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First Synthesis of *β*-Keto Sulfoxides by a Palladium-Catalyzed Carbonylative Suzuki Reaction

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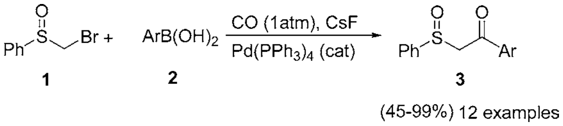
ABSTRACT



An unprecedented palladium-catalyzed three-component cross-coupling reaction between α-bromo sulfoxide, carbon monoxide, and aromatic boronic acids provides a new and efficient approach to the synthesis of *β*-ketosulfoxides. The reaction takes place under mild conditions with a wide range of variously substituted aryl and heteroaryl boronic acids. The carbonylative cross-coupling reaction is strongly favored over competing direct cross-coupling and homocoupling processes, except with boronic acids carrying strong electron-withdrawing substituents.

The cross-coupling reaction is considered one of the most straightforward and general methods for the formation of carbon−carbon bonds.[1] In this area, the transition-metal-catalyzed three-component cross-coupling reaction between organometallic reagents, carbon monoxide, and organic halides is now considered a useful tool for ketone synthesis.[2] Aryl, 1-alkenyl, 1-alkynyl, allyl, benzyl, and alkyl halides have been shown to be suitable electrophiles for this carbonylative cross-coupling reaction.[3] *β*-Hydride elimination associated with alkyl halides with an sp^3 carbon containing *β*-hydrogens does not proceed in the carbonylation reaction because the insertion of carbon monoxide produces the corresponding acylpalladium(II) halides. While various organometallic reagents including magnesium,[4] aluminum,[5] silicon,[6] tin,[7] and boron derivatives[8] have been reported to undergo carbonylative coupling, organoboron reagents, which are generally nontoxic and thermally, air-, and moisture-stable, offer an obvious practical advantage compared to other cross-coupling processes. Due to these advantages, the Suzuki palladium-catalyzed cross-coupling reaction of organoboron reagents with organic halides or pseudohalides to form biaryl derivatives has emerged over the past two decades as an extremely powerful tool in organic synthesis.[9] The palladium-catalyzed three-component cross-coupling of aryl halides, carbon monoxide, and aromatic boronic acids, which is closely related to the Suzuki reaction, also provides convenient access to diaryl ketones.[10] However, the main drawback of the carbonylative Suzuki reaction often lies in the formation of significant amounts of the direct coupling

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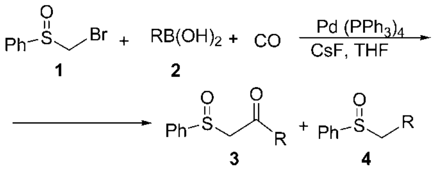
product without carbon monoxide insertion, particularly with electron-deficient aryl halides.

We have recently described a novel Suzuki-Miyaura cross-coupling reaction of α-bromo sulfoxides with aromatic boronic acids.[11a,b] While the usual procedure allows the formation of Csp^2-Csp^2 bonds through the Suzuki cross-coupling reaction, the procedure described by us yields the much less usual[11c−e] formation of a Csp^3-Csp^2 bond. We report here the new palladium-catalyzed three-component cross-coupling of α-bromo sulfoxides, carbon monoxide and aromatic boronic acids. Our present report widens the scope of the palladium-catalyzed carbonylative Suzuki reaction, since for the first time we show that α-bromo sulfoxides are suitable electrophiles for this type of reaction. In addition, this method represents a new approach for the synthesis of β-keto sulfoxides. Three general methods have been reported in the literature for the synthesis of β-keto sulfoxides, namely, i) the reaction of α-sulfinyl anions derived from sulfoxides with esters or nitriles,[12] ii) the oxidation of β-thioethers,[13] and iii) the addition of ketone enolates to sulfinate esters.[14] The first method is used most often, in particular for the synthesis of chiral acyclic β-keto sulfoxides, which are widely used in asymmetric synthesis.[15] Although the synthesis of many enantiomerically pure β-keto sulfoxides has been reported using this method, a major drawback is that only a moderate conversion of the substrate can be achieved due to quenching of the α-sulfinyl anion by the reaction product present in the medium, in addition to limitations in the number of functional groups compatible with the organolithium reagents. Thus, the development of alternative methods of synthesis to overcome these limitations should be of major interest.

An initial experiment was performed with α-bromo sulfoxide **1**, phenyl boronic acid **2a**, CsF and Pd(PPh$_3$)$_4$ (10% mol) as a catalyst under an atmospheric pressure of carbon monoxide (balloon) (Scheme 1).[16] The reaction took place to completion after 2 h and the corresponding keto sulfoxide **3a** was isolated in 80% yield (Table 1, entry 1). Formation of the expected side products, i.e., benzyl sulfoxide **4a** arising from the direct cross-coupling reaction without carbonyl insertion, diphenyl arising from the homocoupling reaction of **2a**, benzophenone resulting from the carbonylative homocoupling reaction of the boronic acid **2a**, and the sulfoxide resulting from dehalogenation, was not significant. The reaction took place under conditions that are considered unfavorable for the carbonylative cross-coupling of aryl halides. In particular, the reaction took place at moderate temperatures under atmospheric pressure, in contrast to the carbonylative cross-coupling reaction of aryl halides in which high temperatures and an overpressure of carbon monoxide are needed to promote the insertion process. The best

Scheme 1



2	R	**2**	R
a	C$_6$H$_5$	**i**	2-CF$_3$C$_6$H$_4$
b	4-MeOC$_6$H$_4$	**j**	3-CH$_3$COC$_6$H$_4$
c	3-MeOC$_6$H$_4$	**k**	3-NO$_2$C6H4
d	2-MeOC$_6$H$_4$	**l**	3-thienyl
e	2-MeC$_6$H$_4$	**m**	2-thienyl
f	4-BrC$_6$H$_4$	**n**	Me
g	2-BrC$_6$H$_4$	**o**	Bu
h	4-CF$_3$C$_6$H$_4$		

Table 1. Palladium-Catalyzed Three-Component Suzuki Cross-Coupling

				yields[a] (%)	
entry	**2**	R	*t* (h)	**3**	**4**
1	**a**	C$_6$H$_5$	3	80[b]	0
2	**b**	4-MeOC$_6$H$_4$	2	95	0
3	**c**	3-MeOC$_6$H$_4$	2	88[b]	0
4	**d**	2-MeOC$_6$H$_4$	2	85[b]	0
5	**e**	2-MeC$_6$H$_4$	2	88[b]	0
6	**b**	4-MeOC$_6$H$_4$	3	93[c]	0
7	**f**	4-BrC$_6$H$_4$	3	54	9
8	**g**	2-BrC$_6$H$_4$	3	45[b]	0
9	**h**	4-CF$_3$C$_6$H$_4$	3	77	23
10	**i**	2-CF$_3$C$_6$H$_4$	3	33[b]	0
11	**j**	2-CH$_3$COC$_6$H$_4$	3	0	0
12	**k**	3-NO$_2$C$_6$H$_4$	3	55[b]	0
13	**l**	3-thienyl	1	99	0
14	**m**	2-thienyl	3	72	0
15	**n**	Me	15	5[d]	0
16	**o**	Bu	18	0	0

[a] Isolated yields. [b] Conversion > 95% calculated from reacted sulfoxide **1**. [c] 5 Mol % of catalyst used. [d] Detected by ^{1}H-NMR.

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(16) **Representative Procedure.** A mixture of α-bromo sulfoxide **1** (0.4 mmol), boronic acid **2** (0.8 mmol), CsF (1.6 mmol), and Pd(PPh$_3$)$_4$ (0.04 mmol) was added to a flask fitted with a reflux condenser and a septum inlet. The flask was flushed with carbon monoxide and then charged with THF (6 mL). The mixture was stirred at 60 °C under an atmospheric pressure of carbon monoxide. After the appropriate reaction time, the mixture was cooled at room temperature, quenched with water (10 mL), and extracted with diethyl ether (2 × 15 mL) and dichloromethane (3 × 15 mL). The combined organic extracts were dried with Na$_2$SO$_4$ and evaporated under reduced pressure.

palladium-to-ligand ratio (1:4) for the three-component coupling with the α-bromo sulfoxide **1** is unusual among carbonylative reactions with aryl halides. With these compounds, deviation from a 1:2 ratio reduces the activity of the catalyst since the coordination sphere of palladium is likely to be too hindered to allow good activity. These facts prompted us to perform a survey of the reaction with a series of representative boronic acids (Table 1). Aryl boronic acids **2b**−**e** substituted with electron-donating groups (Table 1, entries 2−5) were found to be very active in the carbonylative cross-coupling. The position of the electron-donating group in the aromatic ring did not induce noticeable differences in the chemoselectivity or extent of conversion (Table 1, entries 2−5). Thus, good yields were obtained with the relatively hindered o-substituted boronic acids **2d** and **2e** (Table 1, entries 4 and 5). Significant amounts of side products were not detected in any case. Aryl boronic acids substituted with electron-donating groups gave the corresponding keto sulfoxides **3b**−**e** in high yields after short reaction times.

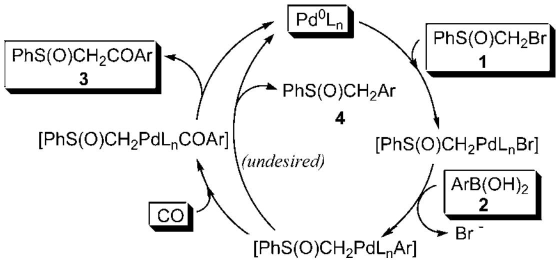
When the amount of catalyst was reduced to 5 mol %, boronic acid **2b** reacted to completion after 3 h (Table 1, entry 6). Reactions were complete much faster in the case of carbonylative cross-coupling than in the case of direct cross-coupling of related substrates, consistent with the known effect of carbon monoxide in accelerating reductive elimination.[17] Aryl boronic acids bearing an electron-withdrawing group in the aromatic ring **2f**−**k** (Table 1, entries 7−12) were less reactive than the parent **2a** or electron-rich aryl boronic acids **2b**−**e**. Therefore, the carbonylation reaction proceeded more slowly and the corresponding keto sulfoxides **3f**−**i** and **3k** were produced in moderate yields. The chemoselectivity for the carbonylative cross-coupling was still favored, but the selectivity progressively decreased as the electron-attracting character of the para substituent in the aryl boronic acid increased (see Table 1, entries 7 and 9). However, the presence of a meta substituent with strong electron-attracting character did not favor the formation of the direct coupling product **4**. Nevertheless, the yield of carbonylative product **3k** was only moderate in this case (Table 1, entry 12).

The carbonylative Suzuki reaction failed with 2-acetylphenyl boronic acid and **2j** (Table 1, entry 11) and proceeded slowly with 2-trifluoromethylphenyl boronic acid (**2i**) (Table 1, entry 10). The finding that the *o*-acetyl and *o*-trifluoromethyl groups, respectively, precluded or retarded the reaction seems to be related to the coordinating ability of the substituent (acting as a ligand) and not to electronic or steric effects. In fact, the reaction took place with other ortho-substituted boronic acids such as **2d**, **2e**, and **2g** which lack heteroatoms or carry heteroatoms in a position that does not allow coordination with the metal (Table 1, entries 4, 5, and 8). Hence, the deceleration or inhibition of the reaction may be related to the presence of fluorine or oxygen atoms that might occupy a place in the coordination sphere of the metal. The required displacement of one ligand for carbon monoxide in the square-planar plane to form a four-coordinate *cis*-carbonyl species before the migration step becomes more difficult.[18]

Even the absence of a direct cross-coupling product can be explained by the same effect, since coordination of the acyl group of the boronic acid might hinder the reductive elimination step. Heteroaryl boronic acids **2l** and **2m**, which had failed to give the direct cross-coupling reaction,[11] reacted under carbonylative conditions to give the corresponding *β*-keto sulfoxides (Table 1, entries 13 and 14). The behavior of boronic acid **2l** was similar to that observed for electron-rich aryl boronic acids, whereas **2m** behaved like an electron-poor aryl boronic acid. Alkyl boronic acids **2n** and **2o** were also tested but unfortunately failed to give the carbonylative Suzuki reaction product (Table 1, entries 15 and 16). In the reaction of **2n**, small amounts of the corresponding product **3n** were detected by NMR analyses of the crude reaction mixture.

The results obtained in the present carbonylative Suzuki reaction are likely not due to the following usually proposed catalytic cycle: Oxidative addition of the organic halide to palladium(0) (step 1), migratory insertion of carbon monoxide (step 2), transmetalation of the arylboronic acid (step 3), and reductive elimination (step 4). However, if it is assumed to occur through a permutation of steps 2 and 3, i.e., carbon monoxide insertion takes place after transmetalation, the experimental results are nicely explained. In fact if carbon monoxide insertion did occur in the second step after oxidative addition, we should expect that a change in the electronic properties of the boronic acid would not produce any significant difference in the selectivity of the carbonylative Suzuki product compared to the direct cross-coupling reaction. Moreover, the carbonylative cross-coupling product should be favored with substituted boronic acids with electron-attracting groups, since in this case transmetalation (third step) is slow and accordingly the competitive direct Suzuki coupling is hindered (Scheme 2).

Scheme 2



By the usual mechanism in our case, the carbonylative cross-coupling should be favored for boronic acids bearing electron-attracting groups, which is just the opposite of the experimental results. Conversely, if carbon monoxide insertion takes place after transmetalation, the aryl group can play

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a role in controlling carbon monoxide insertion. It is known from the carbonylative Suzuki reaction of aryl halides that carbon monoxide insertion occurs faster with electron-rich aryls than with aryl groups with electron-withdrawing substituents. Thus, direct cross-coupling without carbon monoxide insertion is easier with electron-poor aryls, and the selectivity for the carbonylative coupling decreases. We observed the same trend with the different boronic acids assayed. As a consequence, it appears that carbon monoxide insertion is also controlled by an aryl group, but now the aryl group is provided by the boronic acid. Consequently, the hypothesis that insertion occurs after transmetalation accounts for our experimental results.

In conclusion, we have described the first example of a palladium-catalyzed three-component cross-coupling reaction with α-bromo sulfoxides as electrophiles. The reaction takes place under very mild conditions and with high selectivity for a wide range of boronic acids. This method does not require an overpressure of carbon monoxide or special palladium ligands. The mildness of the reaction conditions allows us to obtain β-keto sulfoxides containing functional groups such as $-NO_2$ that would not be available using alternative procedures from the literature such as the addition of the lithium α-sulfinyl anion to esters. Thus, a wide array of β-keto sulfoxides or sulfinyl aromatic ketones functionalized in the ketone ring are readily available. Concerning the reaction mechanism of the carbonylative Suzuki cross-coupling reaction with α-bromo sulfoxides, a modification of the textbook catalytic cycle seems to be necessary for these substrates to account for the results obtained with different aryl and heteroaryl boronic acids. Hence, the chemoselectivity between carbonylative cross-coupling products and direct cross-coupling products in the reaction of α-bromo sulfoxides seems to depend on the electronic character of the aryl group present in the palladium complex. The influence of the aryl group on the control of the migratory insertion of carbon monoxide suggests that this process might occur after the transmetalation step. Thus, the established sequence for the catalytic cycle that explains the carbonylative cross-coupling reactions of aryl halides might be different in the case of α-bromo sulfoxides.

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Supporting Information Available: Experimental details for the synthesis and characterization of compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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