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Lipase/Oxovanadium Co-Catalyzed Dynamic Kinetic Resolution of Propargyl Alcohols: Competition between Racemization and Rearrangement

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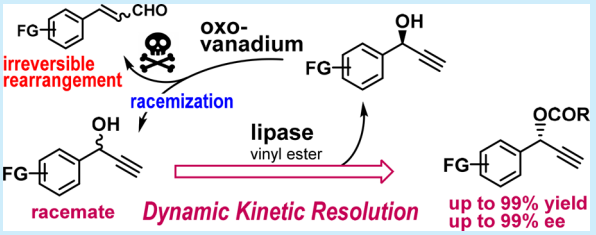
Supporting Information

ABSTRACT: Quantitative conversion of racemic propargyl alcohols into optically active propargyl esters with up to 99% ee has been achieved by lipase/oxovanadium co-catalyzed dynamic kinetic resolution, which combines the lipase-catalyzed enantioselective esterification of the racemic substrates and the in situ racemization of the remaining enantiomers. The success is owed to our discovery of a magic solvent, (trifluoromethyl)benzene, that accelerated the racemization while sufficiently suppressing the common oxovanadium-catalyzed rearrangement of propargyl alcohols to irreversibly produce enals.



The lipase-catalyzed kinetic resolution (KR) of racemic secondary alcohols has been widely used for the preparation of optically active compounds because of its excellent chemo- and stereoselectivity, easy operation, and easy purification of the products;[1] however, it has an inherent limitation that it can yield only 50% at maximum of each optically pure enantiomer. This problem has been overcome by combining KR and in situ racemization of the remaining less reactive enantiomers using a racemization catalyst to produce quantitative yields of optically pure products, and this protocol is called dynamic kinetic resolution (DKR). The racemization is mainly conducted by a redox process, for which more than a dozen Ru/Rh complexes possessing different ligands have been devised.[2,3] Very recently, less expensive Fe complexes were also reported to be useful for similar DKR.[4] These DKR protocols involving redox racemization have been applied to a wide range of secondary alcohols.[2−4] Around the same time, we independently performed a novel DKR of allyl alcohols using our original racemization catalyst V-MPS4 in which oxovanadium moieties are covalently bound to the inner surface of mesoporous silica (MPS) with a pore diameter of 4 nm (Figure 1a).[5] Different from the aforementioned DKR, the V-MPS4-catalyzed racemization proceeds along with 1,3-transposition of the hydroxyl group of allyl alcohols generating a dynamic equilibrium between the two regioisomers [(±)-**I** and (±)-**II**], and lipase catalyzes the chemo- and enantioselective esterification of (*R*)-**I** (Figure 1b). Its small pore size has dramatically improved the compatibility between the oxovanadium moiety and lipases to produce quantitative yields of optically pure allyl esters (*R*)-**III**.

Enantiomerically pure propargyl alcohols and their esters are found as partial structures of natural products and are important building blocks of a range of natural products and pharmaceutical compounds.[6] Their synthetic applications include the preparation of allenes[7] and diverse cyclization reactions such as the Huisgen reaction.[8] Therefore, we have been interested in applying the V-MPS4/lipase co-catalyzed DKR to racemic propargyl alcohols **1** to obtain optically active propargyl esters **2**. However, it has been well-known that the reactions of propargyl alcohols with oxovanadium moieties bring about the 1,3-transposition of the hydroxyl group to form conjugate enals, which is named Meyer−Schuster rearrangement (Figure 1c).[9,10] Thus, once the allenyl vanadates **D** are formed via either the [3,3]-sigmatropic rearrangement of **B** or C−O bond formation at the terminal carbon of a propargyl cation **C**,[10d] the hydrolysis of **D** immediately forms **3** by tautomerization of allenols **E**. This irreversible process is quite different from the aforementioned racemization of allyl alcohols (Figure 1b); the hampered DKR results in a significant decrease in the yields of **2**. We report herein how we could effectively suppress the side reactions to achieve DKR of propargyl alcohols (±)-**1** leading to esters (*R*)-**2** in high chemical and optical yields.

To examine the feasibility of the racemization while suppressing the Meyer−Schuster rearrangement, we studied the time course of the V-MPS4 (5.0 mol %)-catalyzed racemization of an optically pure propargyl alcohol (*S*)-**1a** as a model substrate in a range of organic solvents at 50 °C (Figure 2). The following results are noteworthy. First, the racemization in acetonitrile, which was the most often used solvent in our previous DKR,[5] proceeded slowly to produce **1a** with 69% ee after 12 h. This result was very different from the racemization of allyl alcohols in acetonitrile, where the complete racemization was attained using only 1.0 mol % V-MPS4 at 35 °C within 2 h.[11] Second, iPr_2O was another less

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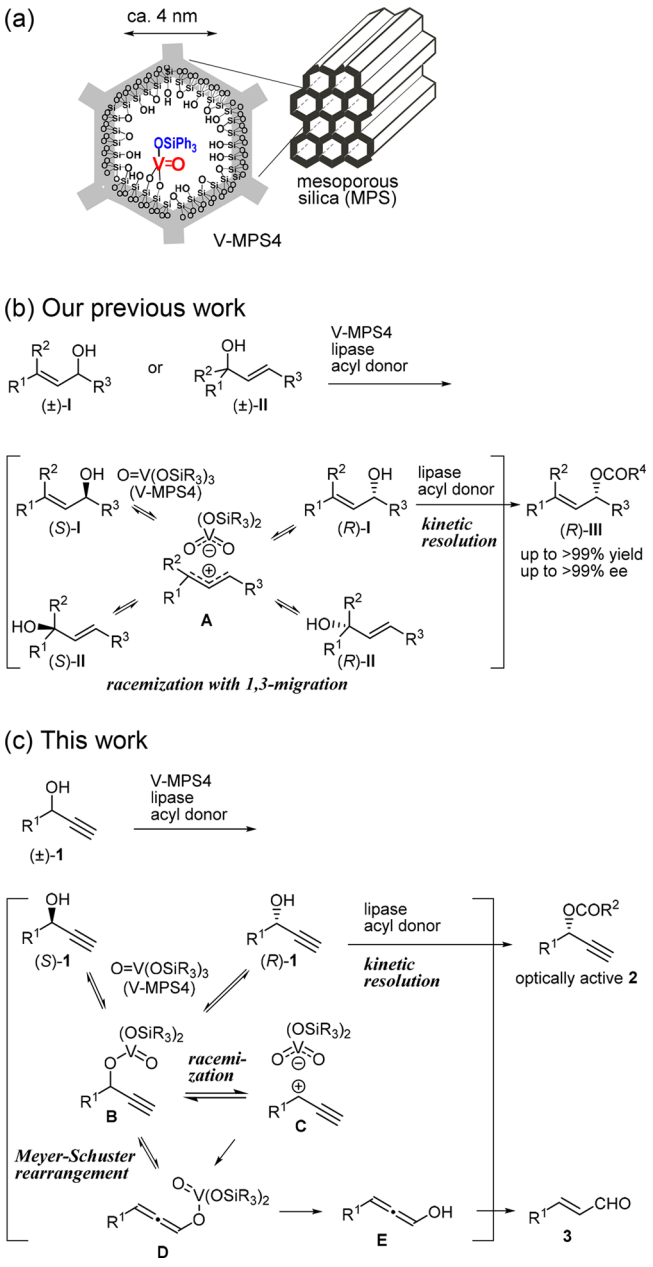

Figure 1. (a) Structure of V-MPS4. (b) Lipase/V-MPS4 co-catalyzed DKR of racemic allyl alcohols (**I** and **II**). (c) Lipase/V-MPS4 co-catalyzed DKR of racemic propargyl alcohols **1** and their Meyer–Schuster rearrangement. O═V$(OSiR_3)_n$ (n = 2 or 3) describes a local structure of the reactive site of V-MPS4.

suitable solvent for producing **1a** with 65% ee after 12 h. Third, the racemization in less polar solvents, such as toluene and dichloromethane, proceeded faster (**1a** with 8% ee was obtained in toluene after 12 h, and complete racemization was observed in dichloromethane within 4 h). Fourth, the faster the racemization proceeded, the higher the yield of **3a** (38% in toluene after 12 h and 62% in dichloromethane at 4 h). Further study led us to the discovery of (trifluoromethyl)-benzene as the best solvent that promoted fast racemization with relative suppression of the formation of **3a**. In addition, acetonitrile was the second choice of solvent because the level of formation of **3a** was much lower in acetonitrile than in iPr$_2$O, whereas the racemization rates were almost the same in these solvents.

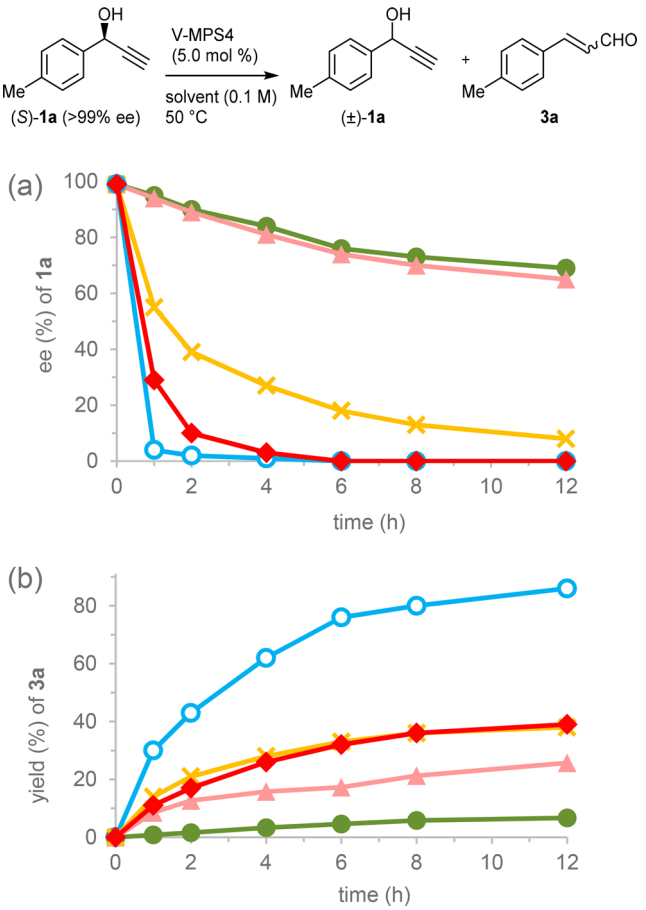

Figure 2. Time course of the reaction of (*S*)-**1a** (99% ee) and V-MPS4 (5.0 mol %) at 50 °C in different solvents. (a) Racemization of (*S*)-**1a** and (b) formation of **3a** based on ^{1}H NMR analysis of the reaction mixture: (●) MeCN, (▲) iPr$_2$O, (×) toluene, (◆) PhCF$_3$, and (○) CH_2Cl_2 (in a sealed tube).

On the basis of these results, we next optimized the conditions of V-MPS4/lipase co-catalyzed DKR of (±)-**1a** (Table 1). First, DKR was conducted in (trifluoromethyl)-benzene at 50 °C for 24 h using commercially available immobilized *Candida antarctica* lipase B (CAL-B)[12] (3 w/w) and vinyl decanoate (2 equiv) with varying amounts of V-MPS4 (entries 1–3). The corresponding ester (*R*)-**2aC** was obtained in >80% yield with high enantioselectivity (97 to >99% ee) in all cases, and the level of formation of **3a** (11–12% yield) was much lower than we expected from the results depicted in Figure 2. A similar DKR of (±)-**1a** (1.4 mmol) using 2.5 mol % V-MPS4 produced (*R*)-**2aC** (83% yield, 97% ee) (entry 4), which was almost the same as DKR using 0.34 mmol of (±)-**1a** (entry 2). Second, almost the same result as that in entry 3 was obtained by a similar reaction at 35 °C (entry 5); however, another reaction at 10 °C did not reach completion in 24 h (entry 6). The recovery of a 14% yield of (*S*)-**1a** with 38% ee showed that both racemization and enzymatic resolution became slower at 10 °C.

Third, the use of vinyl esters with a shorter acyl moiety caused a slight decrease in the yield of esters (*R*)-**2aB** and (*R*)-**2aA** due to the increase in the yield of **3** (compare entry 3 and entries 7 and 8). Fourth, DKR in acetonitrile did not reach completion in 24 h to give (*R*)-**2aC** (74% yield, >99% ee) and (*S*)-**1a** (16% yield, 52% ee) mainly due to the slow racemization, although the formation of **3** was suppressed

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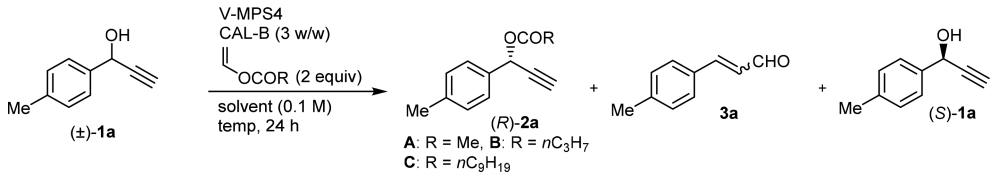
Table 1. Optimization of DKR Conditions of (±)-1a[a]



						(*R*)-2a				(*S*)-1a	
entry	solvent	V-MPS4 (mol %)	R	temp (°C)	conversion (%)		yield (%)[b]	ee (%)	3a yield (%)[c]	yield (%)[b]	ee (%)
1	$PhCF_3$	1.0	*n*-C_9H_{19}	50	93	(*R*)-**2aC**	81	97	11	7	23
2	$PhCF_3$	2.5	*n*-C_9H_{19}	50	100	(*R*)-**2aC**	83	99	12	–	–
3	$PhCF_3$	5.0	*n*-C_9H_{19}	50	100	(*R*)-**2aC**	85	>99	11	–	–
4[d]	$PhCF_3$	2.5	*n*-C_9H_{19}	50	100	(*R*)-**2aC**	83	97	12	–	–
5	$PhCF_3$	5.0	*n*-C_9H_{19}	35	100	(*R*)-**2aC**	82	99	10	–	–
6	$PhCF_3$	5.0	*n*-C_9H_{19}	10	86	(*R*)-**2aC**	81	97	4	14	38
7	$PhCF_3$	5.0	*n*-C_3H_7	50	100	(*R*)-**2aB**	81	99	14	–	–
8	$PhCF_3$	5.0	Me	50	100	(*R*)-**2aA**	77	94	16	–	–
9	MeCN	5.0	*n*-C_9H_{19}	50	84	(*R*)-**2aC**	74	>99	6	16	52
10[e]	CH_2Cl_2	5.0	*n*-C_9H_{19}	50	100	(*R*)-**2aC**	81	>99	17	–	–
11[f]	toluene	5.0	*n*-C_9H_{19}	50	100	(*R*)-**2aC**	77	98	10	–	–

[a]Each reaction was conducted using 0.34 mmol of **1a** except for entry 4. [b]Isolated yield. [c]Yield determined by ^{1}H NMR. An approximate 3:1 mixture of (*E*)- and (*Z*)-**3a** was obtained. [d]Conducted using 1.4 mmol of **1a**. [e]Conducted in a sealed tube. [f]A mixture of two diastereomers of bis[1-(4-tolyl)prop-2-yn-1-yl] ether (**4a**) was formed in 11% yield. The yield is calculated on the basis of the alcoholic moiety and corresponds to a 6% yield based on its molar amount.

(entry 9). However, DKR in dichloromethane produced (*R*)-**2aC** (>99% ee) in an unsatisfactory yield (81%) due to the fast formation of **3a** (17% yield) (entry 10). Toluene was not a favorable solvent because of the formation of another side product **4a**,[13] resulting in a reduced yield of (*R*)-**2aC** (77%) (entry 11). From these results, the DKR in (trifluoromethyl)-benzene (entries 2−4) was chosen as the best among these trials.

DKR of 4-methoxyl derivative (±)-**1b** under the same conditions as entry 3 of Table 1 provided ester (*R*)-**2bC** in low chemical and optical yields (67% yield, 83% ee) along with **3b** (18% yield) and **4b** (7% yield) (Table 2, entry 1). Further investigation by changing the amounts of V-MPS4 and CAL-B and reaction temperature led to a dramatic improvement in the yield and optical purity of (*R*)-**2bC**.[11] For example, reducing the amount of V-MPS4 (0.50 mol %) at 35 °C resulted in the formation of (*R*)-**2bC** (96% yield, 97% ee), whereas the yields of **3b** and **4b** were significantly decreased (entry 2). Because of the fast racemization in (trifluoromethyl)benzene, the amount of V-MPS4 was even reduced to 0.10 mol % to give (*R*)-**2bC** (88% yield, 97% ee) despite the longer reaction time (48 h) (entry 3). On the other hand, we had preliminarily reported that (*R*)-**2bB** (96% yield, 99% ee) was obtained using vinyl butyrate and V-MPS4 (1.0 mol %) in acetonitrile (entry 4), even though we had little information about solvent effects.[5a,14] Now, we have noticed that the high yield of (*R*)-**2bB** is mainly due to efficient suppression of the Meyer−Schuster rearrangement in acetonitrile.

On the basis of these studies, we set up two typical reaction methods for DKR, the use of vinyl decanoate and V-MPS4 in (trifluoromethyl)benzene (method I) and the use of vinyl butyrate and V-MPS4 in acetonitrile (method II), and applied them to various propargyl alcohols (±)-**1**. The results are summarized in Table 2. (±)-**1c** and (±)-**1d** were converted to (*R*)-**2cC** and (*R*)-**2dC** in high yields with high enantioselectivities by method I (entries 5 and 6, respectively). Method I was also useful for the alcohols having electron-rich aromatic moieties, such as (±)-**1e** and (±)-**1f**, to produce (*R*)-**2eC** and (*R*)-**2fC** in around 90% yields with 92 and 98% ee, respectively (entries 7 and 9, respectively). In addition, method II produced a slightly better yield and a slightly better enantioselectivity than method I for these alcohols (entries 8 and 10). Similarly, these two methods were applied to substituted alcohols (±)-**1g−i** to give (*R*)-**2gC**, (*R*)-**2hA**, and (*R*)-**2iB**, respectively, in good yields and enantioselectivities (entries 11−13, respectively). Moreover, the heterocyclic alcohols, such as (±)-**1j** and (±)-**1k**, were converted into (*R*)-**2jB** and (*R*)-**2kC** with high enantioselectivity (entries 14 and 15, respectively). However, alcohol (±)-**1l** having a methoxycarbonyl group at the *para* position was found to be a poor substrate for this DKR to provide (*R*)-**2lC** (>99% ee) in 55% yield along with recovered (*S*)-**1l** (38% yield, 96% ee) (entry 16), which was due to slow racemization of **1l**.

These results show that method I is useful for many of the substrates and allows the use of smaller amounts of V-MPS4 (0.10−0.50 mol %) due to faster racemization in (trifluoromethyl)toluene than in acetonitrile. However, method II generally forms products in chemical and optical yields slightly higher than those produced by method I, even though it is available for substrates having an electron-rich aromatic moiety.

In conclusion, we have discovered that V-MPS4, in which oxovanadium moieties are covalently bound to the inner surface of mesoporous silica (MPS), preferentially catalyzes the racemization of optically active propargyl alcohols in some solvents, even though the oxovanadium compounds have been mostly employed to catalyze the Meyer−Schuster rearrangement of the propargyl alcohols to form the corresponding conjugate enals.[9,10] One of the most significant findings was that the relative rates of rearrangement and racemization are significantly dependent on solvents. In particular, (trifluoromethyl)benzene was found to effectively suppress the rearrangement while accelerating the racemization; acetonitrile was another option for decelerating the rearrange-

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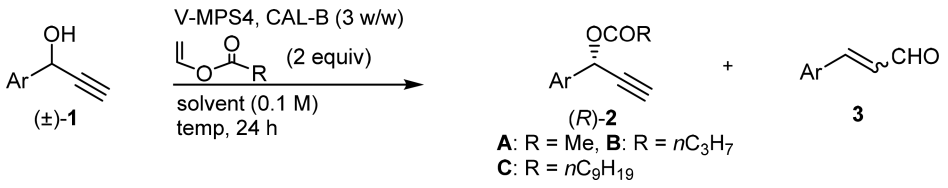
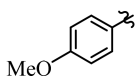
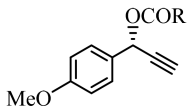
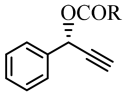
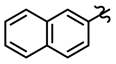
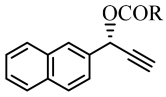
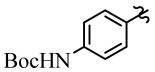
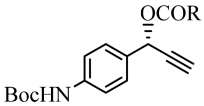
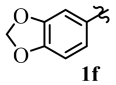
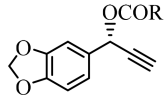
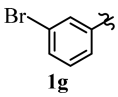
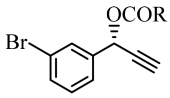
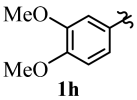
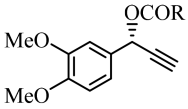
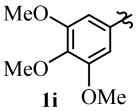
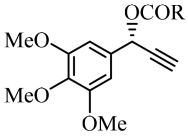
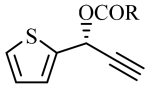
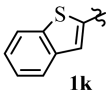
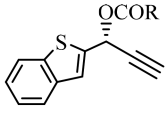
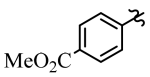
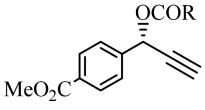
Table 2. Substrate Scope of DKR of Propargyl Alcohols (±)-1



entry	1, Ar	V-MPS4 (mol %)	method[a]	temp (°C)	2 product	2 yield (%)[b]	2 ee (%)	3 yield (%)[c]
1[d]	 **1b**	5.0	I	50		(*R*)-**2bC**	67	83	**3b**, 18
2		0.50	I	35		(*R*)-**2bC**	96	97	**3b**, 2
3[e]		0.10	I	35		(*R*)-**2bC**	88	97	**3b**, 4
4[f]		1.0	II	35		(*R*)-**2bB**	96	99	**3b**, trace
5	 **1c**	5.0	I	50		(*R*)-**2cC**	70	91	**3c**, 14
6	 **1d**	5.0	I	50		(*R*)-**2dC**	84	93	**3d**, 10
7	 **1e**	0.50	I	35		(*R*)-**2eC**	90	92	**3e**, 4
8		1.0	II[g]	35		(*R*)-**2eA**	94	97	**3e**, 6
9	 **1f**	0.50	I	35		(*R*)-**2fC**	88	98	**3f**, 4
10		1.0	II	35		(*R*)-**2fB**	94	99	**3f**, 3
11	 **1g**	5.0	I	50		(*R*)-**2gC**	86	81	**3g**, trace
12	 **1h**	1.0	I[g]	35		(*R*)-**2hA**	86	95	**3h**, 5
13	 **1i**	1.0	II	50		(*R*)-**2iB**	99	99	**3i**, N.D.[h]
14	 **1j**	1.0	II	35		(*R*)-**2jB**	99	98	**3j**, N.D.[h]
15	 **1k**	5.0	I	50		(*R*)-**2kC**	81	92	**3k**, 14
16[i]	 **1l**	5.0	I[j]	50		(*R*)-**2lC**	55	>99	**3l**, 3

[a]Method I: use of vinyl decanoate (R = *n*-C_9H_{19}) in $PhCF_3$. Method II: use of vinyl butyrate (R = *n*-C_3H_7) in MeCN. [b]Isolated yield. [c]Determined by ^1H NMR analysis of the crude product. [d]Bis[1-(4-methoxyphenyl)prop-2-yn-1-yl] ether (**4b**) was formed in 7% yield (for the calculation of the yield, see footnote f of Table 1). [e]Conducted using 0.10 mol % V-MPS4 and 0.6 w/w CAL-B for 48 h. **4b** was formed in 3% yield (see footnote f of Table 1). [f]Cited from ref 5a. [g]Vinyl acetate (R = Me) was used. [h]Not detected. [i](*S*)-**1l** (38% yield, 96% ee) was recovered. [j]CH_2Cl_2 was used in a sealed tube instead of $PhCF_3$.

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ment. By using these specific solvents, we could apply our V-MPS4/lipase co-catalyzed DKR to racemic propargyl alcohols to produce the corresponding optically active esters in >80% yields with 90−99% ee in many cases. Further investigation to clarify the unique nature of (trifluoromethyl)benzene and acetonitrile and applications of our DKR of propargyl alcohols[15] are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00334.

Full experimental data, including synthetic procedures, characterization data, and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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