Asymmetric Synthesis

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Synthesis of *syn* and *anti* 1,4-Diols by Copper-Catalyzed Boration of Allylic Epoxides**

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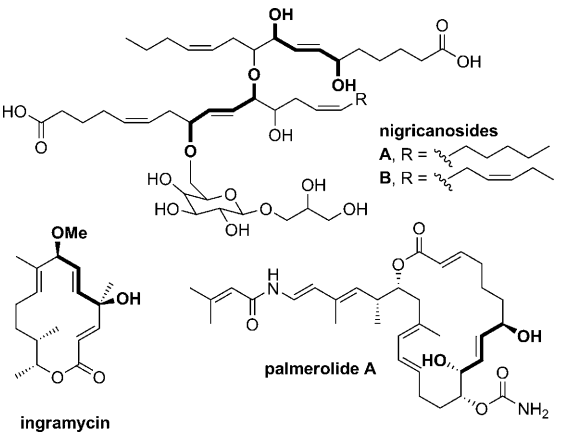
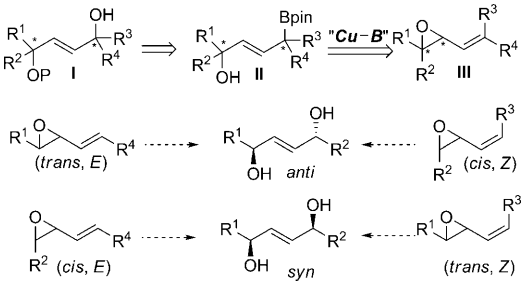
Dedicated to Professor William R. Roush

Stereodefined 1,4-diols are a common feature in a number of biologically active natural products.[1] The nigricanosides,[1a] palmerolide A,[1b] and ingramycin[1c] are three examples of natural products that contain the 1,4-diol subunit.

While a large number of methods have been published for the synthesis of 1,2-, 1,3-, and 1,5-diols, the stereoselective synthesis of 1,4-diols has received less attention. Most of the effort in this field has been focused on the synthesis of symmetrical 1,4-diols,[2] which can be difficult to apply to the total synthesis of complex molecules. Asymmetric reductions of chiral γ-hydroxy ketones,[3] additions of 1-alkyn-3-ols to aldehydes,[4] and olefination reactions[5] are some of the most common ways to access enantiomerically pure nonsymmetrical 1,4-diols. Although good levels of diastereoselectivity can be achieved, two different chiral sources are generally needed to introduce the two oxygenated stereocenters, and their application to total synthesis can be problematic.[6] Recently, an elegant approach was described starting from enantiopure β-hydroxy allylsilanes, but only acyclic *anti* 1,4-diols were obtained with high diastereoselectivity.[7] Therefore, the development of new and general ways to access stereochemically pure *syn* and *anti* 1,4-diols, both cyclic and acyclic and including tertiary alcohols, is a current problem of significant interest in organic synthesis.[8]



Chiral organoboron compounds are versatile synthetic intermediates for the preparation of a wide range of organic molecules. Recently, copper-catalyzed borations of α,β-unsaturated carbonyl compounds[9] and allylic carbonates[10] have emerged as an important tool for the synthesis of enantiopure organoboron compounds. In this context, copper-catalyzed S_N2' addition of diboronates to allylic epoxides (Scheme 1) is



Scheme 1. Proposed diastereoselective synthesis of 1,4-diols. pin = pinacolato.

a potentially powerful transformation for the formation of 2-ene-1,4-diols **I** via the corresponding 1,4-hydroxyboronates **II**. Although formal S_N2' attacks of Cu–B species on allylic carbonates[10] have been described, to the best of our knowledge the only reported Cu^I-catalyzed addition of diboronates to vinyl oxiranes proved to be unsuccessful.[11] Additionally, allylic epoxides provide a new class of functionalized allylic boronates that are difficult to access from other allylic substrates. Some advantages of this methodology would include the well-established catalytic and enantioselective methods for the preparation of allylic epoxides,[12] the ability to form primary, secondary, and tertiary diols, both symmetrical and nonsymmetrical, and the selective introduction of orthogonal protecting groups on the alcohols. Moreover, the method would allow for the synthesis of both *syn* and *anti* 1,4-diols by proper choice of the double-bond and oxirane geometries. Additionally, intermediates **II**, with a valuable, functionalized allylboronate, would be primed for subsequent diastereoselective transformations.[13]

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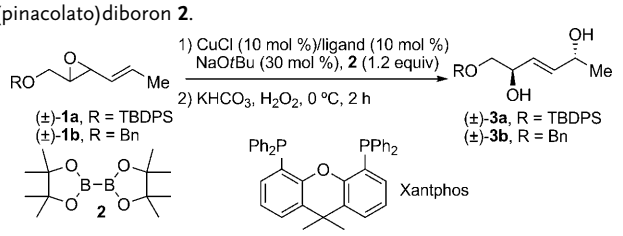
We began by examining the reaction of racemic allylic epoxides (±)-**1a**,**b** (Table 1) with bis(pinacolato)diboron **2** (1.2 equiv) in the presence of catalytic amounts of a ligand (10 mol%), CuCl (10 mol%), and NaO*t*Bu (30 mol%). Using bis[2-(diphenylphosphino)phenyl] ether (DPEphos) in THF at ambient temperature, we observed a rapid conversion of (±)-**1a** to a 1,4-hydroxyboronate. Unfortunately, this intermediate was not stable enough to be isolated, and afforded complex mixtures of unsaturated compounds. However, in situ oxidation of the C–B bond gave *anti* diol (±)-**3a** with moderate diastereoselectivity but complete regioselectivity (Table 1, entry 1).[14]

Table 1: Cu^{I}-catalyzed reaction of allylic epoxides (±)-**1a**,**b** with bis(pinacolato)diboron **2**.



Entry	Epoxide	Ligand	Solvent	*T* [°C]	Yield [%][a]	d.r.[b,c] (*anti*/*syn*)
1	(±)-**1a**	DPEphos	THF	RT	67	68:32
2	(±)-**1a**	Xantphos	THF	RT	81	83:17
3	(±)-**1a**	Bu_3P	THF	RT	–[d]	–
4	(±)-**1a**	Xantphos	toluene	RT	81	82:18
5	(±)-**1a**	Xantphos	THF	0	75	89:11
6	(±)-**1a**	Xantphos	THF	−20	80	92:8
7	(±)-**1a**	Xantphos	THF	−40	60	94:6
8	(±)-**1a**	Xantphos	THF	−78	–	–
9	(±)-**1b**	Xantphos	THF	−20	80	94:6
10[e]	(±)-**1a**	Xantphos	THF	−20	87	92:8

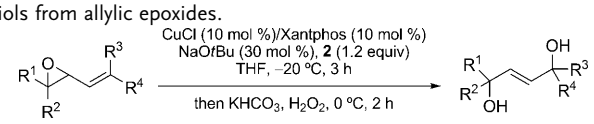
[a] Yield of isolated product over two steps. [b] S_N2 products were not detected. [c] Determined by HPLC analysis. [d] The ^{1}H NMR spectrum of the crude product showed a complex mixture of compounds along with epoxide **1a**. [e] Using 5 mol% CuCl and Xantphos and 15 mol% NaO*t*Bu. TBDPS = *tert*-butyldiphenylsilyl, Bn = benzyl.

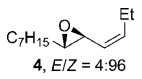
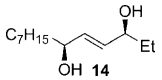
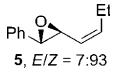
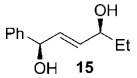
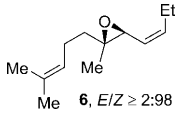
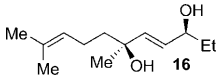
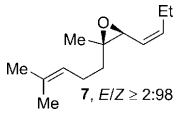
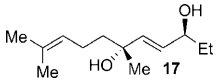
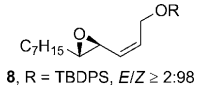
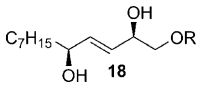
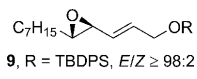
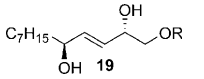
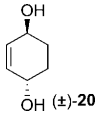
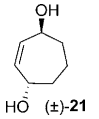
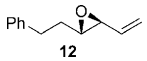
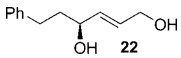
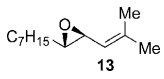
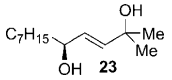
To improve the diastereoselectivity we tried different phosphines. Bu_3P afforded a complex mixture of compounds (Table 1, entry 3) while 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) gave promising results in THF and toluene (Table 1, entries 2 and 4). At lower temperatures (Table 1, entries 5 and 6) we observed higher diastereoselectivities, finding the best results at −20 °C. At −40 °C, the yields were not consistent and we often recovered 20–30% of the starting material, while at −78 °C (Table 1, entry 8) no reaction was observed. Compound (±)-**1b**, with a benzyloxy group, gave similar results (Table 1, entry 9). Moreover, the catalyst loading was reduced to 5% without affecting the diastereoselectivity (Table 1, entry 10).

Using the optimized conditions, the scope of the reaction was then examined with several allylic epoxides (Table 2). We were first intrigued by the stereochemical outcome of *Z*-allylic epoxides. (*Z*)-**4** (*E*/*Z* = 4:96) afforded *syn* diol **14** with high diastereoselectivity (d.r. 6:94; Table 2, entry 1). Phenyl groups attached to the epoxide were also tolerated (Table 2, entry 2), providing *syn* benzylic 1,4-diol **15** (d.r. 8:92).[15] Trisubstituted epoxide **6** (Table 2, entry 3) was found to be an excellent substrate to obtain *syn* diol **16** (d.r. ≥ 98:2) containing a tertiary alcohol. We next changed the geometry of the oxirane ring with epoxide **7** (Table 2, entry 4) and were pleased to find that *anti* diol **17** was obtained as a single isomer. These examples illustrate that by the proper choice of epoxide and double-bond geometries, enantiomerically enriched *syn* and *anti* diols can be readily prepared.

A silyloxy group attached to the double bond (Table 2, entry 5) slightly diminished the diastereoselectivity to 9:91. Unfortunately, this reduction was more noticeable for its *E* counterpart **9**, as *anti* diol **19** was obtained with only moderate diastereoselectivity (d.r. 78:22). Although this result was disappointing, *anti* diols with the same substitution pattern as in **19** were easily obtained with high diastereocon-

Table 2: Cu^{I}-catalyzed diastereoselective synthesis of *syn* and *anti* 1,4-diols from allylic epoxides.

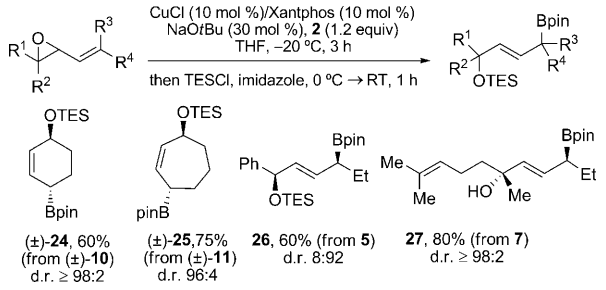


Entry	Epoxide	Diol	Yield [%][a]	d.r.[b] *anti*/*syn*
1	 **4**, *E*/*Z* = 4:96	 **14**	75	6:94[c,e]
2	 **5**, *E*/*Z* = 7:93	 **15**	78	8:92[d,e]
3	 **6**, *E*/*Z* ≥ 2:98	 **16**	80	≥2:98[c]
4	 **7**, *E*/*Z* ≥ 2:98	 **17**	80	≥98:2[c]
5	 **8**, R = TBDPS, *E*/*Z* ≥ 2:98	 **18**	71	9:91[d]
6	 **9**, R = TBDPS, *E*/*Z* ≥ 98:2	 **19**	70	78:22[d]
7	 (±)-**10**	 (±)-**20**	25	≥98:2[c]
8	 (±)-**11**	 (±)-**21**	39	96:4[c]
9	 **12**	 **22**	71	–
10[f]	 **13**	 **23**	48	–

[a] Yield of isolated product. [b] S_N2 products were not detected. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] This result suggests a d.r.value of ≈2:98 for pure *Z*-allylic epoxides. [f] Using 15 mol% CuCl and Xantphos and 45 mol% NaO*t*Bu over 16 h.

trol from epoxides with a silyloxy group attached to the oxirane, as in (±)-**1a** (see (±)-**3a** in Table 1). Cyclic vinyl epoxides (±)-**10** and (±)-**11** provided *anti* diols (±)-**20** and (±)-**21**, respectively, with excellent diastereoselectivity but only moderate yield (Table 2, entries 7 and 8). Addition to a vinyl epoxide with a terminal olefin (Table 2, entry 9) proceeded uneventfully to afford diol **22** in good yield. On the other hand, reaction of allylic epoxide **13** with a trisubstituted alkene required higher catalyst loading for a reasonable conversion (Table 2, entry 10).

At this point we again focused our attention on the versatile 1,4-hydroxyboronate intermediates **II**. We reasoned that in situ protection of the hydroxy group prior to C–B bond oxidation could increase the stability of these compounds and allow for their isolation. Addition of triethylsilyl chloride and imidazole, after the allylic epoxide was consumed, afforded a series of *anti* and *syn* 1,4-silyloxyboronates in good yields and high diastereoselectivities (Scheme 2). We

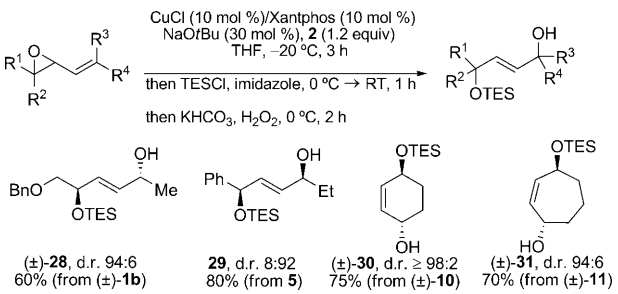


Scheme 2. Diastereoselective synthesis of *syn* and *anti* 1,4-silyloxyboronates. TESCl = triethylchlorosilane, TES = triethylsilyl.

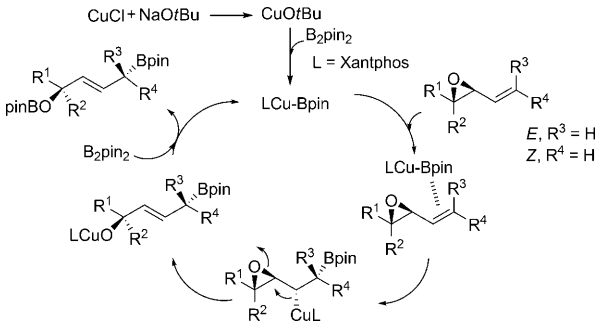
found good yields also for cyclic compounds (±)-**24** and (±)-**25**. This result suggested that the low yields observed for diols (±)-**20** and (±)-**21** might be because of difficulties associated with their isolation. Surprisingly, 1,4-hydroxyboronate **27**, with a tertiary alcohol, was not silylated under standard conditions but was found to be stable. All these compounds were purified by silica gel chromatography and stored for months in the freezer without any observable decomposition.[16]

Additionally, we explored the one-pot Cu^I-catalyzed addition–protection–oxidation process to obtain orthogonally protected 1,4-diols (Scheme 3). Monoprotected *syn* and *anti* 1,4-diols were obtained with excellent diastereoselectivity and overall yield. We believe this mild one-pot addition–protection–oxidation sequence could be very useful in the total synthesis of complex molecules, in which protecting group manipulation is often a challenge.

The observed stereochemical outcome could be explained by an *anti* attack of the boryl–copper intermediate to an allylic epoxide in an s-*trans* conformation.[17,18] A possible mechanism for the Cu^I-catalyzed boration of allylic epoxides is shown in Scheme 4. The diphosphine–copper–boryl complex is first formed from CuO*t*Bu and bis(pinacolato)diboron **2** and formation of a Cu–alkene π complex would next take place.[10b] Addition of the Cu–B bond across the alkene would then give a β-borylalkyl copper intermediate that would



Scheme 3. Diastereoselective synthesis of monoprotected 1,4-diols.



Scheme 4. Proposed mechanism.

undergo elimination with ring opening of the epoxide and formation of a copper alkoxide.[19] The latter regenerates the catalyst with diboron compound **2**.

In summary, the regio- and diastereoselective Cu^I-catalyzed boration of allylic epoxides offers a new approach for the diastereoselective synthesis of *anti* and *syn* 1,4-diols. This method constitutes a formal stereocontrolled hydrolysis of vinyl oxiranes.[20] Enantiomerically enriched 1,4-diols can be prepared from nonracemic epoxides. In situ protection of the new alcohol allows for the isolation of *anti* and *syn* 1,4-silyloxyboronates. Moreover, the one-pot addition–protection–oxidation sequence affords monoprotected *syn* and *anti* 1,4-diols. We believe this one-pot process will be useful in the preparation of a number of diol and triol targets. Studies to establish the full scope of the reaction and applications to the total synthesis of biologically active compounds are under way.

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Keywords: allylic epoxides · borates · copper · diols · natural products

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[16] Oxidation of the C–B bond in **26** followed by deprotection gave diol **15** with the same d.r. as in Table 2 (d.r. 8:92). For the other silyloxyboronates, we assume the d.r. was the same as that for the corresponding diols in Table 2.

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