

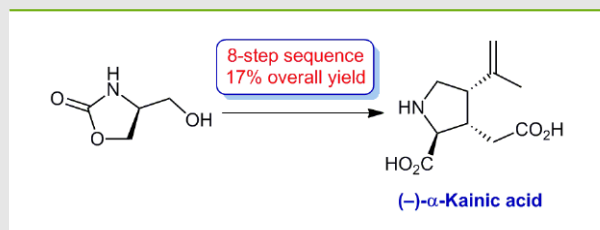
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/06

## SYNSTORIES

■ **Diastereoselective Rhodium-Catalyzed Ene-Cycloisomerization Reactions of Alkenylidenecyclopropanes: Total Synthesis of (-)- $\alpha$ -Kainic Acid**



■ **Ruthenium-Catalyzed C–H Bond Arylations of Arenes Bearing Removable Directing Groups via Six-Membered Ruthenacycles**

■ **Young Career Focus:  
Dr. Paul Davies (University of Birmingham, UK)**

**CONTACT +++++**

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**Dear readers,**

Would you submit your next, very important paper to a low(ish) impact factor (IF) journal? Probably not. What if you are invited to contribute an article for a special issue of a rather low IF journal honoring an eminent

colleague, or a friend? Sometimes it happens, as we all know. Well, a friend is a friend, and an eminent colleague who is retiring or celebrating his 70th birthday deserves something special. Not to mention the bad feeling of submitting on such a special occasion not-so-important data which have been waiting for ages in a drawer. On the other hand, the student who has been working hard for two years on that important piece of research needs a high IF publication for getting a prestigious postdoctoral position. What a struggle! What should I do now? Wait a minute, I just got an idea... a review! Yes, a small review summarizing (once again) the work my group has been doing in the last few years. A review is always good, it normally gets more citations than a research article, so journals very much like reviews, highlights, summaries, whatever may lead to an even negligible increase of that devilish number called Impact Factor. So, let's go for a small review, my student will get an extra publication without spending too much time and effort, the issue's guest editor will be quite happy and I will save my next big paper for a high IF journal. Is it just me, or the situation above is all but uncommon? Have you ever had the same thoughts in a similar situation? Could you let me know, please? Knowing I am not the only one would make me feel much better... although I already know that after this editorial nobody will ever invite me anymore for a special issue!!!

This issue of **SYNFORM** is also special, as it features three articles packed full of outstanding science. The first **SYNSTORY** covers a new ruthenium-catalyzed arylation developed by Professor L. Ackermann (Germany). The second one leads us through a novel synthesis of the neuroexcitatory (–)- $\alpha$ -kainic acid relying on a rhodium-catalyzed cycloisomerization reaction discovered by Professor P. A. Evans (UK). Last but not least, a Young Career Profile that allows us to know more about an up-and-coming young researcher working in the area of catalysis and organic synthesis: Dr. P. Davies (UK).

Enjoy your reading!

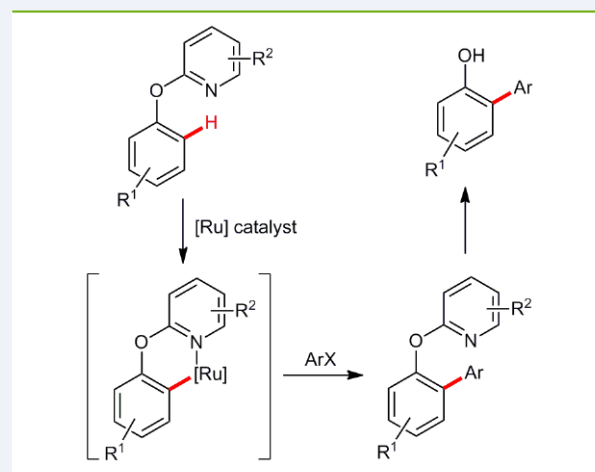
**Matteo Zanda**

Editor of **SYNFORM**

## IN THIS ISSUE

### SYNSTORIES ■ ■ ■ ■

**Ruthenium-Catalyzed C–H Bond Arylations of Arenes Bearing Removable Directing Groups via Six-Membered Ruthenacycles..... A53**



**Diastereoselective Rhodium-Catalyzed Ene-Cycloisomerization Reactions of Alkenylidenecyclopropanes: Total Synthesis of (–)- $\alpha$ -Kainic Acid ..... A56**

**Young Career Focus: Dr. Paul Davies (University of Birmingham, UK)..... A59**

**COMING SOON ..... A62**

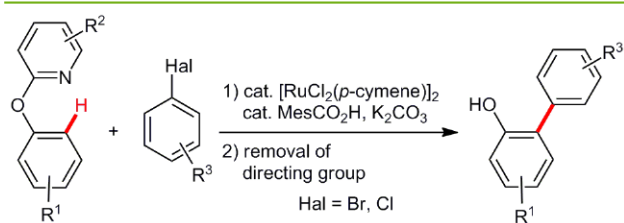
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NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

## Ruthenium-Catalyzed C–H Bond Arylations of Arenes Bearing Removable Directing Groups via Six-Membered Ruthenacycles

*Org. Lett.* **2012**, *14*, 1154–1157



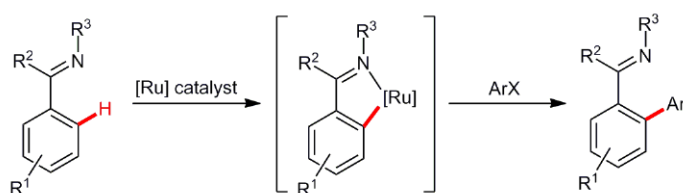
**Scheme 1**

Palladium-catalyzed arylation reactions for the synthesis of biaryls have been well established during the past four decades. In contrast, the corresponding ruthenium-catalyzed transformations are very rare. In recent years, ruthenium catalysts have, however, proven to be valuable tools for sustainable C–H bond arylation, with very recent applications to step-economical syntheses of bioactive compounds in both academia and industry. Despite this considerable recent progress in ruthenium-

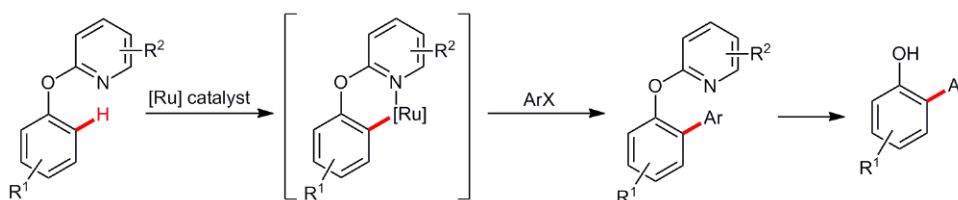
catalyzed C–H bond arylation with aryl halides, all of these methods continued to lack generality. As a direct consequence, ruthenium-catalyzed direct arylation with organic electrophiles as arylation reagents were unfortunately not possible with arenes bearing removable directing groups. Recently, the group of Professor Lutz Ackermann from the Georg-August-Universität, Göttingen (Germany) introduced carboxylates as co-catalysts for widely applicable ruthenium(II)-catalyzed direct arylation in various solvents. More recently, the same group reported an exciting development of this cross-coupling methodology consisting of the direct arylation or arenes bearing a removable pyridyl directing group (Scheme 1).

The breakthrough was largely due to clever mechanistic considerations that overcame the previous limitations (for references see the original paper) arising from the use of substrates, such as aryl imines, forming five-membered ruthenacycles (Scheme 2). “Based on this mechanistic insight, we were able to devise the first ruthenium-catalyzed direct arylation-

*Previous work:*



*This work: six-membered ruthenacycle, removable directing group*



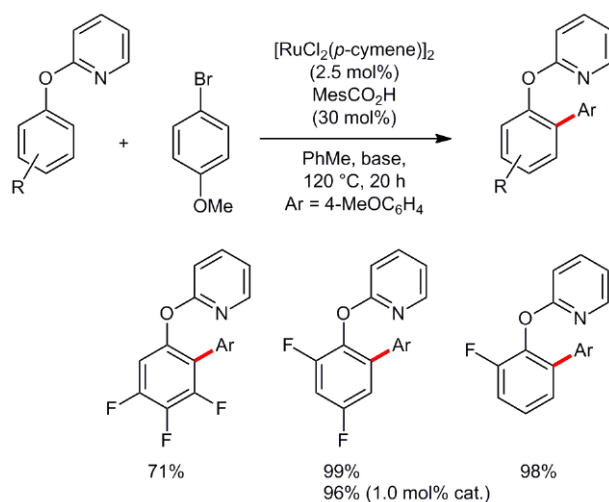
**Scheme 2** The synthetic strategy

tions of arenes via six-membered ruthenacycles that set the stage for a removable directing group strategy," said Professor Ackermann.

The ruthenium-catalyzed cross-couplings occurred efficiently with aryl bromides, as exemplified in the case of *p*-bromoanisole (Scheme 3).

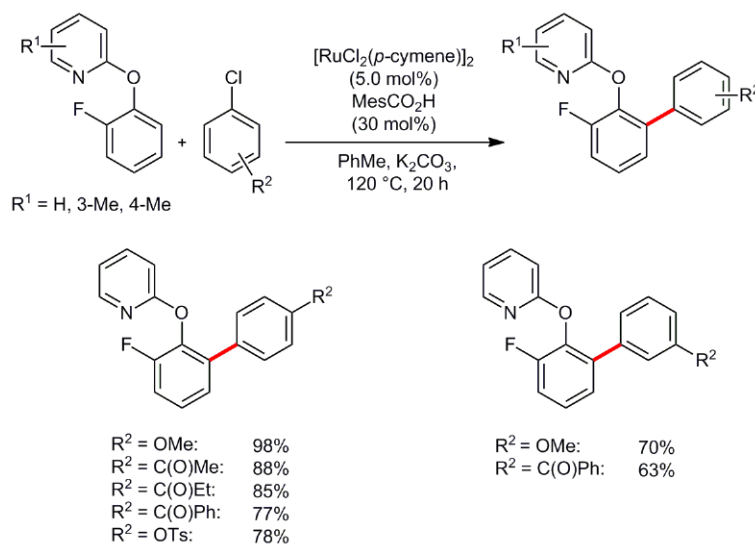
Remarkably, the method also worked well with cheaper aryl chlorides, demonstrating a rather broad scope (Scheme 4).

Professor Ackermann is confident that this methodology will be further validated, becoming a new useful tool in the arsenal of organic reactions. "We expect these findings to stimulate further developments in ruthenium-catalyzed C–H bond functionalizations and to foster applications of direct arylations in, among others, pharmaceutical and agrochemical industries," he concluded.



Matteo Zanda

Scheme 3 Direct arylation with aryl bromides



Scheme 4 C–H Bond arylation with aryl chlorides

*About the authors*

From left: Prof. L. Ackermann, E. Diers



A. Manvar

# Diastereoselective Rhodium-Catalyzed Ene-Cycloisomerization Reactions of Alkenylidenecyclopropanes: Total Synthesis of (–)- $\alpha$ -Kainic Acid

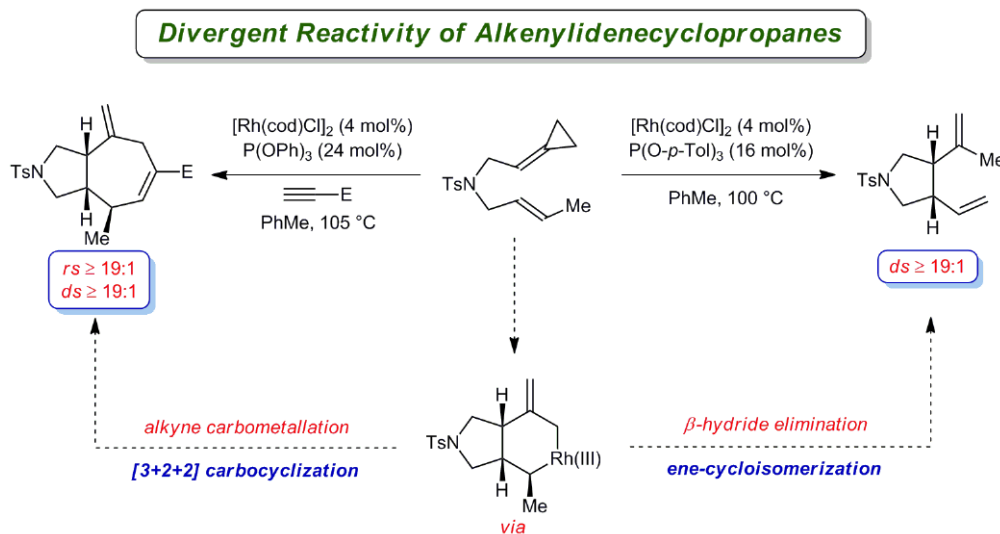
*J. Am. Chem. Soc.* **2012**, *134*, 3635–3638

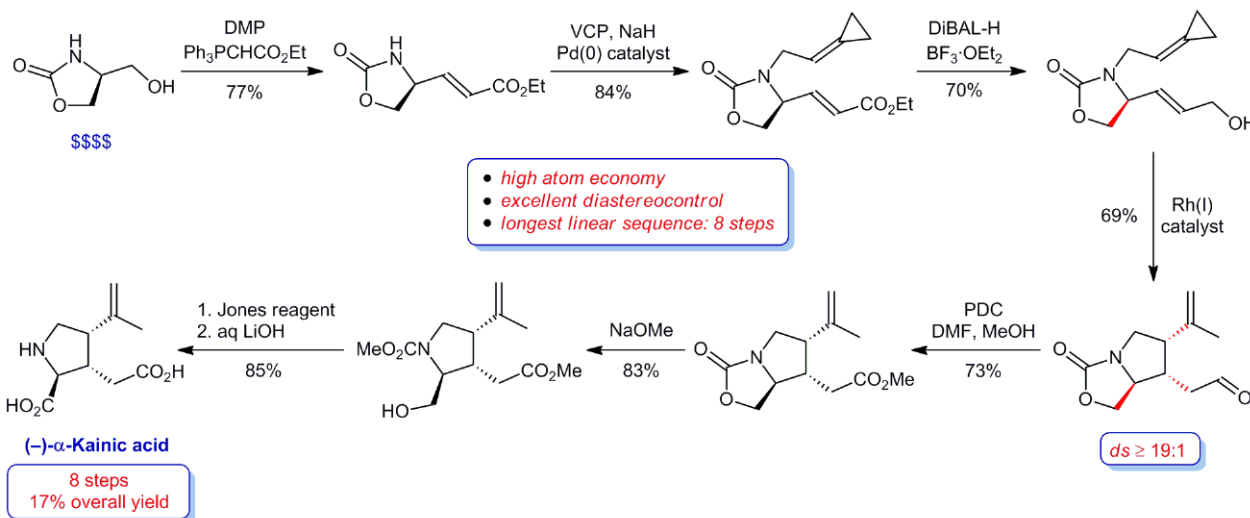
The development of novel reactions that can be readily used for the synthesis of important natural and/or bioactive organic molecules is an extremely timely and competitive area of research that involves many top researchers worldwide. Recently, Professor P. Andrew Evans, who is an Editorial Board member of Thieme's chemistry journal **SYNTHESIS**, and Dr. Phillip A. Inglesby from the University of Liverpool (UK) published an elegant and efficient new rhodium-catalyzed ene-cycloisomerization reaction whose synthetic usefulness was demonstrated in the concise total synthesis of (–)- $\alpha$ -kainic acid, an important neuro-excitatory molecule, which is of current primary interest in neuroscience and drug discovery.

“Our group has been interested in the development of metal-catalyzed higher-order carbocyclization reactions for over a decade,” stated Professor Evans. “We recently published a tutorial review on the highlights of some of the more important developments in this area (*Chem. Soc. Rev.* **2010**, *39*, 2791), which we truly believe have great synthetic potential for the construction of complex molecular architectures embedded in pharmacologically active agents,” he continued. Professor Evans explained that his group has recently become

interested in the reactivity of alkenylidenecyclopropanes (ACPs), which led to the development of a rhodium-catalyzed [(3+2)+2] carbocyclization reaction (*J. Am. Chem. Soc.* **2008**, *130*, 12838). An interesting feature about this work, according to Evans, “is that the carbocyclization proceeds via a metallacyclohexene intermediate, which provides further opportunities to develop new cyclization reactions. This intermediate is rather intriguing since it does not undergo competitive reductive elimination, a process that is extremely facile with palladium,” said Professor Evans. “This observation prompted us to develop the ene-cycloisomerization reaction since we envisioned the pendant alkyl substituent would facilitate  $\beta$ -hydride elimination in the absence of a  $\pi$ -component to generate highly functionalized five-membered rings,” he continued.

Professor Evans noted that “Despite the plethora of ene-cycloisomerization reactions, many of the examples generate five-membered rings with the formation of a single stereogenic center, whereas the use of ACPs generates two new stereogenic centers in a completely diastereoselective manner from what is formally a diene,” which, according to Dr. Inglesby,



Total Synthesis of (-)- $\alpha$ -Kainic Acid

“greatly enhances the synthetic utility of this process, since the geometry of the alkene does not have to be predefined as is the case in related transformations.” Dr. Inglesby also noted that “We recognized early on in the project that we may be able to contribute to the search for an efficient, reliable and practical synthesis of (-)- $\alpha$ -kainic acid, which is an extremely valuable tool for neuroscientific research, since the ene-cycloisomerization adducts closely resemble the core of the natural product.”

Professor Evans stated that “Although I was somewhat skeptical at first due to the number of successful total syntheses of this agent by a ‘who’s who’ list of world-class synthetic chemists, I believe we have successfully accomplished a very nice total synthesis that beautifully demonstrates the synthetic utility of the ene-cycloisomerization reaction.” Dr. Inglesby noted that “The initial stages of the synthesis proved challenging due to considerable epimerization of the enantioenriched stereocenter.” Ironically, this problem was easily avoided by simply changing the order of events, namely a one-pot oxidation/olefination followed by installation of the ACP to facilitate the rapid assembly of the precursor for the key ene-cycloisomerization reaction. “The installation of the *anti,syn*-stereotriad was also not straightforward and required considerable optimization,” according to Dr. Inglesby. “Nevertheless, we certainly feel that this strategy provides a scalable, practical and atom-economical synthesis of this important agent, with only the loss of methanol, ethanol and carbon dioxide,” concluded Dr. Inglesby. ■

## About the authors



From left: Dr. P. A. Inglesby, Prof. P. A. Evans

**P. Andrew Evans** was born in Llangollen (Wales) in 1964. He received his PhD at the University of Cambridge (UK) in 1991 under the supervision of Professor Andrew B. Holmes, FRS, and then completed a NATO postdoctoral fellowship under the direction of Professor Philip D. Magnus, FRS, at the University of Texas at Austin (USA). In 1993, he joined the faculty in the Department of Chemistry and Biochemistry at the University of Delaware, Newark (USA) as an Assistant Professor and was rapidly promoted through the ranks to Professor before moving to the Department of Chemistry at Indiana University, Bloomington (USA) in 2001. In 2006, he

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Matteo Zanda

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moved to his current position as Heath-Harrison Chair of Organic Chemistry in the Department of Chemistry at the University of Liverpool. He has been recognized with numerous honors and awards, including most recently the Pedler Award from the Royal Society of Chemistry. His research interests focus on catalysis in the context of the development of new synthetic transformations that permit the expeditious total synthesis of complex bioactive natural products.

**Phillip A. Inglesby** was born in Liverpool (UK) in 1985. He received his MChem from the University of Liverpool in 2007 where he worked for Dr. Nick Greeves. Later that year, he joined the research group of Professor P. Andrew Evans at the same institution where he carried out his PhD research. This was focused on the development of new rhodium-catalyzed carbocyclization and ene-cycloisomerization reactions as well as their application in complex total synthesis. He has gained recognition both regionally and nationally with numerous awards for his contribution to research. Upon completion of his PhD in 2011, he remained in the Evans group as a Post-doctoral Associate, working on the total synthesis of another complex bioactive natural product.



## Young Career Focus: Dr. Paul Davies (University of Birmingham, UK)

■ **Background and Purpose.** *SYNFORM* will from time to time meet 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 *SYNSTORY* with a **Young Career Focus** presents Dr. Paul Davies, University of Birmingham, UK.

### BIOGRAPHICAL SKETCH



Dr. P. Davies

**Paul Davies** was born and raised in Hertfordshire (UK) before reading for an undergraduate MChem degree (Chemistry with Industrial Experience) at the University of Sheffield (UK) which included a year in the Medicinal Chemistry department at SmithKline Beecham (Harlow, UK). He undertook research with Professor Varinder Aggarwal, moving to the University of Bristol (UK) in 2000, and obtained his PhD in 2003 on the development of palladium-catalyzed cascade reactions and their application in natural product synthesis. Paul then moved to the Max-Planck-Institut für Kohlenforschung (Mülheim, Germany) working with Professor Alois Fürstner on new catalysts in metathesis processes and then on platinum-catalyzed cycloisomerizations. In 2006, Paul was appointed Lecturer in Organic Chemistry at the University of Birmingham (UK). He was promoted to Senior Lecturer in 2012 and heads the Molecular Synthesis and Catalysis research unit at Birmingham. His research group is concerned with the development, study and application of catalysis in organic synthesis, with a particular focus on the discovery of novel transformations. Paul was recently recognized with a Thieme Chemistry Journal Award in 2012.

### INTERVIEW

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

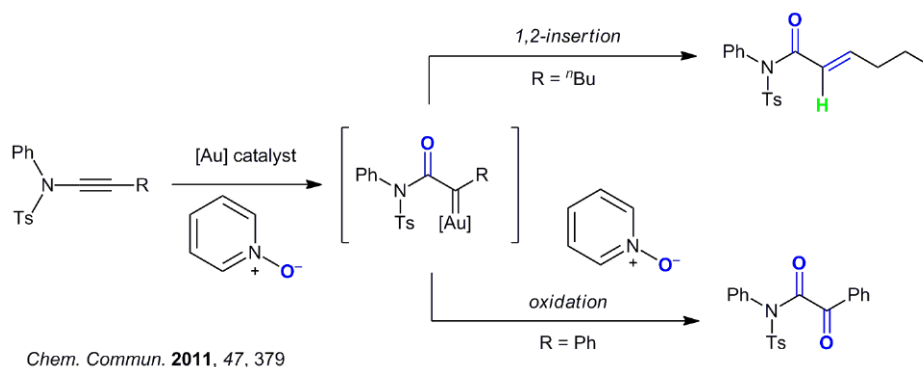
**Dr. Davies** | The main focus of our current research involves the development of new catalysis-based transformations and strategies for synthesis. We are particularly interested in looking at reactivity principles that will help to streamline synthesis.

**SYNFORM** | *When did you get interested in synthesis?*

**Dr. Davies** | My interest in synthesis really took off when I was first exposed to a research environment during my undergraduate degree. Seeing how theory meshed with practice and problem-solving convinced me that synthesis was an appealing and creative science. My PhD was then spent predominantly looking at cascade reactions from which I developed an abiding fascination with new and hopefully improved methods to assemble molecules. I found it tremendously enjoyable to be able to walk into the lab and design and run experiments that would test my own ideas, and then to see the directions the projects would take. Despite not having that much time to get into the lab these days, and so enjoying the practical aspect vicariously alongside my research group co-workers, this potential for discovery underpins my continued interest in synthesis.

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

**Dr. Davies** | Clearly I am biased towards this matter but the role of organic synthesis in both its applied and fundamental forms seems to me to be of ever-increasing importance. Small molecules that have been designed and prepared by synthetic chemists are, and will continue to be, of central importance to our quality of life. There are numerous emerging areas across science, materials and engineering that depend on designed molecules and/or can be advanced by creative input at the molecular synthesis level. Yet, despite all the fantastic advances in synthesis up to this point in time, preparing any given target molecule is far from being a



Scheme 1

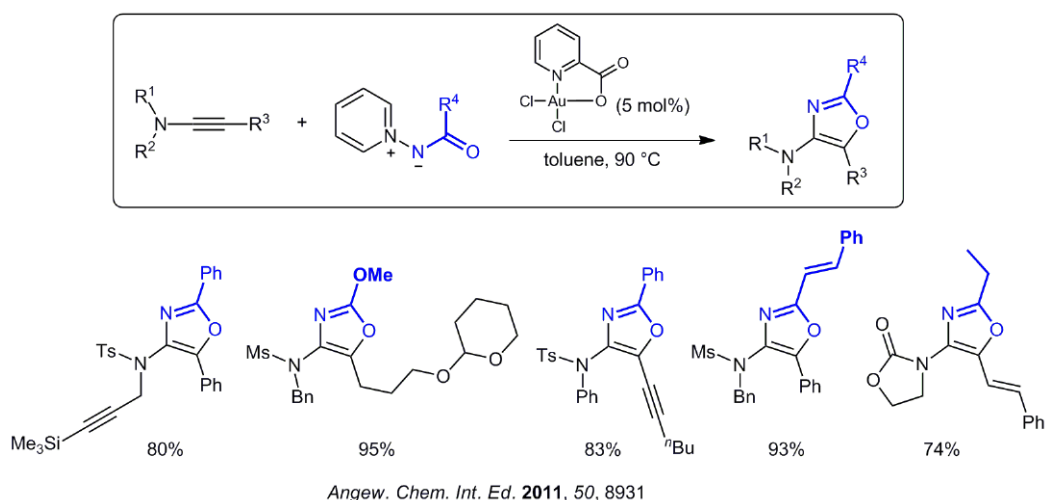
matter of course and in fact takes a huge amount of resource. Considering that we have limited natural resources, coupled with the demand from an increasing population and level of industrialization, there is a major need for us as a society to be able to prepare molecules more rapidly and efficiently while generating less waste. This will come down to increasing our toolbox of methods and strategies, having greater understanding of all aspects of synthesis, and making the most of other technologies.

It is, however, increasingly important that we can convince society of organic synthesis' relevance so that we do continue both in both the short- and long-term to develop sufficient numbers of capable and creative scientists and give them the opportunity to face the challenges of the future.

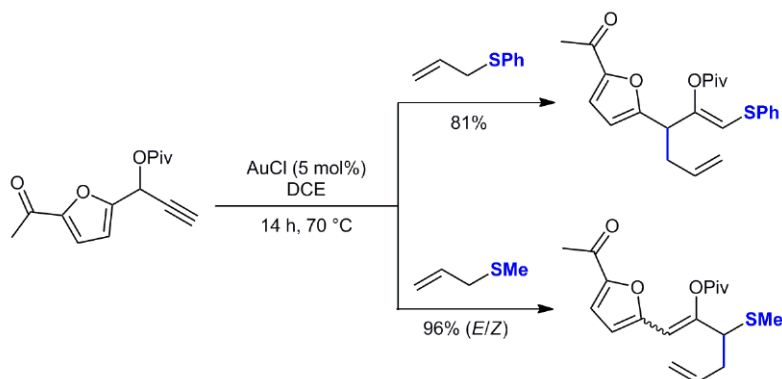
**SYNFORM** | Your research group is active at the frontier of organic synthesis and catalysis. Could you tell us more about your research and its aims?

**Dr. Davies** | Our aims are to design reactions that are highly efficient and practically applicable. Once we have a new process then we are interested in exploring its synthetic utility, mechanistic details, and how the underlying reaction concept can be extended.

We tend to start from the point of exploring a new reactivity principle, keeping an eye on the type of products that could be made. These should either be motifs that have a well-established importance in synthesis, in which case our aim is to provide an improved access, or the products should



Scheme 2



*Chem. Commun.* **2008**, 238; *Pure Appl. Chem.* **2010**, 82, 1537; *Angew. Chem. Int. Ed.* **2009**, 48, 8372; *Synlett* **2012**, 23, 70.

### Scheme 3

be novel structures. While the former type makes it easier to show applicability of a new process, the latter often offers greater opportunities for subsequent discoveries.

A major focus of the group concerns the use of  $\pi$ -acid activation of alkynes due to the synthetic complexity that can be achieved from simple functional groups. From our earliest work on the use of alkynes to generate sulfur ylides we developed a selective intermolecular gold-catalyzed oxidation of ynamides as a direct entry into gold-carbenoid reactivity patterns (Scheme 1). This potentially allows ynamides to be used in place of other carbene precursors. One of the advantages of this approach is that we avoid the need to install a sacrificial functionality, such as the diazo unit which is normally used to enable metal insertion, prior to the reaction that we are really interested in.

More recently, we have brought together our interest in ylides, ynamides and gold catalysis to develop a new strategy to effect intermolecular cycloadditions. A gold-promoted reaction between the nucleophilic atom of an ylide with the ynamide evolves with loss of pyridine as the only waste product to generate an organogold intermediate capable of cyclizing. Using this approach we can prepare oxazoles from new equivalents of *N*-acyl nitrenes with greater control than was previously available (Scheme 2). Highly functionalized products can be prepared due to a combination of readily accessible starting materials, mild conditions and the superb chemoselectivity of the process.

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

**Dr. Davies** | In terms of how it has informed our further research, and hopefully contributed to the wider community, I would say our discovery that we could prepare sulfur ylides directly from an alkyne under gold catalysis (Scheme 3). The first process we developed showed that we could potentially employ organogold species generated in situ as equivalents to metal carbenes normally generated from diazo compounds. The evolution of this research program has taken us into some unexpected areas that I think will make valuable contributions. ■

Matteo Zanda

*(Signature)*

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2012/07

is available from  
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In the next issues:

## SYNSTORIES ■ ■ ■ ■ ■

## ■ Catalytic Asymmetric Hydrogenation of Naphthalenes

*(Focus on an article from the current literature)*■ Benzofurans from Benzophenones and Dimethylacetamide:  
Copper-Promoted Cascade Formation of Furan O1–C2 and C2–C3  
Bonds Under Oxidative Conditions*(Focus on an article from the current literature)*

## FURTHER HIGHLIGHTS + + + +

## SYNTHESIS

Review on: Challenges in the Syntheses of Peptidic Natural  
Products*(by S. C. Stolze, M. Kaiser)*

## SYNLETT

Account on: Method in the Madness – Methodology from Total  
Synthesis*(by R. H. Pouwer, C. M. Williams)*

## SYNFACTS

Synfact of the Month in category “Polymer-Supported  
Synthesis”: [SBA-15-SO<sub>3</sub>H-Confined Acidic Ionic Liquid](#)

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