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

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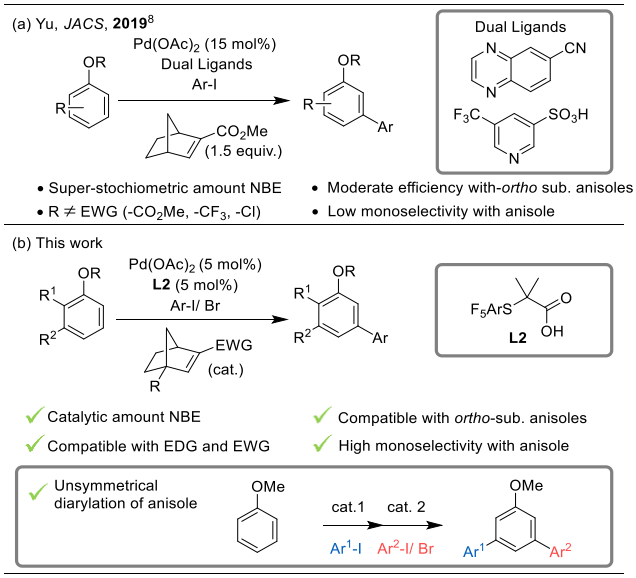
ABSTRACT: Reversing the conventional site-selectivity of C–H activation processes provides new retrosynthetic disconnections to otherwise unreactive bonds. Here, we report the realization of non-conventional site-selectivity through Pd/Norbornene cooperative-catalysis. Specifically, we report a new catalytic system based on Pd/norbornene with an S,O-ligand for the *meta*-C–H arylation of aryl ethers. Furthermore, we demonstrate the unique ability of this system to employ alkoxyarene substrates bearing both electron donating and withdrawing substituents. Additionally, *ortho*-substituted aryl ethers are well tolerated, with the *ortho* constraint overcome through the use of a novel norbornene mediator. Remarkably, the monoarylation of alkoxyarenes is achieved efficiently enabling the subsequent introduction of a second, different aryl coupling partner to rapidly furnish unsymmetrical terphenyls.

1. 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).[1] In recent years, alternative catalytic systems have been developed for the non-directed palladium-catalyzed C–H functionalization of arenes,[2] greatly broadening the substrate scope beyond those bearing DGs. The majority of these examples invoke site-selectivity, which is mainly controlled via electronic effects, with the functionalization occuring at the most electron rich positions of the arene. Consequently, realizing complementary site-selectivity—favoring the functionalization at electron-deficient position— is a major challenge in the field. Beyond the examples that use templates or traceless DGs to achieve the reverse site-selectivity,[3] only few methodologies using non-directed arenes have been reported albeit with low levels of site-selectivity.[4] A more general approach for reversing conventional site-selectivity has been achieved using palladium/norbornene (Pd/NBE) cooperative catalysis, known as the Catellani-type reaction.[5,6] Although the first reports on C–H activation using the Pd/NBE strategy were focusing on substrates bearing DGs, [5b, 7] in 2019 the *meta*-arylation of electron-rich alkoxyarenes was developed by Yu and coworkers (Scheme 1a).[8] In the same year, the group of Dong reported the direct vicinal difunctionalization of thiophenes using the Pd/NBE strategy.[9] Following a similar approach, the functionalization of fluoroarenes, simple arenes[10] and five-membered heteroarenes[11] 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 superstochiometric amounts of NBE, *ii*) the lack of reactivity for substrates bearing electron withdrawing substituents, *iii*) the relatively low reactivity observed for aryl ethers with only *ortho* substituents and *iv*) the impossibility to control the monoarylation of unsubstituted aryl ethers.[8] 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.[5a,12] Threfore, a general and efficient methodology for non-directed *meta*- C–H arylation of alkoxyarenes, ubiquiotous structures in natural products and pharmaceuticals, remains elusive.

Scheme 1. Direct *meta*-C–H Arylation of Aryl Ethers



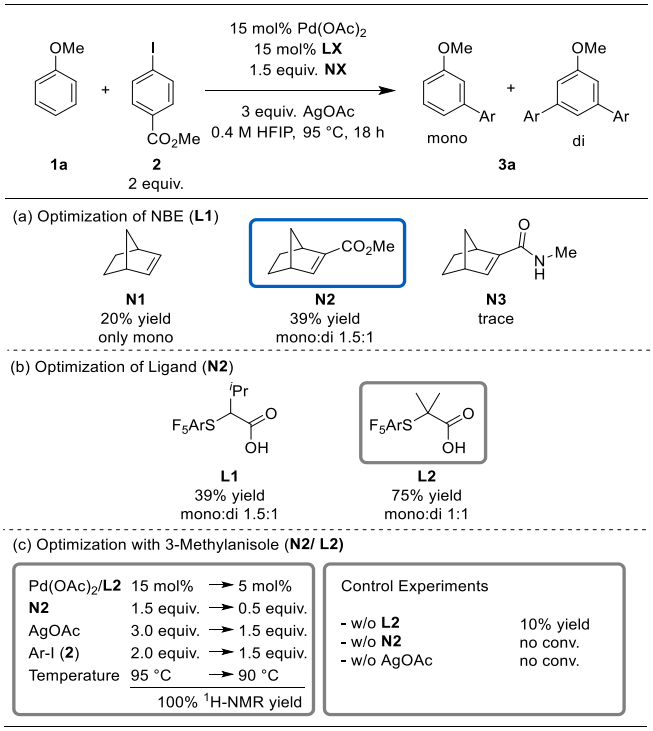
Recently, our group has disclosed a new catalytic system based on Pd/S,O-ligand, capable of promoting Pd-catalyzed C–H functionalization reactions of a wide variety of arenes including simple arenes, thiophenes, anilines and anisoles.[2e,13,14] A unique feature of the Pd/S,O-ligand system is it's high catalytic

activity, allowing for the functionalization of aniline and anisole derivatives bearing several electron withdrawing substituents, substrates that are unreactive using other catalytic systems. We hypothesized that by using our catalytic system based on Pd/S,O-ligand in conjunction with the appropriate choice of the NBE mediator,[15,16] we could overcome the previously mentioned limitations for the *meta*-arylation of alkoxyarenes. Herein, we report a general and efficient C–H arylation of alkoxyarenes with non-coventional site-selectivity, promoted by Pd/NBE catalysis using the Pd/S,O-ligand catalytic system (Scheme 1b). The reaction proceeds using catalytic amounts of NBE on a broad range of alkoxyarene derivatives bearing both electron donating and withdrawing substituents. *Ortho*-substituted alkoxyarenes are efficiently arylated by overcoming the *ortho* constraint through simple selection of the the appropiate NBE mediator. Remarkably, the monoarylation of alkoxyarenes is efficiently achieved allowing, for the first time, the introduction of two different aryl coupling partners.

2. RESULTS AND DISCUSSION

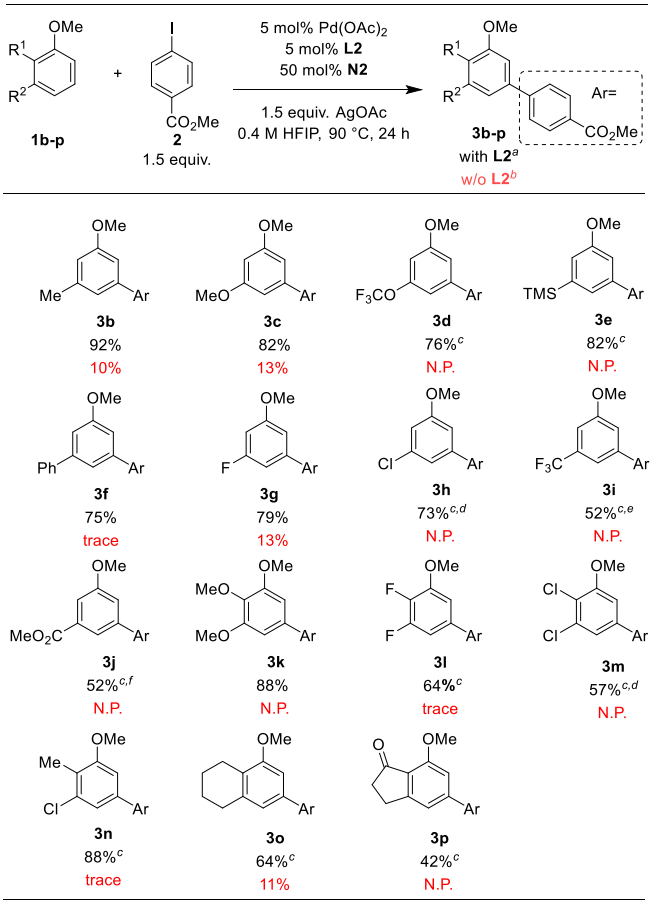
2.1. Scope of the *meta*-arylation of alkoxyarenes. Initially, we applied the conditions reported for the *meta*-arylation of anisole derivatives[8] using anisole and methyl 4-iodobenzoate as model substrates in the presence of 15 mol% of $Pd(OAc)_2$ and the S,O-ligand **L1**, previously used for the C–H olefination of anisoles,[14] and 1.5 equiv. of NBE **N1** (Table 1). Under these conditions, we observed the formation of the *meta*-monoarylated product **3a** in 20% ^{1}H NMR yield. Next, modified norbornenes **N2** (NBE-CO_2Me) and **N3** (NBE-CONHMe) were evaluated in the reaction under previously mentioned conditions. The reaction using **N2** afforded a mixture of mono- and diarylated products **3a** in 39% ^{1}H NMR yield, and with **N3** only traces amount of product was detected (Table 1a). The superior performance of **N2** on this type of transformation is in line with previous reports.[7b,16]

Table 1. **Selected Optimization for *meta*-C–H Arylation**



Next, 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 the isopropyl, furnished **3a** in 75 % ^{1}H NMR yield and a 1 to 1 ratio of mono-, and diarylated products (Table 1b). The same reactions conditions using 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 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. Moreover, no product was observed in the absence of NBE or AgOAc,[17] confirming the crucial role of these reagents play in the reaction.

Table 2. **Scope of *meta*-Substituted Anisoles**

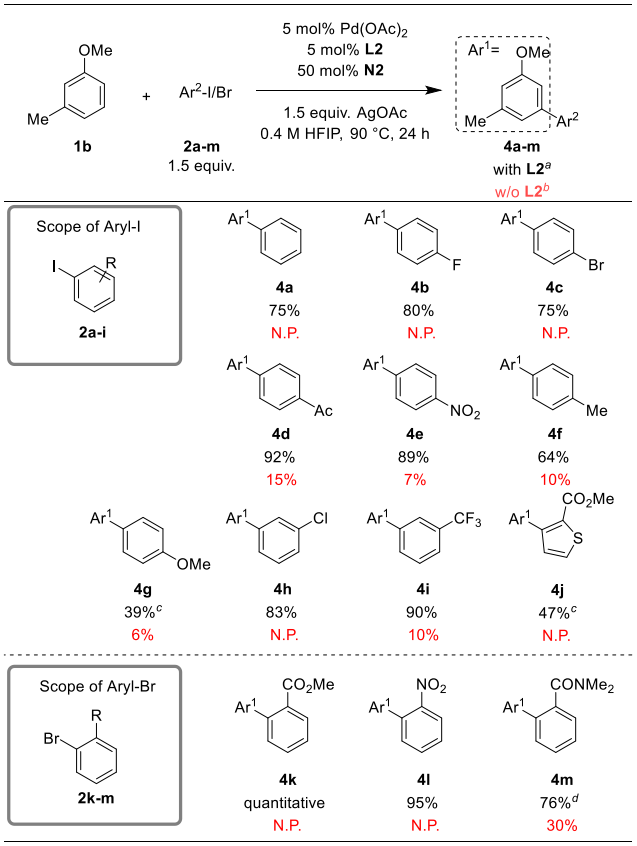


[a]Isolated yield. [b]^{1}H-NMR yield of the crude mixture using CH_2Br_2 as internal standard. [c]10 mol% $Pd(OAc)_2$/**L2** was used. [d]30 mol% NBE **N3** instead of NBE **N2** was used. [e]3.6 equiv. anisole **1i**, 1.0 equiv. aryl iodide **2a,** 20 mol%. **N2**, 2 equiv. AgOAc, 0.2 M HFIP, 70°C, 48 h. [f]2.0 equiv. anisole **1j**, 1.0 equiv. aryl iodide **2a**, 48 h. N.P.: no product. w/o: without.

With the optimized conditions in hand, the scope of *meta*-substituted anisole derivatives was evaluated (Table 2). Anisole derivatives with a OMe-, OCF_3-, 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%.[18] Likewise, 3-substituted anisoles with CF_3- and CO_2Me-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. After demonstrating the generality of the methodology with anisoles bearing both electron donating and withdrawing substituents at the *meta*-position, we studied the reaction using disubstituted anisoles. 2,3-dimethoxy-, difluoro-, dichloro- and 3-chloro-2-methyl- anisoles **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**–**p** in synthetically useful yields (42–64%).

Table 3. **Scope of Aryl Halides**

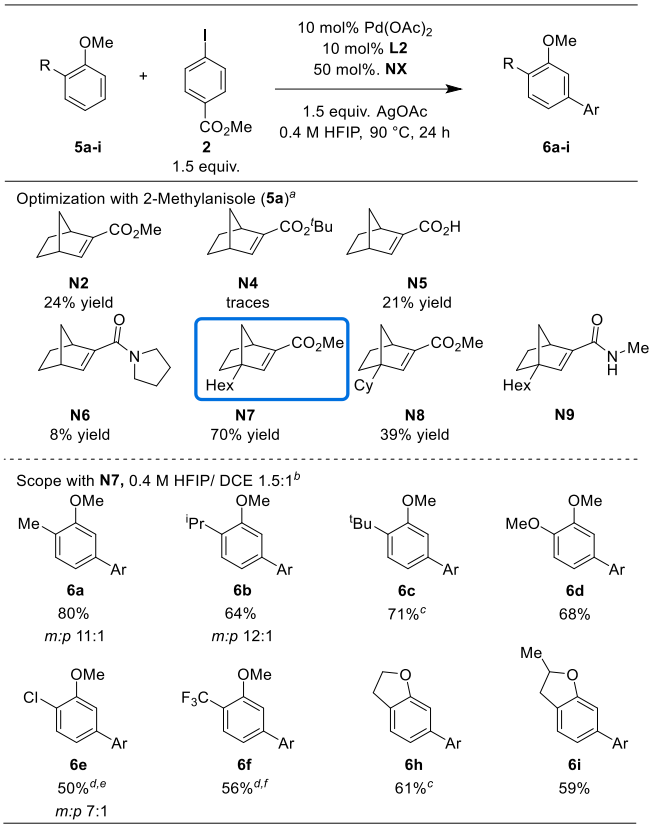


[a]Isolated yield. [b]^{1}H-NMR yield of the crude mixture using CH_2Br_2 as internal standard.[c]10 mol% $Pd(OAc)_2$/**L2** was used [d]1.0 equiv. of aryl-Br **2m** and 1.5 equiv. of 2-methylanisole **1b** were used. N.P.: no product. w/o: without.

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 initial 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 NO_2, were well tolerated, affording the arylated 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. *Ortho*-Substituted aryl bromides with coordinating functional groups that facilitate the oxidative addition (i.e., ester, nitro and amide),[5a,7c,9] were also compatible, providing the desired products **4k–m** 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 all cases, low yields or no product formation were observed, which highlights the key role of 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% ^{1}H 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 *(vide supra)*. Therefore, we decided to explore the effect of NBE modification with 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**. Inspired by the work of Dong,[15] 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 70%. However, increasing the steric hindrance at the bridgehead with NBE **N8** (cyclohexyl) only afforded a 39% yield. Therefore, we continued our investigation with NBE **N7**. When using a solvent mixture of HFIP and DCE in a ratio of 1.5:1, the isolated yield increases up to 80%, providing **6a** as a mixture of regioisomers 11:1 in favor of the *meta*-product.

Table 4. Scope of *ortho*-Substituted Anisoles

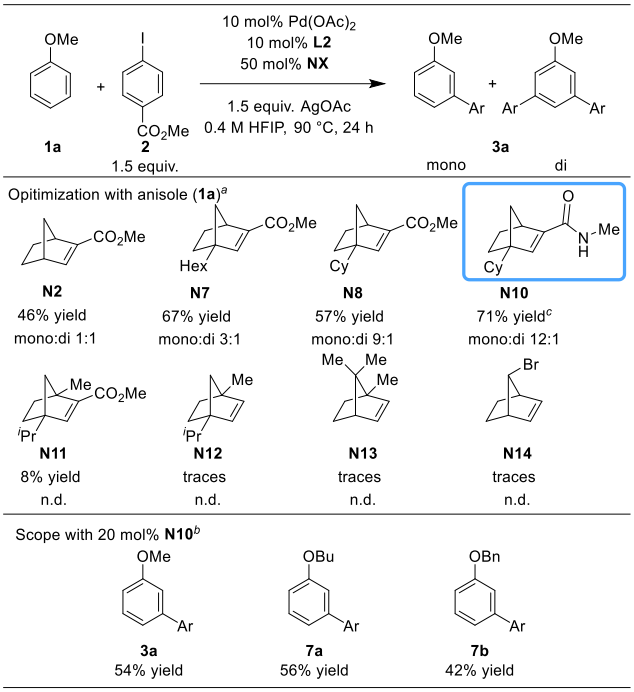


[a]^{1}H-NMR yield of the crude mixture using CH_2Br_2 as internal standard. [b]Isolated yield. [c]2.0 equiv. of Ar-I **2** was used. [d]HFIP (0.4 M) was used as sole solvent. [e]30 mol% NBE **N9** instead of NBE **N7**, 48h. [f]3.0 equiv. anisole **5f**, 1.0 equiv. Ar-I **2**, 40 h.

With the optimized reaction conditions in hand, the scope of the reaction was investigated. *ortho*-substituted anisoles with an isopropyl, *tert*-butyl and methoxy group **5b**–**d** were arylated in high yields (64–71%). Similarly to the reaction of 2-methylanisole, 2-isopropyl anisole provided a mixture of regioisomers *meta*:*para* in a 12:1 ratio. Electron withdrawing substituents, Cl- and CF_3, were well tolerated although some modifications of the standard reaction conditions were required. In both cases, HFIP was used as a sole solvent and longer reaction times were needed. Similar to previous chlorinated anisoles, the modified NBE **N9**,[18] with an amide group, provided the best yield for 2-chloroanisole (**5e**) and 3 equiv. of 2-trifluoromethylanisole (**5f**) were used. Under these conditions, products **6e**–**f** were obtained in synthetical useful yields (50–56%). 2,3-Dihydrobenzofuran (**5h**) and 2,3-dihydro-2-mehtylbenzofuran (**5i**) were successfully *meta*-arylated in good yields (59–61%) with perfect regioselectivity.

Encouraged by the good results using *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 using previously optimized conditions for *ortho*-substituted anisoles in the presence of **N2** provided the *meta*-arylated products in 46% NMR yield as a 1 to 1 mixture of mono- and diarylated products **3a**. As expected, both an increase in yield and mono/di selectivity was achieved using NBEs substituted at the bridgehead position. **N7** provided the arylated products in 67% ^{1}H NMR yield with an improve selectivity of 3:1 in favor of the monoarylated product, while **N8** afforded the arylated products in 57% ^{1} H NMR yield with a 9:1 regioselectivity. The yield and regioselectivity were further improved to 71% and 12:1 ratio mono:diarylated products by changing 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**[15] were evaluated, but low yields were obtained. Additionally, **N13** and **N14**[19] were tested, but only traces amount of product were detected. Next, with the suitable conditions for the highly selective monoarylation 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 **7a**–**b** in 56% and 42% isolated yields, respectively.

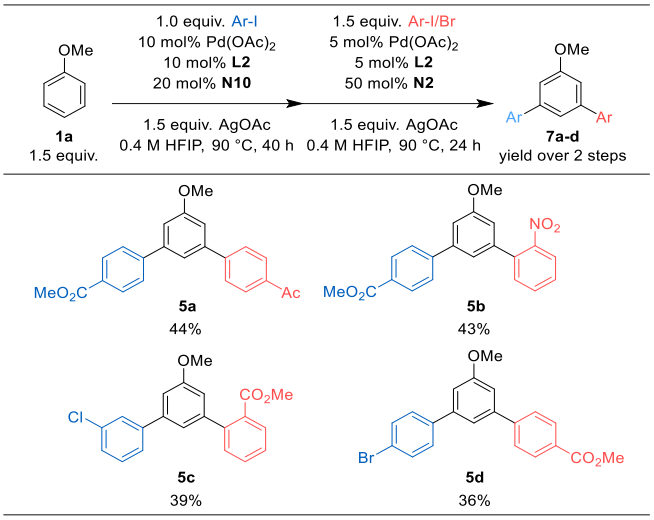
Table 5. Monoarylation of Aryl Ethers



[a]^{1}H-NMR yield of the crude mixture using CH_2Br_2 as internal standard. [b]Isolated yield of the monoarylated product. [c]20 mol% **N10** was used. n.d.: not determined

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* -CO_2Me, -Br and *meta* -Cl substituents in the first step. In the second step, we used aryl iodides with *para*-CO_2Me and -Ac groups and aryl bromides bearing NO_2 and CO_2Me 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.

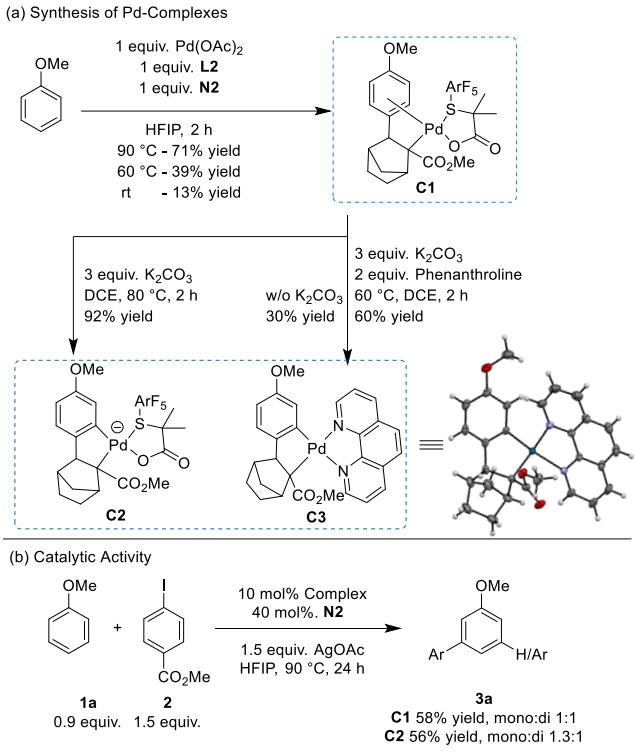
Table 6. Unsymmetrical Diarylation of Anisole



2.2. Mechanistic studies. To get more insights into the mechanism of this transformation, we focused our efforts in the isolation of the intermediates proposed in the catalytic cycle established by Yu.[8] To our delight, the stoichiometric reaction of anisole, $Pd(OAc)_2$, **L2** and **N2** in HFIP at 90 °C afforded, after 2 h, the palladium complex **C1**, which was isolated in 71% yield and fully characterized by NMR and MS spectroscopy. **C1** corresponds to the Pd-complex after the first *para*-C–H activation and NBE insertion (Scheme 2a). The chemical shift of the anisole hydrogens indicates the coordination of palladium to the arene ring, similarly to previous reported examples.[20] Interestingly, **C1** was also obtained at 60 °C and at room temperature in 39% and 13% yield, respectively. These results suggest that the first C–H activation and NBE insertion are not rate limiting steps, in contrast to previously reported DFT calculations,[21] where the initial carbopalladation was proposed to be the rate determining step. In addition to **C1**, we observed the formation of a new complex at 60 °C and at room temperature that we tentatively assigned as the complex coming from the first *ortho*-C–H activation and NBE insertion **C1**-*ortho* (see Supporting Information, Table S11), meaning that **C1** is the thermodynamic Pd-complex. Furthermore, the complex **C1** was also obtained using DCE as solvent albeit in lower yields (< 10 %) at 60 °C after 2 h (50% yield after 18 h). Based on these results and on previously reported observations,[22] we suggest that HFIP has a positive effect on the first C−H activation step. Although under the previously mentioned conditions we did not observe the formation of the complex after the second C−H activation step, we were pleased to find that by adding 3 equiv. of K_2CO_3 to **C1** in DCE at 80 °C, the anionic complex **C2**, with the palladium attached to the *meta*-position of anisole, was isolated in 92% yield. Additionally, the reaction of **C1** with 3 equiv. of K_2CO_3 in the presence of phenanthroline in DCE at 60 °C provided complex **C3** in 60% yield. Single crystals were grown by layering heptane onto a CH_2Cl_2 solution of **C3**, enabling confirmation of the structure by single-crystal X-ray crystallography, with the ORTEP diagram with 50% probability ellipsoids shown in Scheme 2.[23] Complex **C3** corresponds to the complex after the *meta*-C−H activation bearing a phenanthroline ligand and with the typical insertion of NBE in a *cis, exo* manner.[5] Alternatively, complex **C3** was obtained in 30% yield without adding K_2CO_3.

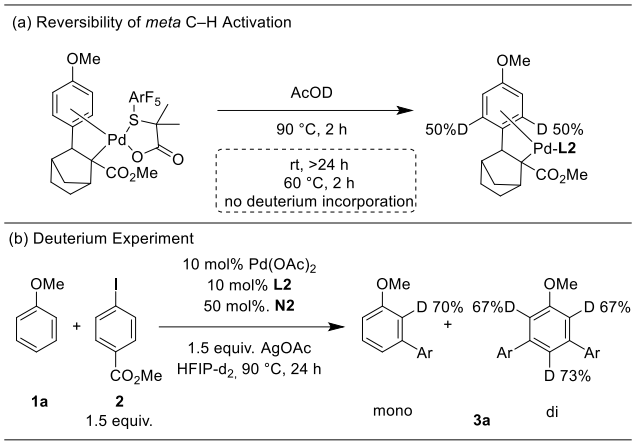
With the complexes **C1** and **C2** in hand, we evaluated their catalytic activity in the reaction of anisole using 10 mol% of **C1** or **C2** under standard reaction conditions, with the addition of 40 mol% **N2**. Gratifyingly, the *meta*-arylated products were obtained in 58% (**C1**) and 56% yield (**C2**), indicating that both species are catalytically active (Scheme 2b)

Scheme 2. Synthesis and Evaluation of Pd-Complexes



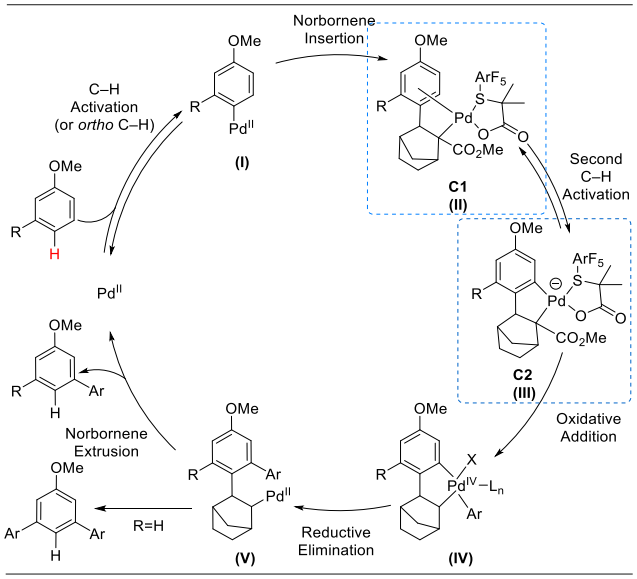
After establishing the catalytic activity of **C1** and **C2**, we investigated the reversibility of the second C–H activation step.[23] We found that **C1** was partially deuterated at the *meta*-position of anisole in the presence of AcOD-d_4 at 90 °C for 2 h, confirming that the second C–H activation step is reversible (Scheme 3a). Therefore, we further explored the reversibility of this reaction at 60 °C and at room temperature, finding no deuterium incorporation was observable. Finally, the reaction of anisole and methyl 4-iodobenzoate under standard reaction conditions using HFIP-d_2 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 70% deuterium incorporation at the *ortho*- and *para*-positions (Scheme 3b), consistent with previously reported results.[8] 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 arrives from both C–H activation at the *para*-position and *ortho*-palladation of the monoarylated product.

Scheme 3. Deuteration Experiments



Based on our results, we propose the catalytic cycle outlined in Scheme 4, with the first and second C–H activation steps being reversible.[23] Furthermore, we suggest, that the first C–H activation step and norbornene insertion are not rate determining steps.

Scheme 4. **Proposed Catalytic Cycle**



3. 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 withdrawing 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge http://pubs.acs.org. Experimental procedures, compounds characterizations, crystallographic data and mechanistic studies. Crystallographic data for compound **C3** have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition no. CCDC 2128582. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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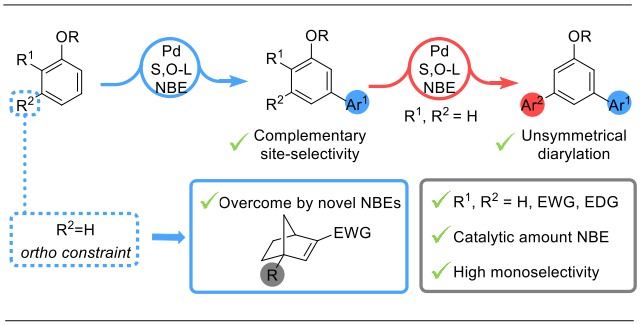
OR
R1
R2
Pd
S,O-L
NBE
Ar1
Complementary
site-selectivity
R1, R2 = H
Ar2
Unsymmetrical
diarylation
R2=H
ortho constraint
Overcome by novel NBEs
EWG
R
R1, R2 = H, EWG, EDG
Catalytic amount NBE
High monoselectivity