

Chemoselective Activation of sp^3 vs sp^2 C–H Bonds with Pd(II)

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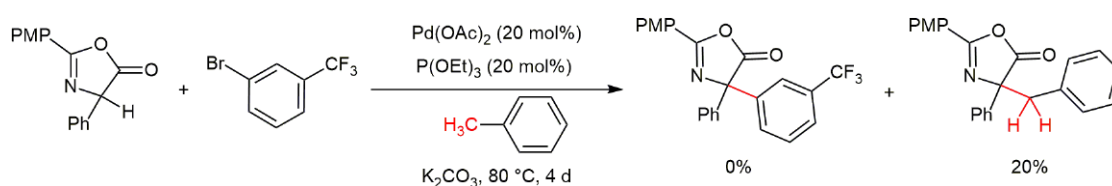
■ Oxidative C–H activation is the most atom-economical process for the construction of carbon–carbon bonds. Yu, White, Sanford, Fagnou and Davies (for references see the original article) have pioneered the activation of $C(sp^3)$ –H bonds with directing groups (heteroatom, allyl, carbene, etc.). The ability of some metals, such as Pd catalysts, to insert selectively into C–H bonds has provided a host of new, useful methods for the synthesis of organic molecules. Considering as an example the Pd-mediated carboxylation of toluene, selective insertion into $C(sp^2)$ –H bonds (110–115 kcal/mol) by palladium is remarkable when considering bond strengths of the competing $C(sp^3)$ –H bonds (benzylic 85–90 kcal/mol). Typically, the arene π -system positions the metal carboxylate for a favorable deprotonative insertion that relies on forming the stronger $C(sp^2)$ –Pd bonds.

The group of Professor Marisa C. Kozlowski at the University of Pennsylvania (USA) has had an ongoing interest in oxidative C–H activation. Initial studies on the chemoselective activation of toluene arose from a serendipitous discovery; in the course of attempting an arylation of azlactones, an unusual benzyl product was observed (Scheme 1). “This is a perfect example of how chance favors the prepared mind,” said Professor Kozlowski. “Since the targeted compound was not observed, many scientists would have moved on. Only the curiosity and diligence of the graduate student undertaking the experiments, Dr. John Curto, brought this result to light. Upon further study, we discovered that a selective insertion into the benzylic position of toluene was occurring under conditions that would typically cause insertion into one of the arene C–H bonds.” In fact, methyl and other alkyl sub-

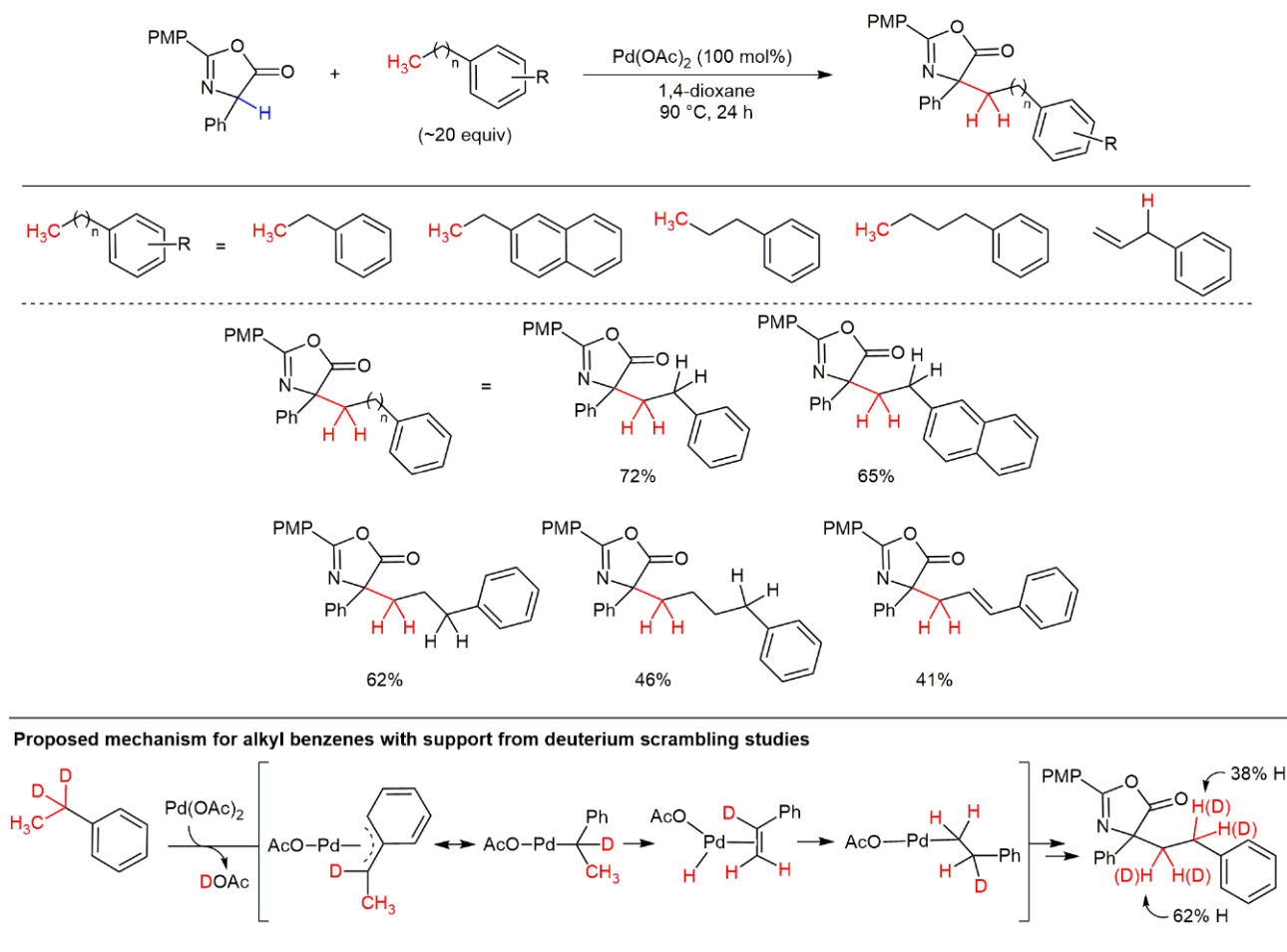
stituents on arenes have been shown to be compatible to many Pd-catalyzed $C(sp^2)$ –H insertions. “Thus, this discovery represents a novel mode of reactivity for Pd,” added Professor Kozlowski, who explained that toluene derivatives are the ideal benzylation reagent because they are stable, commercially available, and easy to handle, while being far more atom-economical than the corresponding benzyl halides.

Professor Kozlowski said: “Our initial success with the selective $C(sp^3)$ –H bond activation of tolyl and methylnaphthyl analogues prompted our exploration of secondary benzylic C–H bonds. Extension of the alkyl chain on benzene to ethyl, propyl and butyl most surprisingly gave rise to the terminal alkylated product (Scheme 2, top). This chemoselectivity provides access to chemical space that would not be feasible via a radical-mediated process.” A mechanism consistent with the C–H activation step involving a benzylic metalation is supported by kinetic isotope effect studies performed by Professor Kozlowski and Dr. Curto. For ethylbenzene, deuterium scrambling supports a zipper mechanism, involving β -hydride elimination and rearrangement of a benzylic palladium species (Scheme 2, bottom). “If the conditions that permit this novel pathway of alkyl benzene activation can be understood, then similar migrations could be achieved in a broad range of known Pd-catalyzed coupling processes,” said Professor Kozlowski.

Upon discovering this novel $C(sp^3)$ –H activation of alkyl arene bonds, a primary goal for the Kozlowski group was to identify catalytic conditions, which would greatly expand the utility of this transformation. “We utilized the UPenn High-Throughput Experimentation Center, one of the few academic



Scheme 1



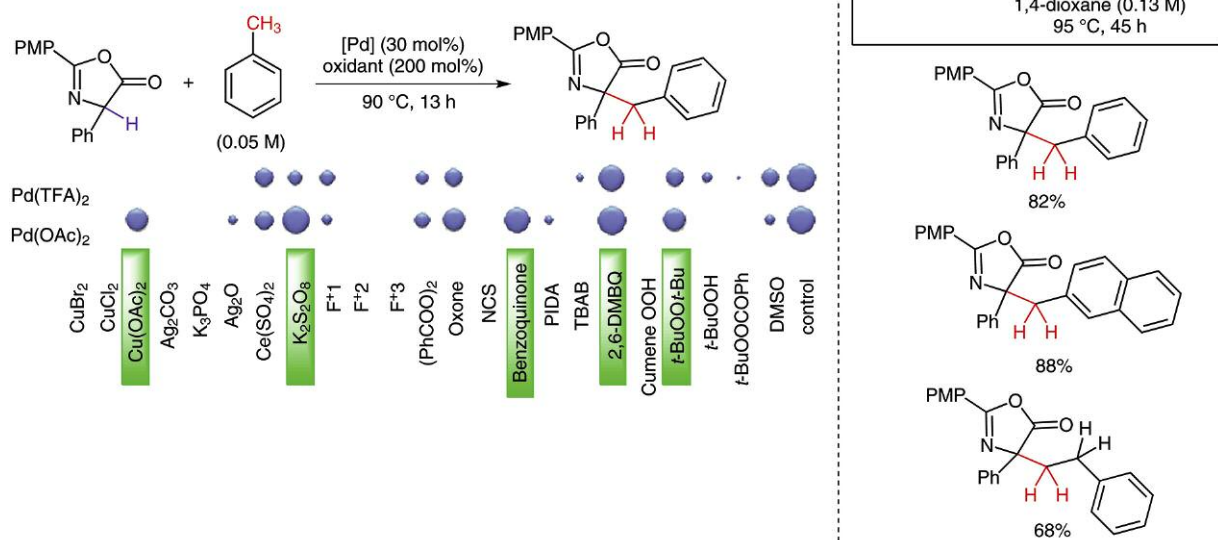
Scheme 2

centers with this technology, to screen multiple variables and rapidly identify trends,” said Professor Kozłowski. “Parallel microscale experimentation (Scheme 3, left) revealed that most transition-metal oxidants used extensively in the Pd-catalyzed $\text{C}(\text{sp}^2)\text{-H}$ processes were ineffective in this transformation. The highlighted oxidants were identified as potential leads and eventually led to the discovery of catalytic conditions using fewer equivalents of the alkyl benzene reaction partner (Scheme 3, right).”

“In summary, a novel reactivity mode for alkyl arenes was discovered from the investigation of a serendipitous result,” said Professor Kozłowski. With a simple system consisting of $\text{Pd}(\text{OAc})_2$ and pivalic acid, catalytic dehydrogenative cross-coupling with a carbon nucleophile occurs readily for the terminal methyl positions of methyl, ethyl, propyl and butyl arenes. Notably, selective $\text{C}(\text{sp}^3)\text{-H}$ insertion is observed in benzylic systems even though $\text{Pd}(\text{OAc})_2$ typically causes

arene $\text{C}(\text{sp}^2)\text{-H}$ insertion. Double $\text{C}-\text{H}$ activation to form a $\text{C}-\text{C}$ bond is a difficult transformation because two different $\text{C}-\text{H}$ bonds need to be activated in a selective manner. “We hope to extend the scope of this technology and are exploring other acidic $\text{C}-\text{H}$ partners. Although the full mechanistic details of this transformation remain to be elucidated, our ongoing efforts lend support for a mechanism that represents a shift in our understanding of Pd,” concluded Professor Kozłowski. ■

Matteo Zanda



Scheme 3

About the authors



Dr. J. Curto

John Curto was born and raised in western Massachusetts (USA). He obtained his undergraduate degree at the College of the Holy Cross in Worcester, MA (USA), where he was first introduced to research while working for Kevin Quinn on the synthesis of small natural products. In 2014, John graduated from the University of Pennsylvania (USA) with a PhD under the guidance of Professor Marisa Kozlowski on the asymmetric

synthesis of α,α -disubstituted α -amino acids and studies on the Pd-catalyzed C(sp³)-H activation of alkyl arenes. John and his wife Barb currently live in Connecticut where John has begun his career as a medicinal chemist.



Prof. M. Kozlowski

Marisa Kozlowski received an A.B. in Chemistry from Cornell University (USA) in 1989 and a PhD under the direction of Paul Bartlett from the University of California at Berkeley (USA) in 1994. After an NSF postdoctoral fellowship with David A. Evans at Harvard University (USA), she joined the faculty at the University of Pennsylvania (USA) in 1997 and is currently Professor of Chemistry. The Kozlowski group's research focuses on the

design of new catalysts and transformations. She has also co-authored 'Fundamentals of Asymmetric Catalysis' with Patrick Walsh.