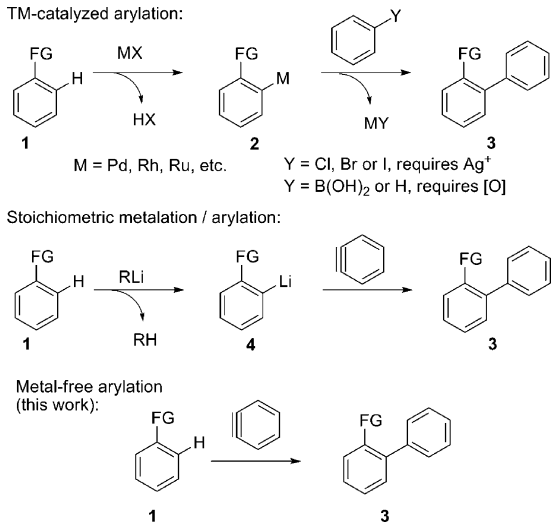
C–H Arylation

DOI: 10.1002/anie.201106150

Transition-Metal-Free Direct Arylation of Anilines**

*Tracey Pirali, Fengzhi Zhang, Anna H. Miller, Jenna L. Head, Donald McAusland, and Michael F. Greaney**

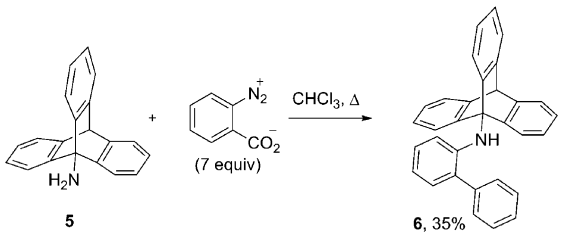
The *ortho*-arylation of aromatic compounds is a principal reaction system in C–H activation chemistry.[1] The transformation uses a functional group to direct a C–H metalation in the *ortho* position, usually by using transition metals (TMs) such as palladium or ruthenium (Scheme 1). A second arene



Scheme 1. *ortho*-Arylation strategies.

reagent then reacts with the metalated intermediate **2** to form a biaryl, **3**, molecules with enormous utility in chemistry and biology. Use of aryl halides in this second step affords a closed catalytic cycle, but stoichiometric silver salts are required to sequester halide.[2] Aryl boronic acids or silanes are effective, but require a stoichiometric oxidizing agent to close the cycle.[3] Simple arenes (Y = H) are potentially the most atom-economical of all coupling partners, but are currently used in hyperstoichiometric quantities and require an external oxidant and high catalyst loadings.[4]

Our interest in the reactive intermediate benzyne[5] led us to speculate whether an equivalent *ortho*-arylation might be possible, by using benzyne as the electrophilic arene and proceeding in the absence of TM catalysis. Benzyne is well known to react with strongly nucleophilic arylmetals such as Grignard reagents and aryllithiums (e.g. **1**→**4**→**3**, Scheme 1),[6] but intermolecular *direct arylation* at a C–H position has yet to be developed as a synthetic process. We chose to investigate anilines as the nucleophilic C–H component, as they are highly reactive in electrophilic aromatic substitution chemistry and functionalized aminoarenes are important building blocks for new medicines and materials. An immediate obstacle to aniline arylation concerns the potential competition between N- and C-arylation, with anilines undergoing N-arylation in high yield when treated with benzyne.[7] To suppress this pathway, we reasoned that steric hindrance around the nitrogen atom might direct benzyne arylation to the *ortho* carbon. Literature precedent for this idea is scant, but a single report from Yamamoto et al. provided some valuable support.[8] For the preparation of a molecular gear, N-phenylation of the hindered amine **5** was required. When treated with a large excess of benzyne, the unexpected double arylation product **6** was formed in low yield, i.e. N-arylation then C-arylation of the resultant hindered aniline (Scheme 2).

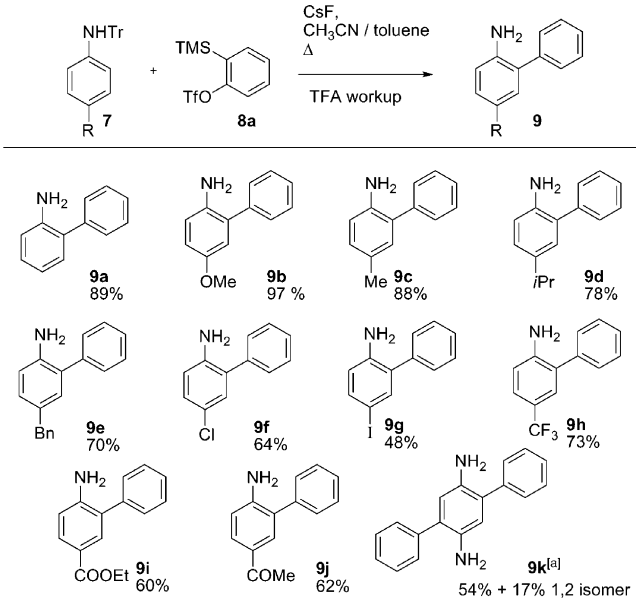


Scheme 2. Yamamoto's arylation of 9-tryptycylamine.

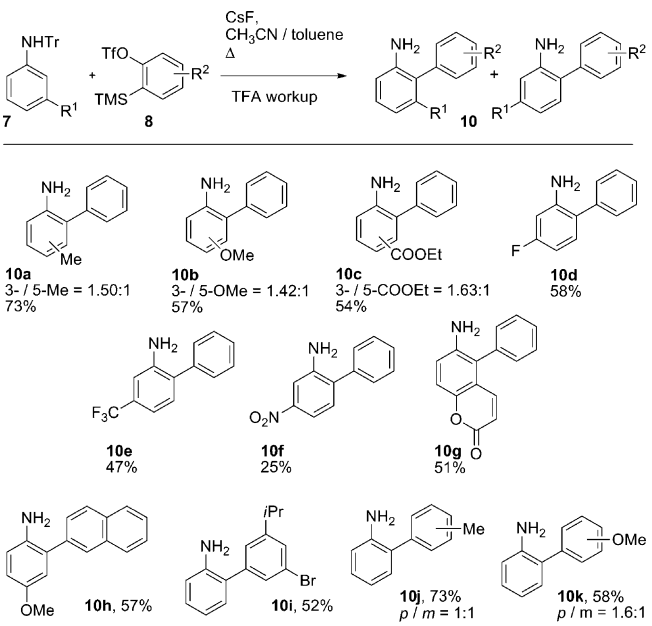
We began our study by using fluoride treatment of silane **8a** as our aryne source. A screen of substrates established that *tert*-butyl and Boc-aniline were not effective, but the larger trityl group did afford the desired C-arylated product **9a**. After some optimization, we defined conditions that afforded *o*-phenylaniline **9a** in an excellent 89% yield, following a TFA workup (Scheme 3). No sign of either diarylated compound, a common side-product in TM-catalyzed *o*-arylations, or *p*-arylated product could be detected.

[*] Dr. F. Zhang, A. H. Miller, J. L. Head, D. McAusland, Prof. M. F. Greaney[#]
School of Chemistry, University of Edinburgh
King's Buildings, West Mains Rd, Edinburgh, EH9 3JJ (UK)
E-mail: michael.greaney@manchester.ac.uk
Dr. T. Pirali[+]
Università degli Studi del Piemonte Orientale
via Bovio 6, 28100 Novara (Italy)
[#] Current address: School of Chemistry, University of Manchester
Oxford Rd, Manchester M13 9PL (UK)
[+] Visiting research fellow from DiSCAFF.

[**] We thank Regione Piemonte, DRUIDI project (visiting research fellowship to T.P.) and the EPSRC for funding (Leadership Fellowship to M.F.G.), and the EPSRC mass spectrometry service at the University of Swansea.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106150.



Scheme 3. Scope of C–H arylation: *para*-substituted anilines. Reaction conditions: trityl aniline **7** (1 equiv), aryne precursor **8a** (1.8 equiv), CsF (3 equiv), toluene/acetonitrile 3:1 (0.1 M), 110 °C for 48 h, 0.6 mmol scale. Then, TFA (1.6 mL), RT for 20 min. Yields of isolated products throughout. [a] 3.6 equiv of **8a** and 6 equiv of CsF used. TFA = trifluoroacetic acid, Bn = benzyl.



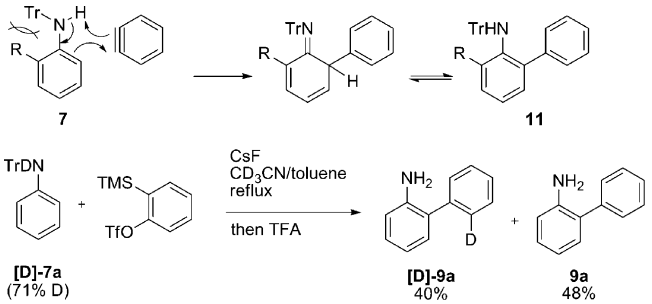
Scheme 4. Scope of C–H arylation: *meta*- and *meta/para*-substituted anilines. Reaction conditions are as shown in Scheme 3. TfO = trifluoromethanesulfonate, TMS = trimethylsilyl.

A study of the scope of the reaction quickly established that *p* and *m* substituents were well tolerated, but *o* substitution was not (recovered starting material). Electron-donating groups such as methoxy (**9b**) and alkyl (**9c–9e**) in the *p* position were excellent substrates, giving high yields of the *o*-phenylated products **9b–9e** (Scheme 3). Electron-withdrawing groups and halogens (e.g. Cl, I, CF_3, CO_2Et, COMe), which can be problematic in metal-based arylation strategies, were also effective, producing the products **9f–9j** in moderate to good yields. The trityl derivative of *p*-phenylenediamine, an important monomer in the plastics industry, underwent diarylation to give a terphenyl in 54% yield, tentatively assigned as the linear isomer **9k**, along with a small amount of the 1,2-terphenyl (Supporting Information).

Simple *m*-substituted substrates were successful in the reaction, but gave mixtures of regioisomers in some cases (Scheme 4). The *m*-Me, *m*-OMe, and *m*-CO_2Et substrates all gave moderate to good yield of product with regioisomeric ratios in the range 1–1.6:1 (**10a–c**). The strongly electron-withdrawing substrates *m*-F, *m*-CF_3, and *m*-NO_2, however, were less efficient but highly regioselective, producing the 1,2,5-trisubstituted compounds exclusively (**10d–f**). *m,p*-Disubstituted substrates were also feasible in the reaction; with the phenylated heterocycle **10g** formed in 51% yield and excellent regioselectivity.

A selection of substituted arynes were studied in the reaction and found to be effective.[9] 1,2-Naphthyne gave a single biaryl in the reaction, assigned as the β isomer on the basis of attack at the more sterically accessible β position[5d] (**10h**). We prepared a novel 3-isopropyl-5-bromoaryne precursor and observed high levels of regiocontrol in arylation. The bulky isopropyl group directs addition to the distal site, producing the bromoaryl product **10i** having a convenient handle for further TM or radical-based functionalizations. 4-Methylbenzyne gave good yields of arylated product **10j**, but in the expected 1:1 ratio as the 4-methyl group does not provide any directing effect in aryne additions. 4-Methoxybenzyne, by contrast, showed a small preference (1.6:1) for addition of the aniline *para* to the MeO group (**10k**).[10]

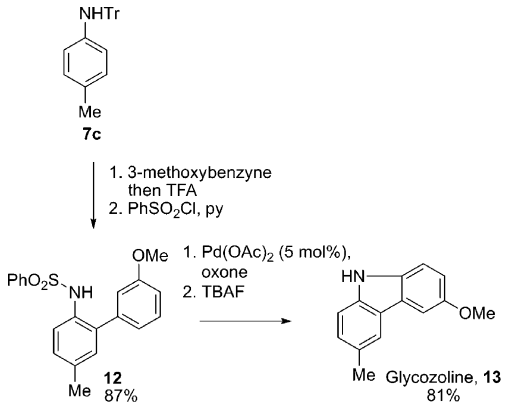
The lack of reactivity for both *o*-substituted substrates, anisole and *N*-trityl-*N*-methylaniline, along with the lack of *o*/*p* mixtures for tritylaniline, points to a hetero-ene reaction as the probable mechanism. Benzynes are well known enophiles,[11] although aryne hetero-ene reactions are uncommon.[8,12] Here, the ene conformation places the large trityl group in close proximity to any *ortho* substituent, a destabilizing interaction when R ≠ H (Scheme 5). A second arylation of the product **11** (R = H) is thus disfavored for the same reason. To probe this mechanism we first ran the reaction in CD_3CN to check for any proton incorporation from the solvent, and observed none. Second, we subjected a deute-



Scheme 5. Mechanistic studies. Tr = trityl.

rium-enriched substrate [**D**]-**7a** to the reaction conditions and observed deuterium incorporation in the product, implicating the ene mechanism as the principal reaction mode for *ortho*-arylation.[13]

The product *o*-arylanilines are important components of natural product and medicinal chemistry syntheses. To exemplify the power of the aryne arylation we carried out a short synthesis of the antibiotic and antifungal natural product glycozoline[14] (Scheme 6). Arylation of tritylated *p*-toluidine with 3-methoxyaryne proceeded in an excellent



Scheme 6. Synthesis of glycozoline. TBAF = tetrabutylammonium fluoride.

95% yield, followed by sulfonylation to give the biaryl **12**. Treatment of **12** with Youn's C–H amination conditions ($Pd(OAc)_2$, oxone)[15] selectively afforded the carbazole in high yield, which was desulfonylated to give glycozoline (**13**) in four steps and 71% overall yield from **7c**.

In conclusion, we have developed a new direct arylation reaction for anilines. The method is distinct from existing methods of arylation, requiring neither stoichiometric metalation with strong lithium or magnesium bases, nor transition-metal catalysis with associated ligands and additives. As a result, the reaction displays excellent functional-group compatibility and operational simplicity. An ene mechanism is implicated, which produces singly *ortho*-arylated products with no possibility of *para* regioisomers. Further studies on aryne C–H arylation are in progress.

Experimental Section

General procedure for *ortho*-arylation: In a vial the *N*-trityl aniline (0.60 mmol, 1 equiv) was dissolved in toluene and acetonitrile (3:1) (0.1M). The benzyne precursor (1.07 mmol, 1.8 equiv) and caesium fluoride (1.79 mmol, 3 equiv) were then added. The vial was then flushed with nitrogen, sealed and stirred at 110°C for 48 h. The volatiles were removed under vacuum and the crude material treated with TFA (1.6 mL). The reaction was then stirred at room temperature for 20 min. [For the preparation of compounds **9a**, **9b**, **9c** and **9d** 2.5 equiv (1.49 mmol) of the aryne precursor was used]. The reaction was diluted with diethyl ether and extracted with HCl 2M (×3). The combined aqueous phases were basified with NaOH aq. 10% and extracted with diethyl ether (×3). The combined organic phases were washed with brine, dried over magnesium sulfate and evaporated. The crude material was purified by column chromatography on silica gel, eluting with hexane/EtOAc mixtures.

5-Benzylbiphenyl-2-amine (**9e**): Purification by column chromatography (hexane/EtOAc 9:1) gave the desired product in 70% yield as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$–7.46 (m, 4H), 7.40 (m, 1H), 7.36–7.32 (m, 2H), 7.28–7.25 (m, 2H), 7.24 (t, $J = 7.2$ Hz, 1H), 7.06–7.03 (m, 2H), 6.77 (d, $J = 8.1$ Hz, 1H), 3.98 (s, 2H), 3.68 ppm (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 141.8$, 141.5, 139.6, 131.5, 131.0, 129.0, 128.9, 128.8, 128.5, 128.0, 127.9, 127.2, 126.0, 116.0, 41.1 ppm. HRMS (ES^+) calcd for $C_{19}H_{18}N^+$ $[M+H]^+$: 260.1434, found: 260.1434.

Received: August 30, 2011
Revised: October 31, 2011
Published online: December 12, 2011

Keywords: anilines · arynes · C–H bond activation

[1] Reviews: a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; b) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074–1086; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; d) X. Chen, K. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115.

[2] a) T. Satoh, M. Kawamura, M. Miura, M. Nomura, *Angew. Chem.* **1997**, *109*, 1820–1822; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740–1742; b) Y. Kametani, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2000**, *41*, 2655–2658; c) R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem.* **2003**, *115*, 116–118; *Angew. Chem. Int. Ed.* **2003**, *42*, 112–114; d) O. Daugulis, Z. G. Zaitsez, *Angew. Chem.* **2005**, *117*, 4114–4116; *Angew. Chem. Int. Ed.* **2005**, *44*, 4046–4048; e) H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879–9884; f) L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285–13293; g) L. Caron, L.-C. Campeau, K. Fagnou, *Org. Lett.* **2008**, *10*, 4533–4536; h) B. Xiao, Y. Fu, T.-J. Gong, J.-J. Dai, J. Yi, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 468–469.

[3] a) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699; b) S. Yang, B. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067; c) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem.* **2007**, *119*, 5650–5654; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554–5558; d) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511; e) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862–1865; *Angew. Chem. Int. Ed.* **2009**, *48*, 1830–1833; f) T. Nishikata, A. R. Abela, S. Huang, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 4978–4979; g) M. J. Tredwell, M. Gulias, N. Gaunt Bremeyer, C. C. C. Johansson, B. S. L. Collins, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 1108–1111; *Angew. Chem. Int. Ed.* **2011**, *50*, 1076–1079.

[4] a) B. Li, S.-L. Tian, Z. Fang, Z. Shi, *Angew. Chem.* **2008**, *120*, 1131–1134; *Angew. Chem. Int. Ed.* **2008**, *47*, 1115–1118; b) G. Brasche, J. Garcia-Fortanet, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2207–2210; c) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331–336.

[5] a) D. McAusland, S. Seo, D. G. Pintori, J. Finlayson, M. F. Greaney, *Org. Lett.* **2011**, *13*, 3667–3669; b) A. A. Cant, L. Roberts, M. F. Greaney, *Chem. Commun.* **2010**, *46*, 8671–8673; c) D. G. Pintori, M. F. Greaney, *Org. Lett.* **2010**, *12*, 168–171; d) A. A. Cant, G. V. H. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew. Chem.* **2009**, *121*, 5301–5304; *Angew. Chem. Int. Ed.* **2009**, *48*, 5199–5202.

[6] T. Truong, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 4243 – 4244, and references therein.
[7] Z. Liu, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 3198 – 3209.
[8] G. Yamamoto, K. Inoue, H. Higuchi, M. Yonebayashi, Y. Nabeta, J. Ojima, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1241 – 1248.
[9] For a recent study on aryne regioselectivty, see: P. M. Tadross, C. D. Gilmore, P. Bugga, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2010**, *12*, 1224 – 1227.
[10] For other reactions with 4-methoxybenzyne showing similar selectivities, see: a) Z. Liu, R. C. Larock, *J. Am. Chem. Soc.* **2005**, *127*, 13112 – 13113; b) H. Yoshida, T. Morishita, J. Ohshita, *Org. Lett.* **2008**, *10*, 3845 – 3847; c) C. Ni, L. Zhang, J. Hu, *J. Org. Chem.* **2008**, *73*, 5699 – 5713.
[11] R. W. Hoffmann, *Dehydrobenzenes and Cycloalkynes*, Academic Press, New York, **1967**, pp. 197 – 199. Recent examples: a) D. A. Candito, J. Panteleev, M. Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 14200 – 14203; b) T. T. Jayanth, M. Jeganmohan, M.-J. Cheng, S.-Y. Chu, C.-H. Cheng, *J. Am. Chem. Soc.* **2006**, *128*, 2232 – 2233.
[12] A. A. Aly, R. M. Shaker, *Tetrahedron Lett.* **2005**, *46*, 2679 – 2682.
[13] The deuterium leakage in the labeling experiment was investigated by preparing a triply labeled substrate, having nitrogen plus both *ortho* positions deuterated. A similar ratio of deuterium transfer in the reaction was observed (see Supporting Information).
[14] D. P. Chakraborty, *Tetrahedron Lett.* **1966**, *7*, 661 – 664.
[15] S. W. Youn, J.-H. Bihn, B. S. Kim, *Org. Lett.* **2011**, *13*, 3738 – 3741.

