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Non-Enzymatic Geometry-Selective Acylation of Tri- and Tetrasubstituted α,α′-Alkenediols

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Abstract: A highly geometry-selective organocatalytic acylation of tri- and tetra-substituted 2-alkylidene-1,3-propanediols has been developed. The highly *E*-selective acylation of various tetrasubstituted 2-alkylidene-1,3-propanediols was achieved in 96 to >99% selectivity for the first time by a non-enzymatic protocol.

Keywords: acylation; geometry; molecular recognition; organocatalysis; tetrasubstituted olefin

Introduction

The selective manipulation of one of multiple hydroxy groups is a fundamental challenge in current organic synthesis.[1] We have developed the organocatalytic regioselective acylation of glycopyranoses[2] and chemoselective monoacylation of linear diols.[3] Preferential formation of a hydrogen bond between catalyst **1** and the primary OH (circled) of the glycopyranoses was proposed to be the origin of the high selectivity (Figure 1). In this paper, we describe the geometry-selective acylation of unsymmetrically substituted alkenediols promoted by organocatalysts (Figure 1, **A**).

The differentiation of hydroxy groups of unsymmetrically substituted 2-alkylidene-1,3-propanediols was expected to be difficult due to the similar intrinsic reactivity of the two primary hydroxy groups.[4] In accordance with the expectation, non-enzymatic methods for geometry-selective acylation of unsymmetrically trisubstituted 2-alkylidene-1,3-propanediols has never been reported, while the highly selective enzymatic acylation of the diols and deacylation of the corresponding diesters have been reported.[5] To the best of our knowledge, however, no methods including enzymatic protocols for the *differentiation of primary hydroxy groups of tetrasubstituted 2-alkylidene-1,3-propanediols* have been reported. Here we report the highly geometry-selective acylation of tri- and tetrasubstituted 2-alkylidene-1,3-propanediols based on recognition of the the substrate structure by artificial organocatalysts.[6,7]

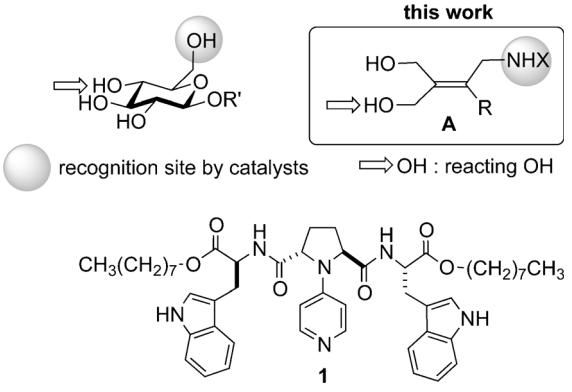
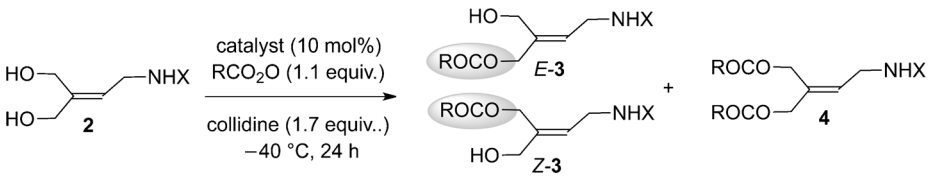


Figure 1. Regioselective acylation catalyzed by **1** and related organocatalysts.

Results and Discussion

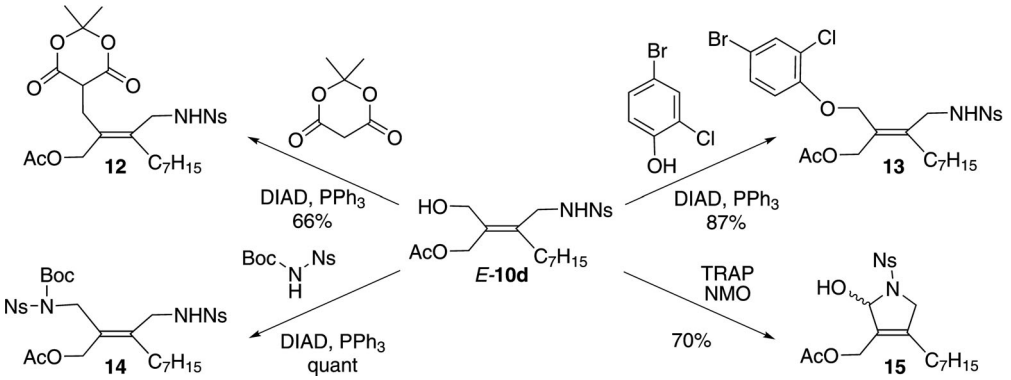
We chose trisubstituted alkenediols **2** with a nitrogen substitutent (Table 1) as the substrate for geometry-selective acylation because versatile functional group transformation of the monoacylate is possible as exemplified in the case of a tetrasubstituted alkenediol (Scheme 1). The NHX group of **2** was expected to affect the regioselectivity by serving as a hydrogen bond donor for the recognition by the catalyst (Figure 1, **A**). The regiochemical profile for acylation of **2** was investigated. Treatment of **2a** (X = Boc) with 1.1 equiv. of isobutyric anhydride in the presence of 10 mol% of DMAP in $CHCl_3$ at −40 °C for 24 h gave

Table 1. Effects of catalysts and of nitrogen protecting groups on geometry selectivity of acylation of trisubstituted alkenediol **2**.[a]



Entry	**2**	X	Cat.	R	Solvent	**3** [%]	*E*-**3**:*Z*-**3**	**4** [%]	Recovery [%]
1	**2a**	Boc	DMAP	*i*-Pr	$CHCl_3$	37	18:82	26	–[c]
2	**2b**	$COCF_3$	DMAP	*i*-Pr	$CHCl_3$	20	14:86	40	–[c]
3	**2c**	Ts	DMAP	*i*-Pr	$CHCl_3$	47	20:80	29	20
4	**2d**	Ns[d]	DMAP	CH_3	$CHCl_3$	56	48:52	14	30
5	**2a**	Boc	**1**	*i*-Pr	$CHCl_3$	52	71:29	14	13
6	**2b**	$COCF_3$	**1**	*i*-Pr	$CHCl_3$	51	42:58	26	23
7	**2c**	Ts	**1**	*i*-Pr	$CHCl_3$	52	63:37	18	30
8	**2c**	Ts	**1**	CH_3	$CHCl_3$	80	84:16	12	8
9[b]	**2c**	Ts	**1**	CH_3	CH_2Cl_2	71	76:24	12	17
10[c]	**2c**	Ts	**1**	CH_3	DMF	50	50:50	15	35
11[d]	**2d**	Ns[d]	**1**	CH_3	$CHCl_3$	85	88:12	8	7

[a] Reactions were run at the substrate concentration of 0.01 M.
[b] Geometry was determined by NOE experiments (see the Supporting Information).
[c] Not determined.
[d] 2-Nitrobenzenesulfonyl.



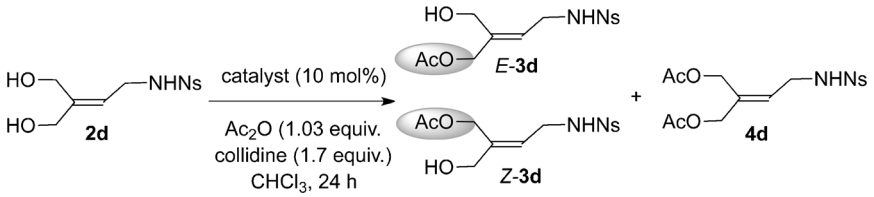
Scheme 1. Geometry-controlled synthesis of tetrasubstituted alkenes.

an 18:82 mixture of *E*-**3a** and *Z*-**3a** in 37% yield with concomitant formation of the diacylate **4a** in 26% yield (entry 1). Similarly, alkenediols **2b** (X = $COCF_3$) and **2c** (X = Ts) gave *Z*-**3b** and *Z*-**3c** as the major monoacylates in DMAP-catalyzed acylations (entries 2 and 3). These results indicate that the *Z*-hydroxy group of **2a**–**2c** has a higher intrinsic reactivity than the *E*-hydroxy group.

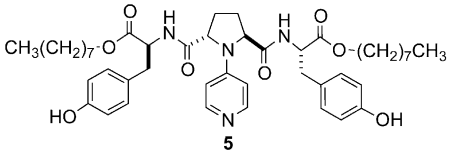
On the other hand, the *E*-acylates were the major monoacylates in the reactions of **2a** and **2c** with isobutyric anhydride in the presence of catalyst **1** (entries 5 and 7). Use of acetic anhydride instead of isobutyric anhydride resulted in the higher *E*-selectivity (*E*-**3c**:*Z*-**3c** = 84:16) (entries 7 *vs.* 8). The highest *E*-selectivity (88:12) was obtained in the acetylation of **2d** [X = 2-nitrobenzensulfonyl (Ns)[8]] (entry 11). The higher ratio of *E*-acylation was associated with the higher yield of monoacylation in the reactions catalyzed by **1** (entries 6–11), while *Z*-selective acylation by DMAP catalysis gave only poor yields of the monoacylates with concomitant formation of significant amounts of the diacylates (entries 1–3). These results may indicate that *E*-acylation catalyzed by **1** proceeds in an accelerative manner (see Table 4).[9]

We then examined various catalysts **5**–**8** for regioselective acylation of **2d** (Table 2). Among the catalysts examined, catalyst **7** gave the highest *E*-selectivity (94:6) in the acetylation at −40 °C (entry 5). Further improved *E*-selectivity (95:5) as well as high yield for monoacylation (95%) were obtained in the acylation

Table 2. Screening of catalysts for geometry-selective acylation of trisubstituted alkenediol **2d**.[a]



Entry	Cat.	Temp. [°C]	**3d** [%]	*E*-**3d**:*Z*-**3d**	**4d** [%]/Recovery [%]
1	DMAP	−40	55	48:52	14/30
2	**1**	−40	85	88:12	8/7
3	**5**	−40	80	92:8	4/16
4	**6**	−40	82	81:19	11/8
5	**7**	−40	90	94:6	2/8
6	**8**	−40	88	81:19	6/6
7	**7**	25	72	86:14	6/15
8	**7**	−60	95	95:5	3/2
9[b]	**7**	−60	82	90:10	5/10
10[c]	**7**	−60	95	93:7	8/~0
11[d]	**7**	−60	71	88:12	17/12



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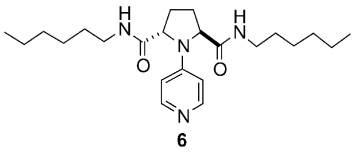

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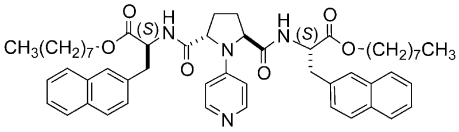

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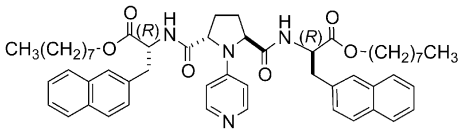

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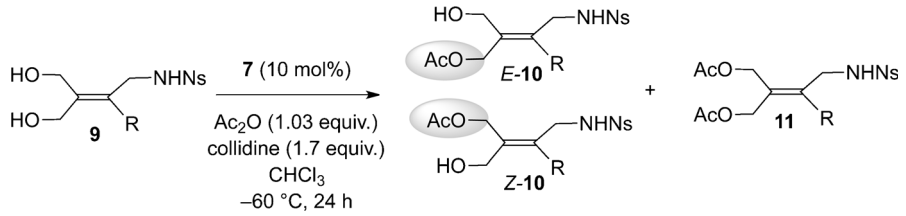
[a] Reactions were run at the substrate concentration of 0.01 M.
[b] Isobutyric anhydride was used as an anhydride.
[c] **2c** (X = Ts) was used as a substrate.
[d] **2e** (X = Tf) was used as a substrate.

of **2d** catalyzed by **7** at −60 °C (entry 8). Use of isobutyric anhydride resulted in a slight decrease in the regioselectivity (*E*:*Z* = 90:10, entry 9). Substrates **2c** (X = Ts) and **2e** (X = Tf) were also examined under the optimized conditions employed in entry 8. Acylation of **2c** and **2e** in the presence of **7** gave the corrrsponding monoacylates in 93% and 88% *E*-selectivity, respectively (entries 10 and 11). Accordingly, Ns-substituted substrate, catalyst **7**, and acetic anhydride were found to be the proper choices for the *E*-selective acylation.

The optimum conditions for *E*-selective acylation of trisubstituted alkenediols catalyzed by **7** were applied to the acylation of tetrasubstituted alkenediols (Table 3).[10] A perfect *E*-selectivity (>99%) was obtained in acetylation of **9a** (R = Me), albeit with only a moderate yield for monoacylation (52%) due to the poor solubility of **9a** in $CHCl_3$ (entry 1). Uniformly high *E*-selectivity (~98:2) and high yields of monoacylation products (93–98%) were observed in the acylation of various tetrasubstituted alkenediols **9b–9f** by use of catalyst **7** (entries 2–6). Slightly lower, yet high *E*-selectivity (96:4) and acceptable yields of monoacylation (73%) were obtained in the acetylation of **9g** (R = Br) (entry 7). The high selectivity associated with the high yield for monoacylation (entries 2–6) again indicates accelerative acylation.[3,9] On the other hand, regiorandom acylation (50:50) proceeded with low yield (31–41%) of monoacylation in DMF (entries 9 and 11). High *E*-selectivity (98:2) was maintained in the acylation of **9c** in $CHCl_3$:DMF = 4:1 with a relatively high mono/diacylation ratio (82/6) (entry 8). Similarly, highly *E*-selective acylation (98:2) took place in $CHCl_3$:DMSO = 4:1 with a moderate mono/diacylation ratio (69/8) (entry 10).

Tetrasubstituted alkenemonool *E*-**10d** thus obtained was readily transformed to highly functionalized alkenes **12**, **13**, **14**, and **15** *via* Mitsunobu C–C, C–O, C–N bond formation, and oxidative C–N bond formation, respectively (Scheme 1). Thus, an example of the geometry-controlled synthesis of tetrasubstituted

Table 3. Geometry-selective acylation of tetrasubstituted alkenediols **9**.[a]



Entry	R	**9**	**10** [%]	*E*-**10**:*Z*-**10**[b]	**11** [%]/Recovery [%]
1	Me	**9a**	52	>99:<1	24/24
2	Et	**9b**	93	98:2	1/2
3	Pr	**9c**	96	98:2	~0/3
4	C_7H_{15}	**9d**	98	98:2	~0/1
5	$CH_2CH_2CH{=}CH_2$	**9e**	97	98:2	~0/3
6	CH_2Ph	**9f**	98	98:2	~0/
7[c]	Br	**9g**	73	96:4[d]	15/12
8[e]	Pr	**9c**	82	98:2	6/~0
9[f]	Pr	**9c**	31	50:50	4/40
10[g]	C_7H_{15}	**9d**	69	98:2	8/6
11[f]	C_7H_{15}	**9d**	41	50:50	14/36

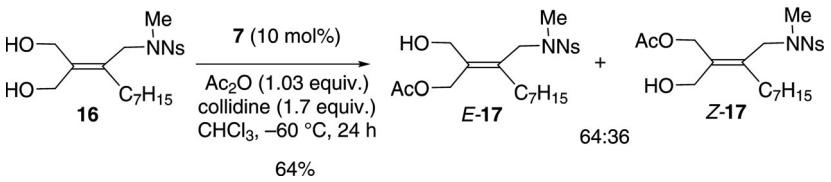
[a] Reactions were run at the substrate concentration of 0.01 M.
[b] Geometry was determined by NOE experiments (see the Supporting Information).
[c] $CHCl_3$/THF (10:1) was used as a solvent.
[d] *E*-**10g** and *Z*-**10g** (R = Br) indicate here that NHNs and OAc are at *E*- and *Z*-geometry to each other, respectively, although this does not follow the nomenclature.
[e] Run in $CHCl_3$:DMF = 4:1
[f] Run in DMF.
[g] Run in $CHCl_3$:DMSO = 4:1.

alkenes with four different substituents was demonstrated.

We then investigated the mechanistic aspects toward the understanding the origins of the extremely high *E*-selectivity of the acylation of tetrasubstituted alkenediols catalyzed by **7**. In order to estimate the effects of N*H*Ns of **9d** on the regioselectivity of the acylation, the corresponding N*Me*Ns derivative, **16**, was treated under the conditions identical to those for the acylation in Table 3 (Scheme 2).

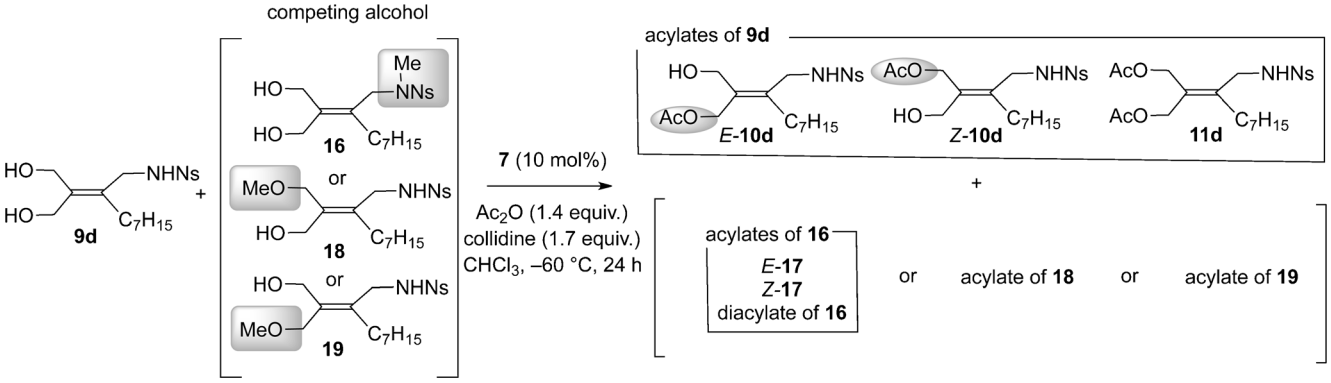
E-Acylation took place predominantly with much less selectivity (*E*-**17**:*Z*-**17** = 64:36) compared to that of **9d**. This result indicates that N*H*Ns of **9d** plays an important role for achieving high geometry-selectivity in the acylation catalyzed by **7**.

The kinetic aspects of the geometry-selective acylation were investigated (Table 4). Competitive acylation reactions between **9d**/**16**, **9d**/**18** (the corresponding *Z*-methoxy derivative of **9d**), and **9d**/**19** (the corresponding *E*-methoxy derivative of **9d**) were performed in the presence of the catalyst **7**. A 1:1 mixture of **9d** and **16** was treated under the reaction conditions identical to those in Table 3 except for the amount of the anhydride (0.70 equiv. for the total amount of the alcohols = 1.4 equiv. for each of the alcohols) (entry 1). A mixture of monoacylates of **9d** (*E*-**10d** in 91% and *Z*-**10d** in 1%), a diacylate of **9d** (**11d** in 3%), monoacylates of **16** (*E*-**17** in 6% and *Z*-**17** in 4%), and a diacylate of **16** (1%) were obtained (yield based on each of the alcohols). Total yield of the acylation of **9d** was 95% and that of **16** was 11%. The relative rate of acylation between **9d** and **16** was determined to be 26 according to the equation shown in the footnote [d] in Table 4.[11] Thus, the acidic hydrogen of NHNs in **9d** is expected to be responsible for the *E*-selective acylation as well as accelerative monoacylation.



Scheme 2. Regiochemical profile of acylation of NMeNs derivative **16** catalyzed by **7**.

Table 4. Competitive acylation between **9d** and **16**, **18**, or **19** in the presence of **7**.[a]



Entry	Competing alcohol	Products [%]	Acylates of **9d** [%][b]/ Acylate(s) of the competing alcohol [%][c]	Fast-reacting alcohol	Relative rate[d]
1	**16**	*E*-**10d** (91), *Z*-**10d** (1), **11d** (3) *E*-**17** (6), *Z*-**17** (4), diacylate of **16** (1)	95/11	**9d**	26
2	**18**	*E*-**10d** (93), *Z*-**10d** (1), **11d** (5) acylate of **18** (5)	99/5	**9d**	89
3	**19**	*E*-**10d** (92), *Z*-**10d** (1), **11d** (3) acylate of **19** (8)	96/8	**9d**	40

[a] Reactions were run at the substrate concentration of 0.01 M.
[b] Sum of the yields of the acylates of **9d** (%).
[c] Sum of the yields of the acylates of **16** for entry 1, and the yield (%) of the acylate of **18** and **19** for entries 2 and 3, respectively.
[d] k(fast-reacting alcohol)/k(slow-reacting alcohol) = ln{1−conversion[1+(A−B)/(A+B)]}/ln{1−conversion[1−(A−B)/(A+B)]}. A = Sum of the yields of the acylates of **9d**, B = Sum of the yields of the acylates of **16** for entry 1, and the yield (%) of the acylate of **18** and **19** for entries 2 and 3, respectively. Conversion was calculated based on the total amount of two alcohols.

Formation of a hydrogen bond between the N*H*Ns and the reactive intermediate (acylpyridinium) generated from catalyst **7** may be the possible origin of the observed phenomena (Figure 2). Alkenediol **9d** underwent acylation 89 times faster than **18** in the presence of **7** on treatment of a 1:1 mixture of **9d** and **18** (entry 2). This suggests that the *Z*-OH of **9d** affects the accelerative acylation of the *E*-OH. On the other hand, the *E*-OH of **9d** does not significantly affect the acylation of the *Z*-OH, since net acylation of *Z*-OH of **9d** {4% = 1% (*Z*-**10d**) + 3% (**11d**)} was comparable with acylation of *Z*-OH of **19** (8%) (entry 3). The relative rate of acylation between **18** and **19** was determined to be 4.8 (fast-reacting alcohol: **18**) by an independent experiment on the kinetic studies under pseudo-first-order conditions using an excess amount (10 equiv.) of acetic anhydride in the presence of **7** at −60 °C. This suggests that the NHNs group is a directing group for *E*-acylation. In addition to the NHNs directing group, another directing group (*Z*-OH) appears be necessary for almost exclusive *E*-selective acylation. All of these results suggest that NHNs and the *Z*-OH of **9** are critically involved in the *E*-acylation probably as hydrogen bond donors. The importance of the hydrogen-bonding interaction between the catalyst and the substrate for selective acylation was also suggested by the solvent effects (Table 3, entries 3, 4 *vs.* 9, 11). Geometry selectivity was ham-

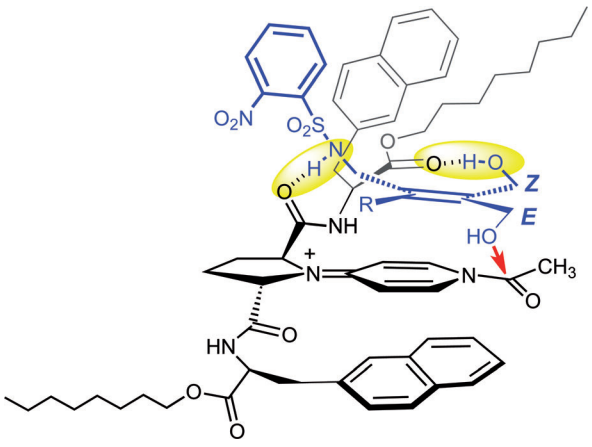


Figure 2. A hypothetical model for the geometry-selective acylation catalyzed by **7**.

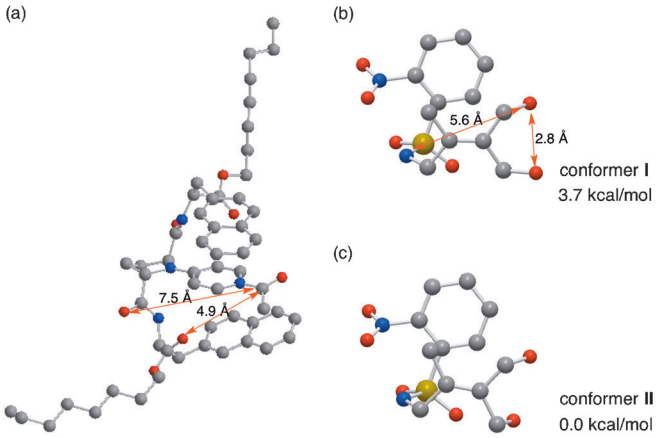


Figure 3. Conformers of the *N*-acetylpyridinium ion of catalyst **7** and the substrate **9a** generated by MacroModel (V 9.0). (a) The most stable conformer of the *N*-acetyl pyridinium ion of **7**. (b) The most stable conformer of **9a** among the conformers without the hydrogen bond between SO_2 and *Z*-OH. (c) The global minimum conformation of **9a**.

pered (50: 50) in the acylation in DMF (entries 9 and 11). Surprisingly, high *E*-selectivity was still maintained in the acylation in $CHCl_3$:DMF = 4:1 and $CHCl_3$:DMSO = 4:1 (entries 8 and 10). These results imply that the hydrogen-bonding interaction between the catalyst and the substrate is still working in such solvents with relatively high polarity. The kinetic study in Table 4 and the regiochemical results in Scheme 2 suggest that the hydrogen-bonding interaction between N*H*Ns group and the *Z*-O*H* of the substrates and the catalyst might be responsible for the selective and accelerative acylation. Based on this assumption, a hypothetical transition state model for the geometry-selective acylation is shown in Figure 2. Since the hydrogen of the NHNs group is the most acidic in the substrate, it would preferentially form a hydrogen bond with an amide carbonyl of the acylpyridinium ion.[12] As the result of the formation of this hydrogen bond, the *Z*-OH of the substrate locates itself near the ester carbonyl group of the catalyst, and may form an additional hydrogen bond between them. The cooperative effect of the two hydrogen bonds would fix the conformation of the substrate at the transition state for acylation, where the *E*-OH is in close proximity to the reactive carbonyl group, resulting in the selective acylation of the *E*-OH.

To estimate the validity of the molecular assembly shown in Figure 2, conformational analyses of substrate **9a** and the *N*-acetylpyridinium ion of catalyst **7** were performed (Figure 3) by a molecular modelling search using MacroModel V 9.0. Conformer II (Figure 3, c) was obtained as the most stable one by a conformational search of **9a**, in which the *Z*-OH forms a hydrogen bond with the oxygen of SO_2 of the Ns group. Since the *Z*-OH of the substrate was suggested to serve as hydrogen bond donor in the selective acylation (Table 4, entry 2), conformer **II** was excluded as the reactive species for the acylation. On the other hand, a stable conformer **I** (Figure 3, b) without the hydrogen bond between SO_2 and *Z*-OH was assumed to be the species responsible for the selective acylation, although conformer **I** was estimated to be 3.7 kcal mol^{-1} less stable than the conformer **II**. In conformer **I**, the distance between the nitrogen atom of the NHNs group and the oxygen atom of the reacting *E*-OH is 5.6 Å, and that between the oxygen atoms of the *Z*-OH and the reacting *E*-OH is 2.8 Å. The most stable conformer of the *N*-acetylpyridinium ion of catalyst **7** was generated with AMBER* force field using the GB/SA solvation model for chloroform (Figure 3, a). The distance between the oxygen atom of the amide carbonyl group and the carbon atom of the reactive acetyl group is 7.5 Å, and that between the oxygen atom of the ester carbonyl group and the carbon atom of the reactive acetyl group is 4.9 Å. These calculated distances between functional groups roughly account for the proposed interaction between the *N*-acetylpyridinium ion and the substrate shown in Figure 2, if the typical hydrogen bond distance (2.7–3.0 Å) is considered. This is merely a hypothetical understanding for the observed selectivity. Efforts for obtaining spectroscopic evidence for the substrate-catalyst interaction are currently underway in our laboratory.

Conclusions

In conclusion, we have developed an organocatalytic method for the *E*-selective acylation of tri- and tetrasubstituted 2-alkylidene-1,3-propanediols. The highly geometry-selective acylation of various tetrasubstituted 2-alkylidene-1,3-propanediols was achieved for the first time by a non-enzymatic protocol.

Experimental Section

General Procedure for Geometry-Selective Acylations of Table 1, Table 2, and Table 3

To a solution of diol substrate (20.0 mg, 1.0 equiv.), catalyst (10 mol%) and 2,4,6-collidine (1.7 equiv.) in solvent (concentration of the substrate: 0.01 M) was added acid anhydride (1.03 equiv.) at the temperature indicated in Table 1, Table 2, and Table 3. The resulting mixture was stirred at the same temperature for 24 h. The reaction was quenched with MeOH (10 mL), and the solvent was evaporated. The residue was dissolved in AcOEt, washed with 1 *N* HCl, brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude compound was purified by preparative TLC (SiO_2, hexane:AcOEt = 1:2) to afford the mono- and diacylates, and the recovered diol substrate. The *E*/*Z* ratio

of the monoacylate was determined by the integration of ^{1}H NMR.

(*E*)-2-(Hydroxymethyl)-4-(2-nitrophenylsulfonamido)but-2-enyl isobutyrate (*E*-3d): colorless oil. ^{1}H NMR ($CDCl_3$): δ = 8.17–8.09 (m, 1H), 7.92–7.84 (m, 1H), 7.81–7.71 (m, 2H), 5.74 (s, 1H), 5.58 (t, J = 6.4 Hz, 1H), 4.53 (s, 2H), 4.16 (s, 2H), 3.88 (t, J = 6.4 Hz, 2H), 2.39 (s, 1H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 171.0, 147.9, 138.2, 133.9, 133.7, 132.9, 131.0, 126.1, 125.4, 65.8, 58.2, 40.5, 20.9; IR (KBr): ν = 3525, 3333, 3099, 3023, 2937, 2889, 1731, 1593, 1540, 1366, 1340, 1239 cm^{-1}; MS (FAB): *m/z* (rel intensity) = 345 ($M+H^+$, 10); HR-MS (FAB): *m/z* = 345.0773, calcd. for $C_{13}H_{17}N_2O_7S$ $(M+H)^+$: 345.0757. The (*E*)-stereochemistry was determined by differential NOE experiments as shown in the Supporting Information.

(*Z*)-2-(Hydroxymethyl)-4-(2-nitrophenylsulfonamido)but-2-enyl isobutyrate (*Z*-3d): colorless oil. ^{1}H NMR ($CDCl_3$): δ = 8.10–8.03 (m, 1H), 7.84–7.77 (m, 1H), 7.73–7.65 (m, 2H), 5.61 (t, J = 7.1 Hz, 2H), 4.55 (s, 2H), 3.99 (s, 2H), 3.82 (t, J = 6.2 Hz, 2H), 2.05 (s, 1H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 171.2, 147.9, 138.0, 133.8, 133.7, 132.9, 131.0, 125.7, 125.4, 64.4, 59.3, 40.6, 20.8; IR (KBr): ν = 3526, 3333, 3099, 3023, 2930, 1731, 1593, 1540, 1441, 1365, 1340, 1238, 1165 cm^{-1}; MS (FAB): *m/z* (rel intensity) = 345 ($M+H^+$, 10), 327 (5); HR-MS (FAB): *m/z* = 345.0755, calcd. for $C_{13}H_{17}N_2O_7S$ $(M+H)^+$: 345.0757. The (*Z*)-stereochemistry was determined by differential NOE experiments as shown in the Supporting Information.

(*E*)-2-(Hydroxymethyl)-3-methyl-4-(2-nitro-phenylsulfonamido)but-2-enyl acetate (*E*-10a): colorless powder; mp 72–75 °C. ^{1}H NMR ($CDCl_3$): δ = 8.15–8.08 (m, 1H), 7.90–7.84 (m, 1H), 7.79–7.73 (m, 2H), 5.82 (s, 1H), 4.64 (s, 2H), 4.17 (s, 2H), 3.82 (d, J = 6.0 Hz, 2H), 2.47 (s, 1H), 2.07 (s, 3H), 1.79 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 171.5, 147.9, 135.8, 133.7, 133.7, 133.1, 132.8, 130.9, 125.4, 63.1 60.3, 45.9, 20.9, 17.1; IR (KBr): ν = 3488, 3220, 2927, 1737, 1543, 1440, 1429, 1381, 1362, 1334, 1295, 1237, 1157, 1031 cm^{-1}; MS (FAB): *m/z* (rel intensity) = 381 ($M+Na^+$, 10), 359 ($M+H^+$, 5); HRMS (FAB): *m/z* = 359.0912, calcd. for $C_{13}H_{17}N_2O_7S$ $(M+H)^+$: 345.0757. The (*E*)-stereochemistry was determined by differential NOE experiments as shown in the Supporting Information.

Procedure for Mitsunobu Reactions in Scheme 1

To a solution of *E*-**10d** (20 mg, 0.05 mmol) in THF were added the nucleophile (0.50 mmol), DIAD (0.15 mmol) and PPh_3 (0.15 mmol) at room temperature. After being stirred for 1 h at room temperature, the solvent was evaporated under vacuum to give a residue. The residue was purified by preparative TLC on silica gel to give the corresponding Mitsunobu products. For the synthesis of **12**, **13** and **14**, Meldrum's acid, 4-bromo-2-chlorophenol and NsNHBoc were employed as nucleophiles to give **12** (yield: 19 mg, 66%), **13** (yield: 28 mg, 87%) and **14** (yield: 36 mg, quant.), respectively.

(*E*)-2-[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl]-3-[(2-nitrophenylsulfonamido)methyl]dec-2-enyl acetate (12): colorless oil. ^{1}H NMR (toluene-d_8): δ = 7.82 (dd, J = 7.8, 1.4 Hz, 1H), 6.91 (dd, J = 7.8, 1.4 Hz, 1H), 6.73 (dt, J = 7.8, 1.4 Hz, 1H), 6.58 (dt, J = 7.8, 1.4 Hz, 1H), 5.99 (t, J = 6.2 Hz, 1H), 4.59 (s, 2H), 3.77 (d, J = 5.9 Hz, 2H), 3.73 (t, J = 5.9 Hz, 1H), 2.71 (d, J = 5.4 Hz, 2H), 1.66 (s, 3H), 1.40–1.09 (m, 18H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (toluene-d_8): δ = 169.7, 164.8, 138.8, 134.2, 132.5, 131.5, 130.6, 130.0, 104.2, 62.4, 45.5, 44.2, 31.8, 30.9, 29.6, 29.1, 28.7, 27.8, 26.6, 25.3, 22.7, 13.9; IR (neat): ν = 3335, 2926, 2855, 1783, 1746, 1542 cm^{-1}; MS (FAB): *m/z* (rel intensity) = 591 ($M+Na^+$, 8), 533 (10), 404 (5), 271 (8); HR-MS: *m/z* = 591.1991, calcd. for $C_{26}H_{36}N_2O_{10}SNa$ $(M+Na)^+$: 591.1988.

(*E*)-2-[(4-Bromo-2-chlorophenoxy)methyl]-3-[(2-nitrophenylsulfonamido)methyl]dec-2-enyl acetate (13): colorless oil. ^{1}H NMR ($CDCl_3$): δ = 8.12–8.06 (m, 1H), 7.84–7.78 (m, 1H), 7.73–7.67 (m, 2H), 7.47 (d, J = 1.8 Hz, 1H), 7.31 (dd, J = 8.7, 1.8 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 5.47 (t, J = 6.0 Hz, 1H), 4.71 (s, 2H), 4.58 (s, 2H), 3.84 (d, J = 6.4 Hz, 2H), 2.17 (t, J = 6.9 Hz, 2H), 2.03 (s, 3H), 1.36–1.24 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 170.8, 153.3, 148.0, 142.2, 133.7, 133.4, 132.8, 132.7, 131.1, 130.6, 129.2, 125.3, 124.5, 115.7, 113.6, 67.0, 62.0, 44.0, 31.7, 31.0, 29.5, 29.1, 28.8, 22.6, 20.9, 14.1; IR (KBr): ν = 3335, 2927, 2856, 1733, 1717, 1541, 1473, 1362, 1241, 1167, 1125, 1025 cm^{-1}; MS (FAB): *m/z* (rel intensity) = 633 ($M+H^+$, 2). 186 (5); HR-MS (FAB): *m/z* = 633.0856, calcd. for $C_{26}H_{33}{}^{81}Br^{35}ClN_2O_7S$ $(M+H)^+$: 633.0860.

(*E*)-2-{[*N*-(*tert*-Butoxycarbonyl)-2-nitrophenylsulfonamido]methyl}-3-[(2-nitrophenylsulfonamido]methyl)dec-2-enyl acetate (14): colorless oil. ^{1}H NMR ($CDCl_3$): δ = 8.32–8.26 (m, 1H), 8.21–8.16 (m, 1H), 7.93–7.87 (m, 1H), 7.81–7.71 (m, 5H), 6.04 (t, J = 6.2 Hz, 1H), 4.67 (s, 2H), 4.51 (s, 2H), 3.85 (d, J = 6.0 Hz, 2H), 2.26 (t, J = 7.8 Hz, 2H), 2.08 (s, 3H), 1.43–1.26 (m, 19H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 171.1, 150.0, 148.0, 147.3, 141.3, 134.4, 133.9, 133.7, 133.5, 133.4, 132.8, 131.9, 130.9, 128.0, 125.5, 124.6, 86.1, 77.2, 61.0, 46.7, 43.4, 31.8, 31.0, 29.6, 29.1, 27.8, 22.6, 21.0, 14.1; IR (KBr): ν = 3336, 3100, 2931, 2858, 1748, 1733, 1716, 1557, 1541, 1472, 1457, 1362, 1223, 1123, 1046 cm^{-1}; MS (FAB): *m/z* (rel intensity) = 727 ($M+H^+$, 5); HR-MS (FAB): *m/z* = 727.2300, calcd. for $C_{31}H_{43}N_4O_{12}S_2$ $(M+H)^+$: 727.2319.

Procedure for the Competitive Acylation of Table 4

A solution of diol **9d**, the competing alcohol **16** or **18** or **19** (1.0 equiv.), catalyst **7** (10 mol% for the total amount of the alcohols) and 2,4,6-collidine (1.7 equiv. for the total amount of the alcohols) in $CHCl_3$ (concentration of the substrate: 0.01 M) was stirred at room temperature for 15 min. After being cooled to −60 °C, acetic anhydride (0.70 equiv. of total amount of the alcohols = 1.4 equiv. for each of the alcohols) was added and stirred at −60 °C for 24 h. The reaction was quenched with MeOH (10 mL), and the solvent was evaporated. The residue was dissolved in AcOEt, washed with 1 *N* HCl, brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude compound was purified by preparative TLC (SiO_2, hexane:AcOEt = 1:2) to afford the mono- and diacylates of **9d** and the competing alcohol. *E*/*Z* ratios of **10d** (monoacylate of **9d**) and **17** (monoacylate of **16**) were determined by the integration of the ^{1}H NMR spectrum.

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References

[1] For non-ezymatic approaches to regioselective acylation of carbohydrates, see: a) T. Kurahashi, T. Mizutani, J. Yoshida, *J. Chem. Soc. Perkin Trans. 1* **1999**, 465–473; b) T. Kurahashi, T. Mizutani, J. Yoshida, *Tetrahedron* **2002**, *58*, 8669–8677; c) K. S. Griswold, S. J. Miller, *Tetrahedron* **2003**, *59*, 8869–8875; d) E. Kattnig, M. Albert, *Org. Lett.* **2004**, *6*, 945–948; e) Y. Demizu, Y. Kubo, H. Miyoshi, T. Maki, Y. Matsumura, N. Moriyama, O. Onomura, *Org. Lett.* **2008**, *10*, 5075–5077.

[2] a) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890–12895; b) Y. Ueda, W. Muramatsu, K. Mishiro, T. Furuta, T. Kawabata, *J. Org. Chem.* **2009**, *74*, 8802–8805.

[3] K. Yoshida, T. Furuta, T. Kawabata, *Angew. Chem.* **2011**, *123*, 4990–4994; *Angew. Chem. Int. Ed.* **2011**, *50*, 4888–4892.

[4] For an example of descrimimation of prochiral primary diols by peptide-based catalysts, see: C. A. Lewis, B. R. Sculimbrene, Y. Xu, S. J. Miller, *Org. Lett.* **2005**, *7*, 3021–3023.

[5] a) T. Schirmeister, H-H. Otto, *J. Org. Chem.* **1993**, *58*, 4819–4822; b) K. Takabe, N. Mase, T. Hisano, H. Yoda, *Tetrahedron Lett.* **2003**, *44*, 3267–3269; c) T. Hisano, K. Onodera, Y. Toyabe, N. Mase, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2005**, *46*, 6293–6295; d) T. Miura, Y. Kawashima, S. Umetsu, D. Kanamori, N. Tsuyama, Y. Jyo, Y. Murakami, N. Imai, *Chem. Lett.* **2007**, *36*, 814–815; e) T. Miura, Y. Kawashima, M. Takahashi, Y. Murakami, N. Imai, *Synth. Commun.* **2007**, *37*, 3105–3109; f) T. Miura, K. Okazaki, K. Ogawa, E. Otomo, S. Umetsu, M. Takahashi, Y. Kawashima, Y. Jyo, N. Koyata, Y. Murakami, N. Imai, *Synthesis* **2008**, 2695–2700; g) T. Miura, S. Umetsu, D. Kanamori, N. Tsuyama, Y. Jyo, Y. Kawashima, N. Koyata, Y. Murakami, N. Imai, *Tetrahedron* **2008**, *64*, 9305–9308.

[6] For excellent recent reviews on (a) organocatalytic acyl transfer reactions and (b) chiral DMAP-type catalysts, see: a) C. E. Müllen, P. R. Schreiner, *Angew. Chem.* **2011**, *123*, 6136–6167; *Angew. Chem. Int. Ed.* **2011**, *50*, 6012–6042; b) R. P. Wurtz, *Chem. Rev.* **2007**, *107*, 5570–5595.

[7] Regioselective acylation of polyol derivatives *via* a molecular recognition process by peptite-based catalysts has been reported. For examples, see: a) ref.[1c]; b) C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744–5747; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616–5619; c) C. A. Lewis, K. E. Longcore, S. J. Miller, P. A. Wender, *J. Nat. Prod.* **2009**, *72*, 1864–1869.

[8] a) T. Fukuyama, C-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374; b) T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353–359.

[9] The importance of the accelerative nature in selective acylation and sulfonylation has been noted, see: a) G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 6496–6502; b) K. W. Fiori, A. L. A. Puchlopek, S. J. Miller, *Nature Chem.* **2009**, *1*, 630–634.

[10] An abstract of Table 3 has been briefly described: T. Furuta, T. Kawabata, in: *Science of Synthesis, Asymmetric Organocatalysis 1, Lewis Base and Acid Catalysts*, (Ed.: B. List), Georg Thieme Verlag, Stuttgart, New York, **2012**, p 529.

[11] The equation was generated by modifying an equation for the selectivity factor of the kinetic resolution, see, H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–331.

[12] The structure of an acylpyridinium ion is tentatively drawn with iminium N^+=C substructure because of the reported X-ray structure of several *N*-acyl-4-dialkylaminopyridinium ions, see: a) P. G. Jones, K. Linoh, A. Z. Blaschette, *Z. Naturforsch. B* **1990**, *45*, 267; b) C. Lohse, S. Hollenstein, T. Laube, *Angew. Chem.* **1991**, *103*, 1678–1679; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1656–1658; c) S. Hollenstein, C. Lohse, T. Laube, *Croat. Chem. Acta* **1992**, *65*, 727–736; d) B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092.

