ORGANIC
LETTERS

2007
Vol. 9, No. 17
3213−3216

# Base-Free Mizoroki–Heck Reaction Catalyzed by Rhodium Complexes

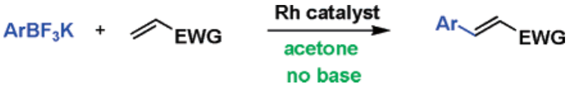
**Rémi Martinez, Florina Voica, Jean-Pierre Genet,* and Sylvain Darses***

*Laboratoire de Synthèse Sélective Organique (UMR 7573, CNRS), Ecole Nationale Supérieure de Chimie de Paris, 11 rue P&M Curie, 75231 Paris cedex 05, France*

*sylvain-darses@enscp.fr; jean-pierre-genet@enscp.fr*

Received May 11, 2007

## ABSTRACT



**A base-free rhodium-catalyzed Mizoroki–Heck (M–H) reaction using potassium aryltrifluoroborates as the arylating agent of alkenes and acetone as a green "oxidant" is described. Thanks to the ready availability of organoboranes, this reaction should constitute an interesting alternative to conventional M–H reactions using aryl halides.**

The arylation of alkenes, the Mizoroki−Heck reaction (M−H),[1] is now recognized to be of genuine synthetic utility for preparing aromatic fine chemicals.[2] In addition to the conventional M−H reaction of unsaturated compounds with organic halides, triflates, or carboxylic acid derivatives, occurring via oxidative addition, the use of organometallic reagents, such as silanes, stannanes or boranes, has attracted much attention.

The palladium(II)-mediated vinylic substitution of organometallic reagents was first reported by Heck,[3] using stoichiometric amounts of palladium(II) salts, more than two decades ago. A catalytic variant, using organoboronic acids, was reported by Uemura et al. in 1994, requiring the use of a base.[4] Since then, several conditions have been developed for the so-called palladium-catalyzed oxidative Heck-type reaction of organometallic reagents with electron-deficient olefins.[5] However, all these reactions require the presence of both excess base and excess oxidant (copper(II) acetate or $O_2$) as the reoxidizing agent, conditions incompatible with the presence of many functional groups. Moreover, large amounts of palladium catalyst are generally required (5−10%) to achieve acceptable yields of the M−H adduct. A variant, using a ruthenium(II) catalyst as a precursor, has been reported, but the reaction still required a regeneration system based on the association of a base and an oxidant.[6]

Alternatively, Lautens[7] and our group[8] have reported M−H reactions using rhodium(I) catalysts[9] for the reaction of boronic acids with styrenes, in the presence of a base but without any oxidizing agent. These conditions were extended

---

[1] (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

[2] Reviews: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Shibasaki, M.; Boden, C. O. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (d) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (f) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.

[3] (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518. (b) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707. (c) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083.

[4] Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85.

[5] Borane: Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313. Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231. Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218. Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212. Yoon, C. H.; Yoo, K. S.; Yi, S. W.; Mishra, R. K.; Jung, K. W. *Org. Lett.* **2004**, *6*, 4037. Enquist, P.-A.; Lindh, J.; Nilsson, P.; Larhed, M. *Green Chem.* **2006**, *8*, 338. Silane: Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893. Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 749. Hirabayashi, K.; Ando, J.-i.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409. Stannane: Hirabayashi, K.; Ando, J.-i.; Nishihara, Y.; Mori, A.; Hiyama, T. *Synlett* **1999**, 99. Parrish, J. P.; Jung, Y. C.; Shin, S. I.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 7127. Others: Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 1484.

[6] Farrington, E. J.; Brown, J. M.; Barnard, C. F. J.; Rowsell, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 169.

[7] Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358.

[8] Amengual, R.; Michelet, V.; Genet, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5905.

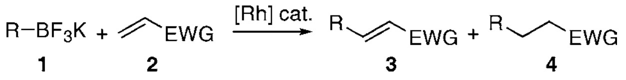
[9] In some rhodium-catalyzed 1,4-additions, the M−H adduct has been observed as a byproduct: Cho, C. S.; Motofusa, S.-i.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 883.

10.1021/ol071098q CCC: $37.00

to other activated alkenes by Lautens, but the reaction still needed added base.[10] Mori reported the rhodium(I)-[11] and iridium(I)-catalyzed[12] M−H reaction of organosilanes with electron-deficient olefins, and more recently it has been shown that $RhCl_3$ could be used in place of Rh(I).[13] However, there are some evident drawbacks in these reactions. First, the presence of a base and/or an oxidizing agent is required for maximum efficiency. Second, in the Rh- or Ir-catalyzed reactions, the Mizoroki−Heck product is generally contaminated by the presence of saturated product[10−13] (1,4-addition adduct), and with some electron-deficient olefins, such as enones, the latter become the major product.

We have recently shown that potassium organotrifluoroborates[14] were highly suitable organoboron reagents in either palladium- or rhodium-catalyzed processes.[15] More particularly, we developed an efficient Heck-type reaction with aldehydes, affording a direct access to ketones.[16] We want to report here a general and efficient process for the Heck reaction, occurring under very mild conditions, in the absence of either added base or oxidant[17,18] and using easily available and stable potassium trifluoro(organo)borates (Scheme 1).

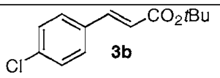
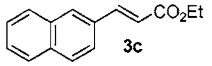
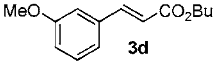
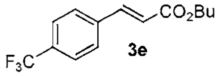
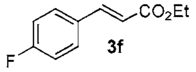
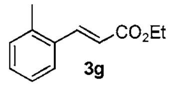
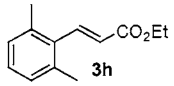
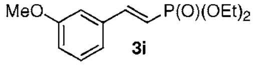
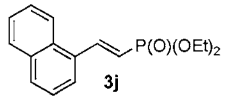
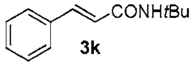
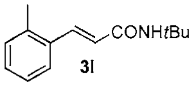
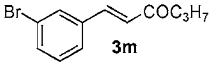
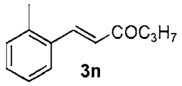
**Scheme 1.** Rhodium-Catalyzed Mizoroki−Heck-Type Reaction with Potassium Trifluoro(organo)borates



To achieve exclusive formation of the Mizoroki−Heck adduct **3** at the expense of the 1,4-addition adduct **4**, several conditions were evaluated in the presence of the rhodium catalyst (Scheme 1). It appeared that, whatever the conditions evaluated, in the presence of water only the saturated product **4** was obtained, a result similar to that observed by Mori et al.[11] On the other hand, under anhydrous conditions, the Mizoroki−Heck product became the only observable product. Among the tested solvents, a binary mixture of dioxane/acetone proved to be the most suitable. Indeed, reaction of potassium phenyltrifluoroborate (**1a**, R = Ph) with butyl acrylate (**2a**, EWG = $CO_2Bu$) using $[Rh(=)_2Cl]_2$ in conjunction with the $PPh_3$ ligand as catalyst afforded quantitative conversion in alkene **3a** (R = Ph, EWG = $CO_2Bu$) as the sole product. Contrary to other Rh- or Ir-catalyzed reactions, we did not observe any traces of the 1,4-addition/protonation adduct **4**.

These conditions proved to be general, and a great variety of M−H adducts were obtained from the reaction of potassium organotrifluoroborates with acrylates (Table 1).

**Table 1.** Rhodium-Catalyzed Mizoroki−Heck Reaction with Potassium Organotrifluoroborates[a]

| entry | product | yield[b] (%) |
|---|---|---|
| 1 |  **3b** | 71 |
| 2 |  **3c** | 89 |
| 3 |  **3d** | 88 |
| 4 |  **3e** | 94 |
| 5 |  **3f** | 85 |
| 6 |  **3g** | 92 |
| 7 |  **3h** | 80 |
| 8 |  **3i** | 86 |
| 9 |  **3j** | 83 |
| 10 |  **3k** | 68 |
| 11 |  **3l** | 83 |
| 12 |  **3m** | 84[c,d] |
| 13 |  **3n** | 86 |

[a] Reactions conducted using 1 mmol of **1**, 2 equiv of **2** with 1.5 mol % of $[Rh(CH_2CH_2)Cl]_2$, and 6 mol % of $PPh_3$ at 80 °C in 2.5 mL of 1,4-dioxane/acetone 4:1. [b] Isolated yields of M−H adduct. [c] 10% of debrominated product was also obtained. [d] 3 equiv of enone was used.

Good to excellent yields were generally achieved with many substitution patterns on the reaction partners. It appeared that the electronic nature of the organoboron reagent did not have a great influence as similar yields and reaction rates were obtained with trifluoroborates bearing either electron-withdrawing or -releasing substituents (entries 3 and 4). It is also noteworthy that reactions of mono- and di-*ortho*-

---

(10) Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, 2006.

(11) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774.

(12) Koike, T.; Du, X.; Sanada, T.; Danda, Y.; Mori, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 89.

(13) Zou, G.; Wang, Z.; Zhu, J.; Tang, J. *Chem. Commun.* **2003**, 2438.

(14) Reviews: (a) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (b) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49.

(15) For some examples, see: (a) Pucheault, M.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2002**, 3552. (b) Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4729. (c) Navarre, L.; Darses, S.; Genet, J.-P. *Chem. Commun.* **2004**, 1108. (d) Navarre, L.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2004**, 69. (e) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719. (f) Pucheault, M.; Darses, S.; Genet, J.-P. *Chem. Commun.* **2005**, 4714−4716. (g) Navarre, L.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2006**, *348*, 317.

(16) (a) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356. (b) Mora, G.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2007**, *349*, 1180.

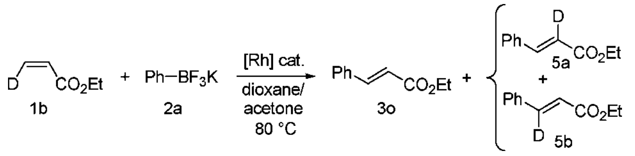
(17) Base-free Heck reaction using aroyl chloride in place of boronic acid has been reported: Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4672.

(18) Under the present conditions, $RBF_3K$ is not decomposed to $RBF_2$ and KF, ruling out KF as a base.

substituted potassium aryltrifluoroborates (entries 6 and 7) with ethyl acrylate afforded the expected M−H adducts **3f** and **3g** in high yield, whereas such *ortho* substitution generally resulted in the formation of high amounts of 1,4-adduct.[10] The reaction is not limited to ethyl acrylate, and other alkenes such as vinylphosphonates or acrylamides participated equally well (entries 8−11). For example, reaction of potassium trifluoro(3-methoxyphenyl)borate with diethyl(vinyl)phosphonate afforded M−H adduct **3i** in 86% yield, as the only reaction product (entry 8). It is noteworthy that reaction of vinyl ketones afforded exclusively the M−H adduct on reaction with aryltrifluoroborates (entries 12 and 13), in sharp contrast with other rhodium-catalyzed processes described.[10,11,13] Indeed, reaction of trifluoro(2-methylphenyl)borate with propyl vinyl ketone allowed the formation of unsaturated ketone **3n** in 86% yield (entry 13).

For the present reaction, a Heck-type mechanism[2] can be envisioned after the transmetalation step of the organometallic to rhodium(I): insertion of the olefin bond into the aryl-rhodium(I) species followed by rotation and $\beta$-hydrogen elimination forms the (*E*)-olefin and generates a rhodium hydride species (Scheme 3). To understand the subsequent transformations of the putative rhodium-hydride and the crucial part played by acetone in this reaction, labeling studies were conducted (Scheme 2).

**Scheme 2**



To our surprise, the reaction of ethyl (*Z*)-3-deuteriopropenoate (**1b**) with potassium phenyltrifluoroborate (**2a**) under standard conditions afforded not only the expected nondeuterated adduct **3o** but also a mixture of monodeuterated adducts **5a** and **5b**, and deuterium scrambling occurred in position α and even in position $\beta$ of the M−H adduct. To determine the origin of this scrambling, ethyl acrylate **1b** was reacted under identical conditions but in the absence of potassium phenyltrifluoroborate. Indeed, we observed complete deuterium scrambling of the substrate, with the reaction mixture after 1 h consisting of an equimolar mixture of the three possible monodeuterated and nondeuterated acrylates. Such deuterium−proton exchange must occur via insertion/$\beta$-hydride elimination sequences in the substrate on reaction with a putative rhodium-hydride species, but we did not study this exchange process any further.

The $^2$H NMR spectra of the crude reaction mixture (Scheme 2 and Figure 1a) revealed the formation of a major deuterated compound at 2.61 ppm, along with traces of monodeuterated products **5a** ($\delta$ = 7.49 ppm) and **5b** ($\delta$ = 6.35 ppm) as well as all three possible double bond monodeuterated acrylates ($\delta$ = 6.15, 5.93, and 5.66 ppm). Upon addition of water, the signal at 2.61 ppm disappeared, and we observed the appearance of a new signal at 3.51 ppm, which was assigned to 2-deuteriopropan-2-ol (Figure 1b). The remainder of the spectra was unchanged. Indeed, the species observed at 2.61 ppm could be assigned to a boron alcoholate derived from 2-deuteriopropan-2-ol, which must be produced during the transmetalation step of potassium phenyltrifluoroborate to the alkoxo−rhodium, formed upon reaction of rhodium-hydride with acetone.

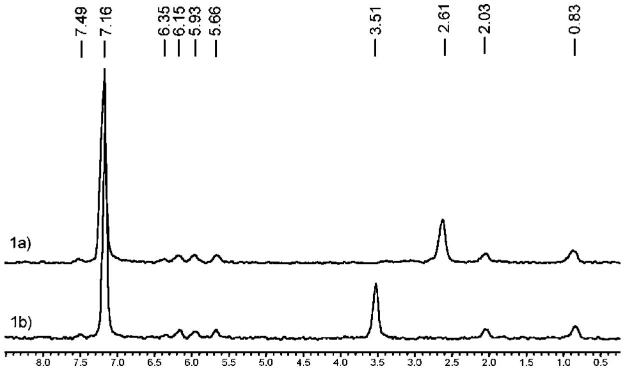
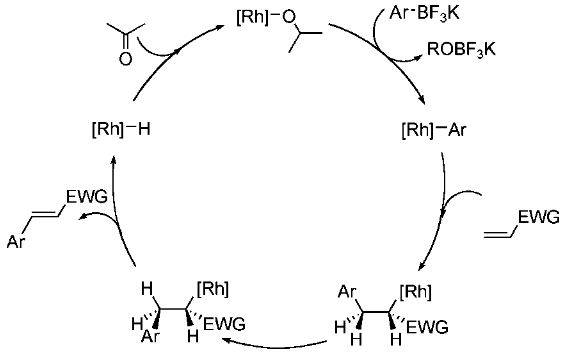


**Figure 1.** (a) $^2$H NMR spectrum of the crude reaction mixture of the rhodium-catalyzed reaction of **1b** with **2a**. (b) $^2$H NMR spectrum after addition of water (benzene-$d_6$, $\delta$ = 7.16 ppm, was used as the internal reference).

Two other minor signals were also observed at 0.83 and 2.03 ppm, which were attributed to ethyl 3-deuteriopropanoate and ethyl 2-deuteriopropanoates, respectively. Indeed, under these conditions, the starting material also acts as a hydride acceptor but to a minor extent, the major path being the hydride transfer to acetone.

The overall mechanism is believed to involve transmetalation of the organometallic reagent to the rhodium(I) complex followed by the insertion of the activated olefin into the aryl-rhodium(I) (Scheme 3). Rotation, followed by *syn*-$\beta$-deuteride elimination from the generated alkyl rhodium(I) complex, would release the M−H adduct and a rhodium(I) deuteride species. The latter may react with

**Scheme 3.** Proposed Reaction Mechanism for the Rhodium-Catalyzed M−H Reaction



acetone to afford an alkoxo−rhodium(I) complex, which is suited for transmetalation with the boron reagent. Transmetalation of organoboron compounds to the alkoxo or hydroxo complex of palladium,[19] rhodium,[16,20] or ruthenium[21] has been described, allowing the regeneration of aryl−metal species. It is worthy to note that the starting alkenes may also react with rhodium hydride, generating a rhodium enolate, which may also be suitable for transmetalation with organoboranes. But the major path remains the hydride transfer to acetone.

We have thus described for the first time a base-free rhodium-catalyzed M−H reaction using potassium aryltrifluoroborate as the arylating agent of alkenes and acetone as a green oxidant. This reaction should be an interesting alternative to conventional M−H reactions using aryl halides,[2] all the more because organoboron compounds, and organotrifluoroborates, are now easily accessible directly from alkenes or arenes via rhodium- or iridium-catalyzed C−H bond activation.[22]

**Acknowledgment.** This work was supported by the Centre National de la Recherche Scientifique (CNRS). R. Martinez thanks the Ministère de l’Education et de la Recherche for a grant.

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

OL071098Q

---

(19) Review: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

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

(21) (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (b) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706.

(22) (a) Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 15334. (b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263. (c) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757 and references therein. (d) Review: Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *603*, 3.