Boronic Acids in the Three-Component Synthesis of Carbon-Substituted Cyclopentadienyl Tricarbonyl Rhenium Complexes

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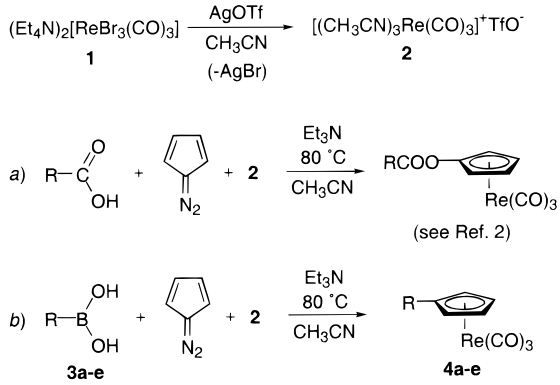
The use of η^5-cyclopentadienyl-tricarbonyl rhenium and technetium complexes in radiolabeling biologically interesting molecules is still rather underdeveloped, despite the excellent structural and chemical properties of such complexes.[1] The main reason for this is that the synthesis of these kinds of complexes is rather difficult and generally requires rather harsh conditions[1a,b] or laborious procedures.[1c] We recently reported[2] a new "three-component" synthesis that provides a convenient way for preparing halo-, carbonyloxy-, and hydroxy-substituted $CpRe(CO)_3$ complexes by a one-pot reaction of diazocyclopentadiene ($C_5H_4N_2$),[3] a rhenium(I) tricarbonyl species (**2**, Scheme 1)[4] and a nucleophile (halide or carboxylate anions) (Scheme 1, eq *a*). The rapidity and simplicity of this reaction made it a promising method for labeling biologically interesting compounds with Re-186, Re-188, and Tc-99m radionuclides.[5] However, so far the functionality linking the organic portion and the metal complex has been limited to an ester group (Scheme 1, eq *a*), which in some cases might undergo a hydrolytic cleavage when used *in vivo*. A carbon−carbon bond would provide a more secure connection between the radioactive metal portion and the organic molecule. To prepare such a carbon−carbon linkage, a palladium-catalyzed cross-coupling reaction might be utilized to connect a previously prepared halo-$CpRe(CO)_3$ complex[2] with an organometallic species.[6] This approach, however, involves long reaction times and often requires additional protection/deprotection steps of sensitive functional groups present on the organic moiety and, thus, is not suitable for short-lived radionuclides such as Tc-99m (6 h half-life).[1c]

Intrigued by the possibility of using a carbon nucleophile instead of a halide or a carboxylate in the three-component reaction,[2] we started to investigate the use of several organometallic reagents with the aim of directly obtaining a carbon-linked $CpRe(CO)_3$ complex in one-pot. We were particularly interested in boronic acids, which have already been successfully employed in Pd-catalyzed cross-coupling reactions.[7] Moreover, in recent years these organometallic species have attracted a great deal of attention, since they are nonflammable, stable to water and air, and easy to handle. We were pleased to find that, as shown in Scheme 1 and Table 1, boronic acids proved to be ideal "masked-carbanion" nucleophiles under our reaction conditions.

Scheme 1



In general, the reaction of $C_5H_4N_2$ and the rhenium(I) tricarbonyl species with the boronic acids **3a**−**e** (Scheme 1, eq *b*, and Table 1) turned out to be slower than with the carboxylates.[2] In fact, using the same amount of nucleophile (2 equiv), longer times (14 h) were required to obtain acceptable yields (42−76%) of the complex (conditions B, Table 1). However, we found that with a 5-fold increase of the concentration of nucleophile (conditions A), satisfactory yields could be obtained within short reaction times (45 min), which are essential in radiolabeling. Both aryl- and vinyl-substituted boronic acids showed a good reactivity,[10] and the effect of a *para*-substituents on the aromatic ring of several phenylboronic acids (**3a**−**d**) was also determined.

The influence of different substitution patterns on the reactivity of boronic acids **3a**−**d** can be qualitatively established looking both at the yields obtained within short reaction times (conditions A) and at the results obtained in a competition experiment reported below. As shown in Table 1 (conditions A), the reactivity of the phenylboronic acids is lowered by electron-withdrawing *para*-substituents, such as an acetyl (**3b**, entry 2, Table 1) or a bromo group (**3c**, entry 3), compared to the unsubstituted phenylboronic acid (**3a**, entry 1), whereas it is significantly increased by an electron-donating group, like a *para*-methoxy group (**3d**, entry 4). This order of reactivity (**3d** > **3a** > **3c** > **3b**) was also confirmed by a competition experiment in which equimolar amounts of boronic acid **3a**−**d** (10 equiv each) were allowed to react with $C_5H_4N_2$ (1.5 eq) and the rhenium precursor **2** (1.0 equiv) at 80 °C for 15 min. NMR analysis of the crude reaction mixture showed the following product ratios, normalized to 1.0 for the unsubstituted phenylboronic acid **4a**: 1.4 (**4d**), 1.0 (**4a**), 0.8 (**4c**), 0.3 (**4b**). The increased reactivity of electron-rich aryl boronic acids in this reaction is just the opposite to what had previously been observed in the Suzuki Pd-catalyzed cross-coupling reaction with the same class of boronic acids.[11] These observations indicate

(1) (a) Wenzel, M. *J. Labelled Compd. Radiopharm.* **1992**, *31*, 641−650. (b) Spradau, T. W.; Katzenellenbogen, J. A. *Organometallics* **1998**, *17*, 2009−2017. (c) Top, S.; El Hafa, H.; Vessières, A.; Quivy, J.; Vaissermann, J.; Hughes, D. W.; McGlinchey, M. J.; Mornon, J.-P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, *117*, 8372−8380.

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(3) (a) Herrmann, W. A. *Chem. Ber.* **1978**, *111*, 2458−2460. (b) Reimer, J. K.; Shaver, A. *J. Organomet. Chem.* **1975**, *93*, 239−252.

(4) (a) Alberto, R.; Schibli, R.; Schubiger, P. A. *Polyhedron* **1996**, *15*, 1079−1089. (b) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, P. A.; Herrmann, W. A.; Artus, G.; Abram, U.; Kaden, T. A. *J. Organomet. Chem.* **1995**, *492*, 217−224. (c) Alberto, R.; Egli, A.; Abram, U.; Hegetschweiler, K.; Gramlich, V.; Schubiger, P. A. *J. Chem. Soc., Dalton Trans.* **1994**, 2815−2820.

(5) Studies using "cold" (nonradioactive) rhenium isotopes can be considered as models for reactions with γ-emitter technetium-99m, due to a high similarity in the chemical behavior of these two metals. See: Boog, N. M.; Kaesz, H. D. Technetium and Rhenium. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, G. F. A., Abel, E. W., Eds.; Pergamon Press: Oxford, U.K., 1982; Vol. 4, pp 161−242.

(6) (a) Lo Sterzo, C.; Miller, M. M.; Stille, J. K. *Organometallics* **1989**, *8*, 2331−2337. (b) Lo Sterzo, C.; Stille, J. K. *Organometallics* **1990**, *9*, 687−694.

(7) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483 and references therein.

(8) Typical experimental procedure: Compound **1** (39 mg, 0.050 mmol) was dissolved in anhydrous CH_3CN (1.5 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing $C_5H_4N_2$ (0.060 mmol), the boronic acid (**3a**−**e**, see Table 1), and triethylamine (see Table 1) in CH_3CN (1 mL). The mixture was heated at 80 °C for the time indicated in Table 1 and then concentrated under vacuum. The crude reaction product was purified by flash chromatography. Characterization data and purification conditions of compounds **4a**−**e** are given in the Supporting Information.

(9) (a) Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem.* **1976**, *110*, 25−37. (b) In our experiments, compound **3e** was synthesized according to a general procedure reported in: Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249−5255.

(10) Alkyl-boronic acids, such as *n*-butyl- and *n*-decyl-boronic acids, showed poor reactivities under our reaction conditions (10 and 14% yields, respectively).

(11) Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149−151.

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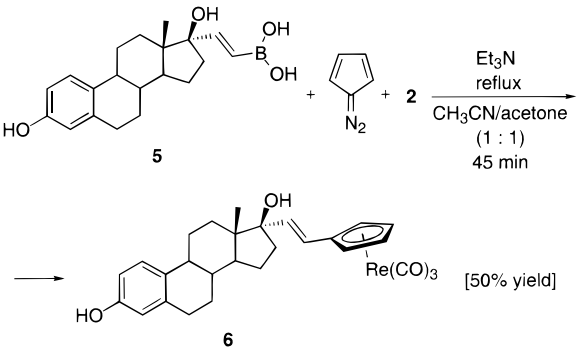
Table 1. Isolated Yields Attained in the Three-Component Reaction of Several Boronic Acids (**3a**−**e**, Scheme 1)[8]

				isolated yield (%)[a]	
entry	boronic acid	R	product	conditions A[b]	conditions B[c]
1	**3a**	phenyl	**4a**	64	59
2	**3b**	4-acetylphenyl	**4b**	34	52
3	**3c**	4-bromophenyl	**4c**	39	50
4	**3d**	4-methoxyphenyl	**4d**	74	42
5	**3e**[9]	1-nonenyl	**4e**	51	76

[a] Yields are based on compound **1**. [b] Conditions A: 10 equiv of boronic acid (**3a**−**e**) and 20 equiv of Et_3N, with respect to the rhenium precursor **1** (Scheme 1), and 45 min reaction time. [c] Conditions B: 2 equiv of boronic acid, 4 equiv of Et_3N, and 14 h reaction time.

Scheme 2



that a higher nucleophilicity of the organometallic precursor is likely responsible for a faster reaction. Moreover, the use of a palladium species such as $Pd(PPh_3)_4$, which is indispensable in the Suzuki coupling of boronic acids,[7] has no effect whatsoever in our reaction. To our knowledge, this is the first example of an uncatalyzed carbon−carbon bond formation reaction involving boronic acids as precursors. We also found that a cyclic boronic ester, namely, 2-phenyl-1,3,2-dioxaborinane, which reacts readily under Suzuki conditions, is completely unreactive in our reaction, showing that the presence of a free boronic acid is essential for the three-component reaction to occur.[12]

As already observed in our previously reported reaction of carboxylates,[2] several functional groups are tolerated. The keto group in **3b** (entry 2) is not affected, and more importantly, the aryl-bromo functionality in **3c** (entry 3), which would be reactive in a Pd-catalyzed reaction, is completely inert. Alcohol and phenolic hydroxyl groups are also tolerated, as shown by the example reported below in Scheme 2.

Encouraged by these results, especially by the excellent reactivity of the vinylboronic acid **3e**[9] (entry 5, Table 1), we decided to try this reaction on compound **5** (Scheme 2),[13] an estradiol derivative containing a vinylboronic acid group in the 17α position.

The rhenium precursor **2**, prepared as shown in Scheme 1,[4] reacted in one pot with boronic acid **5** (5 equiv), Et_3N (10 equiv) and $C_5H_4N_2$ (3 equiv) in refluxing acetonitrile/acetone 1:1 mixture. After 45 min, complex **6** was obtained in 50% isolated yield following flash chromatography. In this case, the cosolvent (acetone) was needed because compound **5** was only partially soluble in pure acetonitrile.[14] A classical organometallic approach to **6** would have required protection/deprotection steps of the two OH groups. However, such additional steps turned out to be unnecessary in the reaction herein reported. An important side reaction, the protodeboronation of the excess of **5**, did occur, producing considerable amounts of 17α-vinylestradiol. Nevertheless, complex **6** could be efficiently purified by chromatography.[14]

In conclusion, the results presented in this report illustrate a marked extension of the three-component reaction toward the preparation of carbon-substituted $CpRe(CO)_3$ complexes, using a very accessible class of organometallic reagents, the boronic acids. The method herein reported is unique since it produces in one pot a carbon−carbon bond between a nucleophile and the Cp ring, in addition to the Cp−rhenium bond formation, without the need for any catalyst. Mild conditions, short times, and good yields suggest that this reaction should have great potential in the radiolabeling of biologically interesting molecules.

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Supporting Information Available: Purification conditions and characterization data of compounds **4a**−**e** and **6** (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) Some preliminary investigations on the reaction mechanism indicate that both carboxylic acids (ref 2) and boronic acids (present paper) react through an initial association between the rhenium precursor **2** (Scheme 1) and the nucleophile. More extensive studies aimed at clarifying the reaction mechanism are currently under investigation in our laboratories.

(13) Nakatsuka, I.; Ferreira, N. L.; Eckelman, W. C.; Francis, B. E.; Rzeszotarski, W. J.; Gibson, R. E.; Jagoda, E. M.; Reba, R. C. *J. Med. Chem.* **1984**, *27*, 1287−1291.

(14) When the reaction is run in pure acetonitrile under the same conditions, the isolated yield of complex **6** is much lower (27%). Use of cosolvents other than acetone either gave lower yield (36% yield with 2-butanone) or completely inhibited the reaction (~0% yield with methanol). Experimental procedure: Compound **1** (39 mg, 0.050 mmol) was dissolved in anhydrous CH_3CN (2 mL) and treated with 40 mg (0.15 mmol) of AgOTf. AgBr was removed by filtration, and the supernatant was added to a solution containing boronic acid **5** (0.25 mmol) and triethylamine (0.50 mmol) in acetone (2 mL). The resulting mixture was treated with $C_5H_4N_2$ (0.15 mmol), heated to reflux for 45 min, and then concentrated under vacuum. The crude reaction product was purified by flash chromatography (Hex/EtOAc/AcOH 75:25:0.2). See Supporting Information for characterization data on compound **6**.