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ARTICLE TYPE

# Rhodium-Catalyzed Synthesis of Unsymmetrical Di(aryl/heteroaryl)methanes Using Aryl/Heteroarylmethyl Ketones via CO-C Bond Cleavage

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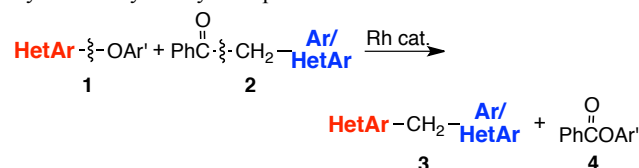
**RhH(PPh<sub>3</sub>)<sub>4</sub> and 1,2-bis(diphenylphosphino)benzene catalyze the reaction of aryl/heteroarylmethyl ketones and aryl heteroaryl ethers giving unsymmetrical diarylmethanes containing one or two heteroarenes in high yields. The reaction does not use alkali metal bases, and therefore does not form large amounts of metal waste.**

The di(aryl/heteroaryl) structure Ar-Ar is an important scaffold for drugs and materials, and the construction of its carbon framework has been extensively studied using the C-C coupling reactions between two aryl *sp*<sup>2</sup>-carbons.<sup>[1]</sup> In contrast, the di(aryl/heteroaryl)methane structure Ar-CH<sub>2</sub>-Ar, a carbon homolog, is much less common,<sup>[2]</sup> although it can be another important scaffold for functional organic molecules, characterized by a more flexible structure possessing two rotating *sp*<sup>2</sup>-C/*sp*<sup>3</sup>-C bonds. This may be due to the lack of efficient and versatile synthetic methods for constructing the structure.

The transition-metal-catalyzed synthesis of di(aryl/heteroaryl)methanes by the C-C bond formation between the *sp*<sup>2</sup>- and *sp*<sup>3</sup>-carbons is attractive, since various heteroaryl products can be obtained by changing the substrate structure. Generally, nucleophilic aryl/heteroarylmethylmetal reagents are reacted with aryl/heteroaryl compounds with halogen-leaving groups,<sup>[3]</sup> and, alternatively, electrophilic arylmethyl halides are reacted with metalated heteroarenes.<sup>[4]</sup> Both methods require the preparation of metalated heteroarenes or methylheteroarenes using stoichiometric amounts of metal, bases, or reducing reagents. Methods not using such stoichiometric metal reagents are rare for the synthesis of di(aryl/heteroaryl)methanes. Miura, Ackermann, and Fagnou reported the Pd-catalyzed reaction of heterocycles and substituted benzyl derivatives such as benzyl carbonates,<sup>[5]</sup> benzyl phosphates,<sup>[6]</sup> and benzyl chlorides<sup>[7]</sup> in the presence of Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, *t*-BuOLi, or NaOAc. Oshima and Yorimitsu reported a 2-pyridylmethyl transfer reaction from 2,4-dimethyl-3-(pyridin-2-ylmethyl)pentan-3-ol to aryl halides in the presence of Cs<sub>2</sub>CO<sub>3</sub>.<sup>[8]</sup> Liu reported the decarboxylative coupling of potassium 2-pyridylacetates or [2-benzoxa(thia)zoly]acetates with aryl halides.<sup>[9]</sup> The reactions entailed the C-C bond activation. Although these methods do not use stoichiometric organometal reagents, they use stoichiometric inorganic bases. In addition, the reactions have a limited scope in terms of the heteroaryl structure in the product because of the limited availability of a heteroarylmethyl component. Note that

very few examples of the synthesis of di(heteroaryl)methane were reported using the conventional methods either by the stoichiometric metal reagent methods<sup>[2b,2d,2e,4b,4d]</sup> or nonstoichiometric methods.<sup>[5,8,9]</sup>

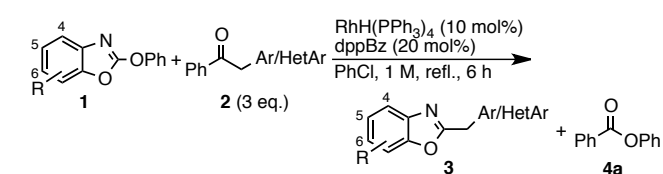
Previously, we reported rhodium-catalyzed acyl transfer reaction between benzyl ketones and thioesters/aryl esters, which entailed the CO-C bond cleavage of unstrained acyclic ketones.<sup>[10]</sup> Described in this study is the rhodium-catalyzed synthesis of unsymmetrical di(aryl/heteroaryl)methanes **3** by the reaction of aryl heteroaryl ethers **1** and aryl/heteroarylmethyl ketones **2** (Scheme 1). This reaction proceeds via the cleavage of the C-O bond of **1** and the CO-C bond of **2**, and C-C bond formation gives **3** containing one or two heteroaryl groups. This method, unlike conventional methods, does not use any alkali metal base, and accordingly large amounts of metal waste are not formed. A wide range of electron-deficient/electron-rich five/six-membered heteroaryl ethers **1** such as 2-benzoxazolyl, 2-benzothiazolyl, 2-thiazolyl, 2-oxazolyl, 2-thienyl, 2-furyl, 2-pyridyl, 4-quinazoliny, and 2-triazyl derivatives were employed. Heteroarylmethyl groups containing 4-pyridyl, 2-benzothiazolyl, 2-thienyl, and 2-furyl groups could be attached to the heteroarene cores. The broad scope of this reaction, which provides various diarylmethanes **3** having one or two heteroarenes, is due to the use of stable substrates for both heteroaryl and aryl/heteroarylmethyl components.

<sup>75</sup> Scheme 1.

When phenyl 2-benzoxazolyl ether **1a** was reacted with benzyl phenyl ketone **2a** (3 equiv) in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub> (10 mol%) and 1,2-bis(diphenylphosphino)benzene (dppBz, 20 mol%) in refluxing chlorobenzene for 6 h, 2-benzylbenzoxazole **3a** and phenyl benzoate **4a** were obtained in 77% and 76% yields, respectively (Table 1, entry 1). No reaction occurred in the absence of the rhodium complex or dppBz. When the molar ratio **2a/1a** was changed from 3 to 2, the yields of **3a** and **4a** decreased to 43% and 43%, respectively. *p*-Chlorophenyl and *p*-methoxyphenyl 2-benzoxazolyl ethers reacted to form **3a** in

moderate yields. The yield of **3a** decreased using phenyl 2-benzoxazolyl thioether, and 2-ethoxy-, 2-methylthio-, 2-chlorobenzoxazole, and benzoxazole did not react under the conditions: The leaving ability appears to be not directly related to the yield of **3a**. Substituted benzyl ketones with either *p*-electron-donating or *p*-electron-withdrawing groups gave aryl 2-benzylbenzoxazoles (entries 2-6). Octyl *p*-cyanophenylmethyl ketone underwent *p*-cyanophenylmethylation (entries 4 and 6). Benzoxazolyl ethers bearing methyl, phenyl, or chloro substituents on the benzene ring could be reacted to form *p*-cyanobenzylloxazole derivatives in high yields (entries 7-12). The reaction was also applicable to heteroarylmethyl ketones containing 4-pyridylmethyl, 2-benzothiazolylmethyl, 2-thienylmethyl, and 2-furylmethyl groups (entries 13-16). This method can transfer heteroarylmethyl groups to aryl heteroaryl ethers, giving various unsymmetrical di(heteroaryl)methanes. Note that heteroatom chelation is not critical for the CO-C bond cleavage, as indicated by the reaction of the substituted benzyl and 4-pyridylmethyl ketones.

**Table 1.** Rhodium-catalyzed aryl/heteroarylmethylation of phenyl 2-benzoxazolyl ethers.

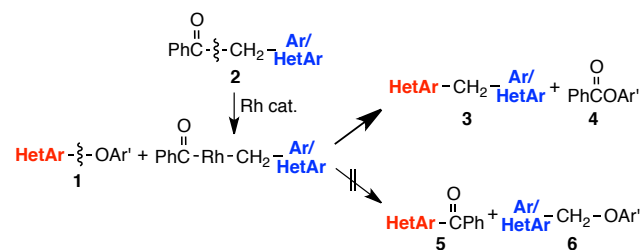


| Entry | R    | Ar/HetAr  | Yield of <b>3</b> /%  |
|-------|------|---|---|
| 1     | H    | Ph  | 77 <sup>a</sup> , 41 <sup>b</sup> , 57 <sup>c</sup> , 23 <sup>d</sup> |
| 2     | H    | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>                | 51  |
| 3     | H    | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>                 | 45  |
| 4     | H    | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>                 | 80, 50 <sup>e</sup>   |
| 5     | H    | <i>p</i> -EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> | 72  |
| 6     | H    | <i>p</i> -NCC <sub>6</sub> H <sub>4</sub>                 | 90, 73 <sup>e</sup>   |
| 7     | 4-Me | <i>p</i> -NCC <sub>6</sub> H <sub>4</sub>                 | 90  |
| 8     | 5-Me | <i>p</i> -NCC <sub>6</sub> H <sub>4</sub>                 | 85  |
| 9     | 5-Cl | <i>p</i> -NCC <sub>6</sub> H <sub>4</sub>                 | 74  |
| 10    | 5-Ph | <i>p</i> -NCC <sub>6</sub> H <sub>4</sub>                 | 61  |
| 11    | 6-Me | <i>p</i> -NCC <sub>6</sub> H <sub>4</sub>                 | 89  |
| 12    | 6Cl  | <i>p</i> -NCC <sub>6</sub> H <sub>4</sub>                 | 78  |
| 13    | H    | 4-pyridyl   | 83  |
| 14    | H    | 2-benzothiazolyl  | 70  |
| 15    | H    | 2-thienyl   | 70  |
| 16    | H    | 2-furyl   | 36  |

<sup>a</sup> Phenyl benzoate **4a** was also obtained in 76% yield. <sup>b</sup> *p*-Chlorophenyl 2-benzoxazolyl ether was used. <sup>c</sup> *p*-Methoxyphenyl 2-benzoxazolyl ether was used. <sup>d</sup> Phenyl 2-benzoxazolyl thioether was used. <sup>e</sup> Octyl *p*-cyanophenylmethyl ketone was used.

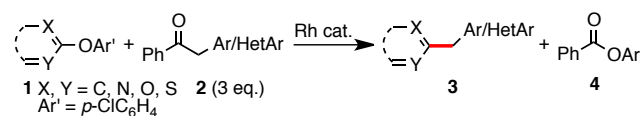
The rhodium catalyst activates the C-O bond of phenyl heteroaryl ethers **1** and the CO-C bond of aryl/heteroarylmethyl ketones **2** providing the product **3** with the concomitant formation of aryl esters **4**. As noted before, the catalysis can directly cleave the CO-C bond.<sup>[10]</sup> Although the mechanism of C-O bond cleavage is not clear, oxidative addition of **2** to low-valent rhodium complex is assumed (Scheme 2). It may also noteworthy that the reaction gave **3** and **4** but not heteroaryl ketones **5** and aryl aryl/heteroarylmethyl ethers **6**, the other mode of the C-O/C-

C metathesis reaction. It may be governed by the thermodynamic stability of the products.



**Scheme 2.**

**Table 2.** Rhodium-catalyzed aryl/heteroarylmethylation of aryl heteroaryl ethers.



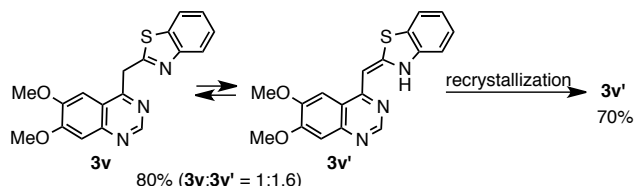
|                                       |                       |                                   |
|---------------------------------------|-----------------------|-----------------------------------|
| <b>3b</b> R = H 75%, 26% <sup>a</sup> | <b>3e</b> R = H 82%   | <b>3g</b> 72%                     |
| <b>3c</b> R = Cl 66%                  | <b>3f</b> R = Ph 93%  |                                   |
| <b>3d</b> R = MeO 60%                 |                       |                                   |
| <b>3h</b> 45%                         | <b>3i</b> R = H 32%   | <b>3k</b> 70%                     |
| <b>3j</b> R = Ph 62%                  |                       |                                   |
| <b>3l</b> R = CH <sub>3</sub> CO 51%  | <b>3m</b> R = CN 35%  | <b>3n</b> 76%                     |
| <b>3o</b> 53%                         |                       |                                   |
| <b>3p</b> 31%                         | <b>3q</b> 62%         | <b>3r</b> 63%                     |
| <b>3s</b> R = H 87%                   | <b>3t</b> R = MeO 80% | <b>3u</b> 65%                     |
| <b>3v</b> X = S 64%                   | <b>3y</b> 89%         | <b>3z</b> 72%                     |
| <b>3x</b> X = O 22%                   |                       | ( <b>3v</b> : <b>3v'</b> = 1:1.6) |

<sup>a</sup> Phenyl 2-benzothiazolyl ether was used.

The reaction was applicable to various 1,3-azoles other than benzoxazoles (Table 2). The *p*-cyanophenylmethylation of 2-benzothiazolyl ethers proceeded in a higher yield using the 2-(*p*-chlorophenoxy) derivative (75%) than using the 2-phenoxy derivative (26%). Benzothiazoles bearing 5-chloro or 5-methoxy substituents could be transformed to the corresponding products **3c** and **3d** in high yields, respectively. *p*-Chlorophenyl ethers containing 1,3-oxazolyl, 1,3-thiazolyl, and 1,3,4-oxadiazolyl

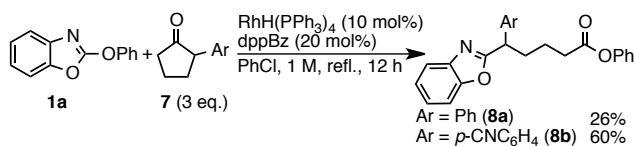
groups reacted with aryl/heteroaryl methyl ketones, and the corresponding products **3e-3k** were obtained. *p*-Chlorophenyl 2-furyl ether and 2-thienyl ether also gave the aryl/heteroarylmethylation products **3l-3p**. The reaction was applied to the synthesis of the *N*-heterocyclic six-membered ring compounds **3q-3z** containing 2-pyridyl, 4-quinazolyl, and 2-triazyl groups. The broad applicability of the rhodium-catalyzed reaction enabled the synthesis of various di(aryl/heteroaryl)methanes.

Note that **3v** equilibrated with the enol form **3v'** (**3v:3v'** = 1:1.6), and recrystallization from CHCl<sub>3</sub> gave pure **3v'** in 70% isolated yield (Scheme 3). Such enolization of diheteroaryl methane has not yet been reported.<sup>[11]</sup>



Scheme 3.

The reaction was applied to a 2-aryl cyclic ketone giving a (heteroaryl)arylmethane with an alkyl substituent at the benzylic position (Scheme 4). The reaction of phenyl 2-benzoxazolyl ether **1a** with 2-(*p*-cyanophenyl)cyclopentanone **7b** gave 1-(2-benzoxazolyl)-1-(*p*-cyanophenyl)pentanoic phenyl ester **8b** in 60% yield.



Scheme 4.

In summary, RhH(PPh<sub>3</sub>)<sub>4</sub> and dppBz catalyze the aryl/heteroarylmethylation of aryl heteroaryl ethers **1** using aryl/heteroaryl methyl ketones **2**, and various di(aryl/heteroaryl)methanes **3** are produced from such a reaction. The reaction entails the C-O bond cleavage of **1** and the CO-C bond cleavage of **2** with concomitant C-C bond formation. The broad applicability of this method is due to the use of stable substrates for both heteroaryl and heteroarylmethyl components. Also note that the chelation of the metal catalyst with the heteroarene is not required for the cleavage of the CO-C bond in the substrates. The nonuse of an alkali metal base is another advantage of this reaction. This catalytic process provides a straightforward synthetic method for unsymmetrical diarylmethanes with one or two heteroaryl groups, which are interesting for both medicinal and material applications.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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