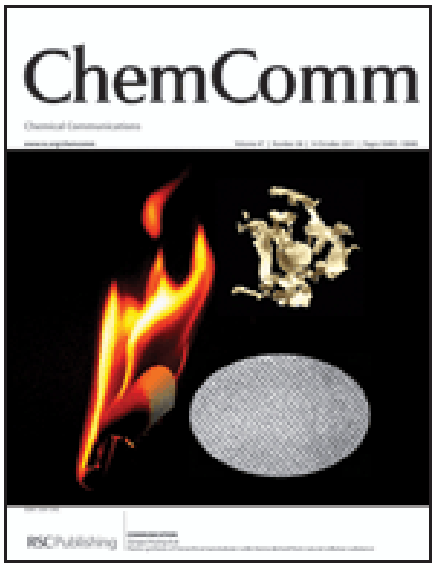
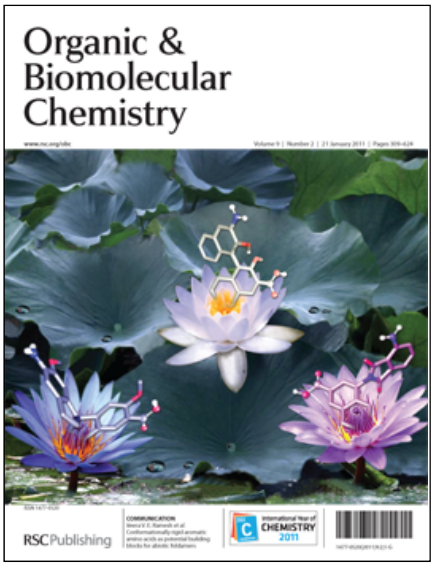




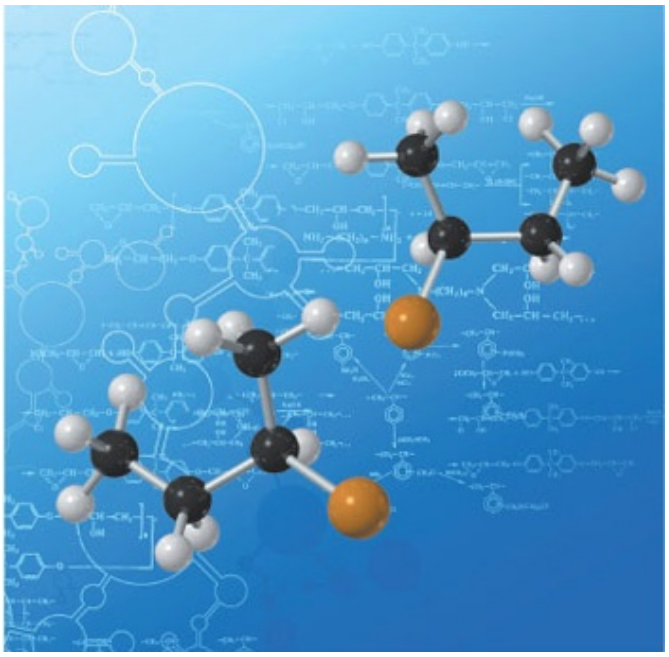
This article is part of the

Organocatalysis

web themed issue

Guest editors: Professors Keiji Maruoka, Hisashi Yamamoto, Liu-Zhu Gong and Benjamin List

All articles in this issue will be gathered together online at www.rsc.org/organocatalysis



ChemComm

Dynamic Article Links

Cite this: *Chem. Commun.*, 2012, **48**, 6981–6983

www.rsc.org/chemcomm

COMMUNICATION

Catalyst-controlled reversal of chemoselectivity in acylation of 2-aminopentane-1,5-diol derivatives†‡

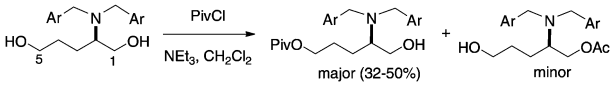
Keisuke Yoshida, Takashi Shigeta, Takumi Furuta and Takeo Kawabata*

Received 8th April 2012, Accepted 15th May 2012
DOI: 10.1039/c2cc32525j

Highly chemo- and regioselective acylation of 2-aminopentane-1,5-diol derivatives has been achieved by organocatalysis. An acyl group can be chemoselectively introduced onto the sterically hindered secondary hydroxy group in the presence of the primary one by virtue of the molecular recognition event of the catalyst.

Development of nonenzymatic approaches toward regioselective acylation of polyol derivatives is one of the current synthetic challenges.[1] We have reported organocatalytic regioselective acylation of carbohydrates[2] and chemoselective monoacylation of linear diols,[3] in which substrate recognition by the catalyst appears to be the origin of the selectivity. Here, we report regio- and chemoselective acylation of 2-aminopentane-1,5-diol derivatives by organocatalysis. The selectivity of acylation was found to be totally catalyst-controlled, independent of the intrinsic reactivity of the diol substrates.

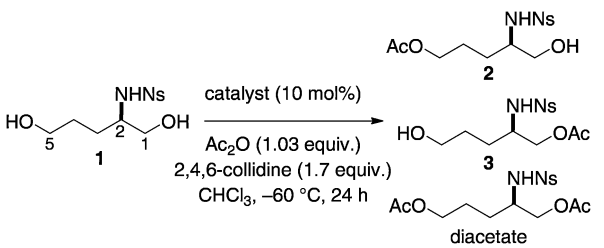
The regioselective acylation of polyol derivatives, including carbohydrates, has been extensively studied using enzymatic protocols.[4] Especially, selective acylation of a primary hydroxy group in the presence of multiple secondary hydroxy groups of carbohydrates has been achieved efficiently. On the other hand, differentiation between the primary hydroxy groups in polyol substrates has been relatively unexplored, probably due to the difficulties resulting from the similar intrinsic reactivity of the primary hydroxy groups. While selective acylation of a primary hydroxy group in primary diol substrates has been reported by enzymatic processes,[5,6] the corresponding non-enzymatic process has scarcely been developed.[7] Hanessian and co-workers reported regioselective monoacylation of (*R*)-*N*-protected-2-aminopentane-1,5-diols, in which the 5-pivalates were obtained as the major acylate in 32–50% yield, which are important building blocks for morphinomimetics (Scheme 1).[8] The regioselectivity of acylation seemed to result from the difference in the intrinsic reactivity of the two hydroxy groups due to steric reasons (substrate-controlled regioselectivity). Inspired by Hanessian's results, we investigated whether the regioselectivity of acylation of *N*-protected (*R*)-2-aminopentane-1,5-diol derivatives could be controlled by the nature of the catalyst.



Scheme 1 Hanessian's example of regioselective acylation based on substrate control.

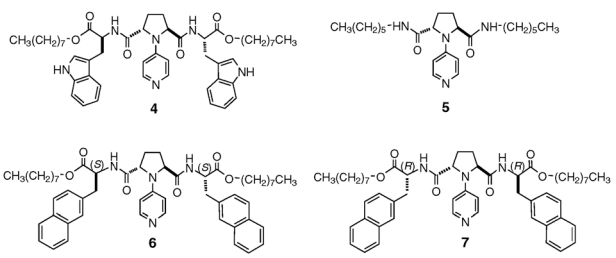
We first examined *N*-(2-nitrobenzenesulfonyl) (Ns)-protected (*R*)-2-aminopentane-1,5-diol (**1**) as a substrate for regioselective acylation (Table 1). The reasons for the choice of the Ns group involves versatile chemical transformation of an NHNs group[9] as well as our previous results from geometry-selective acylation of unsymmetrically substituted 2-alkylidene-1,3-propanediols.[10] Treatment of **1** with acetic anhydride in

Table 1 Effects of catalysts on chemoselectivity of acylation of **1**[a]



Entry	Catalyst	Yield of monoacetates (%)	**2** : **3**	Yield of diacetate (%)
1	DMAP	38	16 : 84	30
2	**4**	70	30 : 70	12
3	**5**	75	83 : 17	15
4	**6**	88	96 : 4	7
5	**7**	95	>99 : <1	3

[a] The reactions were run at the substrate concentration of 0.01 M.



Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan. E-mail: kawabata@scl.kyoto-u.ac.jp; Fax: +81 774 38 3197; Tel: +81 774 38 3190

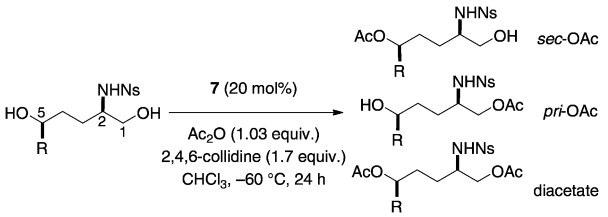
† This article is part of the joint *ChemComm–Organic & Biomolecular Chemistry* 'Organocatalysis' web themed issue.

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, copies of ^{1}H NMR and ^{13}C NMR. See DOI: 10.1039/c2cc32525j

the presence of 4-dimethylaminopyridine (DMAP) in chloroform at −60 °C gave 5-acetate **2** and 1-acetate **3** in a 16 : 84 ratio in a combined yield of 38% with concomitant formation of the diacetate in 30% yield (entry 1). This result indicates that the C(1)–OH is intrinsically more reactive than the C(5)–OH in substrate **1**, and also that the control of over-acylation is difficult in the DMAP-catalyzed acylation even by performing the reaction at −60 °C. Similar regioselectivity favouring the formation of **3** (**2** : **3** = 30 : 70) was observed in the acylation catalyzed by **4** (entry 2), which was reported to be an effective catalyst for regioselective acylation of glycopyranoses and chemoselective acylation of linear diols.[2,3] Contrary to these results, 5-acetate **2** was obtained as the major acylate (**2** : **3** = 83 : 17) in the acylation catalyzed by **5** (entry 3). High regioselectivity (**2** : **3** = 96 : 4) was observed in the acylation of **1** catalyzed by **6** (entry 4). The monoacetates were obtained in the increased combined yield of 88% with diminished formation of the diacetate in 7% yield. Further selective acylation was achieved by catalyst **7**. Treatment of **1** with acetic anhydride in the presence of 10 mol% of **7** gave 5-acetate **2** as the sole monoacetate in 95% yield with only 3% formation of the diacetate (entry 5). Thus, regioselectivity of the acylation of **1** promoted by **7** was found to be totally catalyst-dependent. It was also observed in the acylation reactions in entries 3–5 that the higher ratio of 5-*O*-acylation was associated with the higher ratio of mono/diacylation. These results suggest that 5-*O*-acylation catalyzed by catalysts **5–7** proceeds in an accelerated manner.

The results in Table 1 indicate that 5-*O*-selective acylation can be attained in a catalyst-controlled manner, overcoming the intrinsic higher reactivity of the C(1)–OH of substrate **1**, provided that the regiochemical profile of the DMAP-catalyzed acylation is the measure of substrate-controlled selectivity (entry 1). However, the steric environment around the C(5)–OH in **1** seems to be less hindered compared to that of the C(1)–OH, which was suggested by Hanessian's regiochemical results observed in the acylation of the related substrates (Scheme 1). We then examined acylation of the corresponding derivatives of **1** with a secondary hydroxy group at C(5), **8–11** (Table 2). The primary hydroxy group at C(1) of **8** (R = Me) was acylated almost exclusively in DMAP-catalyzed acylation, indicating the much higher intrinsic reactivity of the primary C(1)–OH than the secondary C(5)–OH (entry 1). Contrary to this result, **8** underwent acylation almost exclusively on the secondary hydroxy group at C(5) in the presence of catalyst **7** (entry 2). Similarly, chemoselective acylation at the secondary hydroxy group was observed in substrate **9** possessing an ethyl substituent at C(5) (entry 3). Surprisingly, acylation took place almost exclusively on the sterically hindered secondary hydroxy group at C(5) of **10** (R = *i*-Pr) in the presence of catalyst **7** (entry 4). Acylation of **11** with a butyl substituent at C(5) took place to give the acylate of the secondary hydroxy group (*sec*-OAc : *pri*-OAc = 98 : 2, entry 5), whereas that of its C(5)-epimer, 5-***epi*-11**, gave the acylate of the primary hydroxy group almost exclusively (*sec*-OAc : *pri*-OAc = 3 : 97, entry 7). The acylation of **11** in the presence of **6**, the diastereomeric catalyst of **7**, gave *ca.* 1 : 1 mixture of the acylates of the

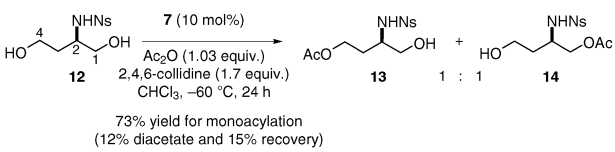
Table 2 Acylation of the secondary *vs.* the primary hydroxy groups catalyzed by **7**[a]



Entry	R	Substrate	Yield of monoacetates (%)	*sec*-OAC : *pri*-OAC	Yield of diacetates (%)	Recovery (%)
1[b]	Me	**8**[c]	90	1 : 99	4	6
2	Me	**8**[c]	79	98 : 2	11	10
3	Et	**9**[d]	78	98 : 2	12	12
4	*i*-Pr	**10**[d]	81	98 : 2	10	9
5	Bu	**11**[c]	76	98 : 2	13	11
6[e]	Bu	**11**[c]	62	46 : 54	14	21
7	Bu	5-***epi*-11**	89	3 : 97	3	7
8[e]	Bu	5-***epi*-11**	72	<1 : >99	0	28

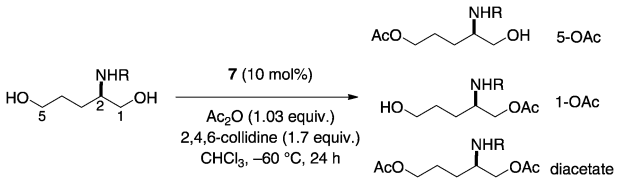
[a] The reactions were run at the substrate concentration of 0.01 M. [b] DMAP (20 mol%) was used as catalyst. [c] The absolute configuration at C(5) was determined by a modified Mosher's method. See ESI. [d] The absolute configuration at C(5) was tentatively assigned according to its reactivity toward chemoselective acylation, see text. [e] Catalyst **6** was employed.

secondary and primary hydroxy groups (entry 6). An exclusive formation of the acylate of the primary hydroxy group among the monoacylates was observed in the acylation of 5-***epi*-11** promoted by **6** (entry 8). The results observed in the acylation reactions in entries 5–8 suggest that chirality of the side chains of catalysts **6** and **7** is responsible for recognition of the substrate chirality. The absolute configuration at C(5) of **8** and **11** was determined by a modified Mosher's method.[11,12] The absolute configuration at C(5) of **9** and **10** was tentatively assigned based on the comparison of their chemoselectivity for acylation with that of **11** and 5-***epi*-11**. The results in Table 2 indicate that highly chemoselective acylation of **8–11** catalyzed by **7** (entries 2–5) was assumed to result from recognition of the distance between the OH group and the NHNs group as well as chirality at C(5) by catalyst **7**. The assumption about length recognition was supported by the reaction of 2-amino-butane-1,4-diol derivative **12** (Scheme 2). Treatment of **12** with the same procedure as that in Table 2 gave 4-acetate **13** and 1-acetate **14** in *ca.* 1 : 1 ratio. The difference of the only one methylene unit between **12** and **1** resulted in a dramatic loss of the regioselectivity in the acylation of **12**. This suggests that catalyst **7** promotes regioselective acylation based on the recognition of the distance between the functionalities in the substrates.



Scheme 2 Loss in regioselectivity of acylation of **12** resulting from one methylene unit difference between **12** and **1** (*cf.* Table 1, entry 5).

Table 3 Effects of solvents, temperature, and nitrogen-protecting groups on chemoselectivity of acylation of 2-aminopentane-1,5-diol derivatives[a]



Entry	R	Substrate	Solvent	Temperature (°C)	Yield of monoacetates (%)	5-OAc : 1-OAc	Yield of diacetate (%)
1	Ns	**1**	$CHCl_3$	20	81	81 : 19	10
2	Ns	**1**	$CHCl_3$	0	85	96 : 4	8
3	Ns	**1**	$CHCl_3$	−20	90	99 : 1	6
4	Ns	**1**	$CHCl_3$	−60	95	> 99 : < 1	3
5	Ns	**1**	THF	−60	47	24 : 76	16
6	Ns	**1**	DMF	−60	35	48 : 52	10
7	Boc	**15**	$CHCl_3$	−60	80	16 : 84	~0
8	Cbz	**16**	$CHCl_3$	−60	49	31 : 69	15
9	Ts	**17**	$CHCl_3$	−60	84	52 : 48	8

[a] The reactions were run at the substrate concentration of 0.01 M.

In order to gain mechanistic insights into the observed chemoselectivity in the acylation of **1** catalyzed by **7**, effects of solvents, temperature, and substrate structure were investigated (Table 3). The selectivity for 5-*O*-acylation of **1** in the presence of **7** increases along with the decrease in the temperature (entries 1–4) and the decrease of the solvent polarity (entries 4–6). This observation indicates that the driving force for the 5-*O*-acylation may involve the hydrogen bonding interaction between substrate **1** and catalyst **7**. The Ns-protecting group of the nitrogen was found to be critical for the 5-*O*-acylation of 2-aminopentane-1,5-diol derivatives. Reactions of *N*-Boc and *N*-Cbz analogues, **15** and **16**, respectively, gave the 1-*O*-acetate as the major acylate (entries 7 and 8) by the similar treatment to that for *N*-Ns derivative **1**. The *N*-Ts derivative **17** underwent regio-random acylation by the similar treatment as above (entry 9). These results suggest that the more acidic hydrogen of the NHNs group in **1** serves as a hydrogen bond donor suitable for the interaction with catalyst **7**. Obviously, further investigations including spectroscopic analyses of the catalyst–substrate interaction are to be carried out for clarifying the mechanism of the regio- and chemoselective acylation promoted by catalyst **7**.

In conclusion, we have developed highly chemo- and regioselective acylation of 2-aminopentane-1,5-diol derivatives promoted by organocatalysts. Catalyst **7** appears to be able to recognize the distance between the functionalities and chirality of the substrates, and promote catalyst-controlled regio- and chemoselective acylation efficiently. By virtue of the molecular recognition event of the catalyst, an acyl group can be chemoselectively introduced onto the sterically much hindered secondary hydroxy group in the presence of the primary one.

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

1 (*a*) T. Kurahashi, T. Mizutani and J. Yoshida, *J. Chem. Soc., Perkin Trans. 1*, 1999, 465; (*b*) T. Kurahashi, T. Mizutani and J. Yoshida, *Tetrahedron*, 2002, **58**, 8669; (*c*) K. S. Griswold and S. J. Miller, *Tetrahedron*, 2003, **59**, 8869; (*d*) E. Kattnig and M. Albert, *Org. Lett.*, 2004, **6**, 945; (*e*) Y. Demizu, Y. Kubo, H. Miyoshi, T. Maki, Y. Matsumura, N. Moriyama and O. Onomura, *Org. Lett.*, 2008, **10**, 5075.

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

3 K. Yoshida, T. Furuta and T. Kawabata, *Angew. Chem., Int. Ed.*, 2011, **50**, 4888.

4 For an excellent review, see: D. Kadereit and H. Waldmann, *Chem. Rev.*, 2001, **101**, 3367.

5 For enzymatic differentiation of unsymmetrical 1,5-diols, see: C. Oger, Z. Marton, Y. Brinkmann, V. Bultel-Poncé, T. Durand, M. Graber and J.-M. Galano, *J. Org. Chem.*, 2010, **75**, 1892.

6 For enzymatic differentiation of unsymmetrically substituted 2-alkylidene-1,3-propanediols, see: (*a*) T. Schirmeister and H.-H. Otto, *J. Org. Chem.*, 1993, **58**, 4819; (*b*) K. Takabe, N. Mase, T. Hisano and H. Yoda, *Tetrahedron Lett.*, 2003, **44**, 3267; (*c*) T. Hisano, K. Onodera, Y. Toyabe, N. Mase, H. Yoda and K. Takabe, *Tetrahedron Lett.*, 2005, **46**, 6293; (*d*) T. Miura, Y. Kawashima, S. Umetsu, D. Kanamori, N. Tsuyama, Y. Jyo, Y. Murakami and N. Imai, *Chem. Lett.*, 2007, 814; (*e*) T. Miura, Y. Kawashima, M. Takahashi, Y. Murakami and N. Imai, *Synth. Commun.*, 2007, **37**, 3105; (*f*) T. Miura, K. Okazaki, K. Ogawa, E. Otomo, S. Umetsu, M. Takahashi, Y. Kawashima, Y. Jyo, N. Koyata, Y. Murakami and N. Imai, *Synthesis*, 2008, 2695; (*g*) T. Miura, S. Umetsu, D. Kanamori, N. Tsuyama, Y. Jyo, Y. Kawashima, N. Koyata, Y. Murakami and N. Imai, *Tetrahedron*, 2008, **64**, 9305.

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

8 S. Hanessian, S. Parthasarathy and M. Mauduit, *J. Org. Chem.*, 2003, **46**, 34.

9 (*a*) T. Fukuyama, C.-K. Jow and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373–6374; (*b*) T. Kan and T. Fukuyama, *Chem. Commun.*, 2004, 353.

10 A Ns-protective group was found to be effective for geometry-selectivity in the acylation of unsymmetrically substituted 2-alkylidene-1,3-propanediols, see: T. Furuta and T. Kawabata, *Science of Synthesis, Asymmetric Organocatalysis 1, Lewis Base and Acid Catalysts*, ed. B. List, George Thieme Verlag KG, Stuttgart, New York, 2012, p. 529.

11 Compounds **8–11** were prepared by addition of Grignard reagents to the corresponding 5-al derivatives, see ESI‡.

12 T. Kusumi, I. Ohtani, Y. Inouye and H. Kakisawa, *Tetrahedron Lett.*, 1988, **29**, 4731.