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Nickel-Catalyzed Borylative Ring Opening of Vinyl Epoxides and Aziridines

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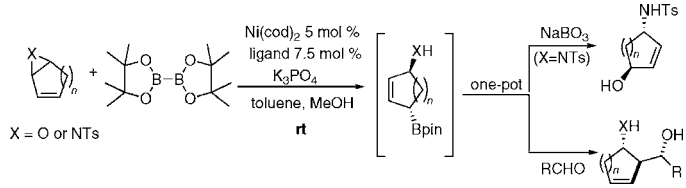
ABSTRACT



A mild ring opening of vinyl epoxides and aziridines with B_2Pin_2 catalyzed by Ni(0)-Binap affords new functionalized allylic boron derivatives which undergo sequential transformations. The uncatalyzed allylation of aldehydes allows obtaining challenging bishomoallylic alicyclic 1,3-diols and 1,3-amino alcohols with remarkably high stereoselectivities. Valuable *trans*-bisallylic 1,4-amino alcohols can be obtained by a simple oxidation.

Functionalized allyl boronates are very useful reagents in advanced organic synthesis, and their preparation by transition-metal-catalyzed formation of carbon−boron bonds is a very active field of research.[1] So far, most protocols have been based on palladium[2] or copper catalysts,[3] while nickel has only recently emerged as a viable alternative.[4] Availability of functionalized allylic boron derivatives remains quite limited, especially in regard to cyclic systems. Furthermore, there is a remarkable lack in the literature concerning the ring opening of small-ring heterocycles by means of a carbon−boron bond formation, with the notable exception of the palladium pincer complex-catalyzed addition of tetrahydroxydiboron to aliphatic aryl-vinyl aziridines.[2b] The use of specialized ligands and the difficult commercial availability of this particular boron reagent can be considered as limiting factors for the widespread use of this method.

We report here a sequential nickel-catalyzed borylative ring opening of vinyl epoxides and aziridines, followed by allylation of aldehydes, with the simultaneous formation of three stereogenic centers with a high stereocontrol.

At the outset of this study, we attempted the borylation of cyclopentadiene monoepoxide **1a**, screening simple combinations of transition metal catalysts and ligands which are known to be effective for the borylation of α,β-unsaturated substrates with bis(pinacolate)diboron (B_2pin_2). Thus the application of copper-catalyzed protocols developed by Miyaura (CuCl, KOAc, DMF, rt),[5] Hosomi [Cu(OTf), Bu_3P, toluene, rt],[6] and Yun (CuCl, *t*-BuONa, THF, MeOH, Josiphos, rt),[7] afforded a complex mixture of unsaturated

(1) (a) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723, and references cited therein. (b) Kennedy, J. W. J.; Hall, D. G. *Boronic acids*; Hall, D. G., Ed.; Wiley VCH: Weinheim, 2006; pp 241−287.

(2) (a) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807. (b) Sebelius, S.; Olsson, V. J.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 10478. (c) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588. (d) Selander, N.; Sebelius, S.; Estay, C.; Szabó, K. J. *Eur. J. Org. Chem.* **2006**, 4085. (e) Selander, N.; Szabó, K. J. *Chem. Commun.* **2008**, 3420.

(3) (a) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Ram Reddy, M. V. *Org. Lett.* **2004**, *6*, 481. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856.

(4) Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 4677.

(5) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982.

(6) Ito, H.; Yamanaka, H.; Tateiwa, J.-I.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821.

(7) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145.

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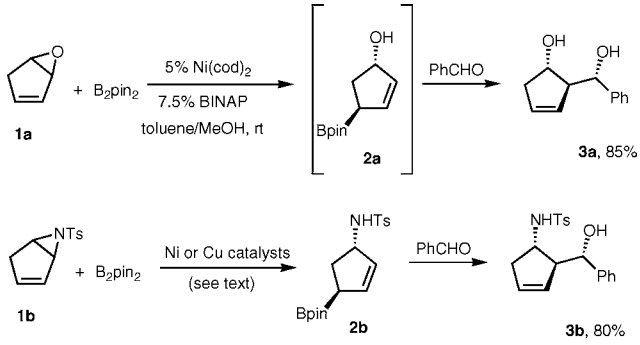
products. Likewise, the use of Pd(0) or Rh(I) catalysts for the borylative ring opening of **1a** with B_2pin_2 was not satisfactory, and complex mixtures were obtained.

To our delight, the use of [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene; 5 mol %) in combination with racemic BINAP (7.5 mol %) in a 30:1 mixture of toluene and MeOH in the presence of anhydrous K_3PO_4 was successful. The ring opening of the epoxide occurred rapidly at room temperature, and 1,4-*trans*-cyclopentenyl boronate **2a** was cleanly obtained, as determined by ^{1}H NMR examination of the crude mixture (Scheme 1).[8]

Scheme 1. Preliminary Results of Metal-Catalyzed Borylative Ring-Opening Allylation



On the other hand, the metal-catalyzed ring-opening borylation of vinyl aziridine **1b** showed some different interesting features. First of all, as well as nickel, also some copper-catalyzed procedures[6,7] were quite effective to obtain with a high yield the allyl boronate **2b**, which, unlike **2a**, turned out to be stable during chromatographic purification.

It should be noted that the reaction without MeOH did not proceed at all. However, with increased amounts of this solvent, also products deriving from the methanolysis of compounds **1a** and **1b** were obtained. The finding of effective reaction conditions to obtain a fast, clean *anti*-S_N2' addition of the boron group to substrates **1a** and **1b** prompted us to explore simple sequential reactions of the in situ formed functionalized allylic boronates. For example, allyl boronates **2a** and **2b** can be directly treated with benzaldehyde without any external Lewis acid additives, to give a clean allylation reaction. It is remarkable that 1,3-diol **3a** and 1,3-amino alcohols **3b**, containing three stereogenic centers, were obtained as single *trans-threo* diastereoisomers after a simple chromatographic purification.[9] The high stereoselectivity obtained (>15:1 d.r. in the crude mixture) is a result of the highly *anti*-stereoselective formation of the intermediate cyclic−allylic boronate and of the subsequent selective carbonyl allylation.[1b] The kinetic resolution of aziridine **1b** with B_2Pin_2 in the presence of Ni(0)-(*R*)-Binap catalyst, aimed at the formation of enantioenriched bisallylic amino alcohol **3b**, proved to not be efficient due to the concomitant methanolysis of the strained ring.[10]

With these results in our hands, representative vinyl epoxide and vinyl aziridine/aldehyde combinations were examined to explore the scope of the sequential borylation−allylation (Table 1). When cyclohexenyl systems **1c** and **1d** were allowed to react with B_2Pin_2 in the presence of Ni(0)-Binap catalyst, they were smoothly converted into the corresponding allylic boronates, which were not isolated but directly treated with benzaldehyde to give the corresponding diol **3c** and amino alcohol **3d** having a *trans-threo* relative configuration (entries 1 and 2, Table 1).[11] The sequential borylation−allylation process proved to be less effective for aliphatic aldehydes. Only for acetaldehyde was it possible to isolate the corresponding adduct **4b** (entry 3), whereas *n*-butanal and 2-methylpropionaldehyde afforded a complex mixture of products (data not shown in Table 1). On the other hand, excellent yields and selectivities were obtained by the use of electron-poor aryl aldehydes (entries 4 and 5) as well as with an electron-rich aldehyde (entry 6).

It should be noted that the methods most generally applied for the synthesis of stereoisomeric 1,3-diols[9] and 1,3-amino alcohols[12] involve multistep processes culminating in a reduction reaction. Furthermore, the preparation of stereohomogeneous alicyclic amino alcohols possessing three stereogenic centers is more difficult to achieve, and the *trans-threo* isomer can be obtained in very low amounts by means of reducing procedures.[13]

Despite the use of a reduced amount of MeOH in the optimized reaction protocol,[11] a competitive methanolysis of vinyl aziridine **1d** was found in the crude mixture (entries 2 and 5). On the other hand, for aliphatic phenyl-vinyl aziridine **1e**,[14] an increased amount of MeOH (13 equiv) was

(8) The 1,4-*trans* relationship of the substituents was deduced by ^{1}H NMR from the small chemical shift difference between the two ring methylene protons and by their characteristic coupling patterns.

(9) The relative configuration of compounds of type **3** was determined by ^{1}H NMR after reduction to the corresponding known saturated compounds: Thompson, S. H. J.; Mahon, M. F.; Molloy, K. C.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Perkin Trans.* **1995**, 379. Also, selected derivation of 1,3-difunctionalized products reported in Table 1 with fosgene and/or acetalization with 2,2-dimethoxypropane were effected (see Supporting Information for details).

(10) Performing the reaction at low temperatures, as well using half equivalent of B_2Pin_2 at room temperature, the kinetic resolution proved to be difficult to control, and the methanolysis of **1b** occurred to a large extent. For example, compound **3b** was obtained (40% ee, at 63% conversion) after chromatographic purification as a 1.8:1 mixture with *N*-(2-methoxycyclopent-3-enyl)-4-methylbenzenesulfonamide.

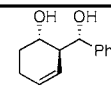
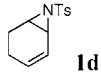
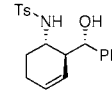
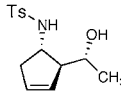
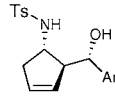
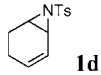
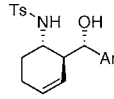
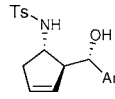
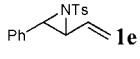
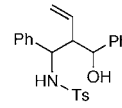
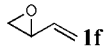
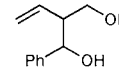
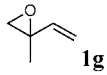
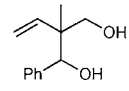
(11) General procedure as follows: A 10 mL Schlenk tube was charged, under argon protection, with Ni(cod)$_2$ (4.20 mg, 0.015 mmol) and K_3PO_4 (154.0 mg, 0.70 mmol). Anhydrous toluene (1.5 mL) and racemic Binap (14.0 mg, 0.0225 mmol) were added, and the resulting suspension was stirred for 10 minutes at 0 °C. The substrate (0.30 mmol) in toluene (1.5 mL) and bis(pinacolato) diboron (114.0 mg, 0.45 mmol) were then added, followed by methanol (0.10 mL, 8.2 equiv). The suspension was vigorously stirred at rt and monitored by TLC (hexanes/AcOEt 7:3) up to complete consumption of the starting material (1−5 h). At this point, the aldehyde (freshly distilled, 0.45 mmol) was introduced at 0 °C, and the reaction mixture was stirred at rt overnight. The reaction was treated with H_2O (3.0 mL), extracted with CH_2Cl_2 (5 mL × 3), and dried ($MgSO_4$). Evaporation of the organic solvent afforded a crude residue which was subjected to flash chromatography (see Supporting Information for details).

(12) For a recent report, see: Davis, F. A.; Gaspari, P. M.; Nolt, B. D.; Xu, P. *J. Org. Chem.* **2008**, *73*, 9619, and references cited therein.

(13) Csomós, P.; Bernáth, G.; Sohár, P.; Csámpai, A.; De Kimpe, N.; Fülöp, F. *Tetrahedron* **2001**, *57*, 3175.

(14) This compound is easily accessible as a ca. 68/32 *cis*/*trans* mixture by addition of allyl sulfur ylides to *N*-tosyl phenyl aldimine: Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Chen, M.-B. *J. Org. Chem.* **1996**, *61*, 4641.

Table 1. Sequential Borylation−Allylation with Aldehydes[a]

entry	substrate	RCHO	dr	product	yield (%)[b]
1	 **1c**	R= Ph	>15:1	 **3c**	65
2	 **1d**	R= Ph	>15:1	 **3d**	72
3	 **1b**	R= CH_3	>15:1	 **4b**	38
4	 **1b**	R= *m*-ClC_6H_4	>15:1	 **5b**	84
5	 **1d**	R= *p*-FC_6H_4	>15:1	 **6d**	75
6	 **1b**	*R*= *o*-OMe C_6H_4	>15:1	 **7b**	95
7[d]	 **1e**	R= Ph	4:1	 **3e**[e]	62
8	 **1f**	R= Ph	2.6:1	 **3f**[e]	55
9	 **1g**	R= Ph	1.6:1	 **3g**[e]	57

[a] Reactions carried out in accordance with the general procedure (see ref 11), unless stated otherwise. [b] Diastereoisomeric ratios determined by ^{1}H NMR examination of the crude mixture. [c] Isolated yields of pure product after chromatographic purification. [d] Reaction carried out with 13 equiv of MeOH. [e] Inseparable mixture.

necessary to effect the borylation. The subsequent addition of benzaldehyde afforded a mixture of diastereoisomeric aliphatic bishomoallylic 1,3-amino alcohol **3e** (entry 7).

From the sequential borylative−allylation of butadiene and isoprene monoepoxides **1f** and **1g** with benzaldehyde, the known bishomoallylic 1,3-diols **3f** and **3g**, respectively,[15] were obtained as unseparable mixtures and with a low stereoselectivity (entries 8 and 9).

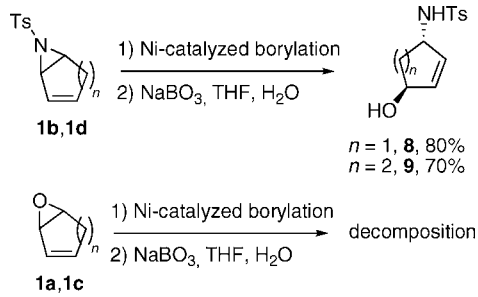
Next, we considered the oxidation of the allylic boron derivatives to the corresponding hydroxy compounds.[16] This transformation corresponds to a formal stereoselective 1,4-addition of a hydroxy group across the double bond of a vinyl-substituted three-membered heterocycle, which has no precedence in the literature. However, the borylation−oxidation sequence was not feasible with vinyl epoxides **1a** or **1c**, while a one-pot oxidation with $NaBO_3$ in THF/H_2O was successful for the allylic boronates derived from aziridines **1b** and **1d** (Scheme 2). Thus, it was possible to obtain very easily carbocyclic amino alcohols **8** and **9**,[17] which are useful

(15) Araki, S.; Kameda, K.; Tanaka, J.; Hirashita, T.; Yamamura, H.; Kawai, M. *J. Org. Chem.* **2001**, *66*, 7919.

(16) Farthing, C. N.; Marsden, S. P. *Tetrahedron Lett.* **2000**, *41*, 4235.

(17) Amino alcohol **9** has been previously prepared by a multistep reaction involving the use of allylic selenides: Shea, R. G.; Fitzner, J. N.; Fankhauser, J. E.; Spaltenstein, A.; Carpino, P. A.; Peevey, R. M.; Pratt, D. V.; Tenge, B. J.; Hopkins, P. B. *J. Org. Chem.* **1986**, *51*, 5243.

Scheme 2. One-Pot Nickel-Catalyzed Borylation−Oxidation of Vinyl Aziridines



building blocks for the synthesis of carbocyclic nucleosides[18] and aminocyclitols,[19] respectively.

(18) Davies, F. A.; Wu, Y. *Org. Lett.* **2004**, *6*, 1269.
(19) For a recent report, see: Pandey, G.; Tiwari, K. N.; Puranik, V. G. *Org. Lett.* **2008**, *10*, 3611.

In conclusion, an unprecedented catalytic regio- and stereoselective borylation of vinyl epoxides and aziridines has been realized in very mild reaction conditions to give high value functionalized allylic boronic derivatives. These compounds can be easily oxidized to synthetically useful bisallylic 1,4-amino alcohols. Alternatively, allylic boronates can be trapped in a one-pot procedure with aldehydes to give alicyclic bishomoallylic 1,3-amino alcohols and 1,3-diols containing three contiguous stereocenters with a high stereoselectivity.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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