ORGANIC LETTERS

2013
Vol. 15, No. 13
3230–3233

# Programmed Selective $sp^2$ C–O Bond Activation toward Multiarylated Benzenes

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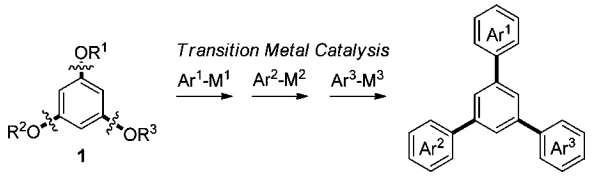
**Received April 26, 2013**

## ABSTRACT




**A variety of important multiarylated benzenes were efficiently synthesized from phloroglucinol derivatives 1 through sequential cross-couplings via Pd-catalyzed C–OTs, Ni-catalyzed C–OC(O)NEt$_2$, and C–OMe bond activation. High selectivity was achieved based on the rational design and inherent diversity in the reactivity of different C–O bonds.**

Multiarylated arenes are important motifs in materials science[1] and drug discovery.[2] Much attention has been paid by chemists to developing synthetic methods toward this motif for a long time. To achieve the multiarylated structures bearing different substituted aryl groups, various kinds of strategies have been established during the last several decades.[3] Among those, transition-metal-catalyzed cross-coupling reactions have been proven to be one of the most powerful tools to construct such structures.[4–7]

The sequential selective cross-coupling reaction is a quite useful method to construct multiarylated arenes. There are mainly two strategies to realize high selectivity. One is

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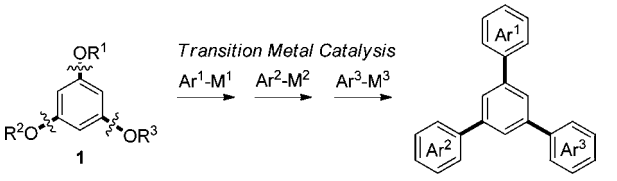
10.1021/ol4011757 
**Published on Web 06/21/2013**

chemoselective activation of different C−X bonds, and another is regioselective activation of one kind of C−X bond. Using the former strategy, our group reported an example to synthesize triarylated benzene with sequential transition-metal-catalyzed activation of C−Cl, C−CN, and C−OMe bonds.[4] With the latter strategy, several groups have developed various methods to synthesize multiarylated arenes and heteroarenes. For example, Miller and co-workers reported a regioselective C−Br bond activation and cross-coupling to construct enantiomerically enriched multiarylated poly arenes.[5]

Due to the high step-economy and atom-economy, direct arylation of aryl C−H bonds became more powerful to synthesize various biaryls. Moreover, multiarylation of aryl C−H bonds has been also realized by many groups. For example, Gaunt and co-workers realized one example of synthesis of multiarylated aniline derivative through copper-catalyzed sequential C−H bond activation.[6] Itami and co-workers developed a sequential palladium-catalyzed cross-coupling to synthesize multiarylated thiophenes via C−H activation.[7] Recently, a sequential Pd-catalyzed arylation of imidazoles and thiazoles has also been reported by Murai and Shibahara.[8]

On the other hand, C−O bond activation has recently drawn much attention due to the easy availability, low toxicity, and environmental friendliness of oxygen-containing compounds.[9] Different types of C−O bonds, including those in sulfates,[10] phosphates,[11] esters,[12] ethers,[13] and even alcohols and phenols,[14] have been readily used as coupling partners. In these reports, the activities of various C−O bonds have been systematically studied. It is found that the reactivity of C−O bonds could be very different and largely depends on the nature of the O-containing leaving group. On the basis of this feature, a substrate containing several different C−O bonds with distinguishable reactivities could be selectively applied to construct multiarylated arenes. Moreover, polyphenols exist widely in nature and are one of the most important structures in biomass. To our knowledge, the synthesis of important multiarylated arenes using commercially available and inexpensive polyphenols as the starting materials has never been reported. Herein, we report a programmed synthesis of multiarylated benzenes via selective and sequential C−O bond activation of phloroglucinol derivatives (Scheme 1).

**Scheme 1.** Programmed Synthesis of Multiarylated Benzenes through Transition-Metal-Catalyzed Sequential $sp^2$ C−O Bond Activation




At the initial stage of the design of sequential activation of the C−O bond in polyphenols, there are two major

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challenges: low reactivity of C−O bonds and poor selectivity in C−O activation. Because of the strong electron-donating ability of most oxygen-containing groups, the C−O bond in polyphenol derivatives will be deactivated by other oxygen-containing substituents. The higher electron density on arenes also hampers the coordination with electron-rich low-valent transition-metal catalysts, which is proposed to lead to oxidative addition of C−O bond in many cases.[12k] Moreover, how to selectively cleave one C−O bond in the presence of other similar C−O bonds is also a big issue.

As is known, a variety of functional groups have been used to protect the aryl C−OH bond. According to the leaving ability of leaving groups and the bond strength, the aryl C−O bonds could be mainly categorized in three parts: (a) relatively less inert C−O bonds, including those in aryl triflates, arenesulfonates, phosphates, and mesylates; (b) inert C−O bonds, including those in carboxylates, carbonates, and carbamates; (c) highly inert C−O bonds, including those in aryl ethers and phenols themselves. Our design is to make use of the different reactivity of the diverse C−O bonds with diverse leaving groups in order to realize high selectivity. Moreover, the introduction of oxygen with electron-withdrawing groups, which always in accordance with the leaving group, would increase its own reactivity and reduce the inhibition to other C−O bonds. Furthermore, different kinds of coupling partners should be carefully chosen to reduce overcouplings.

Based on the rational design, we synthesized phloroglucinol derivative **1** with three kinds of C−O bonds from commercially available phloroglucinol dihydrate (see the Supporting Information).[15] With substrate **1** in hand, we tried the first arylation via C−OTs bond activation. Under the palladium-catalyzed Suzuki−Miyaura cross-coupling conditions, the tosyloxy group could perform as a good leaving group. The C−O bond of aryl carbamates as well as pivalates has been proven to be inactivate under Pd-catalyzed condition.[12k,n,o] The C−O bond of aryl ethers is tolerated under Pd conditions, too.[13i] After systematic optimization based on Buchwald's pioneering report,[16] we found that the reaction proceeded in $^t$BuOH with $Pd(OAc)_2$ as catalyst and XPhos as ligand. In this case, anhydrous $K_3PO_4$ performed as the best base.[17] Both electron-deficient and electron-rich arylboronic acids gave excellent yields. The carbamoyloxy and methoxy group remained in the first arylation, and the cleavage of these two C−O bonds was not observed (Scheme 2). However, due to the deactivation of the C-OTs bond by other two C−O bonds, a little bit higher temperature and longer reaction time were needed in contrast with previous work.[16]

The C−O bond of the carbamate moiety in compound **3** was further selectively activated and underwent Suzuki−Miyaura cross-coupling via nickel catalysis (Scheme 3). Several

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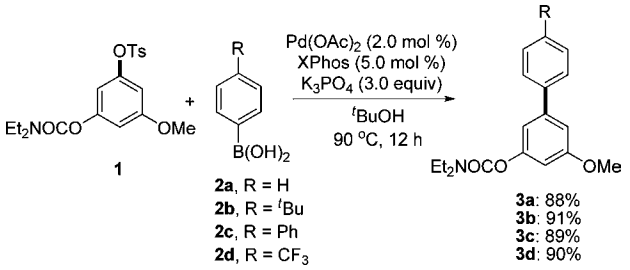
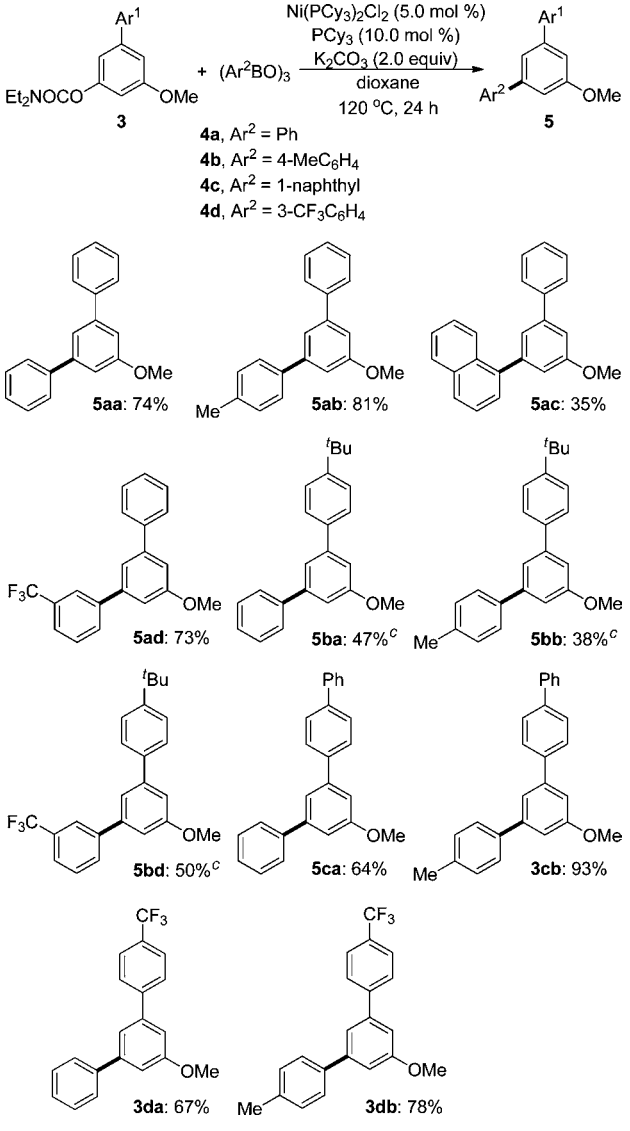
**Scheme 2.** First Step of Arylation via Pd-Catalyzed C−OTs Bond Cleavage



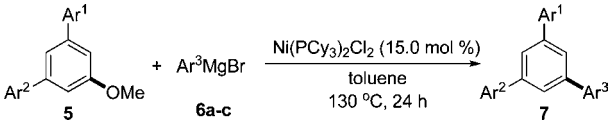

[a] All of the reactions were carried out on a scale of 0.2 mmol of **1** and 0.4 mmol of **2**. [b] Isolated yields.

**Scheme 3.** Second Step of Arylation via Ni-Catalyzed C−OC(O)NEt$_2$ Bond Cleavage[a,b]




[a] All of the reactions were carried out on a scale of 0.2 mmol of **3** and 0.24 mmol of **4**. [b] Isolated yields. [c] Conditions: 10 mol % of $Ni(PCy_3)_2Cl_2$, 20 mol % of $PCy_3$, 48 h.

**Table 1.** Third Step of Arylation via Ni-Catalyzed C–OMe Bond Cleavage[a,b]




| entry | substrate | $Ar^1$ | $Ar^2$ | $Ar^3$ | product and yield |
|---|---|---|---|---|---|
| 1 | **5aa** | Ph | Ph | Ph (**6a**) | **7aaa** (72%) |
| 2 | | | | 4-$^n$BuC$_6$H$_4$ (**6b**) | **7aab** (76%) |
| 3 | | | | 4-Me$_2$NC$_6$H$_4$ (**6c**) | **7aac** (77%) |
| 4 | **5ab** | Ph | 4-MeC$_6$H$_4$ | Ph | **7aba** (66%) |
| 5 | | | | 4-$^n$BuC$_6$H$_4$ | **7abb** (77%) |
| 6 | | | | 4-Me$_2$NC$_6$H$_4$ | **7abc** (70%) |
| 7 | **5ac** | Ph | 1-naphthyl | Ph | **7aca** (41%) |
| 8 | | | | 4-$^n$BuC$_6$H$_4$ | **7acb** (49%) |
| 9 | | | | 4-Me$_2$NC$_6$H$_4$ | **7acc** (47%) |
| 10 | **5ba** | 4-$^t$BuC$_6$H$_4$ | Ph | Ph | **7baa** (51%) |
| 11 | | | | 4-$^n$BuC$_6$H$_4$ | **7bab** (79%) |
| 12 | | | | 4-Me$_2$NC$_6$H$_4$ | **7bac** (65%) |
| 13 | **5bb** | 4-$^t$BuC$_6$H$_4$ | 4-MeC$_6$H$_4$ | Ph | **7bba** (68%) |
| 14 | | | | 4-Me$_2$NC$_6$H$_4$ | **7bbc** (67%) |
| 15 | **5ca** | 4-PhC$_6$H$_4$ | Ph | Ph | **7caa** (74%) |
| 16 | | | | 4-$^n$BuC$_6$H$_4$ | **7cab** (82%) |
| 17 | | | | 4-Me$_2$NC$_6$H$_4$ | **7cac** (80%) |
| 18 | **5cb** | 4-PhC$_6$H$_4$ | 4-MeC$_6$H$_4$ | Ph | **7cba** (56%) |
| 19 | | | | 4-$^n$BuC$_6$H$_4$ | **7cbb** (71%) |
| 20 | | | | 4-Me$_2$NC$_6$H$_4$ | **7cbc** (57%) |

[a] All of the reactions were carried out on a scale of 0.2 mmol of **5** and 0.6 mmol of **6**. [b] Isolated yields.

different conditions, which were developed by Garg, Snieckus, and our group, were tested.[18] It was found that our method[18b] gave the best results for this step with slight modification. This method showed good selectivity for the aryl carbamate moiety while keeping ether C–O bonds untouched.[12n–p,18a,18b] Starting from the biphenyl compounds **3a**–**d**, a variety of terphenyl derivatives **5** were synthesized in moderate to good yields. The substrates **3** with electron-withdrawing groups showed better reactivity than those with electron-donating groups. However, the electronic effect on arylboroxines is not significant. Applying 1-naphthylboroxine **4c** to the reaction would only give the corresponding product **5ac** in low yield, which may arise from low solubility.

Finally, the C–OMe bonds were cleaved and coupled with different aryl Grignard reagents **6a**–**c** in the presence of catalytic $Ni(PCy_3)_2Cl_2$ (Table 1).[19] Using this method, a variety of triarylated benzenes **7** with different functional groups were obtained in moderate to good yields. Due to the low reactivity, poor yields were often obtained for simple anisole substrates. In our reaction, diarylated anisoles **5** performed better due to the electron-withdrawing nature of aryl substituent. The existence of a naphthyl group would decrease the reactivity as well, probably because of the steric hindrance of naphthyl group.

In conclusion, we have developed a general strategy toward multiarylated benzenes via sequential sp$^2$ C–O bond activation of phloroglucinol derivatives. Based on the rational design and analysis of the reactivity of different kinds of C–O bonds, the fully protected phloroglucinol **1** with C–OTs, C–OC(O)NEt$_2$, and C–OMe bonds was synthesized and successfully applied in sequential cross-couplings. It is noteworthy that all of the three cross-couplings took place in high selectivity and good efficiency. Further utilization of this method to functionalize the polyphenol motif in natural products and drugs selectively is ongoing in this laboratory.

**Acknowledgment.** This work was supported by NSFC (No. 20925207, 21072010, 20821062) and the "973" Project from the MOST of China (2009CB825300).

**Supporting Information Available.** Experimental details and NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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