#### **Cross-Coupling**

International Edition: DOI: 10.1002/anie.201708940 German Edition: DOI: 10.1002/ange.201708940

## **Palladium-Catalyzed Cross-Coupling of Nitroarenes**

Yang Yang\*

aromatic substitution  $\cdot$  copper  $\cdot$  cross-coupling  $\cdot$  palladium  $\cdot$  sustainable chemistry

ransition-metal-catalyzed cross-coupling has widely been recognized as an indispensable tool for the synthesis of highly functionalized aromatic compounds.<sup>[1]</sup> With the contributions from numerous research groups over the past decades, a range of carbon- and heteroatom-based nucleophiles can now be utilized in the coupling process, allowing for the rapid construction of C--C, C--N, C--O, and other carbon-heteroatom bonds with excellent functional group compatibility.<sup>[1]</sup> These coupling reactions typically hinge on the use of aryl halides as the electrophilic coupling partner. In an effort to further expand the scope of aromatic electrophiles suitable for cross-coupling, recent studies have focused on the development of novel catalytic techniques to efficiently transform phenol derivatives that are considered to be less reactive.<sup>[2]</sup> Despite these notable advances, it is still highly desirable to engage other classes of widely available aromatic electrophiles in this coupling process.

Nitroarenes constitute a class of easily accessible building blocks that can be conveniently prepared from the parent arenes via Friedel–Crafts nitration.<sup>[3]</sup> In contrast to Friedel– Crafts halogenation, the electrophilic nitration process generally furnishes nitroarene products with good site selectivity. Furthermore, a number of commonly employed aryl halides are synthesized from the corresponding nitroarenes by reduction and subsequent Sandmeyer-type halogenation. In this context, the direct use of nitroarenes as the electrophilic coupling partner would substantially enhance the synthetic utility of cross-coupling chemistry and circumvent many of the problems originating from the need to prepare a stoichiometric quantity of aryl halides from the parent arene.

In 2011, Wu and co-workers described a rhodium-catalyzed C–O bond forming reaction starting from nitroarenes [Scheme 1, Eq. (1)].<sup>[4a]</sup> Later on, the same research group developed an improved protocol for the conversion of nitroarenes to diaryl ethers using a copper catalyst [Eq. (2)].<sup>[4b]</sup> Additionally, an analogous copper-catalyzed C– S cross-coupling of nitroarenes was reported by Shinde et al. [Eq. (3)].<sup>[4c]</sup> Although these methods represent powerful synthetic tools, they suffer from a relatively limited substrate

[\*] Dr. Y. Yang Department of Chemistry, University of California, Berkeley Berkeley, CA 94720 (USA) E-mail: yang89@berkeley.edu

The ORCID identification number for the author of this article can be found under: https://doi.org/10.1002/anie.201708940.

Wu (2011)



**Scheme 1.** Rhodium- and copper-catalyzed carbon-heteroatom bond forming cross-coupling of nitroarenes. EWG = electron-withdrawing group.

scope and electron-withdrawing groups are typically required to ensure excellent yield of the coupled products. In contrast to these C–O/C–S bond forming processes, transition metalcatalyzed C–C and C–N bond forming cross-coupling of nitroarenes remained elusive. Moreover, because of the inherent difficulty associated with the oxidative addition of low valent transition metal catalysts into the  $C(sp^2)$ –NO<sub>2</sub> bond and the lack of alternative  $C(sp^2)$ –NO<sub>2</sub> bond activation mechanisms, the development of a general catalyst system for the coupling of a diverse range of nitroarenes, particularly electron-rich ones, remains a daunting challenge.

Compared to systems derived from other transition metals, palladium-based catalysts are inarguably the most widely used in cross-coupling processes. In stark contrast to coupling reactions utilizing aryl halides and pseudohalides, the palladium-catalyzed cross-coupling of nitroarenes was not previously known. As a related process involving the oxidative addition of palladium into activated  $C(sp^3)$ -NO<sub>2</sub> bonds, in 1982?, Hegedus and Tamura reported a palladium-catalyzed allylic substitution of allylnitro compounds.<sup>[5]</sup> In 2009, Fors and Buchwald reported a palladium-catalyzed conversion of aryl chlorides and triflates to nitroarenes using a catalyst system derived from a bulky monodentate phosphine ligand, t-BuBrettPhos (Scheme 2, L1).<sup>[6]</sup> In this process, the Ar-NO<sub>2</sub> bond forming reductive elimination from  $(L1)Pd^{II}(Ar)(NO_2)$ , which is the microscopically reverse process of nitroarene oxidative addition, was facilitated by the use of t-BuBrettPhos (L1). These results suggested the utility of bulky biarylphosphine ligands in the catalytic transformation of nitroarenes.

Wiley Online Library

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

### Highlights



**Scheme 2.** Palladium-catalyzed nitration of aryl chlorides, triflates and nonaflates. dba = *trans*,*trans*-dibenzylideneacetone, TDA = tris(3,6-dioxaheptyl)amine.

Recently, the groundbreaking work from the group of Nakao and Sakaki demonstrated that an array of nitroarenes could be coupled with arylboronic acids to afford biaryl products in excellent yields (Scheme 3).<sup>[7a]</sup> After an extensive



**Scheme 3.** Palladium-catalyzed Suzuki–Miyaura cross-coupling of nitroarenes and organoboron reagents: selected examples. [a] From the corresponding acetal after hydrolysis. [b] In the absence of 18-crown-6. [c] CsF was used in lieu of  $K_3PO_4$ . acac=acetylacetonate, Cy=cyclohexyl.

optimization, the use of a palladium catalyst generated from the biarylphosphine BrettPhos (L2) was found to be the key to the successful implementation of this challenging transformation. In addition, the use of  $K_3PO_4$  as the base in the presence of 18-crown-6 and a trace amount of water proved crucial for the success of this palladium-catalyzed crosscoupling. Under the optimized reaction conditions, a diverse range of nitroarenes underwent this Suzuki-Miyaura coupling, affording biaryl compounds in excellent yields (1a-1d). Heterocyclic substrates such as a pyridine (1e) and a quinoline (1f) were also compatible with this protocol. Furthermore, electron-rich (1g), electron-deficient (1h), and sterically hindered boronic acids (1i) were readily accommodated under these reaction conditions, further highlighting the synthetic utility of this coupling process.

Nakao and co-workers also developed an efficient C–N cross-coupling process (Scheme 4).<sup>[7b]</sup> A range of nitroarenes with diverse electronic properties represented excellent substrates for this amination process. In addition to secondary amines, primary amines can also be effectively converted under these conditions. Interestingly, commonly used strong bases such as NaOtBu were ineffective for this nitroarene amination.



**Scheme 4.** Palladium-catalyzed C–N cross-coupling of nitroarenes and organoboron reagents: selected examples. [a] CPhos was used instead of BrettPhos. [b]  $K_3PO_4 \cdot nH_2O$  was used as the base and DMF was used instead of *n*-heptane. [c]  $K_3PO_4 \cdot nH_2O$  was used as the base and dioxane was used instead of *n*-heptane.

To gain further insight into the reaction mechanism, stoichiometric reactions using  $(cod)Pd(CH_2TMS)_2$  (cod = 1,5-cyclooctadienyl, TMS = trimethylsilyl), L2 and the nitroarene substrate were also performed (Scheme 5).<sup>[7a]</sup> Treatment of  $(cod)Pd(CH_2TMS)_2$  and L2 with **4a** in THF at 60 °C afforded complex **5a**, demonstrating the oxidative addition of a Pd<sup>0</sup> center into an Ar–NO<sub>2</sub> bond for the first time. On the other hand, reacting  $(cod)Pd(CH_2TMS)_2$  and L2 with **4b** in toluene at room temperature furnished a nitroarene-bound Pd<sup>0</sup>



**Scheme 5.** Stoichiometric studies: oxidative addition of Pd<sup>0</sup> into the Ar-NO<sub>2</sub> bond. C gray, N blue, O red, P orange, Pd green.

Angew. Chem. Int. Ed. 2017, 56, 2-5

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

einheim www.angewandte.org These are not the final page numbers!

# GDCh

complex **5b**. <sup>31</sup>P NMR studies indicated that this Pd<sup>0</sup> intermediate is likely the catalyst resting state. Combined with other mechanistic and computational evidence, it was suggested that this nitroarene cross-coupling proceeds through a classic oxidative addition/transmetalation/reductive elimination mechanism, with the oxidative addition being the ratedetermining step.

In conclusion, the elegant work of Nakao and Sakaki on the cross-coupling of nitroarenes demonstrates invaluable advancements to the field of cross-coupling. In particular, the identification of a Pd<sup>0</sup> species capable of undergoing facile oxidative addition into the Ar–NO<sub>2</sub> bond represents an important addition to the organometallic chemistry of palladium. Furthermore, this work sets the stage for the development of a new class of cross-coupling reactions utilizing broadly available nitroarene substrates, thereby providing an exciting opportunity for accessing value-added coupling products from inexpensive and easily available starting materials. Further efforts to lower the catalyst loading and the reaction temperature will make these nitroarene cross-coupling reactions a powerful tool for the formation of C–C and C–heteroatom bonds.

#### Acknowledgements

I thank the Miller Institute for Basic Research in Science for a research fellowship.

#### **Conflict of interest**

The authors declare no conflict of interest.

- a) A. de Meijere, F. Diederich in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, 2004; b) N. Miyaura, *Cross-Coupling Reactions-A Practical Guide*, Springer, Berlin, 2002.
- [2] a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* 2011, *111*, 1346;
  b) M. Tobisu, N. Chatani, *Acc. Chem. Res.* 2015, *48*, 1717; c) B. Su, Z.-C. Cao, Z.-J. Shi, *Acc. Chem. Res.* 2015, *48*, 886.
- [3] G. Booth, Nitro Compounds, Aromatic; Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, New York, **2012**.
- [4] a) X. Zheng, J. Ding, J. Chen, W. Gao, M. Liu, H. Wu, Org. Lett. **2011**, 13, 1726; b) J. Zhang, J. Chen, M. Liu, X, Zheng, J. Ding, H. Wu, Green Chem. **2012**, 14, 912; c) S. S. Bahekar, A. P. Sarkate, V. M. Wadhai, P. S. Wakte, D. B. Shinde, Catal. Commun. **2013**, 41, 123.
- [5] R. Tamura, L. S. Hegedus, J. Am. Chem. Soc. 1982, 104, 3727.
- [6] B. P. Fors, S. L. Buchwald, J. Am. Chem. Soc. 2009, 131, 12898.
- [7] a) M. R. Yadav, M. Nagaoka, M. Kashihara, R.-L. Zhong, T. Miyazaki, S. Sakaki, Y. Nakao, J. Am. Chem. Soc. 2017, 139, 9423;
  b) F. Inoue, M. Kashihara, M. R. Yadav, Y. Nakao, Angew. Chem. Int. Ed. 2017, 56, 13307-13309; Angew. Chem. 2017, 129, 13492-13494.

Manuscript received: August 30, 2017 Version of record online:

www.angewandte.org

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



## Highlights

### Highlights

Cross-Coupling	
Y. Yang*	

Palladium-Catalyzed Cross-Coupling of Nitroarenes



**Pd at the crossroads**: The palladiumcatalyzed cross-coupling of nitroarenes has eluded chemists for decades. Recently, the first palladium-catalyzed Suzuki–Miyaura and Buchwald–Hartwig cross-couplings of nitroarenes were reported. Mechanistically, this process involves the challenging oxidative addition of LPd<sup>0</sup> into the Ar–NO<sub>2</sub> bond. This process features a broad substrate scope with respect to both the nitroarene and the nucleophilic coupling partners.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

www.angewandte.org

5