S,O-Ligand Promoted meta-C–H Arylation of Anisole Derivatives via Palladium/Norbornene Catalysis

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Abstract: Reversing the conventional site-selectivity of C–H activation processes provides new retrosynthetic disconnections to otherwise unreactive bonds. Here, we report a new catalytic system based on palladium/norbornene and an S,O-ligand for the meta-C–H arylation of aryl ethers that significantly outperforms previously reported systems. We demonstrate the unique ability of this system to employ alkoxyarene substrates bearing electron donating and withdrawing substituents. Additionally, ortho-substituted aryl ethers are well tolerated, overcoming the “ortho constraint”, which is the necessity to have a meta-substituent on the alkoxyarene to achieve high reaction efficiency, by enlisting novel norbornene mediators. Remarkably, for the first time the monoarylation of alkoxyarenes is achieved efficiently enabling the subsequent introduction of a second, different aryl coupling partner to rapidly furnish unsymmetrical terphenyls. Further insight into the reaction mechanism was achieved by isolation and characterization of some Pd-complexes—before and after meta C–H activation—prior to evaluation of their respective catalytic activities.

Introduction

Controlling the site-selectivity in C–H functionalization reactions is a major challenge given that the C–H bond is ubiquitous within organic molecules. In the last two decades, efficient and site-selective metal-catalyzed C–H functionalization reactions have been accomplished using directing groups (DGs). In recent years, alternative catalytic systems have been developed for the non-directed palladium-catalyzed C–H functionalization of arynes, greatly broadening the substrate scope beyond those bearing DGs. In the particular case of Pd-catalyzed C–H arylation reactions, in most of the cases, an excess of the arene is needed, hampering the applicability of these methodologies to substrates of increasing complexity, and directed Pd-catalyzed C–H arylation reactions remain challenging, with only few examples reported. Similar trend is also observed for other transition metals. Achieving selectivity in non-directed C–H functionalization reactions remains equally challenging. The majority of examples invoke site-selectivity that is predominantly controlled via electronic and steric effects, with functionalization occurring at the most electron rich or sterically accessible positions of the arene. Consequently, realizing complementary site-selectivity—favoring the functionalization at electron-deficient position—is a major challenge in the field. Beyond examples that use templates or traceless DGs to achieve reverse site-selectivity, only few methodologies using non-directed arenes have been reported, albeit with low levels of site-selectivity. A more general approach for reversing conventional site-selectivity has been enabled using palladium/norbornene (Pd/NBE) cooperative catalysis, known as the Catellani-type reaction. Although the first reports of C–H activation using the Pd/NBE strategy focused on substrates bearing DGs, in 2019 the meta-arylation of electron-rich alkoxyarenes was achieved by Yu and co-workers (Scheme 1a). In the same year, the group of Dong reported the direct vicinal difunctionalization of thiophenes using the Pd/NBE strategy. Following a similar approach, the functionalization of fluoroa arenes, simple arenes and five-membered heteroarenes at the less reactive (i.e. electron-deficient) site was achieved. Although these examples represent the current state-of-the-art for the palladium-catalyzed C–H functionalization of non-directed arenes for non-conventional site-selectivity, several drawbacks persist. In the particular case of electron rich alkoxyarenes, the main limitations of the methodology are: i) the use of super-stoichiometric amounts of NBE, ii) the lack of reactivity for substrates bearing electron-withdrawing substitutents, iii) the relatively low reactivity observed for aryl ethers bearing small ortho-substituents and iv) the impossibility to control the monoarylation of unsubstituted aryl ethers. The last two limitations are a consequence of the so-called “ortho constraint”, which is the necessity to have an ortho-substituent next to the first activated C–H bond to promote the NBE extrusion from the Pd-complex formed after the meta-C–H functionalization. Therefore, the development of a new catalytic system that overcomes the limitations for non-directed meta-C–H arylation of alkoxyarenes will be of great

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importance, given the ubiquity of this motif in natural products and pharmaceuticals.

Recently, our group has disclosed a new catalytic system based on Pd/S,O-ligand, capable of promoting Pd-catalyzed C–H functionalization reactions on a wide variety of arenes including simple arenes, thiophenes, anilines and anisoles.\[2e, 14\] A unique feature of the Pd/S,O-ligand system is its high catalytic activity, allowing for the functionalization of aniline and anisole derivatives bearing several electron-withdrawing substituents, substrates that are unreactive using other catalytic systems. Additionally, in 2022 the group of Jiao introduced unstrained olefin ligands that bear a S coordination site for use in the Pd-catalysed Catellani reaction.\[15\]

We hypothesized that by using our Pd/S,O-ligand catalytic system in conjunction with the appropriate choice of the NBE mediator\[13, 16\] could overcome the previously mentioned limitations for the meta-arylation of alkoxycarboxylic acids. Herein, we report a general and efficient C–H arylation of alkoxycarboxylic acids, bearing both electron donating and withdrawing substituents. Ortho-substituted alkoxycarboxylic acids are efficiently arylated by overcoming the ortho constraint through simple selection of the appropriate NBE mediator. Remarkably, the monoarylation of alkoxycarboxylic acids is efficiently achieved allowing, for the first time, the introduction of two different arylic coupling partners.

Results and Discussion

Initially, we applied the conditions reported for the meta-arylation of anisole derivatives\[8\] using anisole and methyl 4-iodobenzoate as model substrates in the presence of 15 mol% of Pd(OAc)\(_2\) and the S,O-ligand L1, previously used for the C–H olefination of anisoles.\[14e\] and 1.5 equiv of NBE N1 (Table 1). Under these conditions, we observed the formation of the meta-arylated product 3a in 20 % \(^1\)H-NMR yield. Next, modified norbornenes N2 (NBE-CO\(_2\)Me) and N3 (NBE-COHNMe), pioneered by the group of Yu\[3b\] and Dong,\[17\] respectively were evaluated in the reaction under previously mentioned conditions. The reaction using N2 and N3 afforded a mixture of mono- and diarylated products 3a in 39 % and 36 % \(^1\)H-NMR yield, respectively (Table 1a).

Following this, we evaluated the influence of the S,O-ligand in the reaction using N2 as a mediator (Supporting Information, Table S4). To our delight, the reaction using a slightly modified S,O-ligand L2, bearing a gem-dimethyl group in place of an isopropyl group, furnished 3a in 75 % \(^1\)H-NMR yield and a 1:1 ratio of mono- and diarylated products (Table 1b). The same reactions conditions employing 3-methyl anisole as a substrate provided the meta-arylated product 3b in quantitative yield. Encouraged by this result, we performed an exhaustive optimization of reaction conditions (Supporting Information, Table S5) enabling reductions in catalyst loading to 5 mol%, the use catalytic amounts of N2, decreased amounts of AgOAc and aryl iodide, while maintaining the quantitative yield for 3b (Table 1c). Additionally, further control experiments were performed.

**Table 1**: Selected optimization for meta-C–H arylation.

\[
\begin{align*}
\text{OMe} + \text{CO}_2\text{Me} &\rightarrow \text{Ar} \quad \text{OMe} + \text{Ar}^1 \rightarrow \text{Ar}^2
\end{align*}
\]

(a) Optimization of NBE using L1

(b) Optimization of ligand using N2

(c) Optimization with 3-methylanisole (N2/L2)

\[
\begin{align*}
\text{Pd(OAc)}_2\cdot\text{L2} &\rightarrow 15 \text{ mol\%} \quad 15 \text{ mol\%} \\
\text{R} &\rightarrow 3 \text{ equiv} \quad 1.5 \text{ equiv} \\
\text{AgOAc} &\rightarrow 3 \text{ equiv} \quad 1.5 \text{ equiv} \\
\text{Ac}_2\text{O} &\rightarrow 2 \text{ equiv} \quad 1.5 \text{ equiv} \\
\text{Temperature} &\rightarrow 95 \text{ °C} \quad 90 \text{ °C}
\end{align*}
\]

Control experiments

- w/o L2 10 % yield
- w/o N2 no product
- w/o AgOAc no conv.
performed to enable greater insight into the role of each reagent within the catalytic system. As expected, the reaction without the S,O-ligand dramatically reduced the yield of 3b to 10 %, highlighting the key role of this component in this transformation. Interestingly, the reaction without N2 did not provide 3b and only trace amounts of arylated anisole were detected, highlighting the crucial role of NBE not only to reverse the site-selectivity but also to enable the C–H arylation reaction. Moreover, no product was observed in the absence of AgOAc.\[10\]

With the optimized conditions in hand, the scope of meta-substituted anisole derivatives was evaluated (Table 2). Anisole derivatives with an OMe-, OCF3-, TMS-, and Ph-groups at the meta-position provided the desired meta-arylated products 3c–3f with excellent isolated yields (75–82 %) and perfect regioselectivity. Then, we moved our attention to anisoles bearing electron-withdrawing substituents, as they were demonstrated to be unreactive substrates in the previously reported methodology.\[8\] To our delight, the reaction with 3-fluoroanisole (1g) provided 3g in 79 % yield. When the reaction was performed with 3-chloroanisole (1h), only 18 % yield was obtained. However, upon substitution of N2 with 30 mol % NBE-CONHMe (N3), the yield improved to 73 %. Likewise, 3-substituted anisoles with CF3- and CO2Me-groups 1i–1j revealed low reactivity under standard reaction conditions. Nevertheless, after optimization, the meta-arylated products 3i and 3j were obtained in 52 % yield. In both cases, a higher amount of anisole substrate was needed to obtain these results (3.6 equiv of 1i and 2 equiv of 1j). Anisoles bearing other electron-withdrawing groups, such as NO2, were unreactive under the standard conditions (Supporting Information, Table S9). After demonstrating the generality of the methodology with meta-substituted anisoles, we studied the reaction using disubstituted anisoles. 2,3-Dimethoxy-, difluoro-, dichloro- and 3-chloro-2-methylanisoles 1k–1n were meta-arylated in good yields (57–88 %). Similar to the reaction with 3-chloroanisole (1h), the use of 30 mol % N3 provided the best result for the arylation of 2,3-dichloroanisole (1m). The reaction with 5-methoxytetralin (1o) and 7-methoxy-1-indanone (1p) furnished the arylated products 3o–3p synthetically useful yields (42–64 %). Additionally, we evaluated other successfully reported ligands for C–H functionalization reactions under the optimized reaction conditions utilizing 3-methylanisole (1b) and methyl 3-methoxybenzoate (1j) as substrates (Supporting Information, Tables S6 and S7). From all the ligands tested, the S,O-ligand L2 significantly outperformed the others, confirming the superiority of the Pd/S,O-ligand catalyst.

Next, we decided to explore the generality of the reaction with respect to the aryl halide employed, using 3-methylanisole (1b) as model substrate (Table 3). The starting point was iodobenzene affording the product 4a in a 75 % isolated yield. Electron-withdrawing substituents at the para-position of the aryl iodide, including F-, Br-, Ac- and NO2-, were well tolerated, affording the arylation products 4b–4e in 75–91 % isolated yields. A slightly lower yield of 64 % was obtained when using p-tolyl iodide and a moderate yield of 39 % was obtained when using 4-iodoanisole. Aryl iodides featuring a meta-chloro or trifluoromethyl group were also suitable coupling partners, affording the desired products in 83 % and 90 % isolated yields, respectively. Further evaluation of the reaction with the thiophene iodide derivative 2j afforded 4j in 47 % isolated yield. The ortho-substituted aryl bromides with coordinating functional groups that facilitate the oxidative addition (i.e., ester, nitro and amide)\[5d, 7c, 9\] were also compatible, providing the desired products 4k–4m in excellent yields. It is worth mentioning, that we also performed the reactions outlined in Table 2 and 3 without S,O-ligand, and in the vast majority of cases low yields or no product formation were observed, highlighting the key role of the S,O-ligand in the reaction.

Further evaluation of the reaction was performed with ortho-substituted anisoles (Table 4). Expectedly, the reaction with 2-methylanisole (5a) under the standard conditions, afforded the desired product in only 12 % 1H-NMR yield and 24 % yield using 10 mol % of catalyst. The lack of reactivity against ortho-substituted anisoles is the consequence of the ortho constraint (see above).\[5b, 12, 13\] Therefore, we decided to explore the effect of NBE modification with

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**Table 2: Scope of meta-substituted anisoles.**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>I</td>
<td>1b-p</td>
<td>5 mol % Pd(OAc)2</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>1.5 equiv AgOAc</th>
<th>0.4 M HFIP, 90 °C, 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b-p</td>
<td>Ar = meta-arylated</td>
</tr>
</tbody>
</table>

[1] Isolated yield. [2] 1H-NMR yield of the crude mixture using CH2Br2 as internal standard. [3] 10 mol % Pd(OAc)2/L2 was used. [4] 30 mol % NBE N3 instead of NBE N2 was used. [5] 3.6 equiv anisole 1i, 1.0 equiv aryl iodide 2, 20 mol %. [6] N2, 2 equiv AgOAc, 0.2 M HFIP, 70 °C, 48 h. [7] 2.0 equiv anisole 1j, 1.0 equiv aryl iodide 2, 48 h. N.P.: no product. w/o: without.

the goal of promoting β-carbon elimination. Modification of NBEs N2 and N3 to increase steric bulk did not improve yields, as demonstrated by the performance of the tert-butyl ester N4, tertiary acyclic amide N6, or parent carboxylic acid N5. In 2018, the group of Dong overcame the ortho constraint in the Catellani reaction by using bridgehead-modified NBEs, which facilitates the β-carbon elimination. Inspired by this work, several NBEs with substituents at the bridgehead position were evaluated. To our delight, NBE N7, featuring a hexyl group at the bridgehead position, dramatically improved the yield to 77%. However, increasing the steric hindrance at the bridgehead with NBE N8 (cyclohexyl) only afforded a 39% yield. Next, we tested NBE N9 bearing a hexyl group at the bridgehead position and an amide. Under the standard conditions, 98% 1H-NMR yield was obtained. Further optimization of the reaction conditions allowed to reduce the amount of N9 to 20 mol % while retaining the high yield. The effectiveness of amide-substituted NBEs has been attributed to facilitate the migratory insertion and ortho-palladation steps. Additionally, the use of mixture of HFIP and DCE in a ratio 1.5:1, using N7 provided 6a in 80% isolated yield as a mixture of regioisomers 11:1 in favor of the meta-product.

With the optimized reaction conditions in hand, the scope of the reaction was investigated with both N7 and N9. The ortho-substituted anisoles with an isopropyl, tert-butyl and methoxy groups 5b–5d were arylated in high yields (64–71%) with N7. When using 20 mol % of NBE N9, higher yields (88–92%) were obtained for substrates 5a–5c. Similarly to the reaction of 2-methylanisole, 2-isopropyl anisole provided a mixture of regioisomers (meta:para in a 12:1 ratio) for both N7 and N9. Electron withdrawing substituents, Cl- and CF3-, were well tolerated. For substrate 5e, NBE N9 provided higher yield (50%) than when using N7. Longer reaction times and 3 equiv of 2-trifluoromethyl anisole (5f) were needed to obtain the arylated product 6f in synthetically useful yields. For this substrate, N7 provided slightly higher yield than N9. 2,3-Dihydrobenzofuran (5h) and 2,3-dihydro-2-methylbenzofuran (5i) were successfully meta-arylated in good yields (59–61%) with perfect regioselectivity using N7. Similar results were observed using N9. Encouraged by our promising results with ortho-substituted anisoles, we concentrated our efforts to find a suitable catalytic system for the selective monoarylation of anisole (Table 5). The reaction of anisole employing our previously optimized conditions for ortho-substituted anisoles in the
presence of N2 provided the meta-arylated products in 46 % NMR yield as a 1:1 mixture of mono- and diarylated products 3a. As expected, both an increase in yield and mono/di selectivity was achieved using bridgehead-substituted NBEs. N7 provided the arylated products in 67 % 1H-NMR yield, with a 3:1 improvement of selectivity in favor of the monoarylated product, while N8 afforded the arylated products in 57 % 1H-NMR yield with a 9:1 regioselectivity. The yield and regioselectivity were further improved to 71 % and 12:1 (mono/diarylated products) respectively by converting the ester group to an amide (20 mol %, 71 % and 12:1 (mono:diarylated products) respectively by converting the ester group to an amide (20 mol %, N10). Under these conditions, the monoarylated anisole derivative 3a was isolated pure in 54 % yield. Other NBEs with two substituents at the bridgehead positions N11 and N12 were evaluated, but low yields were obtained. Additionally, N13 and N14 were tested, but only trace amounts of product were detected. Next, with the suitable conditions for the highly selective monoarylolation of anisole, other unsubstituted aryl ethers were evaluated (Table 5). The arylation reaction of butyl phenyl ether and benzyl phenyl ether under the optimized reaction conditions provided the monoarylated products 8a and 8b in 56 % and 42 % isolated yields, respectively.

With this result in hand, we envisioned that a challenging unsymmetrical diarylation of anisole could be achieved in a sequential fashion through the use of two different NBEs. In the first arylation reaction, the aryl iodide is employed as the limiting reagent to ensure its complete consumption, together with 1.5 equiv of anisole and 20 mol % of N10 (Table 6). After a simple filtration through a pad of Celite and evaporation (i.e., no further purification) the crude material was reacted with the second aryl halide in the presence of 5 mol % of Pd/L2 and 50 mol % of N2. In this stepwise approach, we introduced aryl iodides with para- CO2Me, -Br and meta-Cl substituents in the first step. In the second step, we used aryl iodides with para-CO2Me and -Ac groups and aryl bromides bearing NO2 and CO2Me groups at the ortho-position. Under these conditions, we were able to obtain the desired unsymmetrical meta-arylated products in synthetically useful yields over two steps. It is worth mentioning that (as far as we know) this is the first example of unsymmetrical diarylation of non-directed arenes with non-conventional site-selectivity.

To obtain further insights into the mechanism of this transformation, we focused our efforts to isolate the intermediates proposed in the catalytic cycle established by Yu and co-workers.[9] To our delight, the stoichiometric reaction of anisole, Pd(OAc)2, L2 and N2 in HFIP at 90 °C (2 h) afforded palladium complex C1, isolated in 71 % yield and fully characterized by NMR and MS. C1 corresponds to the Pd-complex after the first para-C–H activation and NBE insertion (Scheme 2a). The chemical shift of the anisyl ring protons along with the presence of four broad signals corresponding to the two ortho- and two meta protons, suggests slow rotation around the Csp2–Csp2 bond at r.t., indicating the coordination of palladium to the aren ring is similar to previously reported examples.[20] Interestingly, C1 was also obtained at 60 °C and at r.t. in 39 % and 13 % yield, respectively. These results suggest that the first C–H activation and NBE insertion are not rate limiting steps under our conditions. Indeed, we observed a zero-order dependence of the rate on 1b, further indicating that the first C–H activation is not the rate limiting step (Supporting Information, Table S28).[21] In addition to C1, we observed the formation of a new complex C1-ortho at both 60 °C and r.t. that we assigned as the complex arising from the first ortho-C–H activation and NBE insertion (Scheme 2a),
With the complexes C1 and C2 in hand, we evaluated their catalytic activity in the reaction of anisole using 10 mol % of C1 or C2 under standard reaction conditions, with the addition of 40 mol % N2. Gratifyingly, the meta-arylated products were obtained in 58 % (C1) and 56 % yield (C2), indicating that both species are catalytically active (Scheme 2b).

After establishing the catalytic activity of C1 and C2, we investigated the reversibility of the first[24] and second C–H activation step. We found that C1 was partially deuterated at the meta-position of anisole in the presence of HFIP-d5, at 90 °C for 2 h, confirming that the second C–H activation step is reversible (Scheme 3a). Finally, the reaction of anisole and methyl 4-iodobenzoate under standard reaction conditions using HFIP-d5 as solvent was performed. We observed the monoarylated product with a 70 % deuterium incorporation exclusively at the ortho-position and the diarylated product with around 35 % deuterium incorporation at the ortho- and para-positions (Scheme 3b), consistent with previously reported results.[29] Thus, it is reasonable to propose that the monoarylated product is derived only from the C–H activation at the ortho-position and the diarylated product arises from both C–H activation at the para-position and ortho-palladation of the monoarylated product.

Based on our results, we propose the catalytic cycle outlined in Scheme 4. We have demonstrated that the first and second C–H activation steps are reversible when investigated separately. However, the reversibility of the first C–H activation step cannot be observed in the complete catalytic cycle since the follow-up step is faster. Furthermore, we suggest that the first C–H activation step and norbornene insertion are not rate-determining steps.

**Conclusion**

In conclusion, we have developed a new catalytic system based on Pd/NBE and an S,O-ligand for the meta C–H arylation of aryl ethers that allows—for the first time—to use alkoxyarenes bearing both electron-donating and -with-
drawing substituents. ortho-Substituted aryl ethers are well tolerated by overcoming the ortho constraint in Catellani-type reactions by judicious selection of an appropriate NBE mediator. Remarkably, the monoarylation of alkoxyarenes is efficiently achieved allowing for the unprecedented introduction of two different aryl coupling partners to yield unsymmetrical terphenyls. Moreover, the new catalytic system based on Pd/S,O-ligand only requires catalytic amounts of NBE to obtain the meta-arylated products in good yield. Preliminary mechanistic investigations exclude the first C–H activation to be rate-limiting step. Further applications of this new catalytic system are currently underway in our laboratory.

Supporting Information

Experimental procedures, compounds characterizations, crystallographic data and mechanistic studies.

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Conflict of Interest

The authors declare no conflict of interest.


Deposition Number 2128582 (for C3) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

For experiments proving the reversibility of the first C–H activation step, see Supporting Information.

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