Desymmetrization

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Desymmetrization of *meso*-2-Alkene-1,4-diol Derivatives through Copper(I)-Catalyzed Asymmetric Boryl Substitution and Stereoselective Allylation of Aldehydes**

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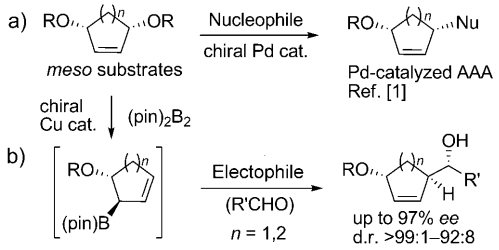
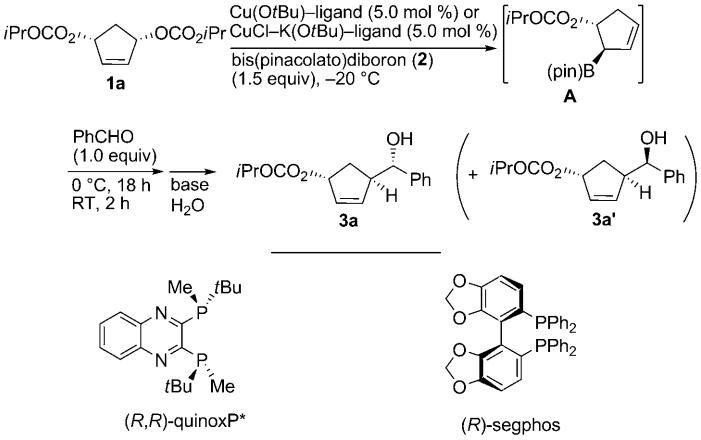
Desymmetrization reactions of *meso* compounds through enantioselective catalysis are a powerful strategy for the synthesis of chiral molecules with multiple stereocenters. One well-known example is the Pd-catalyzed desymmetrization of *meso*-2-alkene-1,4-diol derivatives (Trost's Pd-catalyzed asymmetric allylic alkylation, AAA; Scheme 1a).[1] Such a reaction allows nucleophilic substitution accompanied by differentiation of enantiotopic leaving groups and has been applied to the total syntheses of various natural products.[1] However, the Pd-catalyzed desymmetrization of *meso*-2-alkene-1,4-diol derivatives is limited to the reaction with nucleophiles; desymmetrization with electrophiles, the umpolung version, have not been reported.[2] We report a new desymmetrization procedure: copper(I)-catalyzed asymmetric boryl substitution and stereoselective allylation of aldehydes (Scheme 1b). In this one-pot reaction, the core part of the *meso* substrate is connected to an aldehyde electrophile in a highly diastereo- and enantioselective manner (d.r. > 99:1 to 92:8, up to 97% *ee*), forming the product with three new stereodefined chiral centers. The synthetic utility of this procedure is demonstrated by the concise synthesis of a precursor of the reverse transcriptase inhibitors used to treat HIV, Abacavir and Carbovir.[3] Furthermore, this procedure enables the rapid convergent assembly of more-complex chiral molecules bearing four new stereocenters from *meso*-2-alkene-1,4-diol derivatives with two different aldehyde electrophiles.



Scheme 1. Desymmetrization of *meso*-1,4-diol derivatives. pin = pinacolato.

We recently reported the copper(I)-catalyzed enantioselective synthesis of allylboronates from allylic carbonates with diboron[4–6] and envisaged that this could be used in the desymmetrization of *meso* compounds (Table 1). The reaction

Table 1: Copper(I)-catalyzed asymmetric reaction of allylic carbonates **1a** with diboron **2**.[a]



Entry	Ligand	Solvent	*t* [h]	Yield [%][b]	d.r.[c] **3/3'**	*ee* [%][c]
1	(*R*,*R*)-quinoxP*	toluene	4	87	>99:1	97
2	(*R*,*R*)-quinoxP*	THF	5	87	>99:1	95
3[d]	(*R*,*R*)-quinoxP*	DMI	5	63	>99:1	97
4[e]	(*R*,*R*)-quinoxP*	THF	96	80	>99:1	97
5	(*R*)-segphos	toluene	67	45	>99:1	96
6	(*R*)-binap	toluene	67	49	>99:1	87
7	(*R*,*R*)-Me-duphos	toluene	3	79	>99:1	82
8	(*R*)-(*S*)-josiphos	toluene	67	25	>99:1	46

[a] Conditions: **1a** (0.5 mmol), **2** (0.75 mmol), Cu(O*t*Bu) (0.025 mmol), and ligand (0.025 mmol) in solvent (0.5 mL), then benzaldehyde (0.5 mmol). [b] Yield of isolated product. [c] The d.r. and *ee* values were determined by HPLC on a chiral stationary phase. [d] The reaction was carried out at room temperature. [e] CuCl (15 mol%), K(O*t*Bu) (10 mol%), and ligand (5 mol%) were used to generate the catalyst. DMI = 1,3-dimethyl-2-imidazolidinone, binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, Me-duphos = 1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene), (*R*)-(*S*)-josiphos = (*R*)-(−)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldiphenylphosphine.

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of the carbonate derivative of *meso*-diol (**1a**) and bis(pinacolato)diboron **2** (1.5 equiv) was complete within 4 h in the presence of Cu(O*t*Bu) (5.0 mol%) and a chiral ligand, (*R*,*R*)-QuinoxP* (5.0 mol%)[7] in toluene at −20°C. This reaction was followed by the addition of benzaldehyde (1.0 equiv) at 0°C to produce **3a** in high yield (87%) with excellent diastereo- and enantioselectivities (**3a**/**3a′** > 99:1, 97% *ee*) (Table 1, entry 1).[8] The isolation of the allylboronate intermediate **A** was not successful, but the stereochemical outcome evident in **3a** strongly suggest the formation of the allylboronate **A** with high enantio- and diastereoselectivity.

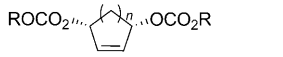
When other solvents were used (THF, DMI), lower yield or enantioselectivity was observed (Table 1, entries 2 and 3). The reaction with a mixture of CuCl (15 mol%) and K(O*t*Bu) (10 mol%), which are more accessible than Cu(O*t*Bu), afforded a comparable result (80%, 97% *ee*, Table 1, entry 4), but required a longer reaction time (96 h). Use of (*R*)-segphos instead of (*R*,*R*)-quinoxP* resulted in a lower yield even after a long reaction time (45%, 96% *ee*, 67 h, Table 1, entry 5). Reactions with other ligands [(*R*)-binap, (*R*,*R*)-Me-duphos, and (*R*)-(*S*)-josiphos] gave lower yields and enantioselectivities (79–25%, 87–46% *ee*, Table 1, entries 6–8).

We next examined the scope of the reaction as shown in Table 2. Reactions with aromatic and aliphatic aldehydes afforded products **3b**–**e** in good yields with high diastereo- and enantioselectivities (93–81% yield, **3**/**3′** > 99:1–92:8, 97–95% *ee*, Table 2, entries 1–4). The reaction with cinnamaldehyde gave the product **3f** in a moderate yield with high selectivity (64%, **3f**/**3f′** > 99:1, 96% *ee*, Table 2, entry 5). (2*R*)-2,3-*O*-Cyclohexylidene glyceraldehyde, which has a chiral center at the α-position to the carbonyl group gave **3g** as an almost single diastereomer in a high yield (Table 2, entry 6, 85%). The six-membered-ring compound **3h** can be obtained in a lower yield at a high temperature (Table 2, entry 7, 43%, **3h**/**3h′** 99:1, 95% *ee*). A substrate with a linear structure (**1c**) also gave products as a mixture of *E*/*Z* isomers (66:34) in low yields with decreased enantioselectivities (36%, 84% *ee* (*E*), 85% *ee* (*Z*), Table 2, entry 8).

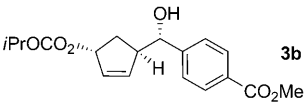
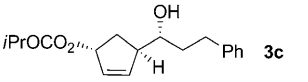
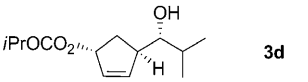
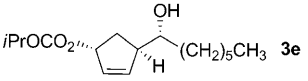
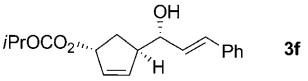
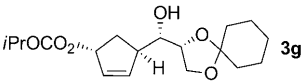
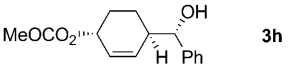
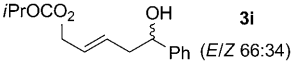
A proposed reaction mechanism is shown in Scheme 2.[9] In the first step the borylcopper(I) intermediate **C** is generated by the reaction between alkoxycopper(I) **B** and diboron **2**. Coordination of the *meso* substrate to the chiral borylcopper(I) intermediate affords complex **D**, and formation of sterically unfavorable **D′** is avoided. Next, the addition of borylcopper(I) across the carbon–carbon double bond produces alkylcopper(I) **E** and subsequent elimination gives the formal *anti*-S_N2' product, allylboronate **A** and a copper(I) carbonate. The alkoxycopper(I) **B** is regenerated by decarboxylation of the copper carbonate. Carbonyl addition of **A** proceeds through a six-membered transition state so that the R^2 group of the aldehyde takes the equatorial position (**F**) to give the adduct **3** after hydrolysis.

The desymmetrization reaction was applied to the concise asymmetric synthesis of an antiviral drug precursor (Scheme 3). The reaction of **1a** with **2** was carried out using the (*S*,*S*)-quinoxP*/Cu(O*t*Bu) catalyst in THF, and then the 4′-hydroxymethyl group was introduced by the reaction of the allylboronate intermediate **G** with aqueous formaldehyde in

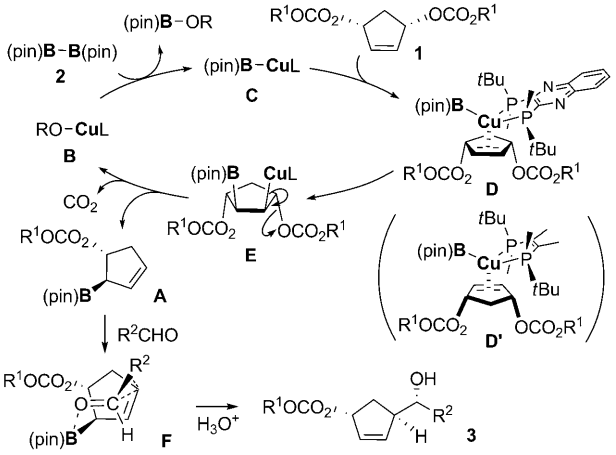
Table 2: Asymmetric synthesis of homoallylic alcohols **3** through desymmetrization of **1a–c** with **2** and subsequent aldehyde allylation.[a]



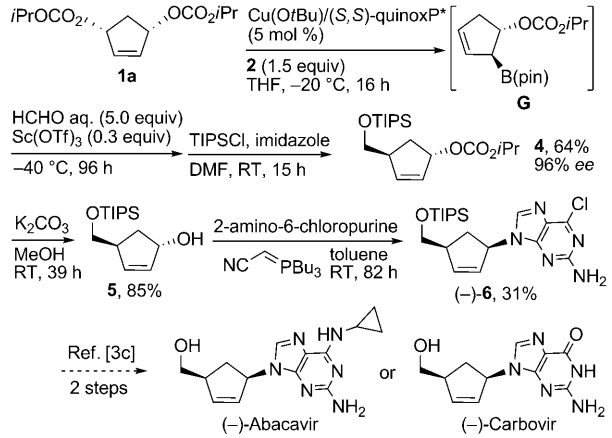
1a, *n* = 1, R = *i*Pr; **1b**, *n* = 2, R = Me — **1c**, R = *i*Pr

Entry	Product	Cond.[b]	Yield [%][c]	d.r.[d] **3**/**3′**	*ee* [%][d]
1[e]	 **3b**	0°C, 23 h	85	>99:1	96
2[e]	 **3c**	0°C, 20 h	85	97:3	95
3[e]	 **3d**	0°C, 96 h	93	92:8	97
4[e]	 **3e**	0°C, 25 h	81	98:2	97
5[e]	 **3f**	0°C, 15 h RT, 3 h	64	>99:1	96
6[e]	 **3g**	RT, 3 h	85	>95:5	–
7[f]	 **3h**	0°C, 13 h RT, 4 h	43	99:1	95
8[g]	 **3i** (*E*/*Z* 66:34)	0°C, 48 h	36	–	84 (*E*)

[a] Conditions: **1** (0.5 mmol), **2** (0.75 mmol), Cu(O*t*Bu) (0.025 mmol), and (*R*,*R*)-quinoxP* (0.025 mmol) in toluene (0.5 mL) at −20°C for 4 h, then aldehyde (0.5 mmol). [b] Conditions for the aldehyde allylation. [c] Yield of isolated product. [d] The d.r. and *ee* values were determined by HPLC on a chiral stationary phase. [e] **1a** was used. [f] **1b** was used. Borylation was carried out at room temperature for 2 h and 50°C for 68 h with 10 mol% Cu(O*t*Bu) and 5 mol% ligand. 1.5 equiv of aldehyde was used. [g] **1c** was used. Borylation was carried out at 50°C for 72 h.



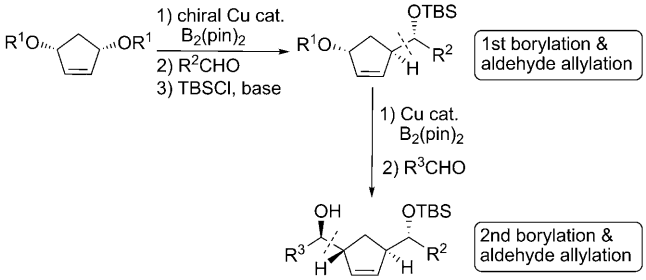
Scheme 2. Proposed mechanism. L = (*R*,*R*)-quinoxP*.



Scheme 3. Concise synthesis of a precursor to established antiviral drugs. TIPS = triisopropylsilyl.

the presence of a Lewis acid catalyst, $Sc(OTf)_3$.[10] The resultant mixture was purified after silyl protection to afford the adduct **4** in 64% yield and 96% *ee*. Hydrolysis of the carbonate moiety of **4** gave **5**, which was subjected to a Tsunoda–Mitsunobu condensation with 2-amino-6-chloropurine to give the drug precursor (−)-**6** in an overall yield of 17% in only three steps from the achiral starting material **1a**.[11,12] This process represents a very short formal synthesis of (−)-Abacavir or (−)-Carbovir (total five steps).[3c]

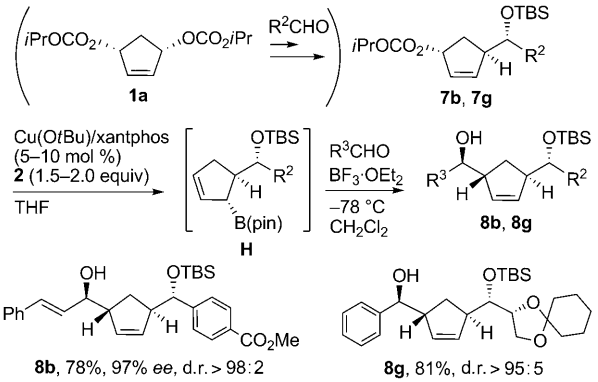
The combination of borylation/aldehyde addition reactions provides a rapid synthesis approach for more-complex chiral molecules (Scheme 4). The enantioenriched products



Scheme 4. Rapid assembly of chiral molecules by repeated borylation/aldehyde addition reactions. TBS = *tert*-butyldimethylsilyl.

obtained by the above reaction are also allylic carbonates; thus we envisaged that these could be substrates for a subsequent borylation/aldehyde allylation and that the core cyclopentene ring of the *meso*-2-alkene-1,4-diol derivatives could be connected with two different aldehyde electrophiles in a stereospecific manner, creating four new chiral centers.

Allylic carbonates **7b** and **7g** were first prepared by TBS protection of **3b** and **3g**, respectively (Scheme 5). Compounds **7b** and **7g** were subjected to a second borylation using an achiral copper(I)/xantphos catalyst.[4a] In contrast to the first borylation of **1**, where *anti*-S_N2'-type boryl substitution proceeds, this second borylation proceeded through *syn*-S_N2'-type pathway to produce allylboronate intermediate **H**. This



Scheme 5. Stereoselective synthesis of **8b** and **8g**. xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

syn/*anti* switch is probably related to the steric properties of **7**. Subsequent Lewis acid catalyzed aldehyde allylation of the allylboronate intermediate **H** gave product **8b** or **8g** in good yields with high stereoselectivities [Scheme 5, **8b**, 78%, 97% *ee*, d.r. > 98:2; **8g**, 81%, d.r. > 95:5].[10] The stereochemical and skeletal structure of the products (**8**) can be modulated easily by changing the aldehyde electrophiles as well as the catalyst ligand [(*R*,*R*)- or (*S*,*S*)-quinoxP*]. This procedure thus serves as a powerful tool for the diversity-oriented synthesis of 1,3-disubstituted five-membered-ring compounds, which often occur as core structures in biologically active compounds.[13,14]

In summary, we have developed a new desymmetrization procedure for *meso*-2-alkene-1,4-diol derivatives through copper(I)-catalyzed asymmetric borylation and stereoselective aldehyde allylation. This reaction was used for the efficient synthesis of chiral molecules, including a drug precursor, and the rapid stereoselective assembly of complex compounds with multiple chiral centers. This reaction is a desymmetrization method complementary to Pd-catalyzed AAA.

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