ORGANIC LETTERS

2008
Vol. 10, No. 14
2975−2978

Rh(I)-Catalyzed Reaction of 2-(Chloromethyl)phenylboronic Acids and Alkynes Leading to Indenes

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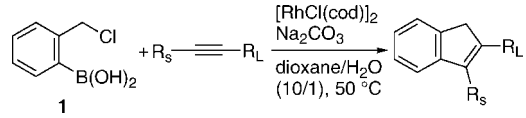
Received April 20, 2008

ABSTRACT



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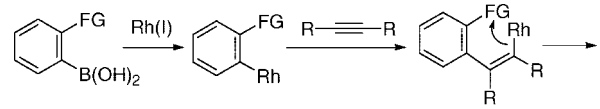
The reaction of 2-(chloromethyl)phenylboronic acid (1) with alkynes in the presence of a Rh(I) complex gave indene derivatives in high yields. The regioselectivity depends on the steric nature of the substituent on the alkynes. A bulky group favors the α-position of indenes.

The development of new reactions that construct carbocycles through carbon−carbon bond formation continues to be a prime issue in synthetic organic chemistry. Recently, the Rh(I)-catalyzed reaction of alkynes with *ortho*-functionalized organoboron reagents leading to carbocycles has been extensively studied.[1] The reactions are triggered by the addition of arylrhodium(I) species **II**, which is generated from the transmetalation of a Rh(I) complex with *ortho*-functionalized arylboronic acids **I** across alkynes to form vinylrhodium(I) complexes **III**. Then, the vinylrhodium moiety in **III** reacts with the intramolecular functional groups (FG) attached at the *ortho* position in the adjacent aryl ring to give carbocycles (Scheme 1). Various functional groups,

Scheme 1. Catalysis Triggered by Addition of *o*-Functionalized Arylboronic Acids



I II III

such as aldehydes and ketones,[2,3] esters,[3a,4] nitriles,[5] α,β-unsaturated carbonyl compounds,[6] ethers,[7] bromides,[8] iodides,[9] and isocyanates,[10] have been known to participate in this and related transformations to construct carbocycles.

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(1) For a recent review, see: Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217–224.
(2) (a) Shintani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1294–1295. (b) Matsuda, T.; Makino, M.; Murakami, M. *Chem. Lett.* **2005**, *34*, 1416–1417. (c) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2006**, *8*, 3379–3381.
(3) (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54–55. (b) Miura, T.; Shimada, M.; Murakami, M. *Synlett* **2005**, 667–669. (c) Miura, T.; Shimada, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7598–7600. (d) Miura, T.; Shimada, M.; Murakami, M. *Tetrahedron* **2007**, *63*, 6131–6140.
(4) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390–1391.
(5) (a) Miura, T.; Nakazawa, H.; Murakami, M. *Chem. Commun.* **2005**, 2855–2856. (b) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339–3341.
(6) (a) Lautens, M.; Marquardt, T. *J. Org. Chem.* **2004**, *69*, 4607–4614. (b) Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3909–3912. (c) Tseng, N.-W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 5338–5339. (d) Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6336–6338.
(7) (a) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094–1095. (b) Miura, T.; Sasaki, T.; Harumashi, T.; Murakami, M. *J. Am. Chem. Soc.* **2006**, *128*, 2516–2517.
(8) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766–5771.
(9) Shintani, R.; Yamaguchi, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799–4801.
(10) Miura, T.; Takahashi, Y.; Murakami, Y. *Org. Lett.* **2007**, *9*, 5075–5077.

10.1021/ol8006887 CCC: $40.75
Published on Web 06/21/2008

Substituted indenes are useful subunits for several applications, for pharmaceutical compounds possessing interesting biological activities,[11] for functional materials,[12] and for indenyl metal complexes as ligands, which are widely utilized in various catalytic reactions.[13] Consequently, much effort has been devoted to the construction of the indene ring system.[14] Our proposal concerns the reaction of 2-(halomethyl)phenylboronic acid (FG = CH_2Br or CH_2Cl in **I**) with alkynes as a possible route for the synthesis of substituted indenes, which are expected to form by the oxidative addition of either a CH_2Br or a CH_2Cl bond to the generated vinylrhodium **III**, followed by reductive elimination. As a result of testing this proposal, we wish to report a new method for the synthesis of indenes from the Rh(I)-catalyzed reaction of 2-(chloromethyl)phenylboronic acid (**1**) and internal alkynes.

When the reaction of 2-(bromomethyl)phenylboronic acid (**2**, 1.5 mmol) with 4-octyne (1 mmol) was carried out in dioxane/H_2O (100/1, 1 mL) at 80 °C in the presence of $[RhCl(cod)]_2$ (0.025 mmol) and Na_2CO_3 (1 mmol) under nitrogen for 20 h, 2,3-dipropyl-1*H*-indene (**3**) was obtained in 12% isolated yield. The use of a higher catalyst loading (0.1 mmol) at the reaction temperature of 50 °C increased the yield to 36%. All attempts to optimize the reaction conditions failed when using **2** as the substrate. After the optimization of the reaction conditions, we were pleased to find that the use of 2-(chloromethyl)phenylboronic acid (**1**) gave high yields of indene derivative **3** (Scheme 2). It was found that the Ir(I) complex, such as $[IrCl(cod)]_2$ is also active in the indene synthesis, but the yield was lower than that in the Rh(I)-catalyzed reaction.

Scheme 2. Rh(I)-Catalyzed Reaction of 2-(Chloromethyl)phenylboronic Acid (1) and 4-Octyne

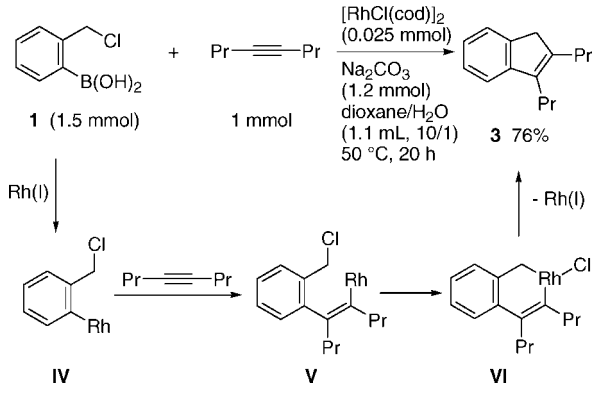
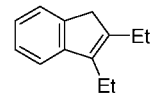
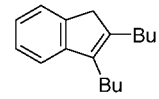
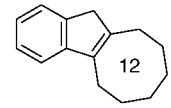
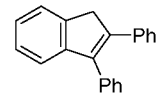
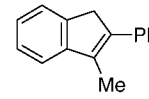
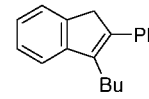
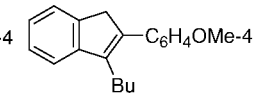
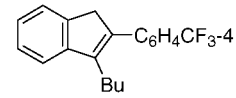
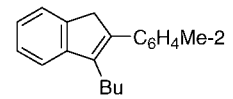
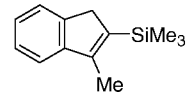


Table 1. Rh(I)-Catalyzed Reaction of Alkynes with 2-(Chloromethyl)phenylboronic Acid (**1**)[a]

alkyne	indene	yield[b]
Et—≡—Et		**4** 79%
Bu—≡—Bu		**5** 74%
		**6** 36% 54%[c]
Ph—≡—Ph		**7** 94% 93%[d]
Me—≡—Ph		**8** 90% (40:1)
Bu—≡—Ph		**9** 90% (26:1)
Bu—≡—C_6H_4OMe-4		**10** 84% (13:1)
Bu—≡—$C_6H_4CF_3$-4		**11** 90% (32:1)
Bu—≡—C_6H_4Me-2		**12** 75% (>50:1)
Me—≡—$SiMe_3$		**13** 25% (4:1) 61% (4:1)[c]

[a] Reaction conditions: alkyne (1 mmol), 2-(chloromethyl)phenylboronic acid (**1**, 1.5 mmol), $[RhCl(cod)]_2$ (0.025 mmol), and Na_2CO_3 (1.2 mmol) in dioxane/H_2O (10/1, 1.1 mL) at 50 °C for 20 h under N_2. [b] Isolated yields. The numbers in the parentheses indicate the regioisomeric ratios determined by GC. [c] $[RhCl(cod)]_2$ (0.05 mmol) was used. [d] $[RhOH(cod)]_2$ (0.025 mmol) was used as the catalyst.

The reaction proceeds as we proposed, as shown in Scheme 2. Transmetalation of Rh(I) with 2-(chloromethylphenylboronic acid (**1**) generates a 2-(chloromethyl)phenylrhodium(I) complex **IV**, to which the insertion of an

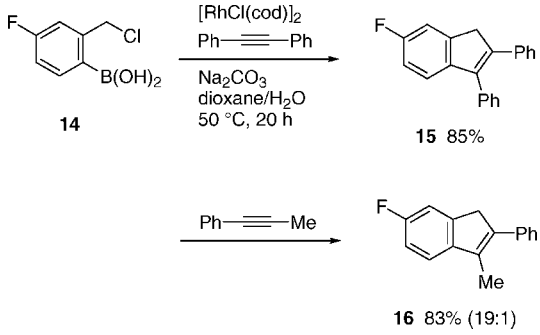
(11) For examples, see: (a) Karaguni, I.-M.; Glusenkamp, K.-H.; Langerak, A.; Geisen, C.; Ullrich, V.; Winde, G.; Moroy, T.; Muller, O. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 709–713. (b) Müller, O.; Gourzoulidou, E.; Carpintero, M.; Karaguni, I.-M.; Langerak, A.; Herrmann, C.; Möröy, T.; Klein-Hitpaß, L.; Waldmann, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 450–454.

(12) For examples, see: (a) Barberá, J.; Raitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296–299. (b) Yang, J.; Lakshmikantham, M. V.; Cava, M. P. *J. Org. Chem.* **2000**, *65*, 6739. (c) Hahn, S. F.; Hillmyer, M. A. *Macromolecules* **2003**, *36*, 71–76.

alkyne gives the vinylrhodium complex **V**. Oxidative addition of C−Cl on the adjacent phenyl ring produces the rhodium(III) species **VI**, which undergoes reductive elimination to give indene **3**. When the reaction was carried out under an ambient pressure of CO, no carbonylation products were obtained, but indene **3** was obtained in low yield, although the exclusive formation of a carbonylation product was observed in the case of FG = Br or Cl.[8] This is due to the unfavorable formation of a seven-membered metalacycle, which is required for CO insertion.

The results of the reaction using various alkynes are summarized in Table 1.[15] Internal alkynes having alkyl and aryl groups gave the corresponding indenes in high yields. The reaction of 1-phenylhexyne gave a regioisomeric mixture of **9** with a ratio of 26:1. It was found that the regioselectivity is affected by the electronic nature of a substituent. Introduction of an electron-withdrawing group, such as CF_3 at the *para*-position on the phenyl ring, increased the regioselectivity of **11** to the ratio of 32:1. On the other hand, the regioselectivity decreased to 13:1 when 1-(4-methoxyphenyl)hexyne was used as the substrate. The steric effects also dramatically affected the regioselectivity, as in the case of 1-(2-methylphenyl)hexyne,

Scheme 3. Rh(I)-Catalyzed Reaction of 2-(Chloromethyl)-4-fluorophenylboronic Acid (**14**) and Alkynes

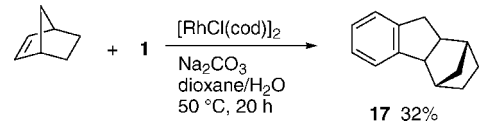


leading to **12**. Alkynes having a silyl group and an ester group were not suitable for the present indene synthesis. The reaction of (trimethylsilyl)phenylacetylene gave a complex mixture involving the corresponding indene derivative in low yield (data not shown in Table 1). The use of (trimethylsilyl)propyne as an alkyne partner gave the corresponding indene **13** in low yield. When the amount of the catalyst loading was increased, the yield of **13** increased, but the regioselectivity was not so high. Alkynes having an ester group, such as methyl 2-butynoate and methyl phenylpropiolate, did not give the corresponding indenes.

The reaction of 2-(chloromethyl)-4-fluorophenylboronic acids (**14**) with diphenylacetylene and phenylpropyne gave the corresponding indenes **15** and **16**, respectively, in high yields (Scheme 3).

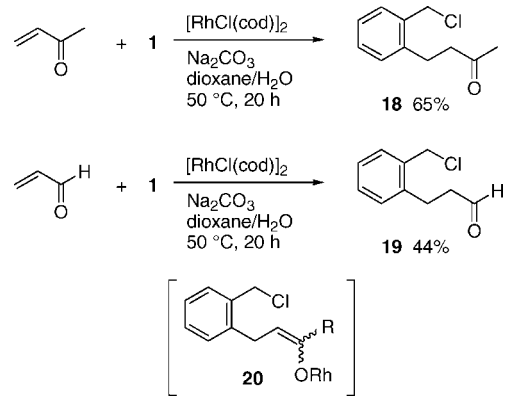
Next, we examined the reaction of alkenes with **1**, which would be expected to lead to the formation of indane derivatives if the reaction proceeds similar to the reaction with alkynes. However, alkenes were not suitable substrates for the present reaction. Even with norbornene, the corresponding indane derivative **17** was obtained in a low yield (Scheme 4), although an arylrhodium species is well-known to react with norbornene or 7-oxanorbornene.[16]

Scheme 4. Reaction of Norbornene with **1**



The conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds catalyzed by the Rh(I) complex, in particular, the asymmetric version, has been extensively studied.[17] Then, we examined the reaction of electron-deficient olefins with **1**. The reaction of 3-buten-2-one with **1** did not give any cyclized products, but a simple 1,4-addition selectively took place to give **18** in good yield (Scheme 5). The reaction of acrolein also afforded only a

Scheme 5. Reaction of α,β-Unsaturated Carbonyl Compounds with **1**



(13) For reviews, see: (a) Zargarian, D. *Coord. Chem. Rev.* **2002**, *233*, 157–176. (b) Calhorda, M. J.; Felix, V.; Veiros, L. F. *Coord. Chem. Rev.* **2002**, *230*, 48–63. See, also: (c) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205–1222.

(14) For recent papers on the catalytic synthesis of indenes, see: (a) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325–3327. (b) Dube, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062–12063. (c) Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251–262. (d) Dong, C.-G.; Yeung, P.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 363–366.

(15) Notes: (a) The use of terminal alkynes did not produce the corresponding indenes under these conditions. (b) The regioselectivities observed in the reactions with unsymmetrical alkynes are mostly parallel to those observed in our preveous report. See ref 8.

(16) Tseng, N.-W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 5338–5339. and references cited therein.

(17) For recent reviews, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196.

conjugate addition product **19**. These results show that protonation of the initially generated rhodium enolate **20** is much faster than intramolecular nucleophilic substitution of a chloride.

In summary, we reported on the development of a new synthetic method to access indene derivatives. The reaction involves the addition of an arylrhodium(I) species to alkynes and the oxidative addition of a C−Cl on the adjacent phenyl ring to the resulting vinylrhodium(I), which undergoes reductive elimination.

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

OL8006887