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Rh-catalyzed Addition of β-Carbonyl Pinacol Alkylboronates to Aldehydes: Asymmetric Synthesis of γ-Butyrolactones

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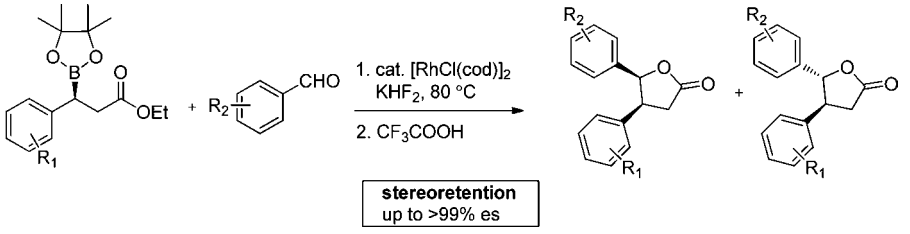
ABSTRACT



The rhodium-catalyzed 1,2-addition of chiral benzylic secondary alkylboronic esters with a coordinating carbonyl group to aldehydes was demonstrated with high levels of enantiospecificity. Pinacol boronic ester derivatives can be employed directly for the addition in the presence of KHF_2 without the use of corresponding trifluoroborate salts where retention of the configuration was observed. Enantiomerically enriched β,γ-diaryl-substituted γ-butyrolactones were synthesized in good yields.

The rhodium-catalyzed addition of organoboron compounds to Michael acceptors or carbonyl compounds has been established as an efficient and reliable tool for carbon−carbon bond formation since it was first reported by Miyaura and co-workers.[1] Excellent results using boronic acids or potassium organotrifluoroborates have been reported in the 1,4-addition and 1,2-addition.[2] However, most of the reactions are limited to aryl- or alkenylboron derivatives that have sp^2-hybridized carbon centers. While much attention has recently been focused on transition metal-catalyzed stereospecific reactions at stereogenic sp^3 carbon centers,[3] the use of alkylboron derivatives in this type of rhodium-catalyzed reaction has been less widely reported. For example, notable advances in the Suzuki-Miyaura cross coupling of alkylboron derivatives have recently been reported.[4]

The use of alkylboron derivatives in the rhodium-catalyzed addition reaction is interesting but challenging due to difficulties involved such as slow transmetalation and side reactions resulting from β-hydride elimination and protodeboronation. Despite these obstacles, Aggarwal and co-workers recently reported the first stereospecific 1,2-addition of potassium alkyl trifluoroborate salts to aldehydes in a highly stereoretentive manner.[5] Encouraged by their report, we thought that β-borylated carbonyl compounds would be interesting molecules to investigate

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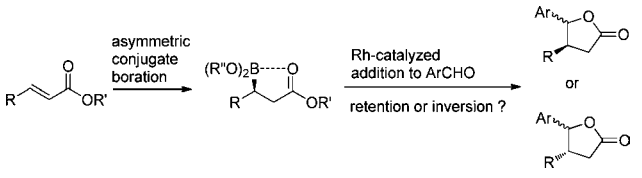
Scheme 1

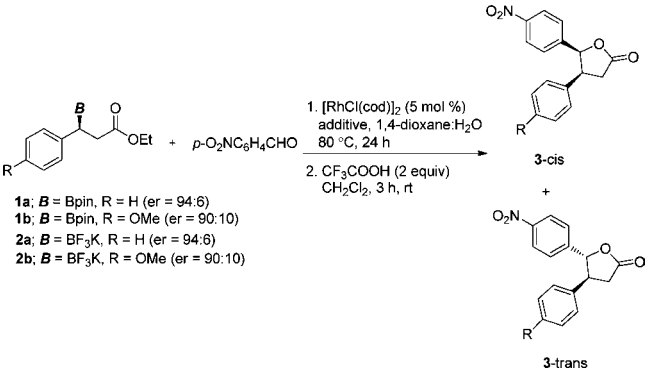


for the Rh-catalyzed addition in view of the stereochemical effect. In the Suzuki-Miyaura coupling, β-borylated carbonyl compounds were reported to display an intriguing stereochemical inversion by the coordinating carbonyl group, as opposed to the usual retention of configuration.[4b,c] Herein, we investigated the rhodium-catalyzed 1,2-addition of chiral alkylboronic esters to aldehydes that produce γ-butyrolactones after cyclization of the resulting adducts (Scheme 1).

Our initial investigation involved carrying out the reaction of boronic esters (**1a**, **1b**) with *p*-nitrobenzaldehyde. The enantiomerically enriched boronic esters were easily prepared by following a developed protocol for the asymmetric conjugate boration of α,β-unsaturated carbonyl compounds[6] while the corresponding trifluoroborate salts (**2**) were prepared by following procedures reported in the literature.[7] Reactions of **1** and **2** were carried out in the presence of 5 mol % $[RhCl(cod)]_2$ in 1,4-dioxane and H_2O (7:1) at 80 °C, followed by an acid treatment (Table 1). With pinacol boronic ester **1a** itself, no substantial conversion was observed under the reaction conditions (entry 1). When the reaction was carried out in the presence of CsF as an additive, both the yield and es[8] (~70%) increased (entry 2), but significant racemization was still observed. Furthermore, in the absence of water, the yield significantly decreased as well as the es value, indicating the importance of water in this addition (entry 3).

Then, we changed the boronic esters to trifluoroborate salts (**2a**, **2b**), expecting a more efficient transmetalation. The addition products were obtained in good yields with high es values (entries 4 and 6). Most interestingly, the chiral center was completely retained[9] and no stereoinversion was observed. To eliminate the preparation and isolation steps

Table 1. Optimization of the 1,2-Addition Reaction of Boronic Esters (**1**) and Trifluoroborate Salts (**2**)[a]



entry	substrate	additive (equiv)	yield (%)[b]	dr (**3**-cis:**3**-trans)[c]	es[d] (%) of **3**-cis	es (%) of **3**-trans
1	**1a**		No rxn			
2	**1a**	CsF (2)	77	1.2:1 (**3a**)	68	77
3[e]	**1a**	CsF (2)	29	1.2:1 (**3a**)	19	1
4	**2a**		82	1.2:1 (**3a**)	98	97
5[f]	**1a**	KHF_2 (1.2)	80	1.2:1 (**3a**)	98	97
6	**2b**		87	1.5:1 (**3b**)	98	94
7[f]	**1b**	KHF_2 (1.2)	85	1.5:1 (**3b**)	98	94

[a] 5 mol % $[RhCl(cod)]_2$ (0.01 mmol) and 1.5 equiv of **1** or **2** (0.3 mmol) relative to *p*-nitrobenzaldehyde (0.2 mmol) were stirred in 1,4-dioxane and H_2O (7:1, 2 mL) at 80 °C for 24 h. [b] Isolated yield of **3**-cis and **3**-trans. [c] The diastereomeric ratio (dr) was determined by HPLC analysis or by ^1H NMR analysis. [d] Enantiospecificity. [e] Anhydrous 1,4-dioxane was used. [f] 5 mol % $[RhCl(cod)]_2$ (0.01 mmol), 1.2 equiv of *p*-nitrobenzaldehyde (0.24 mmol) relative to **1a** or **2a** (0.2 mmol) were used.

of the trifluoroborate salts, we evaluated different additives in the hopes of identifying more effective additives than CsF in the reaction of the pinacol boronic esters. When KHF_2 was employed in the reaction, the desired reaction took place with a high efficiency. After further optimization of the reaction conditions, we demonstrated that the use of 1.2 equiv of *p*-nitrobenzaldehyde and 1.2 equiv of KHF_2, relative to the pinacol boronic esters, led to results comparable to the reactions using excess trifluoroborate salts, generating products in good yields with high es values (compare entries 5 and 7 vs 4 and 6). Again, the addition products were produced without stereoinversion.

Diastereoselection of the addition was not high, and a slight preference for the cis product was obtained as indicated by the diastereomeric ratios of the **3**-cis and **3**-trans products (1.2−1.5:1), which did not vary much under the different conditions. The exact boron species that participates in the reaction remains unclear. Only a few studies of the use of KHF_2 salt in combination with arylboronic acids (sp^2C-B) have been reported[10] so far, while no examples have been reported on the use of the salt

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(8) The enantiospecificity calculated using the following equation [% es = (ee of product/ee of starting material) × 100] indicates the degree of conservation of the enantiomeric purity over the course of the reactions: Denmark, S. E.; Vogler, T. *Chem.—Eur. J.* **2009**, *15*, 11737–11745. Also see ref 4b.

(9) The absolute configurations of the addition products (**3a**-cis and **3a**-trans) were determined by comparing optical rotation data reported in the literature (see Scheme 2). In addition, hydrogenation of **3f**-cis and **3f**-trans gave (*S*)-**5a**, confirming the retention of the configuration of the original stereogenic center. The other products in Table 2 were assigned by analogy.

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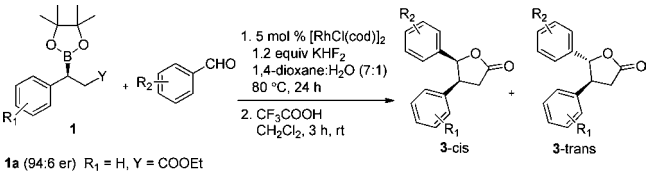
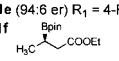
Table 2. 1,2-Addition of the Pinacol Boronic Esters (**1**) to Aldehydes



1a (94:6 er) R_1 = H, Y = COOEt
1b (90:10 er) R_1 = 4-OMe, Y = COOEt
1c (95:5 er) R_1 = H, Y = CN
1d (93.5:6.5 er) R_1 = 4-Me, Y = COOEt
1e (94:6 er) R_1 = 4-F, Y = COOEt
1f 

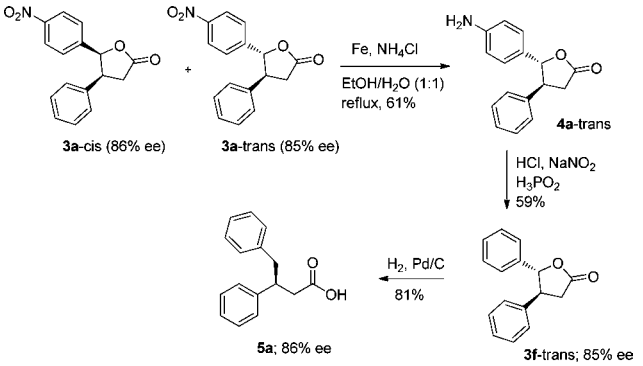
entry	1	R_2	yield (%)[a]	dr[b] (**3**-cis:**3**-trans)	**3**-cis (er)[c]	**3**-trans (er)[c]
1	**1a**	3-NO_2	69	1.5:1 (**3c**)	93:7	92:8
2	**1a**	2-NO_2	73	1.4:1 (**3d**)	93.5:6.5	90:10
3	**1a**	4-CN	77	1.5:1 (**3e**)	92.5:7.5	92.5:7.5
4	**1a**	H	50	1.3:1 (**3f**)	90:10	91:9
5	**1b**	4-CN	80	1.4:1 (**3g**)	89:11	89:11
6	**1c**	4-NO_2	45	1:1 (**3a**)	95:5	94:6
7	**1d**	4-NO_2	82	1.4:1 (**3h**)	93:7	91.5:8.5
8	**1d**	4-CF_3	76	1.2:1 (**3i**)	91.9	90:10
9	**1e**	4-NO_2	56	1.2:1 (**3j**)	87:13	85:15
10	**1f**	4-NO_2	n.f[d]			

[a] Isolated yield of **3**-cis and **3**-trans. [b] The diastereomeric ratio (dr) was determined by ^{1}H NMR. [c] The enantiomeric ratio (er) was determined by chiral HPLC analysis. [d] Not formed. **1f** and protodeboronated byproduct were only detected.

with pinacol boronic esters in the rhodium-catalyzed addition. While *in situ* generation of organotrifluoroborate[11] may be possible, the involvement of intermediate boron species with fluoride coordination cannot be ruled out in the reaction.

With the optimized reaction conditions using KHF_2 as an additive, reactions of a range of different pinacol boronic esters and aldehydes were carried out (Table 2). Most of the reactions directly produced cyclized lactones as the major product after the first step, but the reaction mixture was further treated with an acid for the complete cyclization of acyclic γ-hydroxy esters. Benzylic boron derivatives were reactive in this addition, and electron-donating substituents are allowed on the aromatic ring. A range of chiral β,γ-diarylsubstituted γ-butyrolactones could be synthesized by applying this protocol. In general, the addition was most successful for activated aldehydes possessing an electron withdrawing substituent, resulting in a good addition yield and high es values (>96%). Sterically encumbered 2-nitrobenzaldehyde was a suitable substrate as well, producing the 1,2-addition products in good yield (entry 2). Particularly noteworthy is that the less activated simple benzaldehyde resulted in adducts with high enantiospecificities (es values of 91 and 93%) although

Scheme 2. Derivatization of **3a**-cis and **3a**-trans Lactones



a slightly decreased yield was obtained (entry 4). β-Cyano alkylboronate (**1c**) was a reactive substrate as well, yielding γ-butyrolactones with a high enantiospecificity but with a lower yield than the corresponding ester derivative (entry 6). The reaction of benzylic boronate (**1e**) with an electron-withdrawing aryl substituent was less selective and afforded products with decreased enantiospecificities (entry 9). However, a simple secondary alkylboron compound was inactive in the addition (entry 10).

In this rhodium-catalyzed reaction, the boronate esters play the role of homoenolate equivalents[12] and their original configuration is retained throughout the reaction. If the current addition takes place by a similar mechanism to the additions of arylboronic acids to electrophiles, where transmetalation of an organic group from boron to rhodium is involved, a retentive transmetalation event still occurs in the rhodium catalysis even in the presence of an intramolecularly coordinating carbonyl group to the boron center.[13] This is in contrast to the palladium-catalyzed Suzuki-Miyaura coupling via stereoinvertive transmetalation due to intramolecular coordination of the β-carbonyl group.

Chiral γ-butyrolactones are important structures found in many natural and biologically active compounds.[14] For additional applications of the resulting products, functional group transformations were carried out. When the nitro group of the **3a**-cis and **3a**-trans products were subjected to reduction, interestingly, both diastereomers resulted in **4a**-trans as a single diastereomer through epimerization of the cis-isomer (Scheme 2).[15] Removal

(11) Recent reviews of organotrifluoroborates: (a) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (c) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240–9261.

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(13) For an alternative mechanism without transmetalation to rhodium, see ref 5.

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(15) The reduction of isolated **3a**-cis also gave **4a**-trans as a single product with a yield of ~60%, which indicates the epimerization of the carbinol center during the reaction.

of the amino group produced **3f** without erosion of the initial ee value[16] and hydrogenation of **3f** produced **5a**, the absolute configuration of which was verified by comparison with literature data.[17]

In summary, we showed that rhodium-catalyzed 1,2-addition of chiral alkylboronic esters with a β-coordinating carbonyl group to aldehydes efficiently takes place with a high level of stereoretention. The direct use of organoboronic esters in the presence of KHF_2 is convenient and economical, as it obviates extra preparation and isolation steps of the corresponding organofluoroborate salts with a large excess of KHF_2. This current method offers an interesting homoenolate pathway to chiral γ-butyrolactones.

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

The authors declare no competing financial interest.

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