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Stereoselective Conjugate Addition of Aryl- and Alkenylboronic Acids to Acyclic γ,δ-Oxygen-Substituted α,β-Enoates†

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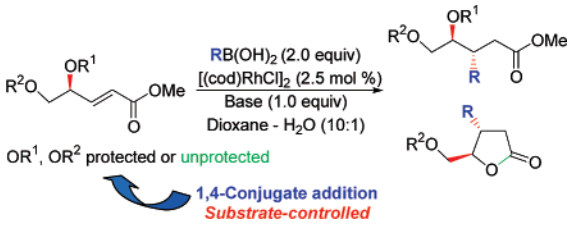
ABSTRACT



The substrate-controlled Rh^{I}-catalyzed conjugate addition of aryl- and alkenylboronic acids to α,β-unsaturated esters which bear γ- and δ-oxygen substituents takes place in a highly *anti* diastereoselective fashion either when using γ-hydroxyl unprotected starting materials or when the γ-oxygen substituent is protected with a nonbulky group. The δ-oxygen substituent plays a role in the stereoselectivity of the reaction, and better results are obtained when this OH-group is protected.

The conjugate addition of organometallic reagents to unsaturated carbonyl compounds is one of the main synthetic methods for C−C bond formation. Among the different procedures reported, the reaction of aryl- and alkenylboronic acids under Rh^{I} catalysis, the Hayashi−Miyaura reaction,[1] has become increasingly popular.[2] The Rh^{I}-catalyzed conjugate addition reaction of organoboronic acids to electron-deficient alkenes can be carried out in water-containing solvents, is widely functional-group tolerant, and is compatible with the presence of unprotected OH and NH groups, which together with the catalytic use of the transition metal and the low toxicity of boron compounds makes this procedure very attractive from an environmental standpoint. In addition, aryl- and alkenylboronic acids can be conveniently prepared by a variety of methods.[3]

Control of the stereoselectivity is crucial in the development of new synthetic methods. In the Rh^{I}-catalyzed conjugate addition reactions of organoboronic acids and their derivatives, this has been achieved by using a variety of chiral ligands attached to the transition metal.[2,4] In contrast, the substrate-controlled stereoselectivity of this reaction has been scarcely explored,[5,6] in particular with regard to conformationally flexible acyclic substrates.

† Dedicated to Prof. Vicente Gotor (Universidad de Oviedo) in honor of his 60th birthday.

(1) First report: Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

(2) Reviews: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465. (e) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (f) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 3, p 55.

(3) For recent leading references on the synthesis of boronic acids and derivatives, see: (a) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399. (b) Zhu, W.; Ma, D. *Org. Lett.* **2006**, *8*, 261. (c) Stefani, H. E.; Cellab, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (d) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757 and references cited therein.

(4) Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D.; Yamamoto, Y.; Miyaura, N. *J. Organomet. Chem.* **2007**, *692*, 428 and references cited therein.

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We report herein the stereoselective Rh^I-catalyzed conjugate addition of aryl- and alkenylboronic acids to the α,β-unsaturated esters **1**−**5**, which bear a γ-oxygen substituent (Figure 1).

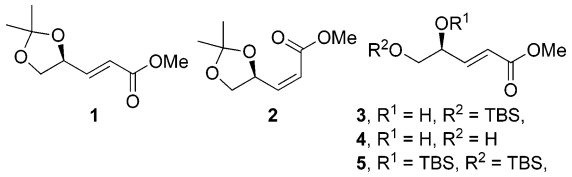
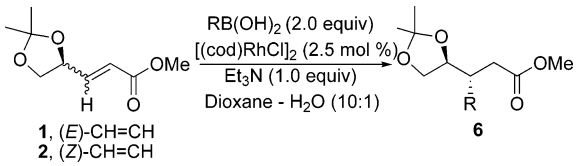


Figure 1. γ,δ-Oxygen-substituted α,β-enoates **1**−**5**.

These types of compounds have been traditionally considered as poor substrates for conjugate addition reactions, as oxygen at the γ-position makes the β-carbon less electrophilic than ordinary α,β-unsaturated esters.[7] Additionally, in comparison with ketones, linear α,β-unsaturated esters are known to be less reactive toward the Rh^I-catalyzed conjugate addition reactions of organoboronic acids.[2] We have chosen for our study the γ,δ-oxygen-substituted α,β-enoates **1**−**5**, which are easily prepared from D-glyceraldehyde acetonide. Substrates **1** and **2** have been used as starting materials for the conjugate addition of arylcuprate reagents, and the products of these reactions are valuable intermediates in the synthesis of natural and pharmaceutical products.[8] Compounds **3** and **4**, with free OH groups, constitute interesting substrates for the evaluation of the stereoselective bias of the Rh^I-catalyzed conjugate addition of organoboronic acids, as OH-free compounds are often not compatible with traditional methods for conjugate addition reactions, such as organocuprate chemistry.[6,9]

At first (Scheme 1) we examined the reaction of compound **1** with several organoboronic acids using $[(cod)RhCl]_2$ as

Scheme 1. Addition of $RB(OH)_2$ to Esters **1** and **2**



catalyst in dioxane−H_2O (10:1) as solvent and in the presence of a base, conditions which are known to be efficient for transmetalation from boron to rhodium and subsequent conjugate addition reaction to α,β-unsaturated esters (Table 1, entries 1−3).

Table 1. Addition of $RB(OH)_2$ to Esters **1** and **2**[a]

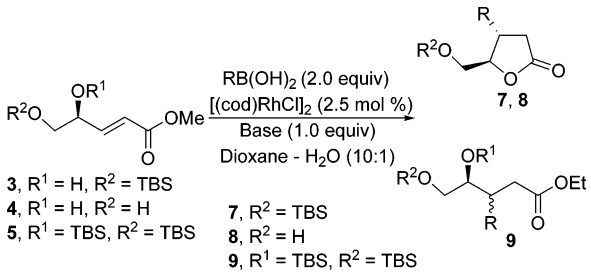
entry	substrate	R	product (de, %; yield, %)[b,c]
1	**1**	C_4H_6	**6a** (>98; 90)
2	**1**	*p*-F-C_4H_6	**6b** (>98; 85)
3	**1**	(*E*)-PhCH=CH	**6c** (>98; 90)
4	**2**	C_4H_6	**6a** (>98; 90)
5	**2**	*p*-F-C_4H_6	**6b** (>98; 85)
6	**2**	(*E*)-PhCH=CH	**6c** (>98; 85)

[a] Reactions carried out at room temperature with 0.2 mmol of esters **1**−**2**, 2.0 equiv of $RB(OH)_2$, and 1.0 equiv of Et_3N with 5 mol % of Rh^I with respect to **1**−**2** in 0.5 mL of dioxane−H_2O (10:1). [b] Diastereomeric excesses determined by integration of the ^1H NMR signals of the reaction crudes. [c] Yield of the isolated product after column chromatography on silica gel.

In all cases we observed high conversion of the starting materials and exclusive formation of the *anti* reaction product **6**. We also found that compound **2**, which differed from **1** in the geometry of the C=C bond, afforded similar results (Table 1, entries 4−6).

Compound **3**, with an unprotected γ-hydroxyl group, did also react (Scheme 2) with aryl- and alkenylboronic acids to afford, in this case, the *trans*-lactones **7** (Table 2, entries 1−5).

Scheme 2. Addition of $RB(OH)_2$ to Esters **3**−**5**



We observed that yields with Et_3N were inferior to those obtained in the corresponding reactions of compounds **1** and **2**. However, the use of $Ba(OH)_2$ afforded high yields of lactones **7**, resulting from the in situ cyclization of the corresponding *anti* open-chain adducts, which were not isolated.

In a similar fashion, compound **4**, with both γ- and δ-hydroxyl groups unprotected (Scheme 2), afforded the

(5) (a) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2571. (b) Chen, Q.; Kuriyama, M.; Soeta, T.; Hao, X.; Yamada, K.; Tomioka, K. *Org. Lett.* **2005**, *7*, 4439.

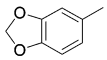
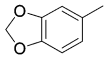
(6) For conjugate additions of R-Rh^I reagents to γ-OH-substituted cyclic enones, see: de la Herrán, G.; Mba, M.; Murcia, M. C.; Plumet, J.; Csáky, A. G. *Org. Lett.* **2005**, *7*, 1669.

(7) Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P. A. *Tetrahedron* **1995**, *51*, 12843.

(8) See for example: (a) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627. (b) Reichard, G. A.; Ball, Z. T.; Aslanian, R.; Anthes, J. C.; Shiha, N.-Y.; Piwinskia, J. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2329. (c) Han, G.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 4281. (d) Manpadi, M.; Kornienko, A. *Tetrahedron Lett.* **2005**, *46*, 4433. (e) Kireev, A. S.; Nadein, O. N.; Agustin, V. J.; Bush, N. E.; Evidente, A.; Manpadi, M.; Ogasawara, M. A.; Rastogi, S. K.; Rogelj, S.; Shors, S. T.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 5694.

(9) For other OH-free directed conjugate additions of RMgX and RLi reagents to open-chain systems, see: (a) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 4235. (b) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035. (c) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1126. (d) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763.

Table 2. Addition of $RB(OH)_2$ to Esters **3**−**5**[a]

entry	substrate	R	base	product (*de* %, yield %)[b,c]
1	**3**	C_4H_6	Et_3N	**7a**, (>98, 60)
2	**3**	C_4H_6	$Ba(OH)_2$	**7a**, (>98, 85)
3	**3**	p-F-C_4H_6	$Ba(OH)_2$	**7b**, (>98, 80)
4	**3**	p-MeO- C_4H_6	$Ba(OH)_2$	**7c**, (>98, 80)
5	**3**		$Ba(OH)_2$	**7d**, (>98, 90)
6	**4**	C_4H_6	$Ba(OH)_2$	**8a**, (75, 80)
7	**4**	C_4H_6	LiOH	**8a**, (75, 80)
8	**4**	C_4H_6	K_3PO_4	**8a**, (60, 80)
9[d]	**4**	C_4H_6	$Ba(OH)_2$	**8a**, (50, 60)
10[e]	**4**	C_4H_6	$Ba(OH)_2$	**8a**, (50, 60)
11	**4**	p-F-C_4H_6	$Ba(OH)_2$	**8b**, (75, 60)
12	**4**	p-MeO- C_4H_6	$Ba(OH)_2$	**8c**, (80, 60)
13	**4**		$Ba(OH)_2$	**8d**, (80, 60)
14	**4**	(*E*)-PhCH=CH	$Ba(OH)_2$	**8e**, (75, 60)
15	**5**	C_4H_6	$Ba(OH)_2$	**9a**, (0, 75)

[a] Reactions carried out at room temperature with 0.2 mmol of esters **3**−**5**, 2.0 equiv of $RB(OH)_2$, and 1.0 equiv of base with 5 mol % of Rh^I with respect to **3**−**5** in 0.5 mL of dioxane−H_2O (10:1). [b] Diastereomeric excesses determined by integration of the ^1H NMR signals of the reaction crudes. [c] Yield of the isolated product after column chromatography on silica gel. [d] Reaction carried out in dioxane−H_2O (10:0.5). [e] Reaction carried out in dioxane−H_2O (8:2).

trans-lactones **8** as the major reaction products (Table 2, entries 6−14). However, the free δ-hydroxyl group influenced the stereochemical outcome of the Rh^I-catalyzed conjugate addition reaction, as the stereoselectivity was lower than when using compounds **1**−**3** as starting materials. As evidenced for the reaction with $PhB(OH)_2$, $Ba(OH)_2$ (entry 6) afforded good yield and diastereoselective excess. Similar results were observed when using LiOH (entry 7), but the use of K_3PO_4 resulted in lower stereoselectivity (entry 8). We also observed an influence of the water content of the reaction medium in the stereoselectivity when using $Ba(OH)_2$ (entries 9 and 10).

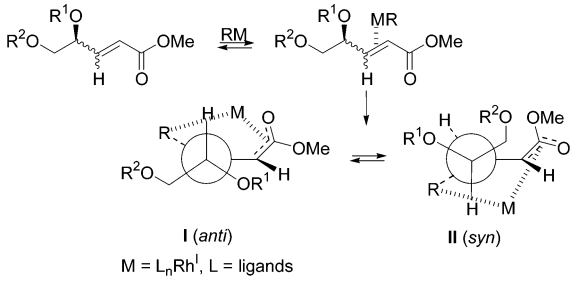
Last, we carried out the Rh^I-catalyzed conjugate addition reaction of $PhB(OH)_2$ to compound **5**, with both γ- and δ-hydroxyl groups protected as bulky TBS-derivatives (Scheme 2). However, a 1:1 mixture of diastereomers **9a** was obtained in this case (Table 2, entry 15).

The stereochemical outcome of conjugate addition reactions of organometallic reagents to γ-alkoxy-α,β-enoates has been addressed by several groups. The diastereoselectivity has been found to be dependent on both the substrate and reagent structures. In a broad sense,[10] chelation-controlled additions of RLi and RMgX reagents or lithium diallylcuprates produce the *syn* adducts with high selectivity. On the other hand, the additions of alkyl-, alkenyl-, and arylcuprates are mainly *anti*-selective. This has been interpreted by nonchelation-controlled models, due to the lower chelation ability of organocopper in comparison with RLi or RMgX reagents. Most of these models explain the diastereoselection on the basis of the steric and electronic interactions which develop upon metal−olefin π-complex formation or simple nucleophilic addition of the RM species. It has also been noted that these types of additions are less diastereoselective with (*Z*)-esters than with (*E*)-esters, and models have been developed to account for this observation.

The Rh^I-catalyzed conjugate addition reaction of organoboronic acids to the acetal-protected esters (*E*)-**1** and (*Z*)-**2** was found to be highly *anti*-selective, irrespective of the double bond geometry. The reaction with the γ-OH-δ-OTBS protected ester **3** was also highly *anti*-selective, while the addition to the γ-OH-δ-OH ester **4** was slightly less stereoselective, although the *anti* isomer was also predominant. On the other hand, no diastereoselectivity was observed with the γ-OTBS-δ-OTBS ester **5**.

Therefore, the predominance of the *anti*-products in these reactions may be understood assuming that diastereoselection takes place upon formation of the oxo-π-allyl-Rh^I intermediate, which may be the rate-limiting step of the catalytic cycle (Scheme 3),[2] and that there is no chelation between the metal moiety and the OR^1 group in this case.[11,12]

Scheme 3. Proposed Stereochemical Course



Both transition state models minimize steric interactions of the metal moiety with both the OR^1 and CH_2OR^2 groups.[13] Model **I**, leading to the *anti* adducts, is sterically destabilized by an $A^{1,3}$-interaction of the α-H with OR,[1] while model **II**, leading to the *syn* adducts, is sterically destabilized by an $A^{1,3}$-interaction of the α-H with CH_2OR.[2] However, model **I** is energetically more favorable than **II**, as the nucleophile

(10) See: (a) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (b) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(11) This is to be compared with the additions of vinyl-Rh^I species to γ-OH-substituted cyclic enones, which may take place under chelation or nonchelation control, and similar additions of Ar-Rh^I species, which take place under nonchelation control. See ref 6.

(12) For OH-directed stereoselectivity in Rh-catalyzed hydrogenation reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307 and references cited therein.

(13) Similar models have been used to interpret the addition reactions of other nucleophiles to γ-hydroxy-substituted α,β-unsaturated esters. See: Kireev, A. S.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 2630 and references cited therein.

enters antiperiplanar to the lowest σ^*-lying orbital of the γ-C−X groups (X = H, OR,[1] CH_2OR^2), which is the γ-C−OR^1 bond, as compared with **II**, where the nucleophile enters antiperiplanar to the γ-C−CH_2OR^2 bond.

Thus, the high *anti* selectivity observed for esters **1** and **3** is the consequence of the combination of a relatively small R^1 group (**1**, R^1 = CH_2-O-acetal; **3**, R^1 = H), which minimizes the steric interaction present in **I**, with a relatively bulky R^2 group (**1**, R^2 = CH_2-O-acetal; **3**, R^2 = TBS), which increases the steric interaction present in **II**. Stereoselectivity is eroded in ester **4**, as the size of R^2 is smaller (**3**, R^2 = H), and completely vanishes in **5**, as the size of R^1 is larger (**5**, R^1 = TBS).

With regard to the *Z*-ester **2**, the high *anti* selectivity may be understood on the basis of prior *Z*−*E* isomerization, which may take place upon complexation of the metal with the double bond. A competition experiment with an equimolecular mixture of **1**, **2**, and $PhB(OH)_2$ showed the exclusive formation of **6a** (50% yield) together with unreacted **1** and **2** in 20:80 ratio. This shows that the (*Z*)-ester **2** reacts slower than the (*E*)-ester **1**, in agreement with the *Z*−*E* isomerization hypothesis.[13]

In conclusion, the Rh^I-catalyzed conjugate addition reaction of organoboronic acids to acyclic γ,δ-oxygen-substituted α,β-unsaturated esters takes place in a highly diastereoselective fashion to afford the *anti* reaction products, either when using γ-hydroxyl unprotected starting materials or when the γ-oxygen substituent is protected with a nonbulky group. The δ-oxygen substituent plays a role in the stereoselectivity of the reaction, and better results are obtained when this OH-group is protected.

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Supporting Information Available: Preparative methods, spectra of compounds **6**−**9**, and procedures for the stereochemical assignment of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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