

## Nickel-Catalyzed Mono-Selective $\alpha$ -Arylation of Acetone with Aryl Chlorides and Phenol Derivatives

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The development of straightforward methods for preparing  $\alpha$ -arylated ketones directly from acetone is of great interest from both economic and synthetic points of view. While the arylation of carbonyl compounds with transition metal catalysts, via the formation of enolate intermediates, represents a powerful and relatively well-established class of carbon–carbon bond-forming reactions,<sup>1</sup> the transposition of this technology to simple acetone has remained – in comparison – rather elusive.<sup>2</sup> For example, this challenging transformation has rarely been achieved using palladium catalysis with aryl halide electrophiles. “From an economic viewpoint, the development of this methodology with more sustainable and cost-effective nickel catalysts appeared as a very valuable alternative, but the transposition to nickel has proven highly challenging,” remarked Professor Abderrahmane Amgoune, from CNRS & Université Lyon 1 (Villeurbanne, France). He continued: “Only a few examples of nickel-catalyzed arylations of substituted ketones were reported and the arylation of acetone had not been documented with nickel catalysts thus far.”

This project emerged from collaborative work between the group of Professor Amgoune, colleagues Dr. Nuno Monteiro and Dr. Anis Tlili (all from Université de Lyon), and Dr. Johannes Schranck from Solvias AG (Switzerland). The story started with a discussion between Professor Amgoune, Dr. Tlili and Dr. Schranck on the potential of Josiphos-type ligands in nickel catalysis, especially for the functionalization of small molecules.<sup>3</sup> “We decided to combine my expertise in synthetic organometallic chemistry and mechanistic studies,<sup>4</sup> with the experience of Dr. Tlili and Dr. Schranck in transition-metal-catalyzed functionalization of small building-block molecules<sup>5</sup> to develop and understand the nickel-catalyzed monoarylation of acetone,” said Professor Amgoune.

Dr. Tlili approached Professor Amgoune and Dr. Monteiro with a preliminary result showing that the combination of Josiphos ligand (see scheme for structure) with Ni(COD)<sub>2</sub> could promote the monoarylation of acetone, albeit in low yield. Professor Amgoune explained: “The collaboration started at that point, and beyond the synthetic interest of this transformation we were also eager to carry out detailed mechanistic studies to unravel the key role of the ligand.”

“We started our investigations with intensive optimization studies that were carried out by graduate student Sary Abou

Derhamine,” explained Professor Amgoune, who continued: “He investigated a large set of reaction conditions and ligands and identified a very practical catalytic system that demonstrated a high compatibility with several functional groups and enabled the formation of complex substrate structures with good to excellent yields (Scheme 1).”

Even more important than its economic interest, nickel catalysts display reactivities that are complementary to those of palladium. In particular, the group took advantage of the ability of nickel to activate C–O bonds to extend the methodology to the unprecedented coupling of acetone with phenol derivatives.

While these optimization studies revealed that the association of Josiphos ligand (SL-J004) and Ni(COD)<sub>2</sub> was a very efficient catalytic system, they also raised several mechanistic questions about the key influence of the ancillary ligand. Strikingly, the researchers discovered that only Josiphos-type ligands were effective under these reaction conditions, moreover they also observed that a second equivalent of ligand was beneficial to the catalytic performance.

“We decided to carry out detailed mechanistic investigations to address these questions,” said Professor Amgoune. He continued: “The mechanistic work – which combined NMR monitoring, isolation and characterization of key catalytic intermediates – was carried out principally by postdoctoral associate Dr. Tetiana Krachko, who succeeded in showing the feasibility of all mechanistic steps of the envisioned catalytic cycle.” Professor Amgoune then went on to credit Dr. Guillaume Pilet with carrying out the X-ray diffraction analysis of isolated Ni(0) and Ni(II) intermediates. He remarked: “These important mechanistic studies revealed that the specific reactivity of (Josiphos)Ni catalyst likely results from an enhanced stabilization of the catalyst resting state Ni(II)-aryl species towards decomposition to unreactive Ni(I) species. We were also surprised to find that the use of an excess of Josiphos ligand was not deleterious for the catalytic reactivity. Indeed, under these conditions we could form a saturated 4-coordinate Ni(bis-phosphine)<sub>2</sub> species that was anticipated to be unreactive, based on previous reports. However, we have shown that the extra ligand may indeed coordinate to Ni(0) at high temperature to give a Ni(Josiphos)<sub>2</sub> species, which was characterized. We think that the steric

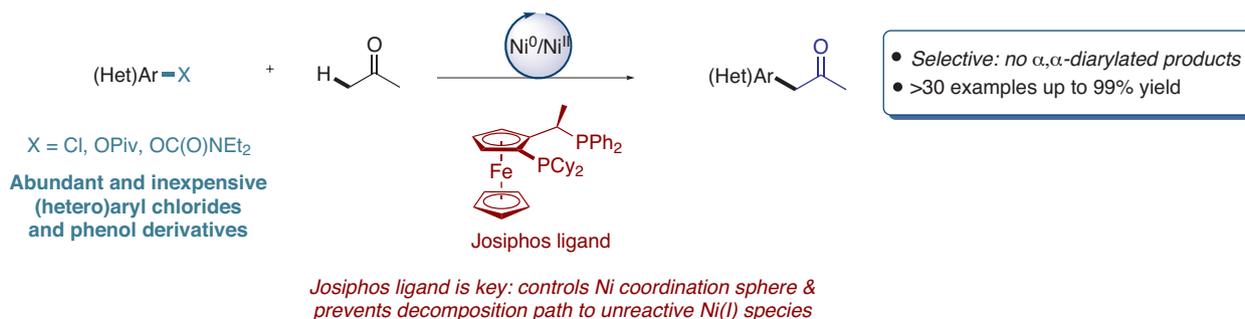
bulk of the Josiphos-type ligand, combined with the specific stereoelectronic properties imparted by the ferrocene backbone, renders the  $\text{Ni}(\text{Josiphos})_2$  very susceptible to ligand exchange with the aryl halide substrate.”

Overall, important fundamental information on the unique behavior of Josiphos-type ligands with nickel emerged from this study. Professor Amgoune concluded: “We are cur-

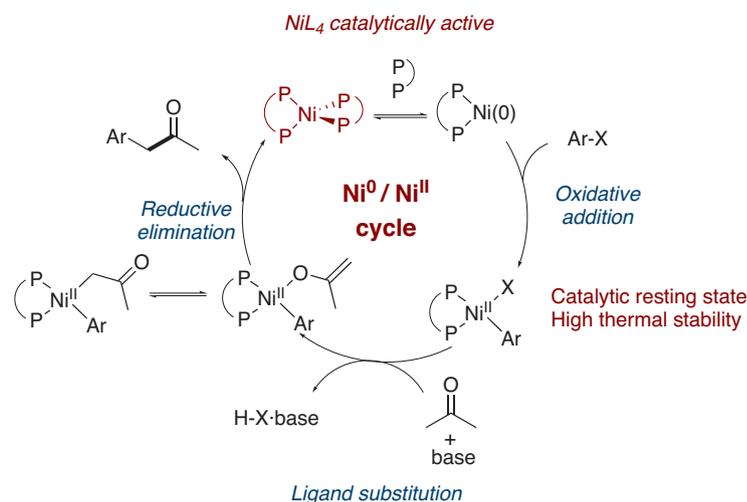
rently seeking to further understand and harness the specific coordination properties of Josiphos-type ligands for the development of new nickel-catalyzed transformations.”

*Mattes Fank*

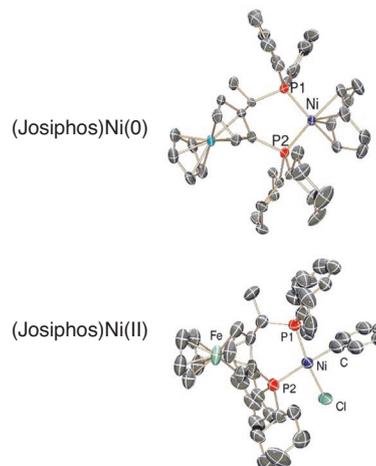
### Synthetic development



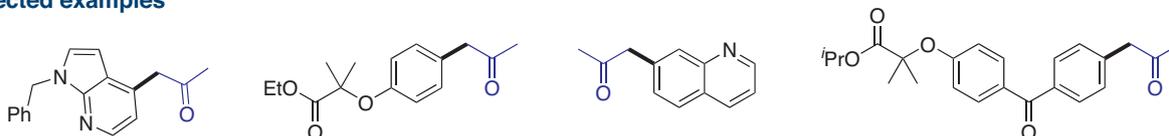
### Key mechanistic insights



### Isolation of catalytic intermediates



### Selected examples



**Scheme 1** Nickel-catalyzed mono-arylation of acetone: synthetic development and mechanistic studies

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## About the authors



Dr. S. Abou Derhamine

**Sary Abou Derhamine** was born in Kfarkouk (Lebanon) and graduated with distinction from the Lebanese University of Beirut (Hadath) with an M.Sc. degree in physical chemistry. Then he was awarded a scholarship for excellence in science from the French government to pursue a Master's degree in molecular chemistry and catalysis at the University of Lyon (France). After that, he carried out a multidisciplinary internship where he worked with physicists, chemists and engineers under the supervision of Prof. B. Masenelli, Dr. A. Quadrelli and Dr. J. Canivet. Subsequently, he completed his Ph.D. in 2020 working in the development of nickel-catalyzed cross-coupling reactions under the guidance of Prof. A. Amgoune and Dr. N. Monteiro at the University of Lyon. In November 2020, he started a postdoctoral position at Total Research & Technology Feluy (Belgium) in collaboration with Prof. Jean-Francois Carpentier (Rennes, France).



Dr. T. Krachko

**Tetiana Krachko** received her Ph.D. (2018) in organophosphorus chemistry from the University of Amsterdam (The Netherlands) under the supervision of Assoc. Prof. J. C. Slootweg. Subsequently, she conducted her postdoctoral research at the same university with Prof. J. N. H. Reek, working on the development of new self-assembled ligands for hydroformylation. Afterwards, she pursued her postdoctoral fellowship at the University of Lyon (France) with Prof. A. Amgoune, performing the synthesis of organometallic complexes and studying their

reactivity for the activation and functionalization of inert bonds. She has been working as a research engineer at the chemical startup Fairbrics (France) since August 2020, focusing on the production of synthetic fibers from carbon dioxide.



Dr. N. Monteiro

**Nuno Monteiro** studied chemistry at the University of Lyon (France) and completed his Ph.D. there in 1992, working on the development of Pd-catalyzed Conia-ene-type cyclizations under the guidance of Jacques Goré and Geneviève Balme. Following a one-year period as a contractual lecturer, he joined the group of Varinder K. Aggarwal (University of Sheffield, UK) as a Marie Curie postdoctoral fellow to work on the synthesis of polyoxin analogues. In 1996 he returned to Lyon where he was appointed as a CNRS researcher. His main research interests have concerned the development of transition-metal-catalyzed methods toward the construction and functionalization of heterocycles, with a recent focus on organofluorine chemistry.



Dr. J. Schranck

**Johannes Schranck** obtained an M.Sc. in chemistry at the University of Rostock in northern Germany. He conducted his Ph.D. studies in the group of Prof. Matthias Beller at the Leibniz-Institute for Catalysis (Germany) as well as with Prof. Mark Stradiotto at Dalhousie University (Canada). In 2014, he joined the catalysis group of Solvias in Basel (Switzerland) to work on the development of industrial asymmetric hydrogenations and

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cross-coupling reactions. Since 2019, Johannes has been leading Johnson Matthey's homogeneous catalysis team as R&D Manager in West Deptford, NJ (USA). In this role he is focused on the development and commercialization of homogeneous catalysis solutions for the global pharmaceutical and fine chemical industry.



*Dr. A. Tlili*

**Anis Tlili** is CNRS Research Fellow. After gaining a Master's degree with Prof. S. Jugé (Dijon, France), he completed his Ph.D. in the group of Dr. M. Taillefer (Montpellier, France) in late 2011. Subsequently, he joined the group of Prof. M. Beller (LIKAT, Rostock Germany) for a postdoctoral stay before taking up a second collaborative postdoctoral position (CEA/ICSN, Paris). In 2014 he was appointed a CNRS research fellow in Lyon. His current

research interests lie in the area of homogeneous catalysis/photoredox catalysis, with particular focus on fluorine chemistry. Anis was recently awarded a JSP Fellowship for the 53<sup>rd</sup> Bürgenstock Conference (2018) and was selected to participate to EuCheMS Young Investigators Workshop in Oxford in 2018.



*Prof. A. Amgoune*

**Abderrahmane Amgoune** received his PhD in 2006 at the University of Rennes (France) under the supervision of Profs. J.-F. Carpentier and C. Thomas. He then moved to the University of Konstanz (Germany) as an Alexander-von-Humboldt postdoctoral research associate with Prof. S. Mecking. In 2008, he was appointed a CNRS research position at the University of Toulouse (France). In 2017, he was promoted to full professor at

the University of Lyon (France). His research interests range from fundamental organometallic chemistry to the development of dual catalytic strategies with transition metals for the functionalization of inert bonds. His work has received several awards, including most recently a nomination as junior member at the Institut Universitaire de France (2019), the Thieme Chemistry Journals Award (2020) and the Young Investigator Award from the French Chemical Society, Organic Chemistry Division (2016).