

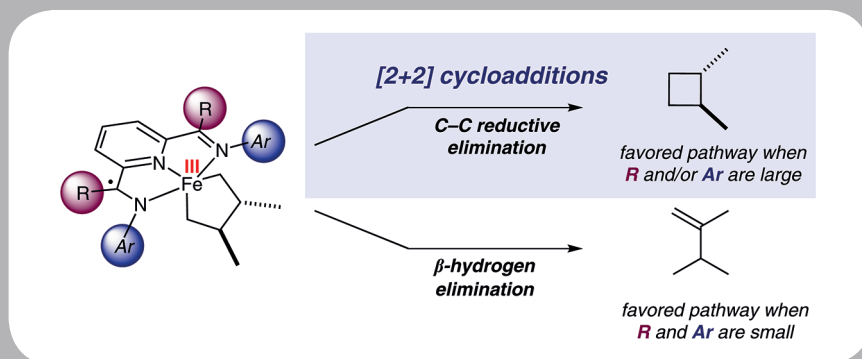
Synform

People, Trends and Views in Chemical Synthesis

2016/01

Iron-Catalyzed Intermolecular [2+2] Cycloadditions of Unactivated Alkenes

Highlighted article by J. M. Hoyt, V. A. Schmidt,
A. M. Tondreau, P. J. Chirik



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Thieme

Dear Readers,

This first issue of 2016 marks the 10th year of publication of SYNFORM, a remarkable milestone for the journalistic-style supplement of the Thieme Chemistry journals. The first issue – actually a number zero – was published in May 2007 and after 10 years I believe Synform has become a well-established and popular non-peer-reviewed publication on “new scientific advances in organic chemistry and related fields of research” as well as on “facts and people from the world of chemical sciences – all this in a stimulating and thought-provoking manner”, as I wrote in my first Editorial. I still remember that it all started when – one year before – I sent an email to Peter Vollhardt proposing my idea of including in SYNLETT and SYNTHESIS a journalistic-type coverage of cutting-edge articles, facts and people in the organic chemistry arena. Peter promised that the idea would be discussed at the next Editorial Board Meeting, and about one month later – to my great delight – Peter got back to me saying that the idea had been approved. I then worked for six months with the fantastic Thieme Chemistry team on the development of the initial concept into a new editorial product: SYNFORM was born! And this year it will be 10 years old! So let’s have a look at the content of this first issue of 2016, which could not be more exciting. The first article of the year covers a *Nature* paper published by Neil Garg, Ken Houk and co-workers (USA) on a breakthrough method for performing a traditionally challenging transformation such as the conversion of amides into esters. The second story covers another *Nature* paper by Daniel Weix and co-workers (USA) on the discovery of a new cross-coupling reaction for preparing asymmetrical biaryls in high yields and broad structural diversity. The third contribution reports on a *Science* paper published by

In this issue

■ Literature Coverage	
Conversion of Amides to Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds	A3
■ Literature Coverage	
Multimetallic Catalyzed Cross-Coupling of Aryl Bromides with Aryl Triflates	A9
■ Literature Coverage	
Iron-Catalyzed Intermolecular [2+2] Cycloadditions of Unactivated Alkenes	A12
■ Young Career Focus	
Young Career Focus: Pablo Barrio Fernández (University of Valencia, Spain)	A15
Coming soon	A18

Contact

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the group of Paul Chirik (USA) describing a groundbreaking method for synthesizing stereodefined cyclobutanes by intermolecular [2+2] cycloadditions of unactivated alkenes. Last but not least, there is the Young Career Focus interview with the up-and-coming researcher Pablo Barrio (Spain).

Happy 10th year of publication, SYNFORM!!

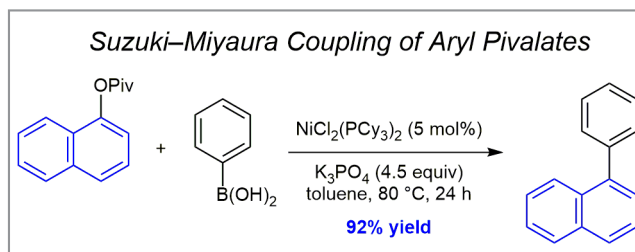


Conversion of Amides into Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds

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.

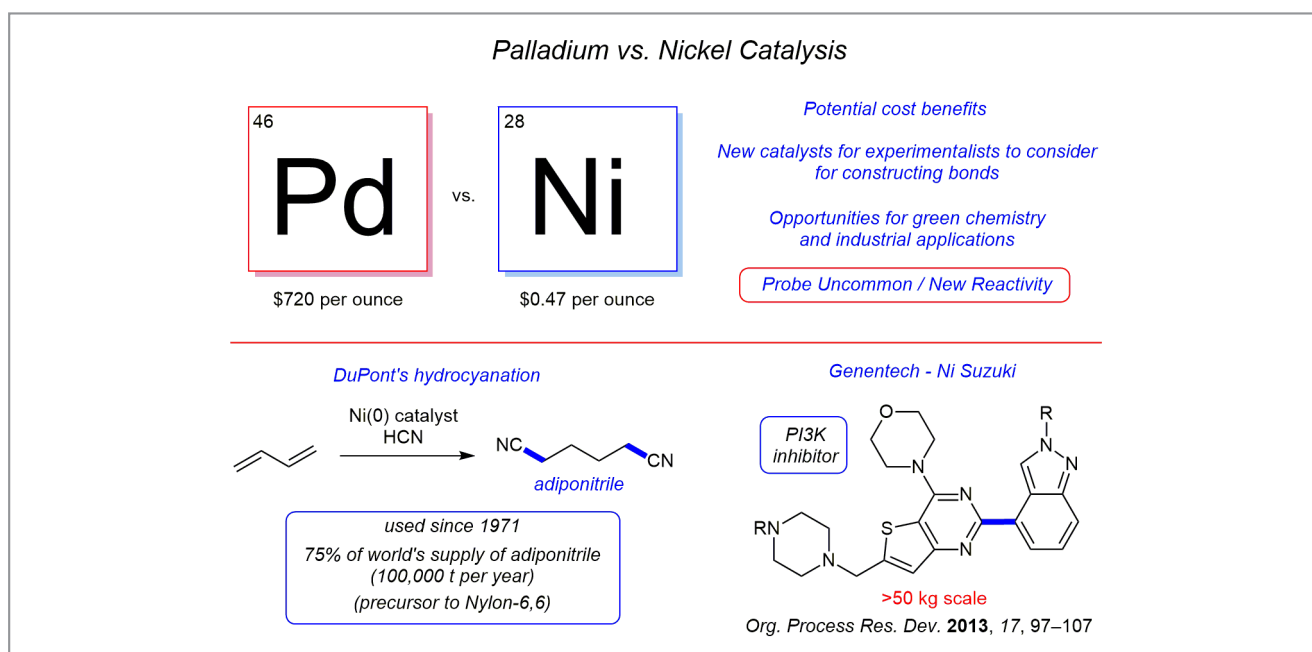
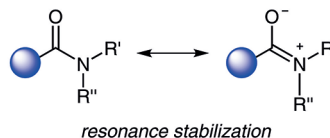


Figure 1

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



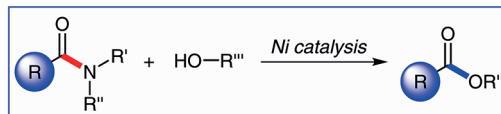
Figure 2

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

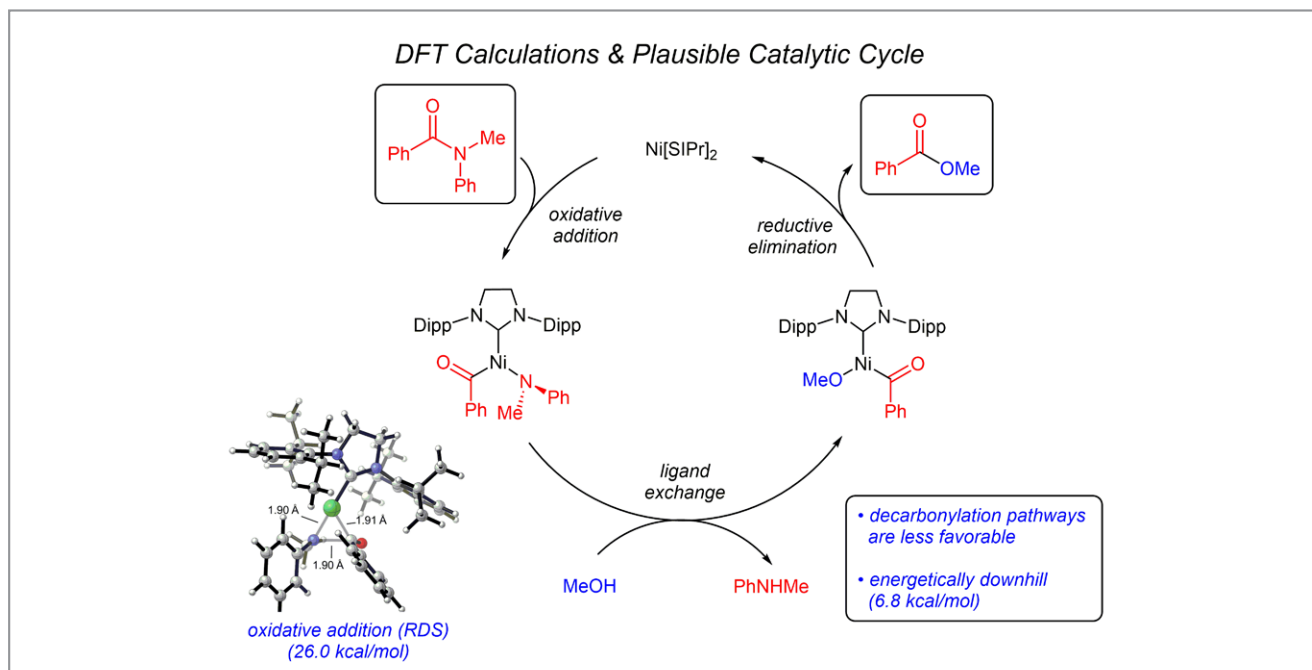
$R =$
aryl or
hetaryl



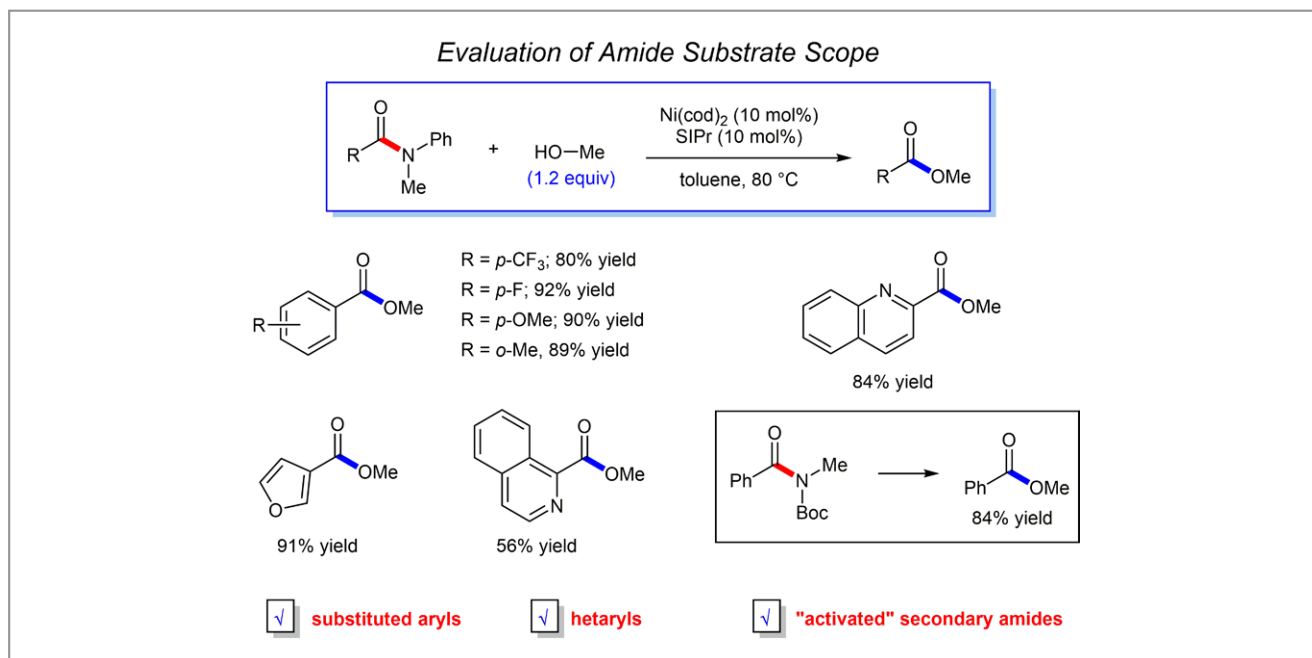
underdeveloped and challenging synthetic transformation

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).

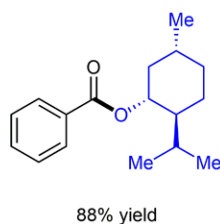
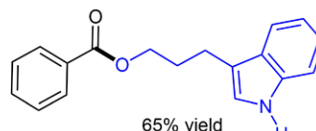
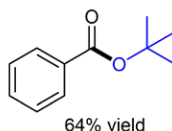
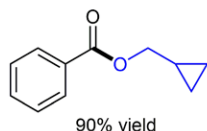
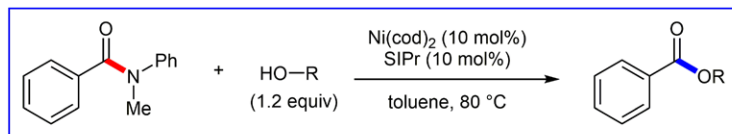


Scheme 3



Scheme 4

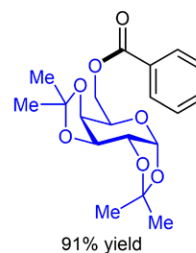
Evaluation of the Alcohol Coupling Partner



simple and sterically hindered alcohols



alcohols containing heterocycles and multiple heteroatoms



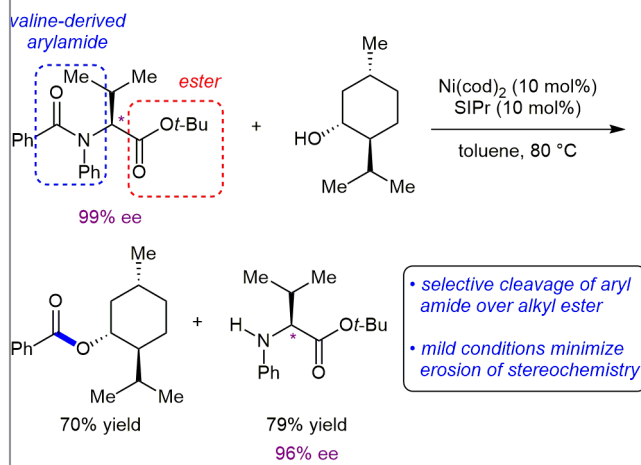
Scheme 5

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."

Amides are back

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

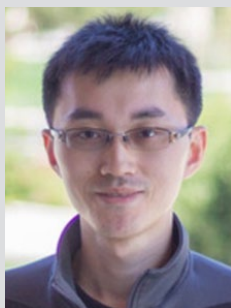
Noah F. Fine Nathel was born and raised in Berkeley, CA (USA). He received a B.A. in chemistry from Cornell University in Ithaca, NY (USA), where he worked in the research group of Professor Geoffrey W. Coates. He obtained his Ph.D. from the UCLA (USA), working under the direction of Professor Neil K. 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.

Multimetallic Catalyzed Cross-Coupling of Aryl Bromides with Aryl Triflates

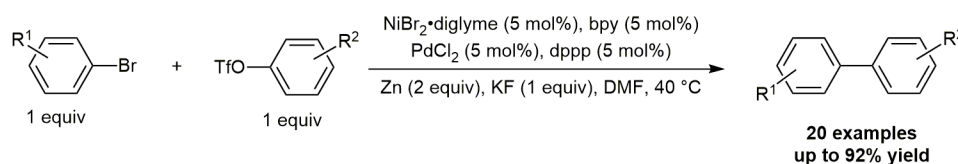
Nature **2015**, 524, 454–457

The ‘classical’ Ullmann reaction is the copper-catalyzed synthesis of symmetric biaryls from aryl halides. Variants of this reaction based on a single metal catalyst have been the object of intensive studies as a means of producing more complex and non-symmetrical biaryls. “The multimetallic catalyzed cross-Ullmann reaction provides two major contributions to the synthetic community: the first, a general method to access unsymmetrical biaryls from widely available starting materials, and second, a guiding principle for the cooperation of two metal catalysts in coupling reactions,” said Professor Daniel Weix at the University of Rochester, New York (USA). While the synthesis of biaryls from arylboron, aryltin, arylzinc, and arylsilicon reagents is well established, in many cases the corresponding aryl halide or aryl pseudohalide would be a more convenient starting material, allowing for increased substrate diversity. The new cross-Ullmann method recently identified by the group of Professor Weix enables the cross-coupling of aryl bromides with aryl triflates with high selectivity and functional group tolerance. Professor Weix explained: “Unsymmetrical biaryls can be isolated in up to 92% yield and both electron-rich and electron-deficient arenes can be employed. These results are promising for the development of other multimetallic catalyzed cross-coupling methods, especially when the substrates may be structurally or electronically similar, as in the formation of dienes (sp^2 – sp^2 coupling) and alkanes (sp^3 – sp^3 coupling).”

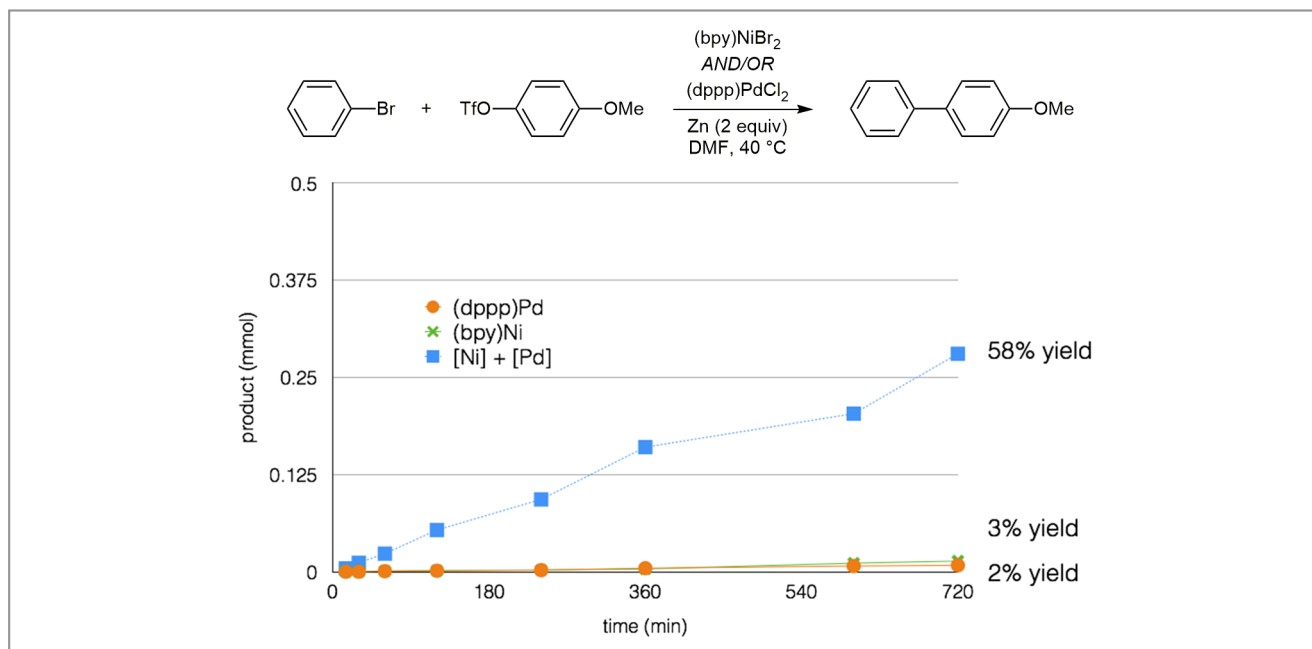
Multimetallic catalysis is represented in several well-known synthetic methods, such as the Wacker oxidation and the Sonogashira coupling. Although it holds great promise, it remains a nascent area in organic chemistry due to the complexity of integrating the reactivity of two metals. Professor Weix said: “Since the founding years of our research program,

we have been interested in multimetallic catalysis and how it could be applied to a reductive cross-electrophile coupling.” He continued: “Also, because of our success in developing methods for the coupling of aryl halides with alkyl halides, we were frequently asked about the potential for a cross-Ullmann reaction. We believed that a cross-Ullmann reaction would be a great vehicle to explore multimetallic catalysis because a general cross-coupling between two aryl halides had not yet been achieved, and the reaction would provide a route to valuable products.” Laura Ackerman – one of the authors of this study – had already spent a year synthesizing and studying the reactivity of various aryl metal complexes and the group knew that in order to design a successful multimetallic reaction, they would need selective activation of each aryl substrate and facile transmetalation between the two catalysts. Professor Weix said: “We hypothesized that the pairing of two reactive catalysts might result in rapid byproduct formation, and conversely, very stable catalysts might not promote any reaction at all. We decided that at least one catalyst should be relatively reactive in comparison to the other.” Due to the group’s experience with nickel catalysis and the myriad of literature on palladium-catalyzed cross-coupling reactions, the authors immediately focused on the combination of two catalysts that they knew possessed orthogonal selectivities for aryl bromides and aryl triflates.

The first nickel- and palladium-catalyzed cross-Ullmann reaction was very promising: Professor Weix and co-workers obtained greater than statistical selectivity; however, the overall product yield and reaction times were not ideal for the practicing synthetic chemist. Professor Weix explained: “Aiming to improve the yields of the reaction, Laura decided to investigate the use of KF as an additive, which had litera-



Scheme 1



Scheme 2

ture precedence for enhancing selectivity in metal-catalyzed cross-coupling reactions.” The third author of this study, Matt Lovell, helped Laura explore the effect of other additives on the multimetallic reaction, and extended the conditions to heteroaryl halides. “While the origin of the cooperation between nickel and palladium warrants further study, it is already apparent that the reaction does not proceed selectively with only one of the two catalysts,” said Professor Weix. “The nickel catalyst rapidly dimerizes aryl bromides before consuming any aryl triflate, while the palladium catalyst is selective for the addition of aryl triflates and is slow to dimerize materials. It appears that throughout the reaction, the arylpalladium intermediate is present in high concentration, while the arylnickel intermediate immediately reacts with the persistent palladium complex once formed.” Professor Weix concluded: “The elucidation of the mechanism of this reaction is an alluring challenge that we are now investigating in our lab. One could imagine that the conditions discovered for this cross-Ullmann reaction could be extended far beyond reductive cross-coupling to other exciting areas, such as cross-dehydrogenative coupling.”

Matt Lovell

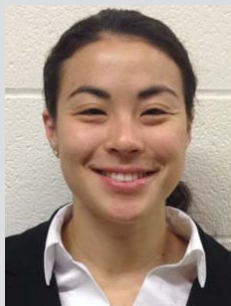
About the authors



M. M. Lovell

Matthew Lovell was born and raised in Munroe Falls, Ohio (USA). He graduated from the University of Rochester (USA) in 2014, majoring in chemistry and psychology. Matt worked in the Weix group for two years (2012–2014), studying nickel- and palladium-catalyzed reactions, and volunteering his time as an emergency medical technician. He is currently starting the first year of his Master's program at Case Western Reserve University (USA) in medical physiology.

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L. K. G. Ackerman

Laura Ackerman was born and raised in Honolulu, Hawai'i (USA). After attending Punahou School, she attended Claremont McKenna College (USA) and majored in chemistry and religious studies while investigating asymmetric reactions under the supervision of Professor Anna G. Wenzel. After graduation in 2009, Laura returned to Hawai'i to conduct research under Professor David A. Vicic at the University of Hawai'i

at Mānoa on copper-promoted trifluoromethylation reactions. In 2010 Laura began researching in the Weix group at the University of Rochester as an NSF graduate fellow, exploring multi-metallic catalytic reactions and nickel-catalyzed cross-electrophile couplings.



Prof. D. J. Weix

Daniel Weix was born in Milwaukee, Wisconsin (USA) in 1978. He received a BA in chemistry at Columbia University (USA) in 2000 while working on helicenes with Professor Thomas Katz. After graduation, Daniel joined the group of Professor Jonathan Ellman at UC-Berkeley (USA) as an NSF graduate fellow in the area of sulfonamide chemistry. He received his PhD in 2005 and moved to Yale University (USA) as an NIH Postdoctoral Scholar under Professor John Hartwig from 2005–2008.

He was appointed Assistant Professor at the University of Rochester (USA) in 2008 and was promoted to Associate Professor in 2014. He has received several awards, including the Thieme Chemistry Journal Award, the Alfred P. Sloan Research Fellowship, the Camille Dreyfus Teacher-Scholar Award, and the Novartis Early Career Award. His research interests are in the development of new mechanisms in catalysis and their application in useful chemical reactions, especially in the area of cross-electrophile coupling.

Iron-Catalyzed Intermolecular [2+2] Cycloadditions of Unactivated Alkenes

Science **2015**, 349, 960–963

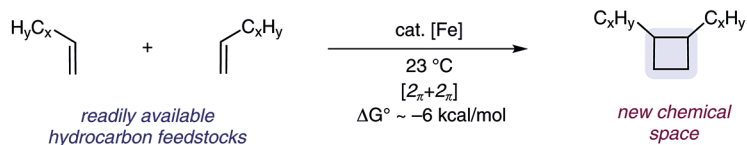
The thermal [2+2] cycloaddition of alkenes leading to cyclobutanes remains a big challenge for chemists as current methodologies rely on photochemical activation and substrates bearing chromophores. For this reason, unactivated alkenes, which are available in large quantities from natural resources, have been outside the scope of [2+2] cycloaddition reactions so far. Recently, a new breakthrough methodology for performing this transformation has been described in a *Science* paper published by Professor Paul Chirik and members of his group from Princeton University (USA). This Fe-catalyzed work is an example of chemistry that has been of long-standing interest to the Chirik group: to develop sustainable catalytic methods employing earth-abundant and environmentally benign first-row transition metals that not only have the potential to replace existing technologies requiring precious metals, but to lead to the discovery of new processes previously unobserved with any catalyst. Professor Chirik said: “Unfunctionalized alkenes and dienes are an attractive substrate class as they are derived from petrochemical and natural sources and are produced on the metric tonne scale annually.” Professor Chirik explained that the development of vast global shale gas reserves and intense efforts for the conversion of methane into higher hydrocarbons has revolutionized supply and created a glut of these feedstocks that will likely only increase in the foreseeable future. Professor Chirik continued: “The realization of new chemical transformations that convert these simple feedstocks into more value-added products is required in order to curb on-site flaring, a practice that currently consumes approximately \$30 billion USD annually and is a major source of CO₂ emissions.”

The synthesis and reactivity of reduced pyridine(diimine) iron dinitrogen compounds in the Chirik group has served as the inspiration for many developments.

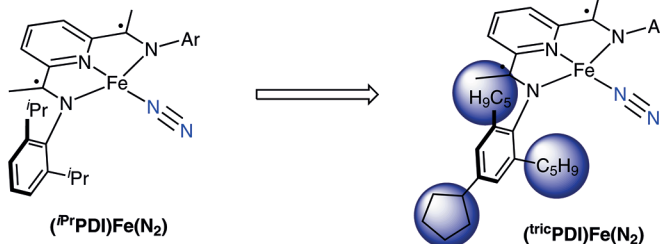
Dr. Marco Bouwkamp was the lead investigator who first discovered the unique reactivity of ^{iPr}PDIFeN₂ to form cyclobutanes from tethered α-olefins (*J. Am. Chem. Soc.* **2006**, 128, 13340). “Since that initial breakthrough,” said Professor Chirik, “a team of graduate students and postdoctoral researchers have tackled the challenge of understanding the distinctive properties of this [2+2] cycloaddition including a mechanistic overview of the process by Dr. Jordan M. Hoyt (*J. Am. Chem.*

Soc. **2013**, 135, 4862) and extension of this reactivity to the analogous cobalt pyridine(diimine) platform by Dr. Valerie A. Schmidt (*J. Am. Chem. Soc.* **2015**, 137, 7903).” During the course of this cobalt study, a new pyridine(diimine) ligand was synthesized in which the 2,6-diisopropyl groups of the aryl imine were replaced with cyclopentyl groups. Professor Chirik said: “While a seemingly subtle change, this cyclopentyl-substituted cobalt compound proved to have an activity comparable to that of ^{iPr}PDIFeN₂, which was previously identified as the most active [2+2] catalyst.” Another significant advance in this project was made by Dr. Sarah K. Russell with the synthesis of ^{Me}PDIFeN₂ (*Inorg. Chem.* **2010**, 49, 2782) and the discovery that it was an effective catalyst for the [2+2] cycloaddition of 1,3-butadiene and ethylene to give vinyl cyclobutane (*J. Am. Chem. Soc.* **2011**, 133, 8858). “Extending the reactivity beyond this singular intermolecular reaction proved challenging, as a loss in selectivity and activity was observed upon changing of the substrates,” explained Professor Chirik.

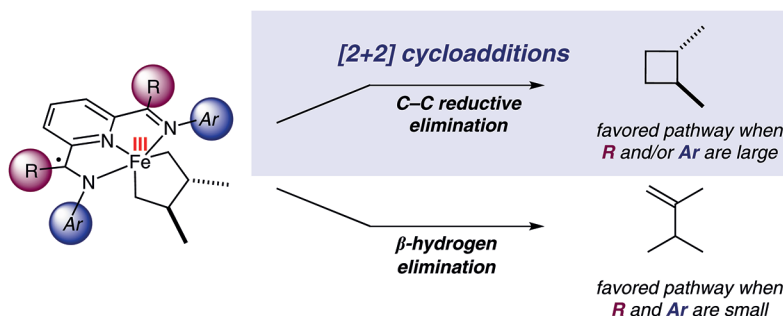
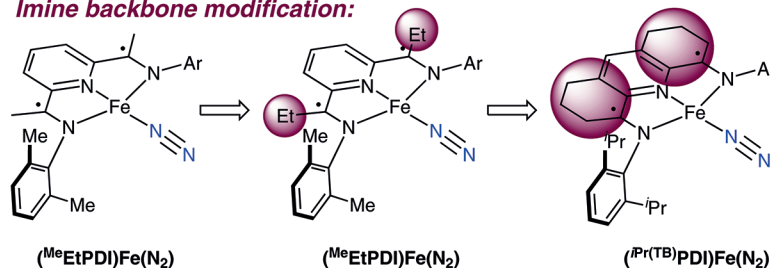
In order to overcome these limitations and with mechanistic insights in hand, new catalysts were rationally designed by the group and the reaction conditions were improved (Scheme 1). Professor Chirik said: “Inspired by the results with cobalt, an iron pre-catalyst bearing the 2,4,6-tricyclopentyl groups on the aryl imine moiety (^{tricyclopentyl}PDIFeN₂) was prepared and found to be active and very selective for the intermolecular [2+2] cycloaddition of alkenes.” Solvent-free conditions were used in order to maximize the activity and remove any waste generation from the reaction. A second catalyst was developed for this transformation and was found to have higher activity, but lower selectivity for the cyclobutane products. Professor Chirik explained: “This was achieved by modifying the ^{Me}PDIFeN₂ catalysts with larger imine ethyl groups forming ^{MeEt}PDIFeN₂. This substitution prevents imine dissociation from the metal center and minimizes byproduct formation.” In order to further prevent imine dissociation, an iron pre-catalyst was prepared in which the imine group was ‘tied-back’ and attached to the pyridine ring (^{iPr(TB)}PDIFeN₂). This modification enabled a significant improvement in the scope and selectivity of diene–alkene [2+2] cycloadditions. Professor Chirik concluded: “With these developed catalysts in hand, we evaluated a series of naturally and petrochemically derived commodity chemicals for the formation of cyclobutanes.



Rational Catalyst Design
Aryl imine modification:



Imine backbone modification:



Scheme 1

Future catalyst development has the potential to further expand the scope of alkene and diene substrates in thermal [2+2] cycloaddition reactions.”

Matthew Farnick

About the authors



Prof. P. J. Chirik

Paul J. Chirik attended Virginia Tech (USA) as an undergraduate before moving to the California Institute of Technology (USA) where he received his Ph.D. working in the lab of Professor John E. Bercaw. After postdoctoral studies at the Massachusetts Institute of Technology (USA) with Professor Christopher C. Cummins, Chirik began his independent career at Cornell University (USA) in 2001, where he was promoted to Associate then to Peter J. W. Debye Professor. In 2011, he relocated to Princeton University (USA) and is currently the Edwards S. Sanford Professor of Chemistry, Associate Director of the Andlinger Center for Energy and Environment and Editor-in-Chief of *Organometallics*.

Valerie A. Schmidt graduated from Towson University (USA) in 2007 before moving to North Carolina to pursue a Ph.D. under the tutelage of Professor Erik J. Alexanian at the University of North Carolina at Chapel Hill (USA). Valerie joined the Chirik group for her postdoctoral studies in 2013 and is a recipient of an NIH NRSA Postdoctoral Fellowship.



Dr. V. A. Schmidt



Dr. J. M. Hoyt

Jordan M. Hoyt attended Florida State University (USA) as an undergraduate where he worked in the lab of Michael Shatruk. After graduating in 2010, Jordan joined the lab of Paul J. Chirik at Cornell University (USA) and shortly thereafter moved with the Chirik group to Princeton University (USA) where he received his Ph.D. in spring 2015.

Aaron M. Tondreau graduated from California State University, Bakersfield (USA) before joining the Chirik group in 2006 where he developed base-metal-catalyzed hydrosilylation reactions. Aaron then went on to pursue postdoctoral studies with Professor Hansjörg Grützmacher at ETH Zurich (Switzerland) and is currently employed at Los Alamos National Laboratory (USA) working with Dr. James Boncella.

Young Career Focus: Professor Pablo Barrio (University of Valencia, Spain)

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 Pablo Barrio (University of Valencia, Spain).

Biographical Sketch



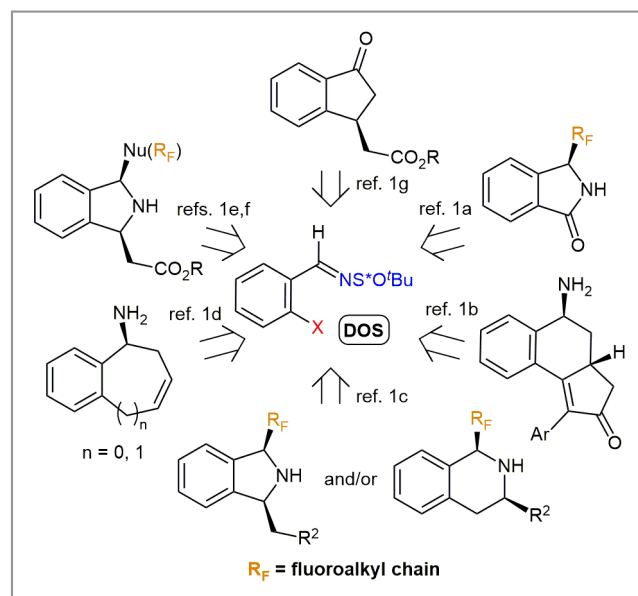
Prof. P. Barrio

Pablo Barrio was born in La Coruña (Spain) in 1979. He studied chemistry at the University of Oviedo (Spain), obtaining his PhD under the supervision of Professor Barluenga. Later, he joined the group of Professor Carreira at ETH Zurich (Switzerland) where he worked as a post-doctoral fellow for two years. Afterwards, he was granted a *Juan de la Cierva* fellowship in the group of Professor Fustero at the University of Valencia (Spain) where he has been working since 2009. He is focused on two topics: the asymmetric synthesis of benzo-fused carbo- and heterocycles using a DOS approach and the chiral Brønsted acid catalyzed allylboration reaction. He is also interested in the use of terphenyls in medicinal chemistry. He has carried out short (2–3 months) stays at Trinity College Dublin (Ireland), Max Planck Institute (Mülheim an der Ruhr, Germany), Gakushuin University (Tokyo, Japan), University of Southern California (Los Angeles, USA) and University of Louisville (Kentucky, USA). He is author of 21 publications in high impact factor journals and has mentored two PhD theses. In 2015 he received the Thieme Chemistry Journals Award.

INTERVIEW

SYNFORM What is the focus of your current research activity?

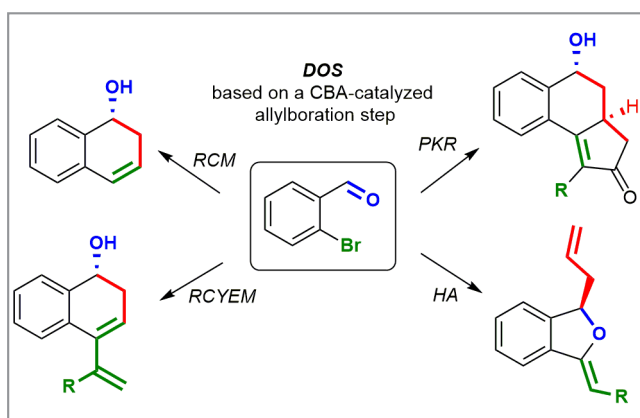
Prof. P. Barrio Currently, we are active in three main research areas. The first two are closely related to each other, while maintaining their independence. More specifically, for the last five years we have been studying the use of *ortho*-halobenzaldehyde-derived Ellman's imines in the context of Diversity-Oriented Synthesis (DOS).¹ We have shown that these compounds are outstanding starting materials for the rapid construction of benzo-fused carbo- and heterocyclic amines in a stereoselective manner. The presence of a halogen at the *ortho* position allows the introduction of appropriate



Scheme 1 DOS strategy from 2-halobenzaldehyde-derived Ellman's imines

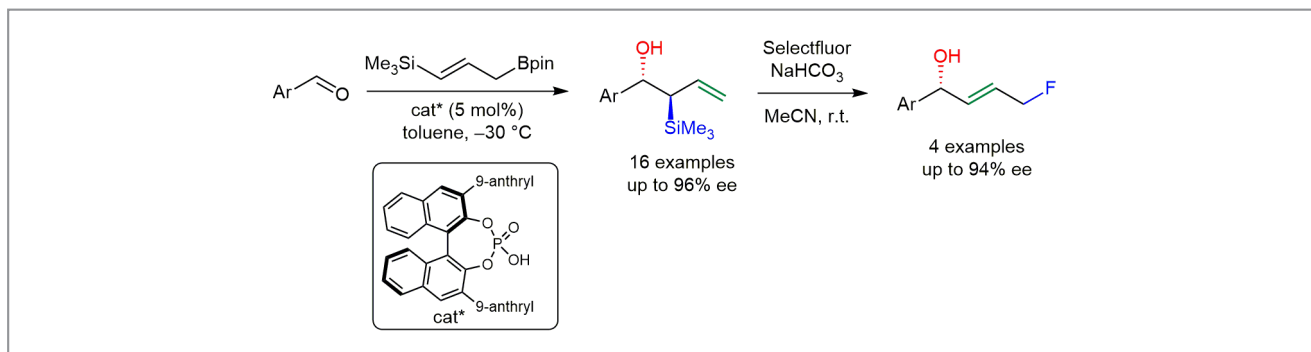
functional groups, by means of well-established palladium-catalyzed cross-coupling chemistry, in the proximity of the reacting center for subsequent cyclization reactions (Scheme 1).

Related to the aforementioned project, we have also studied the reactivity of *ortho*-functionalized benzaldehydes.² Specifically, we have studied the performance of such substrates in the chiral Brønsted acid catalyzed allylboration reaction. Furthermore, we have carried out a similar DOS approach, obtaining a number of benzo-fused carbo- and heterocycles (Scheme 2).



Scheme 2 Chiral Brønsted acid catalyzed allylboration of *ortho*-functionalized benzaldehydes

Lately, we have changed our approach to achieve densely functionalized products, suitable for further derivatization; while we previously used *ortho*-functionalized substrates, we are currently also using γ -functionalized allylboronates, unprecedented in enantioselective catalysis (Scheme 3).³ The α -silylhomoallylic alcohols obtained were further transformed into fluorinated allylic alcohols (Scheme 3).



Scheme 3 γ -Silylallylboronates in the chiral Brønsted acid catalyzed allylboration of aldehydes

Last but not least, the third project deals with medicinal chemistry. In collaboration with Professor Gallego from the Universidad Católica de Valencia, bilaterally substituted terphenyl derivatives were found as effective inhibitors of the replication cycle of the HIV-1 virus. Currently, we are designing and synthesizing a second generation of anti-HIV agents and we also want to extend the applicability of such compounds in order to tackle a second-world pandemic, malaria.

SYNFORM When did you get interested in synthesis?

Prof. P. Barrio I have been interested in science since I was very young. However, the decision to study chemistry was made at the very last moment before I started at university... physics and mathematics were serious options but finally chemistry, being a science much less abstract than physics or mathematics (we do 'touch' our matter of study!), tipped the scales. During my second year as an undergraduate student I met Professor Barluenga who taught me the first organic chemistry course I ever took. I believe that his passion for synthesis played a decisive role in my interest for organic synthesis.

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

Prof. P. Barrio Undoubtedly, sustainability must be one of the major foci in modern synthesis. We have shown that we are able to synthesize very complex molecules in very high levels of selectivity (chemo-, regio-, stereo-), sometimes even mimicking nature's own levels of selectivity. The next challenge is making these beautiful transformations in ways that are as respectful to the environment as possible. Of course, we also must keep asking ourselves questions and coming up with creative solutions for new synthetic challenges. Another

important aspect of modern organic synthesis is interdisciplinarity. We must be able to understand our colleagues in other branches of science and make our solutions understandable to them.

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

Prof. P. Barrio In the first question, I explained the topic of our research in detail; here, I would like to focus a little more on the aims. I won't make high-sounding statements; my motivations are quite humble, if I may say so. First of all, I try to learn. Second, I try to come up with useful synthetic methods... chemistry that is reliable and applicable for the preparation of potentially widely used building blocks, with a special focus on drug discovery. Finally, teaching chemistry to students. I believe that in an academic laboratory this is enough of an aim. Even if this was the only usefulness of our research it would be a very important one. Our research is the means we use to train new chemists. The more they learn from our research, the better chemists they will become. This is a good reason to seek challenging research topics and carry them out in a proficient manner...that the next generation produces better chemists than us.

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

Prof. P. Barrio The part of my work I feel most proud of is everything related to the chiral Brønsted acid catalyzed allylations. This is a research project that I set up within the research group of Professor Fustero. In a couple of years we have made a few interesting contributions to this competitive field that have had high impact. Related to the previous question, I also feel very proud of having mentored a number of students and witnessed how they have turned into mature chemists.

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Coming soon

■ Literature Coverage

Catalyst-Directed Diastereoselective Isomerization of Allylic Alcohols for the Stereoselective Construction of C(20) in Steroid Side Chains: Scope and Topological Diversification

■ Literature Coverage

Highly Stereoselective, Intermolecular Haloetherification and Haloesterification of Allyl Amides

■ Literature Coverage

An Oxazetidine Amino Acid for Chemical Protein Synthesis by Rapid, Serine-Forming Ligations

Further highlights

Synthesis Review: Synthesis of Ynones and Recent Application in Transition-Metal-Catalyzed Reactions

(by G. Dong and co-workers)

Synlett Thieme-IUPAC Prize Account: Our Path to Less Toxic Amphotericins

(by M. D. Burke and co-workers)

Synfacts Synfact of the Month in category "Synthesis of Materials and Unnatural Products": Double Spiros

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 SYNFORM issue 2016/02 is available from January 19, 2016
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 Rüdigerstraße 14, 70469 Stuttgart, Germany,
 ■ Homepage: www.thieme-chemistry.com

Publication Information

Synform will be published 12 times in 2016 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

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