Palladium-Catalyzed Carbonyl Allylation: Synthesis of Enantiomerically Pure α-Substituted Allylboronic Esters

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Received 26 February 2009

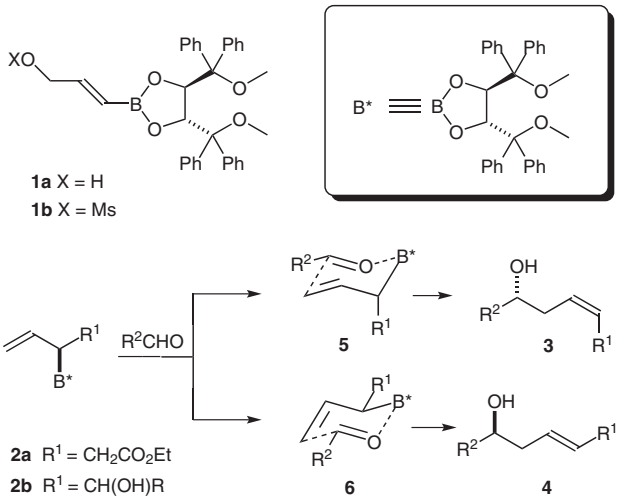
Abstract: Palladium-catalyzed carbonyl allylation of stable alkenylboronic ester with $SnCl_2$ proceeded diastereoselectively to afford α-substituted allylboronic esters; the assignment of their configuration as well as allyl additions are presented.

Key words: boron, allylation, asymmetric synthesis, allyl additions

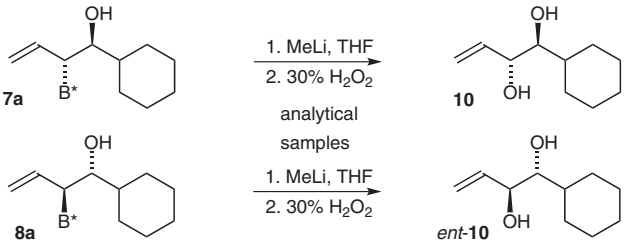
Additions of allylboronic esters to carbonyl compounds giving homoallyl alcohols is one of the most versatile transformations in organic synthesis.[1] Allylboronic esters are nontoxic and easy to handle reagents that add to aldehydes passing through a predictable six-membered transition state, regularly inducing high selectivity. Particularly, reagents with a stereogenic center α to the boronic moiety often afford exceptionally high selectivity. The synthesis of α-substituted allylboronates and their addition to aldehydes was pioneered by Hoffmann (Scheme 1).[2] Different methods have been reported for their synthesis.[3] It was established in our group that [3,3]-sigmatropic rearrangement of the highly stable tartrate derivate **1a**[4] gives allylboronic esters **2a** with a stereogenic center α to boron. Their addition to aldehydes gave homoallylic alcohols with very high diastereo- and enantioselectivity forming almost exclusively *Z*-isomers **3**, with only minor amounts of the *E*-isomer **4** detectable.[3a–3d,5]

The stereochemical course of the reaction depends on the substituent in the α-position and the steric bulk of the boronic ester. The selectivity can be explained in terms of steric and dipolar effects on the two competing transition structures **5** and **6**.[2] In order to extend the approach, we were interested in developing new α-substituted allylboronic esters **2** via the palladium-catalyzed carbonyl allylation reaction. This transformation has been extensively investigated in the past few years.[6] Particularly, the system $Pd^0/SnCl_2$ proved to be very powerful, wherein $SnCl_2$ is used as reducing reagent and various Pd^{2+} complexes as catalyst.[7] Herein, we report for the first time that intermediates **1b** are indeed suitable precursors for the envisaged reaction.

In analogy to a protocol reported by Takahara et al.,[7f] boronic ester **1b** was treated with $PdCl_2(PhCN)_2$, $SnCl_2$, and DMF as solvent with different aldehydes, with *anti*-allylboronic esters **7a–f** being predominantly produced with good yields and selectivity. While the minor diastereoisomers **8a–f** (*anti*) and **9a–f** (*syn*) were detectable in most cases, the phenyl-substituted reagent **7b** was formed exclusively. By increasing the amount of catalyst (from 2–5 mol%) and water (25 equiv), the reaction was accelerated and conversion was complete after 2 hours instead of 20 hours, without any changes in the selectivity (Table 1).[8] Water supports the hydrolysis of the Sn(IV)–Cl bond activating the allyltin intermediate.[9]



Scheme 1 Transition structures for the allyl addition of α-substituted allylboronates **2** to aldehydes

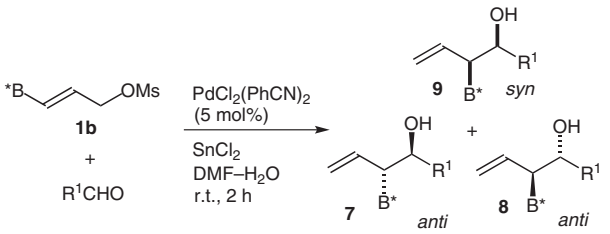


Scheme 2 Assignment of the configuration of boronic esters **7a** and **8a** by chemical correlation

In each case, the diastereoselectivity of the reaction was estimated by examination of the ^1H NMR spectrum of the crude product. The configuration of the products was assigned by means of chemical correlations. Oxidation of **7a** and **8a** (R^1 = *c*-C_6H_{11}) gave the known[10] diols **10** and *ent*-**10** (Scheme 2). The relative stereochemistry of the allyl boronic esters **7** and **8** was also confirmed to be *anti* from the *J* values for the CH(OH)CH(B) protons (3–6 Hz) in ^1H NMR spectrum. In contrast, the corresponding *syn*-isomers **9** showed larger coupling constants (9–11 Hz) for the CH(OH)CH(B) unit.

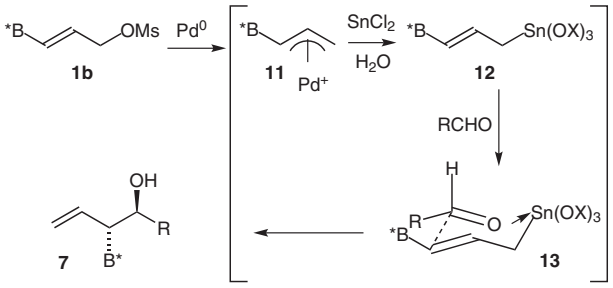
SYNLETT 2009, No. 9, pp 1474–1476
Advanced online publication: 13.05.2009
DOI: 10.1055/s-0029-1217160; Art ID: D06209ST

Table 1 Allylations with Boronic Ester **1b**



Entry	R^1	Yield (%)[a]	Ratio of **7/8/9**[b]
a	*c*-C_6H_{11}	79	78:18:4
b	Ph	79	100:0:0
c	$Ph(CH_2)_2$	80	75:18:7
d	PhCHCH	75	89:11:0
e	Me_2CH	70	78:22:0
f	Me_2CHCH_2	71	77:14:9

[a] Isolated mixture of diastereomers.
[b] As determined by ^{1}H NMR spectroscopy.

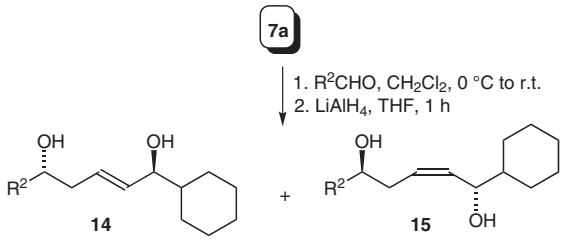


Scheme 3 Proposed mechanism of the palladium-catalyzed allylation

A plausible mechanism of the palladium-catalyzed allylation reaction is shown in Scheme 3. The principle of the process relies on the transient formation of a η^3-allyl palladium complex **11**, which might be transformed into allyltin intermediates **12** that would cause nucleophilic attack to aldehydes furnishing homoallylic alcohols **7**. The carbonyl allylation reaction seems to proceed via a six-membered transition state **13**, with the carbonyl oxygen coordinating to the Sn(IV) species leading to the *anti* products **7**.

The addition of **7** and **8** to different aldehydes produced 3-alkene-1,5-diols with good yields (83–92%) and selectivity (dr up to 85:15, ee >99% for all diastereoisomers; Table 2 and Table 3). The (*R*,*S*)-**7a** diastereomer gave surprisingly selectively the *E*-isomers **14a–c**, while diastereomer (*S*,*R*)-**8a** produced the *Z*-isomers *ent*-**15a–c**. The configuration of all diols **14** and **15** was determined by comparison of the spectroscopic data observed with those previously reported[3k,l] and by the Mosher ester method.[11] The configuration of the diols also indirectly confirmed the assignment of the allylboronic esters **7** and **8**. The observed results are a consequence of the matched/mismatched interaction between the auxiliary (in B*) and the configurations in the *anti* diastereomers thus leading to preferred complementary facial attack to the aldehydes with the α-substituent being in a pseudo-equatorial (**7a**) or pseudo-axial (**8a**) position.

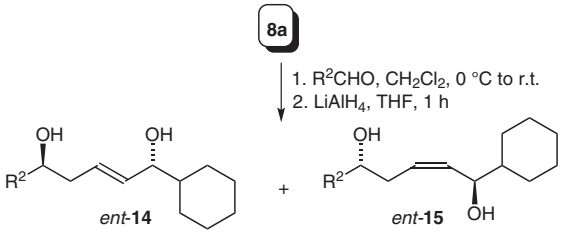
Table 2 Addition of New Reagent **7a** to Various Aldehydes



Entry	R^2	Yield (%)[a]	Ratio (*E*/*Z*)[b]	ee (%)[c]
a	*c*-C_6H_{11}	87	84:16	>99
b	Ph	91	50:50	>99
c	$Ph(CH_2)_2$	92	74:26	>99

[a] Isolated mixture of diastereomers.
[b] The ratio was determined by ^{1}H NMR spectroscopy.
[c] Determined by the Mosher ester method.

Table 3 Addition of New Reagent **8a** to Various Aldehydes



Entry	R^2	Yield (%)[a]	Ratio (*E*/*Z*)[b]	ee (%)[c]
a	*c*-C_6H_{11}	89	16:84	>99
b	Ph	83	33:67	>99
c	$Ph(CH_2)_2$	85	24:76	>99

[a] Isolated mixture of diastereomers.
[b] The ratio was determined by ^{1}H NMR spectroscopy.
[c] Determined by the Mosher ester method.

In summary, the present study demonstrates that boronic esters **1b** can be applied in the palladium-catalyzed carbonyl allylation of aldehydes producing α-substituted *anti*-allylboronic esters **7** and **8**; reagents **7a** and **8a** were demonstrated to add to various aldehydes furnishing enediols **14** and **15**. Further investigations are in progress demonstrating the scope of the sequence and also evaluating the precise nature for the change in facial selectivity during the allyl additions.

Acknowledgment

We gratefully acknowledge the Deutsche Forschungsgemeinschaft for the generous support of our projects. Donations from the BASF

AG, the Chemetall GmbH, and the Wacker AG were greatly appreciated. We thank Colleen Kellenberger and Vera Ophoven for supporting experiments.

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(8) **General Procedure for the Palladium-Catalyzed Carbonyl Allylation of Aldehydes with $SnCl_2$ – Synthesis of 7**

To a solution of **1b** (1.0 mmol) in DMF (3 mL) was added $SnCl_2$ (3.0 mmol), $PdCl_2(PhCN)_2$ (5 mol%), H_2O (25 mmol), and the appropriate aldehyde (1.0 mmol). The solution was stirred at r.t. until the reaction was completed (monitored by TLC, 2 h). The reaction mixture was diluted with Et_2O (120 mL) and washed successively with aq 10% HCl soln (10 mL), sat. $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The extracts were dried over anhyd $MgSO_4$, the solvent was removed under reduced pressure and the crude product subjected to flash column chromatography on SiO_2 (PE–EtOAc, 90:10) and MPLC (PE–EtOAc, 98:2) affording α-substituted allylboronic esters **7**, **8**, and **9** as colorless foams.

Selected Data for 7b

Prepared according to the general procedure: 79% yield of **7b** after flash column chromatography. $[\alpha]_D^{20}$ –93.2 (*c* 1.02, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.85 (dd, $^3J_{2,1}$ = 6.0 Hz, $^3J_{2,3}$ = 9.7 Hz, 1 H, 2-H), 2.02 (d, $^3J_{OH,1}$ = 2.3 Hz, 1 H, OH), 2.97 (s, 6 H, OCH_3), 4.57 (dd, $^3J_{1,OH}$ = 2.3 Hz, $^3J_{1,2}$ = 6.0 Hz, 1 H, 1-H), 4.73 (ddd, $^4J_{4\text{-}E,2}$ = 0.7 Hz, $^2J_{4\text{-}E,4\text{-}Z}$ = 1.9 Hz, $^3J_{4\text{-}E,3}$ = 17.1 Hz, 1 H, 4-H_E), 4.89 (dd, $^2J_{4\text{-}Z,4\text{-}E}$ = 1.9 Hz, $^3J_{4\text{-}Z,3}$ = 10.2 Hz, 1 H, 4-H_Z), 5.29 (s, 2 H, 4′-H, 5′-H), 5.53 (ddd, $^3J_{3,2}$ = 9.9 Hz, $^3J_{3,4\text{-}Z}$ = 9.9 Hz, $^3J_{3,4\text{-}E}$ = 17.1 Hz, 1 H, 3-H), 7.01–7.40 (m, 25 H, arom. CH). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 40.10 (C-2), 51.98 (OCH_3), 72.65 (C-1), 78.22 (C-4′, C-5′), 83.60 (CPh_2OMe), 117.78 (C-4), 126.58, 127.03, 127.62, 127.67, 127.79, 127.86, 128.05, 128.84, 129.89 (arom. CH), 134.25 (C-3), 141.20, 141.31, 143.18 (arom. C_{ipso}). Anal. Calcd (%) for $C_{40}H_{39}BO_5$ (610.29): C, 78.69; H, 6.44. Found: C, 78.26; H, 6.59.

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