ORGANIC LETTERS

2005
Vol. 7, No. 8
1669−1671

Stereoselectivity Control in the Rh(I)-Catalyzed Conjugate Additions of Aryl and Alkenylboronic Acids to Unprotected Hydroxycyclopentenones

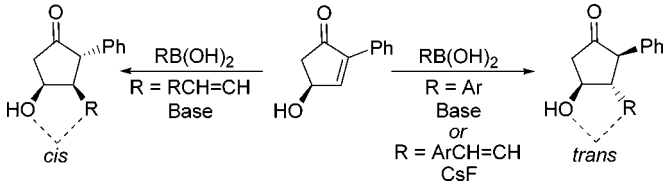
Gabriela de la Herrán, Miriam Mba, M. Carmen Murcia, Joaquín Plumet, and Aurelio G. Csáky*

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

csaky@quim.ucm.es

Received March 3, 2005

ABSTRACT



The stereoselective Rh(I)-catalyzed conjugate addition reaction of aryl and alkenylboronic acids to unprotected 2-phenyl-4-hydroxycyclopentenone is presented. The free OH group on the substrate is responsible for the stereochemistry, which is *cis* for arylboronic derivatives. In the case of the alkenylboronic compounds, the stereochemistry can be tuned to either a *cis* (bases as additives) or *trans* addition (CsF as additive) without the need of protecting groups.

Stereoselective C−C bond-forming reactions are of special importance for the preparation of enantiopure natural compounds and pharmaceuticals. The stereoselective 1,4-addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the preeminent organic synthetic strategies for this purpose.[1] Among the different procedures reported, the conjugate addition of aryl- and alkenylboronic acids using Rh(I) catalysis has been recently developed.[2,3]

We have taken into account that the Rh(I)-catalyzed conjugate addition of aryl- and alkenylboronic acids can be carried out in water media and therefore should be compatible with the presence of a free hydroxyl group in the substrate without the need of protecting groups. We disclose herein that Rh(I) catalysts promote the conjugate addition of organoboronic acids to unprotected 4-hydroxycyclopentenones at room temperature with high diastereoselectivities. In the particular case of alkenylboronic acids, the stereochemisty of the reaction can be tuned to obtain either the hydroxycyclopentanones **2-I** in the presence of base or **2-II** in the presence of CsF.

The Rh(I)-catalyzed conjugate addition of organoboronic acids benefits from the easy preparation of these compounds, which is particularly important in the case of the alkenyl derivatives, as they can be synthesized by hydroboration of alkynes[4] without the need of transmetalation from main group organometallics and is therefore highly functional group tolerant. In addition, these reactions can be carried out in water, which together with the catalytic use of the transition

(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

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

(3) Reviews: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465.

(4) (a) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695. (b) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482. (c) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399. (d) Josyula, K. V. B.; Gao, P.; Hewitt, C. *Tetrahedron Lett.* **2003**, *44*, 7789.

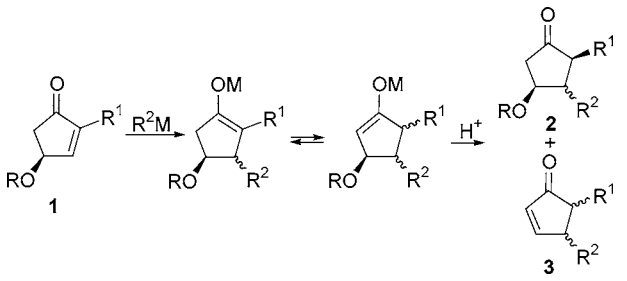
10.1021/ol050462n CCC: $30.25
Published on Web 03/16/2005

metal and the low toxicity of boron compounds, makes this procedure particularly attractive from an environmental standpoint.

Enantioselective versions of Rh(I)-catalyzed conjugate additions have been possible using chiral ligands for rhodium. Although asymmetric catalysis is the best method for the synthesis of optically pure materials, diastereoselective methods are often used in practice. This is particularly important in the manufacture of pharmaceuticals.[5] Among the many unsaturated carbonyl systems that have been subjected to conjugate addition reactions, 4-hydroxycyclopentenones **1** have attracted considerable attention as starting materials for the synthesis of prostaglandins.[6]

Hydroxycyclopentenones can be prepared in optically pure form by a variety of procedures[7,8] and can lead stereoselectively to the functionalized hydroxycyclopentanones **2** by conjugate addition of RM reagents,[7,9] provided isomerization and β-elimination of the enolate intermediate, leading to **3**, is prevented (Scheme 1).

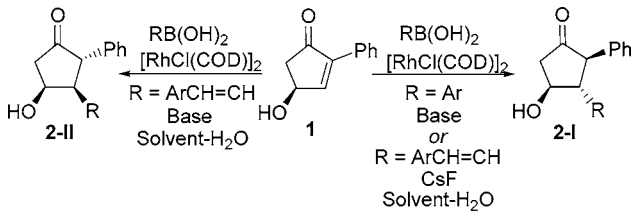
Scheme 1. Addition of RM Reagents to Hydroxycyclopentenones



Most procedures thus far reported based on this synthetic strategy make use of anhydrous reaction conditions and protection of the hydroxyl group in the form of a silyl derivative. In this way, the stereochemistry is sterically controlled by the protecting group affording good yields of the silyl-protected final targets **2-I** in their optically pure form. On the other hand, the stereoselective formation of isomers **2-II** has been only scarcely considered,[10] and the functionalization of 4-hydroxycyclopentenones by means of the catalyzed conjugate addition of organoboronic compounds has not been reported.

Treatment of cyclopentenone **1** (R^1 = Ph, Scheme 2), which has been chosen in this study as model compound, with $PhB(OH)_2$ (1.2 equiv) in dioxane$-H_2O$ (4:1) in the presence of $[RhCl(COD)]_2$ (3% mol) and Cs_2CO_3 (0.1 equiv) at rt gave rise to the formation of the **2a-I** with low yield

Scheme 2. Rh(I)-Catalyzed Conjugate Addition of $RB(OH)_2$ to Hydroxycyclopentenone **1**



2a, R = Ph
2b, R = p-MeO-C_6H_4
2c, R = m-MeO-C_6H_4
2d, R = o-MeO-C_6H_4
2e, R = p-CF_3-C_6H_4
2f, R = PhCH=CH
2g, R = p-Me-C_6H_4CH=CH
2h, R = p-Cl-C_6H_4CH=CH
2i, R = p-CF_3-C_6H_4CH=CH

but excellent stereoselectivity (Table 1, entry 1). Yield optimization was carried out by using other bases (entries 2−4), which lead to either LiOH (0.5 equiv) or Et_3N (1.0 equiv) as the best conditions. Additionally, we found that MeOH$-H_2O$ (6:1) was also a good solvent mixture for this reaction. The results were extended to other substituted arylboronic acids (entries 5−9).

On the other hand, reaction of hydroxycyclopentenone **1** with Ph-CH=CH-$B(OH)_2$ (1.2 equiv) in dioxane$-H_2O$ (4:1) and $[RhCl(COD)]_2$ (3% mol) using either LiOH or Et_3N

Table 1. Conjugate Addition of $RB(OH)_2$ to (*S*)-4-Hydroxy-2-phenylcyclopenten-2-one **1** Catalyzed[a] by $[RhCl(COD)]_2$

no.	cat.[b] (%)	solvent[c]	additive (equiv)[d]	**2**[e] (%)	**2-I/2-II**[f]
1	3	A	Cs_2CO_3 (0.1)	**2a**, 30	98:02
2	3	A	$NaHCO_3$ (0.1)	**2a**, 50	98:02
3	3	A	LiOH (0.5)	**2a**, 85	98:02
4	3	A	Et_3N (1.0)	**2a**, 85	98:02
5	3	B	LiOH (0.5)	**2a**, 90	98:02
6	3	B	LiOH (0.5)	**2b**, 85	98:02
7	3	B	LiOH (0.5)	**2c**, 80	98:02
8	3	B	LiOH (0.5)	**2d**, 70	98:02
9	3	B	LiOH (0.5)	**2e**, 80	98:02
10	3	A	Et_3N (1.0)	**2f**, 50	50:50
11	3	A	LiOH (1.0)	**2f**, 75	60:40
12	3	A	$Mg(OH)_2$ (1.0)	**2f**, 50	60:40
13	3	A	$Ba(OH)_2$ (1.0)	**2f**, 30	40:60
14	3	A	$Zr(OH)_4$ (0.3)	**2f**, 50	02:98
15	3	A	Guanidine (1.0)	**2f**, 90	02:98
16	3	B	LiOH (1.0)	**2f**, 80	05:95
17	3	A	CsF (1.0)	**2f**, 70	75:25
18	12	C	CsF (3.0)	**2f**, 90	98:02
19	3	A	Guanidine (1.0)	**2g**, 85	02:98
20	3	A	Guanidine (1.0)	**2h**, 80	02:98
21	3	A	Guanidine (1.0)	**2i**, 80	02:98
22	12	C	CsF (3.0)	**2g**, 80	98:02
23	12	C	CsF (3.0)	**2h**, 80	98:02
24	12	C	CsF (3.0)	**2i**, 60	98:02

[a] Reactions carried out with 0.17 mmol of **1** and 1.2 equiv of $RB(OH)_2$. [b] Mol percent with respect to **1**. [c] A = dioxane$-H_2O$ (4:1), B = MeOH$-H_2O$ (6:1), C = dioxane$-H_2O$ (2:1). [d] Equivalents with respect to **1**. [e] Isolated yield after flash chromatography on silica gel. [f] Determined from the ^1H NMR ($CDCl_3$, 200 MHz) spectra of the crude samples.

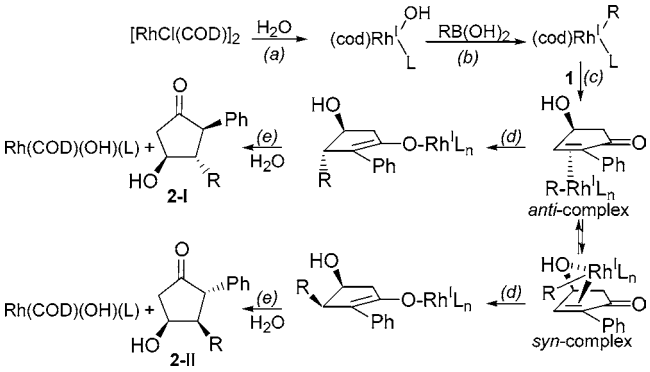
(5) See, for example: Hawkins, J. M.; Watson, T. J. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224.
(6) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley-VCH: Weinheim, 1994; Chapter 5. (b) Collins, C. W.; Djuric, S. W. *Chem. Rev.* **2003**, *93*, 1533.
(7) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeld, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480 and references therein.
(8) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867 and references therein. See also: Csaky, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092.

as base afforded compounds **2f** as a mixture of diastereomers (entries 10, 11). The diastereoselectivity of the reaction was amenable to tuning by the action of the base (entries 12−14), and good de was observed for $Zr(OH)_4$ albeit with low yield. Optimum yield and selectivity for **2f-II** was obtained when using guanidine as the base (entry 15). The solvent had also an influence in the stereoselectivity, and good yield and de in favor of **2f-II** were obtained when using LiOH in MeOH−H_2O (entry 16). However, from all these essays, best results for the selective obtention of isomer **2f-I** (entries 11, 12) did not exceed 20% de.

In the search for selectivity in the formation of isomer **2f-I**, we replaced the bases used up to this moment with fluoride anion.[11] Thus, reaction of cyclopentenone **1** with Ph-CH═CH-$B(OH)_2$ (1.2 equiv) in dioxane−H_2O (4:1) in the presence of $[RhCl(COD)]_2$ (3% mol) and CsF (1.0 equiv) at rt gave rise to the formation of a diastereomeric mixture of compounds **2f** with better diasteroselectivity in favor of **2f-I** (entry 17). Further optimization led to the use of $[RhCl(COD)]_2$ (12% mol) and CsF (3.0 equiv) (entry 18). Similar results were obtained with other alkenylboronic acids (entries 19−21 for isomers **2-II** and entries 22−24 for isomers **2-I**).

In the absence of more mechanistic studies, the stereochemical results may be understood on the basis of the operation of chelating or nonchelating conditions between the hydroxyl group of the substrate and the σ-aryl- or σ-alkenylrhodium(I) intermediate (Scheme 3). Thus, in the

Scheme 3. Stereochemical Outcome



water medium the precatalyst $[RhCl(COD)]_2$ will be transformed in situ into the actual catalyst of the reaction (step a),[12] which will transmetalate (step b) the aryl or alkenyl moiety from boron to rhodium affording a σ-aryl- or σ-alkenylrhodium(I) intermediate. Coordination of these species (step c) to the C═C bond of the substrate may take place on both diastereotopic faces of the unsaturated ketone. However, chelation with the OH group (or even O^- in the basic medium) may stabilize the formation of the *syn*-complex, provided the steric bias of the organic moiety permits it.[13]

Steric interactions with the aryl moiety[14] may shift the equilibrium toward formation of diastereomers **2-I** by migratory insertion (step d) and protonation (step e). These steric interactions may be diminished in the case of the alkenyl-Rh(I) compounds, thus favoring formation of the *syn* intermediate, and migratory insertion and protonation lead to the formation of diastereomers **2-II**.

When fluoride is used as promoter, chelation by the OH group will not favored, either because of the diminished basicity of the medium or via the formation a saturated anionic Rh(I) complex[15] $[(Rh(COD)FR^2L]^-$. In these cases, isomers **2-II** are formed by insertion of the R-moiety away from the OH group.

In conclusion, this work presents the Rh(I)-catalyzed conjugate addition reaction of aryl- and alkenylboronic acids to substrates bearing an unprotected OH group and constitutes the first application of fluoride promotion of this type of reaction. The OH group on the substrate and the reaction conditions (base vs CsF) are responsible for the stereochemistry, which in the case of the alkenylboronic derivatives can be tuned to either a *cis* or *trans* addition without the need of protecting groups. Further development of these findings will allow for the synthesis of new prostaglandin derivatives.

Acknowledgment. Dedicated to Prof. Arlette Solladié-Cavallo on occasion of her retirement. The Ministerio de Ciencia y Tecnología (Proyect PTR1995-0678-OP) and Repsol-YPF are gratefully acknowledged for financial support.

Supporting Information Available: Full experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050462N

(9) (a) West, F. G.; Gunawardena, G. U. *J. Org. Chem.* **1993**, *58*, 2402. (b) West, F. G.; Gunawardena, G. U. *J. Org. Chem.* **1993**, *58*, 5043.

(10) (a) Alkenyl-Al: Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152. (b) Ar−Mg: Csáky, A. G.; Mba, M.; Plumet, J. *J. Org. Chem.* **2001**, *66*, 9026.

(11) The fluoride anion promotes transmetalation from boron to Pd(II) species. This has been extensively used in Suzuki couplings. For recent reviews, see: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83.

(12) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

(13) 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 therein.

(14) From the crystal structures of arylrhodium(I) compounds it is known that the orientation of the aryl group is orthogonal to the square plane of the complex in order to minimize steric interactions with the remaining ligands on the metal. See ref 3a and: (a) Dahlenburg, L.; Yardimciolu, A.; Hock, N. *Inorg. Chim. Acta* **1984**, *89*, 213. (b) Hay-Motherwell, R. S.; Koscmieder, S. U.; Wilkinson, G.; Hussain-Bates, B.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **1991**, 2821. (c) Boyd, S. E.; Field, L. D.; Hambley, T. W.; Partridge, M. G. *Organometallics* **1993**, *12*, 1720. (d) Yamamoto, M.; Onitsuka, K.; Takahashi, S. *Organometallics* **2000**, *19*, 4669.

(15) Alternatively, the formation of a Rh(III) species may be invoked. See: Albrecht, M.; Crabtree, R. H.; Mata, J.; Peris, E. *Chem. Commun.* **2002**, 32.