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Arene–Metal π-Complexation as a Traceless Reactivity Enhancer for C–H Arylation

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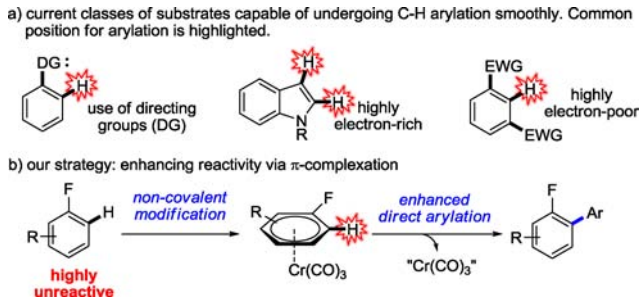
Supporting Information

ABSTRACT: Current approaches to facilitate C–H arylation of arenes involve the use of either strongly electron-withdrawing substituents or directing groups. Both approaches require structural modification of the arene, limiting their generality. We present a new approach where C–H arylation is made possible without altering the connectivity of the arene via π-complexation of a $Cr(CO)_3$ unit, greatly enhancing the reactivity of the aromatic C–H bonds. We apply this approach to monofluorobenzenes, highly unreactive arenes, which upon complexation become nearly as reactive as pentafluorobenzene itself in their couplings with iodoarenes. DFT calculations indicate that C–H activation via a concerted metalation–deprotonation transition state is facilitated by the predisposition of C–H bonds in $(Ar–H)Cr(CO)_3$ to bend out of the aromatic plane.

Carbon–hydrogen arylation is a new and promising tool for constructing biaryl-containing molecules,[1] which has already found important applications in syntheses of organic materials, pharmaceuticals, and natural products.[2] Despite tremendous advances and continuous effort in this field, C–H arylation of arenes is to date almost exclusively limited to three types of substrates (Scheme 1a): (1) arenes bearing a directing group (DG), a functional group capable of coordinating the transition metal catalyst and facilitating C–H activation;[3,4] (2) highly electron-rich arenes;[5] and (3) highly electron-poor arenes, generally requiring two electron-withdrawing groups *ortho* to the C–H bond to be activated.[6] These three approaches are only suitable for arenes bearing an appropriate covalently bonded "reactivity enhancing" substituent. Substrates lacking this feature either are unreactive or must be used in large excesses (often as solvents).[7] Typically, fluorobenzene, with only one electron-withdrawing group, is highly unreactive, and 50 equiv is required to facilitate its C–H arylation, leading to mixtures of *ortho*, *meta*, and *para* biaryls.[7b,f]

Scheme 1. Strategies for Enhancing Reactivity of a C–H Bond toward Direct Arylation



The high reactivity of electron-poor arenes can be explained by a concerted metalation–deprotonation (CMD) process.[6a] In many cases there seems to be a paralleling trend between the reactivity of the arene and the Brønsted acidity of the C–H bond. It is well known that low-valent metal carbonyls such as $Cr(CO)_3$ are able to form stable η^6-complexes with arenes, resulting in a decrease of electron density in the arene, similar to that of a strong electron-withdrawing group, and consequently an increase in acidity.[8] Upon complexation of benzene to $Cr(CO)_3$, its pK_a is lowered by 7 units, an effect similar to that of an *ortho* NO_2 group.[9] This effect also lowers the pK_a at benzylic positions, which has recently been exploited by Walsh et al. in Pd-catalyzed processes.[10] Interestingly, the effect on arene C–H bonds has never been explored in the context of C–H arylation. Thus, we hypothesized that $Cr(CO)_3$ complexes of simple arenes would display greatly enhanced reactivity under CMD-type arylation conditions, compared to the parent arenes. This would lead to a new approach (Scheme 1b) for enhancing the reactivity of simple arenes toward C–H arylation simply by coordinating them to a $Cr(CO)_3$ fragment *without the need for altering their connectivity*.

To test our hypothesis, we chose monofluorobenzenes as benchmark substrates. Direct arylation of 2-fluorotoluene has never been reported. Its complex, **1a**, was prepared, and the reactivity of **1a** toward C–H arylation was examined (Table 1).[11] Initially, we tested Fagnou's well-known catalytic system,[7b] followed by *in situ* oxidative demetalation (Table 1, entry 1).[12] Complex **1a** was incompatible with DMA, and solvent screening revealed $PhCH_3$ as the ideal solvent (entry 2).[13] Carboxylic acid screening showed that 1-$AdCO_2H$ provided similar yields and cleaner reactions compared to $^tBuCO_2H$ (entry 3). Ligandless conditions, initially suggested by Hartwig, were tested unsuccessfully (entry 4).[14] Further Pd catalyst screening revealed that $Pd(PPh_3)_4$ was optimal for this transformation (entries 5–7). Lowering the temperature from 120 to 60 °C provided the best conditions (entry 8), due to increased stability of Cr complex **1a**. The *ortho* regioisomer **3aa** is observed exclusively. The presence of a carboxylic acid is key for achieving high yields, consistent with previous reports on CMD-type C–H activation methodologies (entry 9).[6,7]

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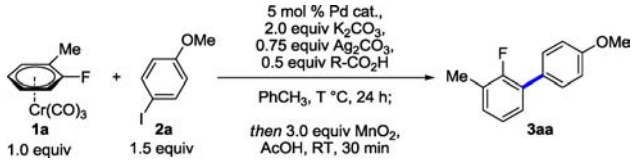
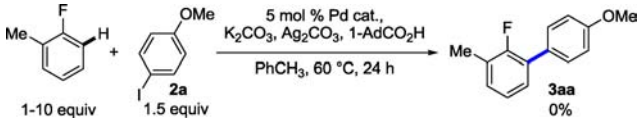
Table 1. Optimization of the Direct Arylation of (2-Fluorotoluene)$Cr(CO)_3$ (1a) with 4-Iodoanisole (2a)[a]



entry	Pd catalyst	R-COOH	T (°C)	3aa yield (%)[b]
1[c]	$Pd(OAc)_2$ + DavePhos	$^tBuCO_2H$	120	0
2	$Pd(OAc)_2$ + DavePhos	$^tBuCO_2H$	120	13
3	$Pd(OAc)_2$ + DavePhos	1-AdCO_2H	120	12
4	$Pd(OAc)_2$	1-AdCO_2H	120	0
5	$Pd(OAc)_2$ + PPh_3	1-AdCO_2H	120	24
6[d]	$Pd(OAc)_2$ + PPh_3	1-AdCO_2H	120	41
7	$Pd(PPh_3)_4$	1-AdCO_2H	120	68
8	$Pd(PPh_3)_4$	1-AdCO_2H	60	90 (89)[e]
9	$Pd(PPh_3)_4$	–	60	64
10	$Pd(PPh_3)_4$	1-AdCO_2H	60	0[f]

[a]Reactions carried out on 0.1 mmol scale with respect to **1a**. 10% of phosphine ligand was used in entries 1–3 and 5. [b]Yield determined by ^1H NMR using an internal standard. [c]Reaction carried out in DMA instead of $PhCH_3$. [d]20% of PPh_3 was used. [e]Isolated yield on 0.5 mmol scale. Reaction carried out for 40 h instead of 24 h. [f]4-Chloroanisole and 4-bromoanisole were used instead of 4-iodoanisole.

Scheme 2. Reaction of Uncomplexed 2-Fluorotoluene



Control experiments with 1–10 equiv of 2-fluorotoluene showed no C–H arylation reaction (Scheme 2), highlighting the outstanding reactivity-enhancing effect imparted by $Cr(CO)_3$ coordination. To determine the extent of this enhancement, we performed a series of competition experiments between $Cr(CO)_3$ complex **1a** and a number of polyfluorobenzenes at short reaction times (Figure 1). Remarkably, the reactivity of

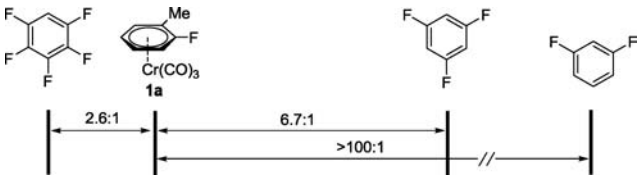
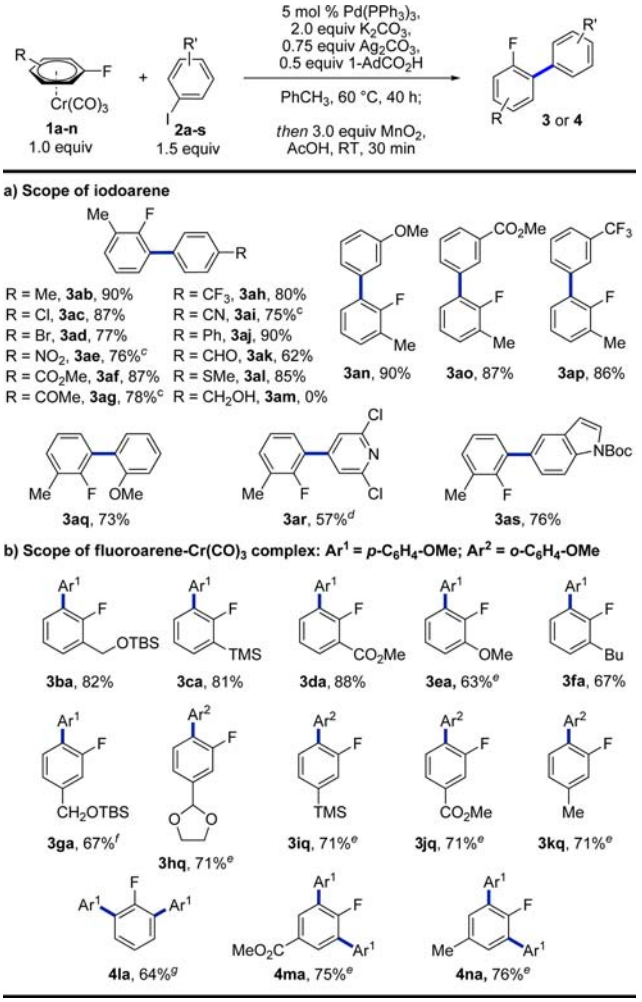


Figure 1. Relative reactivity between Cr complex **1a** and polyfluorobenzenes toward C–H arylation. **1a** and a polyfluoroarene were reacted with **2a** in the same flask. Reactions were stopped at low conversions (10–20%) and ratios determined by ^1H NMR using an internal standard.

complex **1a** toward C–H arylation is close to that of pentafluorobenzene. A KIE of 2.1 was measured for arylation of **1a**, indicating that C–H activation occurs in the turnover-limiting step.

Having validated our hypothesis, we set out to explore the generality of the methodology with respect to the iodoarene coupling partner (Scheme 3a). The optimized conditions were applicable to a wide range of iodoarenes with electron-donating and electron-withdrawing substituents in *para*, *meta*, and *ortho* positions, affording the corresponding biaryl products **3** in

Scheme 3. Scope of the Pd-Catalyzed Direct Arylation of (Fluoroarene)$Cr(CO)_3$ 1a–n with Iodoarenes 2a–s[a,b]



[a]Reactions performed on 0.5 mmol scale. [b]Isolated yields. [c]Reaction time 48 h. [d]Performed at 70 °C with 3 equiv of **2r** and 1.5 equiv of Ag_2CO_3. [e]Performed with 3.0 equiv of **2a** or **2q**. [f]14% of the other *ortho* regioisomer was also obtained. [g]Performed with 4.0 equiv of **2a**.

excellent yields. The reaction is compatible with Cl and Br substituents (**3ac**,**ad**), which would allow for further Pd-mediated transformations, esters (**3af**,**ao**), and ketones (**3ag**). Oxidizable functionalities, like aldehydes (**3ak**) and SMe (**3al**), are compatible, but alcohols need to be protected (**3am**). Pyridine- and indole-based iodoarene compounds can also be used (**3ar**,**as**), albeit higher temperatures are required with **2r** for the reaction to proceed satisfactorily.

We then turned our attention to substitution at the fluoroarene core (Scheme 3b).[11] Functionalities in the *ortho* position such as CH_2OTBS (**3ba**), $SiMe_3$ (**3ca**), CO_2Me (**3da**), and long alkyl chains (**3fa**) were all compatible with the reaction, affording excellent yields of arylated products. Even in the presence of a strongly electron-donating group (MeO) on the fluoroarene, arylation proceeded in good yield (**3ea**). When the substituents were placed in the *meta* position, a second arylation product could be observed in some cases, the major arylation product being at the least hindered position (**3ga**). This could be avoided by employing an *ortho*-substituted iodoarene (**3hq**–**kq**). Finally, with a substituent in the *para* position (**1n**,**m**) or in the absence of a substituent (**1l**), mixtures of single and double

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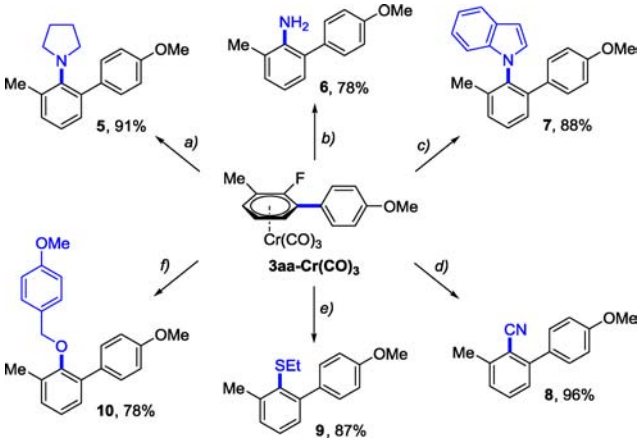
Scheme 4. Nucleophilic Aromatic Substitution Reactions on Arylation Product 3aa-Cr(CO)$_3$[a]



[a]Reagents and conditions: (a) pyrrolidine, K_2CO_3, DMSO; DMSO, 80 °C. (b) NaH, CF_3CONH_2, DMF; NaOH, EtOH. (c) NaH, indole, 15-crown-5-ether, $PhCH_3$; MnO_2, AcOH. (d) KCN, DMSO; DMSO, 80 °C. (e) NaH, EtSH, THF; $h\nu$. (f) NaH, PMB-OH, THF; MnO_2, AcOH.

arylation were obtained. The use of 3-4 equiv of iodoarene allowed for the synthesis of bisarylated adducts **4la–na** in good yields. The reactivity of other electron-poor arenes (Ph-CF_3 and Ph-CO_2Me) toward C–H arylation is also enhanced via $Cr(CO)_3$ complexation; however, poor regioselectivities were observed, leading to complex mixtures of regioisomers and polyarylation.[15]

$Cr(CO)_3$-complexed biaryls can also be isolated before decomplexation, allowing easy functionalization of the C–F bond via a variety of nucleophilic aromatic substitution reactions.[16] For example, arylated complex **3aa-Cr(CO)$_3$** (Scheme 4) was isolated in 72% yield. The C–F bond could then be substituted with N-, C-, S-, and O-nucleophiles, leading to a variety of functionalities in excellent yields: pyrrolidine (**5**), NH_2 (**6**), indole (**7**), CN (**8**), SEt (**9**), and OPMB (**10**).

To probe the origin of enhanced reactivity of $Cr(CO)_3$ complexes **1** toward C–H arylation, DFT calculations were carried out with C_6H_5F or $(C_6H_5F)Cr(CO)_3$ complex (**1l**) and $[Pd(PMe_3)(Ph)OAc]$ (**11**) as the active species effecting C–H activation (Figure 2),[17] which has already been shown to accurately mimic the experimental results of CMD processes for simple arenes.[18,19] The calculated transition state (TS) for **1l** is significantly lower (by 5.7 kcal/mol) than the one calculated for C_6H_5F, consistent with the experimentally observed reactivity.

To gain a better understanding of the different factors involved in the energy difference between the two TSs, distortion–interaction analysis was performed.[19] This analysis separates and quantifies the energy cost for distorting each of the reagents from their minimum energy geometry to the geometry adopted in the TS (ΔG_{dist}) and the energy released in their interaction (ΔG_{int}). This revealed that, while the interaction is less favorable for complex **1l** than for C_6H_5F (by 14.4 kcal/mol), this factor is overcome by the much lower distortion energy cost of **1l** compared to C_6H_5F (by −20.0 kcal/mol).

Ground-state and TS geometries of the arenes are essentially identical except for the C–H bond undergoing activation: in the TS of **1l** this C–H bond is significantly elongated (1.419 vs 1.081 Å in the ground state) and H deviates significantly from the arene plane (33.7° vs 2.1° in the ground state). A study of the

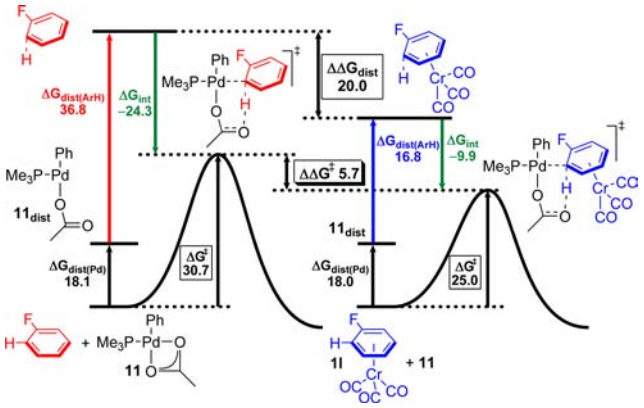
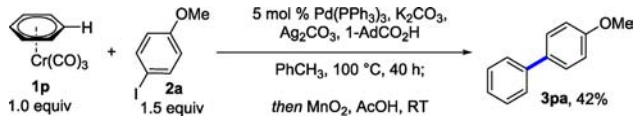


Figure 2. CMD pathway and distortion–interaction analysis for C–H bond activation of complex **1l**. Structures and energies calculated by DFT (B3LYP/DZVP/TZVP). Gibbs free energies (G) in kcal·mol^{-1}. ΔG_{dist}, distortion energy; ΔG_{int}, interaction energy.

contribution of these two factors to ΔG_{dis} for C_6H_5F and **1l** showed that, while the elongation energy is roughly the same in both cases ($\Delta G_{el}(C_6H_5F) - \Delta G_{el}(\mathbf{1l})$ = 1.0 kcal/mol), the bending energy showed a very significant change in favor of complex **1l** ($\Delta G_{bend}(C_6H_5F) - \Delta G_{bend}(\mathbf{1l})$ = 19.1 kcal/mol). Thus, the role of the $Cr(CO)_3$ fragment is to facilitate bending of the H in the TS leading to CMD. This is in stark contrast to previous results for a variety of arenes, where ΔG_{bend} was found to be generally constant and ΔG_{el}, which is directly related to the acidity of the H, was found to be responsible for the differences in reactivity.[19h] Interestingly, a survey of reported crystal structures of $(ArH)Cr(CO)_3$ complexes shows that the arene C–H bonds are generally bent out of the plane toward Cr.[20]

To test the applicability of our approach for enhancing the reactivity of less electron-poor arenes, we examined the effect of complexation on unsubstituted benzene, which has been reported to be 11-fold less reactive than fluorobenzene under CMD conditions.[7b] Gratifyingly, complex **1p** reacted with **2a** under our standard conditions at 100 °C to form the corresponding biaryl product in 42% yield. This demonstrates that our approach is effective even in the absence of an electron-withdrawing group in the arene (Scheme 5).

Scheme 5. Complexation-Enabled Direct Arylation of Benzene



In conclusion, we have demonstrated a novel approach for dramatically enhancing the reactivity of simple arenes toward C–H arylation via π-complexation to $Cr(CO)_3$. This is the first general methodology for direct arylation of monofluorobenzenes affording excellent yields of *ortho*-substituted biaryls with high selectivity. The arylated complexes can be further derivatized, before decomplexation, by reaction with a variety of nucleophiles. Our studies indicate that the observed effect results from a decrease of the energy cost required for distorting the C–H bond of the complexed arene in the CMD transition state. Current studies are directed toward expanding the substrate and reaction scope of this new strategy.

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■ 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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(12) The MnO_2/AcOH system provides a novel, fast, and practical decomplexation procedure. Substrates with functionalities sensitive to oxidation (Scheme 4) can be thermally decomplexed in DMSO at 80 °C or under visible light irradiation.

(13) See SI for complete optimization data.

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