

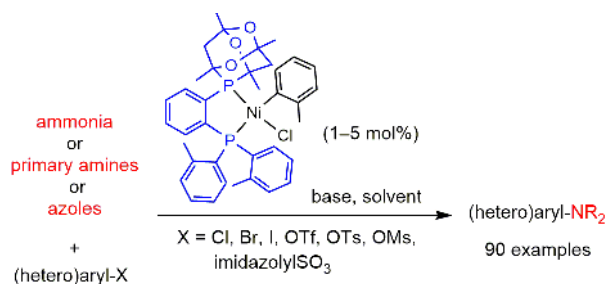
# Synform

People, Trends and Views in Chemical Synthesis

2016/08

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

Highlighted article by C. M. Lavoie, P. M. MacQueen, N. L. Rotta-Loria, R. S. Sawatzky, A. Borzenko, A. J. Chisholm, B. K. V. Hargreaves, R. McDonald, M. J. Ferguson, M. Stradiotto



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## Dear Readers,

I have not yet metabolized the Brexit vote and frankly I am still so bitterly disappointed that I decided to postpone any comment to a future editorial, when hopefully the consequences of Brexit will be clearer.

This August issue of SYNFORM opens with a Young Career Focus interview to Laurean Ilies, a European academic working in Japan, who shares his thoughts on organic chemistry and his research achievements and plans. The first literature coverage article is dedicated to a *PNAS* paper published by Kyoko Nozaki (Japan) who discovered a method for achieving a highly stereocontrolled catalytic all-*syn* polymerization of propylene to polypropylene-type structures. The second contribution covers a *Nat. Commun.* article published by Mark Stradiotto (Canada) describing the use of primary amines and ammonia – which has traditionally been a challenging substrate for arylations – for preparing heteroaryl amines, thanks to an efficient nickel-catalyzed process. Finally, the third article describes a new efficient stereocontrolled synthesis of  $\alpha$ -aryl- and  $\alpha$ -heteroaryl  $\alpha$ -amino ketones catalyzed by chiral N-heterocyclic carbenes, recently reported in *JACS* by Jian Wang (P. R. of China).

Enjoy your reading!



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If you have any questions or wish to send feedback, please write to Matteo Zanda at: [synform@outlook.com](mailto:synform@outlook.com)

## Young Career Focus: Professor Laurean Ilies (The University of Tokyo, Japan)

**Background and Purpose.** SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Laurean Ilies (The University of Tokyo, Japan).

### Biographical Sketch



Prof. L. Ilies

**Laurean Ilies** was born in the county of Transylvania, Romania, the land of mythical vampires, where he studied chemistry at Babes-Bolyai University for two years, before relocating to Japan in 1999 with a scholarship from the Japanese Government. After spending arguably the toughest year of his life learning the Japanese language, he was admitted to The University of Tokyo, where he graduated from the department of chemistry in 2004. He continued his graduate studies at the same university under the supervision of Professor Ei-ichi Nakamura. During this period, he worked on the development of new synthetic methods for  $\pi$ -conjugated molecules, such as a metalative cyclization reaction to create libraries of benzoheterole-containing conjugated molecules. He also investigated the properties of these compounds and designed new *p*-type and *n*-type organic semiconductors for OLEDs. This work earned him a Ph.D. in 2009, and several prizes such as the Incentive Award of the Graduate School of Science (awarded for the best thesis), and the Japanese Society for the Promotion of Science (JSPS) Fellowship. In 2006, he spent several months as a visiting researcher at the University of Chicago (USA), where he worked with Professor Rustem Ismagilov.

In 2009, he was appointed assistant professor at The University of Tokyo, where he continued his collaboration with Professor Ei-ichi Nakamura. His research interest shifted towards the development of sustainable catalysis using base metals such as iron, cobalt, manganese, etc., and with a focus on step-efficient reactions such as C–H activation, annulation, etc. This research earned him several prizes, among them the Banyu Chemist Award (2014), Thieme Chemistry Journals Award (2015), the Young Scientists' Prize from MEXT

(2015), and the Incentive Award in Synthetic Organic Chemistry (2015). In 2014, he was promoted to associate professor.

### INTERVIEW

**SYNFORM** *What is the focus of your current research activity?*

**Prof. L. Ilies** I am working on the creation of new catalysts based on base metals, especially iron, and their application to step-efficient reactions such as C–H functionalization, annulation, etc. I am also interested in the design and synthesis of conjugated molecules for materials science.

**SYNFORM** *When did you get interested in synthesis?*

**Prof. L. Ilies** My love for chemistry started from junior high school, and from that early time my image of chemistry was 'making stuff'. It helped that I was allowed to fool around in the school's lab and do simple experiments (and somehow I managed not to burn it down). During high school I became fascinated by alchemy, and those stories forged my passion for creating new molecules, and for finding new ways to make them.

**SYNFORM** *What do you think about the modern role and prospects of organic synthesis?*

**Prof. L. Ilies** The modern world is abundant in synthetic molecules, plastics, clothes, drugs, semiconductors, etc., and therefore, it is only natural that the role of organic synthesis will continue to grow. In my opinion, organic synthesis will (and should) aim towards efficiency (yield, selectivity, step-,

and atom-economy) and sustainability (green chemistry). Conjugated organic molecules will become more and more important for materials science, and organic synthesis will have to follow suit with the development of synthetic methods to construct complicated  $\pi$ -architectures.

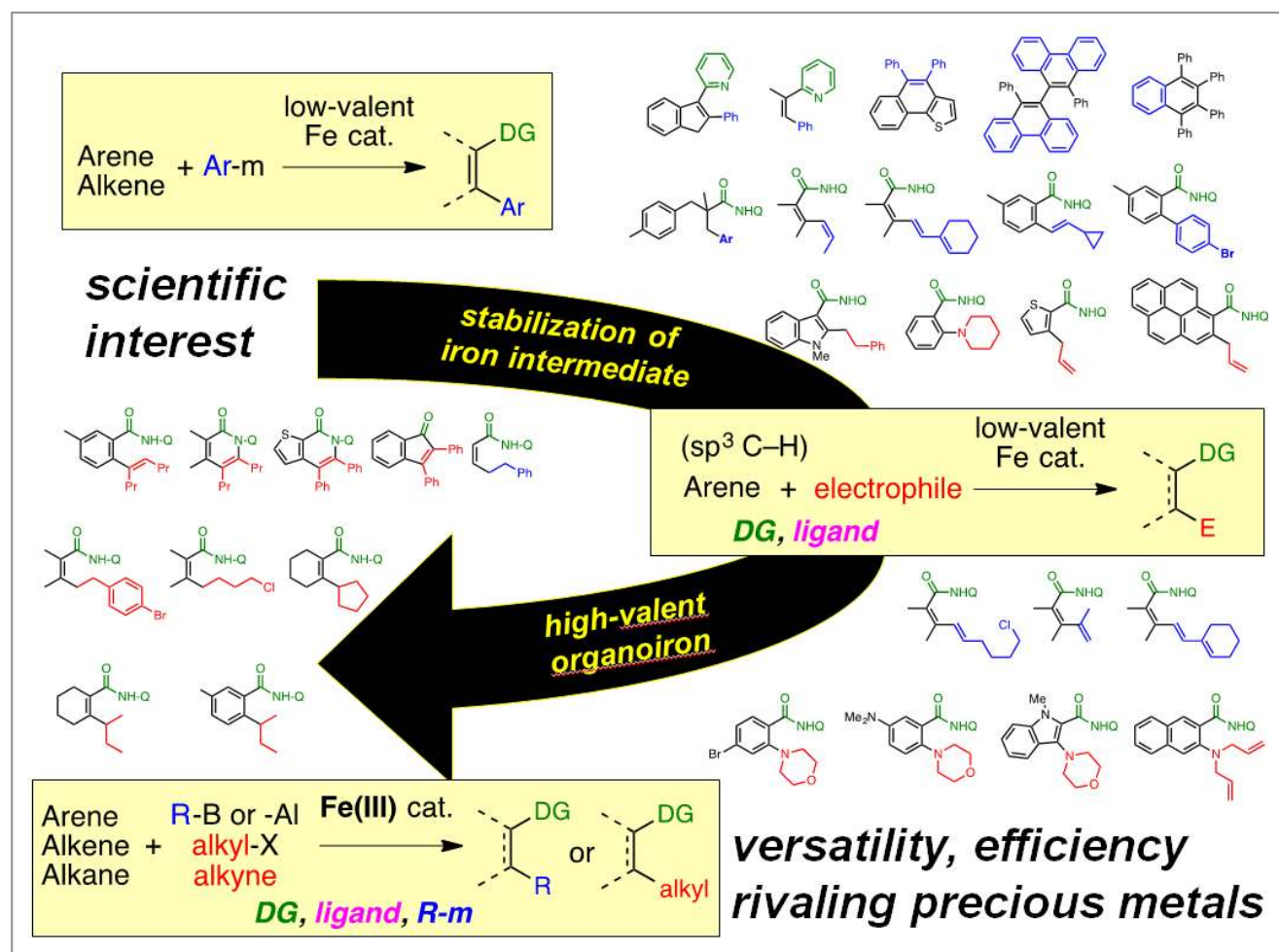
**SYNFORM** Your research group is active in the areas of novel synthetic methods and catalysis. Could you tell us more about your research and its aims?

**Prof. L. Ilies** A main motif of our research is the development of base metal catalysis. We have been particularly active in the area of iron catalysis, because this is the most abundant transition metal, and it is dirt-cheap and virtually non-toxic. We developed an efficient iron catalyst for directed C–H bond activation, but we also explored other reactions such as annulation to make phenanthrenes and naphthalenes, arylation of alkenes at the allylic C–H, and oxidative C–N bond formation.

We were also among the first to develop cobalt catalysis for C–H bond activation, in 2011.

**SYNFORM** What is your most important scientific achievement to date and why?

**Prof. L. Ilies** We struggled for a long time to develop an efficient and versatile iron catalyst for C–H activation. The problem was that we were using an organometallic reagent (zinc or magnesium) as a base, and this was reducing iron to unknown low-valent, highly reactive organoiron species (or a mixture thereof). After much frustration, we learned that a bidentate quinolylamide and a diphosphine ligand possessing a conjugated backbone can stabilize the organoiron species, and by using a milder organometallic reagent such as organoboron or aluminum, we could develop an efficient high-valent iron catalyst. This catalyst enabled a variety of C–H activation reactions such as the reaction of arene- or alkeneamides with vari-



ous organoboron or aluminum compounds with high catalyst turnover, and the reaction of various amides with electrophiles such as alkyl halides, alcohol derivatives, and alkynes.

Handwritten signature in orange ink that reads "Matthew Farnik".

# One-Step Catalytic Asymmetric Synthesis of All-*syn* Deoxypropionate Motif from Propylene: Total Synthesis of (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethyldecanoic Acid

PNAS 2016, 113, 2857–2861

Polypropylene-type structures – termed deoxypropionate motifs – are characterized by alternately methylated alkyl chains containing multiple stereogenic centers and are relatively common in natural products synthesized by bacteria, which assemble these molecules by using propionyl- or methylmalonyl-CoA as a C3 building block. In organic synthesis, however, the stereocontrolled synthesis of enantiomerically pure deoxypropionate-type molecules constitutes a challenging endeavor. Recently, the group of Professor Kyoko Nozaki at The University of Tokyo (Japan) reported a groundbreaking method for the efficient synthesis of the all-*syn* deoxypropionate motif.

Professor Nozaki explained that the work in this paper is the fruit of synergy between polymer chemistry and synthetic chemistry: “Being involved in research on homogeneous transition-metal catalysts for polymerization, we realized that polymerization is one of the most efficient C–C bond-forming reactions and conceived that a skeleton of natural products could be synthesized by oligomerization of olefins. Upon searching such a skeleton, we recognized that the deoxypropionate motif is a partial structure of polypropylene.”

Although great effort has been devoted to the development of highly isospecific propylene polymerization, propylene polymerization catalysts have rarely been utilized for organic synthesis. Professor Nozaki noted that a pioneering report by Kaminsky et al. identified the possible application of asymmetric oligomerization in the synthesis of pheromones.<sup>1</sup> However, those authors did not actually proceed to the syn-

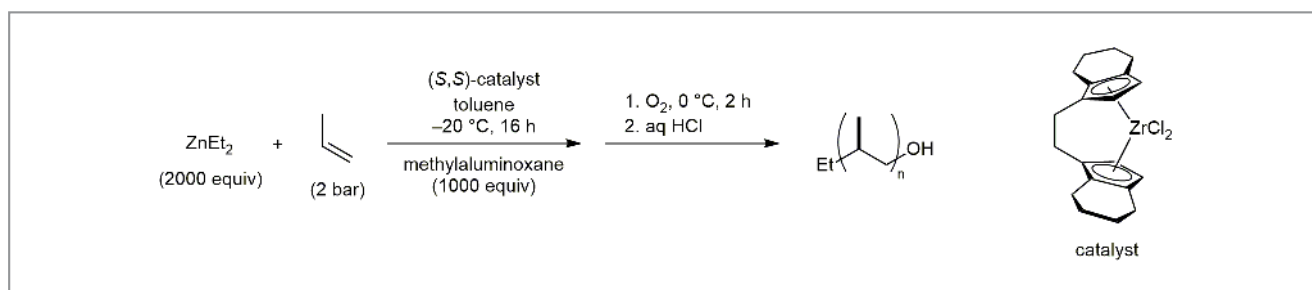
thesis of natural products due to moderate stereoselectivity featured by that process.

“We first tried the oligomerization in the presence of vinyl chloride, expecting fast  $\beta$ -chloride elimination to afford allyl-terminated oligomers as reported in the case of 10-undecen-1-ol.<sup>2</sup> However, this strategy did not work with propylene,” said Professor Nozaki.

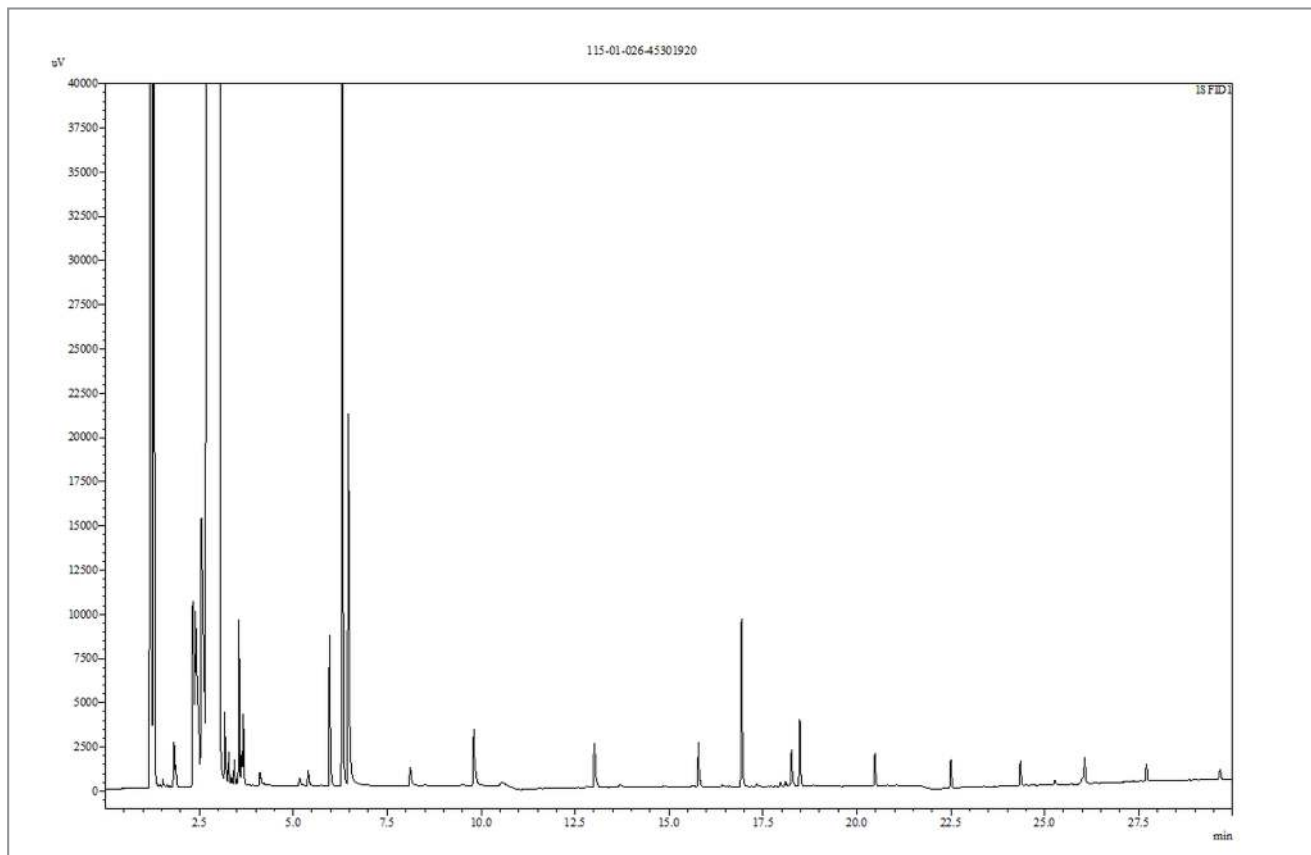
The group focused next on the coordinative chain-transfer polymerization (CCTP).<sup>3</sup> According to the literature of CCTP, trimethylaluminum or diethylzinc was added to the reaction mixture as the chain-transfer agent. When diethylzinc was added, a single peak was observed about once every three minutes in the GC trace; that is, diastereoselective oligomerization of propylene was proceeding (Figure 1)!

Another experimentally problematic part was the oligomer separation. Professor Nozaki remarked: “We assumed that each oligomer could be separated by fractional distillation; however, the amount of the oligomer was too small for fractional distillation.” She continued: “Although preparative gas chromatography was one way to achieve separation, the method is limited on small scale.” After thorough investigation, the group found that oligomers after oxidation were successfully separated by reversed-phase silica gel chromatography (Figure 2). “We were very excited when we saw a series of spots at even intervals in reversed-phase thin-layer chromatography!” said Professor Nozaki.

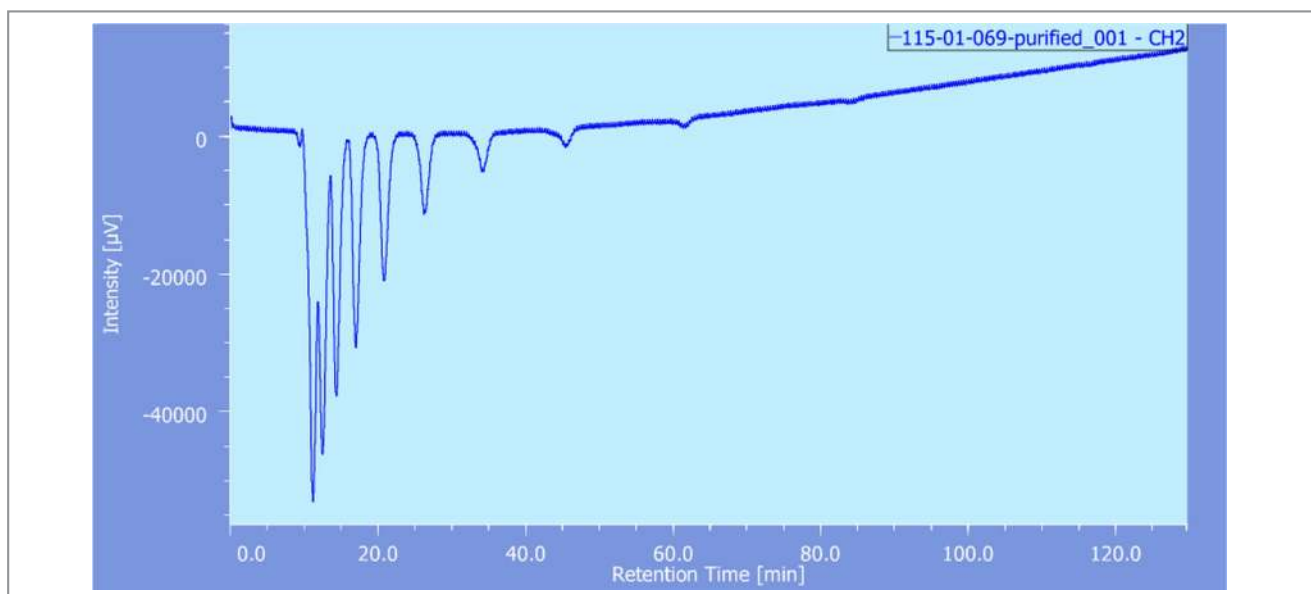
Professor Nozaki concluded: “We envision that our strategy will be extended to the synthesis of other natural products



**Scheme 1** An application of the methodology



**Figure 1** GC trace of a product mixture of the first successful oligomerization in the presence of diethylzinc



**Figure 2** RP-HPLC trace of a mixture of oligomers after oxidation to alcohols

containing the deoxypropionate motif; if the initiating group, an alkyl group bonded originally to the chain-transfer agent, and terminal functionalization can be varied, asymmetric oligomerization could be used for the synthesis of a larger family of natural products.”

*Mattias Farnik*

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## About the authors



From left: Dr. Y. Ota, Prof. K. Nozaki, T. Murayama

**Yusuke Ota** received his B.S. degree in 2011, M.S. degree in 2013 and Ph.D. in 2016 from The University of Tokyo (Japan) under the guidance of Professor Kyoko Nozaki. During that time he joined the group of Professor Bernhard Breit at the University of Freiburg (Germany) as a visiting student. He is now a postdoctoral researcher at The University of Tokyo.

**Toshiki Murayama** received his B.E. degree from The University of Tokyo (Japan) in 2015. He is currently a Ph.D. student under the guidance of Professor Kyoko Nozaki.

**Kyoko Nozaki** is a professor of chemistry and biotechnology at The University of Tokyo (Japan). Her research interest is focused on development of homogeneous catalysts for polymer synthesis and organic synthesis. She received her Ph.D. in 1991 (Professor Kiitiro Utimoto). In 1991, she started her research career as an instructor at Kyoto University (Japan), became an associate professor in 1999, and has occupied her current position since 2003. Her accomplishments include the Organometallic Chemistry directed towards Organic Synthesis (OMCOS) Prize (2003), the Japan IBM Science Award (2005), the Mukaiyama Award (2008), the Saruhashi Prize (2008), the Mitsui Chemicals Catalysis Science Award (2009), ACS 2012 Organometallic Lecturer (2012), and The Award of the Society of Polymer Science, Japan (2013).

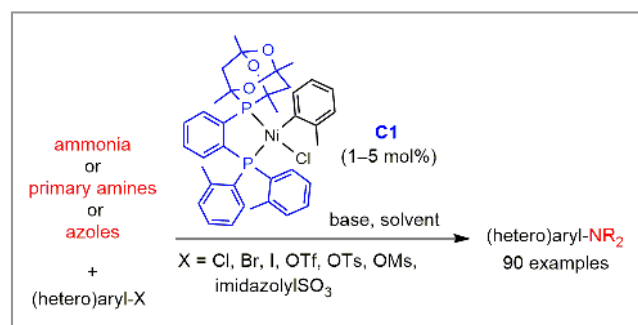
## Challenging Nickel-Catalyzed Amine Arylations Enabled by Tailored Ancillary Ligand Design

*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.<sup>1</sup> 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."<sup>2</sup> 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 Buchwald<sup>3</sup> 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)."<sup>4</sup> 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(sp<sup>2</sup>)–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(sp<sup>2</sup>)–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(sp<sup>2</sup>)-Cl],” said Professor Stradiotto. “However, given the greater propensity for C(sp<sup>2</sup>)-Cl oxidative additions to L<sub>2</sub>Ni(0) relative to L<sub>2</sub>Pd(0),<sup>5</sup> and the potential for rate-limiting C(sp<sup>2</sup>)-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(sp<sup>2</sup>)-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 cycles<sup>6</sup> 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,<sup>7</sup> and in the intervening years the CgP group has been shown to be as sterically demanding as a P(*t*-Bu)<sub>2</sub> fragment, and as electron-poor as phosphites.<sup>8</sup> 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)<sub>2</sub> 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(sp<sup>2</sup>)-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(sp<sup>2</sup>)-N cross-coupling chemistry, our understanding of how this and related ancillary ligands give rise to desirable reactivity within C(sp<sup>2</sup>)-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*

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## 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

# Enantioselective Intermolecular Enamide–Aldehyde Cross-Coupling Catalyzed by Chiral N-Heterocyclic Carbenes

*J. Am. Chem. Soc.* **2016**, *138*, 4706–4709

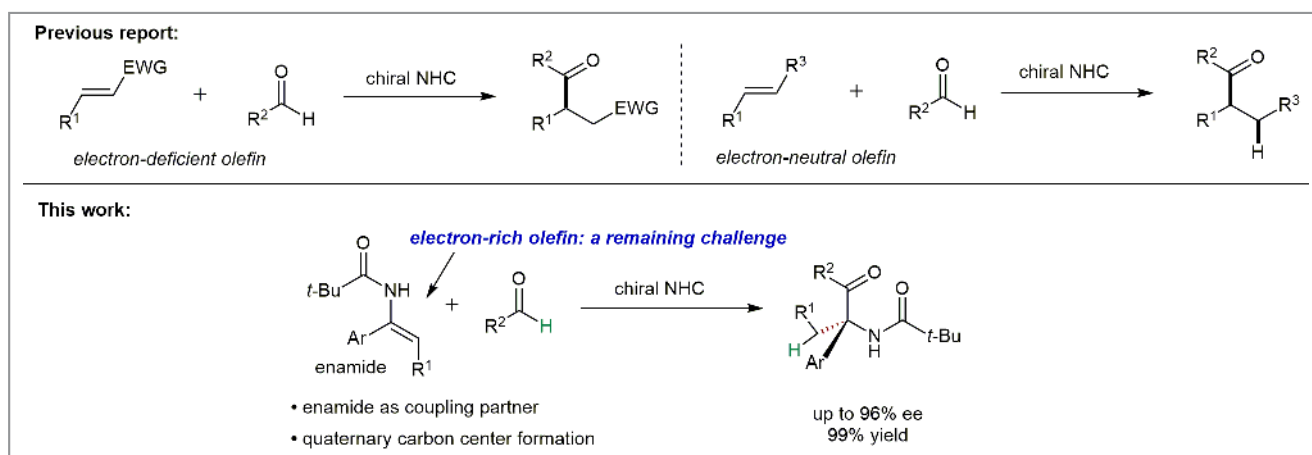
Chiral amines, amino alcohols, amino acids and their derivatives are very important classes of compounds in nature and in biomolecular research. Furthermore, they are very common and important versatile chiral building blocks for the synthesis of chiral ligands, materials, biologically active compounds and drugs. However, the synthesis of these compounds – especially in stereochemically pure form – can still represent a challenging endeavor.

Recently, the group of Professor Jian Wang at the University of Tsinghua (P. R. of China)<sup>1</sup> has reported an efficient method for accessing valuable *N*-acyl-protected amine derivatives in good yields and with high stereochemical purities through an enantioselective intermolecular enamide–aldehyde cross-coupling catalyzed by chiral N-heterocyclic carbenes.

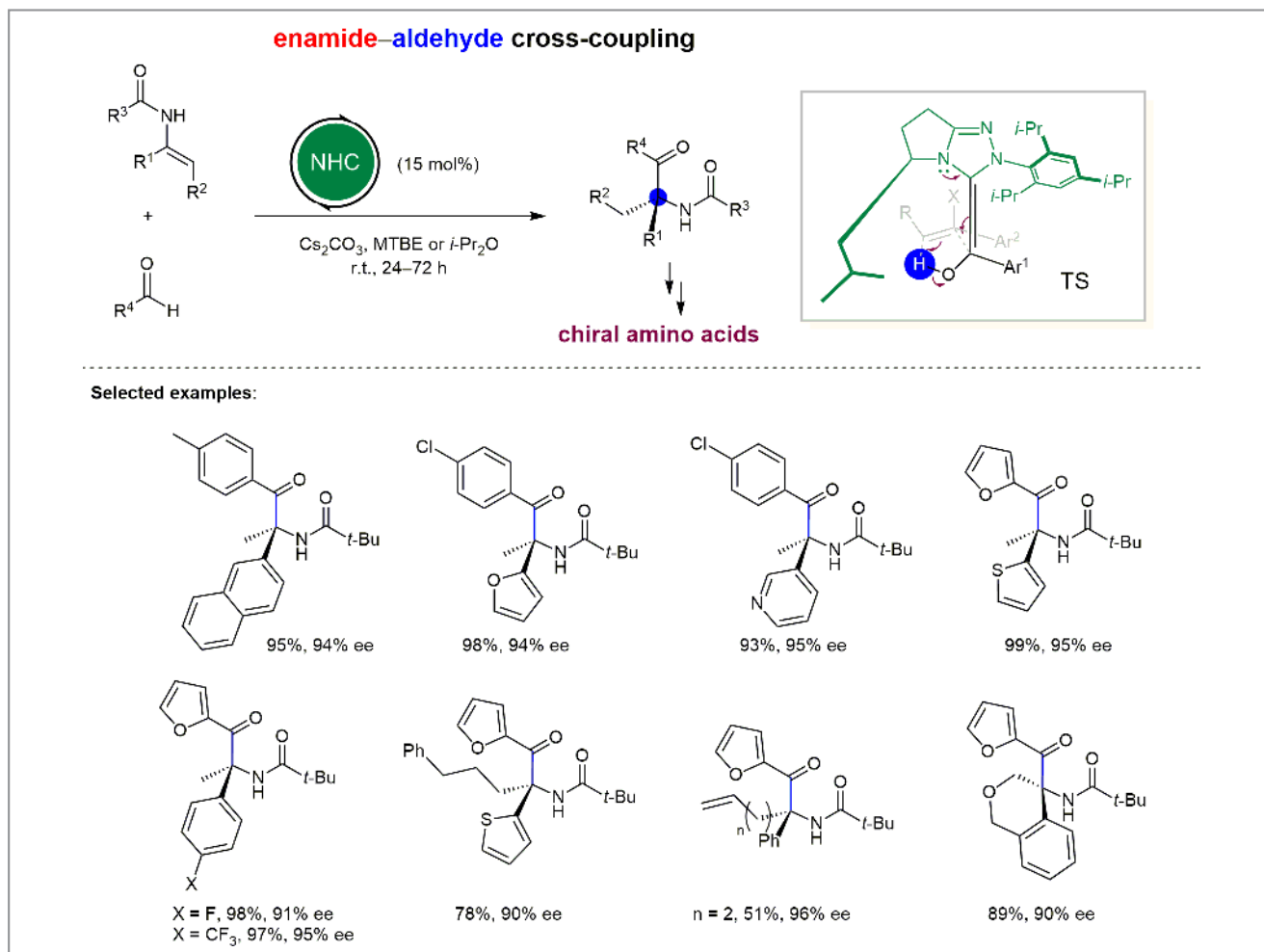
“Our research in NHC-catalyzed intermolecular enamide–aldehyde cross-coupling reactions is focused on the development of efficient and useful methods for C–C bond formation in synthetic chemistry,” said Professor Wang. He continued: “In the past few years, the use of NHC-catalytic strategies to prepare chiral molecules has shown general utility for a number of synthetic transformations. Among them, intermolecular addition reactions have received much attention. Numerous examples of intermolecular asymmetric addition reactions of aldehydes to various olefins have been reported, but generally focused on electron-deficient<sup>2,3</sup> and electron-neutral olefins,<sup>4</sup>

whereas the properties of electron-rich olefins have rarely been exploited in enantioselective NHC-catalyzed cross-coupling reactions. Therefore, we thought it would be welcome to design and develop new strategies involving the use of electron-rich olefins for promoting cross-coupling reactions.” Recently, Professor Wang and coworkers have focused on the development of novel NHC-catalytic methods for enantioselective C–X bond formation. Professor Wang’s group disclosed a novel finding in agreement with their hypothesis: a unique enantioselective cross-coupling was developed to generate *N*-acyl amines under mild conditions, in which electron-rich enamides were utilized as the electrophilic cross-coupling reagents to react with various aldehydes in the presence of NHC catalyst and Cs<sub>2</sub>CO<sub>3</sub> as base (Scheme 1).

At the beginning of this program, a set of experiments evaluating the catalytic system were performed and the reaction was found to occur in the presence of the NHC catalyst. “Pleasingly, we found that the results were excellent, and meticulous optimization of the reaction conditions culminated in good yields and high enantioselectivities,” said Professor Wang. He continued: “To achieve a detailed understanding of the reaction mechanism, a plausible transition state was proposed. The push–pull nature of the Breslow intermediate may promote the formation of this reverse-Cope elimination-like transition state. Several additional experiments revealed that



**Scheme 1** NHC-Catalyzed cross-couplings of aldehydes and olefins



**Scheme 2** Enantioselective intermolecular enamide–aldehyde cross-coupling catalyzed by chiral NHCs

a reverse-Cope elimination-like transition state is possible. Nevertheless, the alternative tautomerization–aza-benzoin mechanism still cannot be completely ruled out.”

From an outlook of the state-of-the-art in organic chemistry, the NHC-catalyzed intermolecular enamide–aldehyde cross-coupling reaction also represents a new protocol for preparing many useful fine chemicals. “The reaction products can be applied to efficiently construct chiral amino alcohols, amino acids, and natural products (Scheme 2),” said Professor Wang.

According to Professor Wang, there are four important features worthy of note in this method: (1) environmental friendliness, as the reaction does not require toxic heavy metals as catalysts; (2) atom economy, as the reaction takes place without loss of atoms in the cross-coupling process; (3) generality, as the broad substrate scope results in the assembly of

valuable and diversified N-protected amines; and (4) quaternary carbon center formation, as the exposure of enamides to aldehydes in the presence of NHC catalyst can produce amines incorporating a quaternary carbon center with high enantioselectivity and in good yields.

Professor Wang and his coworkers concluded: “In this report, the development of a new synthetic solution has enabled us to rapidly construct a diverse set of chiral amines, bearing a quaternary carbon center with high efficiency and good enantioselectivity. Inspired by these new findings, we believe that extending this NHC-catalytic model further towards other cross-coupling reactions could be a long-standing goal for chemists in the future.”

*Matthew Farrel*

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theses, NHC-catalyzed cross-coupling reactions and photocatalysis.

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