ORGANIC LETTERS

2008
Vol. 10, No. 1
129−131

Oxidative Coupling of Arylboronic Acids with Arenes via Rh-Catalyzed Direct C–H Arylation

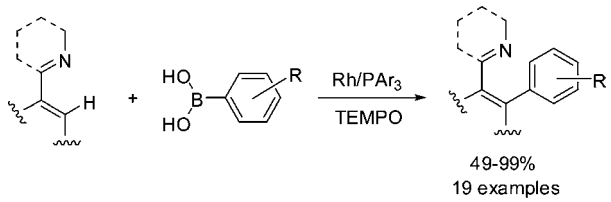
Thomas Vogler and Armido Studer*

Fachbereich Chemie, Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstrasse 40, 48149 Münster, Germany

studer@uni-muenster.de

Received November 5, 2007

ABSTRACT



Oxidative coupling of three different arenes and a thiophene derivative with various arylboronic acids was achieved with a $[RhCl(C_2H_4)_2]_2$/$P[p\text{-}(CF_3)C_6H_4]_3$ catalyst system. Commercially available 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) was used as a stoichiometric oxidant. A 2-pyridyl group and an imine functional group served as ortho-directing groups to mediate the direct C–H arylation by a Rh complex. Moderate to excellent yields were obtained for the coupling reactions.

Biaryls are an important class of compounds which have found widespread application as ligands in asymmetric synthesis.[1] Moreover, they occur in many natural products[2] and are interesting building blocks for the construction of new organic materials.[3,4] Biaryls have been predominantly prepared by metal-catalyzed cross-coupling reactions of aryl halides and aryl metal compounds.[1] More recently, many research groups have focused on the direct arylation of arenes and heteroarenes without preactivation of one of the coupling partners.[5,6] Mostly, Pd catalysis has been used for arene activation,[5] but also Rh-mediated reactions are known.[7] Only a few examples of the direct transition-metal-catalyzed coupling of boronic acid derivatives with arenes or heteroarenes have been published to date.[8,9] Pd and Ru catalysts were applied in these studies. Herein, we present, for the first time, oxidative Rh-catalyzed coupling reactions of various arylboronic acids with four different arenes.[10]

As an oxidant, we selected the commercially available 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO). Op-

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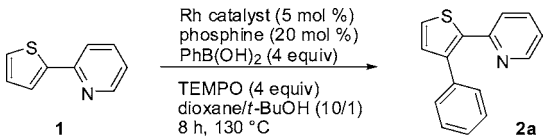
10.1021/ol702659a CCC: $40.75
Published on Web 12/12/2007

timization studies were conducted with thiophene **1**, bearing the ortho-directing 2-pyridyl group,[10b,11] and phenylboronic acid using various Rh catalysts in the presence of excess TEMPO in dioxane/*t*-BuOH at 130 °C in sealed tubes for 8 h (Table 1).

Table 1. Rh-Catalyzed C−H Phenylation Using Various Catalysts

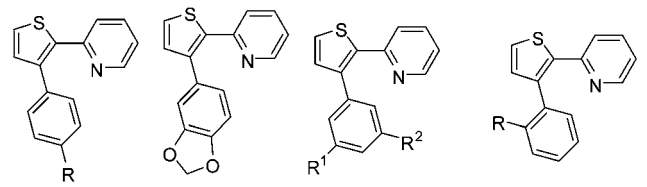


entry	Rh(I) source	phosphine	yield[a] (%)
1	$[RhCl(cod)]_2$	PPh_3	22
2	$[RhCl(cod)]_2$	$P[p\text{-}(MeO)C_6H_4]_3$	27
3	$[RhCl(cod)]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	72
4	$[RhCl(cod)]_2$	dppb[b]	34
5	$[RhCl(coe)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	91
6	$[Rh(OH)(cod)]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	99
7	$[RhCl(C_2H_4)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	99
8[c]	$[RhCl(C_2H_4)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	91
9[d]	$[RhCl(C_2H_4)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	78
10[e]	$[RhCl(C_2H_4)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	88
11[e,f]	$[RhCl(C_2H_4)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	46
12[e,g]	$[RhCl(C_2H_4)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	51
13[e,h]	$[RhCl(C_2H_4)_2]_2$	$P[p\text{-}(CF_3)C_6H_4]_3$	29

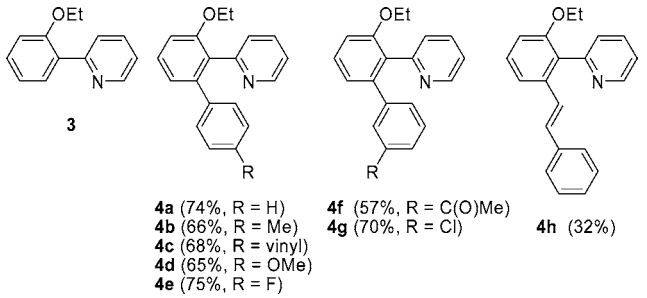
[a] Isolated yield. [b] 10 mol % of dppb was used. [c] 2.0 equiv of TEMPO was used. [d] 2 equiv of $PhB(OH)_2$ was used. [e] Reaction conducted at 90 °C for 13 h. [f] With 20 mol % of TEMPO and oxygen. [g] With 20 mol % of TEMPO and air. [h] With oxygen in the absence of TEMPO.

Combination of $[RhCl(cod)]_2$ with PPh_3 provided **2a** in 22% yield (cod = 1,5-cyclooctadiene, entry 1). The electron-rich phosphine ligand $P[p\text{-}(MeO)C_6H_4]_3$ afforded a slightly higher yield, whereas a satisfactory result (72%) was obtained with $P[p\text{-}(CF_3)C_6H_4]_3$ (entries 2 and 3). The bidentate ligand bis(diphenylphosphino)butane (dppb) afforded a lower yield (34%, entry 4). Further improvement was achieved with the use of $[RhCl(coe)_2]_2$ as a precatalyst (91%, coe = cyclooctene, entry 5). With $[Rh(OH)(cod)]_2$ and $[RhCl(C_2H_4)_2]_2$, biaryl **2a** was formed in quantitative yield (99%, entries 6 and 7). Since $[RhCl(C_2H_4)_2]_2$ is cheaper than $[Rh(OH)(cod)]_2$, all subsequent studies were performed with the ethene-ligated precatalyst. The use of 2 equiv of TEMPO (entry 8) or 2 equiv of phenylboronic acid led to a slightly reduced yield (entry 9). A lower yield was obtained at 90 °C for 13 h (entry 10). The coupling with 20 mol % of TEMPO and oxygen or air as co-oxidants at 90 °C (13 h) provided lower yields (entries 11 and 12). The lowest yield in the series was achieved in the absence of TEMPO with oxygen as the only oxidant (entry 13). The directing 2-pyridyl group is essential since C−H arylation did not occur on 3-methoxythiophene.[7g] It is important to note that no additional base was required for the coupling reaction.

To study the scope and limitations of the oxidative Rh-catalyzed coupling reaction, the arylboronic acid component was systematically varied (9 h reaction time). As expected, an alkyl group at the para position did not influence the reaction outcome to a large extent (**2b**). Interestingly, a vinyl group was inert under the applied conditions (**2c**). Electronic effects at the boronic acid moiety did not play a significant role since similar yields were obtained for electron-rich (**2d**) and for electron-poor arenes (**2e**,**f**). However, steric effects influenced the reactivity. Slightly lower but acceptable yields were achieved for the coupling reaction with ortho-substituted arylboronic acids (**2g**,**h**).



Next, we tested whether C−H activation also works on benzene derivatives. We selected 2-(2-ethoxyphenyl)-pyridine (**3**) as a test substrate. Coupling reactions were conducted under the conditions optimized for thiophene derivative **1**.



Slightly lower yields were obtained for the reactions of **3** with arylboronic acids as compared to the couplings with **1**. Coupling of **3** with para-substituted arylboronic acids afforded the biphenyl derivatives **4a**−**e** in 65−75% yield. As above, electronic effects at the boronic acid moiety did not play an important role. Similar yields were obtained for the coupling of **3** with meta-substituted arylboronic acids (**4f**,**g**). We were also able to show that sluggish coupling with an alkenylboronic acid was possible under the applied conditions. Hence, stilbene derivative **4h** was isolated in 32% yield along with 56% of unreacted substrate **3**.

(10) Oxidative C−H activation using Pd: (a) ref 6. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (d) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. Oxidative coupling of phenols using Rh: Barrett, A. G. M.; Itoh, T.; Wallace, E. M. *Tetrahedron Lett.* **1993**, *34*, 2233.

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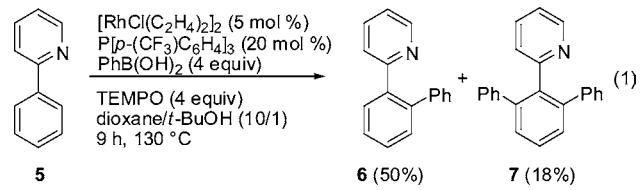
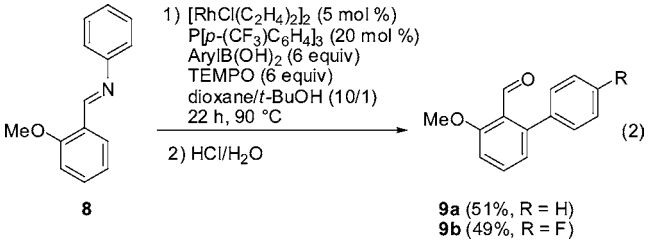


5 **6** (50%) **7** (18%)

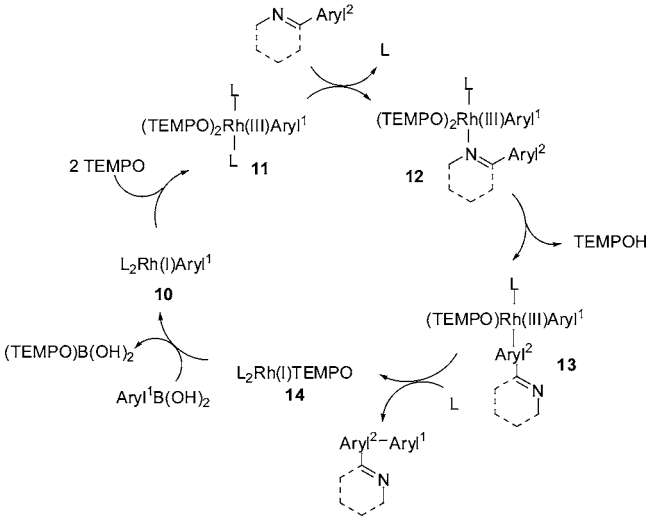
We found that the activating ethoxy group in **3** was not necessary for successful direct C−H arylation. Thus, treatment of pyridine **5** with $PhB(OH)_2$ gave biphenyl derivative **6** in 50% yield along with 18% of the double-arylated compound **7** (eq 1). To broaden the scope of the reaction, we tested whether the 2-pyridyl group could be replaced by another ortho-directing group. Imines have been successfully used in that regard.[12] Therefore, we tested imine **8** in the Rh-catalyzed coupling reaction with $PhB(OH)_2$ and achieved biaryl formation under slightly modified conditions (lower temperature and longer reaction time). The crude product was hydrolyzed to give aldehyde **9a** in 51% yield (eq 2). Similarly, the fluorinated analogue **9b** was prepared in 49% yield.



8 **9a** (51%, R = H) **9b** (49%, R = F)

The proposed mechanism is depicted in Scheme 1. The Rh(I) intermediate **10** is generated via transmetalation of Rh(I) aminoalkoxide **14** with arylboronic acid.[13] Complex **10** is assumed to be oxidized by 2 equiv of TEMPO to give the Rh(III) complex **11**.[14−16] Ligand exchange of a phosphine with the arene bearing the ortho-directing group should then lead to **12**, which eventually undergoes C−H arylation to generate the Rh(III) complex **13** and TEMPOH.[7b,c,e] The TEMPO anion probably acts as base under these conditions. As shown in the experiment, the activation works better when using the electron-poor $P[p\text{-}(CF_3)C_6H_4]_3$ ligand as compared to PPh_3. Therefore, we assume that at least one phosphine ligand is bound to the Rh atom during the direct C−H arylation. Reductive elimination and ligand exchange eventually provide the coupling product and Rh(I) complex **14**.

Scheme 1. Proposed Mechanism (L = $P[p\text{-}(CF_3)C_6H_4]_3$)



In conclusion, we developed an oxidative Rh-catalyzed coupling reaction of arenes and heteroarenes with arylboronic acids via direct C−H arylation. Two different ortho-directing groups can be used to mediate the direct C−H arylation step. TEMPO used as an oxidant is commercially available and no additional base is required for the coupling reaction. To the best of our knowledge, Rh-catalyzed biaryl formation via direct C−H arylation with an external oxidant is unprecedented.[15] We believe that oxidative transformation of readily available Rh(I) complexes using an external stoichiometric oxidant is a highly efficient approach for the generation of the corresponding Rh(III) complexes.[16]

Acknowledgment. We thank Novartis Pharma AG (Young Investigator Award to A.S.), the Fonds der Chemischen Industrie (stipend to T.V.), Dr. Jeffrey R. Simard (Chemical Genomics Centre, Dortmund) for polishing the English, and Ciba Specialty Chemicals for donation of chemicals.

Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702659A

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(15) Direct C−H arylations with Ph_4Sn and tetraphenylborates have been reported; see refs 12c and 11a. However, in these reactions, no oxidant was used. As suggested, insertion of a Rh(I) complex into a C−H aryl bond (aryl-H activation) leads to a HRh(III)aryl species which undergoes further reaction. Our process is different since an external oxidant is necessary and the "C-H-activation" probably occurs via electrophilic aromatic substitution. In fact, without oxidant our reactions did not proceed.

(16) Rh(I) carboxylates can be oxidized with $Cu(OAc)_2$ to the corresponding Rh(III) complexes, which subsequently undergo directed C−H arylation: Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407.