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C–H Homocoupling of Arenes via Pd/S,O-Ligand Catalysis

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Abstract: Non-directed Pd-catalyzed oxidative dehydrogenative homocoupling of arenes is achieved in the presence of an S,O-ligand. The reaction proceeds under aerobic and mild reaction conditions with a wide range of anisole derivatives, providing direct access to symmetric biaryls with excellent *ortho-ortho* or *para-para* regioselectivity. Notably, the use of the arene as the limiting reagent enables late-stage functionalization of complex pharmaceutical molecules. The industrial applicability of this methodology is demonstrated through the synthesis of the Upilexmonomer via the homocoupling of unactivated *o*-xylene.

Keywords: anisole, C–H activation, homocoupling, O-Ligand, oxidative dehydrogenative coupling, Pd/S

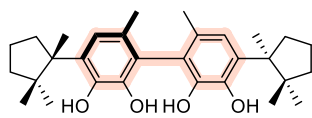
1. Introduction

Symmetrical biaryl scaffolds are ubiquitous moieties in natural products, drugs, agrochemicals, ligands, and organic materials (Scheme 1a).^[1] Since the discovery of the Ullmann reaction on the homocoupling of aryl halides catalyzed by copper salts more than a century ago, other transition metals and functionalized arenes have been successfully used for homocoupling reactions (Scheme 1b).^[2] However, these methods rely on pre-functionalized substrates, which require additional synthetic steps that increase costs and contribute to waste generation.^[3] Alternatively, oxidative dehydrogenative homocoupling, or C–H/C–H coupling, is an efficient and environmentally friendly method for forming C–C bonds by directly activating two C–H bonds, formally releasing only H₂ as a by-product (Scheme 1b).^[3,4] Although the oxidative dehydrogenative homocoupling reaction has been known for decades and several transition metals and arenes have been used for this transformation, there are still some limitations that hinder the applicability of these methods especially in the chemical industry.^[5] These include: use of stoichiometric amounts of metal and/or expensive oxidants, harsh reaction conditions, low conversions/yields, and lack of selectivity

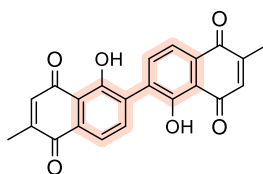
(both regio- and chemoselectivity). To improve conversions and regioselectivities, the use of directing groups has often been employed, generally leading to *ortho-ortho* products.^[6] However, the homocoupling of directing group-free arenes offers the possibility to use simpler substrates and to obtain other regioisomers. In this regard, the homocoupling of activated (hetero) arenes, including anilines, phenols, pyrroles, and thiophenes have been successfully developed.^[7] However, progress with less reactive substrates has been limited and harsh conditions are typically mandatory to achieve high yields.^[8]

Anisoles are versatile and readily available compounds, and their oxidative homocoupling produces symmetrical biaryls essential for the industrial synthesis of polymeric materials and drugs.^[9,1e,1f] Therefore, the development of efficient methods for synthesizing these biaryls have become increasingly important. In this context, one of the most significant contributions in this field was reported by De Vos and coworkers achieving high *para-para* regioselectivity for the homocoupling of unsubstituted anisole employing Pd(OAc)₂ in zeolites.^[10] Other contributions in this field were achieved using PdCl₂ with several acetate-based co-catalysts,^[11] Au nanoparticles^[12] or electrocatalytic methods.^[8b]

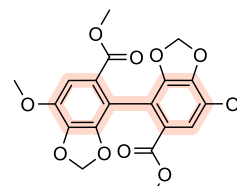
(a) Selected important molecules containing biaryl scaffolds

Bioactive Natural Products & Drugs

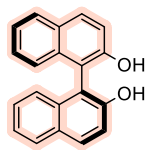
Mastigophorene A



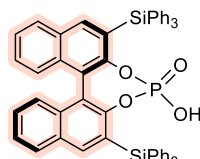
Elliptinone



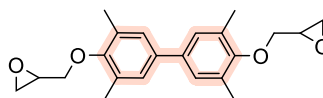
Bifendate (anti-HBV drug)

Ligands & Catalysts

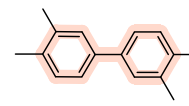
BINOL



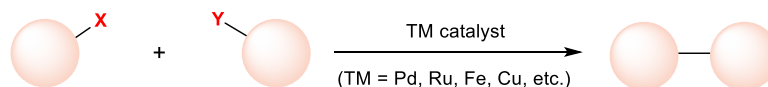
(R)-SL-0103-1

Materials

Epoxy resin monomer YX4000H

Starting material for
Upilex monomer

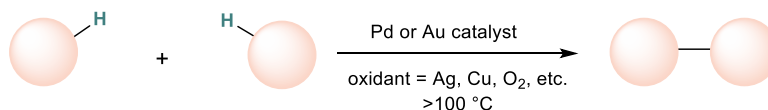
(b) Synthesis of symmetrical biaryls

Transition metal catalyzed C–X/C–Y coupling

X = halogen, OTf, OTs, B(OR)₂, MgX, etc.

Y = halogen, OTf, B(OR)₂, ZnX, MgX, AlR₂, SnR₃, SiR₃, Li, etc.

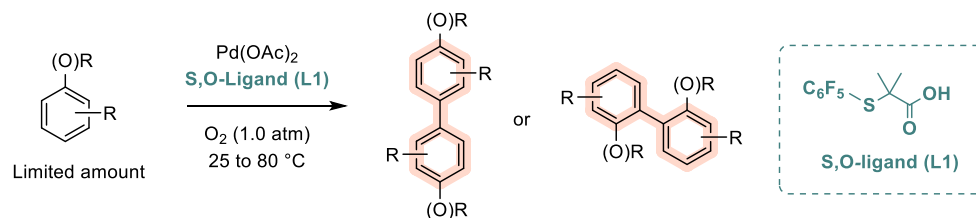
Ball = (Hetero)aryl.

Transition metal catalyzed oxidative dehydrogenative homocoupling

Ball = benzene, toluene, xylene, anisole, etc.

Pd, Cu, Fe, Cr, V catalyst for activated (hetero)arenes: aniline, phenol, pyrrole, thiophene, etc.

(c) This work: Oxidative dehydrogenative coupling



Limited amount

- Mild reaction conditions
- Commercial and stable aryl sources
- Simple set-up and work-up
- Late-stage functionalization

Scheme 1. a) Selected examples of symmetrical biaryls. b) Strategies for the synthesis of symmetrical biaryls. c) **This work:** Oxidative dehydrogenative homocoupling of arenes *via* Pd/S,*O*-ligand.

In 2017, we disclosed the use of a bidentate S,*O*-ligand to enhance the activity of the Pd(II) catalyst to facilitate the C–H functionalization of directing group-free arenes.^[13] This approach was successfully applied to a broad variety of substrates including thiophene,^[14] aniline,^[15] and anisole derivatives for C–H

olefination and arylations reactions.^[16] In this context, during our studies on the direct C–H arylation of 2-methyl anisole using aryl iodides as coupling partners,^[16c] we observed the formation of the homocoupling product. Inspired by these results, we envisioned that biaryl dimers could be synthesized through the

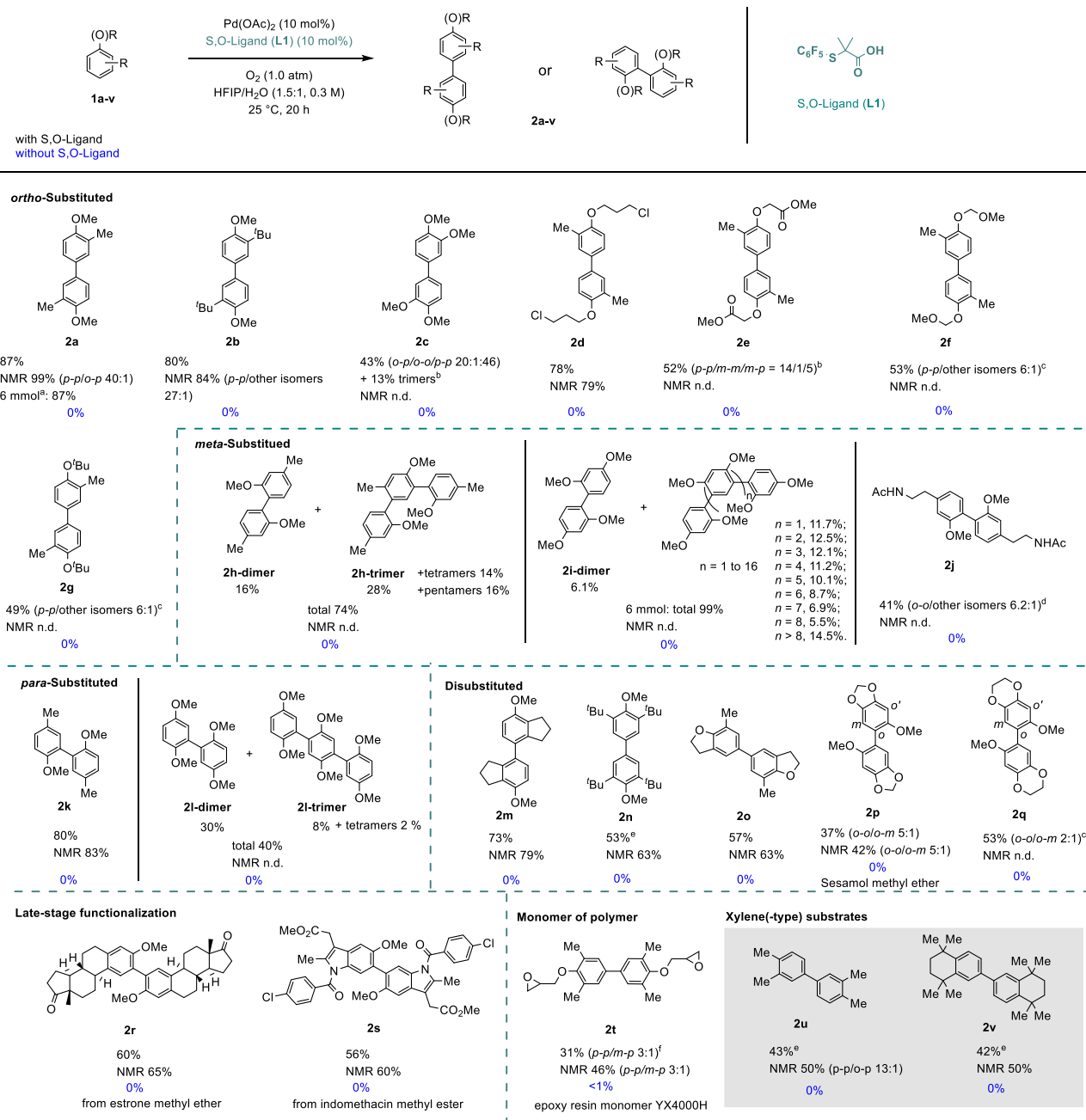
homocoupling of simple arenes under mild reaction conditions using our Pd(II)/S,O-ligand catalytic system. Herein, we present the successful application of a Pd(II)/S,O-ligand catalytic system to efficiently drive the oxidative dehydrogenative homocoupling of various anisole derivatives under remarkably mild conditions, using 1 atm of O₂ at room temperature. This methodology provides a highly efficient approach for synthesizing valuable symmetric biaryl scaffolds and is applicable to the oxidative dehydrogenative homocoupling of bioactive compounds or other non-activated arenes.

To start our investigation, we chose the Pd(II)-catalyzed dehydrogenative coupling of 2-methyl anisole (**1a**) as the model substrate to optimize the reaction conditions. Based on our previous experience in non-directed C–H arylation of anisole derivatives,^[16c] we initially studied the reaction using Pd(OAc)₂, S,O-ligand (**L1**) as the catalyst, with AgOAc serving as the oxidant in hybrid solvent (with H₂O). After an extensive screening of solvents, temperature, ligands and other condition parameters (see Table S1–S9, Supporting Information) the optimal conditions were achieved in the presence of Pd(OAc)₂/S,O-ligand **L1** (10 mol%) in HFIP/H₂O (1.5:1; 0.3 M). Gratifyingly, AgOAc could be replaced by a balloon of O₂ (1 atm), and the reaction was carried out at room temperature leading to the desired *p-p* homocoupling product **2a** in 87% isolated yield with a nearly flawless *para-para* regioselectivity (*p-p/o-p* 40:1). Noteworthy, during the evaluation of different solvents, we observed the significant impact of fluorinated solvents, as reported in C–H activation reactions,^[17] and the essential role of water in this transformation.^[18] Furthermore, the dehydrogenative homocoupling of **1a** was easily scaled up using this procedure. Thus, **2a** was prepared on a 6 mmol scale (1.26 g, 87% isolated yield) employing a reduced catalyst loading (5 mol% Pd(OAc)₂/S,O-ligand **L1**) showcasing the robustness of the methodology.

Encouraged by the results, we decided to examine the scope of the oxidative dehydrogenative homocoupling reaction of anisole derivatives promoted by the Pd(II)/S,O-Ligand **L1** catalytic system (**Scheme 2**). Anisole derivatives bearing *ortho*-substituents (-OMe and -Bu) were well tolerated under our reaction conditions, giving rise to the corresponding products (**2b-c**) in moderate to high yields (43–80%). The reaction of the anisole with the *tert*-butyl substituent (**1b**) showed high regioselectivity in favor of the *p-p* product for steric reasons. When the electron-rich veratrole (**1c**) was used as a starting material the reaction was carried out at 60 °C to achieve a better conversion. The resulting product mixture comprised three isomers alongside trimers (13%). As anticipated, the reaction involving the simplest anisole (**1a**) exhibited notable reactivity but lacked selectivity (Figure S1, Supporting Information). Next, we moved our attention to *O*-substituted 2-methyl anisole derivatives (**1d-g**). Notably, the biaryl product **2d** (78% yield)

was exclusively formed as the sole isomer at room temperature when utilizing *O*-3-chloropropyl anisole **1d**. Conversely, when employing other *O*-alkyl groups, the corresponding products (**2e-g**) were obtained in low to moderate yields at room temperature. To increase the conversion the reactions were carried out at 60 °C and in some cases we introduced catalytic amounts of Cu(OAc)₂ (20 mol%) as a co-oxidant (**2f-g**). Under these conditions, yields of ≈50% and isomeric mixtures were obtained. Subsequently, we moved our attention to *meta*-substituted anisole derivatives and observed that the reactions exhibited *o-o*-selectivity, which can be attributed to the steric effects imposed by the *meta*-substituents. 3-Methylanisole (**1h**) furnished only 16% of *o-o* dimer product (**2h**) together with other oligomers (trimer **28**, tetramers 14%, and pentamers 16%). Following this trend, the reaction of the more activated 1,3-dimethoxy benzene (**1i**) provided a wide range of coupled products, ranging from the smallest **2i**-dimer to the largest **2i**-18-mer. In contrast, the reaction with 3-(2-NHAc ethyl) anisole **1j** showed low reactivity (NMR yield <30%), even when 1.5 equiv. of Cu(OAc)₂ was used as the oxidant, regardless of whether the reaction was conducted at 25 or 60 °C. To improve the conversion, AgOAc was employed as an alternative oxidant. After minor modifications of reaction conditions, using O₂ and a catalytic amount of AgOAc (20 mol%) at 60 °C, the homocoupling product **2j** was formed in 49% yield (*o-o*/other isomers 6.2:1). Next, we demonstrated the efficiency of our Pd(OAc)₂/S,O-Ligand **L1** catalytic system for the homocoupling of *para*-substituted anisole derivatives. The reaction with 4-methylanisole (**1k**) yielded the corresponding dimer (**2k**) as the sole product in an 80% yield. On the contrary, the reaction of the anisole bearing a methoxy group (**1l**) provided a mixture of three products (**2L**-dimer, trimer, tetramer), with the **2L**-dimer homocoupling product forming preferentially (30%). Disubstituted anisoles (**1m-q**) displayed good activity toward homocoupling using our catalytic system. Particularly, perfect *p-p* regioselectivity was observed with anisoles containing two alkyl or one dihydrofuran group on the benzene ring (**1m-o**). The homocoupling of sesamol methyl ether **1p** and 1,4-benzodioxan derivative **1q** provided a mixture of isomers in low to moderate yields (37–53%). The homocoupling reaction using other substituted anisoles bearing electron withdrawing or coordinating substituents were unsuccessful using our catalytic system (Figure S1, Supporting Information).

Next, we extended our catalytic protocol for the late-stage functionalization of structurally complex molecules. To our delight, the homocoupling of estrone methyl ether (**1r**) and indomethacin methyl ester (**1s**) gave the corresponding dimers with perfect regioselectivity in 60% and 56% yields, respectively (**2r** and **2s**). Furthermore, the synthesis of the epoxy resin monomer YX4000H (**2t**) was also realized using our catalytic system. Although the corresponding monomer (**2t**) was



Scheme 2. Scope of substrates. *Conditions:* **1** (0.3 mmol, 1.0 equiv.), Pd(OAc)₂ (10 mol%), **L1** (10 mol%), and O₂ (1 atm) in HFIP/H₂O (1.5:1, 0.3 M) at 25 °C for 20 h; isolated yields. a) **1a** (6.0 mmol), Pd(OAc)₂ (5 mol%), **L1** (5 mol%). b) 60 °C. c) 60 °C, Cu(OAc)₂ (20 mol%). d) 60 °C, AgOAc (20 mol%). e) 60 °C, HFIP (0.3 M), Cu(OAc)₂ (20 mol%). f) 80 °C, HFIP, AgOAc (1.5 equiv.) instead of O₂ (1 atm).

obtained in only 31% yield with low regioselectivity (at 80 °C and 1.5 equiv. of AgOAc), these results still highlight the feasibility of the homocoupling approach for simple arenes containing epoxide groups.

To further prove the versatility of the Pd/S,O-ligand catalytic system in homocoupling reactions, we decided to explore the reactivity of less reactive arenes. To our delight, employing limited amounts of *o*-xylene (0.3 mmol) and catalytic amounts of Cu(OAc)₂ (20 mol%) in HFIP at

60 °C the 3,3',4,4'-tetramethyl-1,1'-biphenyl (**2u**) was produced in good yield (43%) and regioselectivity (*p-p/o-p* 13:1). Similarly, a good yield was obtained using the bulky alkyl-substituted benzene **1v**, resulting in the exclusive formation of the *p-p*-homocoupling product (**2v**).^[19] To confirm the essential role of the S,O-ligand (**L1**), we performed all the reactions in its absence. As expected, no reaction occurred, demonstrating its importance in this transformation (Scheme 2).

Given the industrial importance of the homocoupling product of *o*-xylene as an alternative precursor to the monomer of Upilex,^[20] and encouraged by the results discussed earlier, we decided to explore its synthesis using our catalytic system under neat conditions, given the low cost of *o*-xylene. As shown in **Table 1**, under neat conditions, the desired monomer **2u** was only obtained in trace amounts (Table 1, entry 1). Notably, the inclusion of catalytic amounts of fluorinated solvents significantly improved the yield, albeit at the expense of a slight decrease in selectivity for **2u** (Table 1, entries 2–5). Remarkably, in all cases, excellent chemoselectivity toward the formation of the dimer was achieved. The current study represents an important milestone in the oxidative homocoupling of *o*-xylene for future industrial applications.

To gain insight into the mechanism of this reaction, we began our investigation by studying the reaction kinetics using the initial rates method.^[21] A linear relationship was observed for both Pd/S,O-ligand **L1** and anisole **1a**, with the slope close to one, indicating first-order kinetics for these reagents. A parallel deuterium kinetic isotope effect (KIE) experiment was conducted, yielding a value of 3.7 (Supporting Information). This finding, together with the observed first-order kinetic in catalyst and anisole, indicates that the C–H activation is the rate-determining step.

In summary, we have developed an efficient oxidative dehydrogenative homocoupling reaction of anisole derivatives utilizing a Pd/S,O-ligand catalytic system under mild reaction conditions. Our Pd/S,O-ligand exhibited high catalytic activity across a broad range of anisole derivatives, accommodating both neutral and electron-rich substituents. The desired homocoupling products were obtained in moderate to good yields

and with high *para-para* or *ortho-ortho* regioselectivity using 1 atm of O₂ as the oxidant at room temperature. The developed catalytic system demonstrated compatibility with the late-stage modification of bioactive anisole derivatives. Moreover, the C–H homocoupling of *o*-xylene streamlined the synthesis of the industrial valuable monomer of Upilex. Our approach delivered yields and regioselectivities comparable to those reported in previous studies, with near-perfect chemoselectivity under milder, industry-friendly conditions.

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Conflict of Interest

The authors declare no conflict of interest.

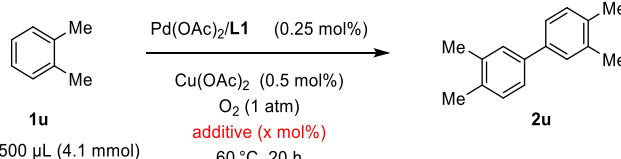
Data Availability Statement

Research data are not shared.

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Table 1. C–H homocoupling of *o*-xylene under neat conditions.



Entry	Additive/[mol%]	Yield ^{a)} [%]	Regio ^{b)} [%]	Chemo ^{c)} [%]
1	none	0.9	88	99.97
2	HFIP (12 mol%)	8.6	71	99.81
3	HFIP (3 mol%)	4.5	69	99.86
4	TFE (12 mol%)	7.8	73	99.76
5	TFA (12 mol%)	4.6	78	99.46
6	AcOH (12 mol%)	0.7	96	99.99

^{a)} Determined by GC analysis, collective biaryl yield, internal standard = *n*-dodecane.

^{b)} % of 3,3',4,4'-tetramethylbiphenyl *versus* all dimers.

^{c)} % of dimers *versus* side products (trimers).

Minimum oxidation product was detected by GC-MS.

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