ChemPubSoc Europe

DOI: 10.1002/chem.201404121

CHEMISTRY
A European Journal
Communication

Organic Synthesis

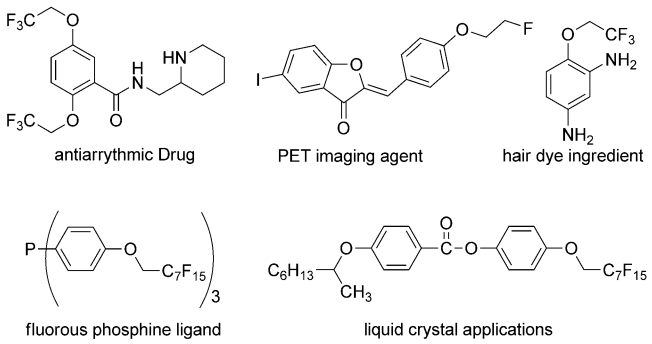
BrettPhos Ligand Supported Palladium-Catalyzed C–O Bond Formation through an Electronic Pathway of Reductive Elimination: Fluoroalkoxylation of Activated Aryl Halides

T. M. Rangarajan,[a, c] Rajendra Singh,*[b] Raju Brahma,[b] Kavita Devi,[b] Rishi Pal Singh,[a] R. P. Singh,*[b] and Ashok K. Prasad[c]

Abstract: We report an unprecedented BrettPhos ligand supported Pd-catalyzed C–O bond-forming reaction of activated aryl halides with primary fluoroalkyl alcohols. We demonstrate that the Phosphine ligand (BrettPhos) possesses the property of altering the mechanistic pathway of reductive elimination from nucleophile to nucleophile. The Pd/BrettPhos catalyst system facilitates the reductive elimination of the oxygen nucleophile through an electronic pathway.

The chemistry of fluorine has been an inviting subject for chemists for more than three decades because of fluorine's excellent and even bizarre physical and chemical properties. In fact, fluorinated organic compounds have found pervasive applications in medicinal,[1a] molecular imaging,[1b] agrochemicals,[1c] and material sciences.[1d–f] Therefore, the incorporation of the fluorine atom and fluorine-containing functional groups into organic molecules has recently received a spectacular growth of interest among chemists.[2,3]

Recently, transition-metal-catalyzed cross-coupling reactions (particularly Pd and Cu) have become a splendid tool not only to couple C–C, C–N, C–O bonds etc.,[4] but also C–F, C–CF_3, C–OCF_3, C–CF_3, and C–SCF_3 bonds. Thanks to the success of fluorination reactions under mild reaction conditions, coupling reactions involving fluorine chemistry have reached an advanced level in all branches of chemistry.[3] By popular demand, transition-metal-catalyzed cross-coupling methodologies have been shown ingress in almost all aspects of chemical syntheses.[3,4] In recent years, aryl fluoroalkyl ethers (Scheme 1) have also been paid as much attention as other fluorinated organic compounds in pharmaceuticals,[5] PET imaging,[1b,6] hair dye ingredients,[7a] pesticides,[7b] liquid-crystal display applications,[7c] fluorous chemistry,[7d] etc. Transition-metal-catalyzed C–O cross-coupling methodologies have become an efficient and alternative tool over traditional methods, such as Williamson ether synthesis, the Ullmann reaction, and alkylation of phenols, as these methods involve harsh reaction conditions, low functional-group tolerance, and carcinogenic reagents.[8]



Scheme 1. Selected examples of aryl fluoroalkyl ether containing compounds in various fields.

Various structural derivatives of phosphine ligated transition-metal-catalyzed cross-coupling methodologies offer a wide scope in the organic synthesis, were initially developed by Buchwald[9,10d,e,12c] and Hartwig groups,[10,12c] and subsequent contributions have been made by Beller[9b,c,10c,11,12c] and others[9b,c,10d,e,12] over last few decades. The electron-rich counterpart of the X-Phos ligand, the so-called electron-rich, relatively bulky BrettPhos ligand (**L1**) (Scheme 2), developed by the Buchwald group,[9f,13a] is one of the most effective supporting ligands that has promisingly facilitated several cross-coupling reactions,[3c,13,14] depicted in Scheme 3.

This catalytic system offered coupling products even with weak nucleophiles, such as a F^- anoin,[14b] trifluoromethyl anion,[14c] and trifluoromethylthio anion.[3c] However, this Pd/BrettPhos catalytic system, albeit it involves an oxidative addition step, failed to give C–O coupling reactions with relatively weak nucleophiles, such as ethyl acetohydroximate,[14e] metha-

[a] T. M. Rangarajan, Dr. R. P. Singh
Department of Chemistry
Sri Venkateswara College, University of Delhi
New Delhi (India)

[b] Dr. R. Singh, Dr. R. Brahma, K. Devi, Dr. R. P. Singh
Fluoroorganic Laboratory
Centre for Fire, Explosive and Environment Safety
DRDO, Delhi (India)
E-mail: rajendra@cfees.drdo.in
rajcfees@gmail.com

[c] T. M. Rangarajan, Prof. Dr. A. K. Prasad
Department of Chemistry
University of Delhi
Delhi (India)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201404121.