ORGANIC LETTERS

2010
Vol. 12, No. 2
308−310

Rhodium-Catalyzed Functionalization of Sterically Hindered Alkenes

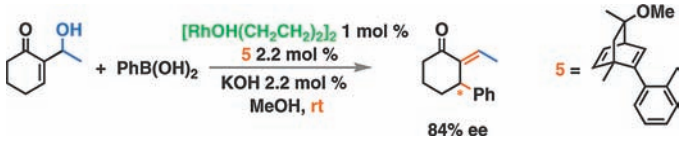
Thomas Gendrineau, Jean-Pierre Genet, and Sylvain Darses*

Laboratoire Charles Friedel (UMR 7223, CNRS), Ecole Nationale Supérieure de Chimie de Paris, 11 rue P&M Curie, 75231 Paris Cedex 05, France

sylvain-darses@chimie-paristech.fr

Received November 17, 2009

ABSTRACT



For the first time the rhodium-catalyzed 1,4-addition of organoboranes to hindered Baylis−Hillman adducts, trisubstituted alkenes, affording highly functionalized alkenes, via addition of the organoboranes and hydroxyelimination, is reported. Moreover, preliminary results have shown that, thanks to the use of a monosubstituted chiral diene ligand, enantio-enriched products were easily accessible, while chiral phosphane ligands were completely inappropriate in this reaction.

The stereoselective and catalytic 1,4-addition reactions of organometallic reagents, mainly boron and zinc, to α,β-unsaturated substrates have provided new synthetic tools in organic synthesis.[1] If the rhodium- or copper-catalyzed additions to disubstituted activated alkenes can be readily achieved under various conditions, the reaction with trisubstituted alkenes is still a challenge. It is only very recently that catalyzed additions to trisubstituted activated alkenes have appeared in the literature.[2,3] In the copper-catalyzed 1,4-addition of organometallic reagents, the groups of Alexakis and Hoveyda have developed efficient catalytic systems for the generation of all-carbon stereogenic centers, upon the addition to β,β-disubstituted Michael acceptors.[4]

On the other hand, in the case of rhodium-catalyzed 1,4-addition reactions, examples are rare of reactions involving trisubstituted activated alkenes. Indeed, construction of stereogenic quaternary centers has been described recently by the groups of Carretero[5] and Hayashi[6] upon the addition of organometallics to β,β-disubstituted Michael acceptors.[7] Some examples of addition to activated arylmethylene cyanoacetates[8] and alkylidene Meldrum's acids have appeared in the literature.[9] However, to our knowledge,

(1) Reviews: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (d) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217. (e) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807. (f) Alexakis, A.; Bäckvall, J.-E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (g) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (h) von Zezschwitz, P. *Synthesis* **2008**, 1809. (i) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547.

(2) (a) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584. (b) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. (c) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988. (d) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416. (e) Lee, K.-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182. (f) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462. (g) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097. (h) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211.

(3) For some recent examples of stoichiometric addition of organometallics to α,β-unsaturated tri- or tetrasubstituted alkenes, see: (a) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Tetrahedron* **2004**, *60*, 6197. (b) Becheanu, A.; Baro, A.; Laschat, S.; Frey, W. *Eur. J. Org. Chem.* **2006**, 2215. (c) Oueslati, F.; Perrio, C.; Dupas, G.; Barré, L. *Org. Lett.* **2007**, *9*, 153. (d) Zimmerman, H. E.; Suryanarayan, V. *Eur. J. Org. Chem.* **2007**, 4091, and references cited therein.

(4) (a) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774. (b) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801.

(5) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961.

(6) (a) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628. (b) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588.

(7) Collier, P. N. *Tetrahedron Lett.* **2009**, *50*, 3909.

(8) Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589.

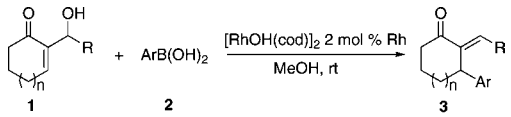
(9) Fillion, E.; Carret, S.; Mercier, L. G.; Trépanier, V. É. *Org. Lett.* **2008**, *10*, 437.

10.1021/ol902646j
Published on Web 12/17/2009

examples of rhodium-catalyzed additions to nonactivated α,α,β-trisubstituted alkenes are rather limited. Indeed, Csákÿ and co-workers have described the diastereoselective conjugate additions of boronic acids to α-substituted hydroxycyclopentenones,[10] and Belyk et al. reported the synthesis of 1,3,4-trisubstituted pyrrolidines via the rhodium-catalyzed addition of boronic acids.[11]

In our continuous interest in rhodium-catalyzed reactions with organoboron derivatives,[12] we recently showed that they add to readily available Baylis−Hillman (BH) adducts in the presence of a rhodium complex, affording stereodefined trisubstituted (*E*)-alkenes under mild conditions via an unusual mechanism.[13] We want to report now the 1,4-addition of boron reagents to α,α,β-trisubstituted BH derivatives, allowing access to highly functionalized cyclic substrates (Scheme 1). Moreover, the use of chiral diene ligands

Scheme 1. 1,4-Addition/β-Hydroxy Elimination on Trisubstituted BH Adducts



n = 1, R = Me (**1a**), Ph (**1b**), 2-FC_6H_4 (**1c**), 4-$NO_2C_6H_4$ (**1d**)
n = 0, R = Me (**1e**), Ph (**1f**)
n = 2, R = Me (**1g**)

allowed the stereoselective control of the generated stereogenic center, affording enantio-enriched substrates.

Preliminary experiments have established that the reaction of BH adduct **1a** with phenylboronic acid (**2a**) was best conducted with $[RhOH(cod)]_2$ as rhodium catalyst precursor.[13c] We were pleased to find that, under these conditions, the reaction occurred smoothly, even at room temperature, using methanol as solvent, affording the adduct **3aa** resulting from the 1,4-addition of the organometallic reagent followed by β-hydroxyelimination with good yields (Table 1, entry 1), even in the presence of 1 mol % of rhodium catalyst. Other six-membered substituted BH adducts reacted equally well with various arylboronic acids (entries 1−10). Most of the reactions were finished in less than 1 h at room temperature, but for some less reactive BH adducts or boronic acids, faster reaction rates were achieved at slightly higher reaction temperature (50 °C, entries 2, 3,

Table 1. Rhodium-Catalyzed Addition of Boronic Acids to Hindered BH Adducts[a]

entry	1	2 (Ar =)	product (3)	yield[b] (%)
1	**1a**	C_6H_5 (**2a**)	**3aa**	91
2	**1a**	4-$MeOC_6H_4$ (**2b**)	**3ab**	82[c]
3	**1a**	4-$CF_3C_6H_4$ (**2c**)	**3ac**	33[c]
4	**1a**	2-naphthyl (**2d**)	**3ad**	39
5	**1b**	**2a**	**3ba**	82
6	**1b**	**2b**	**3bb**	96
7	**1b**	4-MeC_6H_4 (**2e**)	**3be**	81
8	**1b**	3,5-$Me_2C_6H_3$ (**2f**)	**3bf**	57[c]
9	**1c**	**2b**	**3cb**	71[c]
10	**1d**	**2a**	**3da**	65
11	**1e**	**2a**	**3ea**	35
12	**1e**	**2b**	**3eb**	33[c]
13	**1f**	**2a**	**3fa**	76
14	**1f**	3-$MeOC_6H_4$ (**2g**)	**3fg**	52[c]
15	**1g**	**2a**	**3ga**	74[c]

[a] Reactions conducted with 0.5 mmol of **1**, 2 equiv of **2** with 1 mol % of $[RhOH(cod)]_2$ at rt in 1 mL of methanol. [b] Isolated yields of alkene, the isomeric ratio *E*/*Z* being above 95:5. [c] Reaction conducted at 50 °C.

and 9). Under these conditions, electron-deficient or ortho-substituted boronic acids afforded only moderate yields due to competitive proto-deboronation (entries 3 and 4). Other cyclic substrates also reacted (entries 11−15), even if the observed yields were lower with 5-membered methyl-substituted BH substrate **1e** (entries 11 and 12) compared to the phenyl-substituted one **1f** (entries 13 and 14). In all the examined reactions, stereodefined (*E*) trisubstituted alkenes (*E*/*Z* > 98:2) were produced as confirmed by NOE experiments. These substrates, bearing α,β-unsaturated ketone functionality, can be further functionalized by Michael-type addition reactions, providing further opportunities to access, in a straightforward way, more complex structures.[14]

We also evaluated the reactivity of potassium trifluoro(organo)borates[15] because of their attractiveness in terms of higher stability and ease of preparation and purification compared to trivalent organoboranes, and also because these compounds have been shown to be highly suited to rhodium-catalyzed processes.[12] Under quite similar conditions, and with triethylamine as an additive,[16] potassium aryltrifluoroborates **4** added to trisubstituted BH adduct at room temperature (Scheme 2). Indeed, the addition of potassium trifluoro(phenyl)borate to **1a** afforded a 76% yield of the expected product **3aa**. Interestingly, potassium 4-bromophenyltrifluoroborate also underwent 1,4-addition to **1a**, afford-

(10) de la Herran, G.; Mba, M.; Murcia, M. C.; Plumet, J.; Csakÿ, A. G. *Org. Lett.* **2005**, *7*, 1669.

(11) Belyk, K. M.; Beguin, C. D.; Palucki, M.; Grinberg, N.; Da Silva, J.; Askin, D.; Yasuda, N. *Tetrahedron Lett.* **2004**, *45*, 3265.

(12) (a) Pucheault, M.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2002**, 3552. (b) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719. (c) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356. (d) Pucheault, M.; Darses, S.; Genet, J.-P. *Chem. Commun.* **2005**, 4714. (e) Mora, G.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2007**, *349*, 1180. (f) Martinez, R. m.; Voica, F.; Genet, J.-P.; Darses, S. *Org. Lett.* **2007**, *9*, 3213. (g) Navarre, L.; Martinez, R. m.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159.

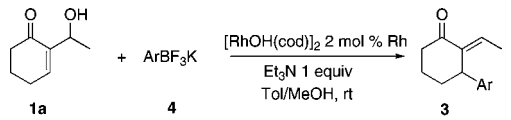
(13) (a) Navarre, L.; Darses, S.; Genet, J.-P. *Chem. Commun.* **2004**, 1108. (b) Navarre, L.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2006**, *348*, 317. (c) Gendrineau, T.; Demoulin, N.; Navarre, L.; Genet, J.-P.; Darses, S. *Chem.−Eur. J.* **2009**, *15*, 4710.

(14) (a) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377. (b) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1112. (c) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807.

(15) Reviews: (a) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (b) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49. (c) Molander, G. A.; Ellis, N. M. *Acc. Chem. Res.* **2007**, *40*, 275. (d) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (e) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288.

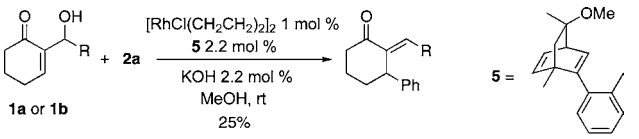
(16) For improved reactivity of RBF_3K with Et_3N, see: (a) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921. (b) Lalic, G.; Corey, E. J. *Tetrahedron Lett.* **2008**, *49*, 4894. (c) Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486.

Scheme 2. Rhodium-Catalyzed Addition of Potassium Trifluoro(organo)borates to Hindered BH Adducts



Ar = Ph (**3aa**) 76%
Ar = 4-BrC_6H_4 (**3ah**) 43%

Scheme 3. Toward an Asymmetric Version



R = Me (**3aa**) ee = 84%
Ph (**3ba**) ee = 84%

ing highly functionalized substrate **3ah**, that can be further functionalized either by 1,4-addition or palladium-catalyzed cross-coupling.

As a potential stereogenic center is generated during the reaction, we evaluated the possibility to produce enantioenriched substrates using this 1,4-addition/β-hydroxyelimination process. Several chiral phosphane ligands, which have been found to be useful in rhodium-catalyzed 1,4-additions,[1] were evaluated. However, whatever the reaction conditions used, the reaction of **1a** with **2a** was totally inhibited in the presence of phosphane ligand, whatever the reaction temperature. On the other hand, we were pleased to find that the use of our recently developed C_1-symmetric chiral diene ligand[17,18] allowed the production of enantioenriched substrates. Indeed, preliminary results have shown that, among the evaluated chiral monosubstituted dienes, ligand **5** was the most suited in terms of enantioselection level (Scheme 3). Under otherwise identical conditions, the addition of phenylboronic acid (**2a**) to BH adduct **1a** afforded enantioenriched **3aa** with an enantiomeric excess of 84%. In the same way, reaction of **2a** with phenyl-substituted BH adduct **1b** afforded the expected adduct **3ba** with an identical enantioselectivity, despite a moderate 25% yield. Further developments are actually underway in order to improve both the reaction yield and enantioselectivity.

It is important to note that the high reactivity of these trisubstituted BH adducts is quite unusual. Indeed, when the same reaction conditions were applied to α-alkyl-substituted cyclic enones, lacking the hydroxy substituent in the β position of the ketone, no reaction occurred. The main difference in the reactivity of this substrate compared to BH adduct relies on the presence of the hydroxy substituent: for the later, the catalytic cycle is terminated by a β-hydroxyelimination,[13] while for the former a protonation of a rhodium enolate must occur.[19] Indeed, it appeared that the rate-determining step with such hindered alkenes is not the olefin insertion, but the protonation step. In the described reaction, the protonation step is bypassed by a more efficient β-hydroxyelimination step.

We have described for the first time a rhodium-catalyzed 1,4-addition of organoboranes to hindered BH adducts. Moreover, preliminary results have shown that, thanks to the use of chiral diene ligands, enantioenriched substrates were easily accessible, while chiral phosphane ligands were completely ineffective.

Acknowledgment. T.G. thanks the Ministère de l'Education et de la Recherche for a grant. The authors thank Diverchim SA for the generous gift of rhodium catalyst precursor.

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

OL902646J

(17) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669, and references cited therein.

(18) For the use of chiral dienes in catalysis, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (c) Review: Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

(19) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.