

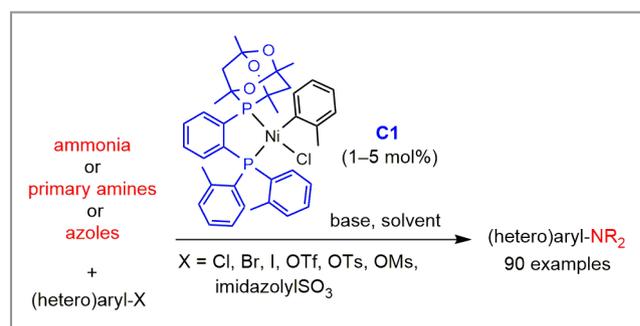
Challenging Nickel-Catalyzed Amine Arylations Enabled by Tailored Ancillary Ligand Design

Nat. Commun. **2016**, *7*, 11073

A primary research focus of Professor Mark Stradiotto's group at Dalhousie University (Halifax, Canada) is on the design and application of new ancillary ligands for use in addressing outstanding reactivity challenges in metal-catalyzed cross-coupling chemistry and beyond. Professor Stradiotto said: "In particular, we are interested in the monoarylation of ammonia and related N–H nucleophiles by use of (hetero)aryl (pseudo)halide reaction partners. While at first glance ammonia appears to be an ideal reagent for the synthesis of sought-after primary (hetero)aryl amines, given that ammonia is one of the most widely produced commodity chemicals, the monoarylation of ammonia has proven to be challenging." He continued: "In addition to catalyst decomposition that can occur in the presence of excess ammonia, the product (hetero)aniline is often a more capable substrate relative to ammonia itself, leading to uncontrolled polyarylation.¹ Achieving selectivity in this difficult transformation presents an exciting challenge from a catalyst design perspective."

Until very recently, only copper- and palladium-based catalysts had proven capable of ammonia monoarylation, with each exhibiting important limitations: reactions involving copper are typically limited to activated aryl bromide or iodide electrophiles under forcing reaction conditions. "In the case of palladium, few catalysts that are capable of operating under mild (room temperature) conditions and/or under high pressure of ammonia are known, and the scope of established reactivity with (hetero)aryl pseudohalides is limited," explained Professor Stradiotto. "Additionally, both the cost of palladium and the potential for bulk palladium supply limitations can be an issue, especially for industrial chemists seeking to establish a process on relatively large scales."² Professor Stradiotto continued: "In this regard, the use of nickel-based catalysts in ammonia monoarylation chemistry represents an attractive alternative to both copper and palladium, given the desirable reactivity properties of nickel in oxidative addition chemistry and its relatively low cost and large abundance (relative to palladium)." He acknowledged: "It should be noted that the use of nickel in cross-coupling chemistry is by no means new: Kumada, Negishi, and others established the utility of nickel in cross-coupling chemistry in the 1970s, and the nickel-catalyzed amination of aryl chlorides was reported by Wolfe and Buchwald³ nearly twenty years ago. Nonetheless,

the first reports of nickel-catalyzed ammonia monoarylation did not appear until 2015, in a pair of independent publications by my research group and that of John Hartwig (UC Berkeley)."⁴ In seeking to identify an ancillary ligand to enable the efficient nickel-catalyzed monoarylation of ammonia, Professor Stradiotto's group employed the common approach of screening ligands that had worked well with palladium in related transformations. Professor Stradiotto explained: "In doing so, my group and the Hartwig group independently identified suitably effective members of the commercially available JosiPhos ligand family. Despite this breakthrough, my group was discouraged by the failure (in our protracted ancillary ligand screen) of other high-performing ligands from the domain of palladium-catalyzed ammonia monoarylation; it became evident to us that simply 're-purposing' ligands from palladium chemistry would not be a universally effective strategy in the development of highly effective nickel catalysts for C(sp²)-N cross-couplings." He continued: "We also thought that it was somewhat ironic to be using an expensive and unnecessarily enantiopure JosiPhos ligand in this chemistry, given our interest in circumventing the use of costly and rare palladium."



Scheme 1

In response, the Stradiotto group initiated a program targeting the development of new ancillary ligands for use in supporting highly effective nickel catalysts for ammonia monoarylation and other challenging nickel-catalyzed C(sp²)-N cross-coupling reactions. "Ligand design in palladium cross-coupling chemistry has focused primarily on bulky *electron-*

rich ancillary ligands to facilitate challenging oxidative additions [e.g., C(sp²)-Cl],” said Professor Stradiotto. “However, given the greater propensity for C(sp²)-Cl oxidative additions to L₂Ni(0) relative to L₂Pd(0),⁵ and the potential for rate-limiting C(sp²)-N reductive elimination with nickel, it occurred to us that sterically demanding yet relatively *electron-poor* bisphosphines might be interesting targets of inquiry. Surprisingly, the design of ancillary ligands specifically for use in enabling nickel-catalyzed C(sp²)-N cross-couplings had not been reported prior to our publication in *Nature Communications*. It is important to recognize that ancillary ligand design in nickel-catalyzed cross-coupling chemistry is likely to play an important function in enabling desirable catalytic performance not only in terms of promoting elementary catalytic steps, but also as a means of favoring desired oxidation states of nickel, given the established viability of both Ni(0)/Ni(II) and Ni(I)/Ni(III) catalytic cycles⁶ and other single-electron transformations. In this vein, developing a repertoire of effective and structurally diverse ancillary ligands will contribute importantly to advancing nickel cross-coupling catalysis in a broad sense.”

With these design criteria in mind Professor Stradiotto and co-workers sought tunable *ortho*-phenylene bisphosphines featuring the 1,3,5,7-tetramethyl-2,4,8-trioxo-6-phosphaadamantane (CgP) group with an adjacent phosphorus donor fragment that could serve as a tuning element in catalyst design. “The study of CgPH dates back to the work of Epstein and Buckler in 1961,⁷ and in the intervening years the CgP group has been shown to be as sterically demanding as a P(*t*-Bu)₂ fragment, and as electron-poor as phosphites.⁸ Notably, the use of the CgP fragment in ancillary ligand design has received only scant attention in palladium cross-coupling chemistry, and had not been used in nickel cross-coupling prior to our report in *Nature Communications*,” said Professor Stradiotto. “After a brief ligand screen focusing on nickel-catalyzed ammonia monoarylation, Chris Lavoie in my group identified a ligand variant featuring CgP and P(*o*-tolyl)₂ donors (‘PAd-DalPhos’) as being particularly effective, and developed an air-stable nickel pre-catalyst (C1) featuring this ligand.”

Professor Stradiotto revealed that exploration of the reaction scope enabled by C1 involved a truly collaborative effort by several members of his group including undergraduates, graduate students, and a postdoc. “Chris Lavoie and Nick Rotta-Loria fleshed out the scope of ammonia monoarylation reactivity involving (hetero)aryl (pseudo)halides including reactions conducted using gaseous ammonia; Preston MacQueen expanded such reactivity to alkylamine and aniline derivatives; Ryan Sawatzky confirmed that such reactions can be carried out by use of ammonium salts under microwave

irradiation and at gram-scale; Andrey Borzenko established transformations involving (aza)indoles and carbazoles; and finally, Alicia Chisholm and Breanna Hargreaves conducted proof-of-principle experiments involving imidazolylsulfonates.” He continued: “The crystallographic work was carried out by Mike Ferguson and Bob McDonald – my long-time collaborators from the University of Alberta (Canada). Featured in our reaction scope are the first documented examples of room-temperature nickel-catalyzed cross-couplings involving primary alkylamines and ammonia, as well as the first examples of ammonia monoarylations employing (hetero)aryl mesylate electrophiles, for which no capable catalyst system is known. In fact, to the best of our knowledge the scope of reactivity demonstrated by C1, both in terms of the reaction conditions and the substrates employed, is unique among all previously reported catalyst systems for C(sp²)-N cross-coupling chemistry (i.e., copper, palladium, nickel or other). In response to the significant interest from both academic and industrial partners, we are in the process of commercializing both PAd-DalPhos and the derived pre-catalyst C1.”

According to Professor Stradiotto, notwithstanding the success of the PAd-DalPhos derived pre-catalyst C1 in challenging C(sp²)-N cross-coupling chemistry, our understanding of how this and related ancillary ligands give rise to desirable reactivity within C(sp²)-N cross-coupling chemistry is still rather poor. “Our presumption is that the mechanism of reactivity is analogous to Pd(0)/Pd(II) chemistry, but this remains to be confirmed,” said Professor Stradiotto, who concluded: “Our hope is that ongoing experimentation in my laboratory focused on further ancillary ligand design, mechanistic studies, computational analysis, and applications in alternative reaction settings, will provide important insights that will direct future development within the field of nickel-catalyzed cross-coupling.”

Dr. Louis-Charles Campeau (Merck, USA) – an expert in this field of research – commented: “As we grapple with the challenges of operating in a world with diminished natural resources, our focus has been on developing and using more sustainable methods for the manufacture of active pharmaceutical ingredients. The use of earth-abundant metals in catalysis is definitely an area of focus for us. The vast majority of ligand development over the last 25 years has focused on precious metals such as Pd, Ir, Ru and Rh. Fundamental research in new ligand scaffolds, such as this work, will be critical to the development of high-performing earth-abundant metal catalysts with low ligand loading, imperative for commercial relevance. The development of the air-stable pre-catalyst system is also a nice touch for practitioners as it simplifies reaction setup and enables catalyst formation. This is particularly important

early on when reactions are first discovered and developed using high-throughput experimentation in micro-arrays, where pre-catalysts are often used to get around catalyst activation issues.”

Mattias Forsberg

REFERENCES

- (1) M. Stradiotto, In *New Trends in Cross-Coupling: Theory and Application*; T. J. Colacot, Ed.; Royal Society of Chemistry: Cambridge, UK, **2014**, 228–253.
- (2) For an excellent webinar on this topic, see: <http://www.acs.org/content/acs/en/acs-webinars/technology-innovation/metal-catalysis.html>.
- (3) J. P. Wolfe, S. L. Buchwald *J. Am. Chem. Soc.* **1997**, *119*, 6054.
- (4) (a) A. Borzenko, N. L. Rotta-Loria, P. M. MacQueen, C. M. Lavoie, R. McDonald, M. Stradiotto *Angew. Chem. Int. Ed.* **2015**, *54*, 3773; (b) R. A. Green, J. F. Hartwig *Angew. Chem. Int. Ed.* **2015**, *54*, 3768.
- (5) V. V. Grushin, H. Alper *Chem. Rev.* **1994**, *94*, 1047.
- (6) J. Montgomery, In *Organometallics in Synthesis: Fourth Manual*; B. H. Lipshutz, Ed.; Wiley: Hoboken, NJ, USA, **2013**, 319–428.
- (7) M. Epstein, S. A. Buckler *J. Am. Chem. Soc.* **1961**, *83*, 3279.
- (8) P. G. Pringle, M. B. Smith, In *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*; P. C. J. Kamer, P. W. N. M. van Leeuwen, Eds.; John Wiley & Sons Ltd.: Chichester, UK, **2012**, 391–404.

About the authors



Prof. M. Stradiotto

Mark Stradiotto received his BSc (Hons.) in Applied Chemistry (1995) and PhD in Organometallic Chemistry (1999) from McMaster University (Canada). After conducting research as an NSERC Postdoctoral Fellow at the University of California at Berkeley (USA) with Professor T. Don Tilley (1999–2001), Mark moved to the Department of Chemistry at Dalhousie University (Canada) where he is now the Alexander McLeod Professor of Chemistry. Mark has been named a Thieme Chemistry Journals Awardee, and was awarded the Canadian Society for Chemistry Strem Chemicals Award for Pure or Applied Inorganic Chemistry. Current research efforts in the Stradiotto group are directed toward developing new classes of ancillary ligands for use with earth-abundant transition metals, with the goal of developing synthetically useful metal-catalyzed substrate transformations that can be employed by end-users in both academic and industrial settings.



Stradiotto Research Group (December 2015). From left to right: A. J. Chisholm, R. S. Sawatzky, C. M. Lavoie, C. Wiethan, C. M. Kelly, Dr. A. Borzenko, C. M. Maccaulay, N. L. Rotta-Loria, Dr. T. Ogawa, J. Clark, B. K. V. Hargreaves, P. M. MacQueen