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Kinetic Resolution of Tertiary Alcohols by Chiral DMAP Derivatives: Enantioselective Access to 3-Hydroxy-3-substituted 2-Oxindoles

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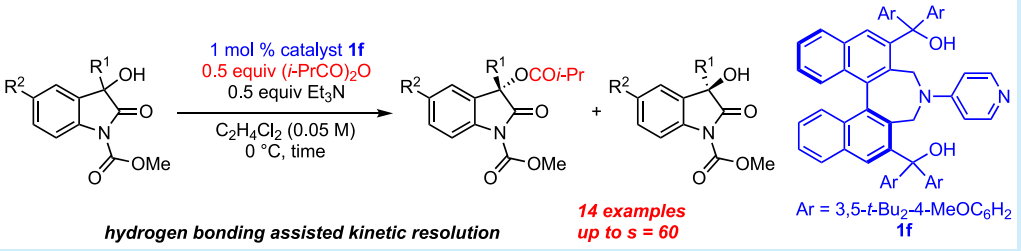

ABSTRACT: We developed an efficient acylative kinetic resolution of 3-hydroxy-3-substituted 2-oxindoles by a chiral DMAP derivative having a 1,1′-binaphthyl with two *tert*-alcohols units. A wide range of 3-hydroxy-3-substituted oxindoles having various functional groups were efficiently resolved (14 examples, up to s = 60) in the presence of 1 mol % of catalyst within 3−9 h. Multigram-scale reactions (10 g) also proceeded with a high s-factor (s = 43) within 5 h.

The optically active 3-hydroxy-3-substituted 2-oxindole skeleton[1] is frequently found in natural products and biologically active molecules. To construct the structure in an enantioselective fashion, various synthetic methods have been extensively studied.[2] For example, the aldol reaction,[3] Friedel−Crafts reaction,[4] the addition of aryl boronic acids,[5] and Morita−Baylis−Hillman reactions of 1,2-unsaturated carbonyls[6] using isatin and other methods[7] have been widely employed. However, limited types of nucleophiles (e.g., enolizable carbonyl compounds for an aldol reaction or electron-rich aromatic compounds for the Friedel−Crafts reaction) could be used in each reaction. Enantioselective hydroxylation of 3-substituted 2-oxindoles[8] and the kinetic resolution of 3-hydroxy-3-substituted 2-oxindoles have also been reported. Regarding the latter case, there are only a few reports on organocatalytic approaches to obtain enantioenriched 3-hydroxy-3-substituted 2-oxindoles. Zhao and co-workers reported the NHC-catalyzed acylative kinetic resolution of 3-hydroxy-3-substituted 2-oxindoles with high s-factors.[9] Very recently, Smith and co-workers reported the acylative kinetic resolution of 3-hydroxy-3-substituted 2-oxindoles by 1−10 mol % of hyperBTM catalyst, which gave an array of enantioenriched products with high s-factors.[10] Extensive experimental and mechanistic studies revealed that C═O···isothiouronium interaction is important for the enantiodiscrimination of tertiary alcohols. Such kinetic resolution approaches are attractive options to access an array of enantioenriched 3-hydroxy-3-substituted 2-oxindoles from the racemate because various substituents (alkyl, aryl, and carbonyl groups) can be incorporated into the starting material in advance, which could not be achieved by the aldol reaction or Friedel−Crafts reaction.

Our research interests involve the development of chiral nucleophilic catalysts[11] for acyl-transfer reactions.[12] Among these, we developed binaphthyl-based chiral *N*,*N*-dimethyl-4-aminopyridine (DMAP) derivatives, which showed drastic rate enhancement and high enantioselectivity in the Steglich-type rearrangement of *O*-acylated oxindoles[11e] and furanyl carbonates,[11k] kinetic resolution of carbinols[11f] and *d*,*l*-1,2-diols,[11g] desymmetrization of *meso*-1,2-diols[11h] and 1,3-diols,[11j,l] and dynamic kinetic resolution of azlactone.[11i] According to our extensive studies on acyl transfer reactions, a polar functional group (*tert*-alcohol or amide) in the catalyst structure is needed to achieve high catalytic activity and high enantioselectivity. To further explore the utility of the catalyst, we selected the kinetic resolution of a sterically congested tertiary alcohol, which is a challenging enantioselective transformation. Our scenario is inspired by the favored transition state revealed by DFT studies in the Steglich-type rearrangement with binaphthyl-based catalyst having two *tert*-alcohol units (Figure 1a).[11e] We expected that the kinetic resolution of 3-hydroxy-3-substituted 2-oxindoles (similar in structure to enolate in Figure 1a) might proceed smoothly with a high s-factor

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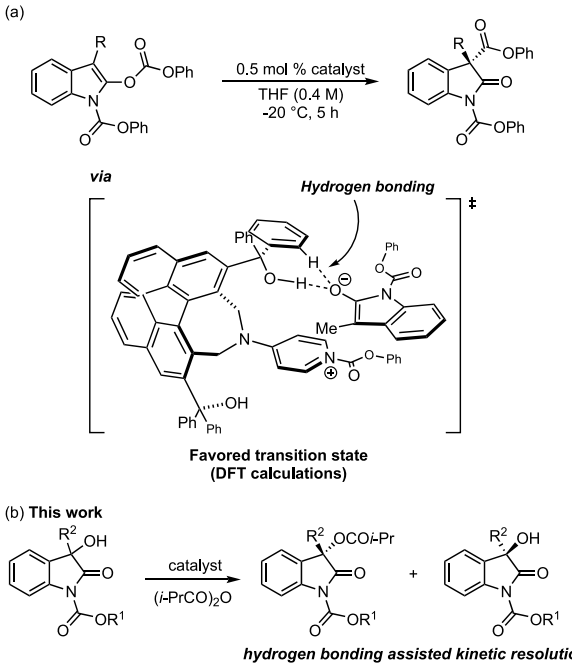


Figure 1. (a) Favored transition state in Steglich-type rearrangement of 2-*O* acylated oxindole derivatives (b) General scheme of the current study.

associated with some sort of hydrogen-bonding interactions between the catalyst and substrate, directly or indirectly (Figure 1b), and raises alternative possibilities to access 3-hydroxy-3-substituted 2-oxindoles in a highly enantioselective fashion.

Herein, we report on the acylative kinetic resolution of various 3-hydroxy-3-substituted 2-oxindoles by using as little as 1 mol % of a chiral DMAP derivative having a 1,1′-binaphthyl with two *tert*-alcohols units. Several control experiments involving the structure of a reaction substrate and a catalyst were also conducted to understand these processes.

We began by identifying the optimal catalyst from a selected library **1a**−**f** for the kinetic resolution of 3-allyl-3-hydroxy 2-oxindoles **2a** in 1,2-dichloroethane ($C_2H_4Cl_2$) at 0 °C for 15 h (Figure 2). As a general tendency, the reactions with 1 mol % of catalysts **1d**−**f** having *tert*-alcohols with 3,5-di- or 3,4,5-trisubstituted aryl group apparently showed higher selectivity factors (s = 33−43) than those from catalysts **1a**−**c** (s = 15−16). Based on these results, we selected catalyst **1f** [Ar = 3,5-(*t*-Bu)$_2$-4-MeOC$_6$H$_2$] as an optimal catalyst for further optimization of the reaction conditions.

Next, the effects of solvent were investigated in the kinetic resolution process (Table 1). The reactions in common organic solvents (CH_2Cl_2, Et_2O, *t*-BuOMe, and toluene, entries 2−5) proceeded in 49−50% conversion but showed less efficient *s*-factors (s = 6−30) compared to that obtained in 1,2-dichloroethane (s = 40, entry 1). Surprisingly, the use of *tert*-amyl alcohol did not significantly reduce the *s*-factor (s = 18, entry 6). According to our previous observations,[11f−j] the protic solvent showed a poor *s*-factor because that should prevent the formation of an effective hydrogen bonding network between the catalyst and the substrate,[13] which is undoubtedly responsible for the high enantioselectivity. Furthermore, the reaction in the optimal solvent ($C_2H_4Cl_2$) with more concentrated conditions (0.1−0.5 M, entries 7−9) showed somewhat lower *s*-factor (s = 32−35). After

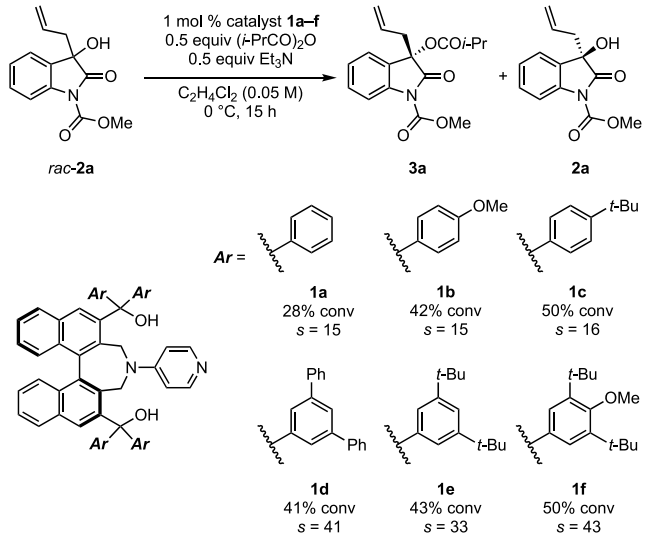
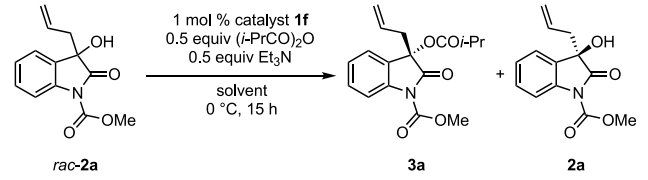


Figure 2. Catalyst screening for the kinetic resolution of *rac*-**2a**.

Table 1. Effect of Solvent in the Kinetic Resolution of *rac*-2a[a]



entry	solvent	conc (M)	conv[b] (%)	er of **3a**[c]	er of **2a**[c]	s[d]
1	$C_2H_4Cl_2$ (1,2-dichloroethane)	0.05	55	90:10	99:1	40
2	CH_2Cl_2	0.05	50	92:8	91.5:8.5	30
3	Et_2O	0.05	51	89:11	90:10	20
4	*t*-BuOMe	0.05	50	90:10	90:10	22
5	toluene	0.05	51	78:22	79:21	6
6	*t*-amyl alcohol	0.05	49	89:11	87:13	18
7	$C_2H_4Cl_2$	0.1	48	93:7	90:10	32
8	$C_2H_4Cl_2$	0.3	49	93:7	92:8	35
9	$C_2H_4Cl_2$	0.5	56	88:12	>99:1	33

[a]Reactions were performed on a 0.1 mmol scale in solvent (0.2 M) under an argon atmosphere. [b]Conversion was determined by enantiomeric excess (ee) of **2a** and **3a**. [c]Enantioselectivities were determined by HPLC analysis. [d]s-Factors were calculated by Kagan's equation.[14]

considering these results and extensive screening of the reaction conditions (see the Supporting Information for details), we selected the following optimal reaction conditions: 1 mol % of **1f**, 0.5 equiv of (*i*-PrCO)$_2$O, and 0.5 equiv of Et_3N in $C_2H_4Cl_2$ at 0 °C.

With the optimal reaction conditions in hand, the kinetic resolution of various 3-hydroxy-3-substituted 2-oxindoles **2a**−**n** was examined (Figure 3). The reactions of alkyl-, vinyl-, or alkynyl-substituted substrates **2a**, **2b**, **2e**, and **2f** could be efficiently resolved with high *s*-factors (s = 41−60), but the *s*-factors were still acceptable when **2c** or **2d** having a sterically demanding substituent (R = *i*-Pr or Cy) was used (s = 27 and 17, respectively). On the other hand, the reaction of aryl- or heteroaryl-substituted substrates **2g**−**j** showed higher *s*-factors (s = 49−60) compared to those of **2a**−**f** (s = 17−60). With **2h** or **2i**, an electron-donating or -withdrawing substituent on the

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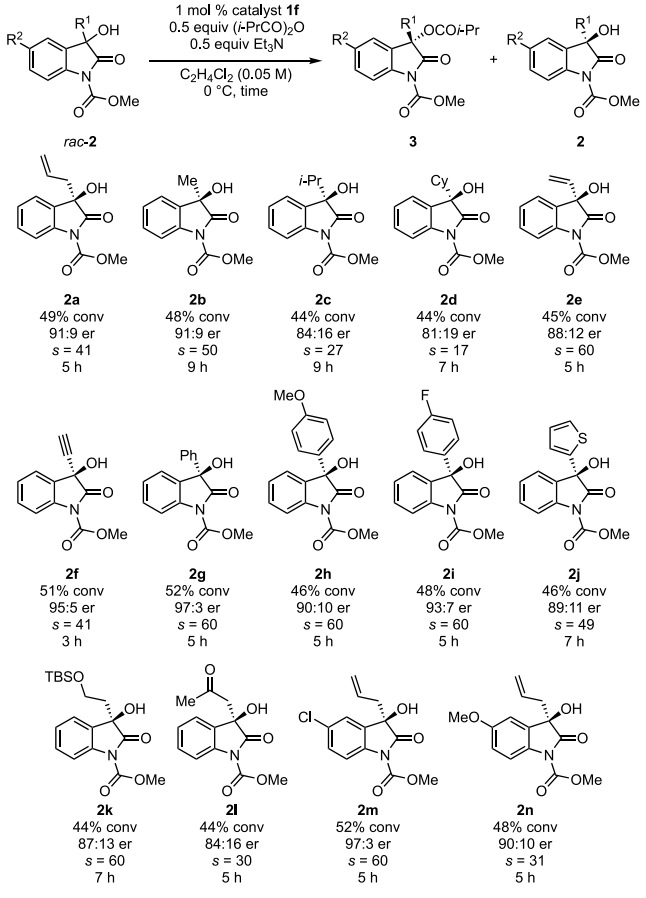


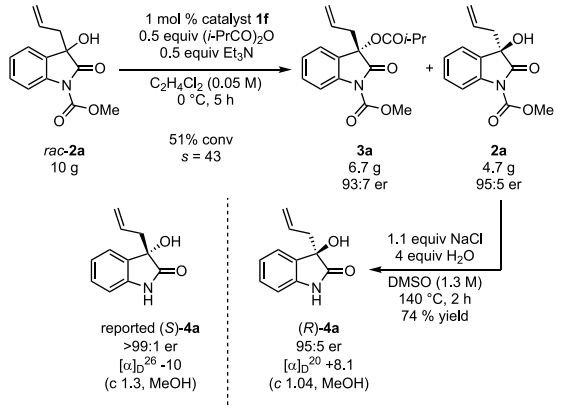
Figure 3. Kinetic resolution of various 3-hydroxy-3-substituted 2-oxindoles with 1 mol % of catalyst **1f**.[15]

aryl group did not significantly affect the *s*-factor (**2h** [*s* = 63, 5 h] vs **2i** [*s* = 60, 5 h]). A polar functional group within the substrate could be tolerated. The use of **2k** having a silyl ether showed an excellent *s*-factor (*s* = 60), and **2l** having a *β*-hydroxy ketone (aldol adduct) showed a good *s*-factor (*s* = 30). In the latter case, we expected dynamic kinetic resolution of **2l** via retro-aldol reaction, but kinetic resolution only proceeded (*s* = 30). 5-Cl- and 5-MeO-substituted substrates **2m** and **2n** also showed good to excellent *s*-factors (*s* = 60 and 31, respectively). According to these experiments, the current kinetic resolution process allowed us to access various enantioenriched 3-hydroxy-3-substituted 2-oxindoles having an *N*-methoxycarbonyl group with *s* = 17−60 within 3−9 h.

We also conducted a multigram-scale reaction with **2a** to test the scalability of this reaction (Scheme 1). With only 19.2 mg (1 mol %) of catalyst **1f**, 10.0 g of *rac*-**2a** was smoothly resolved to give monoacylate **3a** (6.7 g, 93:7 er) and recovered **2a** (4.7 g, 95:5 er) with excellent selectivity (51% conv, *s* = 43) at 0 °C for 5 h. The *N*-methoxycarbonyl group of recovered **2a** was successfully removed by Krapcho-type decarboxylation under mild conditions (NaCl and H_2O in DMSO) to give **4a**, the absolute configuration of which was determined to be *R* by comparison to the reported value for the specific optical rotation of (*S*)-**4a**.[16] Other recovered alcohols **2b**−**n** were also assigned *R* by analogy.

Next, several control experiments regarding substrate structure were carried out to obtain further insight into these reactions. Change of the *N*-protecting group from methoxycarbonyl to *tert*-butoxycarbonyl decreased the *s*-factor

Scheme 1. Kinetic Resolution of *rac*-2a in a Multigram-Scale Reaction and Deprotection of Recovered 2a for Determination of Absolute Configuration



significantly (**2a** vs **2o**, from *s* = 41 to 25) while maintaining its reactivity (∼50% conv within 5 h) (Figure 4). On the other

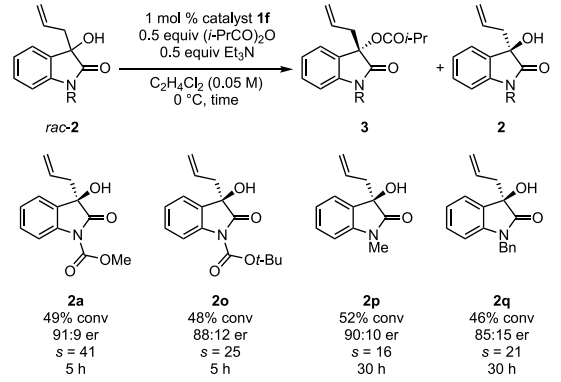


Figure 4. Kinetic resolution of various *N*-protected 3-hydroxy-3-substituted 2-oxindoles **2o**−**q** with 1 mol % of catalyst **1f**.

hand, the use of *N*-alkyl substrates **2p** and **2q**, an *N*-methyl or benzyl group, required a longer reaction time (30 h) for achieving ∼50% conv and resulted in a significant decrease in the *s*-factor (*s* = 16 for **2p**, *s* = 21 for **2q**, respectively). These results suggested that the electron-withdrawing group attached to the nitrogen atom is required for acceleration of the reaction.

One possible explanation for this effect is that the electron-withdrawing group at the *N*-position might increase the acidity of a hydroxy group, which was easily deprotonated by carboxylate ion ($^-$OCO*i*-Pr) fixed by a hydrogen-bonding network (see Figure 6), which accelerates the rate of the reaction. Furthermore, 3-hydroxy-3-substituted 2-benzofuranone was also subjected to kinetic resolution [eq 1]. Thus, the kinetic resolution of **2r** showed a reasonably good *s*-factor (*s* = 28 within 9 h). Compared to *N*-methoxycarbonyl variant **2b**, almost the same reactivity was observed (48% conv for 9 h with **2b** in Figure 3, and 46% conv for 9 h with **2r**). The relatively strong electronegativity of oxygen atom maintains the acidity of the hydroxyl group, which is important for acceleration of the reaction. Finally, the importance of the five-membered moiety was also confirmed (eq 2). The reaction of **2s**, where the five-membered ring is deconstructed, resulted in poor conversion and a low *s*-factor within 26 h (5% conv, *s* = 2) compared to **2a** having a five-membered structure. Overall,

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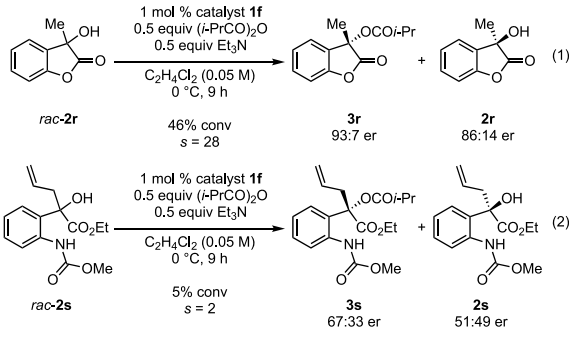

the electronic properties and steric rigidity of the substrate strongly affected the efficiency of the reaction.

Next, we focused our attention on the importance of the *tert*-alcohol unit(s) of the catalyst. The kinetic resolution of *rac*-**2a** was carried out using pseudo-C_2-symmetric catalyst **1f′** (lacking one hydroxy group), C_2-symmetric catalyst **1f″** (lacking two hydroxy groups), and **1g** (elimination of two *tert*-alcohol units) under the optimal conditions for **1f** (Figure 5). The catalyst **1f′** showed lower conversion and *s*-factor

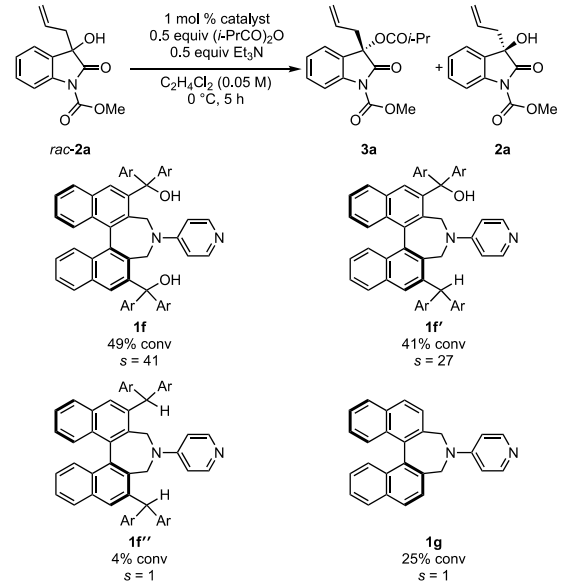

Figure 5. Kinetic resolution of *rac*-**2a** in the presence of catalyst with or without hydroxy group(s) or *tert*-alcohol unit(s).

(41% conv, *s* = 27) but **1f″** and **1g** showed no catalytic activity or enantioselectivity. Interestingly, two sterically demanding $-CHAr_2$ units of **1f″** completely shut down its catalytic activity (4% conv). Accordingly, the hydroxy group of the catalyst enables hydrogen bonding-assisted kinetic resolution, and significantly accelerates the reaction efficiency (**1f″** vs **1f′** or **1f**). Such phenomena were also observed in our previous studies.[11e−h] Based on these observations, and after considering models provided by Spivey and Zipse et al.,[17] Zipse,[18] and Yamanaka and Kawabata et al.,[19] as well as our previous transition states models,[11e−g] we speculated that *N*-methoxycarbonyl group of the substrate is located at far from catalyst to avoid steric repulsion against the catalyst in plausible transition states (Figure 6). The appropriate hydrogen bonding network in the favored transition state should be responsible to the deprotonation of the hydroxy group of the substrate (Figure 6, top). It is deprotonated by a carboxylate

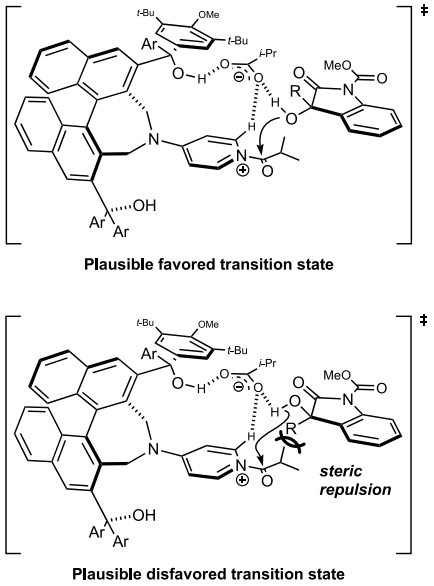

Figure 6. Plausible transition states.

anion[11f,17,19,20] fixed by both a *tert*-alcohol unit and *ortho*-proton of pyridine, followed by acylation to give (*S*)-**3a** and recovered alcohol (*R*)-**2a**. At this stage, the electron-withdrawing *N*-methoxycarbonyl group is responsible for the high acidity of a hydroxy group, accelerating the rate of the reaction (see also Figure 4). In the disfavored transition state (Figure 6, bottom), steric repulsion between the substituent (drawn as R) and the isopropyl group of *N*-acylpyridinium ion might be dominant.

In summary, we have demonstrated that a small amount of catalyst **1f** efficiently promoted the kinetic resolution of 3-hydroxy-3-substituted 2-oxindoles with a high *s*-factor. These transformations required as little as 1 mol % of catalyst **1f** and were relatively faster than previously reported methods.[9a,10] An array of functional groups within the substrate were tolerated and a variety of reactions proceeded with excellent enantioselectivity (14 examples, up to *s* = 60). A multigram-scale reaction (10 g) could be easily conducted within 5 h with 1 mol % of the catalyst **1f**, and deprotection of an *N*-methoxycarbonyl group of recovered alcohol **2a** was also successively achieved in 74% isolated yield by Krapcho-type decarboxylation. Several control experiments on the substrate structure (*N*-protecting group) and the catalyst structure revealed that the substrate with *N*-methoxycarbonyl group is for achieving a high *s*-factor. With regard to the catalyst structure, the catalyst required two *tert*-alcohol units to achieve high enantioselectivity and acceleration of the reaction rate. Further elucidation of the mechanism of the current reaction involving transition states (computational calculations) and application of these products to the synthesis of biologically important molecules are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03956.

Experimental procedures and copies of ^1H and ^{13}C NMR spectra for substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

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