Organocatalysis

DOI: 10.1002/ange.201103470

Scaffolding Catalysts: Highly Enantioselective Desymmetrization Reactions**

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

The use of reversible covalent bonding is a common design feature in synthetic catalysts. For most synthetic catalysts, reversible covalent bonding is used to form a reactive intermediate thereby affording an enhanced rate of reaction (e.g. enamine, iminium, and N-heterocyclic carbene catalysis).[1,2] A less developed area of reversible covalent bonding catalysis uses this bonding to transiently tether reagents (Figure 1).[3] A key aspect of this mode of catalysis is that a

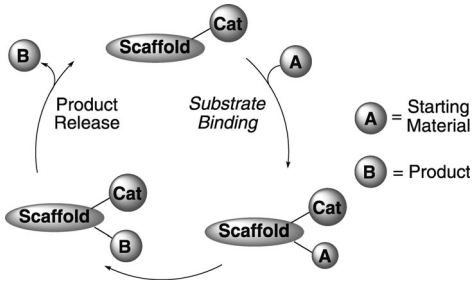


Figure 1. Catalytic cycle for scaffolding catalysis.

part of the acceleration arises from the entropic advantage gained through intramolecularity.[4] We have recently reported the development of phosphine ligands that use reversible covalent bonds between a substrate and the ligand to control regio-, diastereo-, and enantioselectivity in hydroformylation.[5–7] Herein we extend this catalysis design strategy to organic catalysts. In particular, we report the catalytic desymmetrization of meso diols in up to 97% *ee* with high yield at room temperature.

The use of chiral organic compounds as electrophile-transfer catalysts has successfully allowed the kinetic resolution and desymmetrization of alcohol substrates in a variety of transformations; such reactions include acylation,[8,9] phosphorylation,[10] sulfonylation,[11] and silylation.[12,13] Desymmetrization of diol and triol substrates has been accomplished by peptide-catalyzed silylation, acylation, and phosphorylation reactions. These strategies stand out as synthetically practical methods because they afford synthetically useful monoprotected products with no limitation on the theoretical yield. We decided to investigate this reaction as a means of testing a new catalyst motif that incorporates a reversible covalent bond between the catalyst and substrate. Ostensibly, the selectivity in peptide catalysis is due, at least in part, to noncovalent interactions between the substrate and the catalyst that serve to organize the intermediate complex. In comparison, we considered that reversible covalent bonding catalysis might involve a more intimate association between the catalyst and the substrate, and thus lead to enhanced reactivity and/or selectivity. Similar to our phosphine ligand design, we synthesized a bifunctional molecule to serve as a silyl transfer catalyst (Figure 2). The scaffolding

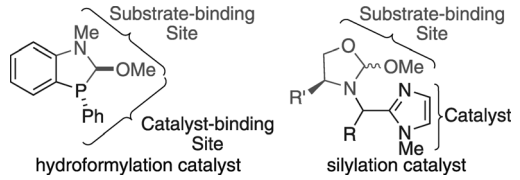
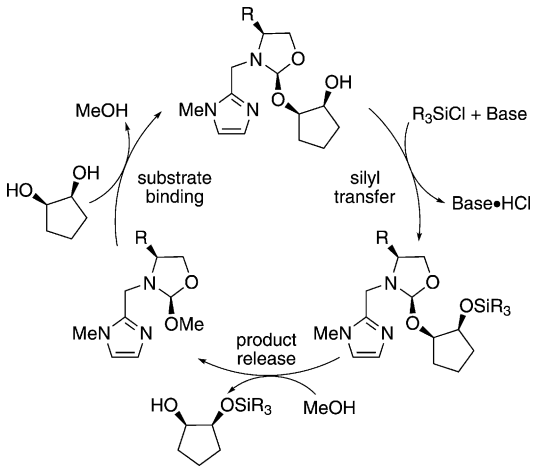


Figure 2. Catalyst design.

catalyst contains a substrate-binding site, which uses reversible covalent bonding, and incorporates an imidazole group as the catalytically active residue (Figure 2). The aim is to reversibly bind the diol, then, through an intramolecular transfer or deprotonation, functionalize the free alcohol (Scheme 1). A unique feature of this catalytic cycle is that



Scheme 1. Proposed catalytic cycle for silylation

[*] X. Sun, A. D. Worthy, Prof. K. L. Tan
Department of Chemistry, Boston College
2609 Beacon St., Chestnut Hill, MA 02467-3860 (USA)
E-mail: kian.tan.1@bc.edu

[**] We thank Professors Marc Snapper and Amir Hoveyda for helpful discussions. We thank Bo Li for X-ray structure analysis of **6.** We thank the ACS-PRF (DNI-5001400) and NIGMS (RO1GM087581) for funding this research. Mass spectrometry instrumentation at Boston College is supported by funding from the NSF (DBI-0619576).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103470.

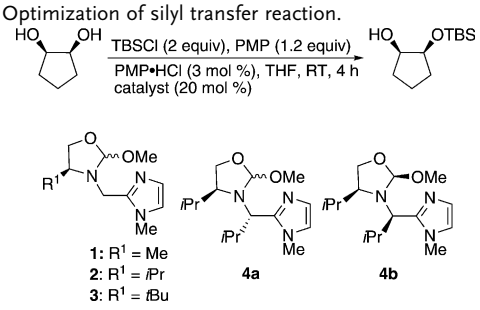
the binding of the catalyst to the substrate is entropically neutral (because an alcohol is released upon binding of substrate). Consequently, the subsequent silylation step is intramolecular but does not have to pay an entropic penalty for bringing the catalyst and diol substrate together. Furthermore, the enantioselectivity in the reaction could be derived from the binding step, functionalization step, or a combination of the two.

To initiate these studies, we developed a catalyst structure that is easy to synthesize and modify. The catalysts in Table 1 are readily synthesized in two steps from amino alcohols. As depicted in Table 1, when employing catalyst **1** in the desymmetrization of 1,2-cyclopentane diol, the monoprotected product forms in 17% yield with −9% *ee* (Table 1, entry 1). Using **2** and **3**, which are derived from valine and *tert*-leucine, respectively, affords the product in modest yield and improved enantioselectivity (Table 1, entries 2 and 3). By optimizing the less expensive valine core structure, it was found that addition of a substituent adjacent to the imidazole ring dramatically affects the selectivity of the reaction. Silylation with **4a** and **4b** show a significant matched and mismatched relationship, with **4b** yielding a product with excellent enantioselectivity (Table 1, entry 5);[14] and **4a** furnishes the opposite product enantiomer in low selectivity (Table 1, entry 4). The high enantioselectivity in the silylation reaction is notable given the fact that the reaction is performed at room temperature. An explanation for the high selectivities at noncryogenic temperatures is the rigid nature of covalent bonding.

Having optimized the catalyst structure, we investigated the substrate scope. A tetrahydrofuran-based substrate affords the product in good yield and enantioselectivity (Table 2, entry 1). The six-membered ring substrates, cyclohexane-1,2-diol, 1,2,3,4-tetrahydro-2,3-naphthalenediol, and cyclohexene-1,2-diol provide comparable yields and enantioselectivities to those of the five-membered ring substrates (Table 2, entries 2–4). Seven- and eight-membered rings also yield the desired product in 90% and 86% *ee*, respectively (Table 2, entry 5 and 6). The substrate scope was expanded to an acyclic substrate, butane-2,3-diol, thus affording the product in 90% *ee* and 78% yield (Table 2, entry 7). The silyl transfer onto both *trans*-cyclohexane-1,2-diol and (*R*,*S*)-pentane-2,4-diol using **4b** as the catalyst yields the products in less than 5% yield; furthermore, *cis*-4-cyclopentane-1,3-diol affords the desired product in 26% yield and 15% *ee*. Given that the proposed mechanism involves intramolecular transfer or deprotonation, a strong proximity effect might account for these observations. Though constraining in terms of substrate scope, a catalyst that recognizes both chirality and proximity has the potential to be a powerful reagent for site-selective reactions.

With these encouraging results, we also investigated the generality of the silyl reagents that can be transferred. The smaller triethylsilyl group is transferred effectively with excellent enantioselectivity (90% *ee*) and yield (94%; Table 3, entry 1) after a reaction time of 1 hour at room temperature. The sterically larger silyl reagent *tert*-butyldiphenyl silyl chloride (TBDPSCl) affords the product in 90% *ee* and good yield (75%; Table 3, entry 2), although extended reaction times are necessary to achieve high conversion. The reaction time can be shortened by increasing the concentration of the reaction mixture (1.0 M in diol), the result being only a small decrease in the *ee* value (Table 3, entry 2). Silylation with the very reactive dimethylphenyl silyl chloride (DMPSCl) results in a decrease in enantioselectivity to 79% (Table 3, entry 3); presumably, the lowered selectivity is a result of background silylation.

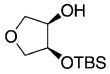
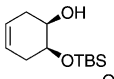
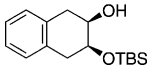
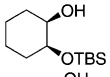
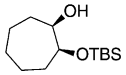
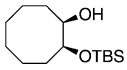
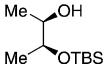
Table 1: Optimization of silyl transfer reaction.



Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**1**	17	−9
2	**2**	19	34
3	**3**	20	40
4	**4a**	25	−16
5	**4b**	84 (92)[c]	97 (94)[c]
6[d]	**4b**	76	92

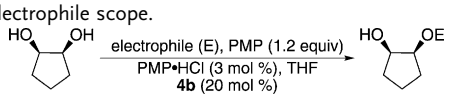
[a] Reaction performed at 0.20 mmol substrate (0.4 M). Yields determined by GC analysis using an internal standard, 1,3,5-trimethoxybenzene. [b] Enantiomeric excess (*ee*) determined by GC analysis. [c] Reaction performed at 0.40 mmol substrate. Yield of product given in parentheses. [d] Reaction performed 0.2 M of diol in *t*BuOH. PMP = pentamethylpiperidine, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

Table 2: Substrate scope with TBSCl.

Entry[a]	Product	Yield [%]	*ee* [%]
1[b]		79	89
2[c]		87	90
3[b]		88	95
4[c]		86	92
5[d]		82	90
6[e]		93	86
7[f]		78	90

[a] All reactions performed with 20 mol% **4b** and 3 mol% PMP·HCl, and are an average of two runs. [b] TBSCl (4 equiv), PMP (1.2 equiv), RT, 24 h. [c] TBSCl (2 equiv), PMP (1.2 equiv), RT, 12 h. [d] TBSCl (4 equiv), PMP (2 equiv), 4 °C, 24 h. [e] TBSCl (4 equiv), PMP (2 equiv), RT, 24 h. [f] TBSCl (4 equiv), PMP (2 equiv), 4 °C, 36 h.

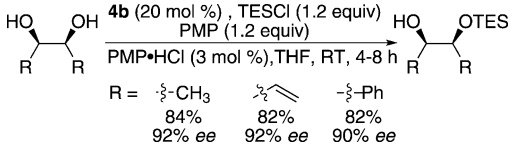
Table 3: Electrophile scope.



Entry	Electrophile	Yield [%][a]	*ee* [%][a]
1[b]	TESCl	94	90
2[c]	TBDPSCl	75 (76)[d]	90 (86)[d]
3[e]	DMPSCl	71	79

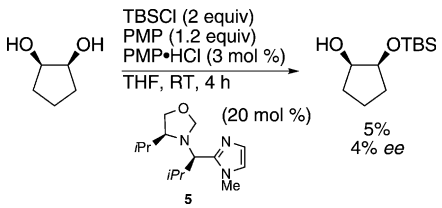
[a] Yields and *ee* values are an average of two runs. [b] TESCl (1.2 equiv), 0.2 M in diol, RT, 1 h [c] TBDPSCl (4 equiv), 0.2 M in diol, RT, 48 h. [d] 1.0 M diol, RT, 24 h. [e] DMPSCl (1.2 equiv), 0.2 M in diol, RT, 1 h. DMPS = dimethylphenylsilyl, TES = triethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

The results with TESCl are a practical improvement over the original TBSCl conditions, because the reaction time is shorter and less silyl chloride is employed. We therefore applied these conditions to butane-2,3-diol, which with TBSCl conditions required a 36 hour reaction time at 0 °C to obtain high enantioselectivity (Table 2, entry 7). With the TESCl procedure, the product is formed with improved selectivity and yield (84 %, 92 % *ee*) after a 4 hour reaction time at room temperature (Scheme 2). Previous attempts with TBSCl to desymmetrize acyclic substrates with vinyl or aryl substitution afforded poor conversion; however, with the new procedure these substrates react with comparable levels of selectivity to the cyclic substrates in 4–8 hours (Scheme 2).



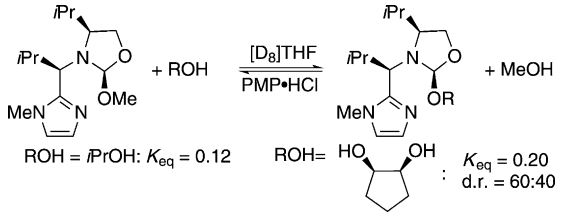
Scheme 2. Silylation with TESCl.

In terms of a mechanism for catalysis and stereoinduction, it is conceivable that either noncovalent bonding (hydrogen bonding) or reversible covalent bonding is responsible for the substrate–catalyst organization. To differentiate these possibilities, hydrogen-bonding solvents were examined. When 1,2-cyclopentane diol was silylated using *t*BuOH as the solvent the product forms in 92 % *ee* (Table 1, entry 6), which is inconsistent with a hydrogen-bonding mechanism. To further validate a reversible covalent bond between the substrate alcohol and the catalyst, we synthesized control catalyst **5**, which lacks a substrate-binding site. Silylation with **5** delivers an almost racemic mixture of the product in low yield (Scheme 3), which is consistent with substrate binding



Scheme 3. Control reaction.

being important for both rate acceleration and enantioselectivity. In support of exchange occurring under the reaction conditions, isopropyl alcohol was added to **4b** in the presence of 10 mol % PMP·HCl and monitored by ^{1}H NMR spectroscopy. Under these reaction conditions, an equilibrium is established with a K_{eq} of 0.12 (Scheme 4).[15] Collectively, these observations strongly support a mechanism that involves reversible covalent substrate–catalyst bonding.



Scheme 4. Exchange of **4b** with isopropanol and substrate.

To learn more about the step in the mechanism that is responsible for selectivity, the structure and stability of the catalysts as well as the catalyst–substrate complexes were examined. First, catalyst **4b** forms only a single diastereomer of catalyst as observed by ^{1}H NMR spectroscopy.[16] Exchange of 4-bromobenzyl alcohol onto **4b** allowed an X-ray structure to be obtained. The X-ray structure shows that the alcohol binds *syn* to the *i*Pr group on the oxazoline ring (**6**; Figure 3). We believe that the two isopropyl groups serve the dual purpose of gearing the substrate binding site in this *syn* relationship and to conformationally restrict the location of the imidazole group. In a second experiment, *cis*-1,2-cyclopentane-diol exchanges with **4b** to form two new species, and reaches equilibrium in approximately 3 hours (Scheme 4).[17] We have tentatively assigned these compounds as being derived from the binding of the enantiotopic alcohols to **4b**. The two new compounds form in a 60:40 ratio, thus suggesting that there is little binding stereoselectivity. The poor selectivity in binding is consistent with the enantioselectivity of the reaction originating from the functionalization step. One explanation for the observed stereoinduction of the catalyst is that when the *R* alcohol binds to the catalyst it places the free alcohol in close proximity to the catalytic site, thus facilitating intramolecular transfer. Conversely, if the *S* alcohol binds, the

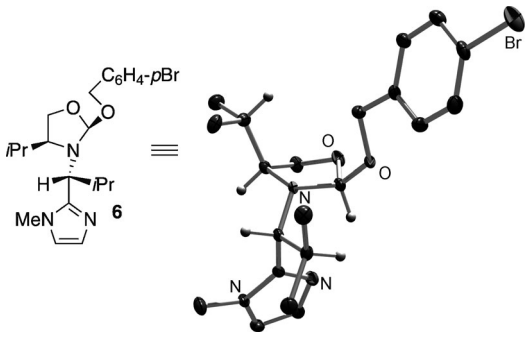


Figure 3. X-ray structure of **6**.[18]ok Thermal ellipsoids shown at 50 % probability.

free alcohol is placed away from the catalytic residue, thereby preventing intramolecular processes. In this way restricting the spatial orientation of the imidazole ring is essential for stereoinduction.

In summary, we have developed a new organic catalyst that uses reversible binding to alcohol substrates to both accelerate and control the selectivity in a desymmetrization reaction. The catalyst is readily synthesized from inexpensive building blocks; furthermore, the modular nature of the synthesis allows derivatives to be rapidly accessed. The rigid covalent bonding between the substrate and catalyst generates a highly enantioselective silylation reaction for a range of 1,2-diols. The ability of the scaffolding catalyst to functionalize substrates through both stereoselectivity and proximity is encouraging for developing these types of catalysts for complex molecule modifications where site-selective catalysis is required. We are continuing to develop these catalysts for other electrophile-transfer reactions, and we envision designing a series of second-generation structures that specifically functionalize *anti* 1,2-diols, *syn*- and *anti* 1,3-diols, and *syn*- and *anti* 1,4-diols.

Experimental Section

A solution of cis-1,2-cyclopentanediol (41 mg, 0.40 mmol), **4b** (22 mg, 0.080 mmol, 20 mol%), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (2.3 mg, 0.012 mmol, 3 mol%) in anhydrous THF (0.50 mL) was added to an oven-dried glass reaction vial. The reaction mixture was stirred at room temperature for 10 min. 1,2,2,6,6-pentamethylpiperidine (87 μL, 0.48 mmol, 1.2 equiv) was added, followed by addition of a solution of *tert*-butylchlorodimethylsilane (120 mg, 0.80 mmol, 2.0 equiv) in anhydrous THF (0.50 mL). After stirring at room temperature for 4 h, reaction mixture was quenched by addition of *N*,*N*-diisopropylethylamine (200 μL) and methanol (60 μL). The mixture was stirred at room temperature for 10 min, and was then concentrated under reduced pressure. Flash column chromatography on silica gel (hexanes/EtOAc = 20/1) afforded pure product as colorless oil (80 mg, 92%, 94% *ee*). GLC analysis using a chiral stationary phase (Supelco Beta Dex 120 (30 × 0.15 mm × 0.25 μm film thickness) was performed using the following conditions: 78 °C for 100 min, 20 °C min^{-1} to 180 °C, 180 °C for 20 min, 15 psi.

Received: May 20, 2011
Published online: July 7, 2011

Keywords: asymmetric catalysis · desymmetrization · organocatalysis · silanes · synthetic methods

[1] For reviews on enamine and iminium catalysis, see: a) P. M. Pihko, I. Majander, A. Erkkilä, *Asymmetric Organocatalysis*, Springer, Berlin, **2010**, pp. 29–75; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; d) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.

[2] For a review on N-heterocyclic carbenes as organic catalysts, see: J. L. Moore, T. Rovis, *Asymmetric Organocatalysis*, *Vol. 291*, Springer, Berlin, **2010**, pp. 77–144.

[3] For recent examples of reversible covalent bonding in organic catalysts that use induced intramolecularity, see: a) T. Sammakia, T. B. Hurley, *J. Am. Chem. Soc.* **1996**, *118*, 8967–8968; b) T. Sammakia, T. B. Hurley, *J. Org. Chem.* **1999**, *64*, 4652–4664; c) T. Sammakia, T. B. Hurley, *J. Org. Chem.* **2000**, *65*, 974–978; d) M. Ghosh, J. L. Conroy, C. T. Seto, *Angew. Chem.* **1999**, *111*, 575–578; *Angew. Chem. Int. Ed.* **1999**, *38*, 514–516; *Angew. Chem.* **1999**, *111*, 575–578; e) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196–4197; f) K. Ishihara, *Tetrahedron* **2009**, *65*, 1085–1109; g) T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 5043–5046; h) T. Maki, K. Ishihara, H. Yamamoto, *Tetrahedron* **2007**, *63*, 8645–8657; i) R. Latta, G. Springsteen, B. Wang, *Synthesis* **2001**, 1611–1613; j) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem.* **2008**, *120*, 2918–2921; *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879; k) T. A. Houston, B. L. Wilkinson, J. T. Blanchfield, *Org. Lett.* **2004**, *6*, 679–681; l) T. A. Houston, S. M. Levonis, M. J. Kiefel, *Aust. J. Chem.* **2007**, *60*, 811–815; m) T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 5047–5050; n) S. M. Levonis, L. F. Bornaghi, T. A. Houston, *Aust. J. Chem.* **2007**, *60*, 821–823; o) G. C. M. Kondaiah, L. A. Reddy, K. S. Babu, V. M. Gurav, K. G. Huge, R. Bandichhor, P. P. Reddy, A. Bhattacharya, R. V. Anand, *Tetrahedron Lett.* **2008**, *49*, 106–109; p) Y. Mori, K. Manabe, S. Kobayashi, *Angew. Chem.* **2001**, *113*, 2897–2900; *Angew. Chem. Int. Ed.* **2001**, *40*, 2815–2818; q) K. Aelvoet, A. S. Batsanov, A. J. Blatch, C. Grosjean, L. G. F. Patrick, C. A. Smethurst, A. Whiting, *Angew. Chem.* **2008**, *120*, 780–782; *Angew. Chem. Int. Ed.* **2008**, *47*, 768–770; r) D. Lee, S. G. Newman, M. S. Taylor, *Org. Lett.* **2009**, *11*, 5486–5489; s) H. Zheng, D. G. Hall, *Tetrahedron Lett.* **2010**, *51*, 3561–3564; t) H. Zheng, R. McDonald, D. G. Hall, *Chem. Eur. J.* **2010**, *16*, 5454–5460; u) see Ref. [4] for more examples.

[4] R. Pascal, *Eur. J. Org. Chem.* **2003**, 1813–1824.

[5] a) T. E. Lightburn, M. T. Dombrowski, K. L. Tan, *J. Am. Chem. Soc.* **2008**, *130*, 9210–9211; b) A. D. Worthy, M. M. Gagnon, M. T. Dombrowski, K. L. Tan, *Org. Lett.* **2009**, *11*, 2764–2767; c) X. Sun, K. Frimpong, K. L. Tan, *J. Am. Chem. Soc.* **2010**, *132*, 11841–11843; d) A. D. Worthy, C. L. Joe, T. E. Lightburn, K. L. Tan, *J. Am. Chem. Soc.* **2010**, *132*, 14757–14759; e) T. E. Lightburn, O. A. De Paolis, K. H. Cheng, K. L. Tan, *Org. Lett.* **2011**, *13*, 2686–2689.

[6] For early examples of reversible covalent bonding with ligands for metal catalysts, see: a) L. N. Lewis, *Inorg. Chem.* **1985**, *24*, 4433–4435; b) L. N. Lewis, J. F. Smith, *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735; c) S. A. Preston, D. C. Cupertino, P. Palma-Ramirez, D. J. Cole-Hamilton, *J. Chem. Soc. Chem. Commun.* **1986**, 977–978; d) A. Iraqi, N. R. Fairfax, S. A. Preston, D. C. Cupertino, D. J. Irvine, D. J. Cole-Hamilton, *J. Chem. Soc. Dalton Trans.* **1991**, 1929–1935.

[7] For reviews on reversible covalent bonding with ligands for metal catalysts, see: a) Y. J. Park, J. W. Park, C. H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222–234; b) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498–2543; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494.

[8] For reviews of organic catalysts used in acyl-transfer reactions, see: a) A. C. Spivey, S. Arseniyadis, *Top. Curr. Chem.* **2010**, *291*, 233–280; b) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174–194; c) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481–2495; d) T. Kawabata, T. Furuta, *Chem. Lett.* **2009**, *38*, 640–647.

[9] For an early example of desymmetrization of 1,2-diols using an organic catalyst, see T. Oriyama, K. Imai, T. Sano, T. Hosoya, *Tetrahedron Lett.* **1998**, *39*, 3529–3532.

[10] a) P. A. Jordan, K. J. Kayser-Bricker, S. J. Miller, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20620–20624; b) B. Sculimbrene, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 10125–10126; c) B. Sculimbrene, A. Morgan, S. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 11653–11656.

[11] a) K. W. Fiori, A. L. A. Puchlopek, S. J. Miller, *Nat. Chem.* **2009**, *1*, 630–634; b) Y. Demizu, K. Matsumoto, O. Onomura, Y. Matsumura, *Tetrahedron Lett.* **2007**, *48*, 7605–7609; c) O.

Onomura, M. Mitsuda, M. T. T. Nguyen, Y. Demizu, *Tetrahedron Lett.* **2007**, *48*, 9080 – 9084.

[12] a) T. Isobe, K. Fukuda, Y. Araki, T. Ishikawa, *Chem. Commun.* **2001**, 243 – 244; b) Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67 – 70; c) Y. Zhao, A. W. Mitra, A. H. Hoveyda, M. L. Snapper, *Angew. Chem.* **2007**, *119*, 8623 – 8626; *Angew. Chem. Int. Ed.* **2007**, *46*, 8471 – 8774; d) Z. You, A. H. Hoveyda, M. L. Snapper, *Angew. Chem.* **2009**, *121*, 555 – 558; *Angew. Chem. Int. Ed.* **2009**, *48*, 547 – 550; e) A. Grajewksa, M. Oestreich, *Synlett* **2010**, 2482 – 2484; f) H. Yan, H. B. Jang, J.-W. Lee, H. K. Kim, S. W. Lee, J. W. Yang, C. E. Song, *Angew. Chem.* **2010**, *122*, 9099 – 9101; *Angew. Chem. Int. Ed.* **2010**, *49*, 8915 – 8917.

[13] For a review on Si–O coupling reactions including metal-catalyzed reactions, see: A. Weickgenannt, M. Mewald, M. Oestreich, *Org. Biomol. Chem.* **2010**, *8*, 1497 – 1504.

[14] In the desymmetrization $<5\,\%$ the bis(silylated) product is observed. Also a control reaction showed no silyl migration during the reaction (see the Supporting Information for details).

[15] The value of this K_{eq} is similar to the value determined for our phosphorous ligand in Figure 2. See Ref. [5a] for details.

[16] Catalysts **1**–**3** form diastereomeric mixtures with ratios between 1.9:1 and 5.7:1. See the Supporting Information for details of each catalyst.

[17] The exchange with *cis*-1,2-cyclopentane diol is significantly faster than isopropanol. The exchange with isopropanol and 10 mol % PMP·HCl takes approximately 12 hours to reach equilibrium. At this time we cannot assign the major and minor diastereomers of substrate bound catalyst.

[18] CCDC 832192 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

