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Very Important Publication

Hydrogen Bonding-Assisted Enhancement of the Reaction Rate and Selectivity in the Kinetic Resolution of *d,l*-1,2-Diols with Chiral Nucleophilic Catalysts

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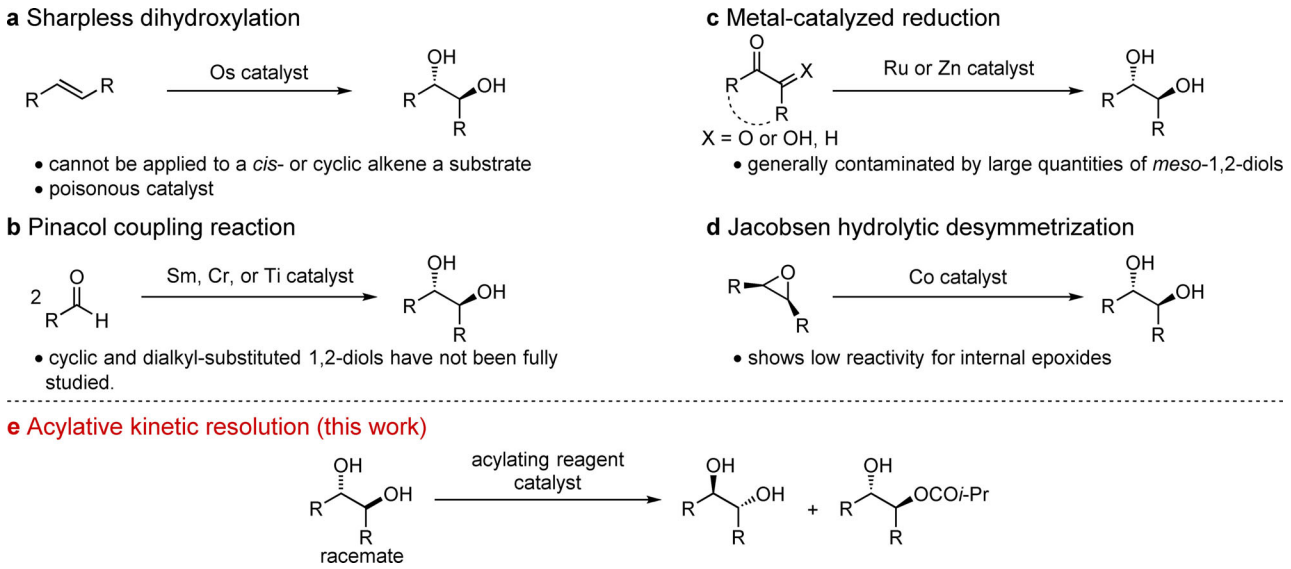
Abstract: An extremely efficient acylative kinetic resolution of *d,l*-1,2-diols in the presence of only 0.5 mol% of binaphthyl-based chiral *N,N*-4-dimethylaminopyridine was developed (selectivity factor of up to 180). Several key experiments revealed that hydrogen bonding between the *tert*-alcohol unit(s) of the catalyst and the 1,2-diol unit of the substrate is critical for accelerating the rate of monoacylation and achieving high enantioselectivity. This catalytic system can be applied to a wide range of substrates involving racemic acyclic and cyclic 1,2-diols with high selectivity factors. The kinetic resolution of *d,l*-hydrobenzoin and *trans*-1,2-cyclohexanediol on a multigram scale (10 g) also proceeded with high selectivity and under moderate reaction conditions: (i) very low catalyst loading (0.1 mol%); (ii) an easily achievable low reaction temperature (0 °C); (iii) high substrate concentration (1.0 M); and (iv) short reaction time (30 min).

Keywords: acylation; chiral nucleophilic catalyst; *N,N*-4-dimethylaminopyridine; *d,l*-1,2-diols; kinetic resolution

Introduction

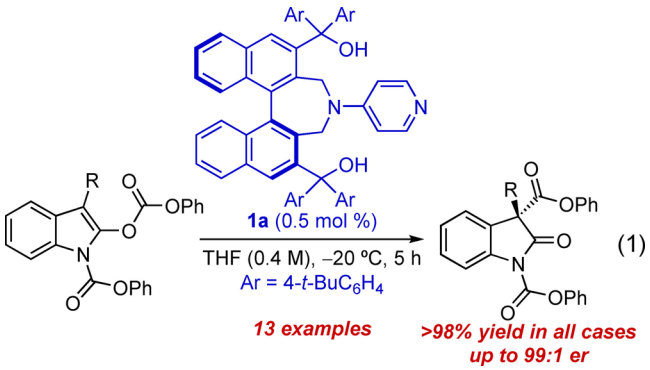
The establishment of a general method for obtaining a pure enantiomer with two or more adjacent chiral carbons is a challenging topic in organic synthesis.[1] An enantiomerically pure 1,2-diol moiety which has two contiguous chiral carbon centers is often found in biologically important molecules,[2] chiral ligands for metal catalysis,[3] auxiliaries,[4] and organocatalysts.[5] A variety of enantioselective methods has been developed to obtain such enantiomerically pure 1,2-diols, including enantioselective Sharpless dihydroxylation,[6] pinacol coupling,[7] reduction of α-hydroxy ketones or 1,2-diketones,[8] and Jacobsen hydrolysis of epoxides[9] (Scheme 1). The enantioselective Sharpless dihydroxylation (Scheme 1a) is a splendid synthetic method that has been frequently used to synthesize chiral building blocks and natural products. However, it has several drawbacks: (i) it requires the use of poisonous osmium(VIII) oxide; (ii) *trans*-alkenes are prepared because the reaction proceeds *via syn*-addition (when a *cis*-alkene is used as a substrate, the reaction gives only *meso*-diol); and (iii) *trans*-1,2-cyclic diols cannot be obtained (*trans*-cycloalkenes have extraordinary ring strain, except for an eight-membered ring). The most satisfactory results with an enantioselective pinacol coupling (Scheme 1b) were reported by Yamamoto,[7d] which also showed high diastereoselectivity and enantioselectivity for a variety of hydrobenzoin-type 1,2-diols, while cyclic and dialkyl-substituted 1,2-diols have not been fully studied (except for 1,2-diol derivatives obtained from cyclohexyl aldehyde). There have been only a few reports on the enantioselective reduction of α-hydroxy ketones or 1,2-diketones to deliver enantiopure 1,2-diols (Scheme 1c), since most metal-catalyzed reductions give the *meso*-isomer as a major product by substrate control.[10] An alternative method for obtaining enantiopure 1,2-diol is the enantioselective hydrolysis of a *meso*-epoxide (Scheme 1d).[9a–f] This reaction is a nearly ideal catalytic enantioselective reaction for obtaining 1,2-diols and offers several advantages (diastereospecific and highly enantioselective, low cost, air- and water-stable, and recyclable catalyst). However, the reaction has mainly been shown to be effective when terminal epoxides are used as substrates (there has been no report of an enantioselective hydrolysis for *cis*-stilbene oxide).[9f] Thus, it cannot cover all the



Scheme 1. Various enantioselective syntheses for 1,2-diols.

various structures of 1,2-diols. On the other hand, racemic acyclic or cyclic 1,2-diols were much easier to access than in the enantioselective variant.[11] Against this background, we were interested in the enantioselective separation of *d,l*-1,2-diol using a chiral catalyst (i.e., kinetic resolution, Scheme 1e), but substrate limitations and over-reactions (e.g., diacylation) sometimes became problematic. Lewis acid-catalyzed acylative kinetic resolutions of diols often proceed with good enantioselectivity, but these reactions needed high catalyst loading (1–5 mol%) and showed unsatisfactory substrate scope (high selectivities were only observed with the use of *d,l*-hydrobenzoin series).[12] Fujimoto,[13] Schreiner,[14] and Yamada[15] have previously reported the efficient kinetic resolution of *d,l*-1,2-diols with organocatalysts. These catalytic systems showed excellent selectivity factors (*s* factors)[16] for a limited number of substrates. For example, Fujimoto's method could be applied to acyclic *d,l*-1,2-diols (*d,l*-hydrobenzoin series), but the use of cyclic and acyclic *d,l*-1,2-diols resulted in moderate *s* factors ($s = 11–20$). In contrast, Schreiner's and Yamada's methods were particularly effective with cyclic *trans*-1,2-diols, but the efficacy of their application to acyclic *d,l*-1,2-diols is unclear. Oriyama reported an organocatalyzed enantioselective acylation of diols with a proline-derived diamine catalyst. It was applicable to the desymmetrization of *meso*-diols with high enantioselectivity, and suppressed undesired over-acylation (required a very low reaction temperature); however, this system was not applied to the kinetic resolution of *d,l*-diols.[17] Accordingly, the development of a general and reliable synthetic method for accessing an array of enantiopure 1,2-diols would be extremely valuable.

Recently, we have developed two classes of chiral *N,N*-4-dimethylaminopyridine (DMAP) derivatives.[18] Among them, binaphthyl-based DMAP derivatives **1a** with hydrogen-bonding substituents at the 3,3′-positions remarkably accelerated the rate of the reaction and showed high enantioselectivity in the Steglich rearrangement of *O*-acylated oxindole derivatives [Eq. (1)].[18d] According to extensive mechanistic studies



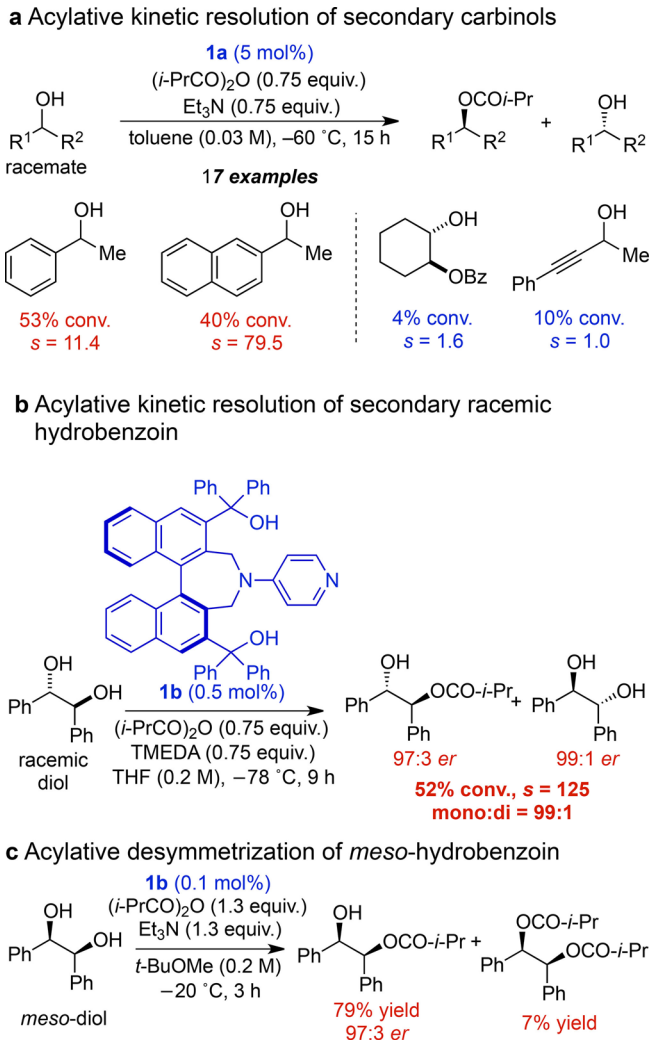
(1)

on the Steglich rearrangement, the reaction system effectively used hydrogen bonding between the catalyst and the counteranion of the *N*-acylpyridinium ion to stabilize the transition state (oxyanion stabilization)[19] to in turn enhance the catalytic activity and enantioselectivity. In this paper, we report the details of the acylative kinetic resolution of acyclic and cyclic *d,l*-1,2-diols using chiral DMAP derivative **1b**, and reveal that hydrogen bonding between **1b** and *d,l*-1,2-diols plays a key role due to enhancement of the reaction rate, enantioselectivity, and mono/di selectivity.

Results and Discussion

In our previous paper, we described the acylative kinetic resolution of racemic carbinols with our catalysts as an example of an *intermolecular* acyl-transfer reaction (Scheme 2a).[18d,e] The reaction proceeded faster than that with the use of DMAP and in moderate to high selectivity, which was achieved by hydrogen bonding between the catalyst and substrate. However, this reaction cannot be applied to compounds other than benzylic carbinols (the use of cyclic or propargylic alcohols gives quite a low selectivity and reaction efficiency), and requires rigorous reaction conditions (high catalyst loading, very low reaction temperature, low substrate concentration). These limitations might be serious problems for kinetic resolutions on a practical scale.

In contrast, our previously reported enantioselective monoacylation of *d,l*- and *meso*-1,2-hydrobenzoins showed excellent results and has the potential

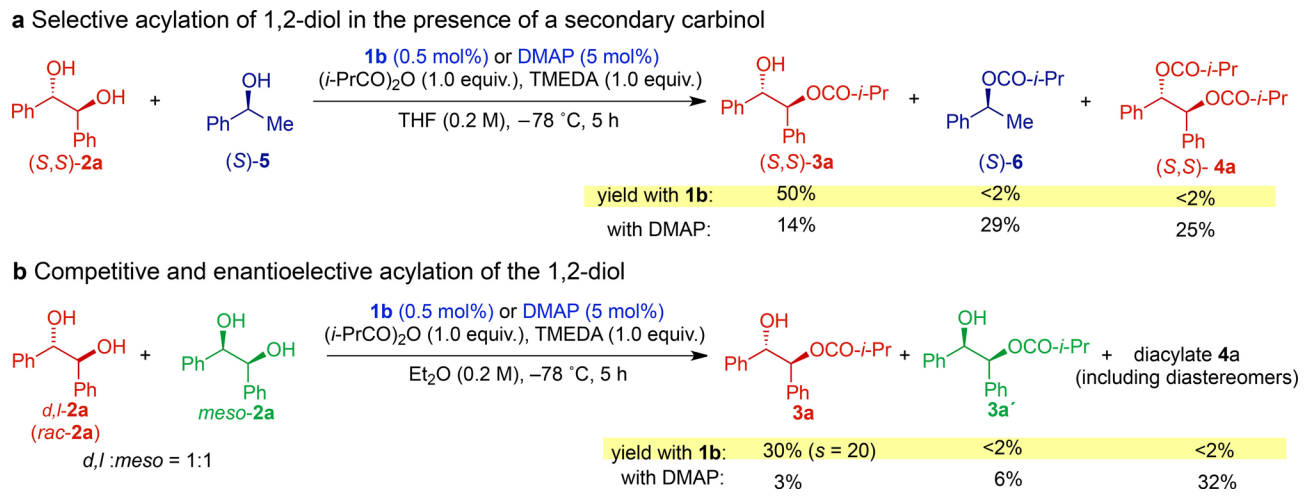


Scheme 2. Enantioselective acylations of various alcohols by our group.

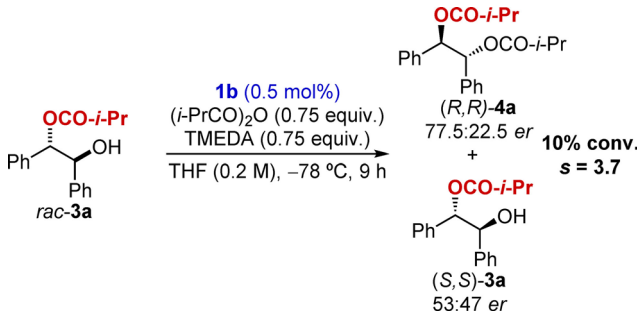
to be an ideal enantioselective reaction system (Scheme 2b and c).[18d] In particular, the acylative kinetic resolution of *d,l*-1,2-diols gave not only excellent *s* factors, but also prevented undesired over-acylation (mono:di = 99:1). These features make this approach advantageous for application at a practical scale.

When a diol is subjected to monoacylation, suppression of the diacylated product (over-acylation) becomes a significant issue. In the ideal kinetic resolution of diols, the monoacylated product should show high selectivity regardless of the *d,l*-1,2-diol structure. In other words, the reaction rate of the first acylation step should be much faster than that of the second acylation step. Our catalyst can evidently recognize the 1,2-diol moiety and accelerate the first monoacylation step. We performed a competitive experiment with (*S,S*)-**2a** and (*S*)-**5** (the fast-reacting enantiomer in the kinetic resolution of racemic alcohol **2a** or **5** with **1b**)[18e] in the presence of 0.5 mol% catalyst **1b**, 1.0 equiv. of isobutyric anhydride, and 1.0 equiv. of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF (0.2 M) at −78 °C for 5 h (Scheme 3a). Although a hydroxy group of (*S,S*)-**2a** was thought to be more sterically hindered than that of (*S*)-**5**, only the selective monoacylation of (*S,S*)-**2a** proceeded to afford (*S,S*)-**3a**, and (*S*)-**6** was not detected. For comparison, we performed the same reaction with 5 mol% of DMAP.[20] Acylation of (*S,S*)-**2a** and (*S*)-**5** proceeded to give a mixture of (*S,S*)-**3a** (14% yield) and (*S*)-**6** (29% yield). Furthermore, a significant amount of diacylate (*S,S*)-**4a** was obtained (25% yield). This control experiment strongly suggested that monoacylation of 1,2-diol using **1b** proceeded much faster than that of a monool. Surprisingly, catalyst **1b** can adequately recognize not only a diol unit but also its diastereomers (Scheme 3b). Although the acylation of two diastereomers, *d,l*-**2a** and *meso*-**2a** (*d,l*:*meso* = 1:1), with 5 mol% of DMAP under slightly modified reaction conditions [1.0 equiv. of isobutyric anhydride, 1.0 equiv. of TMEDA in Et_2O (0.2 M)[21] for 5 h] gave almost the same ratio of two diastereomers of monoacylate (**3a** and **3a'**) in quite low yields and a considerable amount of diacylates **4a**, the use of **1b** only gave **3a** (30% yield) with high enantioselectivity ($s = 20$) as a sole product. It is quite difficult to separate a 1:1 mixture of *d,l*- and *meso*-1,2-diols. Nevertheless, this catalytic process with **1b** allows the reaction with *d,l*-diol selectively in the presence of structurally similar *meso*-1,2-diol.

We also investigated the subsequent kinetic resolution step[22] (Scheme 4). Under the optimized reaction conditions for the kinetic resolution of *d,l*-1,2-diols (see the Supporting Information, Tables S1–5), racemic monoacylate **3a** was barely converted to (*R,R*)-**4a** with very low *s* factor (10% conversion, $s = 3.7$). As a result, the minor enantiomer in the first acylative kinetic resolution step [(*R,R*)-**3a**] was consumed in the



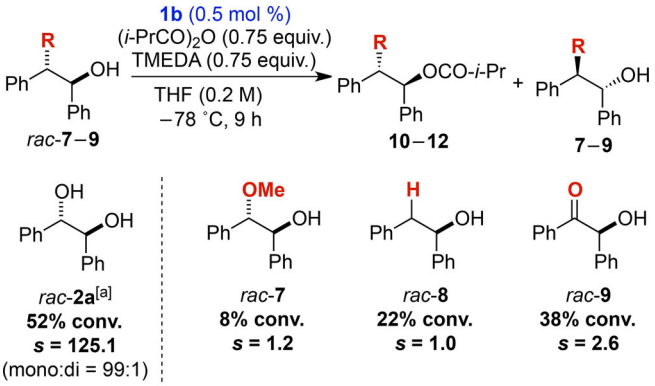
Scheme 3. Catalytic accelerating effect of *d,l*-1,2-diol over monool and *meso*-diol. The reactions were performed on a 0.15 mmol scale under an argon atmosphere. Conversions (±2%) and mono/di ratios were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures. Product yields were determined by ^{1}H NMR spectroscopy using 2-methoxynaphthalene as an internal standard. The *er* values (±1%) were determined by chiral HPLC analysis of the unpurified mixtures. The *s* factors were calculated using Kagan's equation.[16]



Scheme 4. Investigation of the subsequent kinetic resolution step. The reaction was performed on a 0.070 mmol scale under an argon atmosphere. Conversions (±2%) were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures. The *er* values (±1%) were determined by chiral HPLC analysis of the unpurified mixtures. The *s* factors were calculated using Kagan's equation.[16]

second acylation step. This result showed that the enantiomeric ratio of monoacylate **3a** was slightly amplified by the second acylation step, but this subsequent reaction proceeded very slowly. This control experiment clearly showed that the enantiomeric ratio of monoacylate **3a** was determined by the first acylation step, and catalyst **1b** accelerated the rate of the first acylation (i.e., monoacylation of diol **2a** *vs.* acylation of monool **3a**, Scheme 2b *vs.* Scheme 4). This observation supports the notion that catalyst **1b** only gives a monoacylate with high selectivity.

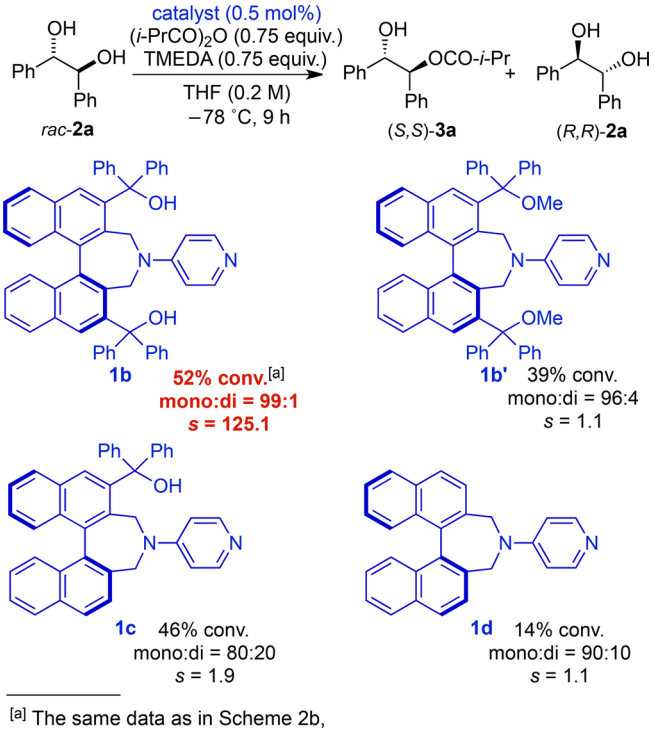
We next investigated in more detail the effect of hydrogen bonding between the hydroxy groups of the catalyst and two hydroxy groups of the substrate by several control experiments. We focused on the structure of the substrate, and performed kinetic resolution for various control substrates (Scheme 5). These experiments clearly indicated that racemic substrates require two adjacent free hydroxy groups to achieve a high *s* factor and conversion. For example, the use of racemic monomethyl-capped 1,2-diol **7**, benzyl phenyl carbinol **8**, and benzoin **9** as substrates gave quite low *s* factors (s = 1.0–2.6) and conversions (8–38% conv.) under the optimal reaction conditions. We presumed that the catalyst **1b** recognizes two adjacent hydroxy groups on the substrate to accelerate the reaction and discriminate between the two enantiomers of the substrate.



[a] The same data as in Scheme 2b.

Scheme 5. Control experiments with various substrates. The reactions were performed on a 0.3 mmol scale under an argon atmosphere. Conversions (±2%) were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures. The *er* values (±1%) were determined by chiral HPLC analysis of the unpurified mixtures. The *s* factors were calculated using Kagan's equation.[16]

Next, we considered the catalyst structure (Scheme 6). The acylative kinetic resolution of **2a** was carried out using four catalyst analogues, including the optimal catalyst **1b**, methyl ether analogue **1b′**, C_1-symmetrical analogue **1c**, and analogue **1d** without *tert*-alcohol units. The use of catalyst **1b** gave an excellent *s* factor and selectivity of monoacylation, whereas catalyst **1b′** gave quite a low *s* factor (s = 125.1 with **1b** *vs.* s = 1.1 with **1b′**). Similarly, the use of catalyst **1c** resulted in a low *s* factor and a significant amount of diacylate was obtained (s = 1.9 and mono:di = 80:20). To our great surprise, catalyst **1d** gave the lowest catalytic activity and almost no enantioselectivity (s = 1.1). These results indicate that the catalyst must have two hydroxy units, and is effective in the enantioselective monoacylation of the *d,l*-1,2-diol series.

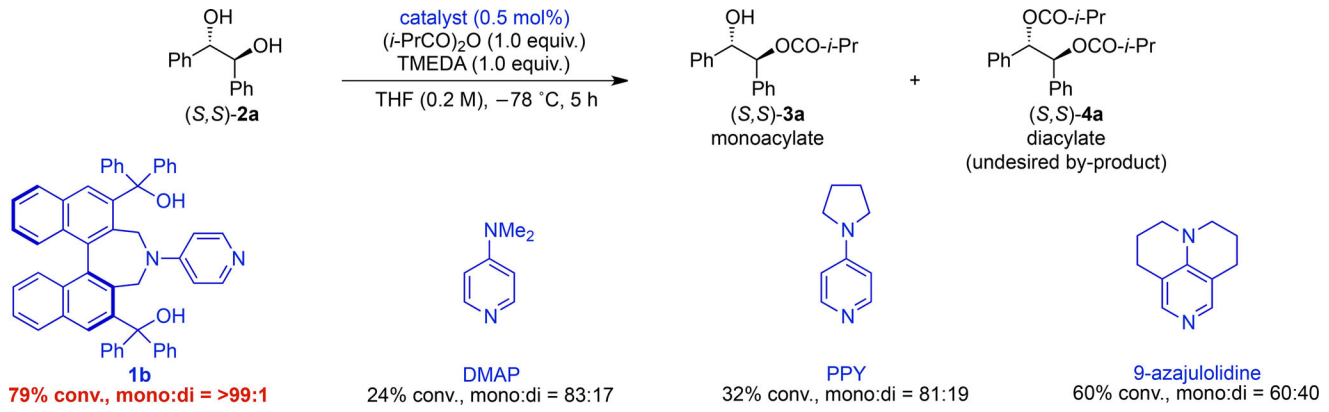


[a] The same data as in Scheme 2b,

Scheme 6. Control experiments focused on hydroxy groups on the catalyst. The reactions were performed on a 0.3 or 0.6 mmol scale under an argon atmosphere. Conversions (±2%) and mono/di ratios were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures. The *er* values (±1%) were determined by chiral HPLC analysis of the unpurified mixtures. The *s* factors were calculated using Kagan's equation.[16]

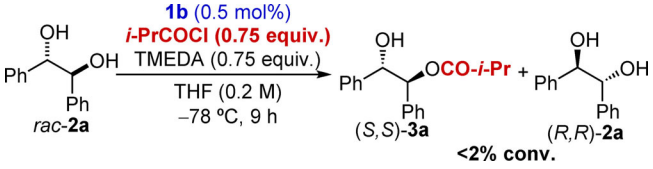
To examine the enhancement of the reaction rate by catalyst **1b**, we next examined the catalytic activity of this reaction system by comparison with commercially available pyridine-based nucleophilic catalysts (Scheme 7). With the use of 0.5 mol% of catalyst **1b**, the monoacylation of (*S,S*)-**2a**, which is the fast-reacting enantiomer (if we exclude the process of kinetic resolution), proceeded in 79% conversion after 5 h and perfectly suppressed over-acylation. The use of 0.5 mol% of DMAP and PPY gave low conversions (24% and 32%, respectively) with a considerable amount of diacylate (*S,S*)-**4a** under the identical reaction conditions. Despite the stoichiometric reaction conditions [1.0 equiv. of $(i\text{-PrCO})_2O$], a large amount of undesirable diacylate was obtained by the use of 9-azajulolidine, which is known to be a highly active pyridine-based nucleophilic catalyst[23] (60% conv., mono:di = 60:40). These results clearly showed that catalyst **1b** selectively accelerated the monoacylation step.

The results of several control experiments regarding the effect of hydrogen bonding (Scheme 4, Scheme 5, and Scheme 6) strongly support the notion that hydroxy groups on **1b** and two hydroxy groups on the substrate play an important role in the rate acceleration and high enantioselectivity. Furthermore, in our previous paper,[18e] we stated that the leaving group of an acylating reagent strongly affected the



Scheme 7. Comparison of various nucleophilic catalysts in the monoacylation of (*S,S*)-**2a**. The reactions were performed on a 0.30 mmol scale under an argon atmosphere. Conversions (±2%) and mono/di ratios were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures.

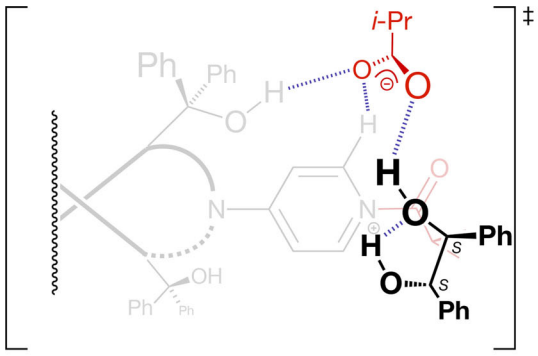
enantioselectivity in the acylative kinetic resolution of a secondary carbinol. We also investigated the benefits of this acylating reagent in this reaction (Scheme 8). The use of 0.75 equiv. of isobutyric chloride instead of isobutyric anhydride under otherwise optimal reaction conditions resulted in almost no conversion with a very low enantioselectivity[24] (<2% conv.). This implies that the leaving group of acylating reagents ($^{-}$OCO-*i*-Pr *vs.* $^{-}$Cl), which comprise the counteranion of *N*-acylpyridinium ion in the transition state, strongly affects the reactivity and enantioselectivity in this kinetic resolution process.[18e,25]



Scheme 8. Investigation of the effect of an acylating reagent. The reactions were performed on a 0.300 mmol scale under an argon atmosphere. Conversions (±2%) were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures.

To summarize these observations, and after considering the explanations offered by Spivey,[26] Zipse,[27] and Kawabata,[28] we speculated that the transition state involves several hydrogen bonding networks among the *tert*-alcohol unit of the catalyst, the *ortho*-hydrogen of the pyridine moiety, the carboxylate anion, and a hydroxy group of the substrate (Figure 1). After formation of the appropriate hydrogen bonding networks in the favored transition state, the more acidic proton of the hydroxy group (activated by a neighboring hydroxy group through *intramolecular* hydrogen bonding) of the substrate is deprotonated by the closest carboxylate anion fixed by the catalyst, and thus another hydroxy group is acylated to give (*S*,*S*)-**3a**. In the disfavored transition state, steric repulsion between the phenyl group (Ph drawn as blue in Figure 1) and the isopropyl group of acylating agent would be dominant. These transition states may explain all of the observations obtained in the control experiments at the present stage. Although computational calculations to elucidate the reaction mechanism and the high selectivity in the transformations are currently conducted, the enormous numbers of possibilities of the alignments prevent us from drawing a conclusion. These results will be reported elsewhere. The hydrogen bonding interactions in acylative kinetic resolution were already studied in detail by Miller (H-bonds between a peptide-based imidazole catalyst and a vicinal amino alcohol[29] or carbinol[30]) and Seidel (H-bonds between a chiral thiourea-DMAP combination catalyst and a vicinal amine).[31] The present study also clearly demonstrates the utility of the hydrogen bonding network in designing enantioselective acyl-transfer reactions.

The kinetic resolution of various 1,2-diols including acyclic and cyclic variants was examined under the optimal reaction conditions (Scheme 9). We initially focused on hydrobenzoin derivatives **2a**–**j** as a substrate (Scheme 9a). The reactions of **2a**–**j** proceeded with good conversions and excellent *s* factors (32–55% conv., $s = 54.0$–180.3, except for **2b**). In all cases, the monoacylated product was obtained with high selectivity (mono:di = >96:4, except for **2b**). Diol **2b**, which contained 2-naphthyl groups, showed a somewhat low selectivity of monoacylation and a low *s* factor (mono:di = 82:12, $s = 6.7$). In contrast, structurally similar diol **2c**, which contains 1-naphthyl groups, showed an excellent ratio of monoacylation and an excellent *s* factor (mono:di = 99:1, $s = 180.3$). This catalytic system could also achieve the separation of enantiomers from *para*-substituted hydrobenzoin derivatives **2d**–**g** with excellent *s* factors even though these molecules have diverse substituents such as electron-donating groups, electron-withdrawing



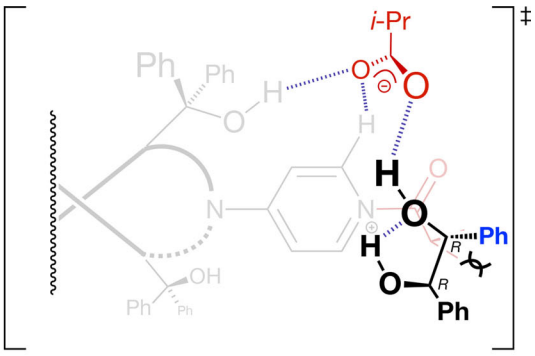
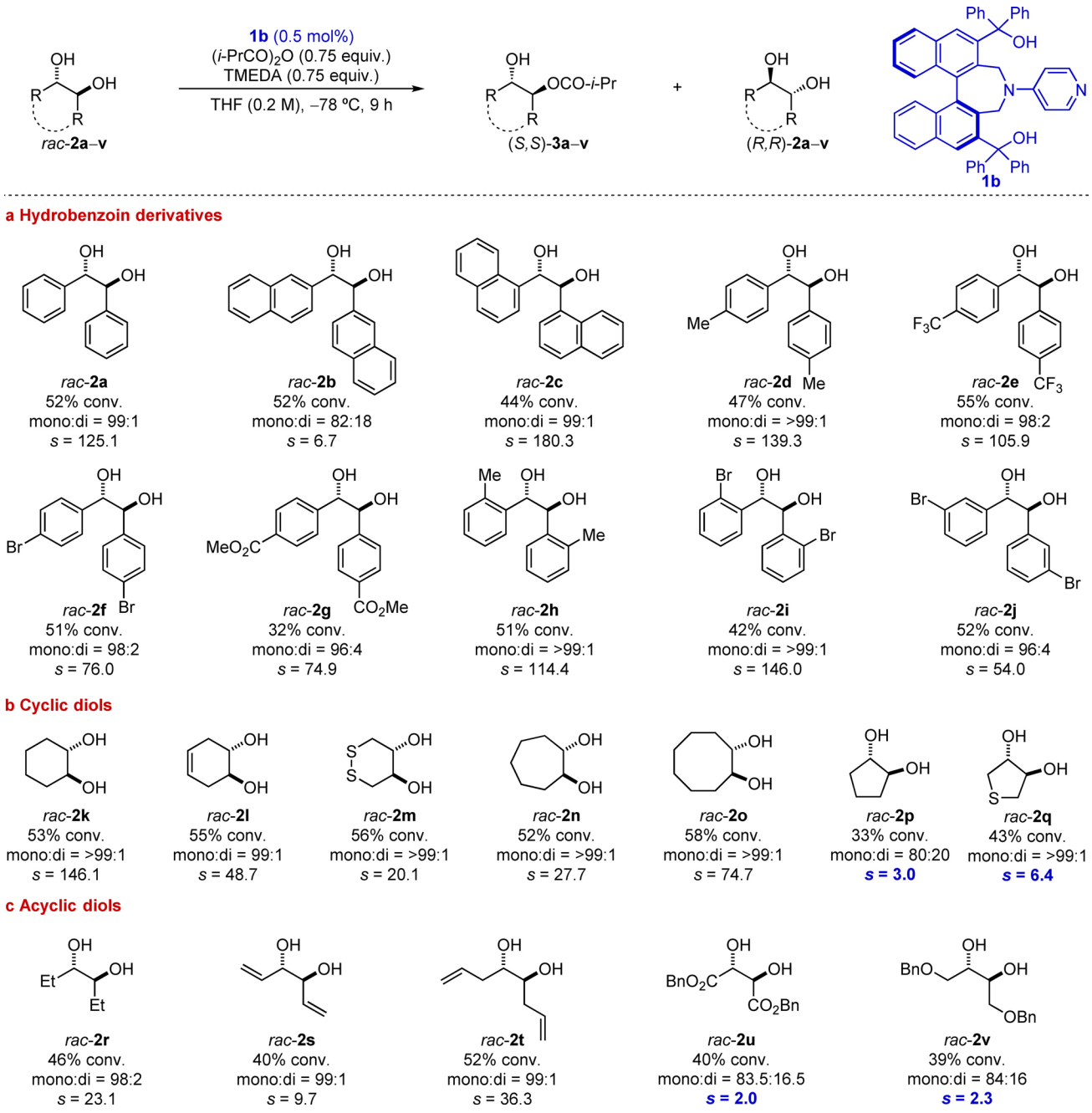


Figure 1. Postulated transition states.



Scheme 9. Substrate scope. The reactions were performed on a 0.30 or 0.60 mmol scale under an argon atmosphere (see the Supporting Information for details). Conversions (±2%) and mono/di ratios were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures. The *er* values (±1%) were determined by chiral HPLC analysis of the unpurified mixtures. The *s* factors were calculated using Kagan's equation.[16]

groups, or hydrogen bond-accepting groups (s = 74.9–139.3). Also, *ortho*- or *meta*-substituted hydrobenzoin derivatives **2h–j** could be resolved with high *s* factors (s = 54.0–146.0).

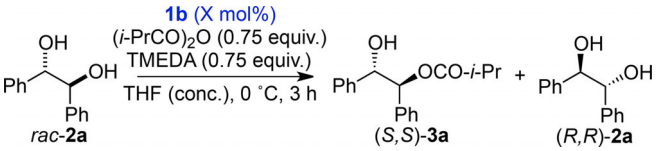
Additionally, this kinetic resolution could be applied to cyclic 1,2-diols in good conversions and with high *s* factors (Scheme 9b). Remarkably, *trans*-cyclohexane-1,2-diol **2k** and its structurally similar variants **2l** and **2m** showed high to excellent *s* factors under the optimal reaction conditions (s 146.1, 48.7, and 20.1, respectively). Diols containing seven-membered **2n** and eight-membered rings **2o** could also be resolved with high *s* factors (s = 27.7 and 74.7, respectively). Unfortunately, this catalytic system could not

be applied to a five-membered ring system (**2p**: $s=3.0$, **2q**: $s=6.4$).

Notably, acyclic diols with alkyl, vinyl, or allyl substituents **2r**–**t** could be resolved under these catalytic systems with moderate to excellent *s* factors ($s=9.7$–36.3, Scheme 9c). It was difficult to resolve these substrates under the kinetic resolution conditions, perhaps because the conformationally flexible nature of acyclic *d,l*-1,2-diol would result in undesirable conformations in the transition state. Thus, there have been only a few reports on the acylative kinetic resolution of acyclic *d,l*-1,2-diols with alkyl substituents with moderate *s* factors.[13,14c] On the other hand, the reactions of acyclic diols **2u** and **2v** with neighboring functional groups resulted in low *s* factors and poor selectivity of monoacylation. While there are no clear explanations for these results, we considered that neighboring functional groups might inhibit the hydrogen bonding between the catalyst and the substrate (Figure 1). To the best of our knowledge, this is the first example of a case where a very small amount of DMAP-based chiral nucleophilic catalyst (0.5 mol% of **1b**) can be applied to various *d,l*-1,2-diols involving acyclic and cyclic substrates with good to excellent *s* factors.

In principle, a practical scale reaction should offer a very low catalyst loading, a higher substrate concentration (to reduce the amount of solvent needed), a high *s* factor ($s>20$),[32] and an easily achievable low reaction temperature. As previously mentioned, catalyst **1b** combined high catalytic activity and excellent chiral recognition for *d,l*-1,2-diols [0.5 mol% of **1b**, THF (0.2 M), −78 °C, 9 h, Scheme 9]. Hence, we reexamined the reaction conditions for a practical scale reaction with maintenance of a synthetically useful *s*-factor ($s>20$).[32] We began by reducing the catalyst loading in THF (0.1 M) at 0 °C for 3 h (Table 1, entries 1–3). The results with 0.1 mol% of catalyst **1b** showed good conversion and a good *s* factor (47% conv.; $s=26.3$; entry 2), and the reaction with 0.05 mol% of catalyst **1b** also proceeded smoothly while maintaining a satisfactory *s* factor (41% conv.; $s=21.6$; entry 3). Since the use of 0.1 mol% of **1b** was thought to be optimal with respect to both conversion and *s* factor, we next performed screening reactions regarding the substrate concentration and reaction time (entries 4–6). A higher substrate concentration (0.5 and 1.0 M) did not significantly affect the *s* factor (entries 4 and 5). Finally, the reaction within a shorter time (0.5 h) under otherwise identical conditions gave monoacylate **3a** and unreacted enantio-enriched **2a** in 52% conversion with a high *s* factor ($s=21.0$, entry 6). For a practical scale reaction, the optimized reaction conditions were determined to be 0.1 mol% of catalyst **1b**, 0.75 equiv. of isobutyric anhydride, 0.75 equiv. of TMEDA in THF (1.0 M) at 0 °C for 0.5 h.

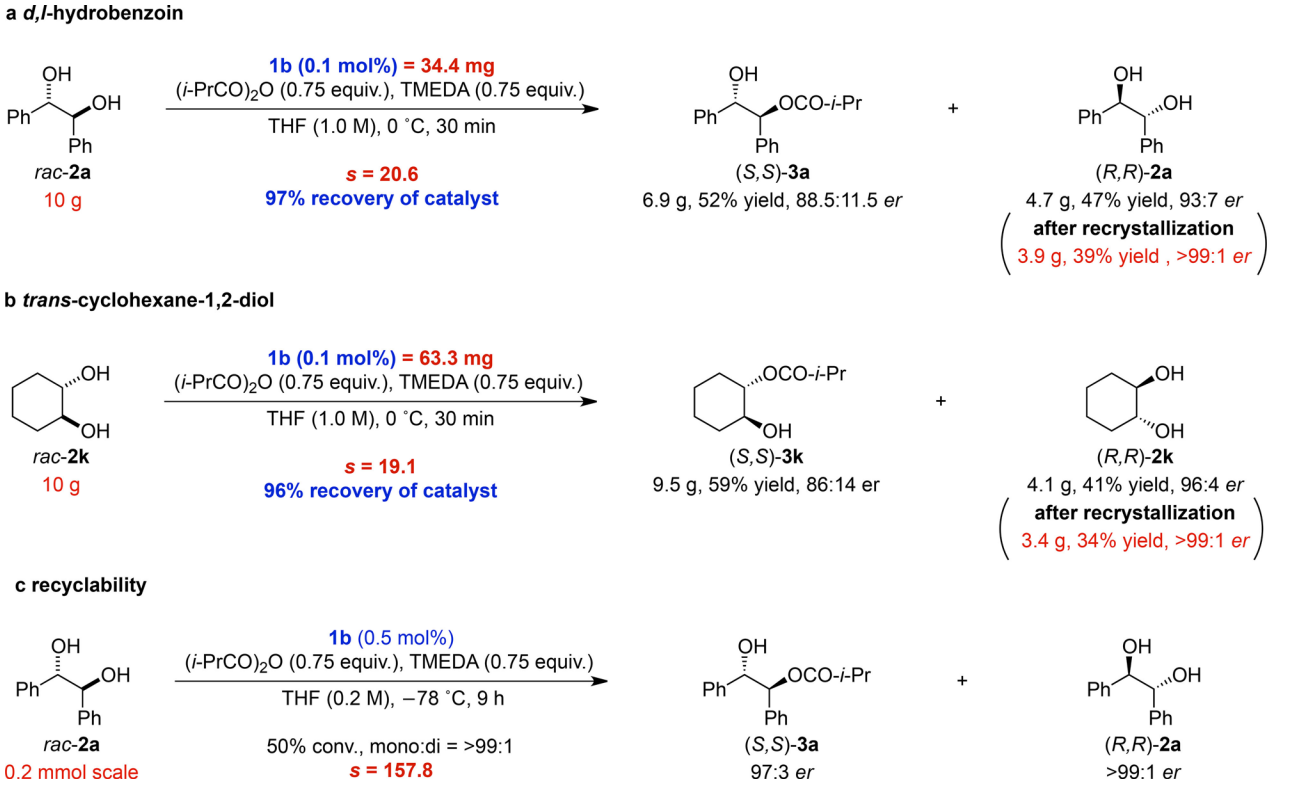
Table 1. Exploration of the conditions for a practical scale reaction.[a,b]



Entry	X [mol%]	Conc. [M]	Conv. [%][c]	*er* of **3a**[d]	*er* of **2a**[d]	*s*[e]
1	0.5	0.1	56	88:12	99:1	31.9
2	0.1	0.1	47	91:9	91:9	26.3
3	0.05	0.1	41	91.5:8.5	84:16	21.6
4	0.1	0.5	58	85:15	99:1	25.9
5	0.1	1.0	56	86:14	97:3	21.6
6[f]	0.1	1.0	52	88:12	93:7	21.0

[a] Performed on a 0.1–0.4 mmol scale under an argon atmosphere.
[b] Mono/di ratios were >98:2 in all cases.
[c] Conversions (±2%) and mono/di ratios were determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures.
[d] The *er* values (±1%) were determined by chiral HPLC analysis of the unpurified mixtures.
[e] The *s* factors were calculated using Kagan's equation.[16]
[f] Stirred for 0.5 h.

With the optimized reaction conditions for a practical scale reaction in hand, we carried out the kinetic resolution of two different substrates on a multigram scale (Scheme 10a and b). The use of 10 grams of racemic hydrobenzoin **2a** under the practical scale conditions (only 0.1 mol% of **1b** = 34.4 mg was used) gave the monoacylate **3a** in 52% yield with 88.5:11.5 *er* along with the recovery of **2a** in 47% yield with 93:7 *er* (purified by column chromatography on silica gel). Recrystallization of recovered **2a** improved the enantiomeric ratio (>99:1 *er*) in 39% yield. Furthermore, catalyst **1b** was recovered in 97% yield. We also conducted a 10 gram-scale reaction with *trans*-cyclohexane-1,2-diol **2k** to give monoacylate **3k** in 59% yield with 86:14 *er* along with the recovery of **2k** in 34% yield with >99:1 *er* (after chromatographic separation and recrystallization), and recovered catalyst **1b** in 96% yield. Both reactions clearly demonstrated the near-perfect selectivity of monoacylation (mono:di = >99:1) and synthetically acceptable *s* factors[32] ($s=20.6$ and 19.1, respectively) even when the reaction was carried out on a multigram scale reaction. Furthermore, the recyclability of **1b** was confirmed by performing the kinetic resolution of racemic hydrobenzoin **2a** (0.3 mmol scale) under the optimal reaction conditions, which showed almost the same *s* factor ($s=157.8$), selectivity of the monoacylate, and conversion (Scheme 10c *vs.* Scheme 9).



Scheme 10. Kinetic resolution on a multigram scale and recyclability. The yields (±2%) refer to isolated material after silica gel chromatography. The *er* values (±1%) were determined by chiral HPLC analysis of the unpurified mixtures. The *s* factors were calculated using Kagan's equation.[16]

Conclusions

We have developed a highly accelerated kinetic resolution of diverse *d*,*l*-1,2-diols with a small amount of high-performance chiral DMAP derivatives (0.1–0.5 mol%). Several key experiments revealed that such transformations were due to a hydrogen bonding network among *tert*-alcohol units and the *ortho*-hydrogen of a pyridine moiety of the catalyst, the carboxylate anion generated by the acylating reagent, and the 1,2-diol moiety of the substrate. The current catalytic system allows the use of hydrobenzoin derivatives with various functional groups, *trans*-1,2-cyclic diols, and acyclic dialkyl-substituted 1,2-diols with an excellent selectivity of monoacylation and high *s* factors (up to $s = 180.3$, 22 examples). The multigram scale reaction using less than 0.1 mol% of the catalyst under the milder reaction conditions also proceeded smoothly with an excellent selectivity of monoacylation and synthetically acceptable *s* factors (**2a**: $s = 20.6$ and **2k**: 19.1, respectively) under reoptimized conditions for the practical scale. Furthermore, the catalyst could be easily recovered in >96% yield and recycled without a loss of catalytic activity or enantioselectivity. We believe that the present method to access highly enantio-enriched 1,2-diols with catalyst **1b** is extremely valuable from a viewpoint of process chemistry for pharmaceutical production. Further applications of this approach for the syntheses of biologically important molecules are now in progress.

Experimental Section

General Procedure for Acylative Kinetic Resolution with 1b

In a dry screw-top test tube, to a solution of substrate (1.0 equiv.), TMEDA (0.75 equiv.), and stock solution of **1b** (0.5 mol%) in THF (0.200 M) was added $(i\text{-PrCO})_2O$ (0.75 equiv.) at −78 °C. The reaction mixture was stirred for 9 h at −78 °C, and then MeOH (5 mL) was added to the reaction vessel at −78 °C. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to another flask using Et_2O to wash the reaction vessel and concentrated under vacuum. The residue was passed through a short pad of silica gel [eluent: hexane/EtOAc or hexane/Et_2O adjusted $R_f = 0.5$ (unreacted substrate)] to give the crude mixture. The conversion and ratio of mono/diacylate were determined by ^1H NMR analysis of the crude mixture. The enantiomeric ratios of monoacylate and recovered substrate were determined by chiral HPLC analysis of the crude mixture. In the case of using a substrate without chromophores, benzoylation of the isolated monoacylate and recovered substrate was conducted. The mono-

benzoate and dibenzoate were used to determine of the enantiomeric ratios by chiral HPLC analysis.

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[20] The reactivity of DMAP is low compared with **1b**, hence 5 mol% of DMAP was used in these control experiments.

[21] Selectivity and product distribution considerably depended on the solvent, probably because the hydrogen bonding networks in the transition state were affected by the solvent. On the use of THF as solvent with **1b**, almost the same amounts of **3a** and **3a′** were obtained. Detailed experimental results are recorded in the Supporting Information.

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