ORGANIC LETTERS

2008
Vol. 10, No. 10
2027−2030

Enantiopure 1,5-Diols from Dynamic Kinetic Asymmetric Transformation. Useful Synthetic Intermediates for the Preparation of Chiral Heterocycles

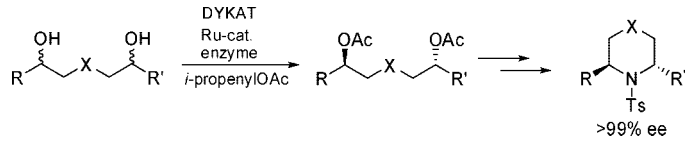
Karin Leijondahl, Linnéa Borén, Roland Braun, and Jan-E. Bäckvall*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

jeb@organ.su.se

Received March 1, 2008

ABSTRACT



Dynamic kinetic asymmetric transformation (DYKAT) of a series of 1,5-diols has been performed in the presence of *Candida antarctica* lipase B (CALB), *Pseudomonas cepacia* lipase II (PS-C II), and ruthenium catalyst 4. The resulting optically pure 1,5-diacetates are useful synthetic intermediates, which was demonstrated by the syntheses of both an enantiopure 2,6-disubstituted piperidine and an enantiopure 3,5-disubstituted morpholine.

The combined metal- and enzyme-catalyzed dynamic kinetic resolution (DKR) has developed into a useful method for the synthesis of enantiopure secondary alcohols.[1−3] The simplicity and scalability of the method has attracted industrial interest,[4] and we recently demonstrated a laboratory procedure[5] on a 1 mol scale using a low catalytic loading. The DKR of secondary alcohols can be extended to the simultaneous DKRs of two chiral sec-alcohol centers, which leads to a dynamic kinetic asymmetric transformation (DYKAT) of diols.[6,7] Recently, efficient procedures for DYKAT of symmetric 1,3- and 1,4-diols were reported,[7] using the second-generation catalyst system.[2a,8]

Chiral 1,5-diols are important synthetic intermediates for the preparation of enantiomerically pure 2,6-disubstituted and 3,5-disubstituted six-membered heterocycles.[9,10] In this communication, we report on a DYKAT of 1,5-diols, leading to diol derivatives in high diastereo- and enantioselectivities.

The diols used in this study for the DYKAT are shown in Figure 1 (**1a**−**g**). The symmetrical diols **1b**, **1c**, **1e**, **1f**, and

(1) (a) Pàmies, O.; Bäckvall, J. E. *Chem. Rev.* **2003**, *103*, 3247–3262. (b) Kim, M. J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587. (c) Pàmies, O; Bäckvall, J. E. *Trends Biotechnol.* **2004**, *22*, 130–135. (d) Martín-Matute, B.; Bäckvall, J. E. *Opin. Chem. Curr. Biol.* **2007**, *11*, 226–232. (e) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327. (f) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563–1601.

(2) (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825. (b) Martín-Matute, B.; Åberg, J. B.; Edin, M.; Bäckvall, J. E. *Chem. Eur. J.* **2007**, *13*, 6063–6072.

(3) (a) Kim, N.; Ko, S.-B.; Kwon, M. S.; Kim, M.-J.; Park, J. *Org. Lett.* **2005**, *7*, 4523–4526. (b) Norinder, J.; Bogár, K.; Kanupp, L.; Bäckvall, J. E. *Org. Lett.* **2007**, *9*, 5095–5098.

(4) Verzijl, G. K. M.; De Vries, J. G.; Broxterman, Q. B. WO 0190396 A1 20011129, CAN 136:4770.

(5) Bogár, K.; Martín-Matute, B.; Bäckvall, J. E. *Beilstein J. Org. Chem.* **2007**, *3*, 50.

(6) (a) Persson, B. A.; Huerta, F. F.; Bäckvall, J. E. *J. Org. Chem.* **1999**, *64*, 5237–5240. (b) Edin, M.; Martín-Matute, B.; Bäckvall, J. E. *Tetrahedron: Asymmetry* **2006**, *17*, 708–715.

(7) Martín-Matute, B.; Edin, M.; Bäckvall, J. E. *Chem. Eur. J.* **2006**, *12*, 6053–6061.

(8) For a mechanistic study of the second-generation ruthenium catalyst, see ref 2b.

(9) (a) Lieandro, E.; Maiorana, S.; Papagni, A.; Pryce, M.; Gerosa, A. Z.; Riva, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1891–1894. (b) Dave, R.; Sasaki, A. *Org. Lett.* **2004**, *6*, 15–18.

(10) (a) Stereodefined 2,6-disubstituted piperidines occur as alkaloids in nature: Strunzand, G. M.; Finlay, J. A. *The alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, **1986**; Vol. 26, p 89. (b) Jones, T. H.; Blum, M. S.; Robertsson, H. G. *J. Nat. Prod.* **1990**, *53*, 429–435. (c) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198–8207.

10.1021/ol800468h CCC: $40.75
Published on Web 04/11/2008

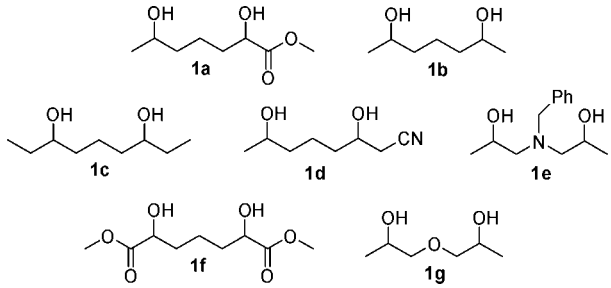
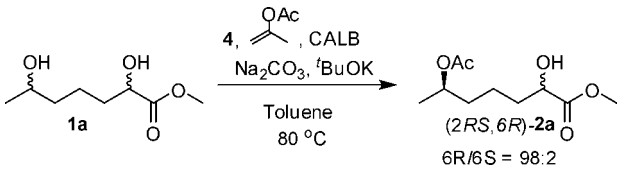


Figure 1. Diols used in the DYKAT.

1g are *dl*/*meso* mixtures, and the unsymmetrical diols **1a** and **1d** are racemic diastereomeric mixtures. Diols **1b**, **1e**, and **1g** were prepared according to literature procedures.[11] The other diols, **1a**, **1c**, **1d**, and **1f**, were synthesized from simple starting materials, and their preparation is given in the Supporting Information.

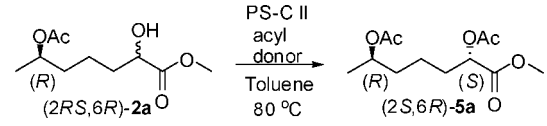
For the development of the enzyme and ruthenium-catalyzed DYKAT process, we chose diol **1a** as a model substrate. Previous studies have shown that *Candida antarctica* lipase B (CALB) is very selective in the acetylation of secondary alcohols as well as diols when a methyl group is the medium-sized group according to Kazlauskas' rule.[12] However, the presence of an ester as the medium-sized group did not allow the acylation to occur,[13] and this was confirmed by the DYKAT of **1a** with CALB that afforded monoacetate (2*RS*,6*R*)-**2a** (Scheme 1). The resulting (2*RS*,6*R*)-monoacetate **2a** was a diastereomeric mixture, in which the acetate carbon (C-6) had the (*R*)-configuration ((6*R*)/(6*S*) = 98:2).

Scheme 1. DYKAT of Diol **1a**



Pseudomonas cepacia lipase, PS-C II, has been used in similar reactions and can also tolerate larger groups, such as esters as the medium-sized groups.[13] However, attempts to use PS-C II for both alcohol centers gave a moderate selectivity at the alcohol next to the methyl group. We therefore decided to use CALB for the first step and PS-C II for the second step. The second acylation using PS-C II was next investigated, and monoacetate (2*RS*,6*R*)-**2a** was used as the substrate to determine the selectivity of that step. Two different acyl donors, isopropenyl acetate (IPA) and vinyl acetate (VA), were used, and in both cases, a pseudo *E* value of 21 was obtained (Table 1, entry 1 vs 2). In the case of IPA, the reaction was slightly slower.

Table 1. Kinetic Asymmetric Transformation of Monoacetate (2*RS, 6R*)-**2a** Using Different Acyl Donors[a]



entry	enzyme	acyl donor	time (h)	*S*,*R*:*R*,*S* diacetate	% diacetate	pseudo *E*
1	0.5 mg of PS-C	IPA	19	95:5	13	21
2	0.5 mg of PS-C	VA	19	94:6	33	21

[a] The reactions were performed on a 0.1 mmol scale using 3 equiv of acyl donor in 1 mL of toluene at 80 °C.

To achieve an efficient DYKAT, a fast epimerization catalyst compatible with the enzyme is required. Our group has used two different catalysts for racemization/epimerization of secondary alcohols in different DKR/DYKAT protocols (Figure 2).[2a,14]

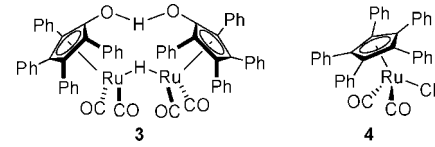


Figure 2. Epimerization catalysts.

Shvo's dimeric catalyst **3** is activated by heat, and both monomers are active in the catalytic cycle. More recently, catalyst **4** was developed in our laboratory.[2a] This catalyst needs activation by base and is very efficient under mild reaction conditions. In order to find out which catalyst would give the most efficient epimerization of the alcohol closest to the carbomethoxy group in diol **1a**, enantiomerically pure monoacetate **2a** was required. The kinetic asymmetric transformation (KAT) of monoacetate (2*RS*,6*R*)-**2a** when run to higher conversion provided enantiopure (2*R*,6*R*)-**2a**, which was further used for the epimerization studies.[15] Both of the catalysts were tested in the epimerization of (2*R*,6*R*)-**2a**, and

(11) (a) **1b** was synthesized by $NaBH_4$ reduction of the 2,6-heptanedione according to: Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675–681. (b) For the synthesis of **1e**, see: Dubois, L.; Fiaud, J.-C.; Kagan, H. B. *Tetrahedron* **1995**, *51*, 3803–3812. (c) For the synthesis of **1g**, see: Sexton, A. R.; Britton, E. C. *J. Am. Chem. Soc.* **1953**, *75*, 4357–4358. (d) Summerbell, R. K.; Jerina, D. M.; Grula, R. J. *J. Org. Chem.* **1962**, *27*, 4433–4436.

(12) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.

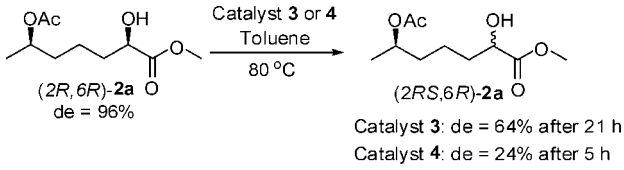
(13) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J. E. *Org. Lett.* **2000**, *2*, 1037–1040.

(14) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650.

(15) The reaction was performed on a 1 mmol scale using 30 mg of PS-C II, 3 equiv of *p*-ClPhOAc as acyl donor in 5 mL of toluene at 60 °C for 48 h, yielding monoacetate (2*R*,6*R*)-**2a** in 41% yield and 96% de.

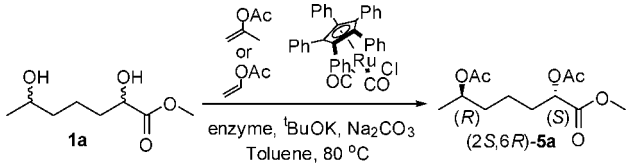
catalyst **4** proved to be the most efficient catalyst, decreasing the de to 24% within 5 h (Scheme 2).

Scheme 2. Epimerization of (2*R*,6*R*)-**2a** Using Catalysts **3** and **4**



We next studied the DYKAT of **1a** using ruthenium catalyst **4** and a combination of the lipases CALB and PS-C II. The DYKAT of diol **1a** was performed as a one-pot, two-step reaction using CALB and PS-C II as the acylation catalysts for the first and the second step, respectively. The results are given in Table 2.

Table 2. DYKAT of **1a**[a]



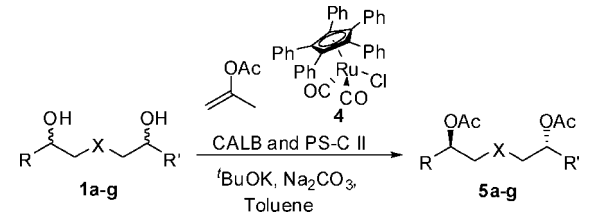
entry	acyl donor (equiv)	equiv of ^{t}BuOK	time (h)	% ee[b]	*anti*/*syn*[c]	% diacetate
1[d]	IPA (6)	0.05	77	99	53:47	21
2[d]	VA (6)	0.05	77	80	61:39	75
3[e]	IPA (6)	0.05	77	95	70:30	96
4[d,f]	IPA (3)	0.025	72	99	79:21	93

[a] Unless otherwise noted, all reactions were performed on a 1 mmol scale in 2.5 mL of toluene with 0.05 equiv of Ru-catalyst, 1 mmol of Na_2CO_3, 30 mg of CALB, and 5 mg of PS-C II at 80 °C under argon. [b] (*S*,*R*−*R*,*S*)/(*S*,*R*+*R*,*S*). [c] ((*S*,*R*+*R*,*S*)/(*R*,*R*+*S*,*S*+*S*,*R*+*R*,*S*)): ((*R*,*R*+*S*,*S*)/(*R*,*R*+*S*,*S*+*S*,*R*+*R*,*S*)). [d] PS-C II was added after 5 h. [e] 10 mg of PS-C II was added after 10 h. [f] The reaction was performed on a 1 mmol scale in 1 mL of toluene with 0.025 equiv of Ru-catalyst, 1 mmol of Na_2CO_3, 2.5 mg of CALB, and 2.5 mg of PS-C II at 80 °C under argon.

The DYKAT conditions were optimized with respect to two different acyl donors, IPA and VA (Table 2, entry 1 vs 2). When 5 mg of PS-C II was added after 5 h and no excess of base was used, IPA gave a higher ee but a slightly lower *anti*/*syn* ratio and a lower conversion than the reaction with VA (entry 1 vs 2). We chose to continue our study using IPA as the acyl donor since it gave a more selective reaction in the CALB-catalyzed acylation, yielding the (6*R*)-monoacetate in 99% ee. Increasing the amount of PS-C II to 10 mg, using IPA as an acyldonor, provided a higher yield and an improved *anti*/*syn* ratio but a lower ee (95% ee) (entry 3). Attempts to further increase the amount of PS-C II were unsuccessful, causing a decrease in both the enantio- and diastereoselectivities. A concentrated reaction, with 2.5 mg of each enzyme (CALB and PS-C II), 3 equiv of IPA, and 2.5 mol % of Ru-catalyst **4** in 1 mL of toluene gave a high yield (93%), an excellent ee (99%), and an *anti*/*syn* ratio of 79:21 (entry 4).[16]

With the optimized results from Table 2 as a guideline, a range of 1,5-diols were acylated, and the results are given in Table 3. It was only for diol **1a** that two different enzymes were employed for the two acylation steps. For all other diols, the same single enzyme (CALB for **1b**−**1e**, **1g**; PS-C II for **1f**) was used for both steps.

Table 3. DYKAT of 1,5-Diols[a]



entry	diol	time (h)	temp(°C)	% ee[b]	*anti*/*syn*[b]	% yield[b,c]
1	**1a**[d,e,f]	72	80	98	80:20	91 (71)
2	**1b**	24	50	>99	96:4	96 (80)
3	**1c**[f]	48	50	>99	94:6	96 (73)
4	**1c**	40	50	>99	96:4	89
5	**1d**[e,f,g]	40	100	>99	94:6	83 (61)
6	**1e**	48	50	>99	>99:1	99 (83)
7	**1f**[e,h]	77	80	37	55:45	77
8	**1g**[i]	46	50	>99	95:5	98 (81)

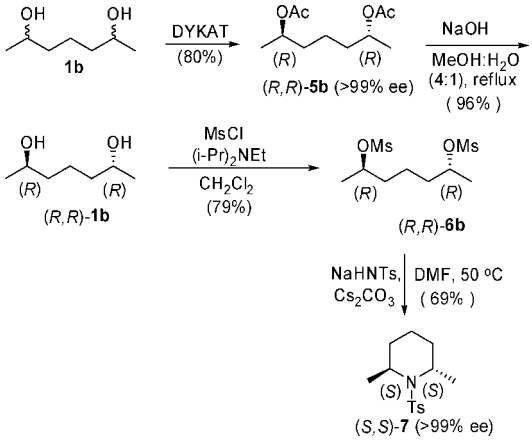
[a] Unless otherwise stated, the reactions were performed on a 1 mmol scale in 1 mL of toluene with 3 equiv of isopropenyl acetate, 2.5−5 mg of CALB, 0.025 equiv of Ru-catalyst, 0.025 equiv of ^{t}BuOK, and 1 mmol of Na_2CO_3 under argon. [b] Determined by chiral GC. [c] Isolated yield in parenthesis. [d] The reaction was run on a 2 mmol scale using 60 mg of CALB, and 20 mg of PS-C II was added after 5 h. [e] 6 equiv of isopropenyl acetate was used. [f] 0.05 equiv of Ru-catalyst, 0.05 equiv of ^{t}BuOK in 2.5 mL of toluene. [g] The reaction was run at 100 °C using 100 mg of CALB. [h] 0.05 equiv of Ru-catalyst, 10 mg of PS-C II, and 0.06 equiv of ^{t}BuOK in 2.5 mL of toluene was used. [i] The reaction was run on a 5 mmol scale.

Using the optimized conditions from Table 2, **1a** was acylated into diacetate **5a** in a good yield and high enantioselectivity (98% ee) within 72 h at 80 °C (Table 3, entry 1). Diacetate **5a** was formed in an *anti*/*syn* ratio of 80:20. Diol **1b**, which is a symmetrical diol with methyl groups as medium-sized groups at each stereogenic center, was transformed into diacetate **5b** in good yield using only CALB and Ru-catalyst **4**. Diacetate **5b** was obtained in excellent enantioselectivity (>99% ee) and high diastereoselectivity (*anti*/*syn* = 96:4) (entry 2). In a similar manner, diol **1c** was transformed into diacetate **5c** in >99% ee (entries 3 and 4). To enable a DYKAT of diol **1d**, the temperature had to be increased up to 100 °C for the epimerization to be efficient, and due to the high temperature, a larger amount of enzyme was required (entry 5). Under these conditions, diacetate **5d** was obtained in an excellent ee with a good diastereoselectivity. DYKAT of **1e** was highly efficient and afforded

(16) A control experiment was run without any enzyme present which gave no detectable amount of diacetate ruling out the potential problem with chemical acylation taking place in the reaction.

diacetate **5e** in high yield and excellent diastereo- and enantioselectivities (entry 6). Diol **1f**, which is a symmetrical diol with carbomethoxy groups as medium-sized groups on each stereogenic center, can be transformed into diacetate **5f** by using PS-C II instead of CALB. When 10 mg of PS-C II was used together with a small excess of base, the diacetate **5f** was formed in 77% yield but with only 37% ee and a very low *anti*/*syn* ratio (55:45) (entry 7). The reason for this low selectivity is most likely that the epimerization is very slow for this substrate in the presence of the enzyme. Finally, diacetate **5g** was obtained from **1g** in excellent enantio- and diastereoselectivities (entry 8).

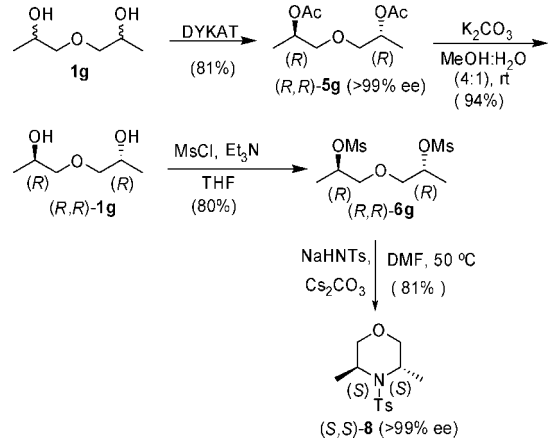
Scheme 3. Synthesis of Piperidine (*S*,*S*)-**7**



To demonstrate the utility of the diacetates **5**, the enantiomerically pure diacetate (*R*,*R*)-**5b** (>99% ee) was hydrolyzed to the corresponding diol, which was subsequently mesylated. Reaction of the thus-formed dimesylate (*R*,*R*)-**6b** with sodium tosylamide (NaNHTs) in DMF at 50 °C afforded the corresponding piperidine (*S*,*S*)-**7** in >99% ee (*trans*/*cis* = 95:5) (Scheme 3).

In a similar manner, the enantiomerically pure diacetate (*R*,*R*)-**5g** (>99% ee) was converted into the corresponding

Scheme 4. Synthesis of Morpholine (*S*,*S*)-**8**



dimesylate (*R*,*R*)-**6g** via diol (*R*,*R*)-**1g**. Reaction of this dimesylate with NaNHTs in DMF afforded *N*-tosyl-protected morpholine (*S*,*S*)-**8** in >99% ee (*trans*/*cis* = 95:5) (Scheme 4).

In conclusion, an efficient enantio- and diastereoselective synthesis of 1,5-diol diacetates via DYKAT has been developed. The enantiopure diacetates are useful building blocks for the enantioselective synthesis of important 2,6-disubstituted and 3,5-disubstituted six-membered heterocycles.

Acknowledgment. This work was financially supported by the Swedish Foundation for Strategic Research, the Swedish Research Council, and AstraZeneca. We thank Dr. Jan-Erik Nyström, AstraZeneca R&D, Södertälje, for fruitful discussions.

Supporting Information Available: Synthesis and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800468H