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Stereoselective Rh^{I}-Catalyzed Tandem Conjugate Addition of Boronic Acids–Michael Cyclization

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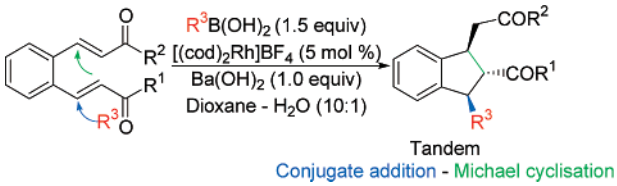
ABSTRACT



The first examples of the stereoselective sequence Rh^{I}-catalyzed tandem conjugate addition of boronic acids to enones–Michael cyclization, is reported. The reaction is carried out in dioxane–H_2O at rt, and 1,2,3-trisubstituted indans are obtained in a highly regio- and stereoselective fashion.

Catalytic tandem transformations initiated by conjugate additions constitute powerful tools for the stereoselective synthesis of complex molecules from readily available starting materials in an atom-economical way. This strategy permits the stereoselective formation of several bonds with a single catalyst in a one-pot operation, without the need for isolation of the intermediates.[1] In particular, tandem sequences initiated by the conjugate addition of a carbon nucleophile to an α,β-unsaturated carbonyl compound followed by intramolecular trapping of the resulting enolate intermediate in a Michael reaction constitute a powerful tool for the synthesis of cyclic molecules.[2]

The formation of carbocycles through sequential carborhodation triggered by the conjugate addition of organoborons to electron-deficient alkenes under Rh^{I} catalysis is particularly attractive.[3,4] Among the different procedures reported for conjugate addition reactions of organometallic reagents to unsaturated carbonyl compounds, the reaction of aryl- and alkenylboronic acids under Rh^{I} catalysis, the Hayashi−Miyaura reaction,[5] has become increasingly popular.[6] This type of reaction can be carried out in water-containing solvents and is widely functional-group tolerant, which together with the catalytic use of the transition metal and the low toxicity of boron compounds makes this procedure attractive from an environmental perspective. In addition,

(1) For recent reviews see: (a) Guo, H.-C.; Ma, J. -A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

(2) See: (a) Saito, S.; Hirohara, Y.; Harahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533. (b) Klimko, P. G.; Singleton, D. A. *J. Org. Chem.* **1992**, *57*, 1733. (c) Cooke, M. P.; Gopal, D. *Tetrahedron Lett.* **1994**, *35*, 2837. (d) Klimko, P. G.; Singleton, D. A. *Synthesis* **1994**, 979. (e) Savchenko, A. V.; Montgomery, J. *J. Org. Chem.* **1996**, *61*, 1562. (f) Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A. *Lieb. Ann. Chem.* **1996**, 899. (g) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911. (h) Yang, J.; Cauble, D. F.; Berro, A. J.; Bauld, N. L.; Krische, M. J. *J. Org. Chem.* **2004**, *69*, 7979. (i) Matsumoto, T.; Masu, H.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2004**, *6*, 4367. (j) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 8019. (k) Hanzawa, Y.; Takebe, Y.; Saito, A.; kakuuchi, A.; Fukaya, H. *Tetrahedron Lett.* **2007**, *48*, 6471. (l) Li, K.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 3765 and references cited therein.

(3) Review: Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217.

(4) For the addition to alkynes followed by conjugate addition, see: (a) Lautens, M.; Marquardt, T. *J. Org. Chem.* **2004**, *69*, 4607. (b) Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem., Int. Ed.* ***2005***, *44*, *4608*.

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

(6) 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, 2005; Chapter 3, p 55.

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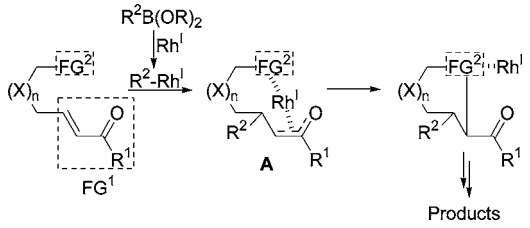
aryl- and alkenylboronic acids can be conveniently prepared by a variety of methods.[7]

The success of a tandem process initiated by the conjugate addition of an organorhodium compound to an unsaturated carbonyl functional group (FG^1) relies on the adequate choice of a secondary functional group (FG^2) suitably placed in the starting material. FG^2 must not react intermolecularly with the R^2-Rh^I compound, but must be reactive enough to trap intramolecularly the oxa-π-allyl-Rh^I intermediate **A** generated in the conjugate addition step (Scheme 1).

Scheme 1. Tandem Process Triggered by Conjugate Addition

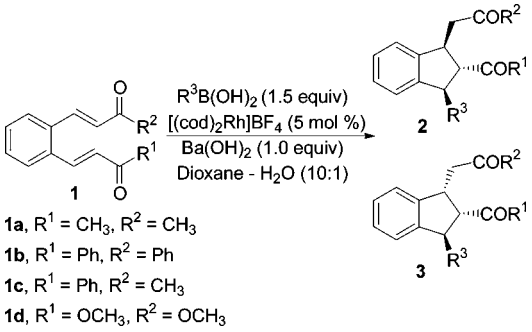


In addition, **A** must be stable enough as not to be protonated in the organic solvent−H_2O reaction medium usually used in these reactions.

In this regard, the combination of enone (FG^1) and ketone (FG^2), i.e., tandem conjugate addition−aldol reaction, has been reported to produce cyclic aldols in a stereoselective fashion,[8] and the combination of α,β-unsaturated ester (FG^1) and nitrile (FG^2) has been reported to produce cyclic β-enamino esters.[9]

We report herein the first examples of the stereoselective sequence Rh^I-catalyzed tandem conjugate addition of arylboronic acids to enones−Michael cyclization (FG^1 = enone, FG^2 = enone). Compounds **1** (Scheme 2) have been chosen

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

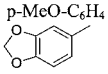
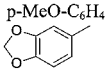


as starting materials to produce 1,2,3-trisubstitued indans, which constitute relevant pharmaceutical scaffolds.[10]

Initial screening of reaction conditions with compound **1a** led to $[(cod)_2Rh]BF_4$ and $Ba(OH)_2$ as the best choices in catalyst and base for the tandem conjugate addition−Michael cyclization process.

Reaction of compound **1a** with arylboronic acids (Table 1, entries 1−5) took place with good yield and diastereo-

Table 1. Addition of $RB(OH)_2$ to Ketones **1a**−**c**[a]

no.	1	R^3	product (yield %)[b]	2/3 ratio[c]
1	**1a**	C_6H_5	90	**2aa**:**3aa** = 90 :10
2	**1a**	p-MeO-C_6H_4	85	**2ab**:**3ab** = 85:15
3	**1a**		85	**2ac**:**3ac** = 85:15
4	**1a**	p-F-C_6H_4	75	**2ad**:**3ad** = 60:40
5	**1a**	o-MeO-C_6H_4	75	**2ae**:**3ae** = 55:45
6	**1a**	Ph-CH=CH	90	**2af**:**3af** = 80:20
7	**1b**	C_6H_5	90	**2ba**:**3ba** = 98:02
8	**1b**	p-MeO-C_6H_4	90	**2bb**:**3bb** = 98:02
9	**1b**		90	**2bc**:**3bc** = 98:02
10	**1b**	p-F-C_6H_4	85	**2bd**:**3bd** = 98:02
11	**1b**	o-MeO-C_6H_4	80	**2be**:**3be** = 98:02
12	**1b**	Ph-CH=CH	90	**2bf**:**3bf** = 98:02
13	**1c**	C_6H_5	90	**2ca**:**3ca** = 90:10
14	**1c**	p-MeO-C_6H_4	90	**2cb**:**3cb** = 90:10
15	**1c**	p-F-C_6H_4	85	**2cc**:**3cc** = 90:10
16	**1c**	o-MeO-C_6H_4	80	**2cd**:**3cd** = 95:05
17	**1c**	Ph-CH=CH	85	**2ce**:**3ce** = 98:02

[a] Reactions carried out at room temperature with 0.2 mmol of substrates **1**, 1.5 equiv of $RB(OH)_2$, and 1.0 equiv of base with 5 mol % of Rh^I with respect to **1** in 0.5 mL of dioxane−H_2O (10:1). [b] Yield of the isolated product mixture after column chromatography on silica gel. [c] Product ratio determined by integration of the ^1H NMR signals of the reaction crudes.

selectivity in favor of the 1,2-*trans*-2,3-*trans*-indans **2a**, with the exception of *p*-F-C_6H_4-$B(OH)_2$ (entry 4) and *o*-MeO-C_6H_4-$B(OH)_2$ (entry 5), which afforded the corresponding products with low diastereoselectivity. Therefore, the reactions of **1a** are sensible both to electronic (para electron-withdrawing group) and steric (ortho electron-donating group) effects. In addition, the tandem process was also successful for the addition of vinylboronic acids (entry 6), which took place with good yield and diastereoselectivity.

On the other hand, the 1,2-*trans*-2,3-*trans*-indans **2b** were obtained in a highly diastereoselective fashion when compounds **1b** were used as starting materials (Table 1, entries 7−12), for the reaction with both aryl- and vinylboronic

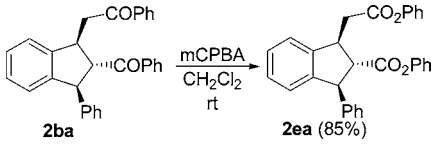
(7) For recent leading references on the synthesis of boronic acids and derivatives, see: (a) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399. (b) Zhu, W.; Ma, D. *Org. Lett.* **2006**, *8*, 261. (c) Stefani, H. E.; Cellab, R.; Vieira, A. S. *Tetrahedron* **2007**,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

(8) (a) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110. (b) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421.

(9) Miura, T.; Harumashi, T.; Murakami, M. *Org. Lett.* **2007**, *9*, 741.

(10) See, for example: (a) Elliott, J. D.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; DeBrosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, C.; Gleason, J. G.; Oeishoff, C. E.; Ohlstein, E. H. *J. Med. Chem.* **1994**, *37*, 1553. (b) Cook, C. E.; Wani, M. C.; Jump, J. M.; Lee, Y.-W.; Fail, P. A.; Anderson, S. A.; Gu, Y.-Q.; Petrow, V. *J. Med. Chem.* **1995**, *38*, 753. (c) Zanoli, P.; Avallone, R.; Baraldi, M. *Phytother. Res.* **1998**, *12*, S114. (d) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550. (e) Clark, W. M. *Curr. Opinion Drug Disc. Devel.* **1999**, *2*, 565. (f) Song, Z. J.; Zhao, M.; Frey, L.; Li, J.; Tan, L.; Chen, C. Y.; Tschaen, D. M.; Tillyer, R.; Grabowski, E. J. J.; Volante, R.; Reider, P. J. *Org. Lett.* **2001**, *3*, 3357. (g) Melikian-Badalian, A. PCT Int. Appl. WO2002030915, 2002.

Scheme 3. Baeyer−Villiger Oxidation of **2ba**



acids. The stereochemical bias was independent of electronic or steric effects in the arylboronic acids, and diastereoselectivity was always higher than that observed for the same reactions with compound **1a**.

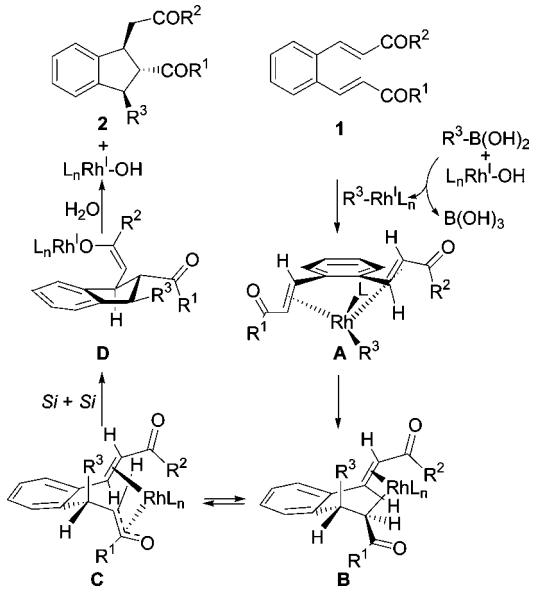
Last, we explored the reaction with the nonsymmetrical starting material **1c**, which features two electronically different unsaturated ketone moieties (alkyl and aryl). The tandem conjugate addition−Michael cyclization of compound **1c** was found to be highly regio- and diastereoselective (Table 1, entries 13−17). Initial conjugate addition of the R-Rh^Ispecies, generated by transmetalation of the boronic acids with the Rh^I catalyst, took place selectively to the unsaturated arylketone moiety, giving rise to compounds **2c**. Again, the diastereoselectivity was independent of electronic or steric effects in the arylboronic acids.

In sharp contrast with the results obtained for ketones **1a**−**c**, the corresponding reactions with ester **1d** ($R^1 = R^2 = OCH_3$) gave rise to a complex mixture of reaction products. However, esters **2e** ($R^1 = R^2 = OPh$) were made available by Baeyer−Villiger oxidation of compounds **2b** (Scheme 3), as exemplified for the synthesis of **2ea**.

The observed diastereoselectivity in the formation of compounds **2** by the tandem conjugate addition−Michael cyclization sequence may be understood on the basis of a Heathcock-like transition state model (Scheme 4).[11] Coordination of the $R^3Rh^IL_n$ species, generated by transmetalation of the corresponding boronic acid, with the alkenyl chains of the starting material may lead to intermediate **A**, which upon conjugate addition to the CH═CH-COR^1 moiety, will afford intermediate **B** in equilibrium with an oxa-π-allyl-Rh^I complex **C**. Intramolecular Michael addition with the

(11) (a) Heathcock, C. H.; Hendreson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. (b) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

Scheme 4. Proposed Reaction Course



CH═CH-COR^2 moiety in a *like* approach (*si* + *si* depicted in Scheme 1) will minimize steric interactions, giving rise to intermediate **D** and compounds **2** after protonation in the reaction medium.

In conclusion, we have developed a new type of tandem annulation reaction triggered by the Rh^I-catalyzed conjugate addition of boronic acids followed by an intramolecular Michael reaction. The sequence affords 1,2,3-trisubstituted indanes in a highly regio- and diastereoselective fashion.

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Supporting Information Available: Preparative methods, NMR spectra, 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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