



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Gold-Catalyzed Direct Arylation

Citation for published version:

Ball, LT, Lloyd-jones, GC & Russell, CA 2012, 'Gold-Catalyzed Direct Arylation', *Science*, vol. 337, no. 6102, pp. 1644-1648. <https://doi.org/10.1126/science.1225709>

Digital Object Identifier (DOI):

[10.1126/science.1225709](https://doi.org/10.1126/science.1225709)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Science

Publisher Rights Statement:

Copyright © 2012 by the American Association for the Advancement of Science. All rights reserved.

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



This is the author's version of the work. It is posted here by permission of the AAAS for personal use, not for redistribution. The definitive version was published in *Science* 337 (6102), DOI: <http://dx.doi.org/10.1126/science.1225709>

Cite as:

Ball, L. T., Lloyd-jones, G. C., & Russell, C. A. (2012). Gold-Catalyzed Direct Arylation. *Science*, 337(6102), 1644-1648.

Manuscript received: 06/06/2012; Accepted: 16/08/2012; Article published: 28/09/2012

Gold-Catalyzed Direct Arylation**

Liam T. Ball,¹ Guy C. Lloyd-Jones,^{1,*} Christopher A. Russell^{1,*}

^[1]School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK.

^[*]Corresponding author; G.C.L.-J. (current address): Guy.Lloyd-Jones@ed.ac.uk, EaStCHEM, School of Chemistry, Joseph Black Building, University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK; C.A.R. e-mail: chris.russell@bris.ac.uk

^[**]Experimental procedures and compound characterization data are both presented in the supplementary materials. L.T.B., G.C.L.-J., and C.A.R. contributed equally to the conception and direction of this work and to the preparation of the manuscript. L.T.B. conducted all of the experimental work. We thank Umicore AG & Co. KG for the generous donation of H₂AuCl₄. L.T.B. thanks the Bristol Chemical Synthesis Doctoral Training Centre, funded by the Engineering and Physical Sciences Research Council (grant EP/G036764/1); AstraZeneca; GlaxoSmithKline; Novartis; Pfizer; Syngenta; and the University of Bristol, for the provision of a Ph.D. studentship. G.C.L.-J. is a Royal Society Wolfson Research Merit Award holder.

Supporting information:

Supporting Online Material can be found at:

<http://www.sciencemag.org/content/suppl/2012/09/26/337.6102.1644.DC1.html>

Synopsis:

Functionalized biaryl building blocks (Ar¹-Ar²) are prepared by site-selective Au-catalyzed arylation of arenes (Ar¹-H) with arylsilanes (Ar²-SiMe₃).

Abstract

Biaryls (two directly connected aromatic rings, $\text{Ar}^1\text{-Ar}^2$) are common motifs in pharmaceuticals, agrochemicals, and organic materials. Current methods for establishing the $\text{Ar}^1\text{-Ar}^2$ bond are dominated by the cross-coupling of aryl halides ($\text{Ar}^1\text{-X}$) with aryl metallics ($\text{Ar}^2\text{-M}$). We report that, in the presence of 1 to 2 mole percent of a gold catalyst and a mild oxidant, a wide range of arenes ($\text{Ar}^1\text{-H}$) undergo site-selective arylation by arylsilanes ($\text{Ar}^2\text{-SiMe}_3$) to generate biaryls ($\text{Ar}^1\text{-Ar}^2$), with little or no homocoupling ($\text{Ar}^1\text{-Ar}^1/\text{Ar}^2\text{-Ar}^2$). Catalysis proceeds at room temperature and tolerates a broad range of functional groups, including those incompatible with cross-coupling. These features expedite biaryl preparation, as demonstrated by synthesis of the nonsteroidal anti-inflammatory diflunisal.

Main text

The biaryl moiety (two directly connected aromatic rings, $\text{Ar}^1\text{-Ar}^2$) is a common functionality in pharmaceuticals [such as Lipitor, Crestor, and Diovan, three of the most widely prescribed drugs in 2010 (1)]; in agrochemicals; and in many modern organic materials, including liquid crystal displays, light-emitting diodes, and conducting polymers. The high value of the biaryl motif is reflected in the myriad strategies for its construction, the majority of which involve transition metal-catalyzed cross-coupling of an aryl halide ($\text{Ar}^1\text{-X}$) and an aryl organometallic ($\text{Ar}^2\text{-M}$) (Fig. 1) (2, 3). Nonetheless, it is widely appreciated that there remains a need for biaryl syntheses that are more concise, more selective, more versatile, or complementary to conventional routes. In response to this need, much effort has been devoted to direct arylation: cross-couplings in which one preactivated partner is replaced by a simple arene [for reviews, see (4–7); for selected examples, see (8–14)].

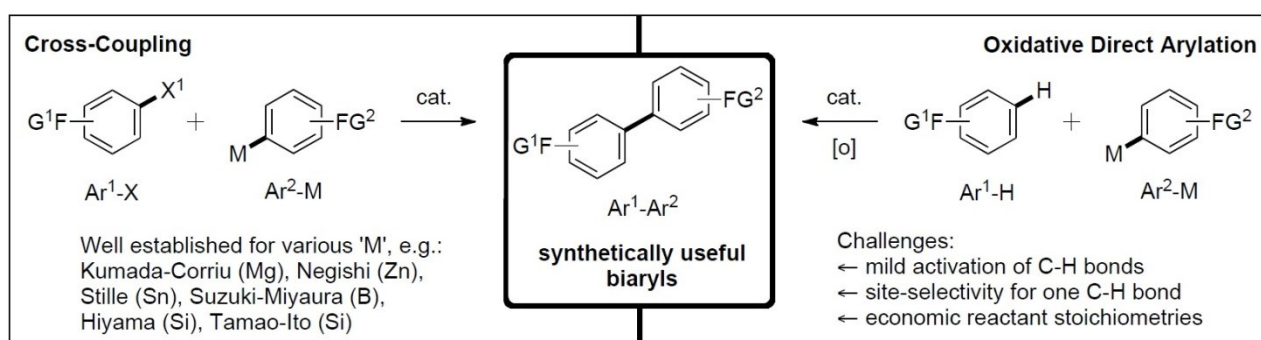


Figure 1. Cross-coupling and oxidative direct arylation approaches to biaryl ($\text{Ar}^1\text{-Ar}^2$) building blocks. X^1 , halide or sulfonate; M, electropositive element (such as Mg, Zn, B, Sn, or Si); $\text{FG}^{1,2}$, functional group (including alkyl, aryl, halogen etc); [O], oxidant; cat., transition-metal catalyst.

Direct arylation of an arene ($\text{Ar}^1\text{-H}$) with $\text{Ar}^2\text{-M}$ constitutes coupling of two nominal nucleophiles and hence requires an oxidant. As a corollary of the oxidative mechanism, functional groups incompatible with traditional cross-coupling may be tolerated; for example, when one or both partners bear additional (pseudo)halogens (i.e., in **Fig. 1**, FG^1 and/or $\text{FG}^2 = \text{X}^2, \text{X}^3$). The mechanistically orthogonal direct arylation approach then facilitates a powerful synthetic strategy for step-economic construction of complex biaryl molecules; for example, delivering versatile halogenated biaryl systems primed for direct entry into the cross-coupling manifold. Although tremendous progress has been made in the field of (oxidative) direct arylation (4–14), delivery of an efficient protocol remains nontrivial. In particular, the inherent low reactivity of a C-H bond (relative to the C-X bond it replaces) must be overcome, and high selectivity must be exhibited for a specific C-H bond in $\text{Ar}^1\text{-H}$, without competition from C-H bonds in the coupling partner ($\text{Ar}^2\text{-M}$) or the product ($\text{Ar}^1\text{-Ar}^2$). Many of the extant methodologies involve harsh reaction conditions, limiting the substrate scope, and employ high catalyst loadings. Moreover, selectivity is frequently achieved by the use of an excess of one coupling partner (for example, as the solvent), and/or substrates incorporating a directing group capable of delivering the transition-metal catalyst to a specific C-H bond (15).

We report a gold-catalyzed direct arylation of simple arenes ($\text{Ar}^1\text{-H}$) with arylsilanes ($\text{Ar}^2\text{-SiMe}_3$) that affords biaryls ($\text{Ar}^1\text{-Ar}^2$) under remarkably mild conditions. The site of arylation is predictable and not dependent on the presence of adjacent, coordinating functionality. Both partners (Ar^1 and Ar^2) can be decorated with a diverse array of functionality, including halogens, thus providing valuable biaryl building blocks.

The stimulus for pursuing the direct arylation described here was provided by two recently disclosed gold-catalyzed processes: the dehydrogenative homocoupling of $\text{Ar}^1\text{-H}$ in the presence of iodine(III), as reported by Tse (16, 17), and a competing homocoupling of $\text{Ar}^2\text{-SiMe}_3$ that we observed in gold-catalyzed oxidative additions to alkenes (18, 19). Whilst these reactions do generate biaryls, they are by definition symmetrical products ($\text{Ar}^1\text{-Ar}^1$ and $\text{Ar}^2\text{-Ar}^2$) and thus of limited value. Arylsilanes are well documented to react via electrophilic aromatic substitution pathways ($\text{S}_{\text{E}}\text{Ar}$), analogously to simple arenes, with *ipso* substitution of the silyl moiety rather than loss of a proton (20). We thus hypothesized that $\text{S}_{\text{E}}\text{Ar}$ might be operative in both homocoupling processes. Extension of this argument raised the tantalizing possibility that site selective gold-catalyzed oxidative heterocoupling of arylsilanes with arenes (to give $\text{Ar}^1\text{-Ar}^2$) should provide a pathway for a synthetically valuable direct arylation. The feasibility of this process was confirmed by a ^{19}F nuclear magnetic resonance (NMR) study of mixtures of mesitylene (1,3,5-trimethylbenzene, $\text{Ar}^1\text{-H}$) with (4-fluorophenyl)trimethylsilane ($\text{Ar}^2\text{-SiMe}_3$) in the presence of a gold(I) precatalyst (Ph_3PAuCl) and an iodine(III) oxidant at 65°C. The desired direct arylation process was detected but accompanied by homocoupling of the arylsilane ($\text{Ar}^2\text{-Ar}^2$), a competing electrophilic substitution of $\text{Ar}^1\text{-H}$ by iodine(III), and further arylation of the biaryl product ($\text{Ar}^2\text{-Ar}^1\text{-Ar}^2$).

Four criteria were identified as key for the delivery of a practical and general direct arylation process, leading us to engage in an extensive program of reaction refinement (21): (i) high selectivity for heterocoupling over

homocoupling; (ii) economic, ideally stoichiometric, quantities of the reactants; (iii) tolerance of a wide range of functionalities; and (iv) efficient catalysis at convenient temperatures, without the need for inert-atmospheres.

Using these criteria as guiding principles, conditions were developed that facilitate high-yielding direct arylation, in the majority of cases with near-complete suppression of all side reactions (Tables 1 and 2). Key developments were using Ph₃PAuOTs as a precatalyst (Table S2), conducting the reaction in the presence of a low concentration of methanol co-solvent at room temperature (Tables S3 and S4), and forming the active oxidant *in situ* from iodobenzene diacetate [PhI(OAc)₂] and camphorsulfonic acid (CSA) (Tables S1 and S4); the latter are both commercially available, bench-stable free-flowing solids. Control reactions established the essential role of a gold precatalyst over other late transition elements or Brønsted/Lewis acid promoters (Table S5) and demonstrated both the innocence of diaryliodonium salt side-products and the absence of uncatalyzed arylation, even at elevated temperatures (Schemes S1 and S2).

Two general sets of conditions were identified, which were tailored to the cost and complexity of the arene: for heavily functionalized or valuable arenes, a 1:1 stoichiometry of coupling partners was used (conditions **A**), whereas for simple or cheap arenes, a 2:1 stoichiometry was used and the precatalyst loading reduced from 2 to 1 mole % (mol %) (conditions **B**). Most reactions proceeded to completion within 20 to 40 hours at room temperature, although some were notably quicker (21). Longer reaction times (up to 80 hours) or higher temperatures (up to 65°C) were required when reactants were sterically hindered (**14**, **31**, and **32**), or when less electron-rich arenes (**4**, **8**, **20**, and **28**) or electron-deficient arylsilanes (**46** and **47**) were coupled, these reactivity trends being consistent with S_EAr elementary steps for both partners. The arylation process exhibits excellent site selectivity with respect to the arene partner (Ar¹-H, Table 1), the position of arylation also being readily predictable based on the well-understood patterns of S_EAr (20). The mildness of the conditions is evident from the reaction of (4-fluorophenyl)trimethylsilane with a range of *ortho*-anisole derivatives under conditions **A**, to give the corresponding biaryls in high yield and with excellent site-selectivity (97 to 99% isomeric purity) (21).

A wide range of functional groups is tolerated, including synthetically useful (pseudo)halogenated species (**1** to **4**), esters and amides (**5** to **8**), and sensitive functionalities remote from the ring, such as primary alcohols (**9** and **10**) and sulfonate (**11**). Biaryl **8** also demonstrates tolerance of an amine in the gold-catalyzed direct arylation; a basic nitrogen moiety is present in all of the 10 most widely prescribed drugs of 2010 (1). In compounds **1** to **8**, **14**, and **17** to **19**, the methoxy substituent itself is of further synthetic potential; for example, directing S_EAr and *ortho*-metallation, or via derivatization, cross-coupling, amination, or reductive cleavage [for a review of catalytic activation of arylmethyl ethers, see: (22)].

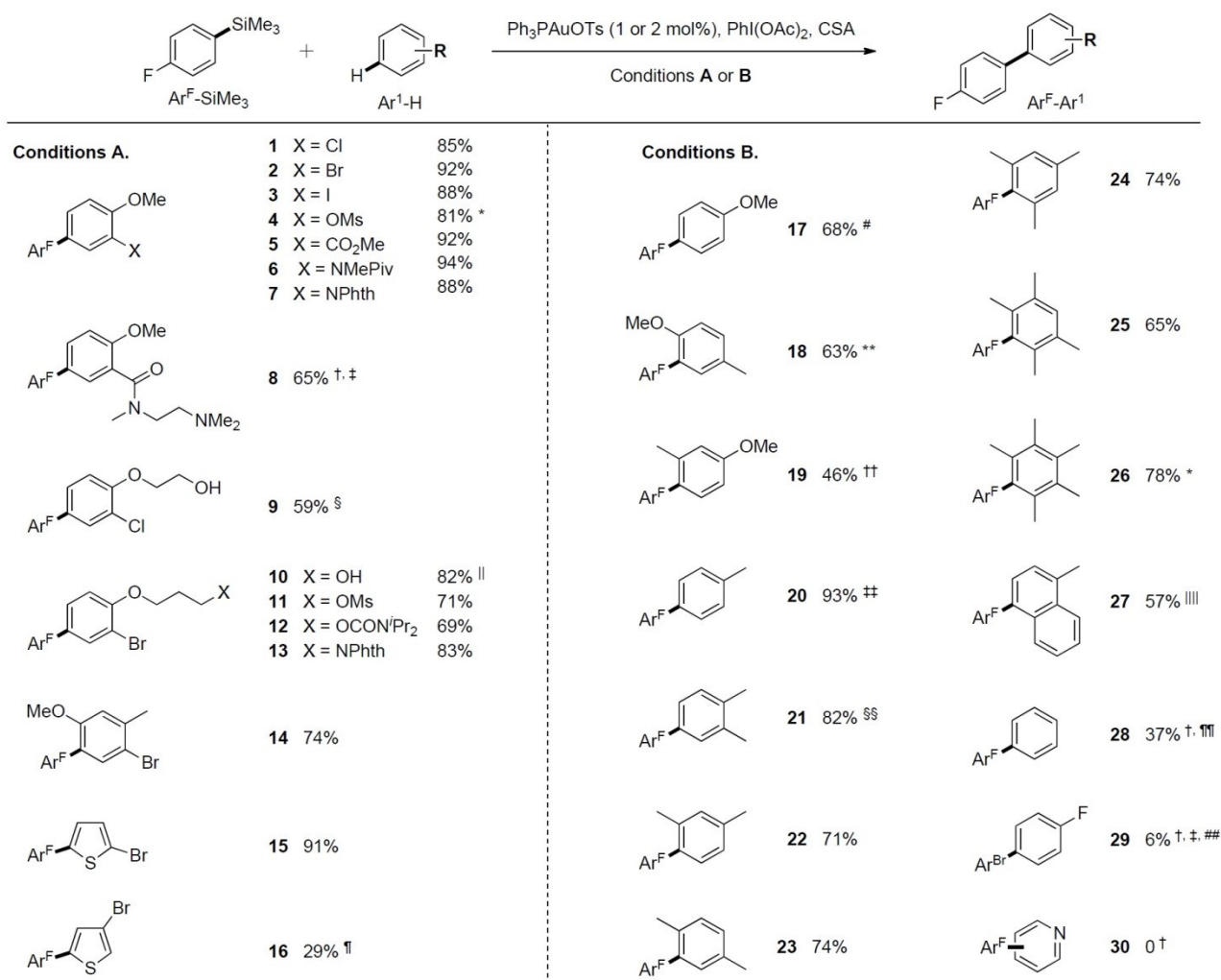


Table 1. Scope of Ar¹-H in Au-catalyzed direct arylation. Conditions: arylsilane (0.50 mmol), PhI(OAc)₂ (0.65 mmol), and CSA (0.75 mmol) in CHCl₃/CH₃OH (50:1) at room temperature, and **A**, Ar¹-H (0.50 mmol) and Ph₃PAuOTs (2 mol %); or **B**, Ar¹-H (1.00 mmol) and Ph₃PAuOTs (1 mol %). Ts, *p*-toluenesulfonyl; Ms, methanesulfonyl; Piv, pivaloyl (COCMe₃); NPhth, *N*-phthalimido.

Simple arenes, including those lacking strongly electronically-activating and/or -directing groups, also proved excellent substrates and were ideal for reaction under conditions **B**; the site-selectivity observed with anisole and toluene, giving biaryls **17** and **20**, respectively, being consistent with S_EAr by a gold(III) electrophile (23). Although the electron-rich 4-methylanisole, in which the position para to the methoxy substituent is blocked, promoted double arylation, **18** was generated with >99.7% discrimination between electronically different sites. In contrast, 3-methylanisole, in which the 4- and 6- positions are similarly activated, underwent arylation to give **19** as a 2:1 mixture of isomers. Arylation even occurred smoothly at C-H bonds flanked on either side by methyl substituents (**24** to **26**), and although the parent naphthalene reacted with low selectivity (**21**), the methyl-substituted analog generated biaryl **27** with >96% site selectivity, in just 5 hours at room temperature.

A preliminary investigation indicated that thiophenes are viable substrates, although, without further optimization, the conditions proved less general [for example, compare **15** (91%, >99.5% site selective) and **16** (29%, 57% site selective)]. The low reactivity of electron-deficient (hetero)arenes, such as PhF (**29**) and pyridine (**30**), is again consistent with an S_EAr mechanism. The selectivity for electron-rich aromatics not only suppresses over-arylation but is also complementary to direct arylation processes that proceed via deprotonation-type mechanisms and favor electron-poor substrates or require *ortho*-directing groups (4–7, 15).

Diverse functionality could also be introduced through the arylating partner (Ar^2-SiMe_3 , Table 2). *Ortho*-substituted arylsilanes that reacted sluggishly at room temperature gave the corresponding biaryls (e.g., **31** and **32**) in excellent yield at 65°C, using a less-reactive iodine(III) oxidant. The synthetically useful halogens and sulfonates (**31** to **36** and **40**) were well tolerated, as were an aldehyde (**37**) and a pivaloyl ester (**41**) that remained in the products without oxidation or transesterification, respectively. Although electron-rich silanes proved more challenging, as a result of arylsilane homocoupling, the selection of appropriate reaction conditions allowed even biaryl **45** to be isolated in reasonable yield. Homocoupling of the arene partner (16, 17) was not observed; instead, the material balance of the less efficient reactions detailed in Table 1 (typically for electron-rich Ar^1-H) comprised diarylation and diaryliodonium side-products (21).

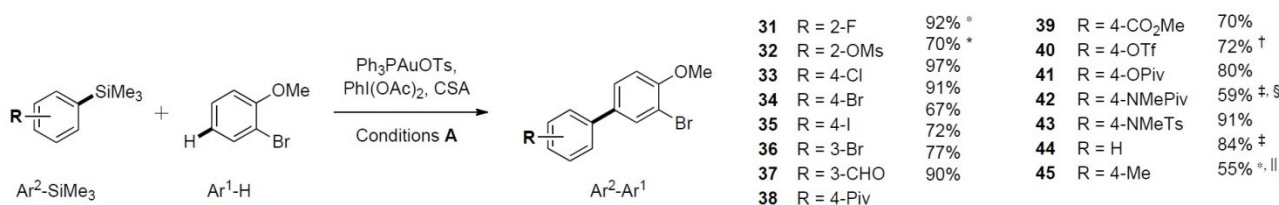


Table 2. Scope of Ar^2-SiMe_3 in Au-catalyzed direct arylation. Reaction conditions are as in Table 1. Tf, trifluoromethanesulfonyl.

The utility of the direct arylation methodology is exemplified by the preparation of diflunisal (Dolobid, Merck & Co.), a non-opioid, nonsteroidal anti-inflammatory drug (24, 25). Unoptimized direct arylation of methyl *ortho*-anisate (X = CO₂Me, **Fig. 2**) with (2,4-difluorophenyl)trimethylsilane afforded the corresponding biaryl **46**; routine demethylation gave diflunisal (69%). Previous methods for forging the key biaryl linkage of diflunisal include Gomberg-Bachmann coupling of a diazonium salt and traditional cross-coupling (21). The power of the direct arylation approach is also evident in a second route to diflunisal, proceeding via biaryl **47**; this iodide intermediate can also serve as a versatile platform for structural diversification via a broad spectrum of stoichiometric and catalytic methodologies, including cross-coupling.

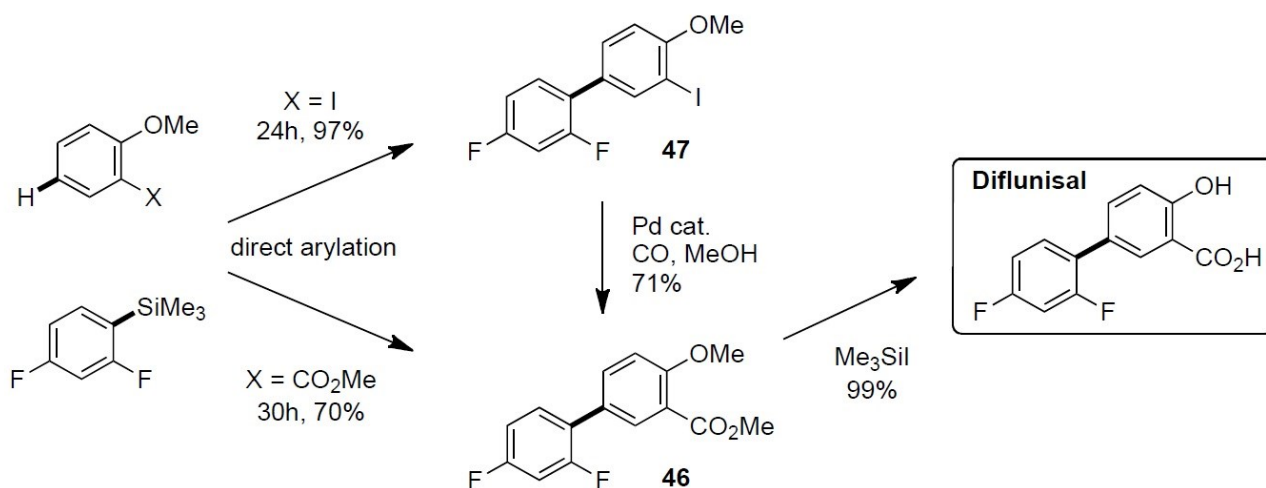


Figure 2. Diflunisal via gold-catalyzed direct arylation; yields are unoptimized. Site selectivity for the arylation step (**46** and **47**) is 98 to 99%.

In summary, compared to many other direct arylations (4–14), gold-catalyzed arylation with arylsilanes is notable for its mild conditions, low loadings, and site selectivity. It also provides complementarity and orthogonality to traditional cross-coupling strategies (2, 3), allowing the strategic linking of the two processes (Fig. 2). Arylsilanes are particularly valuable as substrates, because the stability of the silyl moiety allows it to be installed early in a synthesis, and they are readily handled, lacking the toxicity and/or air sensitivity that can be displayed by the aryl metal complexes traditionally used in cross-coupling. Their synthesis, via silylation of a range of precursors that includes arenes, aryl halides, benzonitriles, and arylmetallics, is generally straightforward (21), and both camphorsulfonic acid and iodobenzene diacetate are commercially available; alternatively, the latter can be very efficiently prepared from iodobenzene with a cheap stoichiometric oxidant (21). In addition, and in contrast to such metals as palladium and nickel, gold residues are regarded as relatively benign, and the Ph₃PAuOTs precatalyst can be prepared in near-quantitative yield (26) in a single step from commercially available precursors. All of these aspects suggest the expedient application of gold-catalyzed direct arylation for the concise construction of synthetically valuable biaryl building blocks for pharmaceutical, agrochemical, and materials chemistry.

Notes and references

- [1] DrugTopics, <http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/252011/727256/article.pdf>; accessed 30 May 2012.
- [2] J. Tsuji, *Palladium Reagents and Catalysis: New Perspectives for the 21st Century* (Wiley, Chichester, UK, 2004).
- [3] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, Palladium-catalyzed cross-coupling: A historical contextual perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **51**, 5062(2012).
- [4] L. Ackermann, R. Vicente, A. R. Kapdi, Transition-metal-catalyzed direct arylation of (hetero)arenes by C-H bond cleavage. *Angew. Chem. Int. Ed.* **48**, 9792 (2009).
- [5] D. Alberico, M. E. Scott, M. Lautens, Aryl-aryl bond formation by transition-metal-catalyzed direct arylation. *Chem. Rev.* **107**, 174 (2007).
- [6] G. P. McGlacken, L. M. Bateman, Recent advances in aryl-aryl bond formation by direct arylation. *Chem. Soc. Rev.* **38**, 2447 (2009).
- [7] T. W. Lyons, M. S. Sanford, Palladium-catalyzed ligand-directed C-H functionalization reactions. *Chem. Rev.* **110**, 1147 (2010).
- [8] M. Lafrance, K. Fagnou, Palladium-catalyzed benzene arylation: Incorporation of catalytic pivalic acid as a proton shuttle and a key element in catalyst design. *J. Am. Chem. Soc.* **128**, 16496 (2006).
- [9] S.-D. Yang *et al.*, Palladium-catalyzed direct arylation of (hetero)arenes with aryl boronic acids. *Angew. Chem. Int. Ed.* **47**, 1473 (2008).
- [10] J. Wen, J. Zhang, S.-Y. Chen, J. Li, X.-Q. Yu, Iron-mediated direct arylation of unactivated arenes. *Angew. Chem. Int. Ed.* **47**, 8897 (2008).
- [11] R. J. Phipps, M. J. Gaunt, A meta-selective copper-catalyzed C-H bond arylation. *Science* **323**, 1593(2009).
- [12] H. Hachiya, K. Hirano, T. Satoh, M. Miura, Nickel-catalyzed direct C-H arylation and alkenylation of heteroarenes with organosilicon reagents. *Angew. Chem. Int. Ed.* **49**, 2202 (2010).
- [13] C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer, M. J. Gaunt, A highly para-selective copper(II)-catalyzed direct arylation of aniline and phenol derivatives. *Angew. Chem. Int. Ed.* **50**, 458 (2011).

- [14] K. Funaki, H. Kawai, T. Sato, S. Oi, Palladium-catalyzed direct C-H bond arylation of simple arenes with aryltrimethylsilanes. *Chem. Lett.* **40**, 1050 (2011).
- [15] S. R. Neufeldt, M. S. Sanford, Controlling site selectivity in palladium-catalyzed C-H bond functionalization. *Acc. Chem. Res.* **45**, 936 (2012).
- [16] A. Kar, N. Mangu, H. M. Kaiser, M. Beller, M. K. Tse, A general gold-catalyzed direct oxidative coupling of non-activated arenes. *Chem. Commun.* 386 (2008).
- [17] A. Kar, N. Mangu, H. M. Kaiser, M. K. Tse, Gold-catalyzed direct oxidative coupling reactions of non-activated arenes. *J. Organomet. Chem.* **694**, 524 (2009).
- [18] L. T. Ball, M. Green, G. C. Lloyd-Jones, C. A. Russell, Arylsilanes: Application to gold-catalyzed oxyarylation of alkenes. *Org. Lett.* **12**, 4724 (2010).
- [19] L. T. Ball, G. C. Lloyd-Jones, C. A. Russell, Gold-catalysed oxyarylation of styrenes and mono- and *gem*-disubstituted olefins facilitated by an iodine(III) oxidant. *Chemistry* **18**, 2931 (2012).
- [20] R. Taylor, *Electrophilic Aromatic Substitution* (Wiley, Chichester, UK, 1990).
- [21] See supplementary materials on *Science Online* for detailed methods and discussion.
- [22] B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, Activation of “inert” alkenyl/aryl C-O bond and its application in cross-coupling reactions. *Chemistry* **17**, 1728 (2011).
- [23] R. O. C. Norman, W. J. E. Parr, C. B. Thomas, The reactions of alkynes, cyclopropanes, and benzene derivatives with gold(III). *J. Chem. Soc. Perkin Trans.* **1**, 1983 (1976).
- [24] W. V. Ruyle, L. H. Sarett, A. R. Matzuk, U.S. Patent 3,714,226 (1973).
- [25] J. Hannah *et al.*, Novel analgesic-antiinflammatory salicylates. *J. Med. Chem.* **21**, 1093 (1978).
- [26] P. Römbke, A. Schier, H. Schmidbaur, Gold(I) organosulfinate and organosulfonate complexes. *J. Chem. Soc. Dalton Trans.* 2482 (2001).
- [27] J. Leonard, B. Lygo, G. Procter, *Advanced Practical Organic Chemistry* (Stanley Thornes, Cheltenham, UK, ed. 2, 1998).
- [28] A. K. Al-Sa'ady, C. A. McAuliffe, R. V. Parish, J. Sandbank, in *Inorganic Syntheses*, S. Kirschner, Ed. (Wiley, N, 2007), vol. 23, pp. 191–194.
- [29] D. Schneider, A. Schier, H. Schmidbaur, Governing the oxidative addition of iodine to gold(I) complexes by ligand tuning. *Dalton Trans.* 1995 (2004).

- [30] L. Kraszkiwicz, L. Skulski, Optimized syntheses of iodylarenes from iodoarenes, with sodium periodate as the oxidant. Part II. Arch. Organic Chem. **6**, 120 (2003).
- [31] M. S. Yusubov, T. Wirth, Solvent-free reactions with hypervalent iodine reagents. Org. Lett. **7**, 519 (2005).
- [32] E. A. Merritt, V. M. T. Carneiro, L. F. Silva Jr., B. Olofsson, Facile synthesis of Koser's reagent and derivatives from iodine or aryl iodides. J. Org. Chem. **75**, 7416 (2010).
- [33] P. Kazmierczak, L. Skulski, L. Kraszkiwicz, Syntheses of (diacetoxyiodo)arenes or iodylarenes from iodoarenes, with sodium periodate as the oxidant. Molecules **6**, 881 (2001).
- [34] T. Dohi *et al.*, Versatile direct dehydrative approach for diaryliodonium(III) salts in fluoroalcohol media. Chem. Commun. 4152 (2007).
- [35] A. M. Stuart, P. L. Coe, D. J. Moody, Fluorodesilylations of fluorophenyltrimethylsilanes with elemental fluorine: Discovery of a novel 1,2-migration of the trimethylsilyl group. J. Fluor. Chem. **88**, 179 (1998).
- [36] L. Hevesi, M. Dehon, R. Crutzen, A. Lazarescu-Grigore, Kinetic control in the cleavage of unsymmetrical disilanes. J. Org. Chem. **62**, 2011 (1997).
- [37] L. Doszczak *et al.*, Prediction of perception: probing the hOR17-4 olfactory receptor model with silicon analogues of bourgeonal and lilial. Angew. Chem. Int. Ed. **46**, 3367 (2007).
- [38] W. E. Brenzovich Jr., J.-F. Brazeau, F. D. Toste, Gold-catalyzed oxidative coupling reactions with aryltrimethylsilanes. Org. Lett. **12**, 4728 (2010).
- [39] B.-H. Ye, Y. Naruta, A novel method for the synthesis of regiospecifically sulfonated porphyrin monomers and dimers. Tetrahedron **59**, 3593 (2003).
- [40] R. Calas, J. Dunogues, J. P. Pillot, C. Biran, N. Duffaut, C-silylation of ketones from chlorotrialkylsilanes and magnesium. J. Organomet. Chem. **25**, 43 (1970).
- [41] K. Hirano, A. T. Biju, I. Piel, F. Glorius, N-heterocyclic carbene-catalyzed hydroacylation of unactivated double bonds. J. Am. Chem. Soc. **131**, 14190 (2009).
- [42] K. Sasaki, D. Crich, Facile amide bond formation from carboxylic acids and isocyanates. Org. Lett. **13**, 2256 (2011).
- [43] M. J. S. Dewar, J. M. W. Scott, 277. The Orton rearrangement. Part II. The reactions of several substituted N-bromoacylanilides in various media causing rearrangement. J. Chem. Soc. 1445 (1957).

- [44] N. Fujikawa *et al.*, Total synthesis of lamellarins D, L, and N. *Tetrahedron* **62**, 594 (2006).
- [45] F. Bruyneel, E. Enaud, L. Billottet, S. Vanhulle, J. Marchand-Brynaert, Regioselective synthesis of 3-hydroxyorthanilic acid and its biotransformation into a novel phenoxazinone dye by use of laccase. *Eur. J. Org. Chem.* **2008**, 72 (2008).
- [46] M. V. Khedkar, S. R. Khan, D. N. Sawant, D. B. Bagal, B. M. Bhanage, Palladium on carbon: An efficient, heterogeneous and reusable catalytic system for carbonylative synthesis of N-substituted phthalimides. *Adv. Synth. Catal.* **353**, 3415 (2011).
- [47] G. Wanag, A. Veinbergs, Kondensation primärer aminoverbindungen mit phthalsäureanhydrid in eisessig. *Chem. Ber.* **75**, 1558 (1942).
- [48] E. Elhalem *et al.*, Design, synthesis, and biological evaluation of aryloxyethyl thiocyanate derivatives against *Trypanosoma cruzi*. *J. Med. Chem.* **45**, 3984 (2002).
- [49] C. J. Barden *et al.*, World Patent WO2008/128321 A1 (2008).
- [50] F. Wu *et al.*, World Patent WO2006/92059 A1 (2006).
- [51] B. Schmidt, F. Hölter, Suzuki-Miyaura cross coupling reactions with phenoldiazonium salts. *Org. Biomol. Chem.* **9**, 4914 (2011).
- [52] J. Qiu, L. Wang, M. Liu, Q. Shen, J. Tang, An efficient and simple protocol for a PdCl₂-ligandless and additive-free Suzuki coupling reaction of aryl bromides. *Tetrahedron Lett.* **52**, 6489 (2011).
- [53] K. Fuchibe, Y. Ohshima, K. Mitomi, T. Akiyama, Low-valent niobium-catalyzed reduction of α,α,α -trifluorotoluenes. *Org. Lett.* **9**, 1497 (2007).
- [54] B. H. Lipshutz, T. B. Petersen, A. R. Abela, Room-temperature Suzuki-Miyaura couplings in water facilitated by nonionic amphiphiles. *Org. Lett.* **10**, 1333 (2008).
- [55] K. W. Quasdorf *et al.*, Suzuki-Miyaura cross-coupling of aryl carbamates and sulfamates: Experimental and computational studies. *J. Am. Chem. Soc.* **133**, 6352 (2011).
- [56] H. Chen *et al.*, Nickel-catalyzed cross-coupling of aryl phosphates with arylboronic acids. *J. Org. Chem.* **76**, 2338 (2011).
- [57] W. Liu, H. Cao, A. Lei, Iron-catalyzed direct arylation of unactivated arenes with aryl halides. *Angew. Chem. Int. Ed.* **49**, 2004 (2010).

- [58] A. Monopoli *et al.*, Glucose as a clean and renewable reductant in the Pd-nanoparticle-catalyzed reductive homocoupling of bromo- and chloroarenes in water. *J. Org. Chem.* **75**, 3908 (2010).
- [59] M. Kamata, C. Satoh, H.-S. Kim, Y. Wataya, Iron(II)-promoted rearrangement of 1,4-diaryl-2,3-dioxabicyclo[2.2.2]oct-5-enes: a mechanism distinct from that postulated previously. *Tetrahedron Lett.* **43**, 8313 (2002).
- [60] T. Deckert-Gaudig, S. Hünig, E. Dormann, M. T. Kelemen, 1,3,5-Tris[(2-hydroxy-3,5-diphenyl)phenyl]benzene and its phenoxy radicals. *Eur. J. Org. Chem.* **2001**, 1563 (2001).
- [61] W. Abitz, D. F. Morf, H.-A. Brauns, German Patent DT 2062956 (1971).
- [62] L. M. Weinstock, A. S. Wildman, D. M. Mulvey, U.S. Patent 4,131,618 (1978).
- [63] M.-A. Gunawan *et al.*, Simple pyridylmethylamines: Efficient and robust N,N-ligands for Suzuki–Miyaura coupling reactions. *Tetrahedron Lett.* **51**, 5392 (2010).
- [64] C. Giordano, L. Coppi, F. Minisci, European Patent EP0494419 A2 (1992).
- [65] S. H. Kim, J.-G. Kim, Organozinc reagents for facile synthetic route to Diflunisal, Fenbufen and Felbinac. *Bull. Korean Chem. Soc.* **32**, 341 (2011).
- [66] R. B. DeVasher, L. R. Moore, K. H. Shaughnessy, Aqueous-phase, palladium-catalyzed cross-coupling of aryl bromides under mild conditions, using water-soluble, sterically demanding alkylphosphines. *J. Org. Chem.* **69**, 7919 (2004).
- [67] T. Rausis, M. Schlosser, The basicity gradient-driven migration of iodine: Conferring regioflexibility on the substitution of fluoroarenes. *Eur. J. Org. Chem.* **2002**, 3351 (2002).
- [68] M. Schlosser, C. Heiss, Exploring structural opportunities: The regioflexible substitution of 1,3-difluorobenzene. *Eur. J. Org. Chem.* **2003**, 4618 (2003).
- [69] J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, Palladium-catalyzed carbonylation reactions of aryl bromides at atmospheric pressure: A general system based on Xantphos. *J. Org. Chem.* **73**, 7102 (2008).
- [70] T. de Haro, C. Nevado, On gold-mediated C-H activation processes. *Synthesis* 2530 (2011).
- [71] M. N. Hopkinson, A. D. Gee, V. Gouverneur, Au(I)/Au(III) catalysis: An alternative approach for C-C oxidative coupling. *Chemistry* **17**, 8248 (2011).

- [72] H. A. Wegner, M. Auzias, Gold for C-C coupling reactions: A Swiss-Army-Knife catalyst? *Angew. Chem. Int. Ed.* **50**, 8236 (2011).
- [73] W. E. Brenzovich Jr. *et al.*, Gold-catalyzed intramolecular aminoarylation of alkenes: C-C bond formation through bimolecular reductive elimination. *Angew. Chem. Int. Ed.* **49**, 5519 (2010).
- [74] A. D. Melhado, W. E. Brenzovich Jr., A. D. Lackner, F. D. Toste, Gold-catalyzed three-component coupling: Oxidative oxyarylation of alkenes. *J. Am. Chem. Soc.* **132**, 8885 (2010).
- [75] E. Tkatchouk, N. P. Mankad, D. Benitez, W. A. Goddard 3rd, F. D. Toste, Two metals are better than one in the gold catalyzed oxidative heteroarylation of alkenes. *J. Am. Chem. Soc.* **133**, 14293 (2011).
- [76] T. Dohi, N. Yamaoka, Y. Kita, Fluoroalcohols: Versatile solvents in hypervalent iodine chemistry and syntheses of diaryliodonium(III) salts. *Tetrahedron* **66**, 5775 (2010).
- [77] H. W. Richter, B. R. Cherry, T. D. Zook, G. F. Koser, Characterization of species present in aqueous solutions of [hydroxy(mesyloxy)iodo]benzene and [hydroxy(tosyloxy)iodo]benzene. *J. Am. Chem. Soc.* **119**, 9614 (1997).
- [78] G. F. Koser, R. H. Wettach, J. M. Troup, B. A. Frenz, Hypervalent organoiodine. Crystal structure of phenylhydroxytosyloxyiodine. *J. Org. Chem.* **41**, 3609 (1976).
- [79] A. S. K. Hashmi, Homogeneous gold catalysis: The role of protons. *Catal. Today* **122**, 211 (2007).
- [80] H. Tohma, M. Iwata, T. Maegawa, Y. Kita, Novel and efficient oxidative biaryl coupling reaction of alkylarenes using a hypervalent iodine(III) reagent. *Tetrahedron Lett.* **43**, 9241 (2002).
- [81] T. Dohi *et al.*, Hypervalent iodine(III): Selective and efficient single-electron-transfer (SET) oxidizing agent. *Tetrahedron* **65**, 10797 (2009).
- [82] E. A. Merritt, B. Olofsson, Diaryliodonium salts: A journey from obscurity to fame. *Angew. Chem. Int. Ed.* **48**, 9052 (2009).
- [83] G. F. Koser, R. H. Wettach, C. S. Smith, New methodology in iodonium salt synthesis. Reactions of [hydroxy(tosyloxy)iodo]arenes with aryltrimethylsilanes. *J. Org. Chem.* **45**, 1543 (1980).
- [84] H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, Copper(II)-catalyzed meta-selective direct arylation of α -aryl carbonyl compounds. *Angew. Chem. Int. Ed.* **50**, 463 (2011).
- [85] Y. Kita *et al.*, Metal-free oxidative cross-coupling of unfunctionalized aromatic compounds. *J. Am. Chem. Soc.* **131**, 1668 (2009).

- [86] T. Dohi *et al.*, Unusual *ipso* substitution of diaryliodonium bromides initiated by a single-electron-transfer oxidizing process. *Angew. Chem. Int. Ed.* **49**, 3334 (2010).
- [87] L. Ackermann, M. Dell'Acqua, S. Fenner, R. Vicente, R. Sandmann, Metal-free direct arylations of indoles and pyrroles with diaryliodonium salts. *Org. Lett.* **13**, 2358 (2011).
- [88] D. Qiu *et al.*, Gold(III)-catalyzed direct acetoxylation of arenes with iodobenzene diacetate. *Org. Lett.* **13**, 4988 (2011).
- [89] A. Pradal, P. Y. Toullec, V. Michelet, Gold-catalyzed oxidative acyloxylation of arenes. *Org. Lett.* **13**, 6086 (2011).
- [90] V. V. Zhdankin, P. J. Stang, Recent developments in the chemistry of polyvalent iodine compounds. *Chem. Rev.* **102**, 2523 (2002).
- [91] V. V. Zhdankin, P. J. Stang, Chemistry of polyvalent iodine. *Chem. Rev.* **108**, 5299 (2008).
- [92] A. Zielinska, L. Skulski, Easy and safe preparations of (diacetoxyiodo) arenes from iodoarenes, with urea-hydrogen peroxide adduct (UHP) as the oxidant and the fully interpreted ¹H- and ¹³C-NMR spectra of the products. *Molecules* **10**, 190 (2005).
- [93] A. Zielinska, L. Skulski, Easy preparation of (diacetoxyiodo)arenes from iodoarenes with sodium percarbonate as the oxidant. *Molecules* **7**, 806 (2002).
- [94] A. McKillop, D. Kemp, Further functional group oxidations using sodium perborate. *Tetrahedron* **45**, 3299(1989).
- [95] Y. Nakao, T. Hiyama, Silicon-based cross-coupling reaction: An environmentally benign version. *Chem. Soc. Rev.* **40**, 4893 (2011).
- [96] A. Postigo, R. A. Rossi, A novel type of nucleophilic substitution reactions on nonactivated aromatic compounds and benzene itself with trimethylsiliconide anions. *Org. Lett.* **3**, 1197 (2001).
- [97] M. Tobisu, Y. Kita, Y. Ano, N. Chatani, Rhodium-catalyzed silylation and intramolecular arylation of nitriles via the silicon-assisted cleavage of carbon-cyano bonds. *J. Am. Chem. Soc.* **130**, 15982 (2008).
- [98] L. J. Gooßen, A.-R. S. Ferwanah, A mild and efficient protocol for the catalytic silylation of aryl bromides. *Synlett* **2000**, 1801 (2000).
- [99] E. Shirakawa, T. Kurahashi, H. Yoshida, T. Hiyama, Diphenylphosphinophenolate: A ligand for the palladium-catalysed silylation of aryl halides activating simultaneously both palladium and silicon. *Chem. Commun.* 1895 (2000).

- [100] Y. Yamanoi, H. Nishihara, Efficient synthesis of arylsilanes by cross-coupling of aromatic compounds with hydrosilanes as silicon sources. *J. Synth. Org. Chem. Jpn.* **67**, 778 (2009).
- [101] M. Bordeau, C. Biran, P. Pons, M. P. Leger-Lambert, J. Dunogues, The electrochemical reductive trimethylsilylation of aryl chlorides: A good route to aryltrimethylsilanes and a novel route to tris(trimethylsilyl)cyclohexadienes. *J. Org. Chem.* **57**, 4705 (1992).