Merry-Go-Round Multiple Alkylation on Aromatic Rings via Rhodium Catalysis

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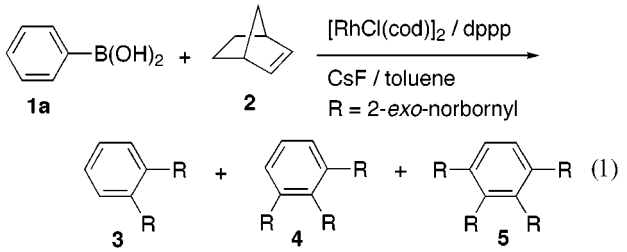
One of the most significant aspects of transition metal complexes is their ability to catalyze multistep reactions. Thus, these complexes may also mediate the continuous formation of multiple carbon−carbon bonds in a single process, and the development of such reactions, for example, domino or cascade sequences, has been the subject of intensive work in the area of transition metal catalysis.[1] We recently reported palladium-catalyzed multiple (two to five times) arylation reactions of aromatic substrates including phenols, aryl ketones, and metallocenes to give oligophenyl compounds. This sequence involves the coupling of intermediary arylpalladium species with aromatic carbons (via C−H cleavage) or with carbanionic species.[2] During the examination of other catalytic multisubstitutions on aromatics, we have found a "merry-go-round type" sequential alkylation that occurs up to four times on aromatic rings using rhodium catalysts and appears to involve a new, intriguing mechanism.

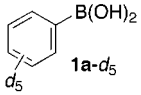
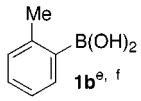
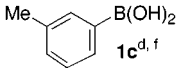
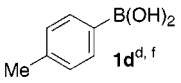
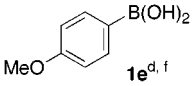
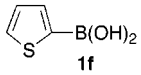
The present reaction employs arylboronic acids **1** and a strained alkene, 2-norbornene (**2**), in the presence of a rhodium catalyst and a base.[3,4] In a representative experiment, a mixture of phenylboronic acid (**1a**), **2** (7 equiv), $[RhCl(cod)]_2$ (1 mol %), dppp [1,3-bis(diphenylphosphino)propane] (2 mol %), and CsF (2 equiv) in toluene was heated at 100 °C for 2 h (eq 1 and Table 1). Analysis of the reaction mixture by GC and GC−MS indicated



that the corresponding 1:4 coupling product was formed predominantly with a selectivity of 80% along with minor amounts of 1:2 and 1:3 products, the total yield being 73%. No other coupling products were detected. Decreasing the amount of **2** to 3 equiv increased the relative amounts of the 1:2 and 1:3 products, enabling us to obtain each of them with ease. The ^1H NMR spectra displayed two to four characteristic aromatic protons confirming that they were 1,2-di-, 1,2,3-tri-, and 1,2,3,4-tetra(2-norbornyl)-benzenes (**3**−**5**), and each product was composed of stereoisomers due to the presence of an asymmetric carbon in the 2-norbornyl group. The IR absorptions due to aromatic C−H bending vibrations were consistent with these substitution patterns. The use of CsF was essential for the reaction to proceed efficiently. Cs_2CO_3 could also be used, but the total yield without any base was less than 5%. The reaction efficiency was also found to be a marked function of ligands used. Thus, the related bidentate phosphine, dppb [1,4-bis(diphenylphosphino)butane], was as effective as dppp, whereas monodentate ligands such as PPh_3 and PCy_3 gave poor yields.

To obtain some insight into the mechanism of this multiple alkylation, phenylboronic-d_5 acid (**1a**-d_5) was reacted with **2**. The yield and product distribution were only slightly affected by the deuteration. The mass spectrum of the tetraalkylated product confirmed that almost all the D atoms in **1a**-d_5 were preserved in the product (Chart 1, **5**-d_5). Its ^1H NMR spectrum indicated that one of the D atoms remained on the aromatic ring and an external hydrogen was introduced as the aromatic one. The other four D atoms were incorporated into the norbornyl substituents. When

Table 1. Reaction of Arylboronic Acids (**1**) with 2-Norbornene (**2**)[a]

1	total product yield[b] (%)	% select[b] (product) mono	di	tri	tetra
1a	73	-[c]	6 (**3**)	14 (**4**)	80 (**5**)
1a[d]	82	-	24	28	48
 **1a**-d_5	65	-	3	9	88 (**5**-d_5)
 **1b**[e, f]	66	4	13	78 (**6**)	5 (**7**)
 **1c**[d, f]	62	-	70 (**8**)	30 (**9**)	-
 **1d**[d, f]	42	-	100 (**8**)	0	-
 **1e**[d, f]	55	-	98 (**10**)	2	-
 **1f**	57	20	6	73 (**11**)	1

[a] Reaction conditions: [**1**]:[**2**]:[$[RhCl(cod)]_2$]:[dppp]:[CsF] = 1:7:0.01:0.02:2 (1 or 2 mmol of **1** was used); at 100 °C for 2 h under N_2. [b] Determined by GLC. Mono, di, tri, and tetra correspond to the numbers of introduced 2-norbornyl group. [c] Not detected. [d] With 3 equiv of **2**. [e] With 5 equiv of **2**. [f] At 135 °C (bath temp).

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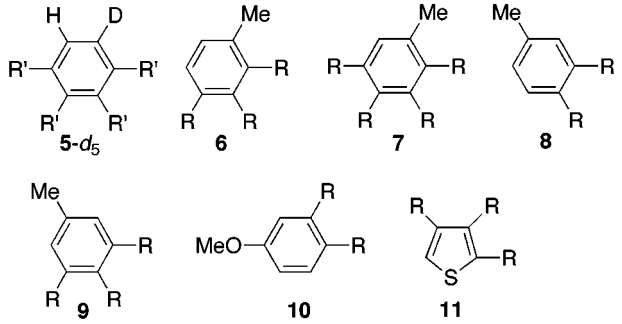
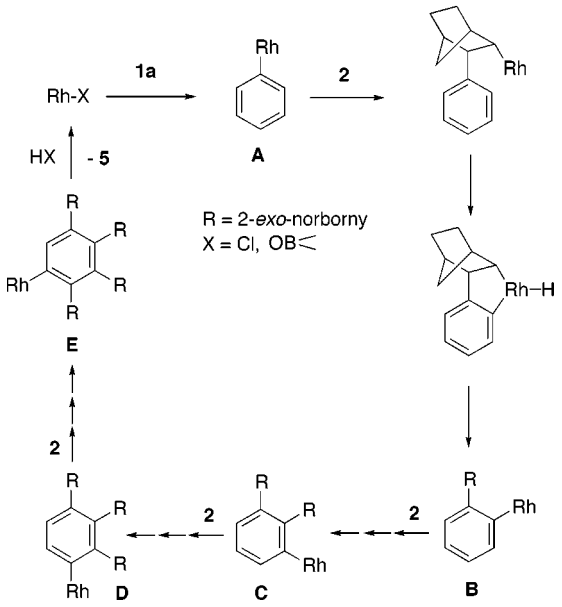
Chart 1. R = 2-*exo*-Norbornyl, R′ = 3-Deuterio-2-*exo*-norbornyl



Scheme 1



the product mixture obtained from the reaction of **1a** with 3 equiv of **2** was treated with $RuCl_3$−$NaIO_4$, which is known to selectively oxidize aromatic moieties of substituted arenes,[5] norbornane-2-*exo*-carboxylic acid was obtained as the single acidic product. Using **1a**-d_5 under the same reaction conditions gave 3-*exo*-deuterionorbornane-2-*exo*-carboxylic acid.

On the basis of the above results, a plausible mechanism for the formation of **5** is illustrated in Scheme 1. The first step may involve the generation of a phenylrhodium species (**A**) by transmetalation[3,6] which is enhanced by CsF.[7,8] Then, insertion of **2** into the phenyl-rhodium bond in an *exo*-fashion[9] followed by cyclorhodation via C−H cleavage and intramolecular reductive elimination gives 2-(2-norbornyl)phenylrhodium species **B**. Subsequently, the insertion-cyclorhodation-reductive elimination process occurs three times, resulting in tetraalkylation of the aromatic ring. The deuterium distribution in **5**-d_5 obtained using **1a**-d_5 supports the formation of the tetrasubstituted phenylrhodium species **E**. Protonolysis by the boronic acid species in the medium may occur in the termination step. The fact that no pentaalkylated product was detected may imply that further insertion of **2** into the final intermediate **E** is inhibited for steric reasons, and thus, the protonolysis is the predominant pathway. Using a reduced amount of **2**, the insertion and the protonolysis occur competitively in the dialkyl- and trialkylphenylrhodium intermediates **C** and **D** to produce **3**−**5** in a comparable yield. The lack of monoalkylated product is attributed to the fact that the insertion of **2** to **B** is extremely fast.

Other arylboronic acids **1b**−**f** are also multiply alkylated (Table 1 and Chart 1). 2-Methylphenylboronic acid (**1b**) was selectively trialkylated to yield 1-methyl-2,3,4-tri(2-norobornyl)benzene (**6**). Interestingly, the formation of a small, but meaningful, amount of tetraalkylated product (pentasubstituted benzene) **7** was observed. This may be due to the fact that the methyl group is relatively small compared to the norbornyl group. 2-Thienylboronic acid (**1f**) also afforded the corresponding trialkylated compound **11** as the predominant product. The reaction of 3-methylphenylboronic acid (**1c**) gave dialkylated product **8** preferentially together with trialkylated derivative **9**. 4-Methyl- and 4-methoxyphenylboronic acids, **1d** and **1e**, gave dialkylated compounds **8** and **10** almost exclusively.

The structures of compounds **6**−**11** are consistent with the sequential mechanism (not involving *o*′-substitution). The product distributions also imply that the alkylation can proceed continuously and selectively until hindered by steric factors. It should be noted that in the palladium-catalyzed dinorbonylation of bromo- and iodobenzenes, (a) successive double-insertion of the alkene into a phenylpalladium species followed by cyclopalladation,[4a,d] or (b) mono-insertion followed by cyclopalladation and the subsequent reaction with another halide molecule[4b,c] occurs selectively. A process leading to 2-alkylphenylpalladium species by protonolysis of the palladacycle in the latter course[10] is partially responsible for the observed products especially when 4-substituted halobenzenes are used.[4a−c] Therefore, the occurrence of sequential substitution appears to be particularly characteristic in rhodium catalysis.

In summary, we have found a new multiple alkylation reaction on aromatic rings which involves a mechanistically fascinating rhodium series of reactions. This sequence provides a straightforward method for the synthesis of a unique class of sterically encumbered aromatic molecules.[11] The scope and limitations as well as the applications of this reaction are under investigation in our laboratory.

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Supporting Information Available: Standard experimental procedure, oxidation method for mixture of **3**−**5**, and characterization data for compounds **3**−**11** (PDF). This material is available free of charge via the Internet at http://www.pubs.acs.org.

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