

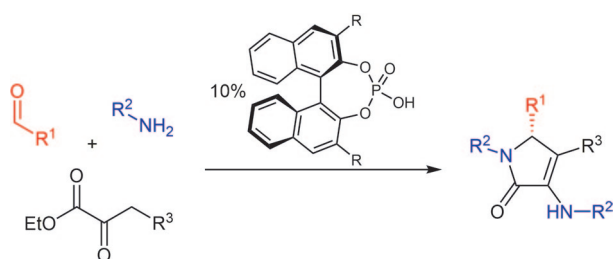
Synform

People, Trends and Views in Chemical Synthesis

2018/06

Brønsted Acid Catalyzed Asymmetric Three-Component Reaction of Amines, Aldehydes and Pyruvate Derivatives: Enantioselective Synthesis of Highly Functionalized γ -Lactam Derivatives

Highlighted article by X. del Corte, A. Maestro, J. Vicario, E. Martinez de Marigorta, F. Palacios



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Dear Readers,

I am delighted to introduce in this June 2018 issue of SYNFORM the first of two interviews to the leading recipients of the SYNTHESIS/SYNLETT Best Paper Awards 2017. The winners of the SYNTHESIS Best Paper Award 2017 are Professor Tõnis Kanger and his co-workers from Tallinn University of Technology (Estonia), with their excellent paper entitled 'Asymmetric Synthesis of 2,3,4-Trisubstituted Piperidines'. In this interview Professor Kanger shares interesting background information regarding the prize-winning article, and discusses current research activities ongoing in his group. The interview follows an article on the recent three-component reaction for synthesizing γ -lactams developed by F. Palacios (Spain) and precedes another Young Career Focus interview with Duncan Brown from Cardiff University (UK). The important task of closing the issue is the capable hands and minds of P.-Q. Huang and X. Lu (P. R. of China) with their novel enantioselective synthesis of vicinal amino alcohols published in *Nature Communications*. I am sure they will not disappoint!

Enjoy your reading!



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

In this issue

Literature Coverage

Brønsted Acid Catalyzed Asymmetric Three-Component Reaction of Amines, Aldehydes and Pyruvate Derivatives: Enantioselective Synthesis of Highly Functionalized γ -Lactam DerivativesA85

SYNTHESIS Highlight

SYNTHESIS Best Paper Award 2017: Asymmetric Synthesis of 2,3,4-Trisubstituted PiperidinesA89

Young Career Focus

Young Career Focus: Dr. Duncan Browne (Cardiff University, UK)A92

Literature Coverage

Dual Catalysis for Enantioselective Convergent Synthesis of Enantiopure Vicinal Amino AlcoholsA96

Coming soon A101

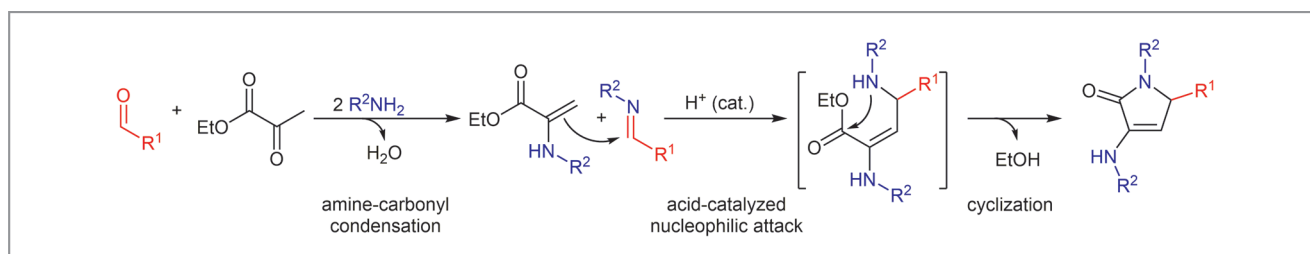
Brønsted Acid Catalyzed Asymmetric Three-Component Reaction of Amines, Aldehydes and Pyruvate Derivatives: Enantioselective Synthesis of Highly Functionalized γ -Lactam Derivatives

Org. Lett. **2018**, *20*, 317–320

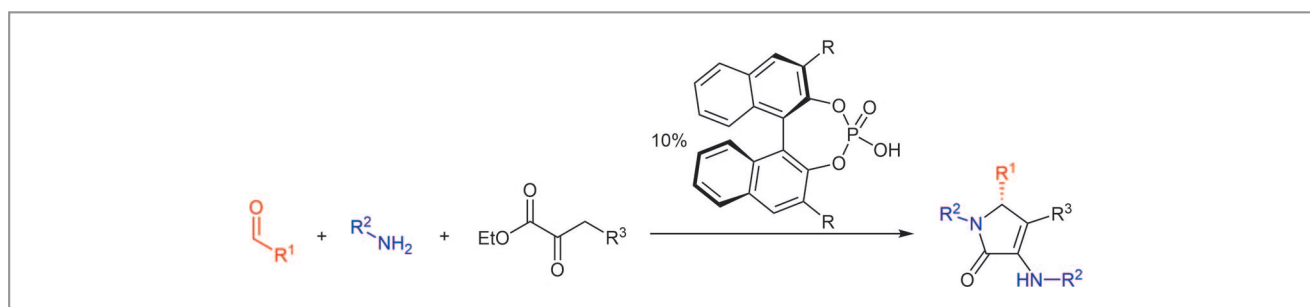
At the heart of diversity-oriented synthesis, multicomponent reactions (MCRs) are valuable synthetic protocols where three or more components react together in a single vessel to afford densely functionalized substrates, where a substantial part of the structure of all the starting materials can be found in the final substrate. Hantzsch dihydropyridine synthesis, Biginelli, Ugi, Passerini, Gröbcke–Blackburn–Bienaymé, Kabachnik–Fields or Strecker reactions are notorious examples of extremely useful MCR protocols. As a contribution to this field, the research group of Professor Francisco Palacios (University of the Basque Country, Vitoria-Gasteiz, Spain) reported a few years ago an acid-catalyzed three component reaction of amines, aldehydes and ethyl pyruvate to afford 3-amino-1,5-dihydro-1*H*-pyrrol-2-ones (*Eur. J. Org. Chem.* **2006**, 2843). “As shown in Scheme 1, this reaction consists of an initial double condensation of amines with aldehydes and ethyl pyruvate, followed by an acid-catalyzed nucleophilic addition of the

resulting enamines to imines with a final intramolecular formation of amide bond, due to the addition of resulting amine to carboxylic group,” explained Professor Palacios. He continued: “The resulting 1,5-dihydro-2*H*-pyrrol-2-ones contain a γ -lactam ring and are the core structures in the skeleton of many bioactive natural products and a wide range of drug candidates that show assorted pharmacological activities.”

Considering the fast development of organocatalysis during recent decades and particularly the Brønsted acid catalyst, the group was intrigued whether the stereocontrolled formation of the C–C bond in their three-component reaction could be achieved if chiral phosphoric acids were used as catalytic species. “Although only a modest enantioselectivity was obtained in the preliminary studies, later on, we were shocked when we discovered that, using diethyl ether as solvent, the enantiomeric excesses were substantially raised,” remarked Professor Palacios.



Scheme 1 Three-component reaction of amines, aldehyde and ethyl pyruvate



Scheme 2 Phosphoric acid catalyzed three component reaction

This remarkable behavior was attributed to the participation of ether molecules in the transition state for the nucleophilic addition process, which may coordinate with the chiral catalyst or even the nucleophile species. Although the enantiomeric excesses were already excellent in diethyl ether, the group tested other ether solvents in order to shed some light on this matter, but no further improvement of the enantioselectivity was observed.

“The optimized experimental conditions were applied to the multicomponent reaction using easily available or commercial starting reagents such as amines, aldehydes and pyruvate derivatives,” said Professor Palacios. Some selected examples are shown in Figure 1. Professor Palacios noted that

regarding the amine substrate, excellent enantiomeric excesses are obtained when weakly activated or deactivated anilines are used as substrates (*p*-toluidine, *p*-bromoaniline, *m*-chloroaniline or *o*-fluoroaniline). “Very good enantioselectivity is also observed when a strongly activated aromatic amine such as *p*-anisidine is used. Regarding the aldehyde component, good enantioselectivities are obtained using the less electrophilic benzaldehyde and good reactivity and enantioselectivity is also achieved using other electron-poor aldehydes such as *p*-trifluoromethylbenzaldehyde,” said Professor Palacios. He continued: “Moreover, although *ortho* substitution is not allowed in the aldehyde substrate, which may be due to steric issues, using *meta*-substituted aromatic aldehydes in the

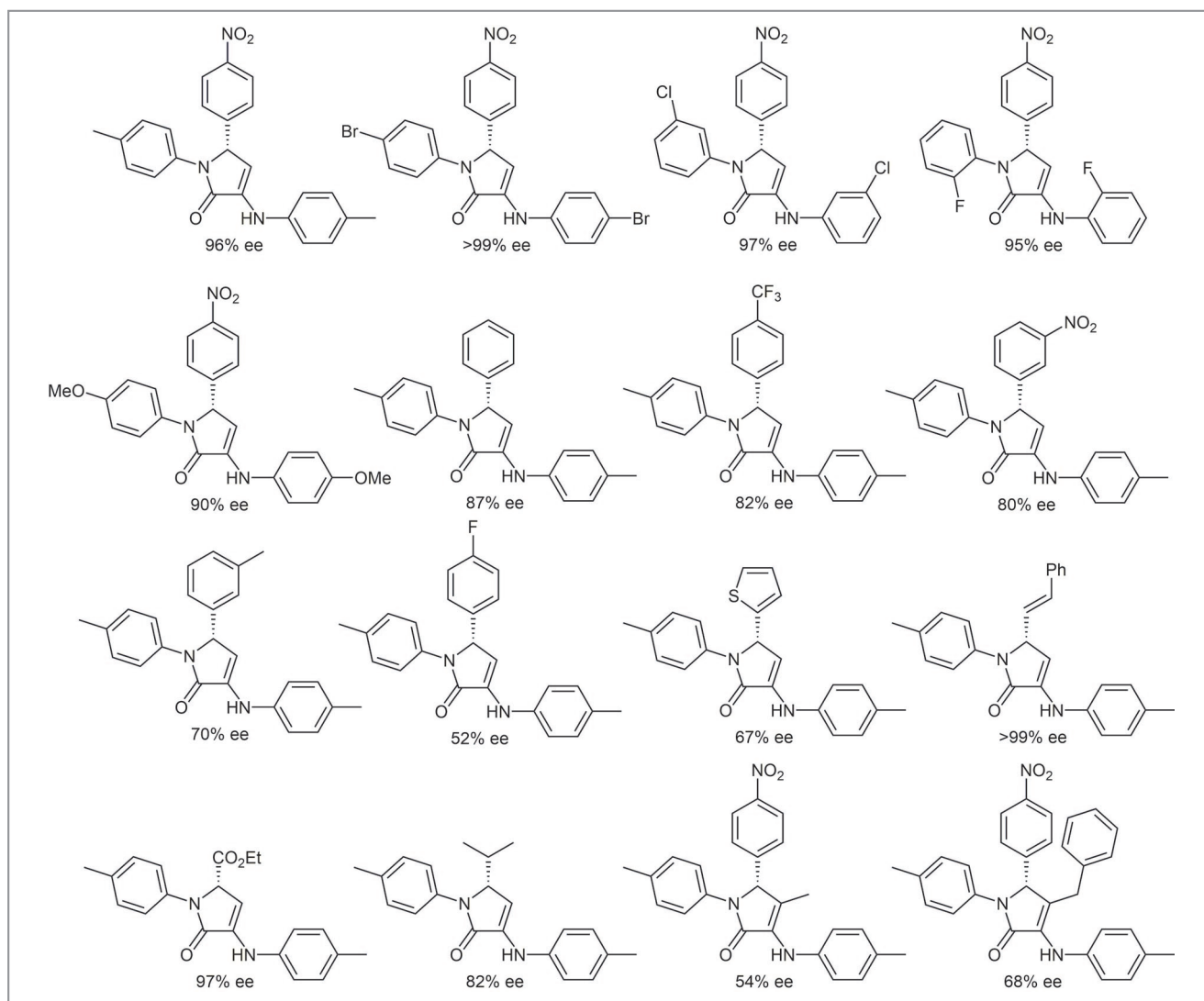


Figure 1 Selected examples for the enantioselective three component reaction

three-component reaction leads to the formation of lactam substrates in good yields." In these cases, while a good ee is observed when *m*-nitrobenzaldehyde is used as substrate, the use of less electrophilic *m*-tolualdehyde requires heating of the reaction, which results in a drop in the ee. "A substantial drop in the ee together with an increase in the reaction time is observed when deactivated *p*-fluorobenzaldehyde is used as substrate. A similar drop in the enantioselectivity, attributed to heating, is observed when heteroaromatic, 2-thiophene-carboxaldehyde is used as electrophile substrate," explained Professor Palacios.

The reaction can also be extended to the use of aliphatic aldehydes as electrophiles, such as cinnamaldehyde or ethyl glyoxalate as well as enolizable aldehydes as *iso*-butyraldehyde, with good to excellent enantioselectivities. Finally, the reaction can be applied to the use of substituted pyruvates as enamine precursors. "However, lower enantioselectivities are obtained, which may possibly be again attributed to the necessity of performing the reaction at higher temperature," Professor Palacios commented.

"In conclusion, this is the first report of a highly enantioselective three-component reaction of pyruvate derivatives, amines and aldehydes to efficiently afford 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones. The enamine chemistry of these lactam substrates is currently under investigation, with special focus on diastereoselective transformations. Moreover, some fluorine- and phosphorus-substituted substrates have been synthesized and the biological activity of racemic and enantiopure substrates is also being investigated," said Professor Palacios.

Mattias Fanch

About the authors



Dr. J. Vicario

Javier Vicario grew up in Imíruri, a small village next to Vitoria-Gasteiz (Basque Autonomous Community, Spain). He graduated in Chemistry in 1998 and then completed his PhD in 2003 under the guidance of Professor Francisco Palacios, at the Faculty of Pharmacy of the University of the Basque Country (Spain), struggling with the chemistry of phosphorylated enamines and hydrazones. Then he joined Ben Feringa's research group at the University of Groningen (The Netherlands), where he completed a two-year postdoctoral period, working mainly in the design of light-driven molecular motors and their attachment to surfaces. In 2006, he moved back to the Faculty of Pharmacy in Vitoria-Gasteiz, where he is currently Associate Researcher in Organic Chemistry. His main research interests include the preparation of new enantiopure amino acid and aminophosphonic acid derivatives, using organocatalytic processes.



Prof. E. Martinez de Marigorta

Edorta Martinez de Marigorta was born in Vitoria-Gasteiz (Basque Autonomous Community, Spain), graduated in Chemistry in 1984 and received his PhD at the University of Basque Country (Spain) under the guidance of Dr. Esther Domínguez on the chemistry of isoquinolines and protoberberines. In 1991–1992 and 1996 he worked with Professor Ian Fleming at the University of Cambridge (UK) on the use of silyl anions in synthesis.

By the end of 1996, he joined the Faculty of Pharmacy and Professor Palacios' group at the University of Basque Country where he is now Associate Professor of Organic Chemistry. His research interests include the chemistry of fluorine- and phosphorus-containing compounds and the preparation of enantioenriched cyclic and acyclic compounds.

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Prof. F. Palacios

Francisco Palacios was born in Vitoria-Gasteiz (Basque Autonomous Community, Spain). He graduated in Chemistry in the University of Zaragoza (Spain) and received his PhD degree in the University of Oviedo (Spain) in 1977 under the supervision of Professor José Barluenga. After two years (1979–1981) of postdoctoral work with Professor Dr. Rolf Huisgen in the Organic Chemistry Institute of the Ludwig Maximilians University (Munich, Germany) working on cycloaddition reactions, he came back to the University of Oviedo as Assistant Professor and became Associate Professor in 1983 at the same University. Since 1991 he has been Full Professor of Organic Chemistry in the University of the Basque Country (Faculty of Pharmacy in Vitoria-Gasteiz, Spain). He has held visiting professorships at the Ecole Nationale Supérieure de Chimie of Montpellier (France) and at the Department of Chemistry of the University of Coimbra (Portugal). His research interests are organic synthesis, organophosphorus chemistry, fluorine chemistry, heterocyclic chemistry, cycloaddition reactions, solid-phase synthesis, design and development of enzyme inhibitors and drug discovery (cancer and neglected tropical diseases).



X. Del Corte

Xabier Del Corte was born and grew up near Bilbao (Basque Autonomous Community, Spain). He graduated in Pharmacy at the University of the Basque Country (Spain) in 2017, with a final degree project related to organocatalytic multicomponent reactions. Currently he is carrying out his PhD thesis in Professor Palacios' research group at the Faculty of Pharmacy of the University of Basque Country in Vitoria-Gasteiz. His current research comprises the development of new organocatalytic processes for the preparation of enantiopure amino acid derivatives.



A. Maestro

Aitor Maestro was born in Vitoria-Gasteiz (Basque Autonomous Community, Spain). He graduated in Chemistry in 2015 and then completed his Master degree in Synthetic Chemistry in 2016 at the University of Basque Country (Spain), working in enantioselective synthesis of aminophosphonates. Then he joined Professor Palacios' research group at the Faculty of Pharmacy of the University of Basque Country in Vitoria-Gasteiz where he is currently carrying out his PhD thesis. His research interests include the synthesis of new amino acid and aminophosphonic acid derivatives and organocatalytic asymmetric processes.

SYNTHESIS Best Paper Award 2017: Asymmetric Synthesis of 2,3,4-Trisubstituted Piperidines

Synthesis 2017, 49, 604–614

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. Tõnis Kanger and his co-workers from the Tallinn University of Technology (Estonia) are the recipients of the SYNTHESIS Best Paper Award 2017. The authors are recognized for their work on the asymmetric synthesis of 2,3,4-trisubstituted piperidines. Paul Knochel, Editor-in-Chief of SYNTHESIS, commented: “The paper describes an asymmetric synthesis of substituted piperidines, which are indeed very important pharmaceutical targets, and this new piperidine synthesis uses two impressive organocatalytic cascades. The selection committee noted not only the scientific value of the paper, but also its presentation. It is a wonderful contribution that we are proud to have published in SYNTHESIS.” SYNFORM spoke with Tõnis Kanger 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



Prof. T. Kanger

Tõnis Kanger received his BSc in 1982 from Tartu University (Estonia) and his PhD in 1990 from the Estonian Academy of Sciences. After postdoctoral studies at the Pierre et Marie Curie University, Paris (France), with Professor Alexandre Alexakis, he returned to Estonia, where he is currently Professor at the Tallinn University of Technology. His research interests are focused on methodology of organic synthesis, asymmetric synthesis and organocatalysis.

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?

Prof. Tõnis Kanger The article deals with the synthesis of substituted piperidines. Piperidine is a very important scaffold in medicinal chemistry, being the third most prevalent ring system in small-molecule drugs. There is a huge range of variety in the biological properties of its derivatives: from the very poisonous coniine isolated from poison hemlock, that was used for the execution of ancient philosopher Socrates, to highly active compounds used in modern medicine. Therefore, it is not surprising that the synthesis of substituted piperidines has been studied thoroughly. It is known that properties of the piperidine derivatives depend on the substitution pattern of the ring. Although the synthesis of fully or densely substituted piperidines is well described, there are few examples of the synthesis of 2,3,4-trisubstituted piperidines. Another important point is stereoselectivity of the substitution. Not only relative stereochemistry but also absolute configuration of the stereocenters is of importance for biological activity. We disclosed a stereoselective method affording 2,3,4-trisubstituted piperidines in high diastereomeric and enantiomeric purities. Obtained derivatives are important intermediates for

the synthesis of various biologically active compounds. Reactive substituents (ester, formyl, or nitro groups) at the piperidine ring can be further converted into other functionalities, adding extra value to the described method.

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

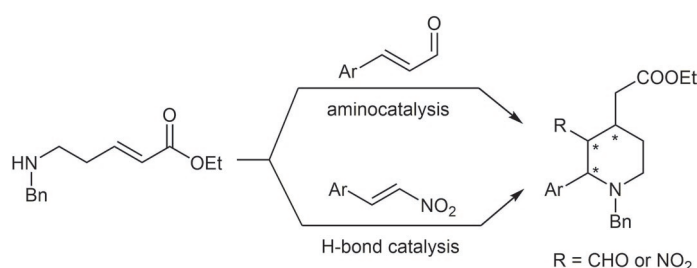
Prof. Tönis Kanger My group has been dealing with asymmetric organocatalysis for several years. The main focus has addressed the efficiency of the reactions. From a synthetic point of view, cascade reactions where several chemical bonds are formed consecutively in one step are the most preferred to increase it. One of the most useful technologies for cascade cyclization reactions is the Michael addition mediated ring closure. To conduct the cascade reaction, multifunctional starting compounds are needed. By choosing a properly substituted Michael donor and acceptor, a variety of cyclic products can be obtained. Planning the first step of the cascade as an aza-Michael reaction provides a platform for the synthesis of heterocycles. We conducted the reaction of *N*-benzyl-5-aminopentenoate with different Michael acceptors (Scheme 1). Depending on the structure of the first Michael acceptor, different activation modes can be used. α,β -Unsaturated carbonyl compounds can be activated via the formation of iminium ions in aminocatalysis, and unsaturated nitro compounds via H-bonding catalysis. In both cases, the first step of the cascade is an aza-Michael addition followed by the second intramolecular conjugated addition. Three stereogenic centers are generated in the course of the reaction. The main goal of our strategy to be addressed was obtaining a single enantiomerically pure stereoisomer. Highly stereodefined reactions must be used for that task. Fortunately, both activation methods are well described in the literature and our experience in this field provided hints for the fast and efficient selection of catalysts.

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

Prof. Tönis Kanger For now, my group is continuously dealing with the problem of efficiency in asymmetric organocatalysis. We have published a triple cascade leading to a pentacyclic product with two quaternary and one tertiary stereocenter in one step in high enantiomeric and diastereomeric purity (*Synthesis* **2018**, *50*, 314). When catalysis is applied in a rearrangement reaction with 100% atom efficiency, it leads to a highly efficient process. We have used this approach for the asymmetric Wittig rearrangement on cyclic and acyclic allyl ethers and these studies are ongoing. Also, we are looking for novel activation methods in catalysis. When a halogen atom is connected to a more electron-withdrawing moiety it becomes electron-deficient, interacting with atoms donating a lone pair. This attractive interaction is called a halogen bond and it is widely exploited in crystal engineering to construct supramolecular complexes and networks. The application of the halogen bond in solution is more challenging. Recently, halogen bond catalysis has received more attention. We have designed and synthesized chiral triazole-based catalysts with easily tunable properties and presently investigate their potential in asymmetric organocatalysis.

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

Prof. Tönis Kanger Synthetic organic chemistry is and will continue to be a cornerstone for the pharmaceutical industry. Organic synthesis is not a solved problem and many challenges concerning selectivity, efficiency and sustainability remain. Although more processes will be automated, synthetic chemists are needed to elaborate novel sustainable methods for selective transformations. We have to learn from Nature.



Scheme 1

It is amazing how efficiently biological machinery works. The development of biomimetic methods and working together with scientists dealing with synthetic biology is one solution to achieve higher efficiency and sustainability in organic synthesis. Today, organic synthesis is a cross-disciplinary research area. Its achievements have impact on materials science, biology, physics, etc. and, on the other hand, these subjects influence the development of organic synthesis. Collaboration and co-operation between universities and industry is essential to facilitate the progress of organic synthesis and tackle scientific challenges.

A handwritten signature in orange ink that reads "Matteo Fanello".

Young Career Focus: Dr. Duncan Browne (Cardiff University, 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. Duncan Browne (Cardiff University, UK).

Biographical Sketch



Dr. D. Browne

Duncan Browne was born in Dunstable (UK). He graduated with an MChem degree in Chemistry with study in industry from the University of Sheffield (UK) during which time he spent one year as an intern at GSK, Stevenage (UK). In 2009, he was awarded a PhD in Organic Synthesis under the supervision of Professor Joseph P. A. Harrity. During this time, he spent 3 months at Syngenta, Jealotts Hill (UK). Following his PhD, he was awarded a one-year Doctoral Prize Fellowship from the EPSRC before moving in 2010 to the ITC and Whiffen Laboratories at the University of Cambridge (UK) as a Post-doctoral Research Associate with Professor Steven V. Ley FRS CBE. There he enjoyed developing new flow chemistry tools, techniques and synthetic methods as well as applying them to industrially relevant processing problems. In 2012, Duncan was appointed as a Fellow in Natural Sciences at Sidney Sussex College (University of Cambridge) and, in 2013, he was made Director of Studies in Natural Sciences. In September 2014, Duncan established his independent research group and became Lecturer in Organic Synthesis & Medicinal Chemistry at Cardiff University (UK). In 2017, he was recognized by both the RSC journals *Green Chemistry* and *Reaction Chemistry and Engineering* as an 'Emerging Investigator' and he was a recipient of a Thieme Chemistry Journals Award.

INTERVIEW

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

Dr. D. Browne My research group is focused on the design and development of new concepts in organic synthesis with specific emphasis on the incorporation of enabling tools and technologies to deliver efficient synthetic processes.

Many of the principles of green chemistry and sustainability can be met by embracing new technologies that are inherently cleaner when compared to the current status quo. By designing new synthetic methods that take full advantage of the capabilities of different enabling technologies, one will end up automatically with greener, cleaner processes. Part of our goal is to explore what the true capabilities of these methods are, both as individual tools and as more complex hybrid designs.

Currently we have a strong focus on mechanochemistry, specifically solvent-free or solvent-minimized processes that take place in high-speed ball mills. We are in search of reactivity or selectivity that is not accessible by other means. Along the way we hope to also gain a better understanding of how reactions can be optimized under these conditions.

SYNFORM *When did you get interested in synthesis?*

Dr. D. Browne I was interested in chemistry from a young age, stimulated by an enthusiastic and encouraging teacher at high-school. I was privileged to have two chemistry teachers at that time. One of my teachers was a former worker at the Ministry of Defense. I remember in one lab practical session we prepared dinitrotoluene! Or at least he led us to believe that's what we were doing; we had to go to a lab at the far end of the science block and work in this strange thing called a fume-cupboard. Looking back, I would like to have seen the NMRs and analytical data for the starting materials and products, as I don't have any evidence that we actually prepared DNT. I remember he stressed that we should keep the reaction very cold to avoid a 3rd nitration reaction leading to TNT; we

were made to neutralize the reaction mixture at low temperature! I enjoyed the excitement of that practical class. It was later on at university, when I spent a year at GSK (Stevenage, UK) and received some encouraging comments (I lacked confidence) about my abilities, that I realized I was capable and really enjoying the subject. My enjoyment still continues today. I like to see a range of chemistry and projects.

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

Dr. D. Browne I think that it is true to say that the breadth of applications of organic chemistry continues to increase and the subject is becoming ever more diverse. Organic chemists

tend to be very creative in their problem solving. The fact that some industrial sectors are shifting (or have already shifted) towards exploring biochemical opportunities has almost certainly caused a spike in creativity in the field; it is a very exciting time. There still exists much excellent work on fundamental synthesis and the design and development of new reactions, but there is also a move towards interdisciplinary applications that align with engineering, sustainability and artificial intelligence. Organic chemists have an excellent ability to keep their science under critical analysis and this helps it to move forward at a rapid pace. Simply look at the rapid growth in photochemistry, electrochemistry and earth-abundant or metal-free catalysis: the capabilities that these methods have delivered already are quite remarkable.



Figure 1

SYNFORM Your research group is active in the area of organic synthesis and new methodology. Could you tell us more about your research and its aims?

Dr. D. Browne Currently we are particularly focused on the area of mechanochemistry. It is becoming more widespread as a technique for molecular synthesis with new mechanochemical reactions being discovered at an increasing frequency. Whilst mechanochemical methods are solvent-free and can therefore lead to improved sustainability metrics, it is more likely that the significant differences between reaction outcomes, reaction selectivities and reduced reaction times will make it a technique of interest to the wider synthetic

community. However, predicting these outcomes *a priori* is a challenge. My research group and I have started out by trying to put together a conceptual framework and understanding of the current state of play of this research area (based on the existing literature) whilst experimentally trying to understand what is required and what the important factors or variables are. My organic chemistry and flow processing training taught me that intuition for reaction optimization comes from a hands-on experience and seeing how product distribution and yields respond to changes in the system. Only then can you get a feeling for the potential phenomena at play. Already we have been on an exciting journey thinking about solid state form, Young's modulus of materials and grinding auxiliaries.

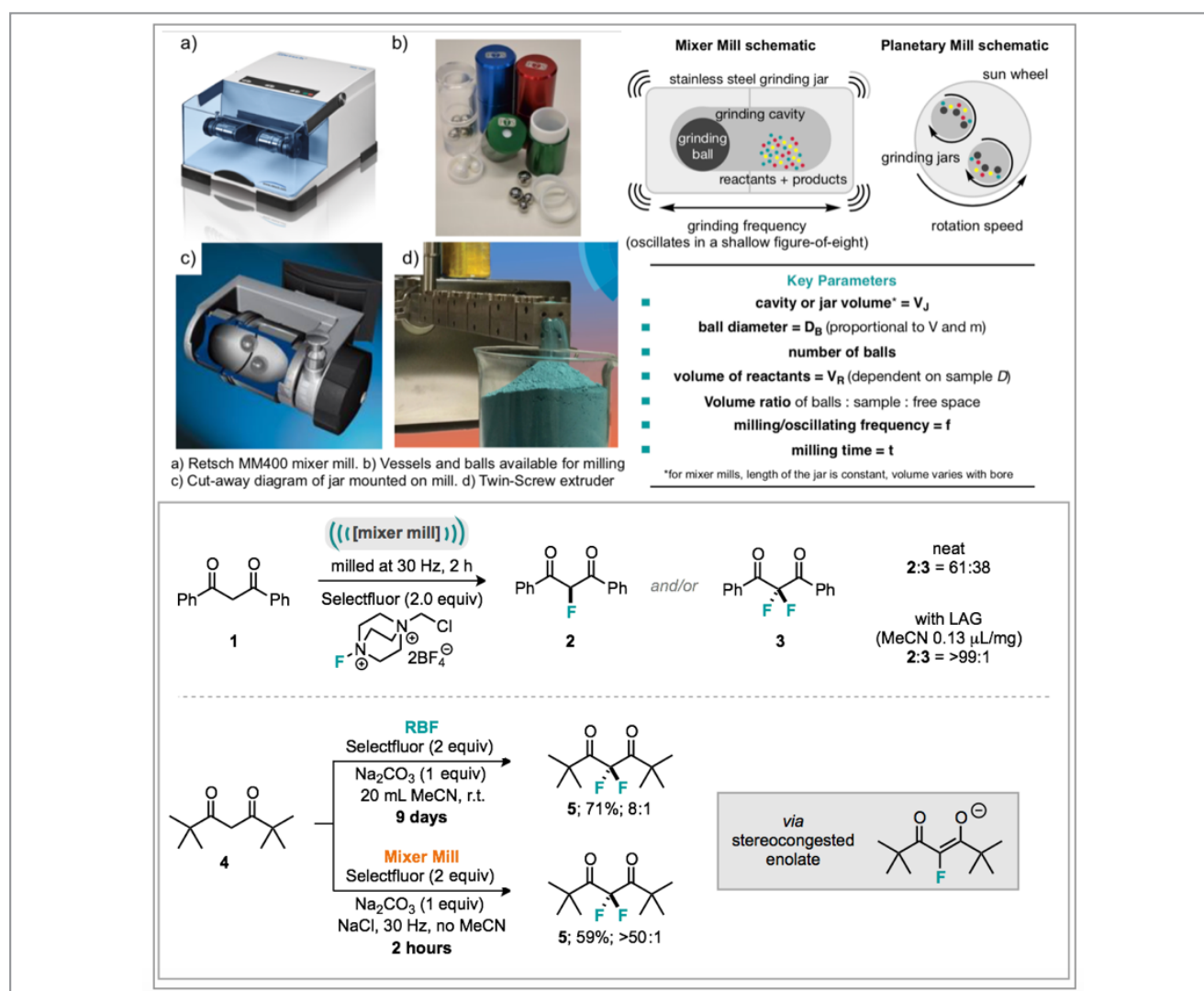


Figure 2

None of which are things I expected or associated with organic chemistry five years ago. It's not to say that organic chemistry has never been conducted using milling devices; it has, and there are many examples. However, the branch of chemistry that has mostly explored the action of milling on product formation is that done by solid-state chemists and those interested in polymorphism, co-crystallization and crystal engineering. We have run several different classes of reactions under milling conditions and have found in at least 50% of cases that there are interesting (unpredictable) outcomes. We aim to get to a point where we understand the process enough to pre-design reactions, reactivity or selectivity only available in the solid state.

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

Dr. D. Browne I take pleasure in the fact that many of the Masters students and visitors that have been part of the research team have gone on to study for PhDs in the UK, Europe and the USA; it pleases me to see them still enthusiastic when they leave! I consider this an important scientific achievement.

Our most exciting lab results are happening right now and are unreported, but have derived from our earlier work on developing an understanding of the technique within the research team. One of our projects started out by simply exploring the mechanochemical fluorination of 1,3-dicarbonyls using Selectfluor. This was initially meant as a prelude or warm-up exercise to the 'real idea', but instead proved interesting at the early stage and developed into its own project (*Green Chem.* **2017**, *19*, 2798). It was observed that upon neat grinding of two equivalents of Selectfluor with dibenzoylmethane, a 61:38 ratio (95% total isolated yield) of monofluorinated to difluorinated dicarbonyls could be isolated. However, upon the addition of acetonitrile (3 equiv or 0.125 mL), the selectivity changed to 100:0 (98% isolated yield) in favor of the monofluorinated product. This was/is a known phenomenon in the area of polymorphism and co-crystallization, that the addition of a liquid can change the outcome of the non-covalently bonded product distribution. The phenomenon is known as Liquid Assisted Grinding (LAG). As an organic chemist, I was skeptical of adding solvent to a reaction that is claimed to be solvent-free! However, the effect is specific to acetonitrile and is real. It appears to slow down the rate of formation of the monofluorinated product, stabilize it once it is reached and prevent it from further fluorination and conversion to the difluorinated product. This observation was explored and held true across a small range of sub-

strates. In this same body of work, we also explored difluorination and noted that the mechanochemical difluorination of 2,2,6,6-tetramethyl-3,5-heptanedione occurred within two hours, whereas the analogous reaction in solvent required nine days to run to completion. I think that this is our most important mechanochemistry work to date. It is one of the first demonstrations that LAG techniques can also have an impact on covalent bond-forming product distributions but it has also served as an inspiration to us to explore this science further.



Dual Catalysis for Enantioselective Convergent Synthesis of Enantiopure Vicinal Amino Alcohols

Nat. Commun. **2018**, *9*, 410

Enantiopure vicinal amino alcohols and derivatives are essential structural motifs in natural products and pharmaceutically active molecules and serve as main stereogenic sources in asymmetric synthesis (Figure 1). Despite numerous efforts devoted to synthesizing these highly valuable compounds, general catalytic enantioselective methods featuring high efficiency and selectivity and, most importantly, broad substrates scopes are still rare, thus representing a challenging endeavor to organic chemists.

Recently, based on a visible-light-induced dual catalytic strategy, a highly effective cross-coupling of nitrones with aromatic aldehydes to give enantiopure vicinal amino alcohols has been demonstrated by Professor Pei-Qiang Huang's group in collaboration with the theoretical group led by Pro-

fessor Xin Lu, both at Xiamen University (P. R. of China). "Our group has long focused on the umpolung construction of carbon-carbon bonds at the *N*- α -carbon and has previously explored two asymmetric methods for preparing enantiopure vicinal amino alcohols from chiral substrates," said Associate Professor Xiao Zheng, who continued: "In these previous works, we developed a SmI_2 -mediated Barbier-type reaction of chiral *N*-Boc *N,S*-acetals with aldehydes/ketones (*Org. Lett.* **2005**, *7*, 553), and a radical cross-coupling of chiral nitrones with aldehydes/ketones (*Org. Biomol. Chem.* **2009**, *7*, 2967) to give the desired enantiopure products (Scheme 1)."

Based on these efficient coupling mechanisms between amine and alcohol moieties, the group further envisioned the exploration of this transformation in a catalytic enantio-

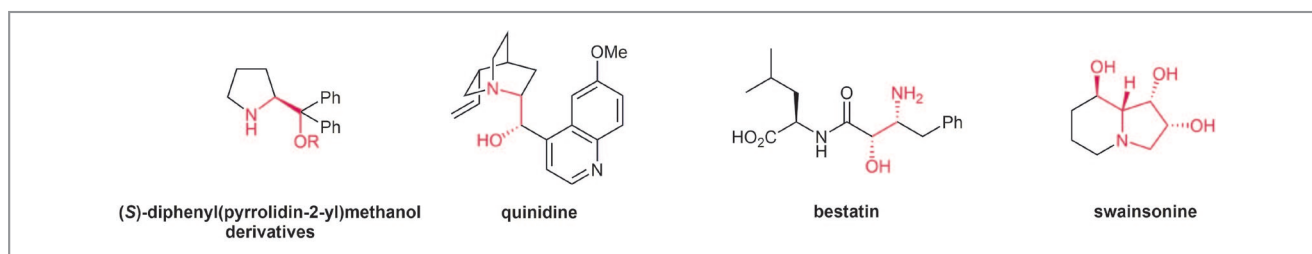
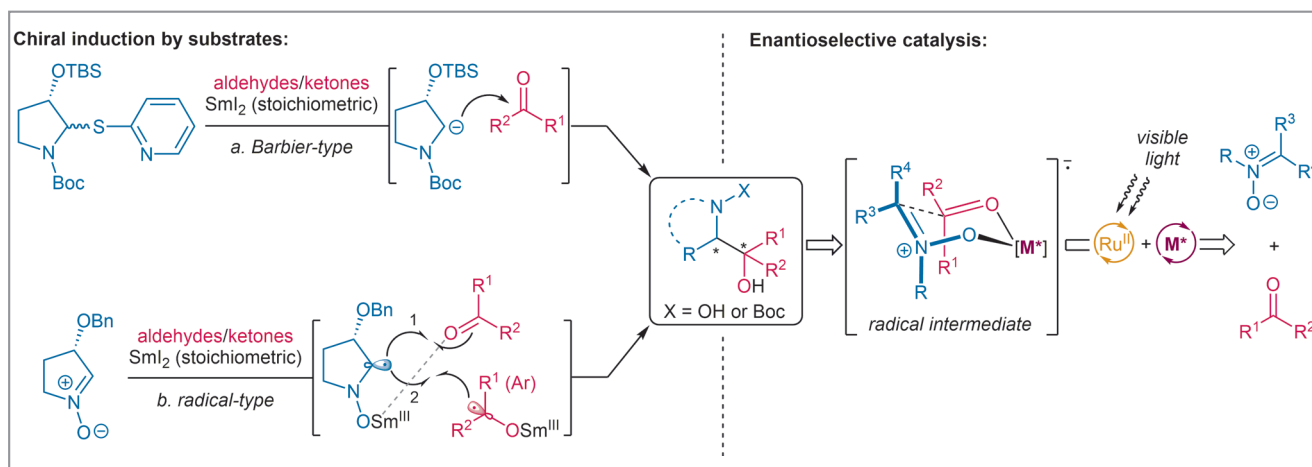


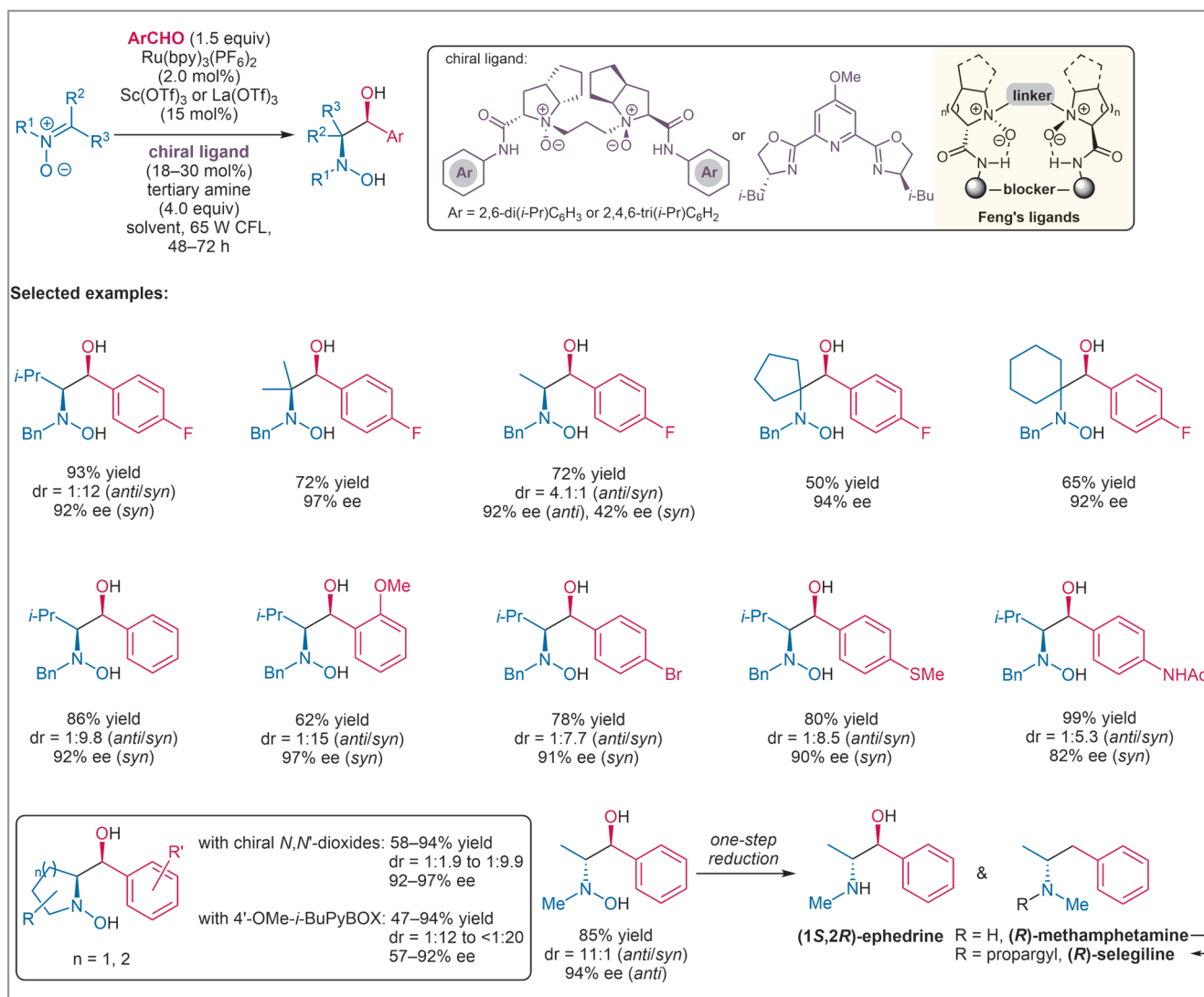
Figure 1 Examples of valuable enantiopure vicinal amino alcohols



Scheme 1 SmI_2 -mediated and catalytic enantioselective design for enantiopure vicinal amino alcohols

selective manner. They decided to prove two interrelated hypotheses: firstly, if an oxophilic chiral Lewis acid could be used to coordinate with nucleophilic oxygen present in the nitrogen-containing substrates and aldehydes/ketones, an enantioselective cross-coupling could be achieved. Secondly, if a catalyzed single-electron transfer (SET) with a low loading of metal could be used to generate α -aminoalkyl radicals or ketyl radicals at low concentration, homocoupling could be inhibited and chiral Lewis acid induced enantioselective cross-coupling would then predominate. If that was the case, a visible-light-induced photocatalytic SET reduction should be the preferred technology, especially considering that the synergistic catalysis of Lewis acid and photocatalyst current-

ly stays at the forefront of modern organic synthesis. "Since samarium ions are Lewis acidic, traditional SmI_2 -promoted radical transformations are obviously unsuitable for enantioselective synthesis, unless stoichiometric amounts of chiral ligands are used," explained Chen-Xi Ye, the graduate student who realized the chemistry. He further commented: "We hypothesized that by using coordinatively saturated photocatalysts in a dual catalytic system, it should be possible to separate Lewis acidity from reducing character, thus enabling flexible stereo-induction via Lewis acid coordinated chiral ligands." With this concept in mind, Chen-Xi Ye began to screen a series of hemiaminals and nitrones, which had been used as substrates to generate α -aminoalkyl radicals in the

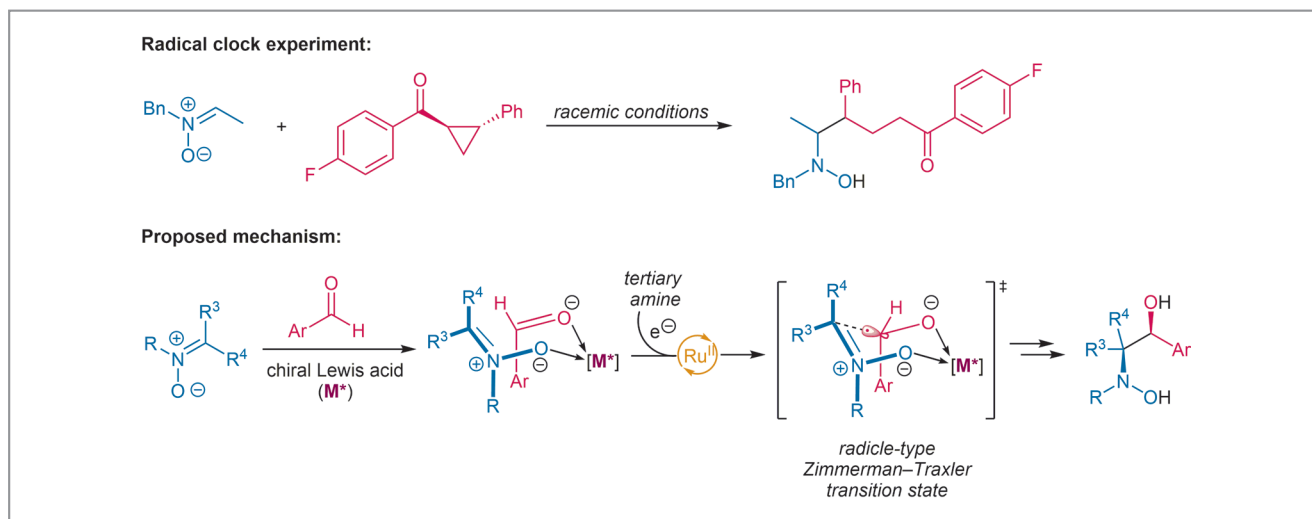


Scheme 2 Selected examples for enantioselective coupling of nitrones and aromatic aldehydes

group's previous works. He subsequently examined a series of photocatalysts/Lewis acids in a novel photocatalytic enantioselective cross-coupling reaction of nitrones and aromatic aldehydes. The optimization of the reaction conditions turned out to be a laborious process, during which $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ with rare-earth ion trifluoromethanesulfonate proved to be an excellent catalytic combination. Even more gratifyingly, chiral ligands such as N,N' -dioxides and PyBOXs were both very effective for chiral induction. Professor Pei-Qiang Huang remarked: "This work represents an important advance in utilizing versatile chiral N,N' -dioxides, which are also known as Feng's ligands (*Acc. Chem. Res.* **2011**, *44*, 574). In fact, this is the first time that Feng's ligands have given a high level of stereoselectivity in a catalytic radical reaction. This should definitely promote the application of such privileged chiral ligands." A number of structurally varied substrates were examined in the dual catalytic system and, for the most part, good to excellent yields and stereoselectivities were obtained. "Although the N,N' -dioxides were potentially reduced under neat reductive photocatalysis conditions, especially in the presence of a Lewis acid, I found that $\text{Sc}(\text{OTf})_3$ -coordinated N,N' -dioxides were stable complexes, which can be used synergistically with $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ to catalyze the enantioselective cross-coupling of many acyclic and cyclic nitrones with aromatic aldehydes efficiently, with high levels of diastereo- and enantioselectivities (Scheme 2)," remarked Chen-Xi Ye. This proved to be a robust technology for the synthesis of enantiopure vicinal N -hydroxyamino alcohols, which could be easily transformed into vicinal amino alcohols or amphetamine derivatives via one-step reduction. Professor Huang

remarked: "Importantly, two pharmaceutically valuable compounds, namely (1*S*,2*R*)-ephedrine and (*R*)-selegiline, were concisely prepared by using our strategy (Scheme 2)."

Professor Xin Lu and his student Yared Yohannes Melcamu conducted in-depth theoretical studies to decipher the reaction mechanism. "With detailed density functional theory (DFT) computational calculations, the starting point and the diastereoselectivity of the reaction could be perfectly unraveled," said Professor Xin Lu, who added: "DFT calculations explained the reason why aliphatic aldehydes were incompatible in this reaction. More importantly, we established a reliable model for predicting the diastereoselectivity of the products by comparing the energies of six-membered-ring transition states." The DFT calculations confirmed that the stereoselectivity of the cross-coupling was induced through a radical-type Zimmerman–Traxler transition state. "Meanwhile, a complex of nitron, aldehyde and Lewis acid was formed favorably at the starting point of the reaction, which led to a more efficient SET reduction by the $\text{Ru}(\text{II})$ photocatalyst, concomitantly inhibiting the homocoupling of both substrates," said Professor Xin Lu. Additionally, an analogous 6-*endo*-trig radical annulation led to a nitroxyl radical-containing intermediate, followed by hydrogen abstraction from $[i\text{-Pr}_2(\text{Et})\text{N}]^+$ to give the chain termination product, which is the desired vicinal hydroxyamino alcohol. "Thus, the role of Hünig's base in this reaction is that of a co-reductant, as well as of an efficient donor for hydrogen and protons. All these results were coherent with experimental studies, thus leading to a convincing mechanistic proposal (Scheme 3)," remarked Professor Lu.



Scheme 3 Mechanistic investigations on the process

Associate Professor Xiao Zheng concluded: "This novel photocatalyst-merged dual-catalytic method features mild conditions, easy operation, broad substrate scope, high yield and stereoselectivity, and has enormous potential for practical use. Based on a deep insight into this reaction, we can accurately predict and understand its stereoselectivity, which will benefit further research and applications of this method. In summary, a concise strategy – which exhibits a high efficiency rivalling those of industrial biosynthetic procedures – has been established to obtain vicinal amino alcohols and amphetamine derivatives. Notably, higher stereoselectivity can be obtained when the temperature of the cross-coupling process is lowered. The synthetic application of this protocol and a significant exploration of photocatalytic generation of α -aminoalkyl radicals from nitrones are still in progress. The latter is expected to lead to more breakthroughs in organic synthesis."

Mattias Farnok

About the authors



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interests cover catalytic radical reaction methods and asymmetric catalysis.

Chen-Xi Ye obtained both his B.Sc. degree (in 2013) and M.Sc. degree (in 2016) from Xiamen University (P. R. of China), where he carried out his research under the supervision of Associate Professor Xiao Zheng and Professor Pei-Qiang Huang. He made up his mind to study abroad, so he is looking for a Ph.D. supervisor. Currently, he works as a research assistant to keep abreast of the advances in chemical synthesis. His research



Y. Y. Melcamu

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Prof. X. Zheng

Xiao Zheng grew up in Xianyou, Fujian Province (P. R. of China). He received his chemistry education at Xiamen University (P. R. of China). After his Ph.D. work with Professor Pei-Qiang Huang, he served as a post-doctoral fellow in the group of Professor Wen-Ge Li of College of Oceanography and Environmental Science of Xiamen University (2003–2005). He joined the faculty of the Department of Pharmaceutical Science of Xiamen University as an Associate Professor in 2005. He served as a research staff in the group of Teck-Peng Loh at the School of Physical and Mathematical Sciences of Nanyang Technological University (Singapore) from 2008–2009. He returned to Xiamen University and joined the faculty of the Department of Chemistry in 2009. His research interests include radical reaction methods and their application for natural product and pharmaceutical relevant molecule synthesis.

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Pei-Qiang Huang was born and grew up in Fujian Province (P. R. of China). He obtained his B.Sc. (1982) from Xiamen University (P. R. of China) and D.E.A. (1984) from the Université de Montpellier II (France) under the direction of Professor B. Castro (INSERM-CNRS). After accomplishing the research work at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette, France) under the supervision of Professor H.-P. Husson, he received his Ph.D. from the Université de Paris-Sud (Orsay, France) in 1987. He served as a postdoctoral fellow in the group of Professor W.-S. Zhou at Shanghai Institute of Organic Chemistry (P. R. of China) from 1988–1990. He was appointed as an Associate Professor at Xiamen University in 1990, and was promoted to Full Professor in 1993. Professor Huang's research team is interested in new synthetic methodologies, total synthesis of natural products, and chemical biology.

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