

Palladium-Catalyzed Direct Cyclopropylation of Heterocycles

Angew. Chem. Int. Ed. **2015**, *54*, 9601–9605

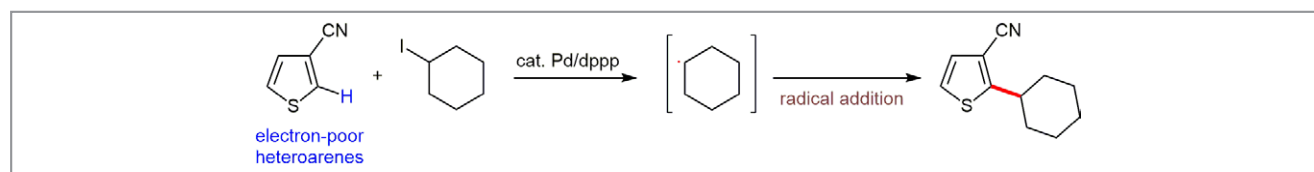
In 2014, Professor Jianrong (Steve) Zhou's group at the Nanyang Technical University in Singapore reported a palladium-catalyzed process for the alkylation of unsaturated heterocycles (*Angew. Chem. Int. Ed.* **2014**, *53*, 13573). The chemistry capitalized on Osborn's initial discovery in the 1970s that phosphine complexes of Pd(0) react with alkyl halides to produce alkyl radicals via single-electron-transfer processes (*J. Am. Chem. Soc.* **1974**, *96*, 7145). Professor Zhou explained: "Under our conditions, the alkyl radicals that were involved in the catalytic bond formation can be trapped by TEMPO. The key step of direct radical addition to heteroarenes without intervention by metal catalysts was further supported by DFT calculations. Suitable substrates included many electron-deficient thiophenes, furans, pyrroles, indoles and pyridines. About 90% of these alkylation products were new entities although they had simple structures. In many cases, good conjugate selectivity of addition was observed. That work was conducted in collaboration with Professor Hajime Hirao on DFT calculations and Professor Jean-Cyrille Hierso in France."

Next, Professor Zhou and co-workers decided to investigate whether a similar radical process was possible by using cyclopropyl iodides together with heterocycles. "Compared with common cycloalkyl analogues, cyclopropyl radicals are

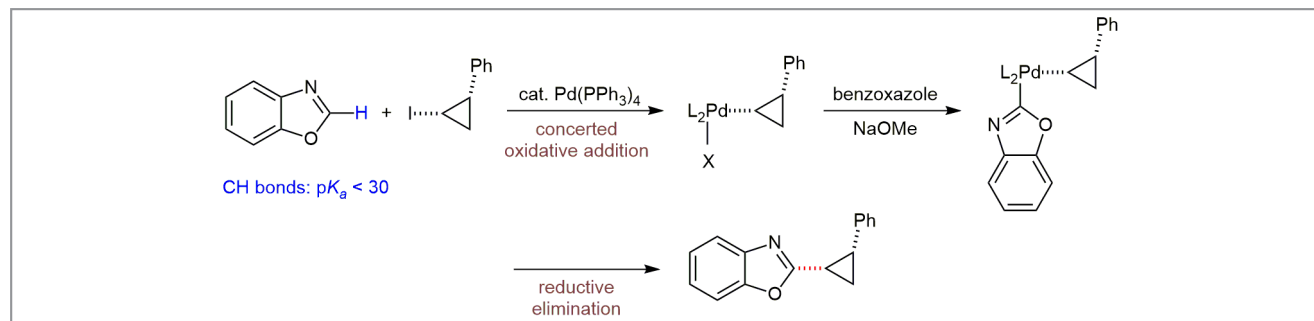
known to be less nucleophilic and they added more slowly to electron-poor heteroarenes," said Professor Zhou. "Cyclopropyl rings are useful pharmacophores, since cyclopropyl rings are small and rigid and their ring substituents have specific orientations in space. They also have high built-in ring strains, which may prompt ring rupture. In the literature, very few methods existed that allowed incorporation of heteroaryl groups directly onto the three-membered rings when we initiated our study."

Professor Zhou continued: "Our new method allowed an efficient cyclopropylation of various heterocycles such as oxazoles, thiazoles and caffeine. Our H/D exchange studies pointed to reversible deprotonation of heterocycles, such as oxazoles, by a base like NaOMe, even in the absence of a palladium catalyst. This finding led us to explore couplings of some electron-poor thiophenes, which have relatively acidic CH bonds with pK_a values less than 30 in DMSO. Indeed, the reactions proceeded as we anticipated."

However, to their surprise, when the Singapore-based researchers tested pure *cis*-2-phenylcyclopropyl iodide under the catalytic conditions at the end of the project, it led almost exclusively to a *cis*-coupling product. This result argued strongly against a radical pathway, as cyclopropyl radicals can undergo inversion of configuration with very low barriers



Scheme 1



Scheme 2

(3–4 kcal/mol). Professor Zhou said: “Now, we believe that the catalytic cycle starts with a concerted oxidative addition of cyclopropyl iodides which is followed by fast transmetalation with anions of heterocycles formed in situ.” Suzuki reaction of cyclopropyl halides was previously reported by Charette to proceed with conservation of the configuration on the three-membered ring.

Professor Zhou concluded: “In retrospect, the main challenge in realizing this transformation was the side reactions lying outside the catalytic cycle, rather than a difficult step in the catalytic cycle. In fact, when the transmetalation step was slow, we found that the oxidative adduct, a cyclopropylpalladium complex, was prone to two side reactions, elimination to form 1,3-dienes and ring opening of cyclopropyl groups to form allylic radicals.”

Mattias Hansch

About the authors



Dr. X. Wu

Xiaojin Wu was born in Yancheng (P. R. of China). He received his B.Sc. degree in chemistry at Soochow University in 2007 and his M.Sc. degree in Professor Shunjun Ji's group in 2010. He then conducted his doctoral studies at the Nanyang Technological University (Singapore) in Professor Jianrong (Steve) Zhou's group from 2010–2015. His thesis research focused on the palladium-catalyzed Heck reaction and alkylation of heteroarenes. He is currently a research fellow in Professor Jishan Wu's lab at the National University of Singapore.



Dr. C.-H Lei

Chuan-Hu Lei was born in Sichuan (P. R. of China). He received his B.Sc. degree in chemistry from Beijing Normal University (P. R. of China) in 2008. Then he joined Professor Mei-Xiang Wang's lab at the Institute of Chemistry, Chinese Academy of Sciences (P. R. of China) as a Ph.D. student and worked on tandem reactions between tertiary enamides and isonitriles for the efficient construction of azacycles. Since 2014, he has been working in Professor Jianrong (Steve) Zhou's group at Nanyang Technological University in Singapore as a research fellow.



Prof. G. Yue

Guizhou Yue was born in Hubei (P. R. of China). From 2008–2011, he received Ph.D. training in the laboratory of Professor Bo Liu at Sichuan University (P. R. of China), working on the total synthesis of lindenane-type sesquiterpenoids. He began his independent research at the Sichuan Agricultural University (P. R. of China) in 2005 and was promoted to associate professor in 2013. His research focuses on the total synthesis of bioactive natural products and transition-metal-catalyzed reactions. In 2014/2015, he was a visiting professor in Professor Steve Zhou's group under the support of Chinese Scholarship Council.



Prof. J. (S.) Zhou

Jianrong (Steve) Zhou was born in Zhejiang (P. R. of China). He received undergraduate education and his Master's degree at the National University of Singapore under the guidance of Professor Teck-Peng Loh. In 2000, he went to MIT (USA) and did his Ph.D. in Professor Gregory Fu's lab where he developed cross-coupling reactions of alkyl halides. From 2005 to 2008, he was a postdoctoral researcher in Professor John Hartwig's group at Yale University (USA) and later moved with him to the University of Illinois at Urbana (USA). In 2008, he started his independent career at Nanyang Technological University (Singapore) with a joint appointment as Singapore National Research Foundation Fellow. Steve's research interests include transition-metal catalysis for fundamental bond-forming processes and mechanistic studies. He likes reading history and politics for leisure.