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Enantioselective Desymmetrization of 1,3-Diols by a Chiral DMAP Derivative

Hiroki Mandai,* Kosuke Ashihara, Koichi Mitsudo, and Seiji Suga*

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Enantioselective Desymmetrization of 1,3-Diols by a Chiral DMAP Derivative

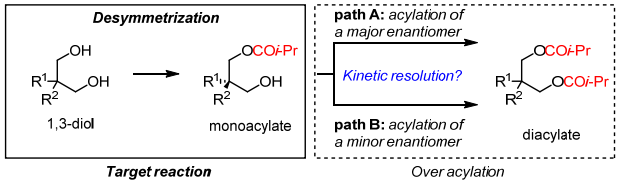
Hiroki Mandai,* Kosuke Ashihara, Koichi Mitsudo, and Seiji Suga*
Division of Applied Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan

E-mail: mandai@cc.okayama-u.ac.jp (HM), suga@cc.okayama-u.ac.jp (SS)

We developed an enantioselective desymmetrization of 1,3-diols by a chiral *N*,*N*-dimethyl-4-aminopyridine (DMAP) derivative containing a 1,1′-binaphthyl with *tert*-alcohol units. The reactions required only 0.1 mol % of catalyst and showed moderate to high chemoselectivity (monoacylation vs. diacylation) and enantioselectivity (14 examples, up to 95:5 er). Several control experiments revealed that diol units in both the substrate and the catalyst are important to achieve high enantioselectivity.

Keywords: chiral DMAP derivative, desymmetrization, 1,3-diol

Enantioselective desymmetrization of prochiral substrates is a promising transformation to obtain optically active compounds in organic synthesis.[1] These processes provide an enantiomer-enriched product in one-step in a theoretical yield of up to 100% with high atom efficiency. Among them, acylative desymmetrization of 2-substituted 1,3-propanediols is quite challenging because the pro-stereogenic center is far from the reaction site, and it is difficult to differentiate enantiotopic alcohols (Scheme 1; target reaction in the solid-line box). In addition, after the first monoacylation, the desired monoacylated product still has a reactive primary alcohol, which would easily be further acylated to give undesired diacylate (Scheme 1; over-acylation in the dotted-line box). A more important issue in this transformation is that the yield and enantiomeric ratio (er) of monoacylate are significantly affected by the second acylation through **path A** (acylation of a major enantiomer of monoacylate) or **B** (acylation of a minor enantiomer of monoacylate). Various methods of desymmetrization of 2- or 2,2-(di)substituted 1,3-diols have been reported using enzymes,[2] metal-[3], or organocatalysts (e.g., silylation,[4] acylation[5], acetalyzation,[6] and acetal cleavage[7]). However, especially in acylative desymmetrization approach with organocatalysts, the chemoselectivity (monoacylation vs. diacylation) and enantioselectivities of monoacylates need further improvements.



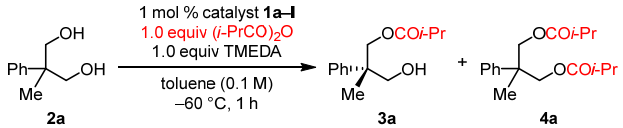
Scheme 1. General scheme for the acylative desymmetrization of 1,3-diol.

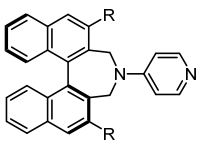
Thus, the development of a high-performance enantioselective catalyst, which accelerates the rate of the first acylation much faster than that of the second acylation, is highly desirable.

Our research interests involve the development of chiral nucleophilic catalysts[8] for acyl transfer reactions.[9] Recently, we developed extremely active and enantioselective pyridine-based catalysts on the basis of a hydrogen bonding strategy.[8e-h] These catalysts efficiently promoted various enantioselective acyl transfer reactions such as Steglich-type rearrangements of *O*-acylated oxindole derivatives,[8e] kinetic resolution of carbinols[8f] and *d*,*l*-1,2-diols,[8g] desymmetrization of *meso*-1,2-diols,[8h] and dynamic kinetic resolution of azlactone.[10] Herein, we report the enantioselective desymmetrization of various 2- or 2,2-(di)substituted 1,3-diols in the presence of pyridine-based catalyst developed by our group. Furthermore, several control experiments were also carried out to better understand these processes.

Initially, the enantioselective acylative desymmetrization of 1,3-diol **2a** was carried out with selected catalysts **1a**–**l** (Table 1). The following reaction conditions were selected after extensive screening of various parameters:[11] 1 mol % of chiral DMAP derivatives **1a**–**l**, 1.0 equiv. of isobutyric anhydride, and 1.0 equiv. of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in toluene at –60 ºC for 1 h.

Table 1. Catalyst screening for the desymmetrization of **2a**[a]





1a: R = C(OH)Ph$_2$
1b: R = C(OH)(3-MeO-C$_6$H$_4$)$_2$
1c: R = C(OH)(4-MeO-C$_6$H$_4$)$_2$
1d: R = C(OH)(4-Me-C$_6$H$_4$)$_2$
1e: R = C(OH)(4-Ph-C$_6$H$_4$)$_2$
1f : R = C(OH)(4-*t*-Bu-C$_6$H$_4$)$_2$
1g: R = C(OH)(3,5-(MeO)$_2$-C$_6$H$_3$)$_2$
1h: R = C(OH)(3,5-(*t*-Bu)$_2$-C$_6$H$_3$)$_2$
1i: R = C(OH)(3,5-(*t*-Bu)$_2$-4-MeO-C$_6$H$_2$)$_2$
1j: R = CO$_2$Et
1k: R = CO$_2$H (HCl salt)
1l: R = CONHPh

entry	catalyst	**3a** (%)[b]	**4a** (%)[b]	**2a** (%)[b]	er of **3a**[c]
1	**1a**	67	3	30	93:7
2	**1b**	48	3	46	92:8
3	**1c**	45	<2	52	93:7

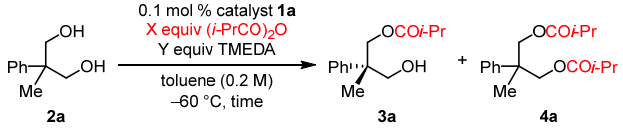
4	**1d**	44	2	55	91:9
5	**1e**	58	4	38	91:9
6	**1f**	45	5	49	90:10
7	**1g**	47	4	50	91:9
8	**1h**	46	4	49	85:15
9	**1i**	32	14	53	83:17
10	**1j**	16	3	83	52:48
11	**1k**	13	<2	87	61:39
12	**1l**	14	2	86	45:55

[a] Reactions were performed on a 0.1 mmol scale in toluene (0.1 M) under an argon atmosphere. [b] NMR yields were determined by ^{1}H NMR analysis using benzylbenzoate as an internal standard. [c] Enantiomer ratios were determined by HPLC analysis using CHIRALCEL OD-H.

The use of catalyst **1a** with *tert*-alcohol units having a diphenyl group gave monoacylate **3a** in moderate yield with good enantioselectivity (entry 1, 67% NMR yield of **3a**; 93:7 er), and undesired diacylate **4a** was almost completely suppressed (3% NMR yield). The use of catalyst **1b–i** with *tert*-alcohol units having an aryl group with various substituents did not dramatically improve the yield of **3a** or the enantioselectivity (entries 2–9: 32–58% yield of **2a**; up to 93:7 er). On the other hand, the reaction with catalyst **1j–l** having carboxylic acid derivatives (-CO_2Et, -CO_2H, or -CONHPh) was slow compared to that with catalysts **1a–i** having *tert*-alcohol units, and the enantioselectivities of **3a** were also moderate (entries 10–12, up to 61:39 er). According to these results, catalyst **1a** was selected as an optimal catalyst for further screening of the reaction conditions.

After further optimization of the reaction conditions (0.1 mol % of **1a**, 1.2 equiv of acylating reagent and TMEDA, and 0.2 M in toluene),[12] we next examined the reaction time and molar ratios of both acylating reagent and TMEDA, which could be a key to suppressing diacylation. (Table 2). When the reaction time was increased from 1 h to 3–12 h (entry 1 vs. entries 2–5), the yield of monoacylate **3a** was improved to a satisfactory level (entry 4, up to 87% NMR yield). However, a small amount of undesired diacylate **4a** (5% NMR yield) and unreacted **2a** (9% NMR yield) were still present even when the reaction time was increased to 12 h (entry 5). Thus, the amount of acylating reagent was reduced to 1.1 equiv to prevent such undesired diacylation, and the amount of TMEDA was increased to accelerate the first acylation (entries 6–9). As expected, when 1.1 equiv of acylating reagent and 1.5 equiv of TMEDA were used, most of **2a** was consumed (1% recovery) and the desired monoacylate **3a** was obtained in 91% NMR yield with 93.5:6.5 er along with a small amount of diacylate **4a** (entry 9). Accordingly, we identified the optimal reaction conditions as follows: 0.1 mol % of **1a**, 1.1 equiv of isobutyric anhydride, and 1.5 equiv of TMEDA in toluene (0.2 M) at –60 °C for 7 h.

Table 2. Effects of reaction time and the molar ratio of acylating reagent and TMEDA[a]



entry	X (equiv)	Y (equiv)	time (h)	**3a** (%)[b]	**4a** (%)[b]	**2a** (%)[b]	er of **3a**[c]
1	1.2	1.2	1	60	2	38	93.5:6.5
2	1.2	1.2	3	79	5	16	92:8
3	1.2	1.2	5	85	5	10	93:7
4	1.2	1.2	7	87	8	5	94:6
5	1.2	1.2	12	84	5	9	93.5:6.5
6	1.1	1.1	7	82	6	11	94:6
7	1.1	1.2	7	90	7	3	94:6
8	1.1	1.3	7	87	5	8	94:6
9	1.1	1.5	7	91	6	1	93.5:6.5

[a] Reactions were performed on a 0.2 mmol scale in toluene (0.2 M) under an argon atmosphere. [b] NMR yields were determined by ^{1}H NMR analysis using benzylbenzoate as an internal standard. [c] Enantiomer ratios were determined by HPLC analysis using CHIRALCEL OD-H.

Next, the desymmetrization of an array of 1,3-diols was examined under the optimal conditions (Figure 1). The reaction of **2a** (R^1 = Ph, R^2 = Me) afforded monoacylate **3a** in high yield with high enantioselectivity (90% isolated yield with 94:6 er) along with 7% of diacylate **4a** and 3% recovery of **2a**. At the same time, we confirmed the possibility of racemization[3e, 13] of enantio-enriched monoacylate **3a**, and found that **3a** was prone to racemize when it was kept at room temperature for >7 days or treated with basic SiO_2.[14] The reaction of substrates with a bulkier alkyl group **2b** (R^1 = Ph, R^2 = Et), **2c** (R^1 = Ph, R^2 = *i*-Pr), or allyl group **2d** (R^1 = Ph, R^2 = allyl) gave monoacylates **3b**, **3c**, or **3d** in good yields but only moderate enantioselectivities (77% yield with 84:16 er for **3b**; 87% yield with 66:34 er for **3c**; 87% yield with 79:21 er for **3d**; respectively). In all cases, undesired diacylates were almost suppressed. The use of substrates **2e–g** with various R^1 = aryl, R^2 = Me groups delivered the desired monoacylate with moderate to high enantioselectivities. However, in the case of **2e** having an electron-rich aryl group (R^1 = *p*-$MeOC_6H_4$, R^2 = Me), the reaction gave a significant amount of diacylate **4e**, probably due to the high nucleophilicity (reactivity) of the monoacylate **3e**. On the other hand, substrate **2g** having an electron-deficient group (R^1 = *p*-$NO_2C_6H_4$, R^2 = Me) also showed poor chemoselectivity of monoacylation. In this case, the solubility of 1,3-diol **2g** was extremely less than that of monoacylate **3g**. Accordingly, once **3g** was generated, it was readily converted to diacylate

4g. The reaction of substrates **2h**–**j** gave monoacylates **3h**–**j** with moderate to high yield and enantioselectivity (54–88% yield and 54:46–95:5 er). The low solubility of substrates also affected the selectivity of monoacylation and diacylation (e.g., **2i** and **2j**). Next, substrates **2k**–**n** with a tertiary carbon atom (R^1 = aryl or alkyl, R^2 = H) were tested under the optimal conditions. Monoacylates were preferentially obtained in 48–88% yield with moderate enantioselectivities (up to 80.5:19.5 er). The reasons for the poor chemo- and enantioselectivity for monoacylates **3k**–**n** are unclear at this time. The absolute configurations of **3a** and **3k** were determined to be *S* after derivatization of **3a** and **3k** to known compounds.[15] Other products were also assigned *S* by analogy. According to these results, the current reaction system could be applied to specific substrates having a quaternary carbon atom (R^1 = aryl, R^2 = Me) in good to high chemo- and enantioselectivities. To expand the substrate generality, a new class of catalysts suitable for such substrates would be required, and the issue of the solubility of 1,3-diols (vs. monoacylate), which greatly affects the chemoselectivity of monoacylation, needs to be addressed.

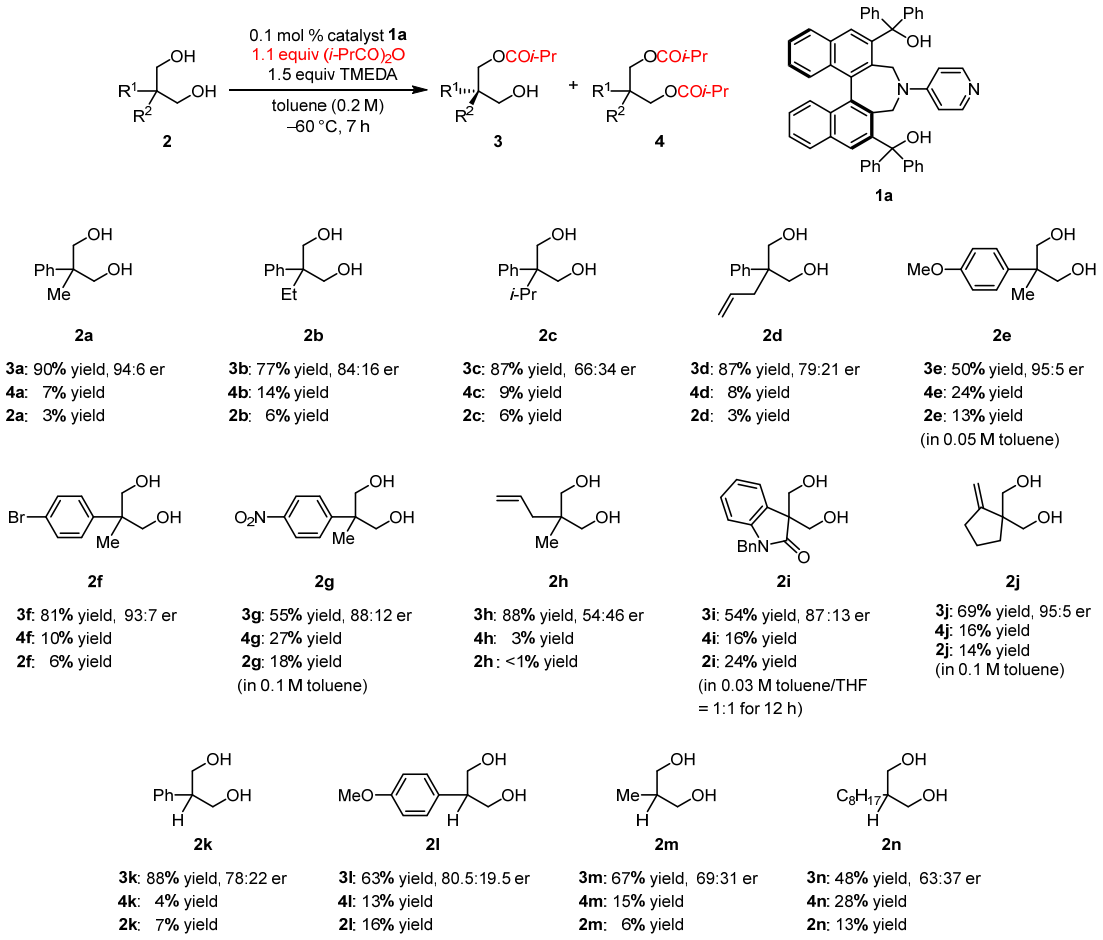


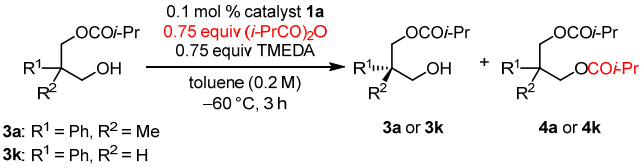
Figure 1. Desymmetrization of various 1,3-diols promoted by catalyst **1a**.

Control experiments to clarify the second acylation process were carried out (Table 3). As mentioned before, controlling such over-reaction is quite challenging because two primary alcohols are too reactive to suppress undesirable over-acylation, which undoubtedly would have a significant impact on the yield and/or enantioselectivity of monoacylate (e.g., Scheme 1). Thus, racemates of monoacylates **3a** (R^1 = Ph, R^2 = Me) and **3k** (R^1 = Ph, R^2 = H) were subjected to the reaction conditions. Consequently, over-acylation proceeded smoothly to give corresponding diacylate **4a** and **4k** in 50% and 59% conversion, respectively, but the selectivity factors were low (*s* =1.8–2.0). In addition, analysis of the recovered starting materials **3a** or **3k** revealed that minor enantiomers in the enantioselective desymmetrization of 1,3-diols **2a** and **2k** were preferentially consumed. This finding suggested that over-acylation preferentially proceeded via **path B** (acylation of a minor enantiomer; the pathway tending to amplifies enantio-enrichment of the monoacylate) in Scheme 1, but its selectivity was rather low.[16]

Next, the importance of the catalyst structure was also investigated. The desymmetrization of **2a** was carried out using pseudo C_2-symmetric catalyst **1a′** (lack of one hydroxy group), and C_2-symmetric catalyst **1a″** (lack of two

hydroxy groups) under the optimal conditions (Figure 2). The catalysts **1a′** and **1a″** were significantly less effective than optimal catalyst **1a** with respect to both catalytic activity and enantioselectivity (65% yield of **3a** with 88.5:11.5 er, and 31% yield of **3a** with 46:54 er, respectively). These results clearly indicated that C_2-symmetric catalyst **1a** with two *tert*-alcohol units is essential to achieve high catalytic activity and high enantioselectivity.

Table 3. Examination of the second acylation step[a]



entry	monoacylate	conv (%)[b]	er of monoacylate[c]	s[d]
1	**3a**	50	62:38	2.0
2	**3k**	59	63:37	1.8

[a] Reactions were performed on a 0.1 mmol scale in toluene (0.2 M) under an argon atmosphere. [b] NMR yields were determined by ^{1}H NMR analysis using benzylbenzoate as an internal standard. [c] Enantiomer ratios were determined by HPLC analysis using CHIRALCEL OD-H. [d] The *s* factors were calculated using Kagan's equation.[17]

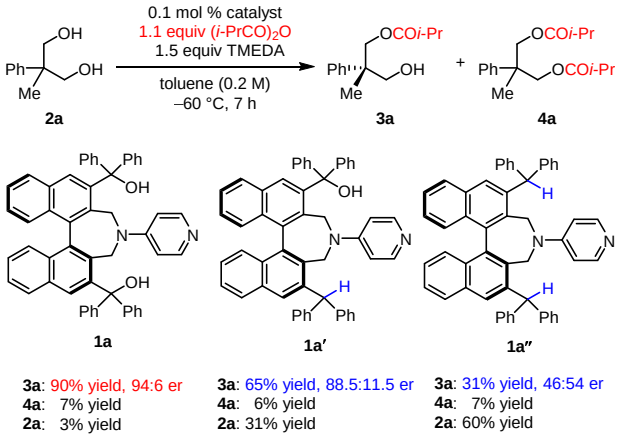


Figure 2. Effects of the *tert*-alcohol unit(s) of the catalyst in the desymmetrization of **2a**

In conclusion, we developed an enantioselective desymmetrization of 1,3-diols by a chiral *N*,*N*-dimethyl-4-aminopyridine (DMAP) derivative **1a** containing a 1,1′-binaphthyl with *tert*-alcohol units. The reactions required only 0.1 mol % of catalyst and showed moderate to high chemoselectivity of monoacylation and enantioselectivity (14 examples, up to 90% yield, and up to 95:5 er). Furthermore, several control experiments revealed that enantioselective acylation proceeded smoothly when 1,3-diols were used, whereas there was almost no enantioselectivity in the second acylation of monoacylate (mono-ol). A catalyst structure having two *tert*-alcohol units is also important for achieving high catalytic activity or enantioselectivity. Further improvements in the enantio- and chemoselectivity of monoacylation are now in progress.

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Supporting Information is available at http://dx.doi.org/10.1246/cl.******.

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11. See the Supporting Information for details.
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15. See the Supporting Information for details.
16. We also check the possibility of transesterification of monoacylate by catalyst **1a**: *Rac*-**3c** was subjected to the optimal reaction conditions (without acylating reagent), but compleate recovery of **3c** with 50:50 er was observed.
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