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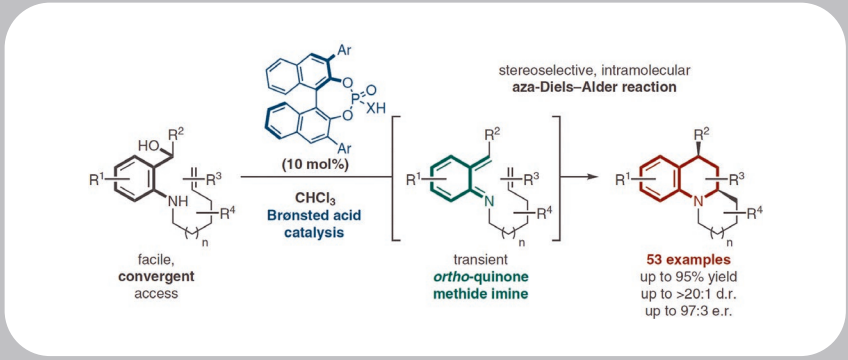
SYNTHESIS Best Paper Award 2022: Asymmetric Synthesis of Fused Tetrahydroquinolines via Intramolecular Aza-Diels–Alder Reaction of *ortho*-Quinone Methide Imines

Highlighted article by F. Hofmann, C. Gärtner, M. Kretzschmar, C. Schneider



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Dear Readers,

In this April issue of SYNFORM we celebrate the first of the two 2022 Thieme Chemistry Best Paper Award winners. Professor Christoph Schneider, together with Fabian Hofmann, Cornelius Gärtner and Martin Kretzschmar from the University of Leipzig (Germany), who are the recipients of the SYNTHESIS Best Paper Award 2022 for their article "Asymmetric Synthesis of Fused Tetrahydroquinolines via Intramolecular Aza-Diels–Alder Reaction of *ortho*-Quinone Methide Imines" (*Synthesis* **2022**, *54*, 1055–1080), are featured in an interview that provides background information on their prize-winning research, as well as about current research activities ongoing in the group. I can anticipate that the SYNLETT Best Paper Award 2022 winners – Professor Todd K. Hyster and co-authors (Cornell University, USA) – will be featured in a forthcoming issue. But there is much more in this issue, starting from the *meta*-selective C–H arylation of phenols reported by L. T. Ball (UK) in *Nat. Chem.* and the enantioselective reductive transformations of secondary amides described in *Sci. Adv.* by P. Q. Huang (P. R. of China). The third Literature Coverage article reports on the iron-catalyzed intermolecular amination of benzylic C(sp^3)–H bonds developed by B. Chattopadhyay (India). The issue is wrapped up by the Young Career Focus interview with Mattia Silvi (UK), who is both a 2023 Thieme Chemistry Journals Award recipient and 2022 ERC Starting Grant Awardee.

Enjoy your reading!

In this issue

SYNTHESIS Highlight
SYNTHESIS Best Paper Award 2022: Asymmetric Synthesis of Fused Tetrahydroquinolines via Intramolecular Aza-Diels–Alder Reaction of *ortho*-Quinone Methide Imines A61

Literature Coverage
***meta*-Selective C–H Arylation of Phenols via Regiodiversion of Electrophilic Aromatic Substitution** A64

Literature Coverage
Multicatalysis Protocol Enables Direct and Versatile Enantioselective Reductive Transformations of Secondary Amides A67

Literature Coverage
Iron-Catalyzed Intermolecular Amination of Benzylic C(sp^3)–H Bonds A70

Young Career Focus
Young Career Focus: Dr. Mattia Silvi (University of Nottingham, UK) A75

Coming soon A78

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

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SYNTHESIS Best Paper Award 2022: Asymmetric Synthesis of Fused Tetrahydroquinolines via Intramolecular Aza-Diels–Alder Reaction of *ortho*-Quinone Methide Imines

Synthesis **2022**, *54*, 1055–1080

Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.

Professor Christoph Schneider, together with Fabian Hofmann, Cornelius Gärtner and Martin Kretzschmar from the University of Leipzig, Germany, are the recipients of the SYNTHESIS Best Paper Award 2022. The authors are recognized for their thorough examination of the title reaction. Mark Lautens, Editor-in-Chief of SYNTHESIS, stated: "The Schneider lab has reported on intramolecular aza-Diels–Alder reactions of *ortho*-quinone methide imines, giving access to biologically relevant tetrahydroquinolines. Key to their success was the use of chiral BINOL phosphoric amides as Bronsted acids. This comprehensive study presents successes and limitations, as well as proposes possible transition states to explain the results. The continuing importance of the Diels–Alder reaction, and its many variants, remains a topic of intense interest 70 years after the award of the Nobel Prize in Chemistry to Diels and Alder."

SYNFORM spoke with Professor Christoph Schneider, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Biographical Sketch

Professor C. Schneider (right) and co-authors Dr. Fabian Hofmann (left), Cornelius Gärtner (second from left), and Dr. Martin Kretzschmar (second from right)

Christoph Schneider received his chemical education at the University of Göttingen (Germany) and obtained a Ph.D. with Prof. Lutz F. Tietze working in the area of natural product synthesis. Subsequently, he was a postdoctoral fellow with Prof. David A. Evans at Harvard University (USA) before returning to Germany to perform independent studies towards his habilitation in Göttingen from 1994 to 1998. Thereafter he was invited for visiting professorships in Szeged (Hungary), Toronto (Canada), and Saarbrücken (Germany). In 2003 he moved to his current position as Full Professor at the University of Leipzig (Germany) where he has remained ever since. Since 2016 he has been an elected member of the review board for organic molecular chemistry within the Deutsche Forschungsgemeinschaft. His research interests are in the area of stereoselective organic synthesis with a focus on catalytic enantioselective transformations and their application towards natural product synthesis.

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INTERVIEW

SYNFORM *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?*

Professor C. Schneider Nitrogen-containing heterocycles are integral constituents of many natural products, in particular within alkaloids, which display a vast array of biological activities, making them ideal candidates for the pharmaceutical industry. However, while natural products have always been an enormous source of inspiration for the development of pharmaceutically active molecules, their exact chemical structure has to be carefully modulated in order to meet the stringent requirements for medicinal applications. In this respect, chemical synthesis continues to be an indispensible tool and state-of-the-art technology to assemble the optimized target compounds with defined properties and the correct three-dimensional configuration.

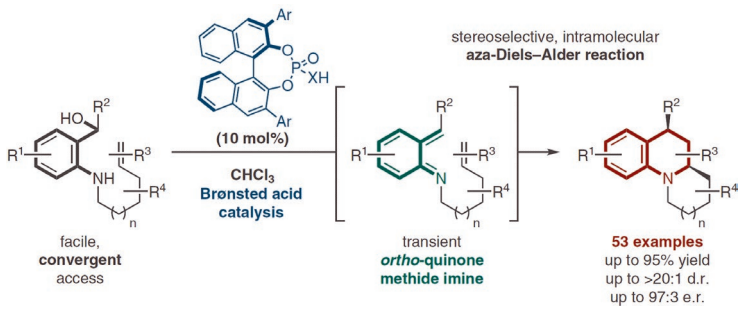
In the present manuscript we have developed the first enantioselective synthesis of benzannulated quinolizidines pursuing a highly straightforward strategy. This structural motif is present in a number of biologically very active compounds. Subjecting readily available *ortho*-amino benzyl alcohols tethered via the nitrogen atom to a suitable dienophile to chiral Brønsted acid catalysis furnishes *ortho*-quinone methide imines as transient 1-azadienes which directly engage the dienophiles in an intramolecular aza-Diels–Alder reaction. Controlled by the chiral phosphoramide catalyst, this cycloaddition proceeds with good yields and good to excellent diastereo- and enantioselectivities. A broad range of substituted quinolizidine products with rather interesting additional pharmacophore motifs embedded into the molecules (such as indoles) have been made available in just a single step. This strategy will likely be of significant value for modern medicinal chemistry as well.

SYNFORM *Can you explain the origin, motivations and strategy used for conducting the award-winning research?*

Professor C. Schneider We have a long-standing interest in asymmetric Brønsted acid catalyzed reactions going all the way back to our discovery of the first enantioselective, vinylogous Mannich reaction in 2008 which evolved into a platform strategy for alkaloid total synthesis over the last decade. More recently, we have been interested in chiral Brønsted acid catalyzed cycloadditions of transient *ortho*-quinone methides, an extremely powerful synthetic strategy for the assembly of benzannulated oxygen heterocycles. From there it was only a small step to extend this concept to the corresponding anilines and the formation and cycloaddition of transient *ortho*-quinone methide imines and the synthesis of nitrogen heterocycles. In a preceding manuscript, we established the first enantioselective intermolecular aza-Diels–Alder reaction. Due to the trivalent nature of the nitrogen atom, and different from the oxygen analogues, we could attach the dienophile directly onto the diene here and conceptualize an intramolecular Diels–Alder reaction. A first report from the Corey group in 1999 demonstrated the general concept in a base-mediated, racemic reaction, while our SYNTHESIS paper established the first catalytic, enantioselective process.

SYNFORM *What is the focus of your current research activity, both related to the award paper and in general?*

Professor C. Schneider Our research continues to focus on novel reaction development and the application of these methods in the context of natural product synthesis. In my opinion this is an ideal training exercise to demonstrate the power and versatility of newly invented methodology. We have just completed a biomimetic, enantioselective total syn-



Scheme 1 Enantioselective synthesis of benzannulated quinolizidines

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thesis of tetrahydrocannabinoids and are currently in the final stages of a total synthesis of the nuphar alkaloids thiobinupharidine and thionuphlutine which display significant cytotoxic activity. Both syntheses utilize our own methodology in their central steps.

In the area of reaction development, we have extended the methodology described in the award paper to cycloadditions of indole and pyrrole methides giving rise to complex nitrogen heterocycles in enantiomerically highly enriched form. In addition, we focus on other Brønsted acid catalyzed, enantioselective transformations which are currently underdeveloped, for example novel Piancatelli and Nazarov cyclizations. Moreover, we strive to attach chiral Brønsted acids onto solid support and thus employ heterogeneous chiral catalysts under continuous flow conditions for the large-scale production of valuable fine chemicals.

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

Professor C. Schneider Organic synthesis continues to be a central discipline within the chemical sciences. Among the major challenges ahead of us, I see difficult carbon–carbon bond-forming reactions effected by chiral catalysts, especially between quaternary chiral centers and within highly functionalized molecules. The prospect of utilizing modified enzymes as chiral catalysts obtained by directed evolution has only recently begun to play a role in organic synthesis. Moreover, protecting-group-free or at least protecting-group-reduced total synthesis is an ambitious, yet worthwhile, goal and would increase the atom economy of a given synthesis. Finally, artificial intelligence and machine learning are just beginning to change the way we execute organic synthesis and will not only affect chemistry, but most certainly revolutionize all branches of sciences.

SYNFORM *What does this award mean to you/your group?*

Professor C. Schneider This award is a wonderful recognition of our group's work and likewise a strong inspiration and encouragement, especially for the PhD students who performed the actual experiments.

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meta-Selective C–H Arylation of Phenols via Regiodiversion of Electrophilic Aromatic Substitution

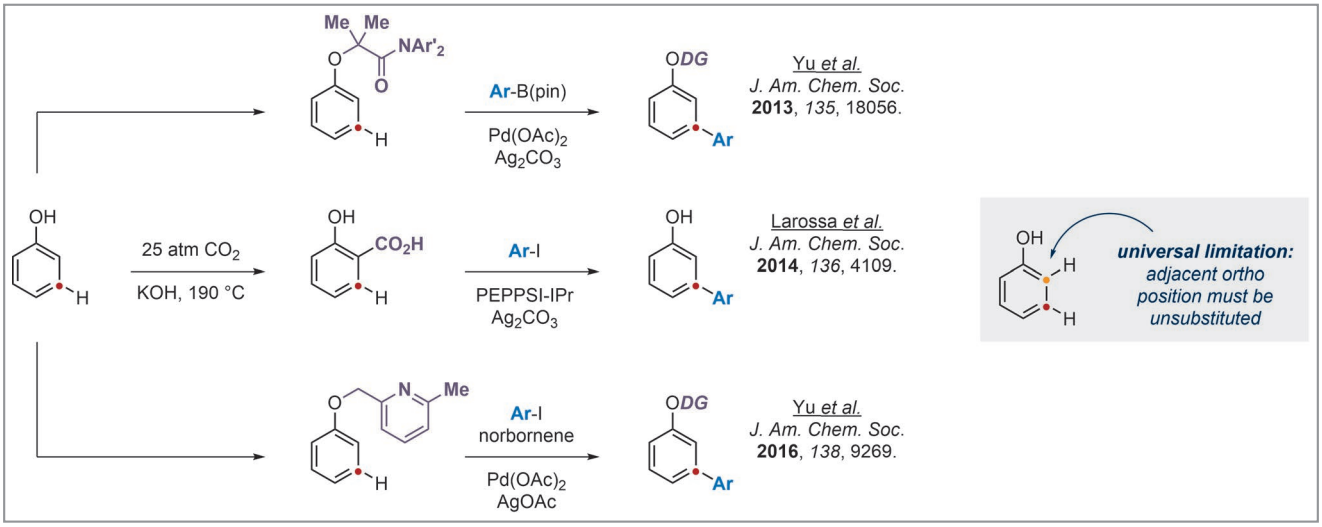
Nat. Chem. **2022**, in press; DOI: 10.1038/s41557-022-01101-0

The *meta*-selective C–H arylation of phenols is an enduring challenge in organic synthesis (*Chem. Rev.* **2022**, *122*, 5682). Not only is the *meta* position deactivated towards electrophilic substitution – the most common reaction manifold for phenols – but it is also beyond the reach of most directing groups that could be appended to the phenolic oxygen. Although this challenge has attracted several pioneering solutions based on Pd-catalyzed C–H functionalization (Scheme 1), these methods do not tolerate an existing *ortho* substituent on the phenol. As such, phenols featuring contiguous substitution patterns (e.g., 2,3-disubstitution) remain severely underrepresented in chemical libraries (*J. Med. Chem.* **2020**, *63*, 13389).

Dr Liam Ball and his team at University of Nottingham (UK) recognized that they could potentially address this limitation using a fundamentally different reaction manifold: Bi(V)-mediated electrophilic arylation. The group recently reported a convenient and highly *ortho*-selective Bi(V)-mediated arylation (*Nat. Chem.* **2020**, *12*, 260). Dr Ball explained: "This appears to proceed *via* an S_EAr-like mechanism in which the "Ar^+" electrophile is added to the π-system of the phenol *prior* to cleavage of the C–H bond. This is obviously very different to Pd-catalyzed C–H functionalizations that typically involve concerted metalation deprotonation, where the new C–C bond is formed *after* the C–H bond is cleaved." The group hypothesized that the electrophilic manifold could be applied equally to the arylation of *ortho*-substituted phenols to give a dienone intermediate which would be prevented from spontaneously rearomatizing. "If we could then induce a dienone–phenol rearrangement," Dr Ball continued, "1,2-aryl migration would effectively form a new Wheland-type intermediate *meta* to the phenolic OH, but without having to actually achieve the initial substitution at this least reactive position."

This hypothesis was borne out in practice (Scheme 2). Following the group's established protocols, telescoped B-to-Bi transmetallation and oxidation converted the bench-stable Bi(III) 'universal precursor' **1** into the active Bi(V) arylating agent **2**, which was then reacted with an *ortho*-substituted phenol to give the corresponding dienone **3** (Scheme 2A). Treatment of isolated dienone **3** with a Lewis acid promoted the 1,2-arylation/rearomatization sequence, giving *meta*-arylated phenol **4**.

Aaron Senior, the first-named author on the paper and a PhD candidate at the time of the work, led reaction development and exploration of substrate scope (Scheme 2B). "The



Scheme 1 Precedent for the *meta*-selective C–H arylation of phenols

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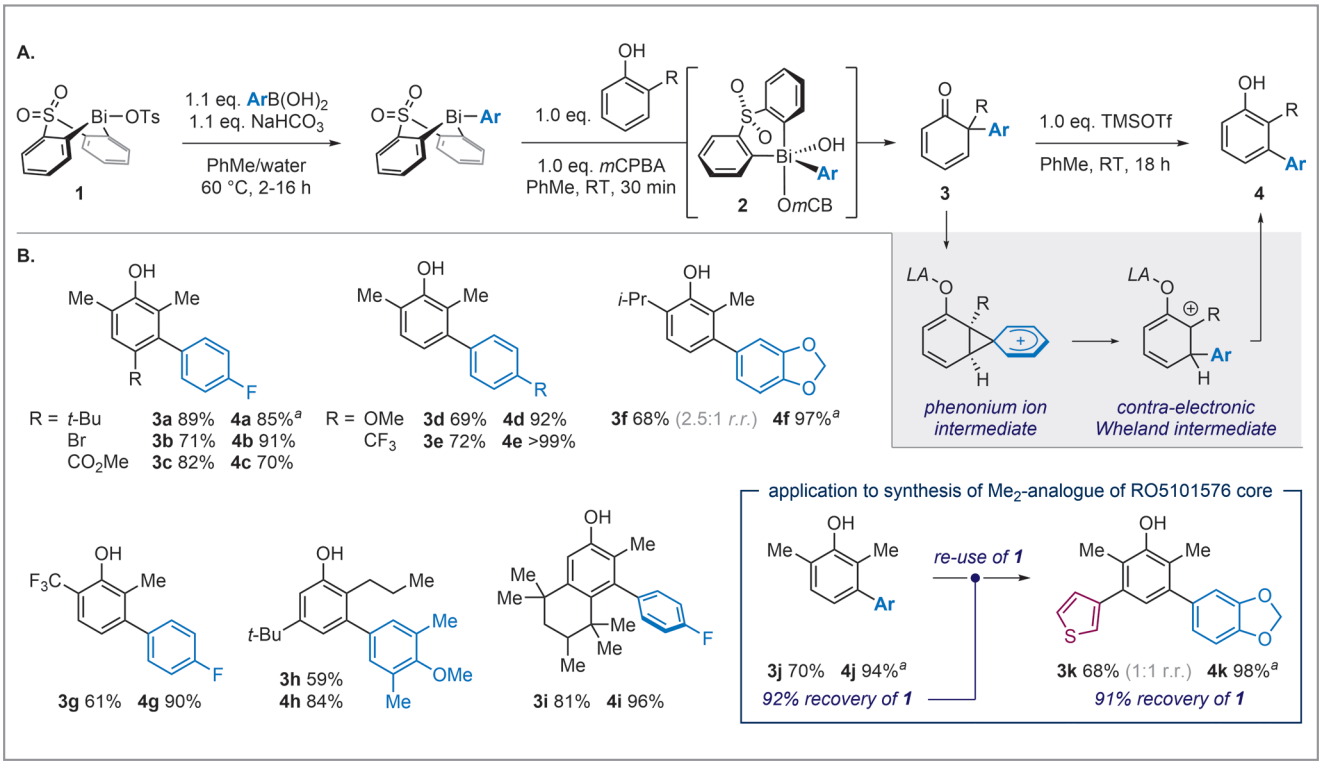

Scheme 2 Selected examples of *meta*-selective C–H arylation via a Bi(V)-mediated arylation/rearrangement sequence. [a] 1,2-Aryl migration performed using $Bi(OTf)_3$ (20 mol%) and NEt_3 (20 mol%) in place of TMSOTf, 60 °C.

process was shown to be compatible with electronically and sterically diverse phenols (**4a–c**) and boronic acids (**4d,e**)," said Dr. Senior. He continued: "Notably, migration occurred smoothly to place the aryl moiety adjacent to even very bulky *tert*-alkyl substituents (*e.g.*, **4a**); in this case, buffered conditions were required to prevent dealkylation via a *retro*-Friedel–Crafts reaction. Non-symmetrical phenols were arylated at the more sterically accessible and more electron-rich *ortho* position (**4f,g**), consistent with the electrophilic nature of the arylation. Substrates with a single *ortho* substituent were also tolerated (**4h,i**), with excellent regioselectivity observed for sterically biased substrates."

A key feature of the methodology is that the bismacyclic reagent 1 can be recovered and re-used. Dr Ball recalled: "Aaron identified the core of RO5101576 as an ideal showcase for the recyclability of the bismacycle [see Scheme 2B, inset]: the same batch of reagent was used in two sequential arylations, with only about 15% of the bismuth being lost over the whole process."

The group used kinetic isotope effects and linear free energy relationships to shed light on the mechanism of the key aryl-migration step. The data were consistent with migration occurring via a phenonium intermediate, in which significant positive charge accumulates on the migrating substituent.

"By combining two known concepts – Bi(V)-mediated arylation and the dienone–phenol rearrangement – we were able to provide a novel solution to a longstanding synthetic challenge," said Dr Ball. He concluded: "The methodology provides a valuable complement to better established approaches to *meta*-selective arylation based on Pd catalysis, and we are excited to continue exploring the opportunities it offers."

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About the authors

Dr. A. Senior

Aaron Senior completed his undergraduate degree at the University of Nottingham (UK) in 2017, which included a Masters project on drug discovery with Dr. Andrew Nortcliffe. He subsequently enrolled in Nottingham's EPSRC Centre of Doctoral Training in Sustainable Chemistry (UK), completing a training year before joining the Ball group in 2018. Aaron completed his PhD in 2022, and is now a Senior Scientist at Pharmaron in Hoddesdon, UK.

Dr. K. Ruffell

Katie Ruffell graduated with an MSc in chemistry from the University of Nottingham (UK) in 2018, following a placement year at GSK Stevenage (UK) and final-year research with Prof. Chris Moody. Her PhD in the Ball group was sponsored by Syngenta, and included a placement at their Jealott's Hill site in 2020. Katie defended her thesis in 2022, and is currently a Senior Scientist at Charles River Laboratories in Saffron Walden, UK.

Dr. L. Ball

Liam Ball obtained his undergraduate degree from the University of Bristol, UK. Following doctoral studies with Dr Chris Russell and Prof. Guy Lloyd-Jones FRS at the University of Bristol (UK, 2009–2013), he moved to the University of Edinburgh, UK, as a postdoctoral researcher with Prof. Guy Lloyd-Jones FRS (2014–2015). In 2015, Liam was appointed Assistant Professor of Organic Chemistry at the University of Nottingham (UK), where he is now an Associate Professor and UKRI Future Leaders Fellow. His research centers on exploiting mechanistic insight in the design and development of new synthetic methods.

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Multicatalysis Protocol Enables Direct and Versatile Enantioselective Reductive Transformations of Secondary Amides

Sci. Adv. **2022**, *8*, eade3431

α-Stereogenic amines are ubiquitous in biologically active natural products, medicinal agents, and agrochemicals (Figure 1). Amides have long been considered as ideal starting materials for the synthesis of functionalized amines, because of their ready availability and high stability. However, the latter property renders the direct conversion of amides into amines challenging, which is particularly true for catalytic asymmetric transformations such as the catalytic, asymmetric reductive alkynylation and reductive alkylation of secondary amides. Indeed, these transformations – according to Professor Pei-Qiang Huang, from Xiamen University (P. R. of China) – remain unconquered.

Professor Huang pointed out to SYNFORM that: "Before addressing the chemistry in the title article, we have engaged in the field of direct transformation of common amides for more than twelve years. In 2010 and 2012, Dr. Kai-Jiong Xiao, one of my former Ph.D. students, developed the first general methods for the reductive bis-alkylation (*Angew. Chem. Int. Ed.* **2010**, *49*, 3037) and reductive mono-alkylation of amides (*tert*-amides: *Chem. Eur. J.* **2010**, *16*, 12792; *sec*-amides: *Angew. Chem. Int. Ed.* **2012**, *51*, 8314) using stoichiometric triflic anhydride as an amide activating agent. In 2016, Dr. Wei Ou, another of my former Ph.D. students, developed the first iridium and copper relay-catalyzed reductive alkynylation of tertiary (*Chem. Commun.* **2016**, *52*, 11967) and secondary amides (*Angew. Chem. Int. Ed.* **2018**, *57*, 11354)." He continued, "After these two steps, it was natural to seek the asymmetric versions of the above-mentioned reactions. In this context, we had obtained some encouraging results (*Org. Lett.* **2019**, *21*, 7587). In particular, we demonstrated recently that the enantioselective reductive cyanation and phosphonylation of secondary amides could be achieved by iridium and chiral thiourea sequential catalysis (*Angew. Chem. Int. Ed.* **2021**, *60*, 8827)."

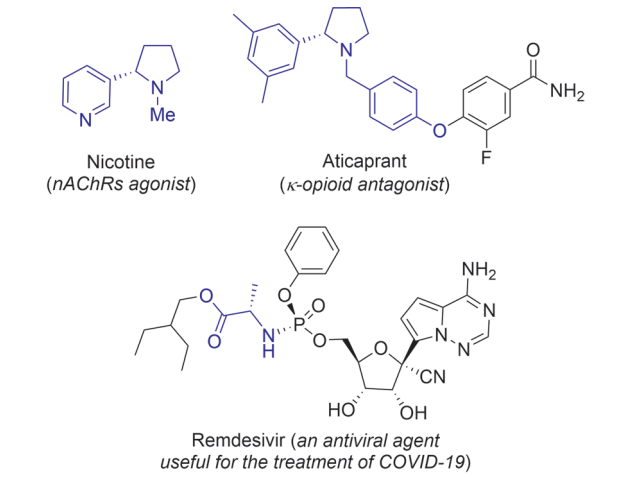
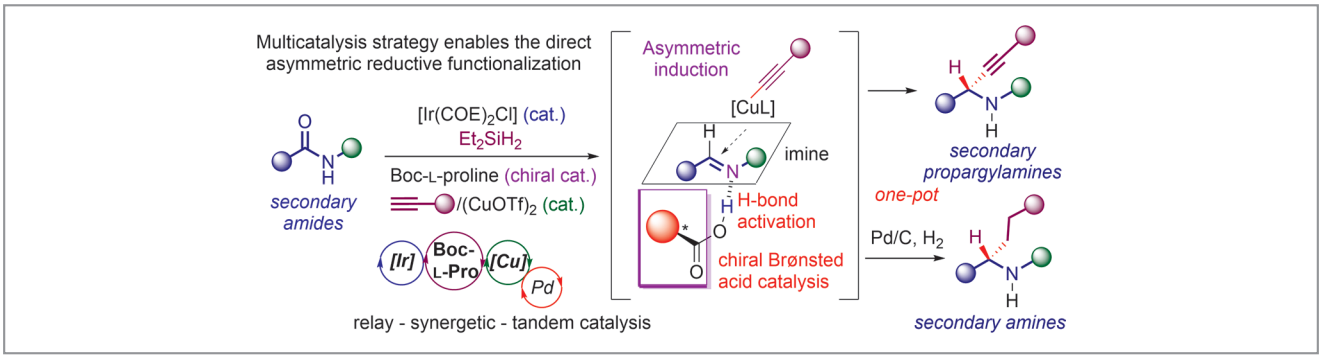


Figure 1 Selected examples of bioactive natural products and medicinal agents featuring an α-chiral amine motif

"Those results inspired me to look for a multi-catalysis system for the enantioselective reductive alkynylation of secondary amides," remarked Dr. Hang Chen, first author of



Scheme 1 The strategy for the direct, catalytic enantioselective deoxygenative alkynylation and alkylation of secondary amides

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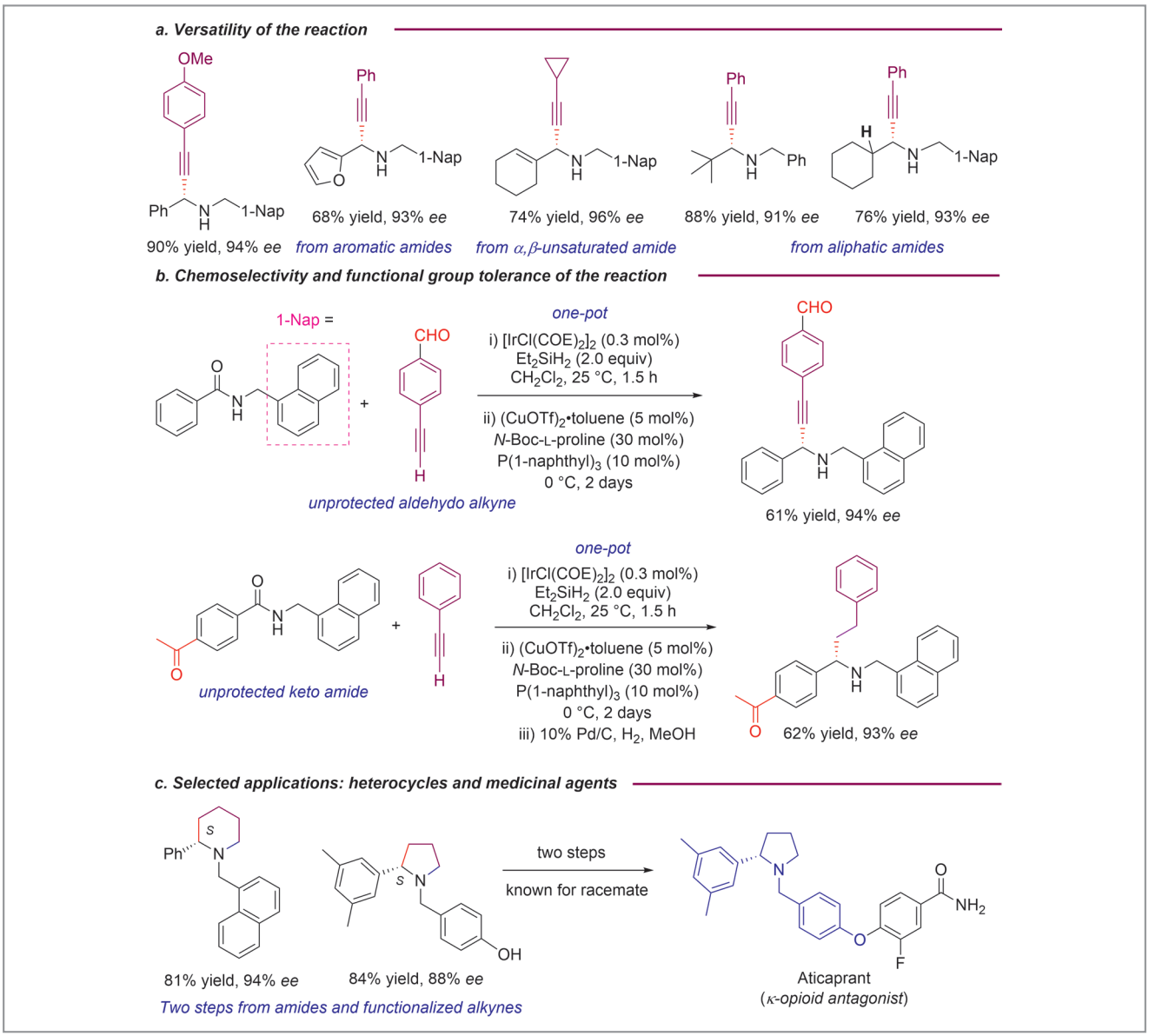
the title article and the Ph.D. student who initiated the project, adding: "The observed significant difference between CuBr and CuOTf in the asymmetric reaction allows us to suggest the asymmetric induction model shown in Scheme 1. Boc-L-proline is an effective Brønsted acid-type organocatalyst to achieve both high enantioselectivity and good yield, which are also influenced by the achiral phosphorus ligands and *N*-protection groups of L-proline."

"The *N*-alkyl group of amides plays an important role in the asymmetric induction," said Zhi-Zhong Wu, Master's student and another first author of the title article. He added: "By further combining the method with Pd/C-catalyzed hydrogenation/hydrogenolysis, we achieved the formal reductive alkylation of secondary amides and thus extended the scope of the reaction, enabling the straightforward catalytic asymmetric synthesis of α-aryl piperidines and α-aryl pyrrolidines, as illustrated by the first asymmetric approach to the medicinal agent aticaprant."

Professor Guo-Qiang Lin at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, an expert of



Scheme 2 Selected examples illustrating the scope and applicability of the method

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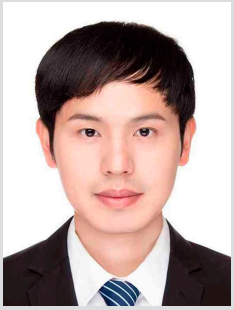
metal catalysis in organic synthesis, commented to SYNFORM that: "The exceptional chemoselectivity and functional group tolerance, allowing the reactions to take place preferentially at the less reactive amide group over the more reactive ester and ketone moieties, and for the use of alkynes bearing ester and unprotected aldehyde groups (Scheme 2) is remarkable, which renders the method promising for applications in the total synthesis of alkaloids and N-containing medicinal agents."

Professor Huang concluded: "Although our method is versatile, the reaction of α-unbranched aliphatic amides gave unsatisfactory results, which prompts us to develop more general methods in the future. It is worth noting that our work was also inspired by recent developments in related fields. We believe that this multi-catalysis strategy will also be applicable to the development of catalytic asymmetric transformations of other carboxylic acid derivatives."

About the authors



Dr. H. Chen

Hang Chen received his B.Sc. from Anhui Normal University and Ph.D. from Xiamen University (P. R. of China), where he worked in the field of methodology development based on the amide transformation under the supervision of Prof. Pei-Qiang Huang and Assoc. Prof. Jian-Liang Ye.

Z-Z Wu

Zhi-Zhong Wu was born in Zhangzhou (P. R. of China) in 1996. He received his Bachelor's (2019) and Master's (2022) degrees from Xiamen University (P. R. of China) under the supervision of Prof. Pei-Qiang Huang, where he worked on catalytic direct transformation of amides.

D-Y Shao

Dong-Yang Shao received his B.Sc. from Wuhan Institute of Technology (P. R. of China). Currently, he is pursuing his Master's degree under the supervision of Prof. Pei-Qiang Huang at Xiamen University (P. R. of China). His current research interests include developing C–C bond formation methods based on amide activation.

Prof. P-Q Huang

Pei-Qiang Huang is a Professor at the College of Chemistry and Chemical Engineering at Xiamen University (P. R. of China). He received his D. E. A. in 1984 from Université de Montpellier II (France) under the direction of Professor B. Castro (INSERM-CNRS). He completed the research work at the Institut de Chimie des Substances Naturelles (ICSN), CNRS under the direction of Professor H.-P. Husson, and received his Ph.D. from the Université de Paris-Sud (Orsay) (France) in 1987. In 1988, he joined Professor W.-S. Zhou's group at the Shanghai Institute of Organic Chemistry (SIOC), CAS (P. R. of China), as a postdoctoral fellow. In 1990, he returned to Xiamen University. The Huang group's research focuses on the development of novel and efficient synthetic methodologies, and the total synthesis of bioactive natural products. He has coauthored several books including 'Efficiency in Natural Product Total Synthesis' (Wiley, 2018) with Z.-J. Yao and R. P. Hsung.

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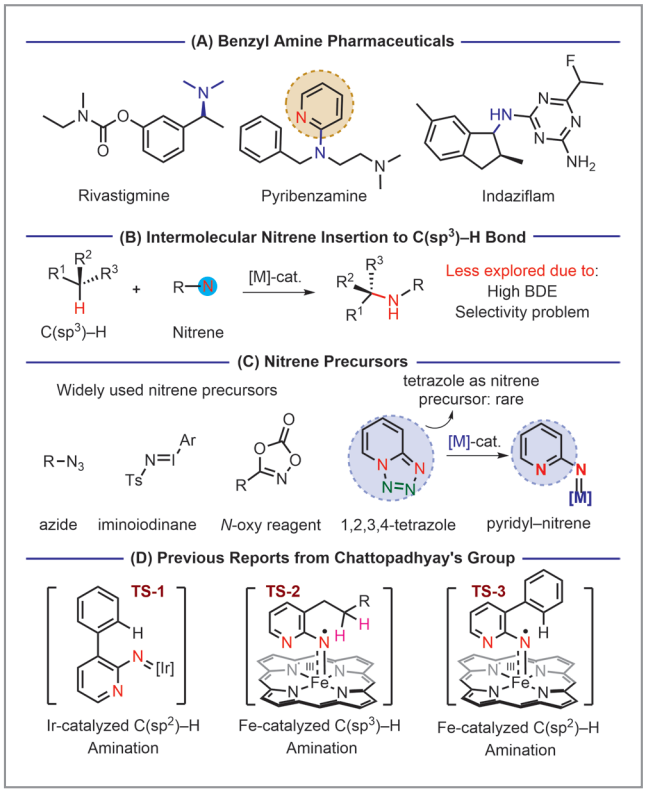
Iron-Catalyzed Intermolecular Amination of Benzylic C(sp^3)–H Bonds

J. Am. Chem. Soc. **2022**, *144*, 21858–21866

Benzyl amines are important motifs in organic chemistry owing to their extensive use in medicinal chemistry, drug discovery and materials science. Professor Buddhadeb Chattopadhyay at the Centre of Biomedical Research (CBMR), Lucknow (India) – whose research group has a strong interest in developing synthetic methods for accessing complex and functionalized benzyl amine frameworks – said: "Many top-selling marketed drugs such as Rivastigmine, Cinacalcet, Tripelennamine, and many more, contain benzyl amine functionalities (Scheme 1, A).[1] While various enzymatic and chemical synthetic methodologies are available for installing an amine functionality, development of a new catalytic process for direct installation of the amine group at a selected C–H bond of an organic molecule remains a vibrant area of research in medicinal and bio-organic chemistry." He added: "Importantly, while the process of C(sp^2)–H bond amination is an established method that has been explored vastly, the amination of aliphatic C(sp^3)–H bonds is much more challenging[2] because of the high bond dissociation energy of the C(sp^3)–H bond, the absence of "active" HOMO or LUMO to interact with the transition metals, as well as problems towards controlling the selectivity (Scheme 1, B). In this context, whereas noble-metal catalysts have received remarkable attention for nitrene transfer reactions, base-metal complexes are relatively less explored for this purpose though they possibly have more efficiency than the noble-metal catalyst."[3]

Professor Chattopadhyay remarked that over the past few years, several efficient C–H amination processes have been developed by employing various nitrene sources, for example, azides,[4] *N*-oxy reagents,[5] and iminoiodinanes (Scheme 1, C).[6] However, the use of 1,2,3,4-tetrazole as nitrene source remained unexplored, although it could be potentially beneficial owing to its additional 2-pyridyl handle for finding new properties related to drug discovery and medicinal chemistry. "In early 1969, Huisgen and Fraunberg studied the reactivity of 1,2,3,4-tetrazole and found that it might be used as a nitrene source for the denitrogenative annulation with nitrile and aryl hydrocarbon amination.[7,8] Moving forward, in 1976 the Wentrup group reported denitrogenative thermal and photochemical nitrene–nitrene rearrangement reactions at very high temperature (>500 °C) under flash vacuum pyrolysis (FVP),"[9] said Professor Chattopadhyay, whose group was inspired by this pioneering work. They had the idea that if they could capture the productive pyridyl metal–nitrene intermediate, it would open numerous opportunities for the discovery of smart technologies that would be extremely welcome in the fields of medicinal chemistry, biochemistry, pharmaceutical chemistry and related areas. Notably, in recent years, Professor Chattopadhyay's group demonstrated that tetrazole can be employed as an effective nitrene precursor[10] for the intramolecular C(sp^2)–H amination via iridium-catalyzed electrocyclization,[11] iron-catalyzed C(sp^3)–H amination and C(sp^2)–H amination via a radical mechanism (Scheme 1, D).[12,13] Professor Chattopadhyay remarked: "After that, we were keen to develop a method for intermolecular amination reaction using tetrazole as nitrene precursor to access 2-pyridyl-substituted benzylamine. In order to establish suitable reaction



Scheme 1 Previous work, challenges and new opportunities

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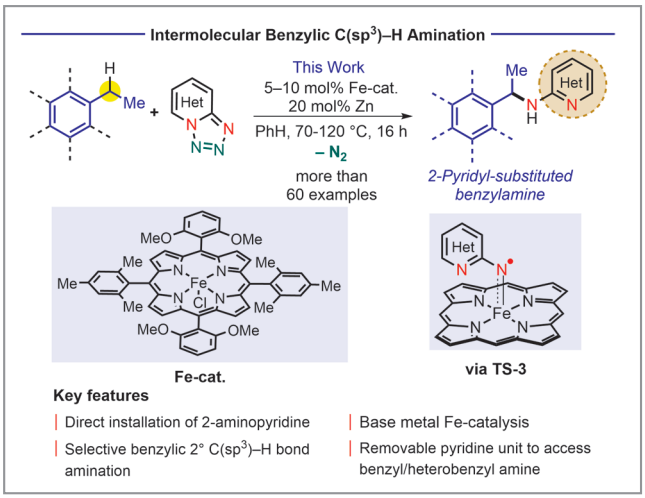
conditions for the C(sp^3)–H amination, we commenced initial studies with simple feedstock ethyl benzene and 5-amide tetrazole, using previously developed conditions. Unfortunately, our previous catalyst systems[11,14] failed for the intermolecular C(sp^3)–H amination, which may be explained by the challenges associated with the difficulty of the intermolecular C(sp^3)–H bond amination."

After screening various catalytic systems, the group found that an iron porphyrin catalytic system containing both electron-donating mesityl and 2,6-dimethoxyphenyl units furnished the expected benzylic amination product in high yield (Scheme 2). Professor Chattopadhyay said: "There are many new findings stemming from this work, such as: i) Intermolecular amination at the more challenging secondary C–H bonds of gaseous hydrocarbons is reported in the literature by utilizing base-metal catalyst systems, such as cobalt or nickel, while intermolecular benzylic C(sp^3)–H amination utilizing 1,2,3,4-tetrazole as a nitrene precursor via iron catalysis is still underdeveloped; in addition, this work differs from many other amination reactions where the nitrogen atom is usually substituted by a protecting group that needs to be removed to allow further elaboration of the products; ii) this method allows for selective amination of the secondary benzylic C(sp^3)–H bond over the weaker tertiary, and sterically accessible primary benzylic C(sp^3)–H bonds; iii) direct installation of 2-aminopyridine into the benzylic and heterobenzylic positions is highly important as this structural motif is found in many bioactive compounds; iv) The reaction conditions are simple and require just 5–10 mol% of the earth-abundant iron catalyst; and v) the scope of the reaction is broad with regards to benzylic substrates and tetrazole precursors."



Scheme 2 Concept of intermolecular C(sp^3)–H amination

Various C(sp^3)–H bonds were assessed for their reactivity (Scheme 3, A). The authors observed that several electronically distinct benzylic C(sp^3)–H bonds underwent intermolecular amination, yielding the aminated products in high yields. Then, the group became interested in submitting pharmaceutically and medicinally important molecules to the C(sp^3)–H amination. "We found that a substrate derived from naproxen (a nonsteroidal anti-inflammatory drug) and estrone (an important metabolite), featuring C–H bonds with different bond dissociation energies, afforded the aminated products with high selectivity and yield," remarked Professor Chattopadhyay. He continued: "Later, the group assessed the scope of various substituted and heterocyclic tetrazoles under the developed amination reaction conditions (Scheme 3, A) and found that the method exhibited excellent effectiveness, delivering the corresponding aminated products in good yields. We also performed several reactions to highlight the synthetic utility of the new intermolecular amination method: i) we synthesized primary amines (Scheme 3, B) from their standard pyridyl amine product; ii) we also synthesized a potential drug molecule Dapoxetine (which inhibits serotonin transport) in good yield from a simple starting material (Scheme 3, C); iii) we performed a large-scale synthesis (3.5 mmol, 62% yield; Scheme 3, D); and iv) we converted the diethyl amide group of the desired product into an important benzyl amine unit in good yield (Scheme 3, E)."

Lastly, to understand the C(sp^3)–H amination reaction, Professor Chattopadhyay and his co-workers proposed a radical mechanism, which is supported by the following mechanistic studies: i) kinetic isotope effect (KIE) experiment (intermolecularly and intramolecularly); ii) radical trapping experiment using TEMPO; and iii) Hammett plot. Based on this body of experimental evidence, the authors proposed the radical mechanism illustrated in Scheme 4. From the KIE value of this amination reaction, Professor Chattopadhyay inferred that C–H bond cleavage might be the rate-limiting step for the intermolecular C(sp^3)–H benzylic amination.

Professor Chattopadhyay summarized his group's work: "We have developed a catalytic system for the intermolecular benzylic C(sp^3)–H amination reaction utilizing 1,2,3,4-tetrazole as nitrene precursors via Fe(II)-based catalysis. This work empowers direct installation of a 2-aminopyridine unit into benzylic and heterobenzylic positions. Moreover, in the literature, we observed that 2-aminopyridine is native to many heterocyclic compounds, but there is a lack of proper focus on it. Furthermore, the 2-aminopyridine alone also exhibits pharmacological activity: crizotinib and lorlatinib are examples of drugs developed by Pfizer to treat non-small cell lung cancer. Cyclometalated complexes with aminopyridines

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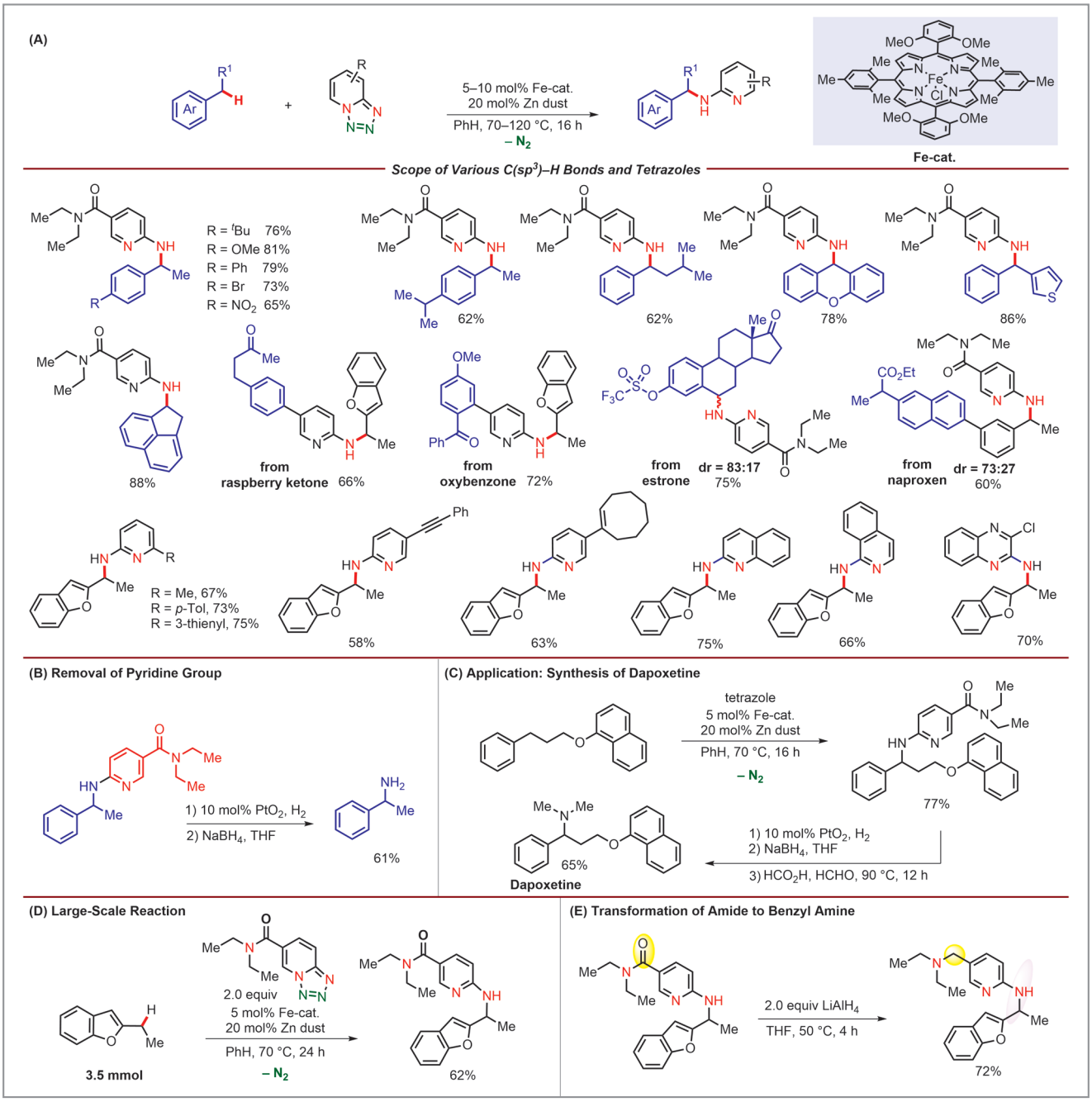

Scheme 3 Intermolecular C(sp³)–H amination and its applications

as ligands also exhibit anticancer activity. These types of moieties highlight the importance of 2-aminopyridine as a bioactive and pharmacological agent."

Professor Chattopadhyay added: "Mechanistic studies revealed that the C(sp³)–H amination proceeds via the formation of a benzylic radical intermediate. This study reports the discovery of a new method for 2-pyridine-substituted benzylamine synthesis using inexpensive, biocompatible base-metal catalysis that should have wide application in the context of medicinal chemistry and drug discovery. In addition, while the denitrogenative transformation of 1,2,3,4-tetrazoles was previously assumed to be not viable, our findings have en-

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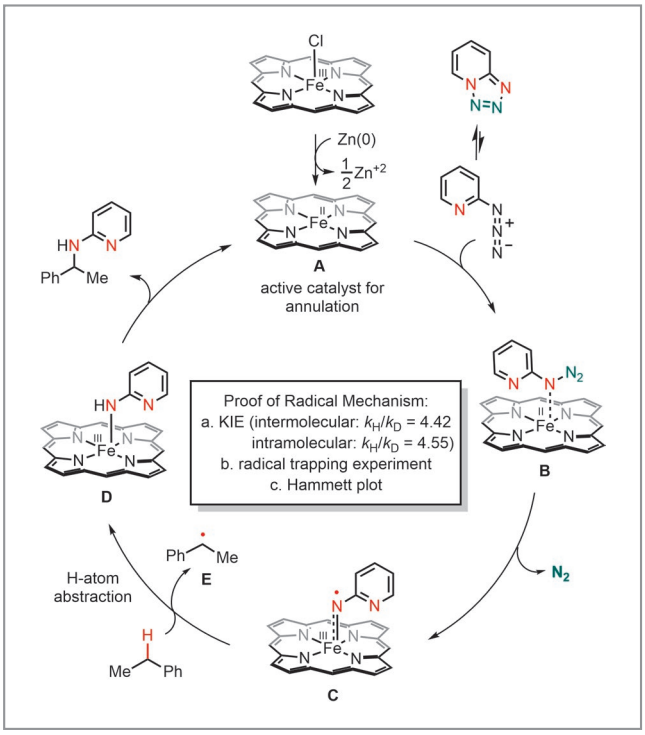

Scheme 4 Radical mechanism for intermolecular C(sp³)–H amination

abled a new area for catalysis research with important implications in organic chemistry." He concluded: "Our future goal will be achieving asymmetric catalysis by developing new chiral catalysts for C–H amination reactions."

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Hillol Khatua was born in West Bengal, India. He received his M.Sc. degree from IIT Bombay (India) in 2017. After that, he joined in the group of Professor Chattopadhyay at the Center of Biomedical Research (CBMR), Lucknow, India in 2017 for his Ph.D. research, focusing mainly on transition-metal-catalyzed denitrogenative annulation and C(sp^3)–H bond amination.

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Dr. S. Roy

Satyajit Roy was born and raised in a small city of West Bengal in India. After completing his Master's degree, he pursued a Ph.D. in the field of transition-metal-catalyzed carbene and nitrene chemistry under the supervision of Professor Chattopadhyay at CBMR. After completing his Ph.D., he moved to the USA where he is currently pursuing postdoctoral studies under the guidance of Professor Rudi Fasan (University of Rochester, NY, USA).

Dr. B. Chattopadhyay

Buddhadeb Chattopadhyay obtained his B.Sc. (2001) in chemistry from Burdwan University and M.Sc. (2003) in chemistry from Visva-Bharati University (India). He completed his Ph.D. in 2009 with Professor K. C. Majumdar. Buddhadeb spent around six years as a postdoctoral research associate at the University of Illinois at Chicago (USA), with Professor Gevorgyan and at Michigan State University, Michigan (USA), with Professor Milton R. Smith, III. In August 2014, he started his independent research career at the Centre of Biomedical Research (CBMR) Lucknow, India as a Ramanujan Fellow. Currently, Dr. Chattopadhyay is an Associate Professor of the same institute. His research interests include metal-catalyzed C–H borylation chemistry (catalyst/ligand engineering) via noncovalent interaction and radical activation chemistry via denitrogenative annulation to get high-valued *N*-heterocycles.

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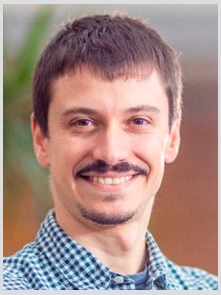
Young Career Focus: Dr. Mattia Silvi (University of Nottingham, UK)

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 Dr. Mattia Silvi (University of Nottingham, UK).

Biographical Sketch



Dr. M. Silvi

Mattia Silvi studied chemistry as undergraduate student at the University Sapienza (Rome, Italy). He then carried out his doctoral studies at the Institute of Chemical Research of Catalonia, ICIQ (Tarragona, Spain) under the supervision of Prof. Paolo Melchiorre, working in the fields of organocatalysis and photochemistry. He also spent part of his PhD at the University of Michigan (Ann Arbor, MI, USA) in the group of Prof. John P. Wolfe working in the field of transition-metal catalysis. After obtaining his PhD in 2015, he moved to the University of Bristol (UK) in the group of Prof. Varinder K. Aggarwal, as a Marie Skłodowska-Curie Individual Fellow, where he carried out research in the fields of boron chemistry, prostanoid synthesis and photochemistry. In 2019, he started his independent career at the University of Nottingham (UK) as a Nottingham Research Fellow. In 2022, he was promoted to tenured assistant professor at the University of Nottingham. Mattia is the recipient of a 2023 Thieme Chemistry Journals Award, a 2022 ERC Starting Grant, a 2020 EPSRC New Investigator Award, and was selected as 2020 outstanding reviewer for the RSC journal Chemical Science. His research interests lie within the fields of organic chemistry, photochemistry and asymmetric catalysis, and these same fields are the focus of his research group's interests.

INTERVIEW

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

Dr. M. Silvi Assembling molecules is a difficult task for scientists. In this regard, organic synthesis often represents a bottleneck in the long process that leads to scientific innovation. Our research focuses on defining new practical and sustainable pathways towards chemical synthesis, thereby extending the strict boundaries that limit chemists' imaginations for the invention of the molecules of tomorrow. We are currently exploring modern tools of organic chemistry, e.g., photoredox catalysis, to develop novel synthetic disconnections and cross-coupling strategies in synthesis.

SYNFORM *When did you get interested in synthesis?*

Dr. M. Silvi During my studies in chemistry, I initially thought I would be more inclined towards analytical chemistry, and I obtained my bachelor's degree in this subject. However, organic synthesis and organic chemistry had such a magnetic effect on me that they quickly steered me towards a different pathway. Indeed, I later obtained both my Master's degree and my PhD in organic chemistry, and since then I have enjoyed assembling organic molecules, solving synthetic puzzles and developing new methodologies. My growth was catalysed substantially by the stimulating research environments in which I carried out my PhD and post-doctoral studies. For this, I am very grateful to my PhD and post-doctoral advisors, Profs. Paolo Melchiorre and Varinder K. Aggarwal, who both inspired me and provided significant support in various steps of my career.

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

Dr. M. Silvi During the last few decades, scientists have developed a remarkable ability to construct organic molecules. The advent of cross-coupling technologies, asymmetric catalysis, and the development of modern tools to tame highly reactive species such as radicals or electronically excited molecules has revolutionised substantially the way we conceive synthetic routes. However, there are open challenges that still need to be addressed. We still heavily rely on the use of non-abundant precious metal catalysts and on reactions with poor atom economy. The advent of C–H functionalisation chemistry has partially tackled these issues, opening new avenues in late-stage functionalisation, but my impression is that much work is still needed to unravel the fundamentals of this chemistry and to control the selectivity in the complex systems that scientists typically face during their real-life applications.

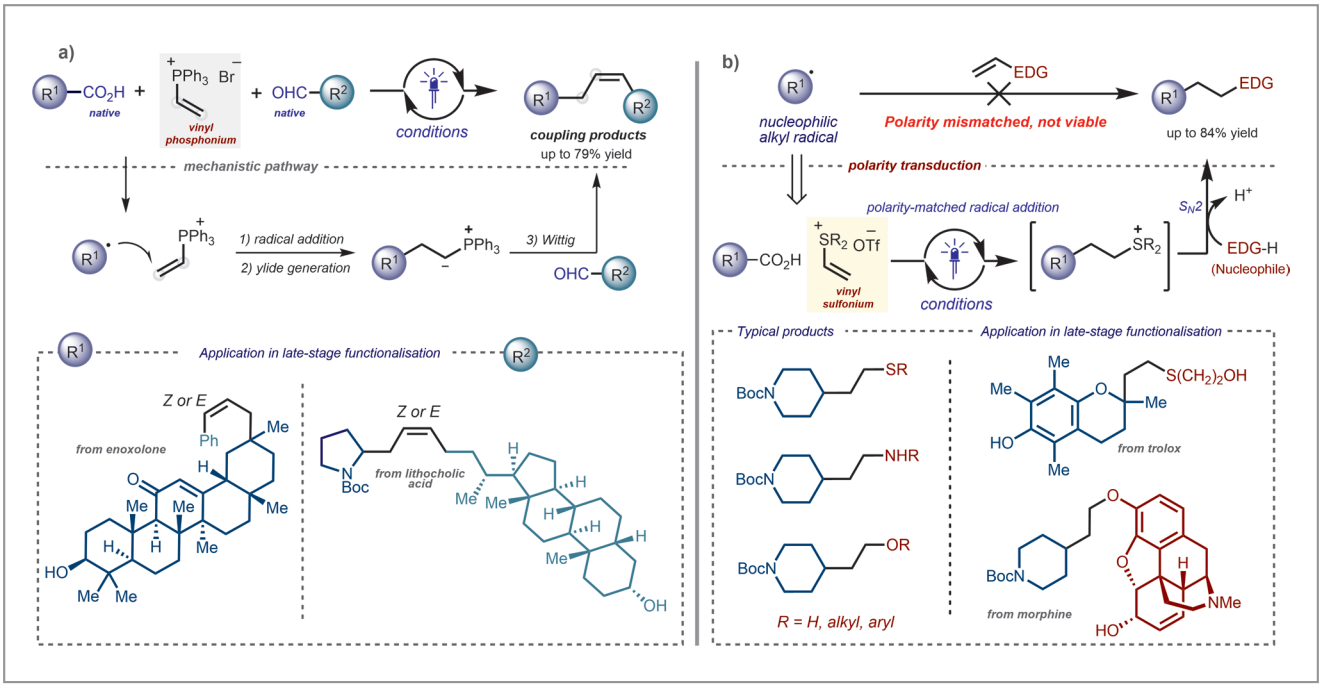
While these are still big challenges, this is a bright moment for organic chemistry. I can't wait to see new adventures in the arena!

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Dr. M. Silvi Currently, our research focuses on the development of novel synthetic methodologies that harness visible light to promote radical reactions. Our ambition is to provide chemists with processes that allow functionalisation of organic molecules in their native form, with high efficiency and selectivity. This means conceiving novel functional-group-tolerant transformations requiring no (or minimal) use of activating group and protecting strategies. We have exciting projects in the pipeline, and in the long term we believe that our research mission will contribute to providing scientists with more sustainable processes, as well as with a versatile synthetic platform for late-stage functionalisation.

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

Dr. M. Silvi Building upon my previous track record in organocatalysis,[1] and radical chemistry,[2] I have recently launched a new research programme in photoredox catalysis. This is a challenging research field for young academics due to the substantial competition with more established research groups. To differentiate our research from others in the area, we chose to investigate the reactivity of unconventional radical traps and harness their potential to address open challenges in organic synthesis.



Scheme 1 Unconventional radical traps explored by Dr. Silvi, and research methodologies developed

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In this regard, we have recently introduced the use of vinyl phosphonium ions in photoredox catalysis, merging radical chemistry with the Wittig reaction (Scheme 1a).[3] The methodology provides an unconventional *conjunctive* coupling strategy for complex sp^3 molecular fragments, forging new C–C bonds using *exclusively native functionalities* in the partners. This was previously considered a challenge for more traditional cross-coupling chemistry and is expected to open new pathways in late-stage functionalisation.

We then introduced vinyl sulfonium ions as novel acceptors in radical conjugate addition chemistry, developing a synthetic strategy that we have termed *polarity transduction* (Scheme 1b).[4] This concept allowed the development of a formal polarity-mismatched radical addition to alkenes, addressing one of the major scope limitations of traditional radical methods.

I believe that having defined such a highly distinctive research line in the very popular field of photocatalysis represents my most significant scientific achievement as an early career researcher. I am grateful to the wide synthetic community for the continuous support and for recognising this achievement through prestigious prizes and awards, including an ERC Starting Grant, an EPSRC New Investigator Award, and a 2023 Thieme Chemistry Journals Award.

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Synform will be published 12 times in 2023 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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