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Application of Scaffolding Catalysts in a Highly Enantioselective Desymmetrization Reaction

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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 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 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] In this publication 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 mono-protected products with no limitation on 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 non-covalent 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 more intimate association between the catalyst and the substrate and lead to enhanced reactivity and/or selectivity. Similar to our phosphine ligand design, to develop a silyl transfer catalyst, we synthesized a bifunctional molecule (Figure 2). The scaffolding catalyst contains a substrate-binding site, which uses a 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 (Figure 3). A unique feature of this catalytic cycle is that the binding of the catalyst

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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 and –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 (34% and 40% ee, table 1, entries 2 and 3). 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 the product with excellent enantioselectivity (97% ee, table 1, entry 5),^[14] while **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 non-cryogenic 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). 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 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 acyclic substrate butane-2,3-diol 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) with a reaction time of 1 h at room temperature. Sterically larger silyl reagent *tert*-butyldiphenyl silyl chloride (TBDPSCI) affords the product in 90% ee and good yield (75%, table 3, entry 2), though 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) with only a small decrease in ee (86% ee, table 3, entry 2). Silylation with the very reactive dimethylphenyl silyl chloride (DMPSCI) results in a decrease in enantioselectivity to 79% (table 3, entry 3); presumably, the lowered selectivity is a result of background silylation.

The results with TESCI 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 36 h reaction time at 0 °C to obtain high enantioselectivity (Table 2, entry 7). With the TESCI procedure, the product is formed with improved selectivity and yield (84%, 92% ee) with a 4 h reaction

time at room temperature (Scheme 1). 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 h (Scheme 1).

In terms of a mechanism for catalysis and stereoinduction, it is conceivable that either non-covalent 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 2), consistent with substrate binding being important for both rate acceleration and enantioselectivity. In support of exchange occurring under the reaction conditions, isopropanol was added to **4b**, in the presence of 10 mol % PMP•HCl and monitored by ¹H NMR. Under these conditions, equilibrium is established with a K_{eq} of 0.12 (Scheme 3).^[15] Collectively, these observations strongly support a mechanism that involves reversible covalent substrate-catalyst bonding.

To learn more about the step in the mechanism that is responsible for selectivity, the structure and stability of catalysts and catalyst-substrate complexes were examined. First, catalyst **4b** forms only a single diastereomer of catalyst as observed by ¹H NMR.^[16] Exchange of 4-bromobenzyl alcohol onto **4b** allowed for an X-ray structure to be obtained, which shows that the alcohol binds *syn* to the *i*-Pr group on the oxazoline ring (Figure 4). We believe 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, reaching equilibrium in ~3 h (Scheme 3).^[17] We have tentatively assigned these compounds as derived from the binding of the enantiotopic alcohols to **4b**. The two new compounds form in a 60:40 ratio, 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 (*R*)-alcohol binds the catalyst it places the free alcohol in close proximity to the catalytic site facilitating intramolecular transfer. Conversely, if the (*S*)-alcohol binds, the free alcohol is placed away from the catalytic residue 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 for derivatives to be rapidly accessed. The rigid covalent bonding between the substrate-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 functionalization *anti*-1–2, *syn*- and *anti*-1,3- and 1,4-diols.

Experimental Section

To an oven-dried glass reaction vial, 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. Reaction was stirred at room temperature for 10 minutes. 1,2,2,6,6-pentamethylpiperidine (87 μ L, 0.48 mmol, 1.2 eq.) was added, followed by addition of a solution of *tert*-butylchlorodimethylsilane (120 mg, 0.80 mmol, 2.0 eq.) in anhydrous THF (0.50 mL). After stirring at room temperature for 4 h, reaction was quenched by addition of *N,N*-diisopropylethylamine (200 μ L) and methanol (60 μ L). The mixture was stirred at room temperature for 10 minutes, and was concentrated. Flash column chromatography (Hex/EtOAc = 20/1) afforded pure product as colorless oil (80 mg, 92%, 94% ee). Chiral GLC Analysis (Supelco Beta Dex 120 (30 $\times$ 0.15 mm $\times$ 0.25 μ m film thickness), 78 $^{\circ}$ C for 100 min, 20 $^{\circ}$ C/min to 180 $^{\circ}$ C, 180 $^{\circ}$ C for 20 min, 15 psi).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. For reviews on enamine and iminium catalysis, see: Pihko PM, Majander I, Erkkila A. Asymmetric Organocatalysis. Springer-Verlag Berlin 2010:29–75. Melchiorre P, Marigo M, Carlone A, Bartoli G. *Angew Chem, Int Ed.* 2008; 47:6138–6171. *Angew Chem.* 2008; 120:6232–6265. Mukherjee S, Yang JW, Hoffmann S, List B. *Chem Rev.* 2007; 107:5471–5569. [PubMed: 18072803] Erkkila A, Majander I, Pihko PM. *Chem Rev.* 2007; 107:5416–5470. [PubMed: 18072802]
2. For a review on *N*-heterocyclic carbenes as organic catalysts see: Moore JL, Rovis T. Asymmetric Organocatalysis. Springer-Verlag Berlin 2010; 291:77–144.
3. For recent examples of reversible covalent bonding in organic catalysts that use induced intramolecularity see: Sammakia T, Hurley TB. *J Am Chem Soc.* 1996; 118:8967–8968. Sammakia T, Hurley TB. *J Org Chem.* 1999; 64:4652–4664. [PubMed: 11674535] Sammakia T, Hurley TB. *J Org Chem.* 2000; 65:974–978. [PubMed: 10814042] Ghosh M, Conroy JL, Seto CT. *Angew Chem, Int Ed.* 1999; 38:514–516. *Angew Chem.* 1999; 111:575–578. Ishihara K, Ohara S, Yamamoto H. *J Org Chem.* 1996; 61:4196–4197. [PubMed: 11667313] Ishihara K. *Tetrahedron.* 2009; 65:1085–1109. Maki T, Ishihara K, Yamamoto H. *Org Lett.* 2005; 7:5043–5046. [PubMed: 16235953] Maki T, Ishihara K, Yamamoto H. *Tetrahedron.* 2007; 63:8645–8657. Latta R, Springsteen G, Wang B. *Synthesis.* 2001; 11:1611–1613. Al-Zoubi RM, Marion O, Hall DG. *Angew Chem, Int Ed.* 2008; 47:2876–2879. *Angew Chem.* 2008; 120:2918–2921. Houston TA, Wilkinson BL, Blanchfield JT. *Org Lett.* 2004; 6:679–681. [PubMed: 14986948] Houston TA, Levonis SM, Kiefel MJ. *Aus J Chem.* 2007; 60:811–815. Maki T, Ishihara K, Yamamoto H. *Org Lett.* 2005; 7:5047–5050. [PubMed: 16235954] Levonis SM, Bornaghi LF, Houston TA. *Aust J Chem.* 2007; 60:821–823. Kondaiah GCM, Reddy LA, Babu KS, Gurav VM, Hude KG, Bandichhor R, Reddy PP, Bhattacharya A, Anand RV. *Tetrahedron Lett.* 2007; 49:106–109. Mori Y, Manabe K, Kobayashi S. *Angew Chem, Int Ed.* 2001; 40:2815–2818. *Angew Chem.* 2001; 113:2897–2900. Aelvoet K, Batsanov AS, Blatch AJ, Grosjean C, Patrick LGF, Smethurst CA, Whiting A. *Angew Chem, Int Ed.* 2008; 47:768–770. *Angew Chem.* 2008; 120:780–782. Lee D, Newman SG, Taylor MS. *Org Lett.* 2009; 11:5486–5489. [PubMed: 19904926] Zheng H, Hall DG. *Tetrahedron Lett.* 2010; 51:3561–3564. Zheng H, McDonald R, Hall DG. *Chemistry-Eur J.* 2010; 16:5454–5460. v) see reference 4 for more examples.
4. Pascal R. *Eur J Org Chem.* 2003; 10:1813–1824.

5. a) Lightburn TE, Dombrowski MT, Tan KL. J Am Chem Soc. 2008; 130:9210–9211. [PubMed: 18576619] b) Worthy AD, Gagnon MM, Dombrowski MT, Tan KL. Org Lett. 2009; 11:2764–2767. [PubMed: 19489593] c) Sun X, Frimpong K, Tan KL. J Am Chem Soc. 2010; 132:11841–11843. [PubMed: 20687551] d) Worthy AD, Joe CL, Lightburn TE, Tan KL. J Am Chem Soc. 2010; 132:14757–14759. [PubMed: 20882977] e) Lightburn TE, De Paolis OA, Cheng KH, Tan KL. Org Lett. 2011; 13:2686–2689. [PubMed: 21504208]
6. For early examples of reversible covalent bonding with ligands for metal catalysts see: Lewis LN. Inorg Chem. 1985; 24:4433–4435. Lewis LN, Smith JF. J Am Chem Soc. 1986; 108:2728–2735. Preston SA, Cupertino DC, Palma-Ramirez P, Cole-Hamilton DJ. J Chem Soc Chem Commun. 1986; 12:977–978. Iraqi A, Fairfax NR, Preston SA, Cupertino DC, Irvine DJ, Cole-Hamilton DJ. J Chem Soc Dalton Trans. 1991; 8:1929–1935.
7. For reviews on reversible covalent bonding with ligands for metal catalysts see: Park YJ, Park JW, Jun CH. Acc Chem Res. 2008; 41:222–234. [PubMed: 18247521] Rousseau G, Breit B. Angew Chem Int Ed. 2011; 50:2450–2494. Angew Chem. 2011; 123:2498–2543.
8. For reviews of organic catalysts used in acyl transfer reactions, see: Spivey AC, Arseniyadis S. Top Curr Chem. 2010; 291:233–280. [PubMed: 21494952] Marinetti A, Voituriez A. Synlett. 2010; 2:174–194. Jarvo ER, Miller SJ. Tetrahedron. 2002; 58:2481–2495. Kawabata T, Furuta T. Chem Lett. 2009; 38:640–647.
9. For an early example of desymmetrization of 1,2-diols using an organic catalyst see Oriyama T, Imai K, Sano T, Hosoya T. Tetrahedron Lett. 1998; 39:3529–3532.
10. a) Jordan PA, Kayser-Bricker KJ, Miller SJ. P Natl Acad Sci USA. 2010; 107:20620–20624. b) Sculimbrene B, Miller SJ. J Am Chem Soc. 2001; 123:10125–10126. [PubMed: 11592903] c) Sculimbrene B, Morgan A, Miller S. J Am Chem Soc. 2002; 124:11653–11656. [PubMed: 12296730]
11. a) Fiori KW, Puchlopek ALA, Miller SJ. Nat Chem. 2009; 1:630–634. [PubMed: 20161563] b) Demizu Y, Matsumoto K, Onomura O, Matsumura Y. Tetrahedron Lett. 2007; 48:7605–7609. c) Onomura O, Mitsuda M, Nguyen MTT, Demizu Y. Tetrahedron Lett. 2007; 48:9080–9084.
12. a) Isobe T, Fukuda K, Araki Y, Ishikawa T. Chem Commun. 2001; 3:243–244. b) Zhao Y, Rodrigo J, Hoveyda AH, Snapper ML. Nature. 2006; 443:67–70. [PubMed: 16957727] c) Zhao Y, Mitra AW, Hoveyda AH, Snapper ML. Angew Chem, Int Ed. 2007; 46:8471–8774. Angew Chem. 2007; 119:8623–8626. d) You Z, Hoveyda AH, Snapper ML. Angew Chem, Int Ed. 2009; 48:547–550. Angew Chem. 2009; 121:555–558. e) Grajewksa A, Oestreich M. Synlett. 2010; 16:2482–2484. f) Yan H, Jang HB, Lee JW, Kim HK, Lee SW, Yang JW, Song CE. Angew Chem, Int Ed. 2010; 49:8915–8917. Angew Chem. 2010; 122:9099–9101.
13. For a review on Si-O coupling reaction including metal-catalyzed reactions see: Weickgenannt A, Mewald M, Oestreich M. Org Biomol Chem. 2010; 8:1497–1504. [PubMed: 20237658]
14. In the desymmetrization <5% bis-silylated product is observed. Also a control reaction showed no silyl migration during the reaction (see 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 between 1.9:1 and 5.7:1. See 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 ~12 h to reach equilibrium. At this time we cannot assign the major and minor diastereomers of substrate bound catalyst.

Figure 1.
Catalytic cycle for scaffolding catalysis

Figure 2.
Catalyst design

Figure 3.
Proposed catalytic cycle for silylation

Figure 4.
X-ray structure of **6**

Scheme 1.
Silylation with TESCl

Scheme 2.
Control reaction

Scheme 3. Exchange of **4b** with isopropanol and substrate

Table 1

Optimization of silyl transfer reaction

1: R₁ = Me 2: R₁ = <i>i</i>-Pr 3: R₁ = <i>t</i>Bu			
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 based on internal standard

^[b] enantiomeric excess (ee) determined by GC

^[c] reaction performed at 0.40 mmol substrate; isolated yield of product.

^[d] reaction performed 0.2 M of diol in *t*-BuOH.

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's 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