JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Site-Selective Catalysis: Toward a Regiodivergent Resolution of 1,2-Diols

Amanda D. Worthy, Xixi Sun, and Kian L. Tan*

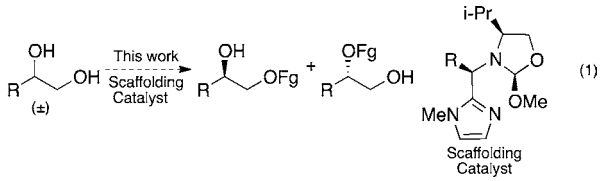
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Supporting Information

ABSTRACT: This paper demonstrates that the secondary hydroxyl can be functionalized in preference to the primary hydroxyl of a 1,2-diol. The site selectivity is achieved by using an enantioselective organic catalyst that is able to bond to the diol reversibly and covalently. The reaction has been parlayed into a divergent kinetic resolution on a racemic mixture, providing access to highly enantioenriched secondary-protected 1,2-diols in a single synthetic step.

Selective manipulation of multiple similar functional groups within a molecular ensemble is a significant challenge in chemical synthesis. This problem is generally addressed by employing reaction sequences wherein the more reactive groups are functionalized first.[1] The ability to functionalize a less reactive position in the presence of a more reactive group may enable new synthesis strategies. The challenge of such a transformation is that most synthetic catalysts cannot change the energetics of the reaction coordinate sufficiently to overcome inherent biases in substrate reactivity.

Notable exceptions are enzymes that routinely functionalize less reactive sites within a complex molecule.[2] Enzymes are able to achieve these dramatic changes in selectivity by binding substrates in a specific orientation that places the target functional group near a catalytic residue. The entropic price for this exquisite control is paid through multiple enthalpically favored interactions between the substrate and the amino acids that line the substrate binding pocket. In analogy to enzymes, synthetic catalysts are able to functionalize less reactive sites when they use noncovalent substrate binding as a critical component in determining the overall selectivity.[3] For example, both Miller[3f] and Kawabata[3c] have reported catalysts that functionalize glucose at the C4 position. In both cases it is postulated that noncovalent interactions are used to bind to the more accessible primary hydroxyl, which directs the reaction to the more hindered site. The size of these organocatalysts is relatively large (although significantly smaller than enzymes), reflecting the need to have a well-defined array of noncovalent interactions to overturn the inherent reactivity. As a complementary method, using reversible covalent bonding[4,5] instead of noncovalent interactions would allow for efficient substrate−catalyst association through a single point of contact, minimizing the catalyst architecture devoted to substrate binding while retaining the proximity effects necessary to achieve site selectivity. Recent work by Taylor and co-workers has shown that covalent interactions in boron-based catalysts can be used to functionalize sugars selectively.[6] We report a chiral organic catalyst that uses reversible covalent bonding between the catalyst and the substrate to functionalize a secondary alcohol in preference to an adjacent primary alcohol. Because the catalyst is chiral, the enantiomers of a racemic mixture react at different rates, resulting in a regiodivergent silylation of a racemic mixture (eq 1). This delivers the

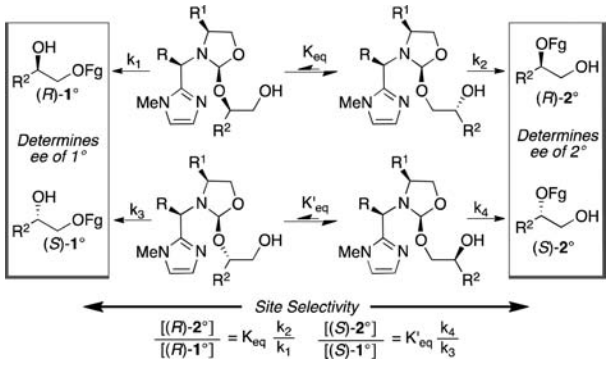


(1)

protected secondary alcohol product with excellent enantioselectivity in a single synthetic step (up to >98% ee; see Table 2).[7,8]

We thought that a scaffolding catalyst previously developed for the desymmetrization of 1,2-diols[9] could be used to perform the site-selective functionalization of a secondary hydroxyl over a primary hydroxyl. As shown in Scheme 1, each enantiomer of

Scheme 1. Curtin−Hammett Kinetics as a Basis for Site and Enantioselectivity



the diol has an independent site selectivity based on both the affinity of the 1° or 2° hydroxyl for the catalyst (K_{eq} and K'_{eq}) and the relative rates of functionalization (k_1 vs k_2 and k_3 vs k_4).[10] We hypothesized that one of the enantiomers of the diol would allow us to combine the binding selectivity and stereoselectivity effectively to overturn the large inherent

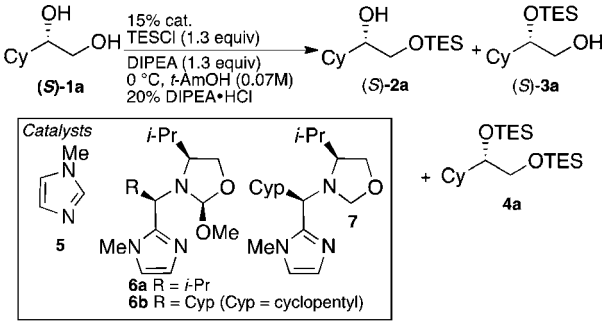
Received: March 20, 2012
Published: April 19, 2012

   dx.doi.org/10.1021/ja3027086 | J. Am. Chem. Soc. 2012, 134, 7321−7324

substrate bias for primary functionalization. In this report, we show that the scaffolding catalyst gives dramatically different site selectivities for the enantiomers of the diol, resulting in an effective divergent kinetic resolution.

To simplify this complex problem, the site-selective silylation of a single enantiomer of terminal 1,2-diol (*S*)-**1a** was investigated (Table 1). As expected, a control reaction

Table 1. Catalyst Screening for 2° Alcohol Protection



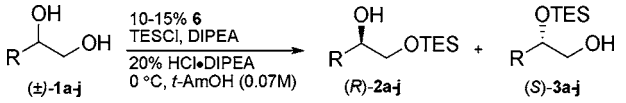
entry	catalyst	yield of **4a** (%)[a]	**2a**:**3a**[a]	yield of **3a** (%)[a]
1	**5**	9	98:2	<2
2	**6a**	5	18:82	58
3	**6b**	5	12:88	76 (74[b])
4	7	8	91:9	<1
5[c]	**6b**	7	>98:2	<2

[a]GC yields and selectivities based on an internal standard (trimethoxybenzene). [b]Isolated yield of **3a**. [c](*R*)-**1a** was used as the substrate.

examining silylation with triethylsilyl chloride and catalysis with *N*-methylimidazole resulted in silylation of the primary alcohol (**2a**:**3a** = 98:2; Table 1, entry 1). Preliminary studies showed that under acetal exchange conditions, primary alcohols have ∼8-fold higher affinity for **6a** than secondary alcohols do (see the Supporting Information), suggesting that the binding selectivity alone would not be sufficient to overturn the inherent substrate bias (98:2). Using **6a** in the silylation of (*S*)-**1a** resulted in a dramatic change in selectivity, with the secondary-protected product being favored (**2a**:**3a** = 18:82; Table 1, entry 2). Furthermore, switching to scaffold **6b** increased the selectivity to **2a**:**3a** = 12:88 (Table 1, entry 3) with an isolated yield of 74% for (*S*)-**3a**. The net site selectivity change is between 2 and 3 orders of magnitude relative to *N*-methylimidazole. A second control reaction using as the catalyst compound **7**, which does not have a substrate binding site, resulted in selective formation of the primary-protected product (**2a**:**3a** = 91:9; Table 1, entry 4), demonstrating the necessity of covalent bonding between the substrate and the catalyst. This reaction was also the only one that suffered from low conversion (33% conv), consistent with the fact that covalent bonding to the catalyst is also necessary for rate acceleration. Application of **6b** to (*R*)-**1a** resulted in a complete reversal in site selectivity, with silylation of the primary alcohol occurring almost exclusively (Table 1, entry 5).

These foregoing results suggested that kinetic resolution of the racemic substrate could be achieved. When the racemic substrate was silylated under the standard conditions, both the primary- and secondary-silylated products were enantioenriched, with **3a** forming in 97% ee in favor of the *S* configuration and **2a** in 81% ee favoring the *R* configuration (Table 2, entry 1). Such a kinetic resolution falls under the

Table 2. Substrate Scope for Regiodivergent RRM[a]



		2		3	
entry	R	yield (%)	ee (%)	yield (%)	ee (%)
1[b]	Cy	52	81	41	97
2[c]	$(CH_2)_3CH_3$	54	79	40	98
3[b]	$CH_2CH(CH_3)_2$	53	82	40	98
4[d]	CH_3	48	70	36	92
5[e]	CH_2Ph	46	80	40	96
6[c]	CH_2OBn	56	74	40	99
7[f]	CH_2OPh	44	78	32	96
8[d]	$CH{=}CH_2$	53	57	37	91
9[b]	CH_2Cl	52	90	45	97
10[b]	CH_2Br	50	91	41	98

[a]Yields and ee's are averages of two runs; ee's were determined by GC or HPLC analysis. In all cases, **2** and **3** were separable by SiO_2 column chromatography, so the isolated yields are of the pure constitutional isomers. [b]Run with 15% **6b**, 1.3 eq triethylsilyl chloride (TESCl) and diisopropylethylamine (DIPEA) for 45 min. [c]Run with 10% **6a**, 1.2 eq TESCl and DIPEA for 1.5 h. [d]Run with 15% **6b**, 1.2 eq TESCl and DIPEA for 25 min. [e]Run with 10% **6b**, 1.2 eq TESCl and DIPEA for 45 min. [f]Run with 15% **6a**, 1.4 eq TESCl and DIPEA for 45 min.

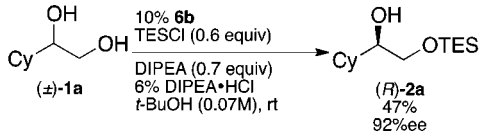
category of a regiodivergent reaction on a racemic mixture (regiodivergent RRM).[11−13]

Investigation of the substrate scope for the resolution revealed that the reaction is permissive of both sterically demanding groups[14] such as cyclohexyl and *sec*-butyl (Table 2, entry 3) and smaller alkyl groups such as butyl (Table 2, entry 2). In most cases, the enantioselectivity of the secondary-protected product was found to be ≥96% ee; exceptions included Me and vinyl substituents (92 and 91% ee, respectively; Table 2, entries 4 and 8). The methyl and vinyl substrates highlight the importance of stereoselectivity as a means of controlling site selectivity, because as the smallest substituents they are the most challenging to differentiate. Both vinyl and OPh groups also pose the additional challenge that the secondary alcohol is electronically deactivated toward silylation. Consequently, background silylation (including bis-silylation) becomes more competitive with 2° alcohol functionalization, lowering the overall yield of **3**. When R is benzyl or OBn, the reaction proceeds in good yield (40%) with high enantioselectivity (96 and 99% ee; Table 2, entries 5 and 6). Additionally, both Cl and Br substituents are tolerated under the reaction conditions and provide excellent enantioselectivities for **3** (Table 2, entries 9 and 10).

The divergent resolution allows for access to (*S*)-**3a**−**j** with high ee, but the formation of (*R*)-**2a**−**j** occurs with more modest enantioselectivities. The lower enantioselectivities for (*R*)-**2a**−**j** directly result from the site selectivity observed for the (*S*)-diol (Table 1, entry 3; also see the boxes in Scheme 1). The formation of (*R*)-**2a**−**j** is faster than that of (*S*)-**3a**−**j**, suggesting that silylation of the primary alcohol is also catalyzed by **6**.[15] Therefore, analogous to a standard kinetic resolution, the enantioselectivity for (*R*)-**2** can be increased by lowering the overall conversion. However, unlike a traditional kinetic resolution, which generally is effective at providing starting material in high ee,[16,17] the divergent resolution makes it possible to isolate the products in high yield with high ee. For example, using 0.6 equiv of TESCl leads to the isolation of (*R*)-

dx.doi.org/10.1021/ja3027086 | J. Am. Chem. Soc. 2012, 134, 7321−7324

2a (R = Cy) in 47% yield with 92% ee (eq 2) versus 52% yield with 81% ee using 1.3 equiv of TESCl (Table 2, entry 1). From



(2)

a practical perspective, these results mean that either the 1°- or 2°-protected products can be accessed in high enantioselectivity simply by adjusting the amount of TESCl employed.

The synthesis of enantioenriched diols is a process that has been achieved using several noteworthy enantioselective reactions, including asymmetric dihydroxylation of olefins,[18] hydrolytic kinetic resolution of terminal epoxides,[19] and asymmetric diboration/oxidation of olefins and alkynes.[20] However, accessing compounds where a secondary alcohol is protected in the presence of a primary alcohol would require an additional 2−3 synthetic steps from the enantiopure diol. Using the regiodivergent RRM not only resolves the enantiomers of the starting material but also chemically differentiates the primary and secondary alcohols. This procedure can also be used for selective functionalization of the secondary over the primary hydroxyl of enantioenriched 1,2-diols in a single step. The ability to overturn the large substrate bias is made possible by implementing a catalyst that is highly stereoselective and has a preference for binding less hindered hydroxyls covalently. We believe that exploiting binding selectivity and proximity will be a productive means of functionalizing inherently less reactive sites on complex molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, compound characterization, equilibrium data, and estimations of site selectivities for (*R*)- and (*S*)-diols from Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

kian.tan.1@bc.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We dedicate this paper to Robert G. Bergman on the occasion of his 70th birthday. We thank Omar DePaolis for experimental support and the Alfred P. Sloan Foundation (K.L.T.), the LaMattina Fellowship (X.S. and A.D.W.), NSF (CHE-1150393), and NIGMS (R01GM087581) for funding of this project. Mass spectrometry instrumentation at Boston College is supported by funding from the NSF (DBI-0619576).

■ REFERENCES

(1) For reviews of synthetic strategy, see: (a) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657. (b) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530. (c) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707. (d) *Strategies and Tactics in Organic Synthesis*, Vol. 5; Harmata, M., Ed.; Elsevier: London, 2004. (e) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, Germany, 2003. (f) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1995.

(2) For examples of site-selective enzymatic reactions, see: (a) Thibodeaux, C. J.; Melançon, C. E.; Liu, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9814. (b) Thibodeaux, C. J.; Melançon, C. E.; Liu, H. *Nature* **2007**, *446*, 1008. (c) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465.

(3) (a) Jordan, P. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2907. (b) Yoshida, K.; Furuta, T.; Kawabata, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 4888. (c) Kawabata, T.; Furuta, T. *Chem. Lett.* **2009**, *38*, 640. (d) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944. (e) Lewis, C. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616. (f) Griswold, K. S.; Miller, S. J. *Tetrahedron* **2003**, *59*, 8869.

(4) For reviews of the use of reversible covalent bonding in catalysis, see: (a) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450. (b) Tan, K. L. *ACS Catal.* **2011**, *1*, 877.

(5) For a recent example of a catalyst that uses temporary intramolecularity in enantioselective catalysis, see: MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100.

(6) (a) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 13926. (b) Lee, D.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 3724. (c) Chan, L.; Taylor, M. S. *Org. Lett.* **2011**, *13*, 3090.

(7) For examples of catalyzed silyl transfer, see: (a) Rodrigo, J. M.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2011**, *13*, 3778. (b) Grajewksa, A.; Oestreich, M. *Synlett* **2010**, 2482. (c) Yan, H.; Jang, H. B.; Lee, J.-W.; Kim, H. K.; Lee, S. W.; Yang, J. W.; Song, C. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 8915. (d) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 547. (e) Yu, Z.; Mitra, A. W.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8471. (f) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (g) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243.

(8) For a review of Si−O coupling reactions, including metal-catalyzed reactions, see: Weickgenannt, A.; Mewald, M.; Oestreich, M. *Org. Biomol. Chem.* **2010**, *8*, 1497.

(9) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167.

(10) For a review of Curtin−Hammett and Winstein−Holness kinetics, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(11) For reviews of divergent kinetic resolutions, see: (a) Miller, L. C.; Sarpong, R. *Chem. Soc. Rev.* **2011**, *40*, 4550. (b) Kumar, R. R.; Kagan, H. B. *Adv. Synth. Catal.* **2010**, *352*, 231. (c) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

(12) For an example of a regiodivergent RRM using silyl transfer, see ref 7a.

(13) In this case, the formation of constitutional isomers is derived from site selectivity, so a more appropriate term maybe site-divergent RRM. Regioselectivity generally refers to differentiation of positions within the same functional group; in this case, we are differentiating the same type of functional group within the same molecule, which is site selectivity.

(14) Attempts at silylating 3,3-dimethyl-1,2-butanediol (R = *t*-Bu) resulted in no protection of the secondary hydroxyl. These results suggest that the current catalyst system is unable to overcome the large substrate bias for primary alcohol protection for this substrate.

(15) Reacting (*R*)-**1a** with control catalyst **7** resulted in modest conversion (60% conv) and a low yield of (*R*)-**2a** (16%), suggesting that covalent bonding between **6b** and (*R*)-**1a** is necessary for efficient catalysis.

(16) For a review of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(17) For an example of kinetic resolution of 1,2-diols via silylation, see ref 7e.

(18) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(19) (a) White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.*

2002, *124*, 1307. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.
(20) (a) Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234. (b) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210. (c) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702.