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Tuning Reactivity and Site Selectivity of Simple Arenes in C–H Activation: Ortho-Arylation of Anisoles via Arene–Metal π-Complexation

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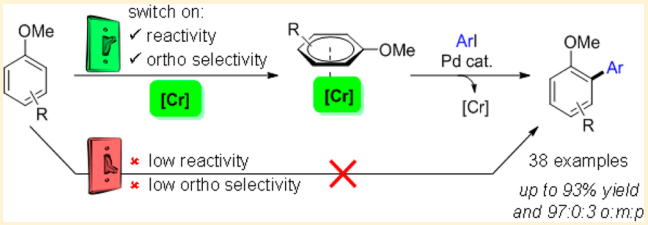
Supporting Information

ABSTRACT: Current approaches to achieve site selectivity in the C–H activation of arenes involve the use of directing groups or highly electron-poor arenes. In contrast, simple arenes, such as anisole, are characterized by poor reactivity and selectivity. We report that π-complexation to a $Cr(CO)_3$ unit enhances the reactivity of anisoles providing an unprecedented *ortho*-selective arylation. This mild methodology can be used for the late stage functionalization of bioactive compounds containing the anisole motif, allowing the construction of novel organic scaffolds with few synthetic steps.



INTRODUCTION

Over the past decade, C–H arylation has emerged as a powerful methodology for the synthesis of biaryls,[1] important motifs in pharmaceuticals, agrochemicals, organic materials, and natural products.[2] Arenes containing a wide variety directing groups can now be readily ortho-arylated.[3] Some progress has also been made in recent years toward achieving selective meta- and para-arylation.[4,5] However, C–H arylation of so-called simple arenes,[6] that is arenes without a directing group, remains a challenge: (1) their low reactivity results in large amounts of the arene being generally required and (2) useful regioselectivity is rarely obtained, thus limiting these reactions to symmetrical substrates. The only exceptions are highly electron-deficient substrates, such as polyfluorobenzenes, where the more acidic C–H bonds can be readily activated.[7] In this context, the efficient arylation of anisole, a ubiquitous motif in biologically active compounds (Scheme 1a),[8] still represents a remarkable reactivity and selectivity challenge (Scheme 1b).[9]

Fagnou's initial report on the Pd-catalyzed direct arylation of anisole with *para*-bromotoluene[6b] highlighted its low reactivity and poor site selectivity (o:m:p 25:50:25). Subsequent reports on Pd-catalyzed oxidative couplings with anisole described the formation of mixtures of regioisomers with a preference for the para isomer.[6d,9c,f] Conversely, Fe-,[9i] Rh-,[9e] and Ir-catalyzed[9b,g] and metal-free couplings[9h,j] show a slight preference for the ortho isomer (59:41 to 71:29 of o:m+p). Besides the overall lack of regioselectivity, all of these reported methodologies also require a large excess of anisole (10–100 equiv) and high reaction temperatures (100–180 °C). Groundbreaking developments were reported in 2011 by the groups of Yu[5a] and Gaunt,[5b] with two elegant examples of highly regioselective Pd- and Cu-catalyzed para-arylation reactions of anisoles (Scheme 1b). In both methods, the regioselectivity of arylation was associated with a sterics-biased electrophilic-type pathway. Here we report the first example of an ortho-selective direct arylation of anisoles (Scheme 1c),[10] using a π-complexation strategy for the enhancement of reactivity and regioselectivity.

Recently, our group reported that π-complexation of a strongly electron-withdrawing $Cr(CO)_3$ unit to fluorobenzene greatly enhances its reactivity toward C–H arylation via a proposed concerted metalation–deprotonation (CMD) pathway.[11] We initially hypothesized that the increased reactivity was due to the formation of a highly electron-poor arene, resulting in weaker C–H bonds. However, computational studies indicated that a more facile out-of-plane bending of the C–H bond to adopt the CMD transition state geometry was the dominating factor. Thus, we reasoned that this effect may also operate on electron-rich arenes, allowing a previously inaccessible CMD pathway. Interestingly, computational studies by Fagnou and Gorelsky[12] showed that, despite the general low reactivity of anisole, a CMD process would selectively proceed at the ortho position. Therefore, we hypothesized that π-complexation could have a triple effect on the reactivity of anisole: (1) enhance reactivity toward a CMD process, avoiding the need for using a large excess of the arene; (2) eliminate S_EAr-type reactivity (and therefore para-reactivity), and (3) afford the CMD-preferred ortho-regioisomer.

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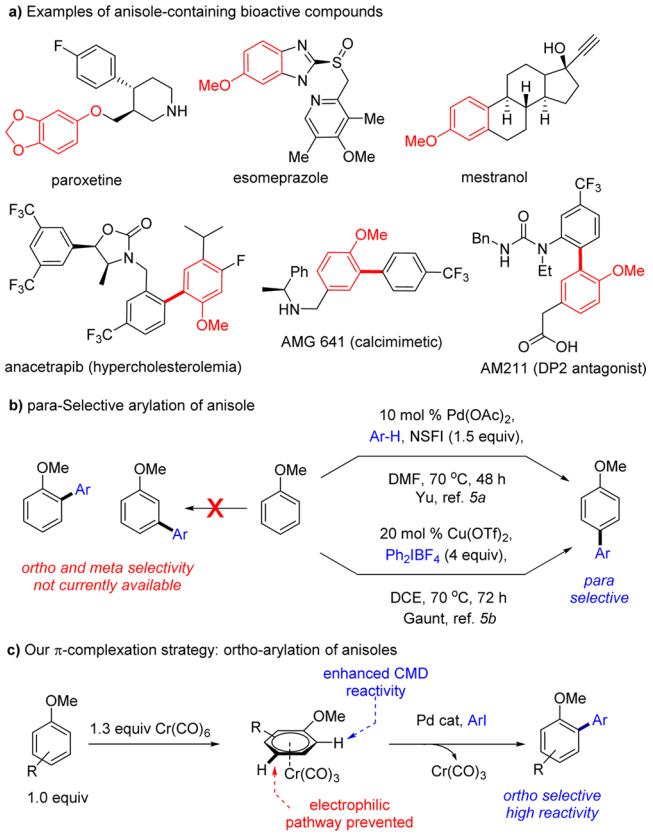
Scheme 1. Regioselective *Ortho*-Arylation of Anisole via Arene–Metal π-Complexation



RESULTS AND DISCUSSION

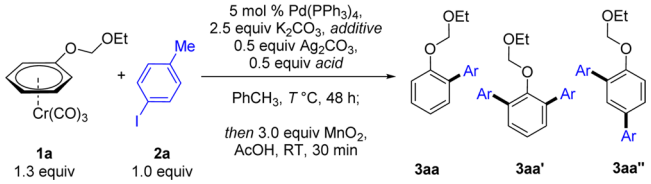
To test our hypothesis, we chose (ethoxymethoxy)benzene as a benchmark substrate (Table 1). Chromium complexes of anisoles are easily prepared, and **1a** was obtained in high yield (81%) from reaction of 1.0 equiv of the arene with 1.3 equiv of $Cr(CO)_6$. Initially, we tested the catalytic system previously developed in our group, followed by in situ demetalation (Table 1, entry 1). Gratifyingly, biaryl **3aa** was obtained in good yield (58%) and excellent ortho-selectivity, confirming that π-complexation for enhancement of reactivity is not exclusive to electron-poor arenes. Screening of different carboxylic acid cocatalysts (Table 1, entries 1–4) showed that acids with low a pK_a, such as *p*-NO_2–C_6H_4–CO_2H (pK_a 3.4), provide no reactivity, while *p*-NMe_2–C_6H_4–CO_2H (pK_a 4.9) can impart similar reactivity to that of 1-AdCO_2H (pK_a 5.0). We hypothesized that a more reactive catalytic system may be achieved by addition of an organic base soluble in toluene, which could assist in the deprotonation of 1-AdCO_2H. Screening of basic additives (entries 5–7) showed that the highly hindered amine TMP (2,2,6,6-tetramethylpiperidine)[13] provided **3aa** in high yield and with excellent ortho-selectivity (o:m:p 95:0:5).[14] The reaction proceeded in lower yields in the absence of K_2CO_3 or 1-AdCO_2H, and not at all in the absence of Ag_2CO_3 (entries 9–11). Finally, a control experiment with 20 equiv of (ethoxymethoxy)benzene (entry 12) gave no yield of the C–H arylation product, highlighting the outstanding reactivity-enhancing effect imparted by $Cr(CO)_3$.

With the optimal reaction conditions in hand, we set out to explore the generality of the method with respect to different substituted anisoles (Scheme 2).[15] Varied alkyl substitution at the oxygen was possible, with the corresponding biaryls **3aa**–**3da** obtained in high yields and with high ortho-selectivities, even when using a sterically hindered isopropyl substituent (**3da**). Para- and meta-substituted anisole complexes led to the corresponding biaryl products in excellent yields (**3ea**–**3la**) and complete regioselectivity. It is noteworthy that a strongly electron-withdrawing CO_2Me para-substituent is compatible with the reaction, with the regioselectivity still being governed by the MeO group (**3la**). Furthermore, more electron-rich arenes, containing two MeO groups (**3ma**–**3oa**), were still highly reactive under the reaction conditions, strongly supporting our hypothesis that reactivity in this case does not correlate with electron density at the arene. Interestingly, ortho-substituted anisole, **1r**, provided only a low yield of product **3ra**. This may result from a C–OMe conformation with increased steric hindrance at the ortho-C–H bond. Indeed, while the MeO group in **1r** would be projected toward the ortho-C–H bond, when this conformation is prevented via ring closure, as in dihydrobenzofuran (**1s**), high reactivity is restored. This effect was used to impart complete regioselectivity in the direct arylation of the unsymmetrical 1,4-hydroquinone derivative **1t**.

We then explored the compatibility of our reaction conditions with a variety of functional groups in the aryl iodide coupling partner. Our optimized conditions were applicable to a wide range of electron-donating and -withdrawing substituents in the ortho, meta, and para positions, affording the corresponding biaryl products **3ka**–**3ko** in excellent yields (Scheme 3). In particular, the reaction is compatible with Cl and Br substituents (**3ke**, **3kf**), which would allow for further Pd-catalyzed cross-couplings, as well as esters, ketones, and thioethers among other functionalities.

C–H functionalization is an attractive tool for late-stage functionalization of bioactive compounds.[16] Steroidal derivatives possess broad spectrum utility in modern medicine and currently find wide application as adjuvants in cancer

Table 1. Optimization of the Direct Arylation of Complex 1a and 4-Iodotoluene (2a)[a]



entry	R–CO_2H	additive (2 equiv)	T (°C)	3aa:3aa′:3aa″ yield (%)[b]
1	1-AdCO_2H	–	60	58:3:1
2	PhCO_2H	–	60	34:1:1
3	*p*-NO_2–C_6H_4–CO_2H	–	60	0:0:0
4	*p*-NMe_2–C_6H_4–CO_2H	–	60	52:3:5
5	1-AdCO_2H	piperidine	60	0:0:0
6	1-AdCO_2H	Et_3N	60	57:3:3
7	1-AdCO_2H	TMP	60	78:3:5
8	1-AdCO_2H	TMP	50	69:3:5
9[c]	1-AdCO_2H	TMP	60	52:5:6
10	–	TMP	60	39:2:1
11[d]	1-AdCO_2H	TMP	60	0:0:0
12[e]	1-AdCO_2H	TMP	60	0:0:0

[a]Reactions carried out on 0.1 mmol scale with respect to **2a**. [b]Yield determined by ^{1}H NMR of the crude using an internal standard. [c]No K_2CO_3 was added. [d]No Ag_2CO_3 was added. [e]20 equiv of (ethoxymethoxy)benzene were used instead of complex **1a**.

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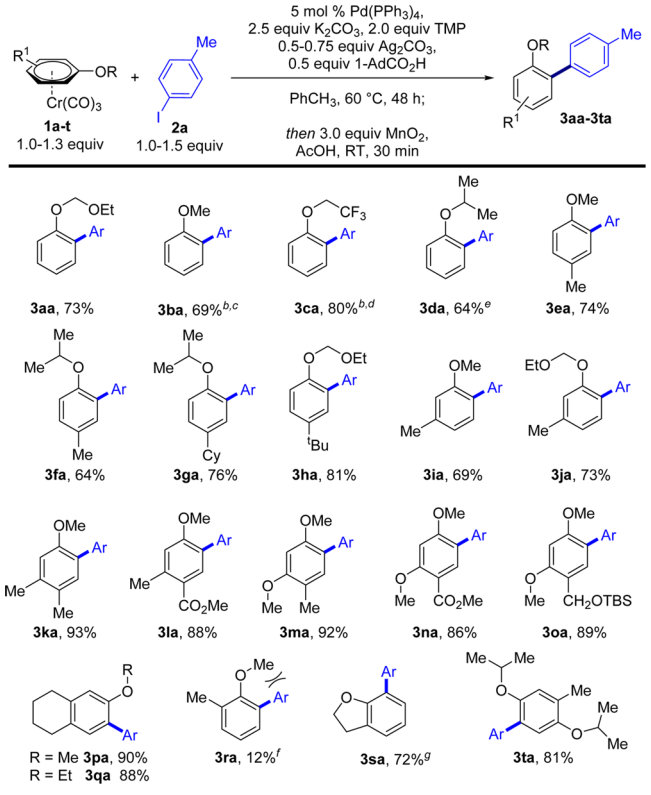
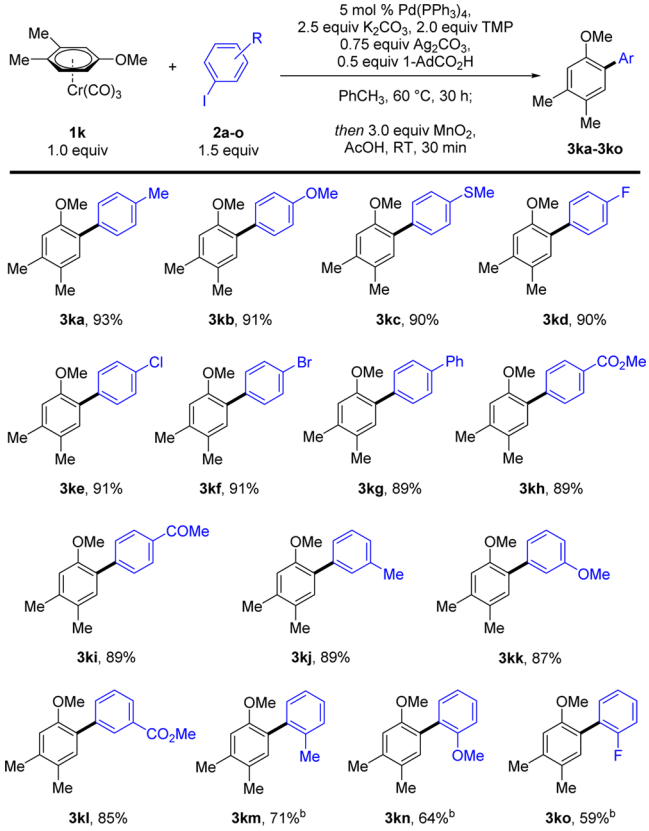
Scheme 2. Scope of the Direct Arylation of Anisole–$Cr(CO)_3$ Complexes 1a–t with 2a[a]



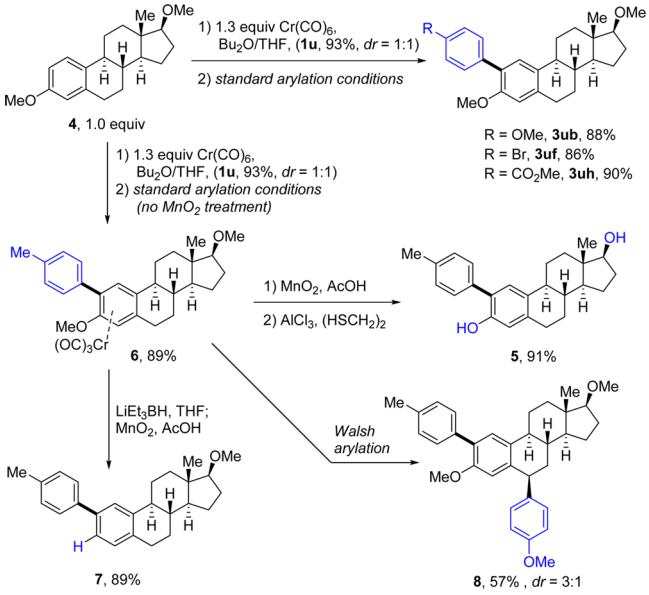
[a]Reactions carried out on a 0.5 mmol scale with respect to the limiting reagent. Yields are of isolated product. [b] Performed with *p*-NMe_2–C_6H_4–CO_2H. [c] o,p-Bisarylated product **3ba′′** (3%) was also obtained. [d] o,p-Bisarylated product **3ca′′** (4%) was also obtained. [e] o,p-Bisarylated product **3da′′** (7%) was also obtained. [f] o,p-Bisarylated product **3ra′′** (3%) was also obtained. [g] Performed without TMP.

Scheme 3. Scope of the Direct Arylation of Complex 1k with Iodoarenes 2a–o[a]



[a]Reactions carried out on a 0.5 mmol scale with respect to the limiting reagent. Yields are of isolated product. [b] Performed with 2.0 equiv of **2** for 40 h.

Scheme 4. Late-Stage Functionalization of Estradiol Derivatives *via* Metal–Arene π-Complexation



chemotherapy.[17,18] We explored the applicability of our novel approach to the selective ortho-arylation of estradiol (Scheme 4). Cr-complexation of dimethylestrone (**4**) yielded complex **1u** in 93% yield and a 1:1 diastereomeric mixture. Application of our methodology to this mixture with different iodoarenes provided the desired arylated adducts (**3ub**, **3uf**, and **3uh**) with complete regioselectivity and excellent yields. Treatment with $AlCl_3$ allowed simultaneous demethylation of both hydroxyl groups, producing aryl-estradiol derivative **5** in excellent yield. Furthermore, the air-stable Cr-complexed biaryls could also be easily isolated in high yields, and the $Cr(CO)_3$ unit was then utilized to control other functionalizations on the steroid core. Reaction of **6** with $LiEt_3BH$ allowed demethoxylation to steroid derivative **7**.[19] Application of Walsh's benzylic arylation conditions to **6** allowed selective arylation at the less hindered benzylic position, forming **8** with good yield and diastereoselectivity.[20]

Anisole is approximately 10^4 times less reactive than 1,3,5-trifluorobenzene under standard CMD-type reaction conditions.[6b,7a] Interestingly, competition experiments indicate that anisole complex **1b** is 4.7 times more reactive than 1,3,5-trifluorobenzene, showcasing a 4 orders of magnitude enhancement of reactivity toward C–H arylation of anisole after complexation.[21,22] A competition experiment between deuterated complex **1p**-5,7-d_2 and **1q** highlighted the latter as 2.0 times more reactive, consistent with the KIE previously measured for complexed fluorobenzene,[11] suggesting a similar reaction pathway is in operation.

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CONCLUSIONS

In conclusion, we have demonstrated that π-complexation of a $Cr(CO)_3$ unit to anisole-type arenes can "switch on" a highly ortho-selective Pd-catalyzed direct arylation process. Our method allows for the easy ortho-arylation of a range of (di)alkoxybenzenes. The high reactivity achieved with just 1 equiv of the arene under mild conditions (no strong acids/bases, 60 °C) makes this approach suitable for the late-stage functionalization of anisole-containing bioactive compounds. In addition, the Cr-unit can be used as a handle for further transformations on and around the arene, allowing for quick access to a variety of structures from a common precursor. This process is likely occurring via a concerted metalation−deprotonation type pathway, which is normally not accessible to electron-rich arenes.

EXPERIMENTAL SECTION

General Procedure A: Preparation of Arene Chromium Tricarbonyl Complexes (1). A flame-dried round-bottom flask equipped with a magnetic stirrer and a reflux condenser was charged with $Cr(CO)_6$ (6.50 mmol, 1.3 equiv), evacuated, and backfilled with Ar. The required O-substituted phenol (5.00 mmol, 1.0 equiv) was added to the flask, followed by the addition of anh. nBu_2O and THF (9:1 v/v, 0.15 M). The resulting suspension was subjected to freeze−pump−thaw cycles (3 × 30 min) and then refluxed (external temperature 150 °C) for 48 h. The solution was then cooled down to room temperature and filtered through a short pad of silica. The silica pad was washed with Et_2O (3 × 20 mL), and the organic layer was then concentrated *in vacuo*. Recrystallization from a cold mixture of hexane/Et_2O 9:1 provided the arene tricarbonyl chromium complex **1**.

*(Ethoxymethoxy)benzene Tricarbonyl Chromium (**1a**, Table 1).* General procedure A was applied by using $Cr(CO)_6$ (1.43 g, 6.5 mmol, 1.3 equiv) and (ethoxymethoxy)benzene (0.760 g, 5 mmol, 1.0 equiv). Recrystallization from cold hexane gave the title product **1a** as a yellow solid in 81% yield (1.17 g, 4.06 mmol). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) = 5.84 (app. t, J = 6.6 Hz, 2H), 5.54 (d, J = 6.4 Hz, 2H), 5.22−5.16 (m, 3H), 3.75 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ (ppm) = 235.6, 143.2, 97.7, 95.4, 89.0, 83.2, 66.5, 16.0. IR: ν = 3096, 1949, 1843, 1531, 1226, 1082, 959 cm^{-1}. Mp: 78−80 °C. HRMS EI+ m/z calcd $C_{12}H_{13}CrO_5$: $[M + H]^+$ 289.0163; found: $[M + H]^+$ 289.0162.

General Procedure B: Direct Arylation of Arene Tricarbonyl Chromium Complexes 1 with Iodoarenes 2 (Excess of Chromium Tricarbonyl Complex). To an oven-dried microwave 10 mL glass vial equipped with a round stirrer bar, the following reagents were added in this order: K_2CO_3 (172.5 mg, 1.25 mmol, 2.5 equiv), 1-$AdCO_2H$ (45.0 mg, 0.25 mmol, 0.5 equiv), Ag_2CO_3 (70 mg, 0.25 mmol, 0.5 equiv), $Pd(PPh_3)_4$ (5 mol %, 28.9 mg, 0.01 mmol), the required arene $Cr(CO)_3$ complex **1** (0.65 mmol, 1.3 equiv), and iodoarene **2** (0.50 mmol, 1.0 equiv). $PhCH_3$ (0.3 mL, 1.7 M) and 2,2,6,6-tetramethylpiperidine (170 μL, 1.00 mmol, 2.0 equiv) were added, and the glass vial was sealed with a disposable microwave cap. The resulting mixture was stirred for 48 h at 60 °C. The reaction was then cooled down, and AcOH (2 mL) was slowly added with moderate stirring. After 5 min, MnO_2 (130 mg, 1.50 mmol, 3 equiv) was added in small portions and the black suspension was vigorously stirred for 30 min. The suspension was then loaded on a short silica plug (2 cm × 4 cm) and eluted with Et_2O (30 mL) before concentrating in vacuo. Purification via flash chromatography column on silica gel provided the required biaryl product.

*2-(Ethoxymethoxy)-4′-methyl-1,1′-biphenyl (**3aa**, Table 1).* General procedure B was applied with arene chromium complex **1a** and 4-iodotoluene **2a**. Flash chromatography (gradient 1−5% Et_2O in hexane) that was performed prior to demetalation afforded the corresponding biaryl $Cr(CO)_3$ complex. AcOH (2 mL) and MnO_2 (130 mg, 1.5 mmol, 3 equiv) were then added, and the black suspension was vigorously stirred for 30 min. The suspension was then loaded on a short silica plug (2 cm × 4 cm) and eluted with Et_2O (30 mL). Removal of solvent in vacuo afforded the title **3aa** as a colorless oil in 73% yield (88.6 mg, 0.366 mmol). Crude ^{1}H NMR of the reaction shows an isomer ratio o:o,o:o,p = 26:1:1.7 which corresponds to an o:m:p = 95:0:5 ratio. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43 (d, J = 7.6 Hz, 2H), 7.35−7.20 (m, 5H), 7.07 (app t, J = 6.8 Hz, 1H), 5.16 (s, 2H), 3.66 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.19 (t, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 154.6, 136.7, 135.9, 131.9, 131.0, 129.6, 128.9, 128.5, 122.2, 115.8, 93.9, 64.4, 21.3, 15.2. IR: ν = 2976, 1600, 1485, 1218, 1103, 993 cm^{-1}. HRMS EI+ m/z calcd $C_{16}H_{21}O_2N$: $[M+NH_4]^+$ 260.1645; found: $[M+NH_4]^+$ 260.1647.

General Procedure C: Direct Arylation of Arene Tricarbonyl Chromium Complexes 1 with Iodoarenes 2 (Excess of Iodoarene). To an oven-dried microwave 10 mL glass vial equipped with a round stirrer bar, the following reagents were added in this order: K_2CO_3 (172.5 mg, 1.25 mmol, 2.5 equiv), 1-$AdCO_2H$ (45.0 mg, 0.250 mmol, 0.5 equiv), Ag_2CO_3 (105 mg, 0.375 mmol, 0.75 equiv), $Pd(PPh_3)_4$ (5 mol %, 28.9 mg, 0.010 mmol), the required arene $Cr(CO)_3$ complex **1** (0.5 mmol, 1.0 equiv), and iodoarene **2** (0.75 mmol, 1.5 equiv). $PhCH_3$ (0.3 mL, 1.7 M) and 2,2,6,6-tetramethylpiperidine (170 μL, 1 mmol, 2.0 equiv) were added, and the glass vial was sealed with a disposable microwave cap. The resulting mixture was stirred for 30 h at 60 °C. The reaction was then cooled down, and AcOH (2 mL) was slowly added with moderate stirring. After 5 min, MnO_2 (130 mg, 1.5 mmol, 3 equiv) was added in small portions and the black suspension was vigorously stirred for 30 min. The suspension was then loaded on a short silica plug (2 cm × 4 cm) and eluted with Et_2O (30 mL) before concentrating in vacuo. Purification via flash chromatography column on silica gel provided the required biaryl product.

*2-Isopropoxy-4′,5-dimethyl-1,1′-biphenyl (**3fa**, Scheme 2).* General procedure C was applied with arene chromium complex **1f** and 4-iodotoluene **2a**. Flash chromatography (gradient 0.01−5% DCM in hexane) afforded the title product **3fa** as colorless oil in 64% yield (77.1 mg, 0.321 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.49 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 7.18 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.4, 2.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.35 (septet, J = 6.0 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 1.25 (d, J = 6.0 Hz, 6H) . ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 152.9, 136.3, 136.2, 132.2, 131.8, 130.6, 129.5, 128.9, 128.7, 116.2, 71.4, 22.2, 21.3, 20.7. IR: ν = 3021, 2975, 1492, 1230, 1110, 953 cm^{-1}. HRMS EI+ m/z calcd $C_{17}H_{21}O$: $[M + H]^+$ 241.1587; found: $[M + H]^+$ 241.1587.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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