k**	**10k**	48	96	95
9	**4l**	**10l**	48	98	66
10	**4m**	**10m**	48	97	88
11	**4n**	**10n**	48	96	83
12	**4o**	**10o**	48	93	74
13	**4p**	**10p**	48	95	61[d]
14	**4q**	**10q**	48	96	71

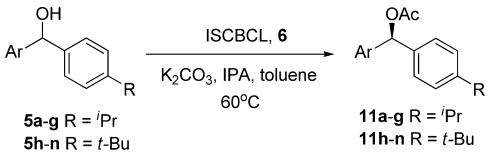
[a]The reaction of **4a** was performed at 25 °C and those of the rest at 60 °C. [b]Isolated yield. [c]Absolute configurations were confirmed by comparing their optical rotations with the literature data (see the Experimental Section). [d]Determined after being deacetylated.

The DKR of diarylmethanols **5a–n** was performed with solutions containing substrate (0.1 mmol), ISCBCL (3 mg), **6** (5 mol %), K_2CO_3 (0.1 mmol), and IPA (1.5 equiv) in toluene at 60 °C. The DKR of three substrates (**5a**, **5h**, and **5i**) provided satisfactory results in both yield and enantiopurity

dx.doi.org/10.1021/jo3027627 | J. Org. Chem. 2013, 78, 2571–2578

(entries 1, 8, and 9, Table 5). In other cases, the yields were significantly reduced owing to the oxidation of substrates to the corresponding ketones. In particular, *p*-methoxy-substituted diarylmethanol **5d** was highly susceptible to oxidation, thus resulting in the lowest yield (entry 4).[18] As expected, the DKR reactions of *p*-*tert*-butyl-substituted substrates (entries 8−14) in general provided the products of higher enantiopurity than those of their *para*-isopropyl-substituted counterparts (entries 1−7).

Table 5. DKR of Diaryl Carbinols with ISCBCL



5a-g R = ^{i}Pr
5h-n R = *t*-Bu

11a-g R = ^{i}Pr
11h-n R = *t*-Bu

entry	substrate	product	time (h)	yield[a] (%)	ee (%)
1	**5a**	**11a**[b]	36	93 (86)	91
2	**5b**	**11b**	36	65 (57)	91
3	**5c**	**11c**	36	61	85
4	**5d**	**11d**	36	19	61
5	**5e**	**11e**	48	75	75
6	**5f**	**11f**	48	65	79
7	**5g**	**11g**	48	46	83
8	**5h**	**11h**	36	89 (87)	95
9	**5i**	**11i**	48	84 (76)	95
10	**5j**	**11j**	48	55	94
11	**5k**	**11k**	60	42	87
12	**5l**	**11l**	48	76	71
13	**5m**	**11m**	60	69	86
14	**5n**	**11n**	60	68	93

[a]Determined by ^{1}H NMR. Isolated yields are given in parentheses. [b]Absolute configuration was confirmed by comparing the optical rotation of its hydrolyzed product with the literature value (see the Experimental Section).

CONCLUSION

More than 40 secondary alcohols, which can be classified into eight different types (II−IX) according to the nature of two substituents at the hydroxymethine center, were examined as the substrates of ISCBCL for KR and DKR. They include boron-containing alcohols, α-chiral propargyl alcohols, and diarylmethanols. Most of them were accepted by ISCBCL with useful to high enantioselectivity. The results prove that ISCBCL is particularly useful in the resolution of sterically demanding substrate types (VIII and IX) with two bulky substituents at the hydroxymethine center. The DKR reactions of 41 secondary alcohols performed by the combination of ISCBCL and a ruthenium-based racemization catalyst provided good yields and high enantiopurities for about half of them. We thus conclude that ISCBCL is a superb enzyme for the KR and DKR of secondary alcohols.

EXPERIMENTAL SECTION

Determination of the Enantioselectivity of ISCBCL. ISCBCL was prepared according to the procedure described previously.[6] The enantioselectivity of ISCBCL for each substrate was determined with its ISCBCL-catalyzed transesterification in the presence of IPA in toluene. In a typical procedure, isopropenyl acetate (1.5 equiv) was added to a 4 mL vial containing ISCBCL (1 mg), substrate (0.2 mmol), and anhydrous toluene (0.2 M). The resulting solution was then shaken at 25−60 °C until the reaction reached 40−50% conversion. After being diluted with methylene chloride, the reaction mixture was filtered through a Celite pad, concentrated, and then analyzed by HPLC or GC to determine the enantiomeric excesses of remaining substrate and acetylated product. The enantioselectivity (E) of ISCBCL was then calculated using the equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$ where $c = ee_s/(ee_s + ee_p)$.

DKR of 2a−g. The DKR reactions were performed with solutions containing substrate (0.3 mmol), ISCBCL (3 mg), **6** (5 mol %), K_2CO_3 (41 mg, 0.3 mmol), and IPA (1.5 equiv) in toluene at 60 °C for 24−72 h according to the standard procedure described previously.[6]

*(R)-3-Acetoxy-1-(trimethylsilyl)-1-butyne (**8a**):* 51 mg (92% yield, 99% ee); $[\alpha]^{17}_D$ = +117 (c = 1.0, $CHCl_3$) [lit.[19] $[\alpha]^{20}_D$ = +119 (c = 2.2, $CHCl_3$, 99% ee)]; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.47 (q, J = 6.72 Hz, 1H), 2.08 (s, 3H), 1.48 (d, J = 6.72 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.0, 103.8, 89.7, 60.9, 21.7, 21.4, 0.0; GC conditions: β-dex 120, inlet temp 250 °C, FID detector temp 300 °C, oven initial temp 60 °C (2 min), rate 1 °C/min, oven final temp 70 °C (30 min), retention times 33.42 min (S), 34.09 min (R).

*(R)-3-Acetoxy-1-(trimethylsilyl)-1-pentyne (**8b**):* 55 mg (92% yield, 99% ee); $[\alpha]^{18}_D$ = +123 (c = 0.9, $CHCl_3$) [lit.[20] $[\alpha]^{20}_D$ = +126.5 (c = 1.0, $CHCl_3$, 99% ee)]; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.34 (t, J = 6.50 Hz, 1H), 2.09 (s, 3H), 1.83−1.71 (m, 2H), 1.00 (t, J = 7.45 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.1, 102.7, 90.5, 65.7, 28.3, 21.3, 9.5, 0.0; GC conditions: β-dex 120, inlet temp 250 °C, FID detector temp 300 °C, oven initial temp 60 °C (2 min), rate 1 °C/min, oven final temp 75 °C (35 min), retention times 44.07 min (S), 44.83 min (R).

*(R)-3-Acetoxy-1-(trimethylsilyl)-1-hexyne (**8c**):* 59 mg (93% yield, 98% ee); $[\alpha]^{18}_D$ = +101 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.39 (t, J = 6.65 Hz, 1H), 2.08 (s, 3H), 1.78−1.68 (m, 2H), 1.50−1.38 (m, 2H), 0.95 (t, J = 7.31 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.1, 102.9, 90.4, 64.4, 37.1, 21.3, 18.5, 13.8, 0.0. Enantiomeric excess (ee) was determined by GC after deprotecting TMS with TBAF. GC conditions: β-dex 120, inlet temp 250 °C, FID detector temp 300 °C, oven initial temp 60 °C (2 min), rate 2 °C/min, oven final temp 90 °C (0 min), retention times 14.27 min (R), 14.76 min (S); TOF-MS (ESI+) calcd for $[C_{11}H_{20}O_2Si + Na]^+$ 235.1130, found 235.1130.

*(R)-3-Acetoxy-1-(trimethylsilyl)-1-heptyne (**8d**):* 64 mg (94% yield, 97% ee); $[\alpha]^{17}_D$ = +92.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.38 (t, J = 6.72 Hz, 1H), 2.08 (s, 3H), 1.79−1.70 (m, 2H), 1.47−1.27 (m, 4H), 0.95−0.88 (m, 3H), 0.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.1, 103.0, 90.4, 64.6, 34.7, 27.3, 22.4, 21.3, 14.1, 0.0. Enantiomeric excess (ee) was determined by GC after deprotecting TMS with TBAF. GC conditions: β-dex 120, inlet temp 250 °C, FID detector temp 300 °C, oven initial temp 60 °C (2 min), rate 4 °C/min, oven final temp 100 °C (10 min), retention times 14.6 min (R), 15.09 min (S); TOF-MS (ESI+) calcd for $[C_{12}H_{22}O_2Si + Na]^+$ 249.1287, found 249.1265.

*(R)-3-Acetoxy-1-(trimethylsilyl)-1-octyne (**8e**):* 70 mg (97% yield, 92% ee); $[\alpha]^{18}_D$ = +71.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.38 (t, J = 6.65 Hz, 1H), 2.08 (s, 3H), 1.79−1.68 (m, 2H), 1.49−1.37 (m, 2H), 1.35−1.27 (m, 4H), 0.94−0.86 (m, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.1, 103.0, 90.4, 64.6, 34.9, 31.4, 24.8, 22.6, 21.3, 14.1, 0.0. Enantiomeric excess (ee) was determined by GC after deprotecting TMS with TBAF. GC conditions: β-dex 120, inlet temp 250 °C, FID detector temp 300 °C, oven initial temp 60 °C (2 min), rate 4 °C/min, oven final temp 100 °C (20 min), retention times 20.99 min (R), 21.65 min (S); TOF-MS (ESI+) calcd for $[C_{13}H_{24}O_2Si + Na]^+$ 263.1443, found 263.1426.

*(R)-3-Acetoxy-1-(trimethylsilyl)-1-nonyne (**8f**):* 74 mg (97% yield, 92% ee); $[\alpha]^{17}_D$ = +74.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.38 (t, J = 6.65 Hz, 1H), 2.08 (s, 3H), 1.79−1.69 (m, 2H), 1.48−1.36 (m, 2H), 1.35−1.24 (m, 6H), 0.93−0.85 (m, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.1, 103.0, 90.4, 64.6, 35.0, 31.8, 28.9, 25.1, 22.7, 21.3, 14.2, 0.0. Enantiomeric excess (ee) was determined by GC after deprotecting TMS with TBAF. GC conditions: β-dex 120, inlet temp 250 °C, FID detector temp 300 °C,

dx.doi.org/10.1021/jo3027627 | J. Org. Chem. 2013, 78, 2571−2578

oven initial temp 60 °C (2 min), rate 4 °C/min, oven final temp 100 °C (25 min), retention times 32.44 min (*R*), 33.69 min (*S*); TOF-MS (ESI+) calcd for $[C_{14}H_{26}O_2Si + Na]^+$ 277.1600, found 277.1580.

*(R)-3-Acetoxy-3-cyclohexyl-1-(trimethylsilyl)-1-propyne (**8g**):* 69 mg (91% yield, 84% ee); $[\alpha]^{17}_D$ = +69.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.24 (d, *J* = 6.14 Hz, 1H), 2.09 (s, 3H), 1.88−1.59 (m, 6H), 1.34−0.99 (m, 5H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.2, 101.9, 91.0, 68.7, 42.0, 28.7, 28.2, 26.4, 25.9, 25.8, 21.2, 0.0. Enantiomeric excess (ee) was determined after deprotection of TMS and acetyl with K_2CO_3. GC conditions: β-dex 120, inlet temp 250 °C, FID detector temp 300 °C, oven initial temp 80 °C (2 min), rate 1 °C/min, oven final temp 130 °C (0 min), retention times 37.86 min (*S*), 38.48 min (*R*); TOF-MS (ESI+) calcd for $[C_{14}H_{24}O_2Si + Na]^+$ 275.1443, found 275.1412.

DKR of 3a−f. The DKR reactions were performed with solutions containing substrate (0.1 mmol), ISCBCL (1−2 mg), **6** (4 mol %) or **7** (4 mol %), K_2CO_3 (14 mg, 0.1 mmol), and IPA (1.5 equiv) in toluene at 25−40 °C for 24−108 h according to the standard procedure described previously.[6] Ruthenium catalyst **6** was employed in most cases except DKR of **3c**, in which **7** was used instead. The DKR reactions of **3a**,**b** were carried out 25 °C and the rest at 40 °C.

*(R)-1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-ethyl acetate (**9a**):* 26 mg (89% yield, 98% ee); $[\alpha]^{25}_D$ = +103.8 (*c* = 0.5, $CHCl_3$) [lit.[21] $[\alpha]^{24}_D$ = +81.8 (*c* = 1.0, $CHCl_3$, >99% ee)]; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 5.88 (q, *J* = 6.6 Hz, 1H), 2.07 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.34 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.3, 144.8, 135.0, 125.3, 83.8, 72.3, 24.8, 22.2, 21.3. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV=217 nm, retention times 5.92 min (*S*), 19.5 min (*R*); TOF-MS (ESI+) calcd for $[C_{16}H_{23}BO_4 + Na]^+$ 313.15871, found 313.15532.

*(R)-1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-propyl acetate (**9b**):* 28 mg (92% yield, >99% ee); $[\alpha]^{25}_D$ = +118.4 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.79 (d, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 5.66 (t, *J* = 6.8 Hz, 1H), 2.07 (s, 3H), 1.93−1.78 (m, 2H), 1.33 (s, 12H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.4, 143.6, 134.9, 125.9, 83.8, 76.6, 29.2, 24.9, 21.2, 9.82. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 18.5 min (*R*); TOF-MS (ESI+) calcd for $[C_{17}H_{25}BO_4 + Na]^+$ 327.17436, found 327.17210.

*(R)-1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-but-3-enyl acetate (**9c**):* 25 mg (78% yield, 94% ee), $[\alpha]^{16}_D$ = +59.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.79 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.80 (t, *J* = 6.8 Hz, 1H), 5.75−5.61 (m, 1H), 5.09−5.02 (m, 2H), 2.69−2.52 (m, 2H), 2.07 (s, 3H), 1.33 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.2, 143.1, 134.9, 133.2, 125.8, 118.1, 83.8, 75.1, 40.7, 24.9, 21.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 5.45 min (*S*), 13.7 min (*R*); TOF-MS (ESI+) calcd for $[C_{18}H_{25}BO_4+Na]^+$ 339.17436, found 339.17345.

*(R)-1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-butyl acetate (**9d**):* 27 mg (85% yield, 94% ee), $[\alpha]^{14}_D$ = +76.2 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.74 (t, *J* = 6.9 Hz, 1H), 2.06 (s, 3H), 1.94−1.67 (m, 2H), 1.33 (s, 14H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.3, 144.0, 134.9, 125.8, 83.8, 75.9, 38.4, 24.9, 21.3, 18.7, 13.8. HPLC condition: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 5.58 min (*S*), 16.0 min (*R*); TOF-MS (ESI+) calcd for $[C_{18}H_{27}BO_4 + Na]^+$ 341.19001, found 341.18906.

*(R)-1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-pentyl acetate (**9e**):* 29 mg (87% yield, 94% ee), $[\alpha]^{20}_D$ = +52.3 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.72 (t, *J* = 6.9 Hz, 1H), 2.06 (s, 3H), 1.95−1.70 (m, 2H), 1.39−1.12 (m, 16H), 0.86 (t, *J* = 4.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.4, 143.9, 134.9, 125.8, 83.8, 76.1, 36.0, 27.6, 24.9, 22.4, 21.3, 13.9. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 5.28 min (*S*), 15.2 min (*R*); TOF-MS (ESI+) calcd for $[C_{19}H_{29}BO_4 + Na]^+$ 355.20566, found 355.20604.

*(R)-1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-heptyl acetate (**9f**):* 32 mg (88% yield, 94% ee), $[\alpha]^{16}_D$ = +37.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 5.72 (t, *J* = 6.9 Hz, 1H), 2.06 (s, 3H), 1.95−1.69 (m, 2H), 1.36−1.24 (m, 20H), 0.86 (t, *J* = 4.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.4, 144.0, 134.9, 125.8, 83.8, 76.1, 36.3, 31.7, 29.0, 25.4, 24.9, 22.6, 21.3, 14.0. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 5.44 min (*S*), 17.6 min (*R*); TOF-MS (ESI +) calcd for $[C_{21}H_{33}BO_4+Na]^+$ 383.23696, found 383.23644.

DKR of 4a−q. The DKR reactions were performed with solutions containing substrate (0.1 mmol), ISCBCL (1−3 mg), **6** (4 mol %), K_2CO_3 (14 mg, 0.1 mmol), and IPA (1.5 equiv) in toluene at 25−60 °C for 24−48 h according to the standard procedure described previously.[6] The DKR reaction of **4a** was carried out 25 °C and the rest at 60 °C.

*(R)-1,3-Diphenylprop-2-ynyl acetate (**10a**):* 16 mg (65% yield, 68% ee), $[\alpha]^{25}_D$ = +2.48 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.59 (d, *J* = 1.58 Hz, 2H), 7.48−7.46 (m, 2 H), 7.40−7.39 (m, 3 H), 7.38−7.32 (m, 3 H), 6.70 (s, 1H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.9, 137.2, 131.9, 129.0, 128.8, 128.7, 128.3, 127.8, 122.1, 87.1, 85.6, 66.1, 21.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 0.5 mL/min, UV = 217 nm, retention times 14.6 min (*S*), 15.8 min (*R*); TOF-MS (ESI +) calcd for $[C_{17}H_{14}O_2 - OAc]^+$ 191.08608, found 191.08575. The product was hydrolyzed by the treatment with K_2CO_3 in water-MeOH to give the corresponding alcohol: $[\alpha]^{25}_D$ = +3.32 (*c* = 1.0, $CHCl_3$) [lit.[22] $[\alpha]^{22}_D$ = +5.1 (*c* = 0.5, $CHCl_3$, 88% ee)].

*(R)-1-(4-Fluorophenyl)-3-phenylprop-2-ynyl acetate (**10b**):* 24 mg (90% yield, 19% ee), $[\alpha]^{27}_D$ = +2.95 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.58−7.56 (m, 2H), 7.48−7.46 (m, 2H), 7.33−7.31 (m, 3H), 7.09 (t, *J* = 8.62 Hz, 2H), 6.67 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.8, 164.6, 131.9, 129.9, 128.9, 128.3, 121.9, 115.8, 115.5, 87.3, 85.3, 65.4, 21.1. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.38 min (*S*), 7.00 min (*R*); TOF-MS (ESI +) calcd for $[C_{17}H_{13}FO_2 - OAc]^+$ 209.07665, found 209.07613.

*(R)-3-Phenyl-1-p-tolylprop-2-ynyl acetate (**10d**):* 25 mg (95% yield, 24% ee), $[\alpha]^{27}_D$ = +3.19 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.50−7.46 (m, 4H), 7.32−7.30 (m, 3H), 7.21 (d, *J* = 7.89 Hz, 2H), 6.67 (s, 1H), 2.37 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.9, 139.0, 134.3, 131.9, 129.4, 128.8, 128.3, 127.8, 122.2, 86.9, 85.8, 66.0, 21.3, 21.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 7.17 min (*S*), 7.36 min (*R*); TOF-MS (ESI +) calcd for $[C_{18}H_{16}O_2 - OAc]^+$ 205.10173, found 205.10191.

*(R)-4,4-Dimethyl-1-phenylpent-2-ynyl acetate (**10g**):* 22 mg (97% yield, 99% ee), $[\alpha]^{25}_D$ = +28.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.50 (dd, *J* = 7.60, 1.90 Hz, 2H), 7.37−7.35 (m, 3H), 6.49 (s, 1H), 2.08 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.9, 137.8, 128.6, 127.8, 126.5, 96.3, 75.2, 65.9, 30.8, 27.5, 21.3. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 96/4, flow rate = 0.5 mL/min, UV = 217 nm, retention times 4.35 min (*R*), 4.73 min (*S*). The product was hydrolyzed by the treatment with K_2CO_3 in water−MeOH to give the corresponding alcohol: $[\alpha]^{25}_D$ = +31.0 (*c* = 1.0, $CHCl_3$) [lit.[22] $[\alpha]^{28}_D$ = +21.3 (*c* = 0.5, $CHCl_3$), 75% ee].

*(R)-1-(4-Fluorophenyl)-4,4-dimethylpent-2-ynyl acetate (**10h**):* 24 mg (97% yield, 95% ee), $[\alpha]^{25}_D$ = +29.6 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.51 (dd, *J* = 8.77, 5.41 Hz, 2H), 7.05 (t, *J* = 8.70 Hz, 2H), 6.45 (s, 1H), 2.08 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 168.8, 163.5, 128.6, 128.0, 114.5, 95.5, 74.0, 64.2, 29.7, 26.5, 20.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 0.5 mL/min, UV = 217 nm, retention times 8.88 min (*R*), 9.68 min (*S*).

*(R)-1-(4-Chlorophenyl)-4,4-dimethylpent-2-ynyl acetate (**10i**):* 25 mg (96% yield, 95% ee), $[\alpha]^{25}_D$ = +27.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.45 (d, *J* = 8.46 Hz, 2H), 7.33 (d, *J* = 8.55

dx.doi.org/10.1021/jo3027627 | J. Org. Chem. 2013, 78, 2571−2578

Hz, 2H), 6.44 (s, 1H), 2.08 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.8, 136.5, 134.6, 129.2, 128.7, 96.7, 74.8, 65.2, 30.7, 27.5, 21.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate =0.5 mL/min, UV = 217 nm, retention times 8.86 min (*R*), 10.4 min (*S*).

*(R)-1-(4-Bromophenyl)-4,4-dimethylpent-2-ynyl acetate (**10j**):* 30 mg (97% yield, 92% ee), $[\alpha]^{25}_D$ = +33.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.50 (d, *J* = 8.53 Hz, 2H), 7.38 (d, *J* = 8.42 Hz, 2H), 6.42 (s, 1H), 2.08 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.8, 137.0, 137.1, 129.5, 122.8, 96.7, 74.8, 65.2, 30.7, 27.5, 21.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 0.5 mL/min, UV = 217 nm, retention times 9.02 min (*R*), 10.8 min (*S*).

*(R)-4,4-Dimethyl-1-p-tolylpent-2-ynyl acetate (**10k**):* 23 mg (96% yield, 95% ee), $[\alpha]^{25}_D$ = +31.4 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.41 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.95 Hz, 2H), 6.45 (s, 1H), 2.35 (s, 3H), 2.06 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.9, 138.6, 134.9, 129.2, 127.8, 96.1, 75.3, 65.8, 30.1, 27.5, 22.4, 21.3. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 96/4, flow rate = 1.0 mL/min, UV = 217 nm, retention times 4.54 min (*R*), 5.07 min (*S*).

*(R)-1-(4-Methoxyphenyl)-4,4-dimethylpent-2-ynyl acetate (**10l**):* 26 mg (98% yield, 66% ee), $[\alpha]^{25}_D$ = +19.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.45 (d, *J* = 8.64 Hz, 2H), 6.89 (d, *J* = 8.51 Hz, 2H), 6.44 (s, 1H), 3.81 (s, 3H), 2.06 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.0, 159.9, 130.1, 129.3, 113.8, 96.1, 75.4, 65.6, 55.3, 30.8, 27.5, 21.3. Enantiomeric excess (ee) was determined after hydrolysis of acetate. HPLC conditions: Chiralcel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 8.85 min (*S*), 10.5 min (*R*).

*(R)-1-(3-Bromophenyl)-4,4-dimethylpent-2-ynyl acetate (**10m**):* 30 mg (97% yield, 88% ee), $[\alpha]^{25}_D$ = +34.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.66 (t, *J* = 1.83 Hz, 1H), 7.45−7.42 (m, 2H), 7.26−7.23 (m, 1H), 6.43 (s, 1H), 2.10 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.7, 140.1, 131.7, 130.8, 130.1, 126.3, 122.5, 96.9, 74.6, 65.0, 30.7, 27.5, 21.2. Enantiomeric excess (ee) was determined after hydrolysis of acetate. HPLC conditions: Chiralcel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 0.5 mL/min, UV = 217 nm, retention times 12.4 min (*S*), 13.4 min (*R*).

*(R)-4,4-Dimethyl-1-m-tolylpent-2-ynyl acetate (**10n**):* 23 mg (96% yield, 83% ee), $[\alpha]^{25}_D$ = +32.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.34−7.26 (m, 3H), 7.16−7.14 (m, 1H), 6.45 (s, 1H), 2.37 (s, 3H), 2.08 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.9, 138.2, 137.7, 129.4, 128.5, 128.4, 124.8, 96.2, 75.3, 65.9, 30.8, 27.5, 21.4, 21.3. Enantiomeric excess (ee) was determined after hydrolysis of acetate. HPLC conditions: Chiralcel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.65 min (*S*), 9.55 min (*R*).

*(R)-1-(3-Methoxyphenyl)-4,4-dimethylpent-2-ynyl acetate (**10o**):* 24 mg (93% yield, 74% ee), $[\alpha]^{26}_D$ = +16.5 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.28−7.25 (m, 1H), 7.10−7.08 (m, 2H), 6.90−6.87 (m, 1H), 6.46 (s, 1H), 3.82 (s, 3H), 2.09 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 169.9, 159.6, 139.3, 129.5, 120.1, 114.4, 113.2, 96.3, 76.0, 65.7, 55.2, 30.8, 29.7, 21.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 5.48 min (*R*), 6.30 min (*S*).

*(R)-1-(Furan-2-yl)-4,4-dimethylpent-2-ynyl Acetate (**10p**).* This product was unstable so it was converted by the treatment with K_2CO_3 in water−MeOH to the corresponding alcohol: 21 mg (95% yield, 61% ee), $[\alpha]^{26}_D$ = +12.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.39 (dt, *J* = 1.75, 0.88 Hz, 1 H), 6.43 (d, *J* = 0.75 Hz, 1 H), 6.33 (d, *J* = 1.34 Hz, 1 H), 5.43 (s, 1 H), 2.50 (s, 1H), 1.26 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 153.9, 142.8, 110.2, 107.5, 94.8, 76.1, 58.2, 30.8, 27.4. HPLC conditions: Chiralcel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 8.60 min (*S*), 10.0 min (*R*).

*(R)-4,4-Dimethyl-1-(naphthalen-2-yl)pent-2-ynyl acetate (**10q**):* 27 mg (96% yield, 71% ee), $[\alpha]^{26}_D$ = +10.9 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.97 (s, 1H), 7.86−7.81 (m, 3H), 7.50 (d, *J* = 3.15 Hz, 1H), 7.49−7.47 (m, 2H), 6.64 (s, 1H), 2.10 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 169.9, 135.2, 133.4, 128.4, 128.3, 127.7, 127.1, 126.5, 126.2, 125.7, 124.4, 96.1, 76.3, 66.1, 30.8, 27.7, 22.5. Enantiomeric excess (ee) was determined after hydrolysis of acetate. HPLC conditions: Chiralcel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 9.36 min (*S*), 10.5 min (*R*).

DKR of 5a−n. The DKR reactions were performed with solutions containing substrate (0.1 mmol), ISCBCL (3 mg), **6** (5 mol %), K_2CO_3 (14 mg, 0.1 mmol), and IPA (1.5 equiv) in toluene at 60 °C for 36−60 h according to the standard procedure described previously.[6] The products from the DKR reactions of **5a**, **5b**, **5h**, and **5i** were isolated and characterized.

*(R)-(4-Isopropylphenyl)(phenyl)methyl acetate (**11a**):* 23 mg (86% yield, 91% ee), $[\alpha]^{25}_D$ = +18.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.34−7.16 (m, 9H), 6.86 (s, 1H), 2.95−2.81 (m, 1H), 2.14 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.0, 148.5, 140.3, 137.5, 128.4, 127.7, 127.1, 126.9, 126.5, 33.7, 23.9, 21.3. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.9 min (*R*), 7.6 min (*S*); TOF-MS (ESI+) calcd for $[C_{18}H_{20}O_2-OAc]^+$ 209.1330, found 209.1306. The absolute configuration was confirmed by comparing the optical rotation of the hydrolyzed product with the literature value. (*R*)-(4-Isopropylphenyl)-(phenyl)methanol, $[\alpha]^{25}_D$ = +6.3 (*c* = 1.0, $CHCl_3$) [lit.[23] $[\alpha]^{24}_D$ = +11.2 (*c* = 0.8, $CHCl_3$, 86% ee)].

*(R)-(4-Fluorophenyl)(4-isopropylphenyl)methyl acetate (**11b**):* 16 mg (57% yield, 91% ee), $[\alpha]^{25}_D$ = +12.8 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.33−7.17 (m, 6H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.83 (s, 1H), 2.93−2.84 (m, 1H), 2.14 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.0, 163.9, 160.6, 148.7, 137.3, 136.2, 136.2, 128.9, 128.8, 127.0, 126.6, 115.5, 115.2, 76.1, 33.8, 23.9, 21.2. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.3 min (*R*), 6.8 min (*S*); TOF-MS (ESI+) calcd for $[C_{18}H_{19}FO_2 - OAc]^+$ 227.1236, found. 227.1199

*(R)-(4-tert-Butylphenyl)(phenyl)methyl acetate (**11h**):* 25 mg (87% yield, 95% ee), $[\alpha]^{25}_D$ = +21.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.36−7.24 (m, 9H), 6.86 (s, 1H), 2.15 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.0, 150.8, 140.3, 137.1, 128.4, 127.7, 127.0, 126.8, 125.4, 34.5, 31.2, 21.3. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.3 min (*R*)), 7.3 min (*S*); TOF-MS (ESI+) calcd for $[C_{19}H_{22}O_2 - OAc]^+$ 223.1487, found 223.1467.

*(R)-(4-tert-Butylphenyl)(4-fluorophenyl)methyl acetate (**11i**):* 23 mg (76% yield, 93% ee), $[\alpha]^{25}_D$ = +14.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.36−7.21 (m, 6H), 7.02 (t, *J* = 8.6 Hz, 2H), 6.84 (s, 1H), 2.14 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 170.0, 163.9, 160.6, 150.9, 136.9, 136.2, 128.9, 128.8, 126.7, 125.4, 115.5, 115.2, 34.1, 31.2, 21.3. HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm, retention times 6.0 min (*R*), 6.9 min (*S*); TOF-MS (ESI+) calcd for $[C_{19}H_{21}FO_2 - OAc]^+$ 241.1392, found 241.1377.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra and GC/HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Research Foundation of Korea (project nos. 2012R1A1A2006595 and 2012-007235) and the POSTECH Basic Science Research Institute for financial support of this work. We thank Dr. Hirose (Amano Pharmaceutical Co.) for providing technical information on *Burkholderia cepacia* lipase.

■ REFERENCES

(1) Books: (a) *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000. (b) *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*; Drauz, K., Waldmann, K., Ed.; Wiley-VCH: Weinheim, 2002; Vols. *I*–*III*. (c) Borncheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2006. (d) *Future Directions in Biocatalysis*; Matsuda, T., Ed.; Elsevier Science: Amsterdam, 2007. (e) *Asymmetric Organic Synthesis with Enzymes*; Gotor, V., Alfonso, I., Garcia-Urdiales, E., Eds.; Wiley-VCH: Weinheim, 2008.

(2) Reviews on chemoenzymatic DKR: (a) Martin-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Biol.* **2007**, *11*, 226–232. (b) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999–1015. (c) Kim, Y.; Park, J.; Kim, M.-J. *ChemCatChem* **2011**, *3*, 271–277.

(3) For the (*R*)-selective chemoenzymatic DKR of secondary alcohols, see: (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825. (b) 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. (c) Thalen, L. K.; Bäckvall, J.-E. *Beilstein J. Org. Chem.* **2010**, *6*, 823–829. (d) Do, Y.; Hwang, I. C.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2010**, *75*, 5740–5742. (e) Thalen, L. K.; Sumic, A.; Bogar, K.; Norinder, J.; Persson, A. K. A.; Bäckvall, J.-E. *J. Org. Chem.* **2010**, *75*, 6842–6847. (f) Lee, J. H.; Kim, N.; Kim, M.-J.; Park, J. *ChemCatChem* **2011**, *3*, 354–359. (g) Lihammar, R.; Millet, R.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2011**, *353*, 2321–2327. (h) Ema, T.; Nakano, Y.; Yoshida, D.; Kamato, S.; Sakai, T. *Org. Biomol. Chem.* **2012**, *10*, 6299–6308. (i) Sato, Y.; Kayaki, Y.; Ikariya, T. *Chem. Commun.* **2012**, *48*, 3635–3637.

(4) For the (*S*)-selective chemoenzymatic DKR of secondary alcohols, see: (a) Kim, M.-J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494–11495. (b) Borén, L.; Martín-Matute, B.; Xu, Y.; Córdova, A.; Bäckvall, J–E. *Chem.—Eur. J.* **2006**, *12*, 225–232. (c) Kim, M.-J.; Lee, H.; Park, J. *Bull. Korean Chem. Soc.* **2007**, *28*, 2096–2098.

(5) For the nonenzymatic DKR of secondary alcohols, see: Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149–15153.

(6) Kim, H.; Choi, Y. K.; Lee, J.; Lee, E.; Park, J.; Kim, M.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10944–10948.

(7) (a) Magnusson, A. O.; Takwa, M.; Hamberg, A.; Hult, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4582–4585. (b) Vallin, M.; Syren, P.-O.; Hult, K. *ChemBioChem* **2010**, *11*, 411–416.

(8) (a) Engström, K.; Vallin, M.; Syrén, P.-O.; Hult, K.; Bäckvall, J.-E. *Org. Biomol. Chem.* **2011**, *9*, 81–82. (b) Engström, K.; Vallin, M.; Hult, K.; Bäckvall, J.-E. *Tetrahedron* **2012**, *68*, 7613–7618.

(9) (a) Itoh, T.; Matsushita, Y.; Abe, Y.; Han, S. H.; Wada, S.; Hayase, S.; Kawatsura, M.; Takai, S.; Morimoto, M.; Hirose, Y. *Chem.—Eur. J.* **2006**, *12*, 9228–9237. (b) Abe, Y.; Hirakawa, T.; Nakajima, S.; Okano, N.; Hayase, S.; Kawatsura, M.; Hirose, Y.; Itoh, T. *Adv. Synth. Catal.* **2008**, *350*, 1954–1958. (c) Abe, Y.; Yoshiyama, K.; Hayase, S.; Kawatsura, M.; Itoh, T. *Green Chem.* **2010**, *12*, 1976–1980.

(10) (a) Schultz, T.; Pleiss, J.; Schmid, R. D. *Protein Sci.* **2000**, *9*, 1053–1062. (b) Guieysse, D.; Salagnad, C.; Monsan, P.; Remaud-Simeon, M.; Tran, V. *Tetrahedron: Asymmetry* **2003**, *14*, 1807–1817.

(11) For empirical rules or active-site models for predicting the enantioselectivity of some lipases, see: (a) Xie, Z.-F.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1990**, *1*, 395–402. (b) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665. (c) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129–6139. (d) Kim, M.-J.; Cho, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1411–1413. (e) Naemura, K.; Fukuda, R.; Takahashi, N.; Konishi, M.; Hirose, Y. *Tetrahedron: Asymmetry* **1993**, *4*, 911–918. (f) Naemura, K.; Fukuda, R.; Konishi, M.; Hirose, K.; Tobe, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1253–1256. (g) Naemura, K.; Fukuda, R.; Murata, M.; Konishi, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2385–2394. (h) Naemura, K.; Murata, M.; Tanaka, R.; Yano, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 3285–3294. (i) Jing, Q.; Kazlauskas, R. J. *Chirailty* **2008**, *20*, 724–735.

(12) For the previous lipase PS-catalyzed transesterification of TMS-propargyl alcohols, see: (a) Takano, S.; Setoh, M.; Yamada, O.; Ogasawara, K. *Synthesis* **1993**, 1253–1256. (b) Allevi, P.; Ciuffreda, P.; Anastasia, M. *Tetrahedron: Asymmetry* **1997**, *8*, 93–99. (c) Meert, C.; Wang, J.; De Clercq, P. J. *Tetrahedron Lett.* **1997**, *38*, 2179–2182.

(13) For the previous lipase-catalyzed transesterification of **3a**, see: Andrade, L. H.; Barcellos, T. *Org. Lett.* **2009**, *11*, 3052–3055.

(14) For the synthesis of Ru complex, see: (a) 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. (b) Lee, J. H.; Kim, N.; Kim, M.-J.; Park, J. *ChemCatChem* **2011**, *3*, 354–359.

(15) (a) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983. (b) Mao, J.; Xie, G. *Curr. Org. Chem.* **2009**, *13*, 1553–1564. (c) Lin, L.; Wang, R. *Curr. Org. Chem.* **2009**, *13*, 1565–1576.

(16) Ariza, X.; Garcia, J.; Gworges, Y.; Vicente, M. *Org. Lett.* **2006**, *8*, 4501–4504.

(17) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

(18) The yield increased to 80% if IPA as the acyl donor was replaced by *p*-chlorophenyl acetate, but the enantiopurity of product was disappointingly low (30% ee).

(19) Marshall, J. A.; Chobanian, H. *Org. Synth.* **2005**, *82*, 43–45.

(20) Lian, X.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8255–8258.

(21) Andrade, L. H.; Barcellos, T. *Org. Lett.* **2009**, *11*, 3052–3055.

(22) Usanov, D. L.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 1286–1289.

(23) Morikawa, S.; Michigami, K.; Amii, H. *Org. Lett.* **2010**, *12*, 2520–2523.