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Desymmetrization of *meso*-Glycerol Derivatives Induced by L-Histidine-Derived Acylation Catalysts

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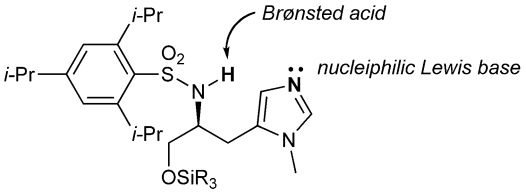
Abstract: The desymmetrization of *meso*-glycerol derivatives bearing a 3-pyrroline-1-carbonyl (Pyroc) directing group is demonstrated through an enantioselective acylation reaction promoted by L-histidine-derived bifunctional catalysts. The desired monoacylated products are obtained in good yields (up to 74%) with high enantioselectivities (up to 99% *ee*).

Keywords: asymmetric acylation; desymmetrization; glycerol; L-histidine; Pyroc (3-pyrroline-1-carbonyl) group

Enantioselective transformations of C_2-symmetrical molecules are among the most useful reactions in asymmetric synthesis. In particular, optically active glycerol derivatives are valuable chiral building blocks for the synthesis of natural products and bioactive compounds. For the synthesis of these chiral building blocks, various methods have been developed for the desymmetrization of *meso*-diols through enantioselective acylation.[1] Although some methods have been reported for the desymmetrization of acyclic *meso*-1,3-diols with good yields and enantioselectivities,[2–5] there are only a few examples of the desymmetrization of *meso*-glycerol derivatives through enantioselective acylation.[2] In 2005, Miller and colleagues reported peptide-based catalysts[6] for the desymmetrization of glycerol derivatives.[2a] Although Miller's reaction was highly enantioselective (>90% *ee*), the desired monoesters were obtained in moderate yields along with significant amounts of undesired diesters. The non-enzymatic organocatalyzed desymmetrization of *meso*-glycerol derivatives is still a challenging issue in organic chemistry.

We previously reported the kinetic resolution of racemic secondary alcohols and carboxylic acids through asymmetric acylation promoted by L-histidine-derived bifunctional catalysts **1** (Figure 1).[7,8]



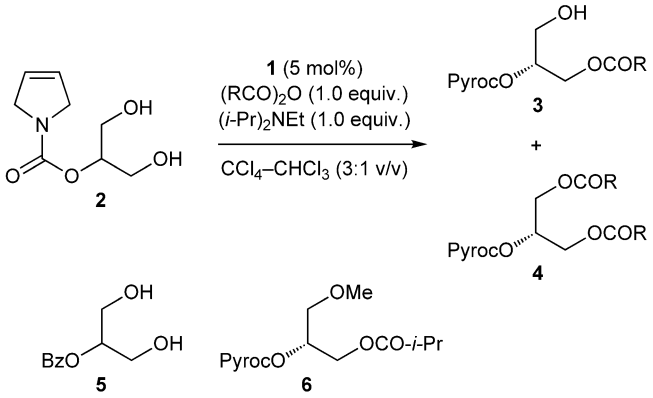
1a: R_3Si = *t*-$BuPh_2Si$ (TBDPS)
1b: R_3Si = $(TMS)_3Si$ (TTMSS)

Figure 1. L-Histidine-derived bifunctional acylation catalysts **1**.

Catalysts **1** contain an *N*-methylimidazole moiety as a nucleophilic base and a sulfonamidyl proton as a Brønsted acid, and induce high-level kinetic resolution through hydrogen bonding between the sulfonamidyl proton and a Brønsted basic site of the substrates. The 3-pyrroline-1-carbonyl (Pyroc) group is a useful directing group of substrates in **1**-catalyzed kinetic resolutions.[7d] The strong Brønsted basicity of Pyroc plays a key role in high-level asymmetric induction through the formation of strong hydrogen bonding with the sulfonamidyl proton of **1**. In addition, Pyroc can be selectively removed *via* DDQ oxidation[9] followed by hydrolysis through the use of NaOH[10] without any loss of stereochemical integrity. We report here the desymmetrization of *meso*-glycerol derivatives bearing a Pyroc group by a **1**-catalyzed asymmetric acylation reaction.

First, the desymmetrization of 2-*O*-Pyroc-glycerol **2** with a carboxylic anhydride (1.0 equiv.) was examined in the presence of **1** (5 mol%) and $(i\text{-Pr})_2$NEt (1.0 equiv.) (Table 1). Although the use of a less polar

Table 1. Desymmetrization of 2-*O*-Pyroc-glycerol **2**.



Entry	**1**	R	*T* [°C], *t* [h]	Yield of **3** [%]	*ee* of **3** [%]	Yield of **4** [%]	Ratio **3**/**4**
1	**1a**	*i*-Pr	−20, 3	37	98	16	2.3
2[a]	**1a**	*i*-Pr	−20, 3	24	58	10	2.4
3[b]	**1a**	*i*-Pr	−20, 3	17	99	28	0.61
4[c]	**1a**	*i*-Pr	−20, 12	55	98	6	9.2
5	**1a**	*i*-Pr	r.t., 3	61	81	13	4.7
6	**1b**	*i*-Pr	r.t., 3	61	91	15	4.1
7	**1b**	Cy	r.t., 15	74	93	13	5.7
8	**1b**	Et	r.t., 2	63	94	12	5.3
9	**1b**	*t*-Bu	r.t., 48	71	86	12	5.9

[a] 2-*O*-Benzoylglycerol **5** was used as a substrate.
[b] The reaction was conducted in the presence of **6** (0.7 equiv., 98% *ee*).
[c] 3 equiv. of $(i\text{-Pr})_2$NEt were used.

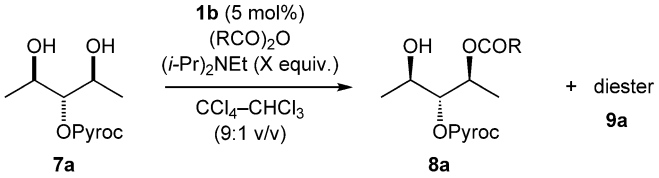
solvent such as CCl_4 is the most suitable for obtaining high enantioselectivity, the reaction of **2** was carried out in CCl_4-$CHCl_3$ (3:1 v/v) due to the poor solubility of **2** in CCl_4. When the reaction with isobutyric anhydride (R = *i*-Pr) was conducted in the presence of **1a** at −20 °C, the corresponding monoester (*R*)-**3** (R = *i*-Pr) was obtained in 37% yield with 98% *ee* along with diester **4** (16%) (entry 1). On the other hand, 2-*O*-benzoylglycerol **5** showed poor reactivity and enantioselectivity under the same reaction conditions (24% yield, 58% *ee*, entry 2). These results indicated that the Pyroc group successfully acted as a directing group in the **1a**-catalyzed desymmetrization of **2**.

Despite the high enantioselectivity of the **1a**-catalyzed desymmetrization of **2**, the yield of **3** did not increase further even when the reaction time was prolonged. The catalysis of **1a** might be inhibited by the interaction of generated **3**, since the reaction was significantly prevented by the addition of optically active (*R*)-**6** (0.7 equiv., 98% *ee*) (entry 3). To overcome this problem, the reaction conditions were investigated. We found that the use of 3 equivalents of $(i\text{-Pr})_2$NEt significantly improved the yield of **3** to 55% and suppressed the generation of **4** to 6% (entry 4). Alternatively, when the reaction was conducted at ambient temperature, the yield of **3** increased to 61%, while the enantioselectivity decreased to 81% *ee* (entry 5). These reaction conditions might successfully prevent the interaction between **1a** and **3**. The use of bulkier catalyst **1b** gave improved enantioselectivity without any loss of reactivity (61% yield, 91% *ee*, entry 6).

The reactivity and enantioselectivity of the **1**-catalyzed asymmetric acylations depended on the carboxylic anhydrides.[7] For the present **1b**-catalyzed desymmetrization of **2**, the use of cyclohexanecarboxylic anhydride (R = Cy) gave the best results (74% yield, 93% *ee*, **3**/**4** = 5.7, entry 7). Under the present reaction conditions, racemization of these monoesters through acyl migration was not observed. Less bulky carboxylic anhydride (R = Et) gave the corresponding ester with high enantioselectivity in rather lower yield (63% yield, 94% *ee*) (entry 8). More bulky pivalic anhydride (R = *t*-Bu) showed poor reactivity (entry 9).

We next examined the desymmetrization of the secondary *meso*-1,3-diol **7a** (Table 2). The solubility of **7a** in less polar solvents was good enough for the reaction to proceed in CCl_4-$CHCl_3$ (9:1 v/v). The reactivity of **7a** was lower than that of **2**, and the reaction required a prolonged reaction time to give the corresponding monoester **8a** in an appreciable yield. When the reaction of **7a** with $(CyCO)_2O$ (1.0 equiv.) was conducted at ambient temperature for 24 h, **8a** was obtained in 59% yield with 89% *ee* (entry 1). The use

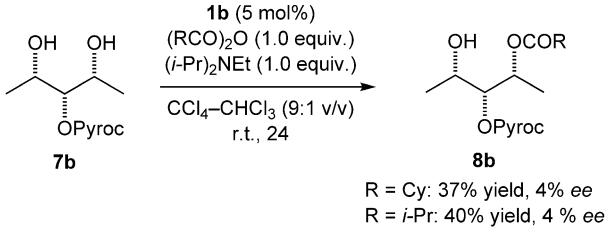
Table 2. Desymmetrization of 3-*O*-Pyroc-2,3,4-pentanetriol **7a**.



Entry	R (equiv.)	X	*T* [°C], *t* [h]	Yield of **8a** [%]	*ee* of **8a** [%]	Ratio **8a**/**9a**
1	Cy (1.0)	2	r.t., 24	59	89	3.1
2	*i*-Pr (1.0)	2	r.t., 12	34	92	1.5
3	Cy (1.3)	3	r.t., 4	71	94	3.1
4	Cy (1.3)	3	10, 12	70	89	2.5
5	Cy (1.3)	3	0, 24	64	94	2.4

of $(i\text{-PrCO})_2O$ significantly decreased the yield of **8a** and the ratio of **8a** to diester **9a**, although the enantioselectivity was high (entry 2). To improve the yield of **8a**, the reaction of **7a** was conducted with 1.3 equivalents of $(CyCO)_2O$ and 3 equivalents of $(i\text{-Pr})_2NEt$. As a result, the reaction at ambient temperature gave an increased yield and enantioselectivity of **8a** (71% yield, 94% *ee*, entry 3). However, the reaction at lower temperature (0–10 °C) did not improve the enantioselectivity (89–94% *ee*) and the ratio of **8a** to **9a** (2.4–2.5) (entries 4 and 5). On the other hand, the desymmetrization of diastereomeric secondary *meso*-1,3-diol **7b** showed poor reactivity and enantioselectivity (Scheme 1).

In the **1**-catalyzed kinetic resolution of racemic secondary alcohols, intermolecular hydrogen bonding between the sulfonamidyl proton in **1** and the carbamoyl oxygen of the substrates has been proposed to promote the acylation by a proximity effect with high enantioselectivity.[7] Based on this intermolecular hydrogen bonding, plausible transition-state assemblies **10** and **11a** were proposed for the present desymmetrization of **2** and **7a** (Figure 2). In these transition-state assemblies, pro-(*R*) hydroxy groups of **2** and **7a** would be placed close to the acylammonium moiety and acylated selectively. In addition, the pro-(*S*) hydroxy proton might be interact with the sulfonyl oxygen to stabilize the conformation of the transition state. In contrast, for the desymmetrization of **7b**, steric repulsion between the methyl group (R^b) and



Scheme 1. Desymmetrization of **7b**.

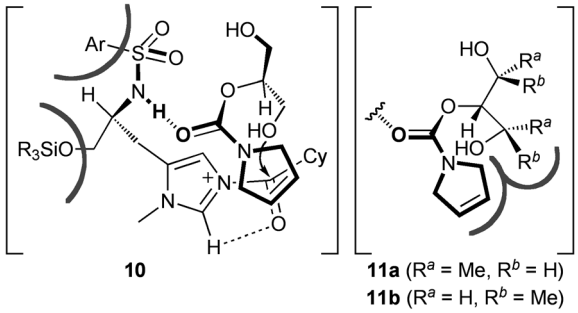
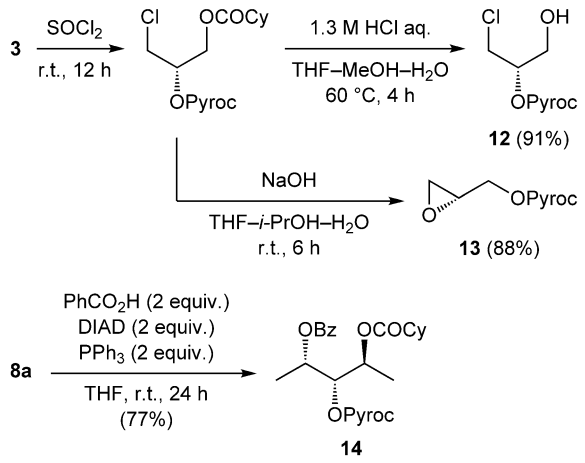


Figure 2. Plausible transition-state assemblies **10** and **11**.

the Pyroc group would direct the pro-(*R*) hydroxy group outside in the transition-state assembly **11b**, which might cause poor reactivity and enantioselectivity.

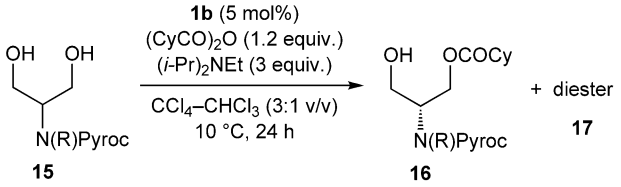
The obtained optically active monoester **3** is a useful chiral building block for the synthesis of various bioactive natural products. Chlorination of the primary hydroxy group of (*R*)-**3** with $SOCl_2$ gave the corresponding chroride quantitatively. Subsequent selective removal[7d] of the cyclohexanecarbonyl group with aqueous HCl gave **12** in 91% yield (2 steps) (Scheme 2). On the other hand, alkaline hydrolysis of cyclohexanecarboxylate gave **13** (88%, 2 steps from **3**) *via* the migration of Pyroc group to the primary hydroxy group.[11] Compounds **12** and **13** were obtained without any loss of stereochemical integrity. In addition, Mitsunobu reaction of **8a** using $PhCO_2H$, DIAD and PPh_3 gave the corresponding benzoate **14** in 77% yield with inversion of the stereochemistry of the secondary hydroxy group.

For further application of the present method, we investigated the desymmetrization of *meso*-2-amino-1,3-propanediols[4] bearing a Pyroc group at the 2-position (Table 3). First, the desymmetrization of *N*-Pyroc-2-amino-1,3-propanediol **15a** (R = H) was examined in $CHCl_3$ due to the poor solubility of **15a**. The reaction with $(CyCO)_2O$ (1.2 equiv.) gave the corresponding monoester **16a** in 64% yield with 59% *ee*



Scheme 2. Transformations of optically cctive **3** and **8a**.

Table 3. Desymmetrization of *N*-Pyroc-2-amino-1,3-propanediols **14**.



Entry	**15** (R)	Yield of **16** [%]	*ee* of **16** [%]	Ratio **16**/**17**
1[a]	**15a** (H)	64	59	2.4
2	**15b** (Me)	60	55	2.7
3	**15c** (Bn)	15	11	0.45

[a] The reaction was conducted in $CHCl_3$.

(entry 1). The moderate enantioselectivity was probably due to the high polarity of the reaction solvent. Therefore, we next examined the desymmetrization of *N*-methyl and *N*-benzyl derivatives **15b** and **15c**, both of which could be dissolved in CCl_4-$CHCl_3$ (3:1 v/v). Disappointingly, the yield and enantioselectivity of **16** decreased with an increase in the steric bulkiness of the substituent on the nitrogen (entries 1–3). Furthermore, the desymmetrization of **15c** predominantly gave the corresponding diester **17c** (**16c**/**17c** = 0.45, entry 3). Steric hindrance of the substituents on the nitrogen, which would be directed to the catalyst in the transition-state, might prevent interaction with the catalyst.

In conclusion, we have demonstrated the desymmetrization of acyclic *meso*-1,3-diols by asymmetric acylation induced by bifunctional catalyst **1b**. A Pyroc group successfully acted as a directing group through intermolecular hydrogen bonding for high-level asymmetric induction.

Experimental Section

Representative Procedure for the Desymmetrization of *meso*-1,3-Diols

To a solution of *meso*-1,3-diol (0.24 mmol) and **1** (0.012 mmol) in $CHCl_3$ (1.2 mL) and CCl_4 (3.6 mL) were added $(i\text{-Pr})_2$NEt (41.8 mL, 0.24 mmol) and carboxylic anhydride (0.24 mmol) at ambient temperature or −20 °C (for each reaction temperature). After being stirred at ambient temperature or −20 °C (for each reaction temperature), the reaction mixture was treated with aqueous 0.1 M HCl solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc 2:1→1:2) to give the desired monoester. The *ee* value was determined by HPLC analysis.

(*R*)-1-Hydroxy-3-(isobutyryloxy)propan-2-yl 2,5-Dihydro-1*H*-pyrrole-1-carboxylate (3, R = *i*-Pr): $[\alpha]_D^{24}$: −13.7 (*c* 1.0, $CHCl_3$) for 96% *ee*; HPLC (Daicel Chiralcel AS-H, hexane-2-propanol 19:1, flow rate 1.0 mL min^{-1}): t_R = 47.4 (major enantiomer), 52.0 (minor enantiomer) min; IR (KBr): ν = 3443, 1737, 1710, 1688, 1429, 1327, 1192, 1159, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.9 Hz, 6H), 2.59 (septet, *J* = 6.9 Hz, 1H), 2.76 (br s, 1H), 3.77 (br s, 2H), 4.09–4.24 (m, 4H), 4.31 (d, *J* = 5.0 Hz, 2H), 5.01 (tt, *J* = 5.0, 5.5 Hz, 1H), 5.75–5.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 33.8, 52.8, 53.2, 61.7, 62.4, 73.6, 125.4, 125.5, 154.2, 176.8; HR-MS (FAB): *m/z* = 258.1339, calcd. for $C_{12}H_{20}NO_5$ [(M + H)$^+$]: 258.1341.

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