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

Paolo Ricci,† Katrina Krämer,‡ 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.
‡School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, U.K.

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 of 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-bromotoluene⁶b 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,⁶f Conversely, Fe⁶b,⁹ Fe₃₈,⁹ and Ir-catalyzed⁶g,⁹ and metal-free couplings² 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 Yu³ and Gaunt⁵b 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 steric-biased electrophilic-type pathway. Here we report the first example of an ortho-selective direct arylation of anisoles (Scheme 1c),⁶h 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 metatation–deprotonation (CMD) pathway.¹⁰ 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 Gorelsky¹² 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_Ar-type reactivity (and therefore para-reactivity), and (3) afford the CMD-preferred ortho-regioisomer.
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, 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 di- and tri-substituted anisoles (Scheme 2).15 Varied alkyl substitution at the ortho-C−H bond imparted by Cr(CO)3.6

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).3a 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 CO2Me 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–3ra), 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 3a. 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.
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 AlCl3 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 LiEt3BH 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 104 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-d2 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.

Anisole is approximately 104 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-d2 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.
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. arene Cr(CO)3 complex to anisole-type arenes can show an isomer ratio o:o,o,o,p = 26:1:1.7 which corresponds to an o:m:p = 95:0.5 ratio. 1H NMR (400 MHz, CDCl3): δ (ppm) = 7.43 (d, J = 7.6 Hz, 2H), 7.35−7.20 (m, 2H), 7.07 (app t, J = 6.9 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). 13C NMR (101 MHz, CDCl3): 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 ESI+ m/z calcld C11H11O3N· [M+NH4]+ 260.1645; found: [M+NH4]+ 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: K2CO3 (172.5 mg, 1.25 mmol, 2.5 equiv), 1-AdCO2H (105 mg, 0.375 mmol, 0.75 equiv), Pd(PPh3)4 (5 mol %, 28.9 mg, 0.010 mmol), the required arene Cr(CO)3 complex 1 (0.5 mmol, 1.5 equiv), and iodoarene 2 (0.75 mmol, 1.5 equiv). PhCH3 (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 min at 60 °C. The reaction was then cooled down, and AcOH (0.05 mL) was slowly added with moderate stirring. After 5 min, MnO2 (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 Et2O (30 mL). Removal of solvent in vacuo afforded the title product 3aa as a colorless oil in 46% yield (67.7 mg, 0.227 mmol). 1H NMR (400 MHz, CDCl3): δ (ppm) = 7.20 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 7.6 Hz, 2H), 7.18 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.45 (septet, J = 6.0 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 1.25 (d, J = 6.0 Hz, 6H). 13C NMR (101 MHz, CDCl3): δ (ppm) = 152.9, 136.3, 136.2, 152.2, 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 ESI+ m/z calcld C11H11O3N· [M+H]+ 241.1857; found: [M+H]+ 241.1857.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

igor.larrosa@manchester.ac.uk

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the European Research Council for a Starting Research Grant (I.L.), the Engineering and Physical Sciences Research Council (EPSRC), QMUL for a studentship (K.K.), and EPSRC National Mass Spectrometry Service (Swansea).

REFERENCES

(1) For recent reviews on direct arylation reactions and Pd-catalyzed C−H activation methodologies, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. Chem. Rev. 2007, 107, 174. (b) Ackermann, L; Vicente, R.; Kapdi, A. R. Angew. Chem., Int. Ed. 2009, 48, 9792. (c) Chen, X.;
(a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. J. Am. Chem. Soc. 2012, 134, 5042.
(b) Wei, Y.; Magano, J.; Dunetz, J. R. J. Am. Chem. Soc. 2013, 135, 2116.
(c) Chen, F.; Neufeldt, S. R.; Sanford, M. S. R. J. Am. Chem. Soc. 2013, 135, 8754.
(d) Yeung, C. S.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J.; Baran, P. S. Org. Lett. 2013, 15, 5528.
(e) Ackermann, L.; Pospech, J.; Fagnou, K. J. Am. Chem. Soc. 2010, 132, 458.
(f) Gulevich, A. V.; Gorelski, S. I.; Lapointe, D.; Fagnou, K. J. Am. Chem. Soc. 2010, 132, 1661.
(g) Itoh, K.-i.; Higashino, T.; Hayashi, T. J. Am. Chem. Soc. 2012, 134, 15537.
(i) Liu, W.; Cao, H.; Lei, A. Angew. Chem., Int. Ed. 2014, 53, 1172.
(j) Hussain, I.; Sharif, M. J. Pharmacol. Exp. Ther. 2014, 3520.
(k) Arroniz, C.; Denis, J. G.; Ironmonger, A. Nature 2013, 51, 1661.
(l) Arroniz, C.; Ironmonger, A.; Rassias, G.; Larrosa, I. J. Org. Chem. 2013, 78, 110.
(m) Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. Synlett 1994, 349.
(n) Fujita, K.; Nonogawa, M.; Yamaguchi, R. Chem. Commun. 2012, 48, 10437.
(o) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Chem. Rev. 2011, 111, 563.
(p) Magano, J.; Dunetz, J. R. Chem. Rev. 2011, 111, 2177.
(q) For selected examples of ortho-arylations see: (a) Gutstein, D. E.; Krishna, R.; Johns, D.; Surks, H. K.; Dansky, H. M.; Shah, S.; Mitchell, Y. B.; Arena, J.; Wagner, J. A. Clin. Pharmacol. Ther. 2012, 91, 109. (d) Lopez, L.; Mendoza, F. J.; Agrilera-Tejero, E.; Perez, J.; Guerrero, F.; Martin, D.; Rodriguez, M. Kidney Int. 2008, 73, 300. (e) Bain, G.; Lorenz, D. S.; Stubbins, K. J.; Broadhead, A. R.; Santini, A. M.; Prodanovich, P.; Darlington, J.; King, C. D.; Lee, C.; Baccei, C.; Stearns, B.; Troung, Y.; Hutchinson, J. H.; Prasit, P.; Evans, J. F. J. Pharmcol. Exp. Ther. 2011, 338, 290.
(r) For examples of meta-arylation: (a) Phipps, R. J.; Gaunt, M. J. Science 2009, 323, 1593. (b) Phipps, R. J.; Gaunt, M. J. Angew. Chem., Int. Ed. 2011, 50, 463. (c) Wang, L.; Dastbaravadeh, N.; Li, G.; Gu, J.-Q. J. Am. Chem. Soc. 2013, 135, 18056. (d) Luo, J.; Preciado, S.; Larrosa, I. J. Am. Chem. Soc. 2014, 136, 4109.
(r) For recent reviews on “undirected” C–H activation, see: (a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Angew. Chem., Int. Ed. 2012, 51, 10236. (b) Lafrance, M.; Fagnou, K. J. Am. Chem. Soc. 2006, 128, 16496.
(c) Stuart, D. R.; Fagnou, K. Science 2010, 326, 1172. (d) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. Chem. Sci. 2010, 351, 331. (e) Liu, W.; Cao, H.; Lei, A. Angew. Chem., Int. Ed. 2010, 49, 2004. (f) Wang, X.; Leow, D.; Yu, J.-Q. J. Am. Chem. Soc. 2011, 133, 13864.
(s) For selected examples: (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. J. Am. Chem. Soc. 2006, 128, 8754. (b) Wei, Y.; Kan, J.; Wang, M.; Su, N.; Hong, M. Org. Lett. 2009, 11, 3346. (c) Sun, Z.-M.; Zhang, J.; Manan, R. S.; Zhao, P. J. Am. Chem. Soc. 2010, 132, 6935. (d) Rene, O.; Fagnou, K. Org. Lett. 2010, 12, 2116. (e) Chen, F.; Min, Q.-Q.; Zhang, X. J. Org. Chem. 2012, 77, 2992. (f) Wang, Y.-N.; Guo, X.-Q.; Zhu, X.-H.; Zhong, R.; Cai, L.-H.; Hou, X.-F. Chem. Commun. 2012, 48, 10437.
(t) For selected examples of para-arylation: (a) Wang, X.; Leow, D.; Yu, J.-Q. J. Am. Chem. Soc. 2011, 133, 13864.