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WHAT'S HOT IN CHEMISTRY, September/October 2009

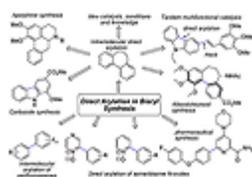
A Surprisingly Simple Way to Couple Arene Molecules Together

by John Emsley



The field of C-H bond activation is being revolutionized in a way that would never have been anticipated five years ago. Influential papers are appearing which not only challenge existing ideas of what is possible, but which also offer technical advances. Paper #8 describes the successful catalytic cross-coupling of two different aromatic compounds using a palladium catalyst. What is particularly surprising is the way this catalyst can distinguish between different aromatic C-H bonds.

[+] enlarge



Direct Arylation in Biaryl Synthesis.

The paper comes from Keith Fagnou and David Stuart of the Center for Catalysis Research and Innovation at the University of Ottawa, Canada

(figure to the left). It promises to revolutionize synthetic arene chemistry and might well become important commercially because molecules with linked arene groups appear in several guises. They are part of light-emitting diodes, liquid crystals, and pharmaceutical compounds.

Bonding together two molecules with aromatic rings (arenes) is not easy, and a great deal of effort has gone into ways to do this. These have involved activating the two rings, for example by the addition of a halide to the point of contact on one ring

Chemistry Top Ten Papers

Rank	Papers	Cites Mar-Apr 09	Rank Jan-Feb 09
1	Y. Kamihara, <i>et al.</i> , "Iron-based layered superconductor La[O _{1-x} F _x]FeAs (x = 0.05-0.12) with T _c = 26 K," <i>J. Am. Chem. Soc.</i> , 130 (11): 3296-7, 19 March 2008. [Tokyo Inst. Technol., Yokohama, Japan] *273SL	142	1
2	C. de la Cruz, <i>et al.</i> , "Magnetic order close to superconductivity in the iron-based layered LaO _{1-x} F _x FeAs systems," <i>Nature</i> , 453 (7197): 899-902, 12 June 2008. [6 U.S. and China institutions] *311WV	69	2
3	H. Takahashi, <i>et al.</i> , "Superconductivity at 43 K in an iron-based layered compound LaO _{1-x} F _x FeAs," <i>Nature</i> , 453 (7193): 376-8, 15 May 2008. [Nihon U., Tokyo, Japan; Tokyo Inst. Technol., Japan] *301AI	39	3
4	X.L. Li, <i>et al.</i> , "Chemically derived, ultrasmooth graphene nanoribbon semiconductors," <i>Science</i> , 319(5867): 1229-32, 29 February 2008. [Stanford U., CA] *267SX	31	4

and putting an electropositive group on the other. Even the production of these preliminary reactants, however, may require several stages, and this means lower overall yields and the generation of unnecessary waste in the form of solvents, catalysts, and reagents.

Fagnou and Stuart's method dispenses with the formation of activated reactants and uses a catalyst that will do the job directly and selectively. It results in the desired cross-coupling product and does not promote the reaction of each arene with itself. The reaction investigated was the attachment of a benzene ring to an indole derivative. The type and position of the group attached to the indole was varied, and this could result in yields as high as 84%. When microwave heating was used it cut reaction times from 48 to 5 hours.

Various catalytic conditions were tried and an optimal activity was achieved with palladium(II) trifluoroacetate in combination copper(II) acetate, 3-nitropyridine and cesium pivalate (aka 2,2-dimethylpropionate). The catalyst appears to be a palladium(II) species and the 3-nitropyridine is thought to play a role in stabilizing palladium(0) which is generated at the end of the catalytic cycle prior to its being re-oxidized to active palladium(II) by the copper salt. The role of cesium pivalate was less clear, but Fagnou speculates that it could assist in the formation of a palladium(II) pivalate complex which might be involved at some stage.

Reaction products were analyzed by gas chromatography-mass spectrometry, which showed that one product was the dominant one: the benzene ring attached to the indole carbon at position 3, while the other product, in which the benzene was attached to the alternative position 2, accounted for 10% or less. The product with two benzenes occupying both positions 3 and 2 accounted for at most 4%, and that was observed only in a few reactions. There was no evidence of the coupling of indole to indole or benzene to benzene.

As Fagnou tells *Science Watch*: "One of the biggest challenges associated with the oxidative arene cross-coupling reaction described in our paper is that the catalyst must establish regiocontrol at both of the aromatic coupling partners. We also found that by making minor modification to the substrate and reaction conditions, a complete change in regiochemistry could be produced." (See D.R. Stuart, *et al.*, *J. Am. Chem. Soc.*, 129: 12072, 2007.)

What alerted Fagnou to the potential of palladium(II) catalysts to be so selective was a study of the direct arylation of perfluorobenzenes; that work was published in *J. Am. Chem. Soc.* (M. Lafrance, *et al.*, 128[27]: 8754-6, 2006). He says his team are now looking at the fundamental physical parameters governing reactivity, using newly acquired knowledge to establish new chemical transformations.

As Fagnou observes, "Instead of asking how we might change the substrate in order to achieve a desired reaction, we are holding the organic components as invariable, and striving to modify only the catalyst and the reaction conditions. My hope is that 20 years from now, reactions at unactivated C-H bonds will be taken for granted, just as we take much of the available reactivity at modified substrates for granted today." ■

5	N. Tian, <i>et al.</i> , "Synthesis of tetrahedral platinum nanocrystals with high-index facets and high electro-oxidation activity," <i>Science</i> , 316 (5825): 732-5, 4 May 2007. [Xiamen U., China; Georgia Tech, Atlanta] *163RR	29	†
6	B. Tian, <i>et al.</i> , "Coaxial silicon nanowires as solar cells and nanoelectric power sources," <i>Nature</i> , 7164(449): 885-9, 18 October 2007. [Harvard U., Cambridge, MA] *221LY	29	7
7	J. Peet, <i>et al.</i> , "Efficiency enhancement in low-bandgap polymer solar cells by processing with alkane dithiols," <i>Nature Mater.</i> , 6(7): 497-500, July 2007. [U. Calif., Santa Barbara] *184NH	21	5
8	D.R. Stuart, K. Fagnou, "The catalytic cross-coupling of unactivated arenes," <i>Science</i> , 316(5828): 1172-5, 25 May 2007. (U. Ottawa, Canada) *171GQ	20	†
9	P.D. Jadzinsky, <i>et al.</i> , "Structure of a thiol monolayer-protected gold nanoparticle at 1.1 angstrom resolution," <i>Science</i> , 318(5849): 430-3, 19 October 2007. [Stanford U., CA] *221LW	20	†
10	A.I. Hochbaum, <i>et al.</i> , "Enhanced thermoelectric performance of rough silicon wires," <i>Nature</i> , 451(7175): 163-7, 10 January 2008. [U. Calif., Berkeley; Lawrence Berkeley Natl. Lab., CA] *249GA	19	†

SOURCE: Thomson Reuters Hot Papers Database. Read the Legend.

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