VIP Asymmetric Catalysis

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Kinetic Resolution of 1,2-Diols through Highly Site- and Enantioselective Catalytic Silylation**

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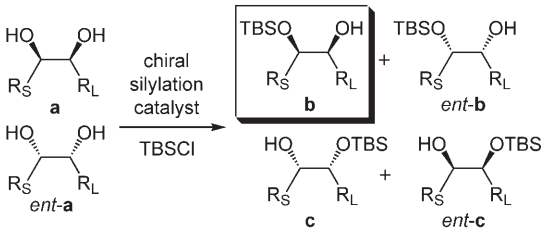
1,2-Diols are components of a variety of biologically active molecules; facile access to this class of building blocks in high enantiomeric purity is thus an important objective.[1] Catalytic protocols delivering diols that are not available through asymmetric dihydroxylation[2] (e.g., *syn*-1,2-diol products from *cis* alkenes)[2,3] and which furnish differentiated hydroxy groups are particularly desirable. We have developed an efficient method for kinetic resolution[4] of three classes of acyclic 1,2-diols through catalytic asymmetric silylation.[5,6]

Enantioselective silylation of a chiral 1,2-diol is more complex than that of the related *meso* isomers[5] and necessitates a higher degree of precision from the chiral catalyst. An effective kinetic resolution, as expected, must involve preferable reaction with one enantiomer of the substrate (rate of **a**→**b** ≫ *ent*-**a**→*ent*-**b**; Scheme 1). This class

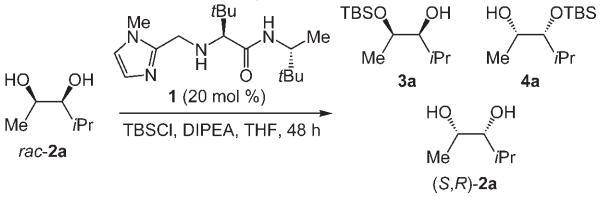


Scheme 1. Effective kinetic resolution demands high site selectivity as well as enantioselectivity. R_S and R_L are small and large R groups, respectively. TBS = *tert*-butyldimethylsilyl.

of transformations, however, demands an additional and critical attribute: it is imperative that silylations proceed with high site selectivity[7] (rate of **a**→**b** ≫ **a**→*ent*-**c**; Scheme 1). Kinetic resolution of a 1,2-diol, therefore, does more than challenge a catalyst's ability to promote preferential silylation of one enantiomer; it illustrates the extent to which a catalyst can differentiate between two hydroxy sites—the smaller the difference in size between R_S and R_L (Scheme 1), the more discriminating the catalyst needs to be.

We began by studying the kinetic resolution of *rac*-**2a** (Table 1). Catalyst **1**, a small molecule (MW = 308.5 g mol^{-1}) that was recently identified to be effective in promoting

Table 1: Initial studies on catalytic kinetic resolution of diol **2a**.[a]



Entry	*T* [°C]; Conv. [%][b]	**3a**:**4a**[c]	Recovered **2a** *ee* [%][c]	Product **3a** *ee* [%][c]	k_{rel}[b]
1	4; 61	>98:<2	70	45	5
2	−15; 53	>98:<2	82	71	16
3	−30; 30	>98:<2	38	88	24
4	−50; 27	>98:<2	34	93	35

[a] Conditions: 1.0 M in diol, 1.25 equiv *N*,*N*-diisopropylethylamine (DIPEA), 1.0 equiv TBSCl. [b] Conversions and k_{rel} values calculated by the methods of Kagan.[9] [c] Ratios of **3a**:**4a** and *ee* values determined by chiral GLC analysis (see the Supporting Information for details).

enantioselective silylations of *meso* diols,[5] initiates asymmetric silylation. Moderate selectivity is obtained at 4 °C (Table 1, entry 1; $k_{rel} = 5$). At lower reaction temperatures, selectivity increases (Table 1, entries 1–4), and, at −50 °C, catalytic resolution proceeds with $k_{rel} = 35$ (Table 1, entry 4). In all cases, the silyl ether derived from reaction of the more hindered carbinol is not detected (<2% by GLC analysis).[8] Further investigations allowed us to establish conditions that provide **2a** in 96% *ee* and 44% yield after purification (see Table 2, entry 1).

A variety of *syn*-1,2-diols can be catalytically resolved (Table 2); selectivities are usually at useful levels ($k_{rel} > 10$).[10] Several additional points merit mention: 1) Reactions proceed with high site selectivity; in most cases, little (3% and 2% in Table 2, entries 4 and 5, respectively) or none of the isomeric silyl ether **4** is generated (<2% in Table 2, entries 1–3, and 6). Only with substrates bearing a carboxylic ester (Table 2, entries 7 and 8) is 14% of isomer **4** formed (see below for further discussion). 2) As a result of high site selectivities, unreacted diols and silyl ethers are obtained in useful yields. Under the conditions shown in Table 2, designed for maximal unreacted substrate enantiomeric purity, *syn*-1,2-diols are recovered in 30–48% yield and in 87 to >98% *ee*. 3) The selectivity (97:3 site selectivity; $k_{rel} = 29$) in Table 2,

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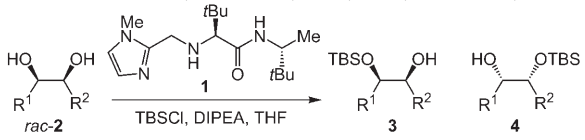
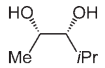
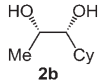
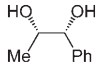
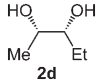
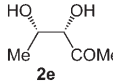
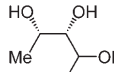
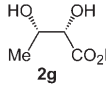
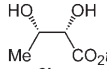
Table 2: Kinetic resolution of secondary alcohols by catalytic asymmetric silylation.[a]



Entry	Recovered diol (**2**)	Equiv. **1**; Conv. [%][b]	*T* [°C]; *t* [h]	**3**:**4**[c]	Recovered **2** yield [%][d]; *ee* [%][c]	Product **3** yield [%][d]; *ee* [%][c]	k_{rel}[b]
1	 **2a**	0.3; 55	−50; 72	>98:<2	44; 96	48; 81	35
2	 **2b**	0.3; 51	−50; 48	>98:<2	48; 91	50; 88	48
3	 **2c**	0.3; 70	−15; 72	>98:<2	30; 96	68; 39	8
4	 **2d**	0.3; 57	−40; 48	97:3	36; 98	50; 73	29
5	 **2e**	0.3; 57	−40; 48	98:2	34; 91	45; 71	17
6	 **2f**	0.3; 55	−30; 24	>98:<2	44; >98	52; 80	>50
7	 **2g**	0.3; 64	−30; 72	86:14	32; 87	34; 78[e]	25[f]
8	 **2h**	0.3; 65	−30; 72	86:14	34; 90	44; 77[g]	25[f]

[a] Conditions: see Table 1 and the Supporting Information for details. [b, c] See Table 1. [d] Yields of isolated material. [e] Minor silyl ether isomer was isolated in 6% yield with 82% *ee*. [f] k_{rel} calculated on the basis of ee_{rsm} and *ee* of major product isomer (see reference [9]). [g] Minor silyl ether isomer was isolated in 8% yield and 88% *ee*.

entry 4 indicates the highly discriminating nature of **1**.[11] Accordingly, the corresponding diol that carries an Et and an *i*Pr group undergoes less than 2% conversion. 4) Reactions in Table 2, entries 7 and 8 proceed with lower site selectivity (86:14) than the reaction with ketone **2e** (Table 2, entry 5) and are mechanistically informative. The slower reacting enantiomer is predominantly involved in the formation of the minor silyl ether, which may form through complex **II** (vs. **I**, Figure 1). It is unlikely that reaction via **II** is caused by steric factors; there is little size difference between an Et (Table 2, entry 4) and a carboxylic ester unit, and the results in entries 7 and 8 (Table 2) are nearly identical (i.e., the difference in size between a CO_2Et and a CO_2tBu makes little or no difference in site selectivity). It is, however, plausible that intramolecular hydrogen bonding involving the more Lewis basic (vs. ketone) ester carbonyl and the adjacent OH enhances α-hydroxy nucleophilicity. Alternatively, the Lewis basic carbonyl may be involved in activation[5,12] of the silyl chloride (hexacoordinated silane) and delivery of the silyl chloride to the proximal alcohol.[13] 5) The protocol delivers chiral diols that might otherwise require a lengthier synthetic route to prepare. Synthesis of dihydroxybutanoates (Table 2, entries 7 and 8), previously obtained by multistep manipulation of substrates obtained from the chiral pool, is a case in point.[14] 6) Although yields of the isolated products are lower in this resolution process than in the alternative asymmetric dihydroxylation, higher enantioselectivities can be obtained. For example, catalytic asymmetric dihydroxylation affords the diols in entries 2 and 3 (Table 2) in only 56 and 72% *ee*, respectively.[2]

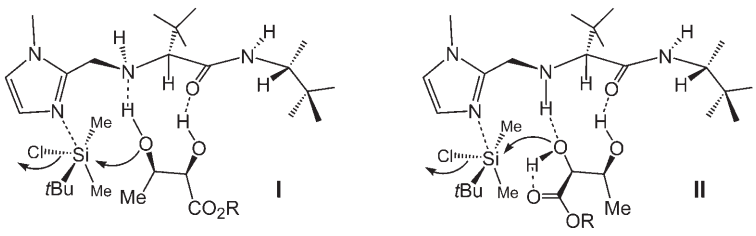
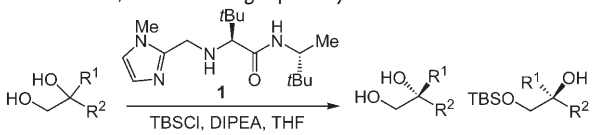


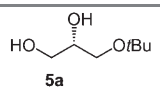
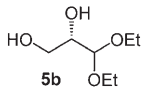
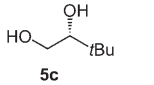
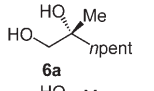
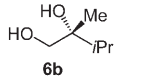
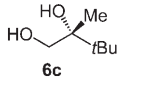
Figure 1. Transition-state models that account for lower site selectivity of ester-containing substrates.

Catalytic asymmetric silylation of primary alcohols that are adjacent to a secondary or a tertiary carbinol constitutes another synthetically useful class of transformations (Table 3). Reactions of diols bearing a secondary (Table 3, entries 1–3)[15] as well as those that carry a tertiary (entries 4–6) carbinol proceed with exceptional site selectivity (>98% primary silyl ether); k_{rel} values of 12 to greater than 50 are obtained, except for the transformation in entry 1 ($k_{rel}=8$). The findings in Table 3 point to the general trend that particularly efficient processes can be expected with substrates that carry a more sterically demanding secondary or tertiary alcohol (Table 3, entry 1 vs. 2 and 3 and entry 4 vs. 5 and 6). It should be noted that catalytic asymmetric dihydroxylations of 1,1-disubstituted olefins that bear aliphatic substituents typically proceed in less than 90% *ee*.[2]

Enantioselective silylations are simple to perform. The structurally robust catalyst is easy to prepare and commercially available (Aldrich); commercially available silyl chloride is utilized as well (no purification), and reactions can be carried out in air. Racemic substrates can be accessed on a gram scale and used in catalytic asymmetric

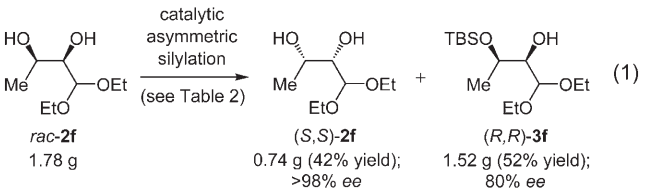
Table 3: Kinetic resolution of 1,2-diols bearing a primary alcohol.[a]



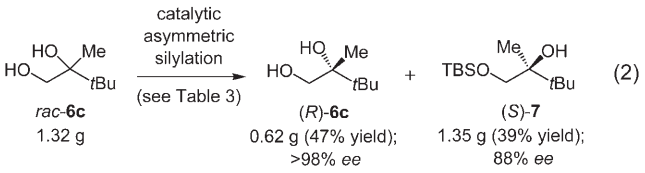
Entry	Recovered diol	Equiv. **1**; Conv.[%][b]	*T* [°C]; *t* [h]	Recovered **5/6** yield [%][d]; *ee* [%][c]	Product yield [%][d]; *ee* [%][c]	k_{rel}[b]
1	 **5a**	0.2; 56	−78; 24	38; 74	46; 57	8[e]
2	 **5b**	0.2; 55	−78; 24	25; 84	55; 68	14[e]
3	 **5c**	0.2; 55	−78; 24	42; >98	44; 76	>50
4	 **6a**	0.3; 52	−78; 96	42;[f] 94	50; 58	12
5	 **6b**	0.3; 54	−78; 40	44; >98	52; 84	>50
6	 **6c**	0.2; 52	−78; 24	45; >98	49; 91	>50

[a–d] See Tables 1 and 2; >98% primary silyl ether observed in all cases. [e] The *ee* values for these cases have ±5% margin of error (k_{rel} values have error bars of ±1). [f] Small amount of product de-silylation upon purification causes slightly higher than expected recovered starting material (rsm) yield.

silylation; the examples in Equations (1) and (2) illustrate this point. By adjustment of conversion, silyl ethers are obtained



(1)



(2)

in high enantioselectivity and yield. As an example, silyl ether **7** is isolated in 45% yield and 98% *ee* (45% conversion) when the reaction is performed at 1.0 M (vs. 1.4 M for substrate recovery; see the Supporting Information for details).

The studies outlined herein furnish, to the best of our knowledge, the first efficient method for kinetic resolution of *syn*-1,2-diols (Table 2) and vicinal diols that bear a tertiary alcohol (Table 3, entries 4–6). The findings disclosed herein enhance the utility of catalytic asymmetric silylation by demonstrating that chiral catalyst **1** is able to provide excellent site- as well as enantioselectivity. Such attributes have significant implications regarding chiral catalyst and synthetic-method design and development; investigations along these lines are in progress.

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[9] H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–330.
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[11] For catalytic asymmetric reactions involving differentiation of a Me and Et substituent, see: a) G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 6496–6502; b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86; c) K. Arai, M. M. Salter, Y. Yamashita, S. Kobayashi, *Angew. Chem.* **2007**, *119*, 973–975; *Angew. Chem. Int. Ed.* **2007**, *46*, 955–957.
[12] S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774–3789, and references therein.
[13] *N*-methylimidazole affords a 4:1 mixture of isomers, perhaps as a result of the same factors. Catalytic asymmetric silylation of the more Lewis basic *n*Bu amide affords silyl ether isomers in 1:4.4

ratio ($OSiR_3$ α to amide is predominant; 46% *ee*); the low *ee* value may be the result of (noncatalytic) amide-directed silylation.

[14] a) S. M. Mahalingam, N. Sathyamurthy, I. S. Aidhen, *Adv. Synth. Catal.* **2005**, *347*, 715–717; For a chiral auxiliary approach, see: b) D. J. Dixon, S. V. Ley, A. Polara, T. Sheppard, *Org. Lett.* **2001**, *3*, 3749–3752.

[15] For alternative approaches to catalytic kinetic resolutions of 1,2-diols bearing a primary and a secondary carbinol, see: a) F. Iwasaki, T. Maki, O. Onomura, W. Nakashima, Y. Matsumura, *J. Org. Chem.* **2000**, *65*, 996–1002; b) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315; and reference [10b].

