Homogeneous Catalysis

DOI: 10.1002/anie.201107874

Iterative Asymmetric Allylic Substitutions: *syn*- and *anti*-1,2-Diols through Catalyst Control**

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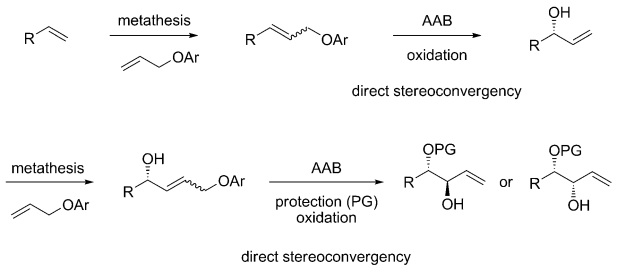
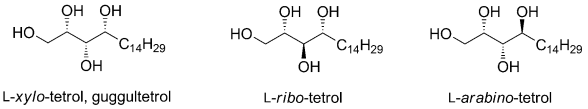
The iterative introduction of multiple contiguous stereocenters of any possible configuration remains a challenging aspect of catalytic asymmetric chemistry because of chiral substrate/chiral catalyst mismatch.[1] Though outstanding examples of catalytic iterative syntheses of 1,3- and 1,5-dialkyl compounds and diols are known,[2] an iterative method that gives vicinal optically active polyols remains elusive because of the proximity of the chiral centers.[3] Herein, we report an efficient iterative approach to 1,2-diols and polyols by using a sequence of copper-catalyzed asymmetric allylic boronation (AAB) and cross-metathesis reaction.

Recently, copper(I)-catalyzed boronations have emerged as a selective tool for the synthesis of chiral organoboron compounds.[4] Among these transformations, AAB reactions have been reported by three research groups, including ours.[4a–e] We have shown that a 6-membered-ring *N*-heterocyclic carbene/copper(I) catalyst (6-NHC-Cu^{I}) exhibits direct stereoconvergency, which allows the use of *E/Z* mixtures produced by cross-metathesis reaction.[4a]



1) Catalyst control versus substrate control,
2) Easy and flexible elongation method (e.g., metathesis),
3) Functional group differentiation.

Chiral 1,2-diols are ubiquitous subunits in natural products, such as carbohydrates and polyketides, and are widely applied in organic synthesis as chiral ligands or auxiliaries. Preparation of *syn*-1,2-diols with high stereocontrol is straightforward by using the Sharpless asymmetric dihydroxylation.[5] Preparation of *anti*-1,2-diols is more challenging, but can be achieved by asymmetric epoxidation and ring opening,[6] chiral auxiliary mediated aldol reactions,[7a–c] Lewis base catalyzed aldol reactions,[7d] organocatalyzed aldol reactions,[7e–g] allene hydroboration/aldehyde allylboration reaction,[8] as well as nucleophilic addition to α-oxyaldehydes or aldehydes.[9] Despite great improvement, catalytic methods that give high *anti*-selectivity cannot provide the *syn*-1,2-diol by simply switching to the opposite stereoisomer of the catalyst, and stoichiometric methods rely on substrate control to achieve the desired selectivity, thereby limiting the scope of the method.[10]



L-*xylo*-tetrol, guggultetrol L-*ribo*-tetrol L-*arabino*-tetrol

A strategy in which an optically pure substrate can react with one enantiomer of a catalyst to give a differentiated *syn*-1,2-diol and with the other enantiomer to give a differentiated *anti*-1,2-diol would be an ideal method and is currently unavailable, despite the fact that catalyst-controlled diastereoselectivity is known.[11,12] We envisioned that an iterative asymmetric allylic boronation in which the boronation step is catalyst-controlled would provide a method fulfilling these ideals, and that such a method would be useful for the preparation of carbohydrates, polyketides, and other important polyols (e.g., natural lipid guggultetrol and stereoisomers, see above).[13]

We recently introduced the annulated optically active 6-NHC-Cu^{I} catalyst, which shows excellent activity and the capacity to perform allylic substitutions stereoconvergently.[4a,g] A modification of the model that we used to justify this stereoconvergent property prompted us to hypothesize that the complex might also perform catalyst-controlled allylic substitution reactions. We predict that substrates will approach the 6-NHC-Cu^{I} complex from an orientation that places the chiral center away from the catalyst (Scheme 1).[14]

First, we tested our hypothesis by performing allylic substitutions on a series of optically active alcohols and ethers (Table 1). Although the products of the allylic substitution are bifunctional 2-hydroxy or ether boronates that in themselves are widely useful,[15] we decided to showcase our method by converting the products to the corresponding alcohols. We observed that both allylic alcohol and ether substrates provided the desired catalyst-controlled activity (Table 1).

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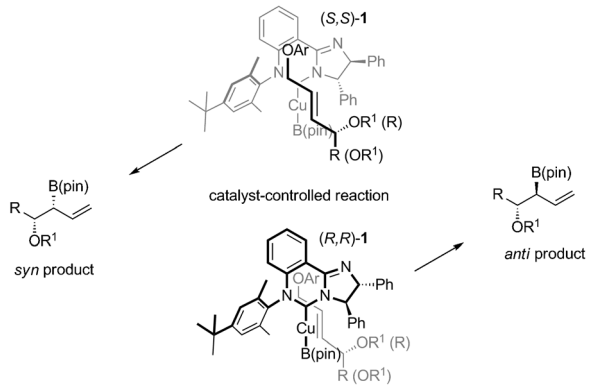
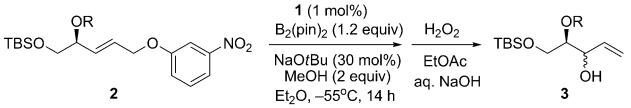
[**] The authors thank NSF (CHE-0809261), Pfizer, Corning Glass, and FSU support and FSU VP of Research and Dean of A&S for NMR upgrades.

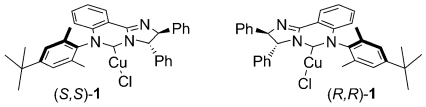
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107874.



Scheme 1. Our model for catalyst control. pin = pinacolato.

Table 1: Screening of protection groups.[18]



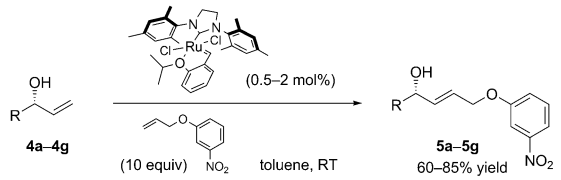


Entry	Catalyst	**2** (R)[a]	*syn*/*anti*[b]	Yield [%][c]
1	(*S*,*S*)-**1**	**2a** (H)	**95:5**	>**95**, **76**[d]
2		**2b** (Me)	82:18	78
3		**2c** (MOM)	94:6	75
4		**2d** (TBS)	n.d.	n.d.
5	(*R*,*R*)-**1**	**2a** (H)	**3:97**	>**95**, **71**[d]
6		**2b** (Me)	<2:98	>95
7		**2c** (MOM)	2:98	79
8		**2d** (TBS)	n.d.	n.d.
9	*rac*-**1**	**2a** (H)	46:54	>95

[a] **2** was synthesized from D-mannitol.[19] [b] Ratio of *syn*/*anti* was determined by ^{1}H NMR analysis of crude mixtures. [c] Yields were determined by ^{1}H NMR spectroscopy. [d] Yields of isolated products after in situ protection with TESOTf and 2,6-lutidine.[19] Results in bold mark optimized reactions. n.d. = not determined. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

We found that the size of the ether controlled diastereoselectivity and yield. The largest protecting group, TBS, did not react (Table 1, entries 4 and 8), while the MOM ether produced the desired products with high selectivity for both catalyst enantiopodes (Table 1, entries 3 and 7). The methyl ether produced the *anti* product with excellent yield and selectivity (Table 1, entry 6), however, the selectivity of the *syn* product was modest (Table 1, entry 2). In order to minimize steric interactions between catalyst and substrate, an allylic alcohol was used as starting material, and the alcohol was not only compatible with the reaction but provided both high yield and selectivity (Table 1, entries 1 and 5). From these data, we conclude that the size of the group adjacent to the allylic substitution site controls whether the reaction exhibits substrate or catalyst control. The boronate products were easily oxidized to give *syn*- and *anti*-1,2-diols. Furthermore, if doubly differentiated diols are the desired product, in situ protection with silyl triflate and lutidine[4f,17] prior to oxidation works well (Table 1, entries 1 and 5, and Scheme 3, **10**→**11**). We found that the ratio of product was maintained at 46:54 (*syn*:*anti*) during the entire course of the reaction with a racemic mixture of catalyst **1** and optically pure alcohol substrate (Table 1, entry 9).[16]

Substrates **5a**–**5g**[19] were readily prepared from allylic alcohols by cross-metathesis reaction that was catalyzed by the Hoveyda-Grubbs catalyst (Scheme 2).[20] The starting



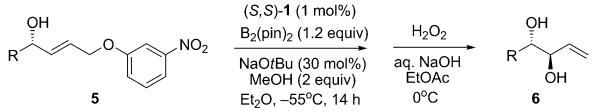
Scheme 2. Cross-metathesis reaction for the substrate synthesis.

materials **4a**–**4f** were synthesized by our asymmetric allylic substitution method,[4a] **4g** was prepared from (−)-linalool. Allylic alcohols are ideal substrates as they significantly accelerated the cross-metathesis reaction by hydrogen bonding to the chloride ligand on the catalyst.[20b–d] In most cases, the cross-metathesis provided the *E* isomers (>10:1) of the desired products with reasonable yields. Remaining starting materials could be recovered and reused. Not surprisingly, we found that ten equivalents of 3-nitrophenyl allyl ether suppressed formation of the homodimer of **4**.

We then used substrates **5a**–**5g** to assess the substrate scope of the catalyst-controlled method.[22] We observed good to excellent selectivity for both chiral catalysts ((*S*,*S*)-**1** and (*R*,*R*)-**1**) with the same enantiomeric series of starting materials **5** (Tables 2 and 3), thus demonstrating that the stereochemical selectivity is mostly dictated by the catalyst and not the substrate. In some examples, slightly higher selectivity was obtained in the *anti* series, which indicates that some minor double asymmetric induction occurs (Tables 2 and 3, entries 1 and 3–5, respectively). The mismatched (*R*,*R*)-**1** complex resulted in low yield and selectivity for the cyclohexyl-bearing substrate (Table 3, entry 6) and the matched complex (*S*,*S*)-**1** provided near perfect selectivity (Table 2, entry 6), thus, the impact of the double asymmetric induction increases with an increased size of the R group. Interestingly, only *syn* product was obtained by using a tertiary alcohol substrate (Tables 2 and 3, entries 7, respectively), thus indicating that the quaternary center controls catalyst–substrate interactions more dominantly than the hydroxy group.

To underscore the value of this methodology, we synthesized the fully differentiated L-*ribo*-tetrol and protected D-*arabino*-tetrol. For L-*ribo*-tetrol, we started the synthesis by performing our asymmetric allylic boronation on substrate **9** followed by oxidation and cross-metathesis to give **10**

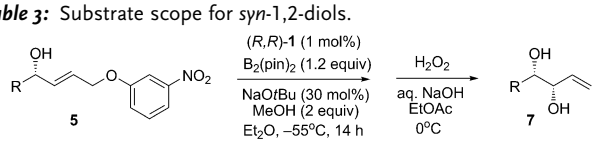
Table 2: Substrate scope for *anti*-1,2-diols.



Entry	5 (*ee* [%])[a]	6	Yield [%][b]	d.r.[c] *anti/syn*
1	**5a** (96)	**6a**	81	98:2
2	**5b** (93)	**6b**	90	95:5
3	**5c** (–)	**6c**	87	95:5
4	**5d** (94)	**6d**	93	97:3
5	**5e** (92)	**6e**	88	94:6
6	**5f** (99)	**6f**	91	>98:2
7[d]	**5g** (>98)	**6g**	–	–

[a] *ee* values were determined using precursor **4**.[21] [b] Yields of isolated products. [c] Ratio of *anti/syn* was determined by ^{1}H NMR analysis of crude mixtures. [d] Opposite configuration was used with (*R*,*R*)-**1**. Enantiomer of product is shown for better understanding. TBDPS = *tert*-butyldiphenylsilyl.

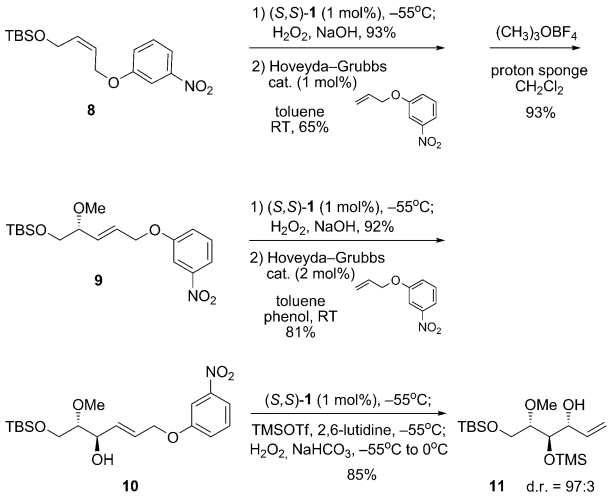
Table 3: Substrate scope for *syn*-1,2-diols.



Entry	5 (*ee* [%])[a]	7	Yield [%][b]	d.r.[c] *syn/anti*
1	**5a** (96)	**7a**	85	95:5
2	**5b** (93)	**7b**	93	95:5
3	**5c** (–)	**7c**	85	93:7
4	**5d** (94)	**7d**	93	95:5
5	**5e** (92)	**7e**	72	91:9
6	**5f** (99)	**7f**	52	88:12
7[d]	**5g** (>98)	**7g**	71	>98:2

[a] *ee* values were determined using precursor **4**.[21] [b] Yields of isolated products. [c] Ratio of *anti/syn* was determined by ^{1}H NMR analysis of crude mixtures. [d] Opposite configuration was used with (*S*,*S*)-**1**. Enantiomer of product is shown for better understanding.

(Scheme 3). The cross-metathesis reaction using these highly oxygenated substrates was significantly improved by adding phenol (30% without phenol, 81% with phenol).[20c] Substrate **10** was then converted into **11** in excellent yield by

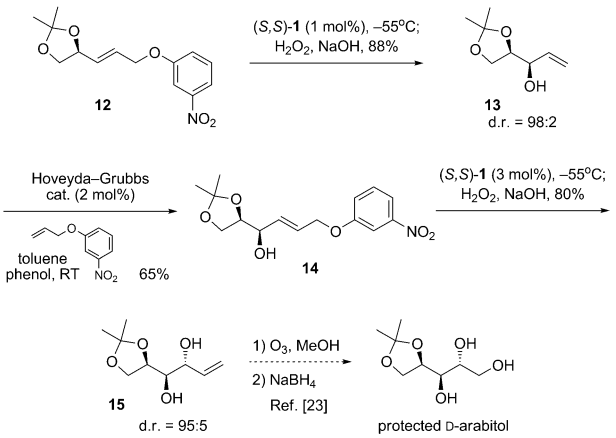


Scheme 3. Iterative synthesis of fully differentiated L-*ribo*-tetrol.

a three-step one-pot process that included an asymmetric allylic boronation, TMSOTf protection, followed by oxidation of the C–B bond using H_2O_2 and $NaHCO_3$.

To synthesize D-*arabino*-tetrol, an AAB reaction was performed on substrate **12** followed by oxidation to give **13** in 88% yield (Scheme 4). Compound **14** was obtained by cross-metathesis reaction of **13** in 65% yield. D-*arabino*-tetrol was obtained in 80% yield through another AAB reaction. Compound **15** is easily transformed to D-arabitol in two steps by using previously reported methods.[23]

In summary, we have shown a catalyst-controlled asymmetric reaction for the synthesis of *syn*- and *anti*-1,2-diols. Diols could be easily differentiated by in situ protection with silyltriflates. We have also demonstrated an iterative synthetic methodology for the highly diastereoselective preparation of



Scheme 4. Iterative synthesis of D-*arabino*-tetrol derivative.

a fully differentiated L-*ribo*-tetrol and protected D-*arabino*-tetrol. We are currently investigating the application of the stereoconvergent AAB method to produce non-diol products and application of this iterative strategy described herein to produce natural products.

Experimental Section

Typical reaction conditions for cross-metathesis: A 7 mL screw-top vial was equipped with a stirrer bar and charged with allylic alcohol **4** (1.0 equiv) and 1-(allyloxy)-3-nitrobenzene (10 equiv) in toluene. Hoveyda-Grubbs second-generation catalyst (0.5–2 mol%) was added in at least two portions until the reaction was complete (progress of the reaction was monitored by ^{1}H NMR spectroscopy). After 1 h, the reaction mixture was directly loaded onto silica gel and purified by column chromatography (hexanes→hexanes:EtOAc = 5:1). Starting materials were recovered and the desired products were isolated with a small amount of homodimer of nitrophenyl ether. The solid homodimer was easily removed by trituration with hexanes or methanol.

Typical reaction conditions for allylic substitution reaction: Allylic aryl ether (0.10 mmol) and bis(pinacolato)diboron (30 mg, 0.12 mmol) were dissolved in Et_2O (0.8 mL). NaO*t*Bu (3 mg, 0.030 mmol) was added to the reaction mixture. The reaction mixture was then cooled to −55 °C and MeOH (8 μL, 0.20 mmol) was added. Et_2O (0.2 mL) was then added to wash the sides of the Schlenk tube. After 5 min, 6-NHC-Cu^I catalyst **1** (< 1.0 mg, 0.0010 mmol) was added. After 14–18 h, the reaction mixture was diluted with EtOAc (1 mL), followed by addition of H_2O_2 (5 equiv) and 1M NaOH (2 equiv). The mixture was warmed to 0 °C and stirred for 30 min. Water was added and the organic phase was separated. The aqueous phase was extracted two times with EtOAc. The combined organic layers were dried and concentrated under rotary evaporator. The resulting residue was purified by column chromatography (hexanes→hexanes:Et_2O = 3:1) to afford the desired products. Diastereoselectivity was determined by ^{1}H NMR spectroscopy of the crude mixture.

Received: November 9, 2011
Published online: February 1, 2012

Keywords: allylic substitution · boronation · copper · homogeneous catalysis · iterative asymmetric reaction

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[11] For the synthesis of differentiated diols, see: a) D. Cartigny, K. Püntener, T. Ayad, M. Scalone, V. Ratovelomanana-Vidal, *Org. Lett.* **2010**, *12*, 3788 – 3791; b) S. M. Lim, N. Hill, A. G. Myers, *J. Am. Chem. Soc.* **2009**, *131*, 5763 – 5765; c) C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem.* **2008**, *120*, 6275 – 6278; *Angew. Chem. Int. Ed.* **2008**, *47*, 6180 – 6183; d) Y. Zhao, A. W. Mitra, A. H. Hoveyda, M. L. Snapper, *Angew. Chem.* **2007**, *119*, 8623 – 8626; *Angew. Chem. Int. Ed.* **2007**, *46*, 8471 – 8474; e) Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67 – 70. For more references, see Ref. [6b, 7 (except 7e), and 9].

[12] For selected examples of catalyst-controlled asymmetric reactions, see: a) G. Muncipinto, P. N. Moquist, S. L. Schreiber, S. E. Schaus, *Angew. Chem.* **2011**, *123*, 8322 – 8325; *Angew. Chem. Int. Ed.* **2011**, *50*, 8172 – 8175; b) G. D. Joly, E. N. Jacobsen, *Org. Lett.* **2002**, *4*, 1795 – 1798. For more references, see Ref. [2, 3].

[13] a) S. Dev, *Pure Appl. Chem.* **1989**, *61*, 353 – 356; b) K. R. Prasad, A. Chandrakumar, *Tetrahedron* **2007**, *63*, 1798 – 1805; c) S. George, G. Suryavanshi, A. Sudalai, *Tetrahedron: Asymmetry* **2010**, *21*, 558 – 561.

[14] We also recognized that *cis* substrates would give the same configuration based upon our model.

[15] a) J. Kister, P. Nuhant, R. Lira, A. Sorg, W. R. Roush, *Org. Lett.* **2011**, *13*, 1868 – 1871; b) E. Fernández, J. Pietruszka, W. Frey, *J. Org. Chem.* **2010**, *75*, 5580 – 5589; c) R. Lira, W. R. Roush, *Org. Lett.* **2007**, *9*, 533 – 536; d) E. M. Flamme, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 13644 – 13645.

[16] This result shows that the matched and mismatched reactions have almost the same rate for alcohol substrates.

[17] M. Penner, V. Rauniyar, L. T. Kaspar, D. G. Hall, *J. Am. Chem. Soc.* **2009**, *131*, 14216 – 14217.

[18] We found that 30 mol% of NaO*t*Bu was needed to provide reproducible outcomes, although in many cases a lower loading provides high yields. We also attempted to alter the amount of methanol added and found that less than one equivalent resulted in leftover starting material. We propose that methanol accelerates the reaction rate by promoting the formation of methyl pinacolyl borate. Temperature was optimized between 0 and −55 °C and the lower temperature was found to provide the highest selectivity.

[19] Preparation details are included in the Supporting Information.

[20] a) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370; for hydrogen bonding effect, see: b) A. H. Hoveyda, P. J. Lombardi, R. V. O'Brien, A. R. Zhugralin, *J. Am. Chem. Soc.* **2009**, *131*, 8378 – 8379; c) G. S. Forman, A. E. McConnell, R. P. Tooze, W. J. van Rensburg, W. H. Meyer, M. M. Kirk, C. L. Dwyer, D. W. Serfontein, *Organometallics* **2005**, *24*, 4528 – 4542; d) T. R. Hoye, H. Zhao, *Org. Lett.* **1999**, *1*, 1123 – 1125.

[21] For ease of separation, we determined the *ee* value of **4** and assumed that it would not change under the metathesis reaction conditions that are used to prepare **5**. Our assumption is supported by Ref. [20b] and the high d.r. that was observed.

[22] We attempted the use of a number of leaving groups, including 3,5-dimethylphenyl ether, which provided similar selectivity at 0 °C (see Ref. [4a]). The 3-nitrophenyl ether appears to be the best leaving group in combination with our catalyst.

[23] W. R. Roush, P. T. Grover, *Tetrahedron* **1992**, *48*, 1981 – 1998.

