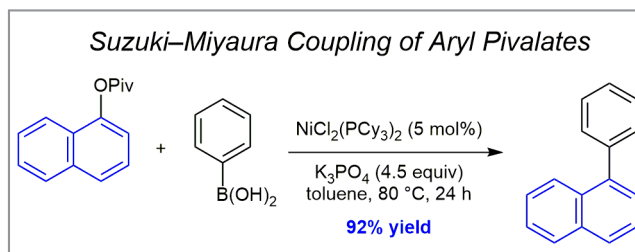


Conversion of Amides into Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds

Nature **2015**, 524, 79–83

The amide function is ubiquitous in natural compounds as well as in man-made molecules and materials. It is generally very stable and poorly reactive owing to its resonance-stabilized C–N group that imparts a planar geometry to amides. In contrast, carboxylic esters are generally reactive under a variety of mild conditions; therefore, it is not surprising that a number of direct methods are available to the chemist for converting esters into amides (amino-de-alkoxylation reaction) but very few for achieving the opposite transformation. Recently, Professors Neil Garg and Ken Houk from the University of California, Los Angeles (UCLA, USA) reported in *Nature* a groundbreaking method for converting amides into esters with a high degree of efficiency.

Professor Garg's group has been interested in transition-metal-catalyzed cross-couplings for some time. Professor Garg said: "Seven years ago, we reported cross-couplings of pivalate esters that were mediated by nickel catalysis (*J. Am. Chem. Soc.* **2008**, 130, 14422). From these efforts and related efforts by other labs, such as Shi's (*J. Am. Chem. Soc.* **2008**, 130, 14468)



Scheme 1

and Chatani's (*Angew. Chem. Int. Ed.* **2008**, 47, 4866), we became intrigued by the idea of using non-precious metal catalysis to activate bonds that were classically considered inert." Professor Garg explained that although nickel is less commonly used compared to palladium, nickel catalysis has been used for decades in DuPont's synthesis of adiponitrile, a precursor to Nylon-6,6, and has recently seen growing use in both academic and pharmaceutical contexts.

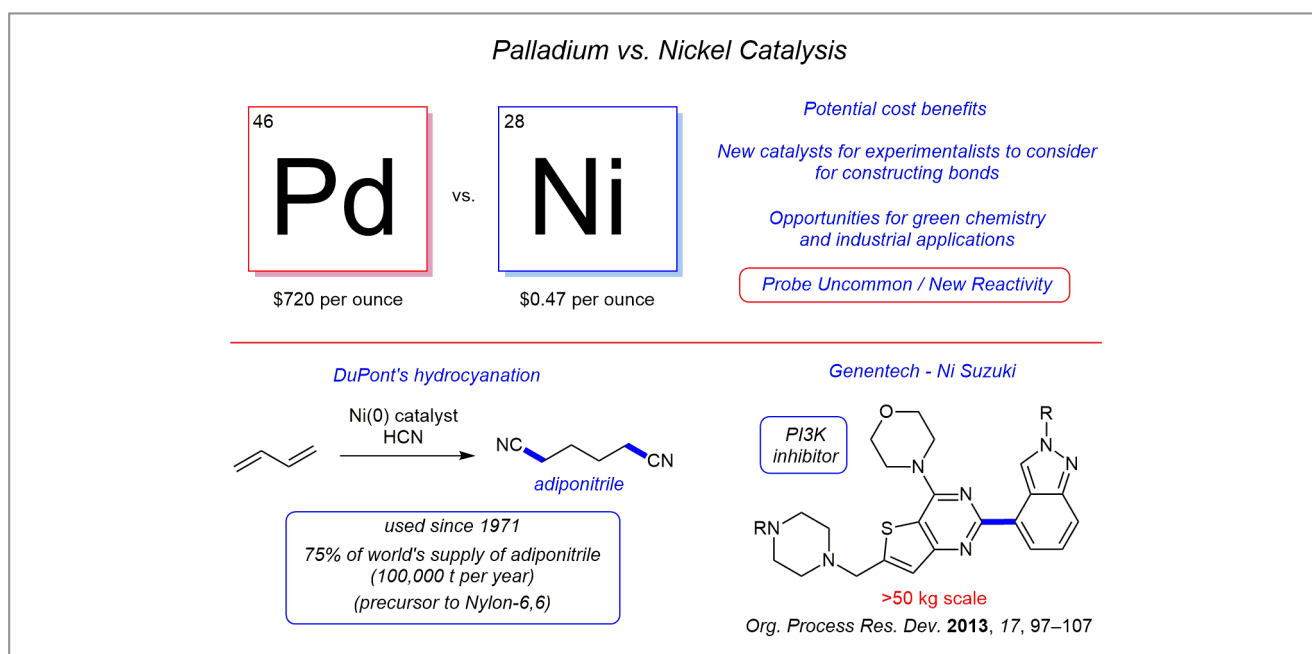
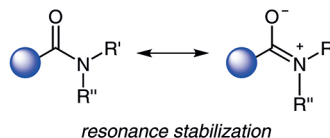


Figure 1

Harnessing Amides as Synthetic Building Blocks

Amides

widely studied for decades
amide stability is well understood



Linus Pauling (1901–1994)

amide planarity
protein structure, α -helix
1954 Nobel Prize in Chemistry

L. Pauling, R. B. Corey *PNAS* 1951, 37, 729–740



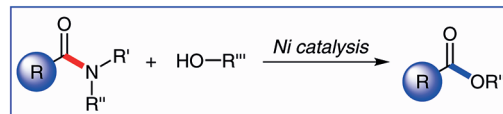
Figure 2

Professor Garg continued: “Bearing this in mind, our laboratory has been collaborating with Ken Houk’s group on using nickel catalysis to break acyl C–heteroatom bonds. In our most recent study, we reported the activation of amide C–N bonds. The work was done by a tremendous team of experimentalists, Liana Hie, Noah Fine Nathel, Tejas Shah, and Emma Baker (Garg lab), and computational chemists Xin Hong, Yun-Fang Yang, and Peng Liu (Houk lab). Amide activation was an exciting area to explore, since amide C–N bonds are often considered as being ‘inert’ due to resonance stabilization, as taught to us by Nobel Laureate Linus Pauling in the 1950s.”

Working closely with Houk’s team, Professor Garg and his co-workers found that *N*-alkyl anilides can be converted into esters using nickel catalysis. Professor Garg remarked: “The choice of *N*-substituent is important in ensuring that the overall reaction is thermodynamically feasible and that C–N bond cleavage can occur with an appropriate Ni/ligand combination. The reaction is thought to proceed by Ni/NHC-mediated oxidative addition, ligand exchange, and reductive elimination.”

Nickel-Catalyzed Conversion of Amides to Esters

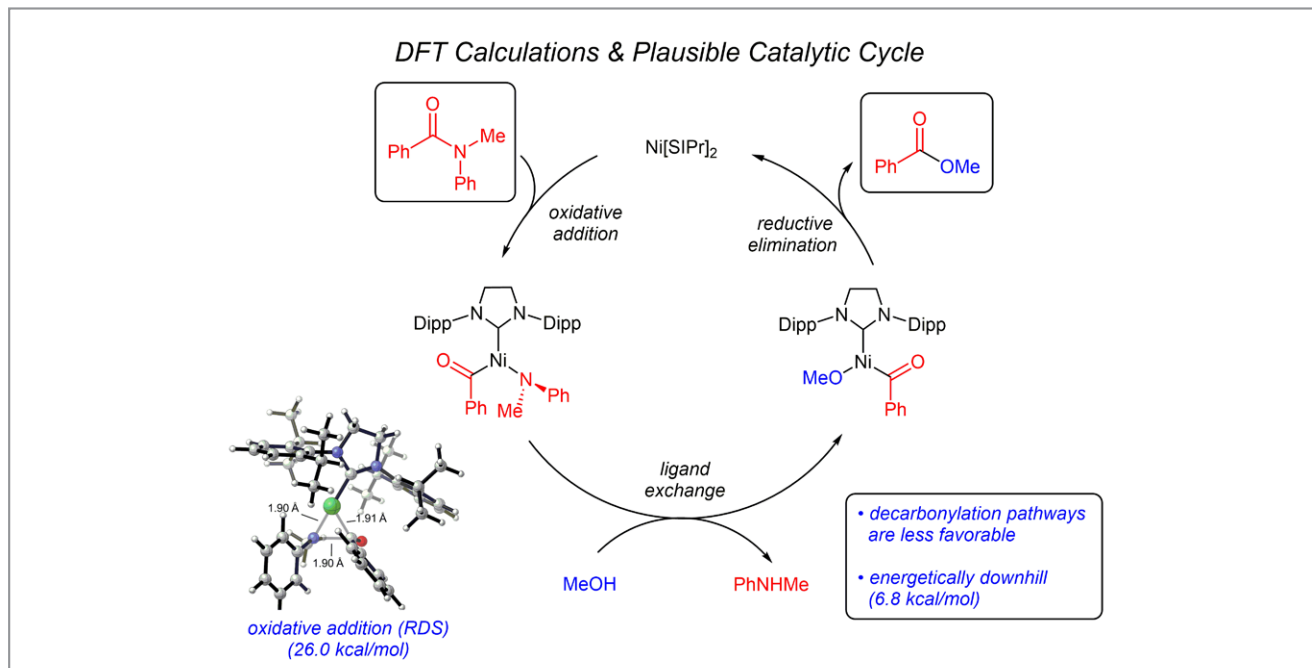
$R =$
aryl or
hetaryl



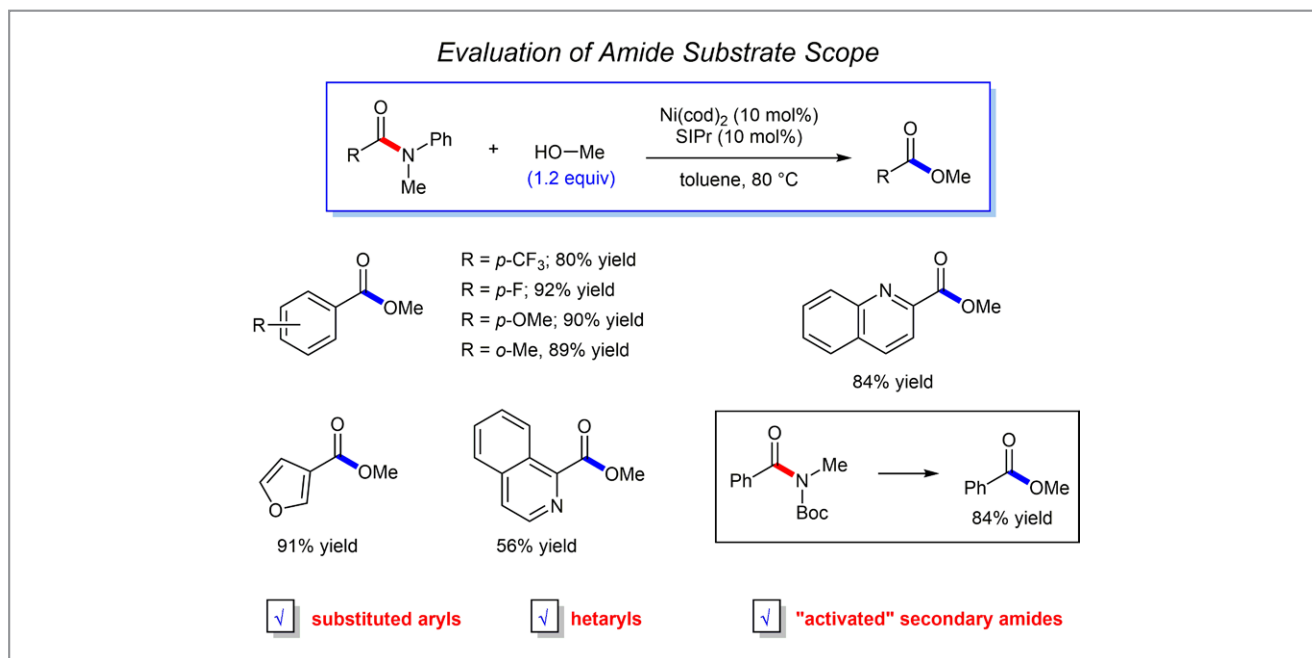
underdeveloped and challenging synthetic transformation

Scheme 2

The methodology tolerates heterocycles, such as quinolines, isoquinolines, indoles, and furans. Moreover, even hindered alcohols can be used (with only 1.2 equiv being necessary).

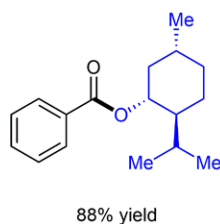
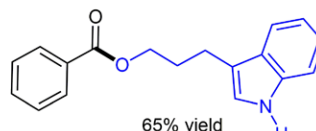
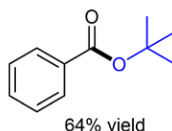
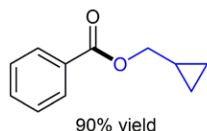
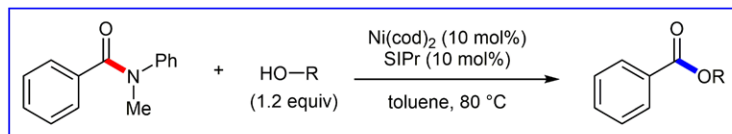


Scheme 3



Scheme 4

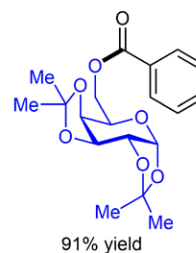
Evaluation of the Alcohol Coupling Partner



simple and sterically hindered alcohols



alcohols containing heterocycles and multiple heteroatoms



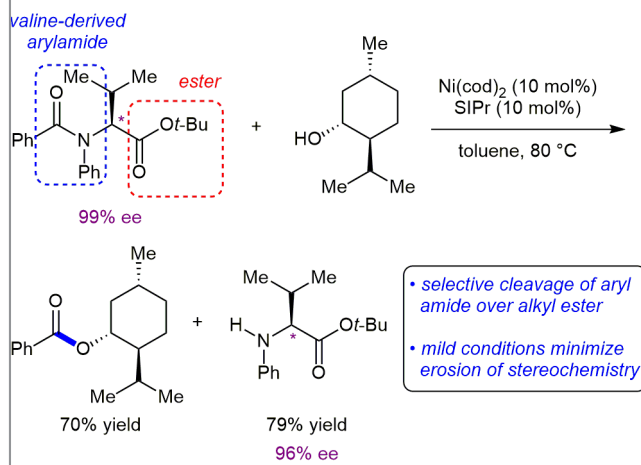
Scheme 5

One of the most exciting features of this methodology, said Professor Garg, is that the reaction conditions are exceptionally mild. "As such, the conversion of amide into ester can be performed in the presence of epimerizable stereocenters or ester functional groups."

When it comes to using amides in C–N bond cleavage processes, perhaps the most commonly used methodologies are the displacement of Weinreb amides or reduction using the Schwartz reagent. Professor Garg concluded: "We expect that our study will provide a new entryway into harnessing amides as synthons to construct C–heteroatom or C–C bonds. As most chemists may not traditionally consider amides as their go-to synthetic building blocks, we hope that overcoming this thinking will lead to new and unique transformations that exploit amide C–N bond cleavage using non-precious metal catalysis."

Matthew Farnish

Cleavage of Valine-Derived Amide



Scheme 6

About the authors



Prof. N. Garg

Neil Garg received a B.S. in chemistry from New York University (USA) where he did undergraduate research with Professor Marc Walters. During his undergraduate years, he spent several months in Strasbourg (France) while conducting research with Professor Mir Wais Hosseini at the Université Louis Pasteur as an NSF REU Fellow. Neil obtained his Ph.D. in 2005 from Caltech (USA) studying under the direction of Professor Brian Stoltz.

He then joined Professor Larry Overman's laboratory at the University of California, Irvine (USA) as an NIH postdoctoral scholar. Neil joined the faculty at UCLA (USA) in 2007 and rose to the rank of Full Professor in 2013. His laboratory develops synthetic strategies and methodologies, such as transformations mediated by non-precious metal catalysis.



Prof. K. N. Houk

Kendall N. Houk was born in Nashville, Tennessee (USA), on February 27, 1943. He received his A.B. (1964), M.S. (1966), and Ph.D. (1968) degrees at Harvard University (USA), working with R. A. Olofson as an undergraduate and R. B. Woodward as a graduate student in the area of experimental tests of orbital symmetry selection rules. In 1968, he joined the faculty at Louisiana State University (USA), becoming Professor in 1976. In 1980,

he moved to the University of Pittsburgh (USA), and in 1986, he moved to UCLA (USA), becoming a Distinguished Professor in 1987. From 1988–1990, he was Director of the Chemistry Division of the National Science Foundation. He was Chairman of the UCLA Department of Chemistry and Biochemistry from 1991–1994. He currently holds the Saul Winstein Chair at UCLA and his group specializes in computational organic chemistry.



E. L. Baker

Emma L. Baker was raised in the small town of Cresco, Iowa (USA). She received her B.A. degree in chemistry from Grinnell College, Iowa (USA) in 2013. She is currently a Ph.D. student at the UCLA (USA) studying under the mentorship of Professor Neil K. Garg. Her research focuses on the activation of amide C–N bonds using nickel catalysis.



Dr. N. F. Fine Nathel

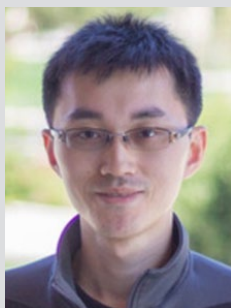
Noah F. Fine Nathel was born and raised in Berkeley, CA (USA). He received a B.A. in chemistry from Cornell University in Ithaca, NY (USA), where he worked in the research group of Professor Geoffrey W. Coates. He obtained his Ph.D. from the UCLA (USA), working under the direction of Professor Neil K. Garg. His research in the Garg group focused on reaction discovery using nickel catalysis, the total syntheses of indolactam alkaloids, and studying mechanistic aspects of aryne intermediates. Noah is currently a postdoctoral scholar at the California Institute of Technology in Pasadena, CA (USA), working in the research group of Professor Robert H. Grubbs.



L. Hie

Liana Hie received her B.S. degree in chemistry from the University of California, Davis (USA) in 2009, where she worked on the chemoenzymatic synthesis of heparan sulfate oligosaccharide analogues in the lab of Professor Xi Chen. She is currently a fifth-year Ph.D. student at UCLA (USA) working under the mentorship of Professor Neil K. Garg. Her research in the Garg lab focuses on the development of nickel-catalyzed couplings.

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Dr. X. Hong

Xin Hong received his B.Sc. (chemistry, 2010) degree from the University of Science and Technology of China (Hefei, P. R. of China) and his Ph.D. (chemistry, 2014) from UCLA (USA) under the guidance of Professor Kendall N. Houk. He then worked as a postdoctoral scholar in Professor Houk's lab focusing on organometallic reactions. In 2015, Xin joined the group of Professor Jens K. Nørskov as a postdoctoral scholar at the Department of Chemical Engineering at Stanford University (USA). His current research focuses on the reaction mechanism of CO₂ electro-reduction.



Dr. Y-f. Yang

Yun-fang Yang was born and raised in Handan (P. R. of China). She received her Ph.D. in chemistry from Peking University (Beijing, P. R. of China) in 2013 under the guidance of Professor Yun-dong Wu. In 2014, she joined the group of Professor Kendall N. Houk as a postdoctoral scholar at the Department of Chemistry and Biochemistry at UCLA (USA). Her current research focuses on computational studies of mechanisms and stereoselectivity of organic reactions.



Prof. P. Liu

Peng Liu obtained his B.S. degree from Peking University (Beijing, P. R. of China) in 2003 and his M.S. degree from the University of Guelph (Canada) in 2006. He received his Ph.D. degree in 2010 and then performed postdoctoral studies with Professor Kendall N. Houk at UCLA (USA). He joined the faculty of the University of Pittsburgh (USA) as an Assistant Professor of chemistry in 2014. His research focuses on computational studies of transition-metal-catalyzed reactions.



T. K. Shah

Tejas K. Shah was born and raised in Piscataway, NJ (USA). He received his BA in chemistry and molecular biology & biochemistry from Rutgers University in New Brunswick (USA), where he performed undergraduate research with Professor Daniel Seidel. He is currently a fifth-year graduate student in Professor Neil K. Garg's laboratory at ULCA (USA). His graduate studies are focused on utilizing heterocyclic arynes and nickel catalysis in organic synthesis.