# Chemoselective Palladium-Catalyzed Deprotonative Arylation/ [1,2]-Wittig Rearrangement of Pyridylmethyl Ethers

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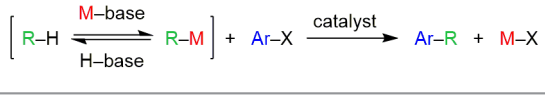
Transition-metal-catalyzed cross-coupling reactions are among the most useful and versatile methods in the field of synthetic organic chemistry, especially to form key carbon–carbon bonds. A long-standing goal of this chemistry is to develop efficient methods to provide valuable compounds found in natural products and bioactive small molecules. While classical approaches use prefunctionalized nucleophiles, recent trends in the area of the cross-coupling chemistry involve direct functionalization of simple starting pronucleophiles (Scheme 1).

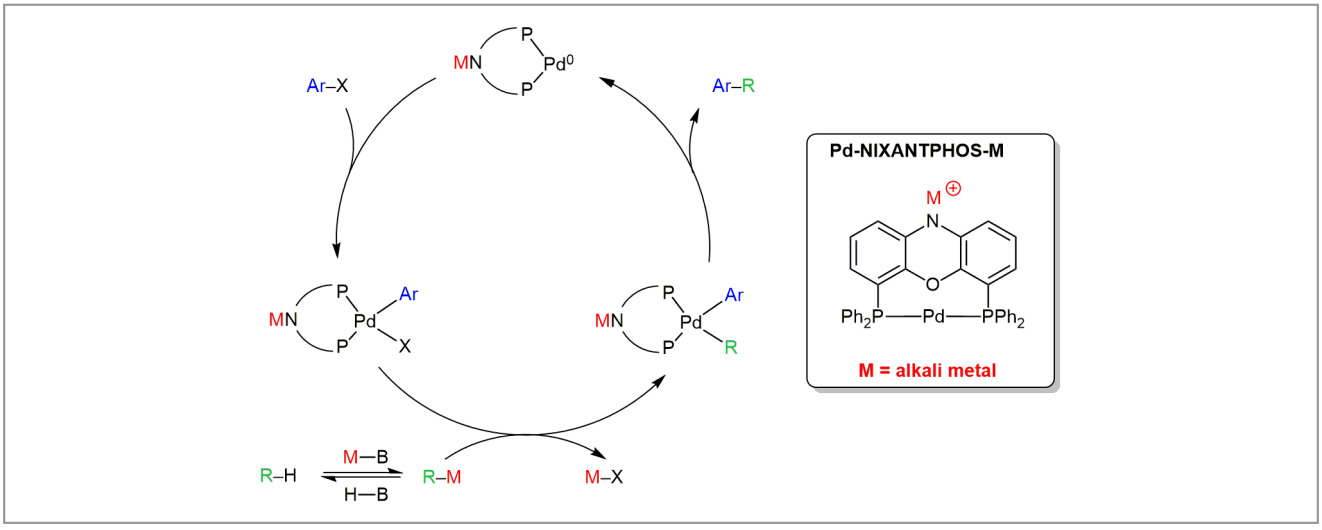



**Scheme 1** Deprotonative cross-coupling process (DCCP)

Recently, Professor Patrick J. Walsh's group at the University of Pennsylvania (USA) has been interested in the functionalization of weakly acidic C($sp^3$)–H bonds ($pK_a$ > 25) through a deprotonative cross-coupling process (DCCP), wherein a weakly acidic C–H of the substrate is deprotonated by a base and functionalized in the presence of a transition-metal catalyst (Scheme 2). The scope of substrates they reported to date includes diarylmethanes, amides, sulfoxides, *N*-Boc-benzylalkylamines, benzyl thioethers, benzylic phosphonates, benzyl imines, and 2-aryl-1,3-dithianes, among others.

"One of the most significant outcomes of our initial investigations is that van Leeuwen's NIXANTPHOS ligand exhibits extraordinary reactivity under basic reaction conditions (*J. Am. Chem. Soc.* **2012**, *134*, 13765)," said Professor Walsh. The role of bases in the reaction is essential to accomplishing this process. Professor Walsh explained: "First, the base reversibly deprotonates the pronucleophiles (R–H in Schemes 1 and 2). Likewise, NIXANTPHOS' free N–H is deprotonated under the reaction conditions and the resulting heterobimetallic catalyst (Pd-NIXANTPHOS-M) displays exceptional reactivity when compared with other bidentate phosphine-based palladium catalysts (Scheme 2)."

Graduate student Byeong-Seon Kim envisioned a unified approach to access a series of important pyridyl-containing building blocks. Professor Walsh and co-workers considered the synthesis of a series of aryl(pyridin-2-yl)methanol cores, intrigued by the idea of using pyridylmethyl derivatives (Figure 1).




**Scheme 2** In situ generated Pd/NIXANTPHOS heterobimetallic catalyst in the deprotonative cross-coupling process (DCCP)

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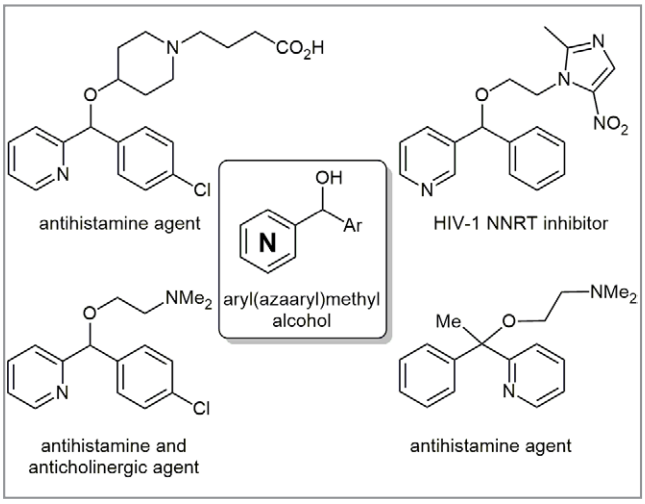
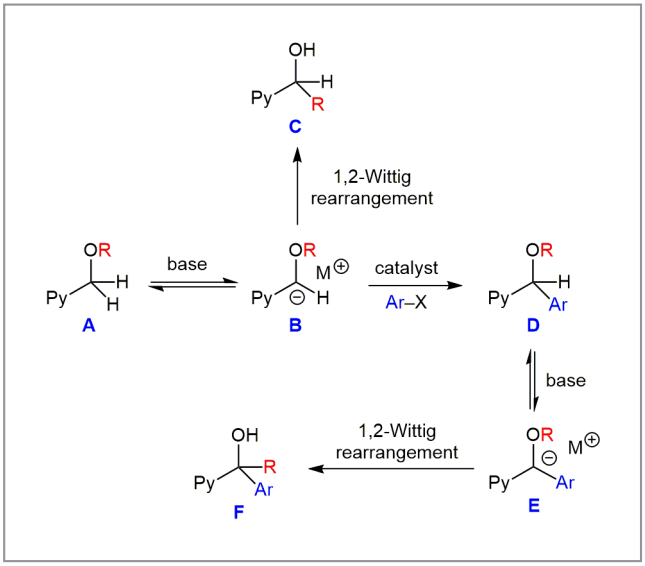



**Figure 1** Selected pharmacologically active compounds containing aryl(azaaryl)methyl alcohol derivatives

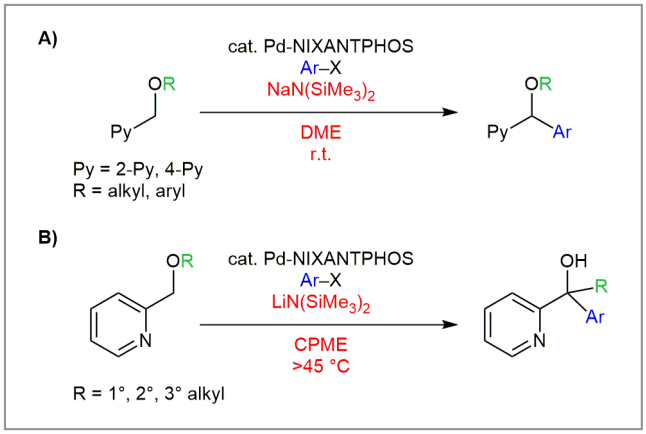
The strategy in this work (Scheme 3) entails deprotonation of the pyridylmethyl ether (**A**) to generate anion **B**, which can undergo a [1,2]-Wittig rearrangement to form **C**. "The anion **B** must be intercepted by the palladium catalyst faster than it undergoes the [1,2]-Wittig rearrangement," explained Professor Walsh. "Interception of anion **B**, through transmetalation to the catalyst, enters into the cross-coupling manifold affording pyridylmethyl ether **D**."




**Scheme 3** Working model of chemoselective palladium-catalyzed deprotonative arylation/[1,2]-Wittig rearrangement of pyridylmethyl ethers

Professor Walsh remarked: "The next challenge is the control of the [1,2]-Wittig rearrangement. Compound **D** possesses a more acidic benzylic C–H than pyridylmethyl ether **A**, and deprotonation of **D** will lead to the [1,2]-Wittig rearrangement via **E** to form **F**."

A number of reaction parameters were examined to either promote or inhibit the [1,2]-Wittig rearrangement, including the base, solvent, and temperature. "We found that remarkable chemoselectivity was possible by a choice of the base's main group metal (Na vs. Li), the solvent (DME vs. CPME), and the reaction temperature (room temperature vs. > 45 °C) (Scheme 4)," explained Professor Walsh. It was found that the [1,2]-Wittig rearrangement of the arylation product **D** is retarded at room temperature by a coordinating solvent like DME, particularly when the sodium base is used. In contrast, operating at 45 °C with the lithium silylamide in non-coordinating solvents favors the [1,2]-Wittig rearrangement.

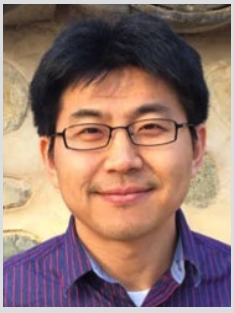



**Scheme 4** Chemoselective (A) arylation of 2- or 4-pyridylmethyl ethers and (B) tandem arylation/[1,2]-Wittig rearrangement of 2-pyridylmethyl ethers

"The work showed that both reaction pathways are compatible with electron-deficient, -rich, -neutral, *ortho*-substituted, and heterocyclic aryl bromides," said Professor Walsh. "Moreover, the arylation occurs with 2- or 4-pyridylmethyl ethers, showing that the reaction does not require a directed metalation for deprotonation. However, the 4-pyridylmethyl derivatives were not suitable for tandem arylation/[1,2]-Wittig rearrangement under the optimized conditions," he continued. "It is worth pointing out that the scalability of both arylation and tandem arylation/[1,2]-Wittig rearrangement reactions were illustrated with 5 mmol scale reactions to provide the product of either arylation or tandem arylation/[1,2]-Wittig rearrangement."

Professor Walsh concluded: "With high chemoselectivity, structural diversity can be forged from a common set of substrates. This is particularly true with tandem reactions, where several bonds are formed under nearly identical conditions without isolation of intermediates, addition of new reagents, or modification of reaction parameters." He continued: "This straightforward technique enables rapid preparation of various types of aryl(azaaryl)methyl derivatives, making it ideal for applications in the field of organic synthesis." The Walsh group has also shown that pyridylmethyl silyl ethers are good substrates for the arylation reaction (Scheme 3, **A** → **D**, R = $SiR_3$, *Org. Lett.* **2016**, *18*, 1590).

## About the authors



*B.-S. Kim*

**Byeong-Seon Kim** was born in Andong (South Korea). He received his B.Sc. in chemistry from Korea University (South Korea) in 2003 and M.Sc. in Professor Deok-Chan Ha's group in 2005. He was a research scientist at Korea Institute of Science and Technology (KIST, Seoul, South Korea) for one year. He is currently a Ph.D. student at the University of Pennsylvania (USA) under the supervision of Professor Patrick J. Walsh. His current research interest is in the field of homogeneous catalysis to develop fundamental bond-forming reactions and its application in new synthetic methods.

*Prof. F. Gao*

**Feng Gao** was born in Chengdu (P. R. of China). He received his B.Sc. in pharmacy science from Sichuan University (P. R. of China) in 2002 and Ph.D. in medicinal chemistry of natural products under the guidance of Professor Feng-Peng Wang in 2009. Then he moved to Sichuan Agricultural University (P. R. of China) where he was promoted to associate professor in 2010. From August 2013 to August 2014, he joined Professor Patrick J. Walsh's group at the University of Pennsylvania (USA) as a visiting scholar. His current research focuses on homogeneous catalysis and its application in natural products chemistry.

*Prof. P.-J. Walsh*

**Patrick J. Walsh** received his B.A. from UC San Diego (USA, 1986) and Ph.D. in chemistry at UC Berkeley (USA) with Professor Robert G. Bergman (1991). He was an NSF postdoctoral fellow with Professor K. B. Sharpless at the Scripps Research Institute (La Jolla, USA). Moving across town from 1994–1999, he was an assistant professor at San Diego State University (USA) and also Professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana (Mexico) from 1996–1999. In 1999, he moved to the University of Pennsylvania (USA) where he was promoted to Professor in 2005, and to the Alan G. MacDiarmid Professor of Chemistry in 2008. Walsh's interests are in asymmetric catalysis, development of new synthetic methods, reaction mechanisms, and inorganic synthesis. With Professor Marisa Kozlowski, Walsh co-authored "Fundamentals of Asymmetric Catalysis" (University Science Books, 2008).

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