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Deng, K.-Z.; Sukowski, V.; Fernández-Ibáñez, M.Á.

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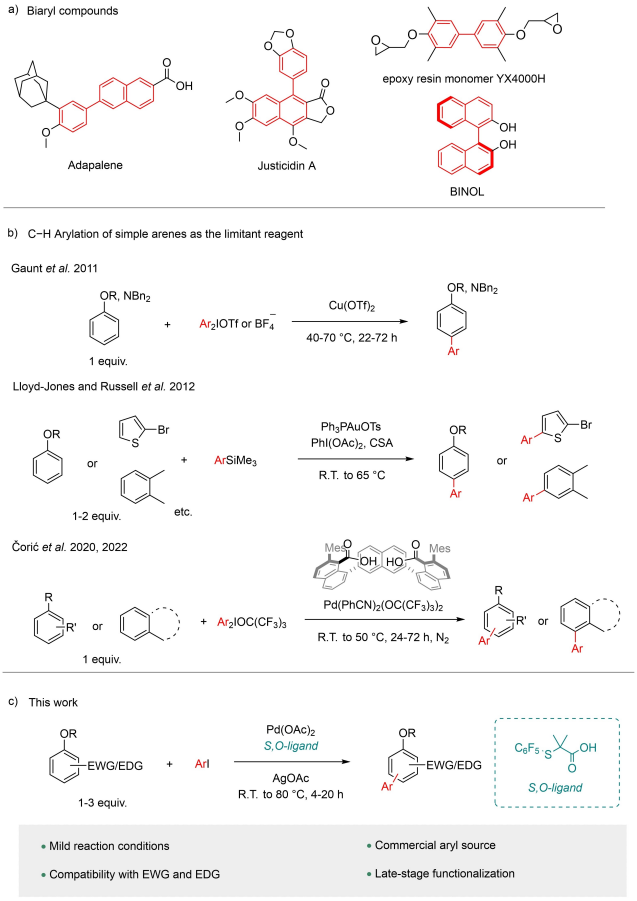
C-H Activation

Non-Directed C–H Arylation of Anisole Derivatives via Pd/S,O-Ligand Catalysis

*Ke-Zuan Deng, Verena Sukowski, and M. Ángeles Fernández-Ibáñez**

Abstract: Non-directed C–H arylation is one of the most efficient methods to synthesize biaryl compounds without the need of the prefunctionalization of starting materials, or the installment and removal of directing groups on the substrate. A direct C–H arylation of simple arenes as limiting reactants remains a challenge. Here we disclose a non-directed C–H arylation of anisole derivatives as limiting reagents with aryl iodides under mild reaction conditions. The arylated products are obtained in synthetically useful yields and the arylation of bioactive molecules is also demonstrated. Key to the success of this methodology is the use of a one-step synthesized S,O-ligand.

Biaryl scaffolds are of great importance as they are present in a wide range of pharmaceuticals, bioactive molecules, natural products, functional materials and ligands in organic synthesis (Scheme 1a).[1] Over the past few years, C–H arylation employing transition metals has emerged as a potent chemical strategy for constructing biaryl linkages. In contrast to traditional cross-coupling reactions, the C–H arylation may omit the use of pre-functionalized arenes resulting in a more atom- and step-economic process.[2] However, the control of the site-selectivity in these reactions is still an open issue. Up to the present day, chelation-assisted strategies (directed C–H activation) have marked significant milestones in C–H activation, addressing challenges related to reactivity and selectivity inherent to C–H bonds.[3] Alternatively, non-directed C–H arylation is not limited to substrates containing directing groups and can reach sites that are typically inaccessible by the directed C–H activation approach.[4] In most of the reported non-directed strategies, an excess of the arene and harsh reaction conditions are required to ensure high reactivity with the transition metal catalysts.[5] Despite significant advances that have been made in this field, non-directed C–H arylation of simple arenes as a limiting reactant remains synthetically challenging, with only a few examples reported (Scheme 1b).[6]



Scheme 1. a) Selected examples of biaryl compounds. b) C–H arylation of simple arenes as the limiting reagent. c) This work: C–H arylation of anisole derivatives using aryl iodides.

An elegant example in the field of non-directed C–H arylation was reported in 2011 by Gaunt and co-workers. In this work the *para*-arylation of electron-rich anisole and aniline derivatives using copper-based catalyst was reported.[6a] Year after, Russel and co-workers described the gold-catalyzed direct arylation of simple arenes with arylsilanes to afford biaryls under milder reaction conditions.[6b] More recently the group of Čorić, has pioneered a novel approach of spatial anion control to tailor catalytic sites for C–H bond activation and achieved non-directed C–H arylation of arenes at ambient temperature.[6c,d] Despite the importance of these strategies, limitations regarding reaction

[*] K.-Z. Deng, V. Sukowski, Prof. Dr. M. Á. Fernández-Ibáñez
van't Hoff Institute for Molecular Sciences,
University of Amsterdam,
Science Park 904, 1098 XH Amsterdam, The Netherlands
E-mail: m.a.fernandezibanez@uva.nl

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conditions, availability of arylation agents and scope still remained.

In addition to the above examples, the direct C–H arylation of arenes with aryl iodides has been accomplished by using norbornene mediators.[7] The key to the success of these arylation reactions is that the presence of norbornene in the palladacycle intermediate facilitates the oxidative addition of the aryl iodide. However, to the best of our knowledge, achieving non-directed C–H arylation of arenes as the limiting reactant with aryl iodides without the use of mediators remains elusive.

In 2017, our research group pioneered a novel catalytic system based on Pd/S,O-ligand, to promote the Pd-catalyzed C–H functionalization reactions on a wide variety of arenes encompassing simple arenes, thiophenes, anilines, and anisoles.[7,8] A unique feature of the Pd/S,O-ligand system is its high catalytic activity, allowing the functionalization of substrates that are unreactive with other catalytic systems. We envisioned that our Pd/S,O-ligand catalytic system under optimal reaction conditions could effectively address the aforementioned limitations for the non-directed C–H arylation of simple arenes. Herein, we report a general and efficient arene-limited non-directed C–H arylation of anisole derivatives with aryl iodides using the Pd/S,O-ligand catalytic system (Scheme 1c).

The reaction between 2-methylanisole (**1a**) and methyl 4-iodobenzoate (**2a**) was used for the optimization of the reaction conditions. Based on our previous report on the C–H olefination of anisoles, we initially studied the reaction using $Pd(OAc)_2$, AgOAc, and S,O-ligand **L1** as the reagents for the non-directed C–H arylation.[8g] Additionally, solvents, temperature, S,O-ligands, and other Pd-based catalysts were evaluated (see Tables S2–S10, Supporting Information). The best conditions were achieved using 10 mol % of $Pd(OAc)_2$/S,O-ligand **L1** in a mixture of HFIP:H_2O at 60 °C, requiring up to 4 h to obtain high yield and site-selectivity (Scheme 2, 80 % yield, 95 : 5 *para*/*meta* selectivity). Consistent with previous observations,[9] the use of fluorinated solvents was key to obtaining the desired arylated product. Remarkably, we found that the addition of water to the reaction as a co-solvent had a positive effect in increasing both yield and regioselectivity, while inhibiting the undesired homocoupling of aryl iodide (Supporting Information, Tables S2 and S5). Gratifyingly, when we scaled up the reaction of 2-methylanisole (**1a**) to 5 mmol using only 5 mol % of catalyst, the arylated product **3a** was obtained with a yield (73 %) and site selectivity (95 : 5 para/meta) comparable to the original value (Scheme 2).

To establish the scope of the non-direct C–H arylation catalyzed by $Pd(OAc)_2$/**L1**, we first selected a representative family of anisoles containing different functional groups. The results are summarized in Scheme 2. The reaction of *ortho*-substituted anisoles bearing electron-donating groups (**1b** and **1c**) with the aryl iodide **2a** furnished the desired biaryl products **3b** and **3c** in high yields and *para*-selectivities. Notably, when the more electron-rich veratrole (**1d**) was used as the starting material, the reaction could be carried out at room temperature leading to the corresponding product **3d** with 62 % yield. Anisoles containing *ortho*-substituted electron-withdrawing groups were also compatible under the reaction conditions, although 3 equiv. of the arene were required to obtain the target products **3e**-**3h** with good yields and high site-selectivities. Similar results were obtained using an *O*-substituted anisole **1i**. We attribute the high *para*-selectivities observed with *ortho*-substituted anisoles to steric reasons, as we have previously rationalized with aniline substrates.[8d] As expected, unsubstituted anisole (**1j**) and *tert*-butoxybenzene (**1k**) were arylated without exhibiting regioselectivity.

Subsequently, we moved our attention to *meta*-substituted anisole derivatives. In the case of 1,3-dimethoxy benzene (**1l**) a mixture of mono- and di-arylated products (**3l**) was obtained at room temperature with a notably high selectivity for the monoarylated compound (64 % isolated yield).[6a] For other *meta*-substituted anisole derivatives the corresponding products were obtained in low to good yields (29 % to 61 %) showcasing a remarkable preference for the *ortho*-position. However, the reaction with **1q** exhibited affinity for the *para*-position yielding the desired product in good yield.[6d] Next, we demonstrated the efficiency of our $Pd(OAc)_2$/**L1** catalytic system for the arylation of *para*-substituted anisoles (**1r**–**u**) yielding the corresponding *ortho*-arylated products in synthetically useful yields. Interestingly, the reaction with 1-methoxynaphthalene (**1v**) provided the *para*-arylated product **3v** as the only regioisomer. Further, we investigated the C–H arylation of dihydrobenzofuran derivatives. The simplest 2,3-dihydrobenzofuran (**1w**) was arylated in good yields although with poor selectivity. Higher yields and selectivities were obtained for the *ortho*-methyl substituted dihydrobenzofuran (**1x**). Encouraged by the results, we extended our catalytic system for the late-stage functionalization of structurally complex molecules. Gratifying, the C–H arylation of estrone methyl ether and nonsteroidal anti-inflammatory indomethacin methyl ester gave the corresponding arylated products in 75 % and 61 % isolated yields (**3y** and **3z**), respectively. Also, we successfully extended our approach for the C–H arylation of other substrates, such as 2-methylthiophene (**1aa**) and *o*-xylene (**1ab**). Although the promising results obtained with these substrates (46 % and 53 % yields, respectively) demonstrate the versatility of our catalytic system, anisole derivatives bearing a CF_3– or NO_2– group or the simple phenol showed low reactivity under standard conditions (Supporting Information, Figure S1).

Next, we evaluated the scope of the reaction by employing a variety of aryl iodide counter partners and 2-methylanisole (**1a**) as the model substrate (Scheme 3). The C–H arylation of **1a** with iodobenzene, under our optimal conditions, furnished the product **4b** in a moderate yield (45 %). Aryl iodides bearing electron-withdrawing groups at the *para*-position were well tolerated yielding the corresponding arylated products **4c**–**4f** and **4j** in moderate to excellent isolated yields (41 to 90 %) and high *para*-selectivity. Similarly, aryl iodides featuring a *meta*-CO_2Me (**2h**) or -CF_3 (**2i**) groups were successfully used as the counter partner. Nonetheless, a slightly lower yield was achieved for the electron-richer aryl iodide **2g**. With these results in hand, we envisioned promoting the C–H arylation

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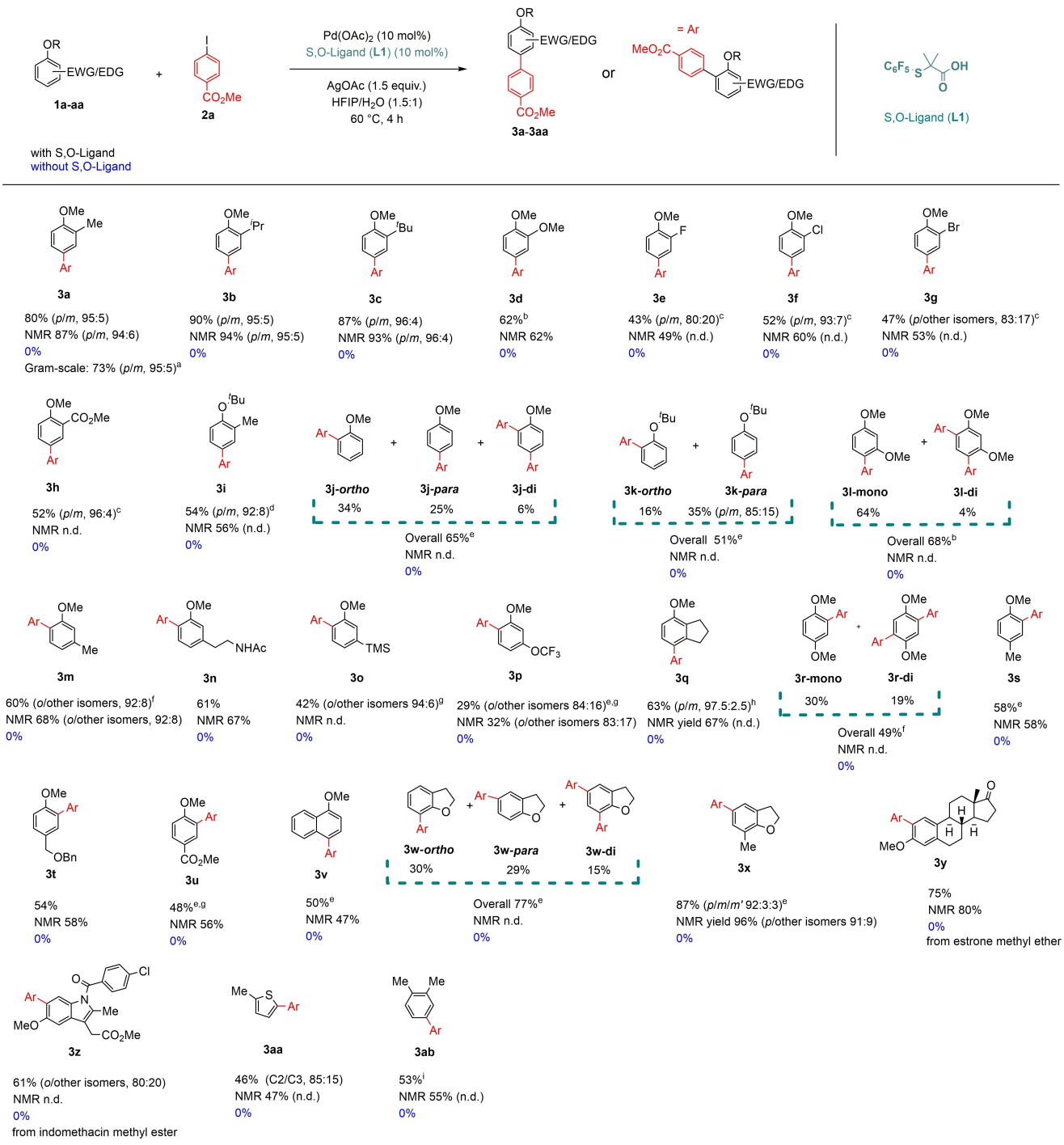

Scheme 2. Scope of anisole derivatives. **1** (0.25 mmol, 1.0 equiv.), **2a** (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), **L1** (10 mol%) and AgOAc (1.5 equiv.) in $HFIP/H_2O$ (1.5:1, 0.4 M) at 60 °C for 4 h; isolated yields. [a] **1a** (5.0 mmol), $Pd(OAc)_2$ (5 mol%), L1 (5 mol%). [b] **1** (2 equiv.), 25 °C, 20–40 h. [c] **1** (3 equiv.), $HFIP/H_2O$ (1.5:1, 0.6 M), 60 °C, 20 h. [d] 80 °C, 20 h. [e] **1** (2 equiv.). [f] 25 °C, 20 h. [g] 20 h. [h] **1** (2 equiv.), 40 °C. [i] 40 °C, 20 h.

of **1a** using L(−)-borneol derivative **2j** as the aryl source. This approach afforded the arylated product **4j** in good yield and high *para*-selectivity. As anticipated, the reactions did not proceed without the S,O-ligand, except for the product **4g** (<5% NMR yield), highlighting the pivotal role of this component in this transformation. Additionally, we performed the reaction with methyl 4-bromobenzoate as a coupling partner, but only 12% NMR yield of the arylated product was observed (Supporting Information, Figure S1), which is consistent with the observed reactivity of 4-bromo iodobenzene (**2e**). We also observed that *ortho*-substituted aryliodides or heteroaryl iodides, among others, were not efficient coupling partners (Supporting Information, Figure S1).

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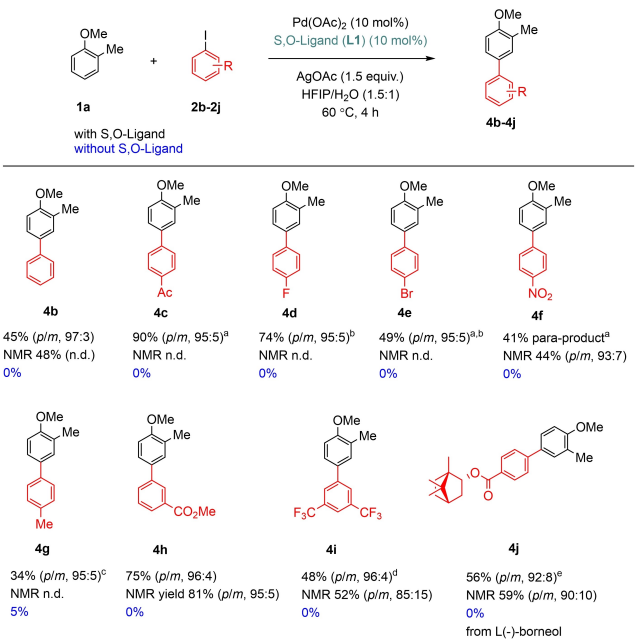
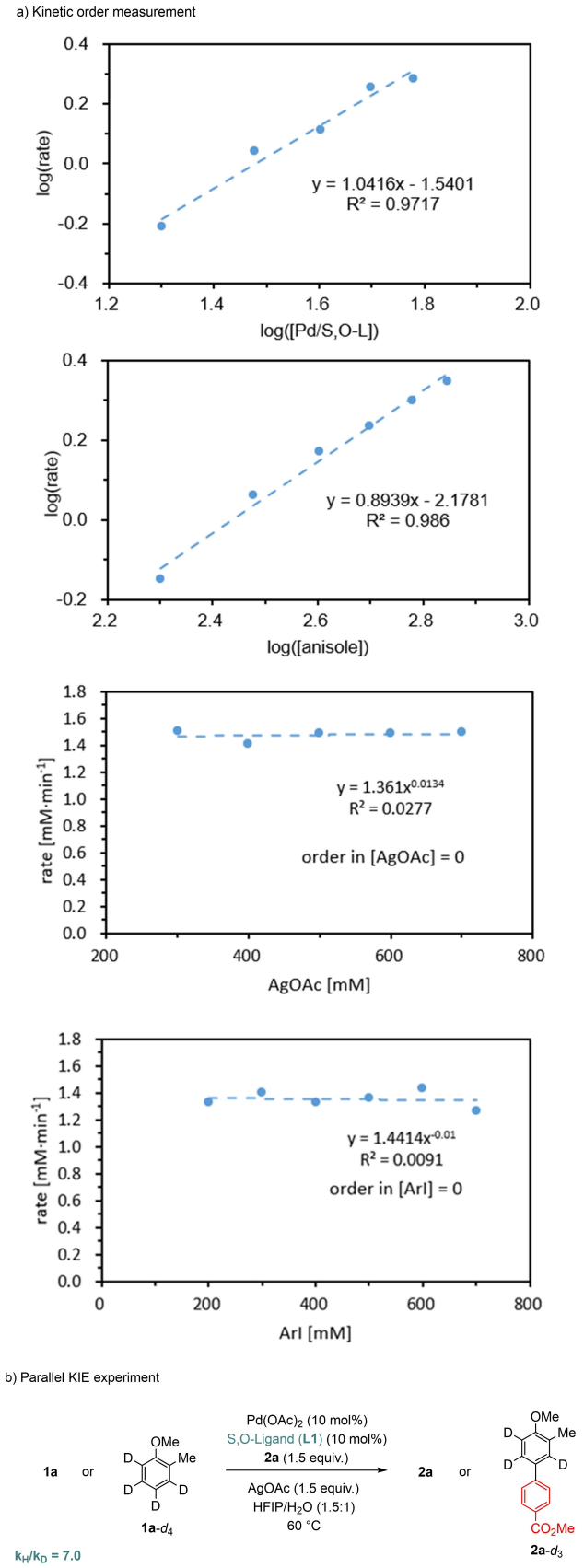


Scheme 3. Scope of aryl iodides. **1a** (0.25 mmol, 1.0 equiv.), **2** (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), **L1** (10 mol%) and AgOAc (1.5 equiv.) in $HFIP/H_2O$ (1.5:1, 0.4 M) at 60 °C for 4 h; isolated yields. [a] **1** (2 equiv.). [b] 20 h. [c] **1** (3 equiv.), 20 h. [d] **1** (2 equiv.), 80 °C. [e] 80 °C.

To gain some insights into the mechanism of these Pd-catalyzed C–H arylation reactions, we performed several kinetic studies. The kinetic order of each reagent was determined using the initial rate method.[10] Scheme 4a shows the plot of the logarithm of the reaction rate against the concentration of the reagent. A straight line with a slope of nearly one was measured for Pd-catalyst and 2-methylanisole, revealing a first order in these reagents. No significant change in the reaction rate was observed using different concentrations of aryl iodide or AgOAc. These results, together with the large KIE observed ($k_H/k_D = 7$) indicated that the C–H activation is the rate limiting step (Scheme 4b).

We then performed a series of control experiments to better understand the mechanism of this C–H arylation reaction. In these transformations, the biaryl compound resulting from the homocoupling of the aryl iodide is a commonly observed by-product. This by-product should result from the oxidative addition of the aryl iodide to Pd(0) species that may be formed during the reaction. First, we tried to understand whether the Pd(0) is formed from the reduction of $Pd(OAc)_2$ under the reaction conditions,[11] or whether it is formed during the C–H arylation reaction. Thus, the reaction was carried out in the absence of 2-methylanisole (**1a**) using 0.5 equiv. of catalyst ($Pd(OAc)_2$/S,O-ligand) under otherwise the same reaction conditions (Table 1, entry 1). No formation of the biaryl by-product **3a′** was observed, indicating that no Pd(0) is directly formed by the reduction of $Pd(OAc)_2$. Next, we added 2-methylanisole (**1a**) in different amounts, from 0.1 equiv. to 0.5 equiv., and we observed the formation of the biaryl by-product **3a′** in



Scheme 4. a) Kinetic order measurement. b) KIE determined from absolute rates of two parallel reactions.

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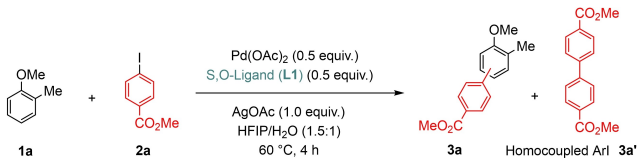
Table 1: Control experiments.



Entry	**1a** (equiv.)	**2a** (equiv.)	Yield of **3a**/%[a]	Yield of **3a'**/%[a]
1	0	1	0	0
2	0.1	1	5	5
3	0.2	1	11	9
4	0.5	1	21	14

[a] ^{1}H NMR yield of the crude mixture using CH_2Br_2 as internal standard.

similar or lower yields than the desired arylated product **3a**. These results strongly suggest that Pd(0) is formed during the C–H arylation reaction, which is consistent with a Pd(II)/Pd(0) mechanism, involving Pd(II) species for the C–H activation and arylation steps, followed by reductive elimination to yield the arylated product and Pd(0) species.[2f]

In conclusion, we have developed a direct C–H arylation of anisoles as a limiting reagent using readily accessible aryl iodides. Key to the success of the methodology was the use of a more active Pd/S,O-ligand catalyst. The reaction proceeds with both aryl ethers bearing electron donating and electron withdrawing groups and with different aryl iodides under mild reaction conditions. The current methodology is also applicable for late-stage arylation of bioactive molecules, including natural products and drugs. Preliminary mechanistic investigations suggest that the C–H activation is the rate-limiting step and that a Pd(II)/Pd(0) manifold is operative.

Supporting Information

Experimental procedures, compounds characterizations, crystallographic data and mechanistic studies. The authors have cited additional references within the Supporting Information.[12–24]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C–H activation · Arylation · Non-directed · Pd/S,O-Ligand · Anisole

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