Communication

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

Paolo Ricci, Katrina Kramer, Xacobe Couso Cambeiro, and Igor Larrosa

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja405936s • Publication Date (Web): 20 Aug 2013

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

Paolo Ricci‡, Katrina Krämer‡, Xacobe C. Cambeiro and Igor Larrosa*

School of Biological and Chemical Sciences, Queen Mary University of London, Joseph Priestley Building, Mile End Road, E1 4NS, London, U.K.

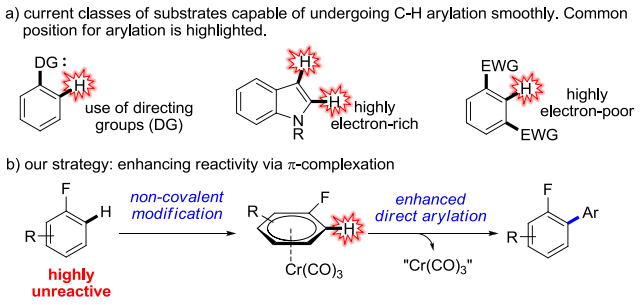
Supporting Information Placeholder

ABSTRACT: Current approaches to facilitate C-H arylation of arenes involve either the use of strongly electron-withdrawing substituents or of directing groups. Both of these approaches require the 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, which greatly enhances 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 metallation-deprotonation (CMD) transition state is facilitated by the predisposition of C-H bonds in $(CO)_3$Cr-Ar-H to bend out of the aromatic plane.

C-H arylation is a new and promising tool for the construction of biaryl containing molecules,[1] which has already found important applications in the synthesis 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 are either 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 are required to facilitate its C-H arylation which leads to mixtures of *ortho*, *meta* and *para* biaryls.[7b,f]

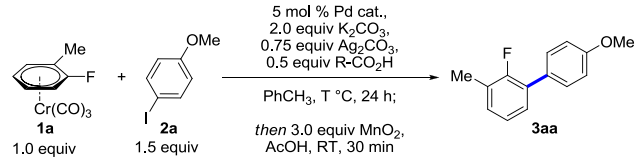
It has been shown that the high reactivity of electron-poor arenes can be explained by a concerted metallation-deprotonation process (CMD).[6a] In many cases there seems to be a paralleling trend between reactivity of the arene and the Brønsted acidity of the C-H bond. It is well known that low valent 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 to $Cr(CO)_3$, the p*K*a of benzene is lowered by 7 units, a similar effect as that of an *ortho* NO_2 group.[9] This effect also lowers p*K*a at benzylic positions, which has recently been exploited by Walsh and coworkers 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 the $Cr(CO)_3$ 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 towards C-H arylation simply by coordinating them to a $Cr(CO)_3$ fragment *without the need for altering their connectivity*.

Scheme 1. Strategies for enhancing reactivity of a C-H bond towards direct arylation



In order to test our hypothesis we chose monofluorobenzenes as benchmark substrates. The direct arylation of 2-fluorotoluene has never been reported. Its complex, **1a**, was prepared and the reactivity of **1a** towards C-H arylation was examined (Table 1).[11] Initially, we tested Fagnou's well-known catalytic system,[7b] followed by *in situ* oxidative demetallation (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 than ^{t}BuCO_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]

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

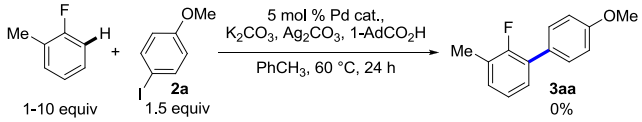


entry	Pd cat	R-COOH	T (°C)	**3aa** (%)[b]
1[c]	Pd(OAc)$_2$+DavePhos	^{t}BuCO$_2$H	120	0
2	Pd(OAc)$_2$+DavePhos	^{t}BuCO$_2$H	120	13
3	Pd(OAc)$_2$+DavePhos	1-AdCO$_2$H	120	12
4	Pd(OAc)$_2$	1-AdCO$_2$H	120	0
5	Pd(OAc)$_2$+PPh$_3$	1-AdCO$_2$H	120	24
6[d]	Pd(OAc)$_2$+PPh$_3$	1-AdCO$_2$H	120	41
7	Pd(PPh$_3$)$_4$	1-AdCO$_2$H	120	68
8	Pd(PPh$_3$)$_4$	1-AdCO$_2$H	60	90 (89)[e]
9	Pd(PPh$_3$)$_4$	–	60	64
10	Pd(PPh$_3$)$_4$	1-AdCO$_2$H	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] The yield was determined by ^{1}H NMR using an internal standard. [c] The reaction was carried out in DMA instead of PhCH$_3$. [d] 20% of PPh$_3$ was used. [e] Isolated yield on 0.5 mmol scale. The reaction was carried out for 40 h instead of 24 h. [f] 4-Chloroanisole and 4-bromoanisole were used instead of 4-iodoanisole.

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

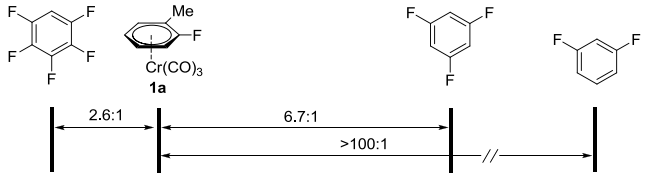
Scheme 2. Reaction of uncomplexed 2-fluorotoluene



Having validated our hypothesis we set out to explore the generality of the methodology with respect to the iodoarene coupling partner (Scheme 3, a). The optimized conditions were applicable to a wide range of iodoarenes with electron-donating and electron-withdrawing substituents in *para*, *meta* and *ortho*, affording the corresponding biaryl products **3** in excellent yields. The reaction is compatible with Cl and Br substituents (**3ac-d**), which would allow for further Pd-mediated transformations, esters (**3af** and **3al**), ketones (**3ag**). Oxidisable 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-s**), albeit higher temperatures are required in the case of **2r** for the reaction to proceed satisfactorily.

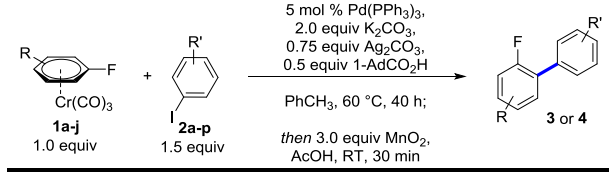
We then turned our attention to the substitution at the fluoroarene core (Scheme 3, b).[11] Functionalities in *ortho* such as CH$_2$OTBS (**3ba**), SiMe$_3$ (**3ca**), CO$_2$Me (**3da**) and long alkyl chains (**3fa**) were all compatible with the reaction, affording

Figure 1. Relative reactivity between Cr-complex 1a and polyfluorobenzenes towards C-H arylation[a]

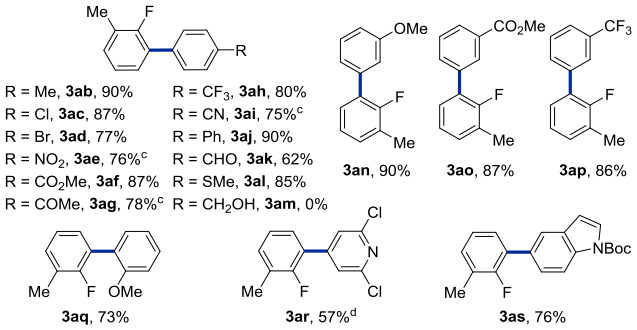


[a] **1a** and a polyfluoroarene were reacted with **2a** in the same flask. Reactions were stopped at low conversions (10-20%) and ratios determined by ^{1}H NMR using an internal standard.

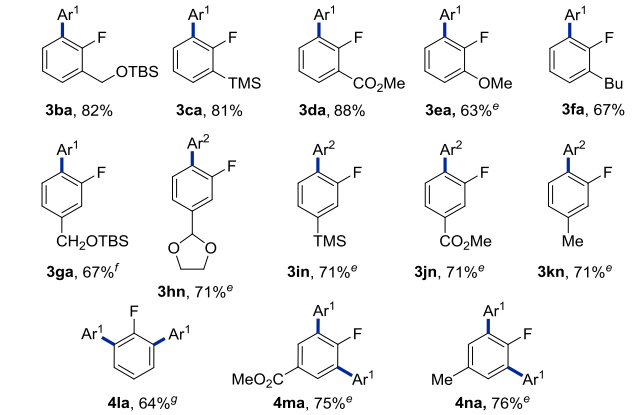
Scheme 3. Scope of the Pd-catalysed Direct Arylation of (fluoroarene)Cr(CO)$_3$ 1a-j with iodoarenes 2a-p. [a,b]



a) Scope of iodoarene



b) Scope of fluoroarene-Cr(CO)$_3$ complex: Ar^1 = *p*-C$_6$H$_4$-OMe; Ar^2 = *o*-C$_6$H$_4$-OMe



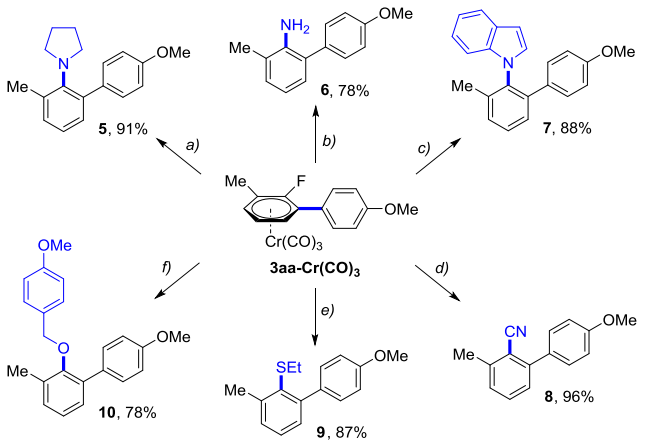
[a] Reactions were performed on 0.5 mmol scale. [b] Isolated yields. [c] Reaction time was 48 h. [d] Performed at 70 °C with 3 equiv of **2o** and 1.5 equiv of Ag$_2$CO$_3$. [e] Performed with 3.0 equiv of **2a** or **2n**. [f] 14% of the other *ortho* regioisomer was also obtained. [g] Performed with 4.0 equiv of **2a**.

excellent yields of the arylated products. Even in the presence of a strongly electron-donating group (MeO) on the fluoroarene the 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, with the major arylation product being at the least hindered position (**3ga**). This could be avoided by employing an *ortho*-substituted iodoarene (**3hn-kn**). Finally, with a substituent in *para*-position (**1n-m**) or in the absence of a substituent (**1l**),

mixtures of mono and double arylation were obtained. The use of 3 equiv of iodoarene, allowed for the synthesis of the bisarylated adducts **4la-ma** in good yields. The reactivity of other electron-poor arenes (Ph-CF_3 and Ph-CO_2Me) towards 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]

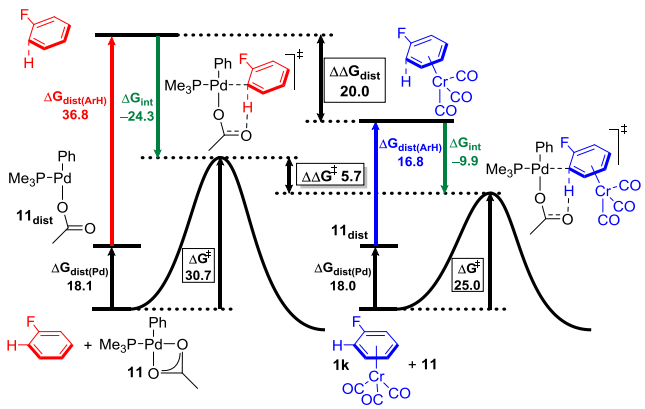
The $Cr(CO)_3$ complexed biaryls can also be isolated before decomplexation which allows easy functionalization of the C-F bond via a variety of nucleophilic aromatic substitution reactions.[16] For example, arylated complex **3aa-Cr(CO)$_3$** (Scheme 4) was isolated in 72% yield. The C-F bond could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

Scheme 4. Nucleophilic aromatic substitution reactions on arylation product 3aa-Cr(CO)$_3$.



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; hv. f) NaH, PMB-OH, THF; MnO_2, AcOH.

Figure 2. CMD pathway and distortion-interaction analysis for C-H bond activation of complex 1k.[a]



[a] 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.

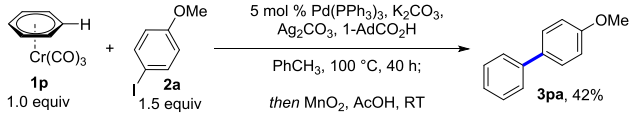
In order to probe the origin of the enhanced reactivity of $Cr(CO)_3$ complexes **1** towards C-H arylation, DFT calculations were carried out with C_6H_5F or C_6H_5F-$Cr(CO)_3$ complex (**1k**) and [$Pd(PMe_3)(Ph)OAc$] (**11**) as the active species effecting the C–H activation (Figure 2),[17] which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

To gain better understanding of the different factors involved in the energy difference between both TS, 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 **1k** than for C_6H_5F (by 14.4 kcal/mol), this factor is overcome by the much lower distortion energy cost of **1k** compared to C_6H_5F (by –20.0 kcal/mol).

The ground state and TS geometry of the arenes are essentially identical except for the C-H bond undergoing activation: in the TS of **1k** this C-H bond is significantly elongated (1.419 Å versus 1.081 Å in the ground state) and the H is significantly deviated from the arene plane (33.7° versus 2.1° in the ground state). A study of the contribution of these two factors to ΔG_{dis} for C_6H_5F and **1k** showed that while the elongation energy is roughly the same in both cases (ΔG_{el}(C_6H_5F)–ΔG_{el}(**1k**) = 1.0 kcal/mol), the bending energy showed a very significant change in favor of complex **1k** (ΔG_{bend}(C_6H_5F)– ΔG_{bend}(**1k**) = 19.1 kcal/mol). Therefore, the role of the $Cr(CO)_3$ fragment is to facilitate the bending of the H in the TS leading to concerted metallation-deprotonation. 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, 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 towards the 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 towards C-H arylation via π-complexation to $Cr(CO)_3$. This is the first general methodology for the direct arylation of monofluorobenzenes affording excellent yields of *ortho*-substituted biaryls with high selectivity. The arylated complexes can be further derivatised, 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 towards expanding the substrate and reaction scope of this new strategy.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

* i.larrosa@qmul.ac.uk

Author Contributions

‡These authors contributed equally.

ACKNOWLEDGMENT

We are grateful to the European Research Council for a Starting Research Grant (I.L.), Marie Curie Foundation for an Intra-European Fellowship (X.C.C.), QMUL for a studentship (K.K.) and EPSRC National Mass Spectrometry Service (Swansea).

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[13] See SI for complete optimization data.

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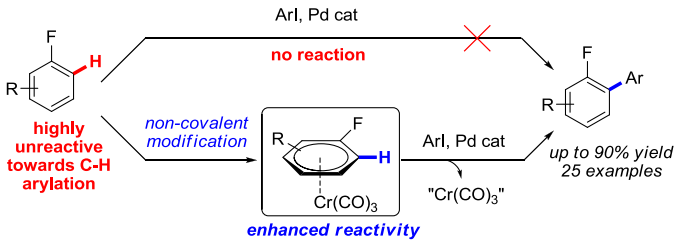
ArI, Pd cat
no reaction
F
H
R
highly unreactive towards C-H arylation
non-covalent modification
F
R
H
Cr(CO)3
enhanced reactivity
ArI, Pd cat
"Cr(CO)3"
F
Ar
R
up to 90% yield
25 examples