SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/04

SYNSTORIES ■ ■ ■ ■

■ Intermolecular [3+2] Cycloaddition of Cyclopropylamines with Olefins by Visible Light Photocatalysis

■ Nickel-Catalyzed C–H/C–O Coupling of Azoles with Phenol Derivatives

■ Young Career Focus:
Professor Sylvain Canesi (Université du Québec à Montréal, Canada)

CONTACT ++++

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Dear readers,

Recently I was talking to a colleague about professional social networks, and he was of the opinion that some of them are very useful not just to keep in touch with colleagues, friends and former students around the world, but

also for acquiring every sort of information useful at professional level, from job openings to recent trends in research (including the attendance of webinars) and even some kind of gossip. Personally, I am not a heavy user of these social networks (actually I am not even on Facebook...) and I think I am spending already too much time online answering to e-mails and retrieving information on the web. However, yesterday I decided to have a closer look at one of these websites, where I have been registered for the last three years without even updating my profile, and I had the impression that the whole world was there, I could even find some of my old school mates! After a couple of hours, I had to admit to myself that professional social networks are indeed a very useful tool, provided one does not become addicted. So, I decided I will try to get more involved and make a better use of this tool although I am strongly determined not to become a slave! Will I succeed? I'll let you know... The other decision I've made is that I will continue to live without Facebook. At least for the moment...

As you know, there is another tool for staying in touch with the community of organic chemists and receive exclusive information on the most exciting breakthroughs and discoveries: it's **SYNFORM**! This issue, for example, explains how Professor N. Zheng (USA) was able to develop his amazing photocatalyzed cycloaddition between cyclopropylamines and olefins. In the second **SYNSTORY** Professor K. Itami takes us through his superb Ni-catalyzed cross-coupling reaction producing heterobiaryls from azoles and phenols. Last but not least, Professor S. Canesi (Canada) is the protagonist of the Young Career Focus.

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

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Intermolecular [3+2] Cycloaddition of Cyclopropylamines with Olefins by Visible Light Photocatalysis

Angew. Chem. Int. Ed. **2012**, *51*, 222–226

■ There is an upsurge of interest in using visible light for promoting the formation of carbon–carbon bonds. This is motivated by both environmental and economic reasons, given the abundance and widespread availability of solar energy. However, photoredox catalysts such as ruthenium or iridium polypyridyl complexes are normally needed to achieve efficient visible-light-promoted synthetic processes. In this process, Ru(I) and Ir(II) are oxidatively photo-excited to Ru(II) and Ir(III), respectively, and amines are used as sacrificial electron donors to reduce these oxidized cations back to the original oxidation state. Recently, the group of Professor Nan Zheng

from the University of Arkansas (USA) designed a new, more atom-economical process employing amines as both the substrates and the sacrificial donors. The new reaction is an intermolecular [3+2] cycloaddition that transforms cyclopropylamines and olefins into ring-expanded cyclopentyl amines.

“Although visible-light photocatalysis using Ru complexes was known back in the 1970s, its use in organic synthesis has been scattered,” said Professor Zheng. “Seminal works from MacMillan, Yoon, Stephenson, Akita, and others have reinvigorated this field. There has been a flurry of activity in this field recently,” he acknowledged. “We were interested in the

Selected examples of cycloaddition products

fate of nitrogen radical cations generated under visible-light photocatalysis. To capture the potential of these odd-electron species, we soon realized that we needed to couple downstream irreversible processes with the initial oxidation of amines,” continued Professor Zheng. “By accident, we stumbled onto cyclopropylamines, which turned out to be an ideal class of compounds to meet this requirement.” Professor Zheng explained that the groups of Cha, Six, and others (see the original paper for references) have explored the synthetic applications of cyclopropylamines, but most of these applications are focused on intramolecular cycloadditions, whereas the chemistry developed by his group is focused on the intermolecular variant. “The conditions used in this chemistry are also much milder than in the intramolecular cycloaddition that often requires a stronger oxidant such as CAN and/or ultraviolet light. We think this chemistry adds a new dimension of cyclopropylamines’ synthetic application,” said Professor Zheng.

According to Professor Zheng, two notable features of this chemistry are that it is cheap and really easy to set up. “The light sources, 13 W compact fluorescent light bulbs from GE, are purchased from local Walmart stores,” he said. “Disposable test tubes from VWR are used to run these reactions. The operation is very straightforward and requires mixing of the catalyst, reagents, and solvents, degassing, and shining the light.” This chemistry produces some new and interesting small amines, particularly bicyclic ones. “These compounds are nonpolar, lipophilic, and therefore should be able to easily cross the blood–brain barrier,” added Professor Zheng. “They could be explored as a new scaffold to treat brain diseases such as Alzheimer’s disease.”

Professor Zheng revealed that this project was undertaken following an accidental discovery. “During our previous studies on the cleavage of N–N bonds by visible-light photocatalysis, postdoctoral fellow Mingzhao Zhu discovered that upon exposure to visible light, air, and a Ru(II) catalyst, *N*-cyclopropyl-*N*-phenylhydrazine was converted into an unstable product. Because of its instability, we could not figure out its structure. Ryan Spencer Shinabery meticulously studied this reaction using a combination of screening and in situ monitoring by GC–MS and ^1H NMR,” he continued. “During these studies, he made a keen observation about the reaction: the N–N bond of the hydrazine was initially cleaved to form *N*-cyclopropylaniline that was next converted into the unknown product. With this observation, we finally solved the structure of the unknown product, which is an endoperoxide.” At that point, Professor Zheng and his co-workers speculated that the endoperoxide was formed by an initial opening of the cyclopropyl ring followed by subsequent trapping of the re-

Reaction setup

sulting radical cation by oxygen in air. “We further tested this hypothesis by successfully trapping the radical cation with electron-deficient olefins such as styrene to form a cyclopentane derivative. Another postdoctoral fellow, Soumitra Maity, expanded this chemistry to different cyclopropylamines and completed the majority of the examples in the paper,” said Professor Zheng.

“We are really excited by the potential of visible-light photocatalysis,” continued Professor Zheng. “Visible-light photocatalysis used to be, and may still be, considered a niche area rather than mainstream chemistry because it can only perform a limited number of chemical processes. I hope our work, along with that of others in this field, will slowly change the organic community’s perception of this chemistry and one day it will become a major tool at the organic chemist’s disposal. Our group chemistry is evolving and starting to branch out to other classes of amines and carbon–carbon π -bonds,” he concluded. ■

Matteo Zanda

About the authors

From left: Prof. N. Zheng, Dr. S. Maity, R. S. Shinabery

Nan Zheng was born in China and did his undergraduate studies at the University of Science and Technology of China (USTC). He earned his Ph.D. (2005) under the tutorship of Professor William R. Roush at the University of Michigan, Ann Arbor (USA), where he studied the total synthesis of pectenotoxin 2. Then, he took up an NIH postdoctoral position in Professor Stephen L. Buchwald's group at MIT (Cambridge, USA) and developed a couple of methods based on Pd- or Cu-catalyzed C–H bond functionalization and C–N bond formation. Since July 2008, he has been an Assistant Professor at the University of Arkansas (Fayetteville, USA). His independent research is focused on visible-light photocatalysis.

Soumitra Maity is a postdoctoral fellow in Professor Zheng's group. Originally from West Bengal (India), he received his B.Sc. in chemistry from Ramakrishna Mission Residential College, Narendrapur (India) in 2002 and his M.Sc. in 2004 from Calcutta

University (India). His Ph.D. research was carried out at the Indian Association for the Cultivation of Science (Kolkata, India) with Professor Subrata Ghosh and focused on the synthesis of natural products. After successfully defending his Ph.D. thesis, Maity moved to the USA in September 2010 to work with Professor Zheng at the University of Arkansas to develop new methods for the formation of C–C and C–N bonds by visible-light photocatalysis.

Ryan Spencer Shinabery is a fourth-year undergraduate student in Professor Zheng's group. He is originally from Little Rock, Arkansas (USA). Since joining the Zheng group in May 2010, he has obtained a number of undergraduate research awards including a prestigious Summer Undergraduate Research Fellowship from the American Chemical Society's Division of Organic Chemistry. He plans to enter a graduate school upon graduation in May 2012.

Dr. M. Zhu

Mingzhao Zhu was a postdoctoral fellow in Professor Zheng's group. He obtained his B.Sc. and M.Sc. in organic chemistry from Lanzhou University (P. R. of China) and his Ph.D. from Leibniz Institute of Plant Biochemistry/Martin-Luther-Universität Halle-Wittenberg (Halle, Germany). Prior to joining the Zheng group, he did postdoctoral studies with Professor Markus Kalesse at Leibniz University of Hannover (Germany) and Professors Björn Åkermark and Berit Olofsson at Stockholm University (Sweden). He started the projects on visible-light photocatalysis in the Zheng group. Currently, he is a postdoctoral fellow at Texas A&M University (College Station, USA).

Nickel-Catalyzed C–H/C–O Coupling of Azoles with Phenol Derivatives

J. Am. Chem. Soc. **2012**, *134*, 169–172

Scheme 1

■ Biaryls and heterobiaryls are ubiquitous motifs in pharmaceuticals, natural products, and organic materials alike, and therefore the construction of these scaffolds has been a topic of great importance in chemistry. As widely announced within the chemical community and beyond, research in ‘palladium-catalyzed cross-coupling reactions’ was awarded the Nobel Prize in Chemistry in 2010, highlighting its significance. Since cross-coupling reactions are undoubtedly among the most reliable methods for constructing biaryls and heterobiaryls, many chemists have contributed to their improvement over the last few decades. However, these reactions generally require the use of: (i) metalated arenes/heteroarenes as aryl nucleophiles, which are synthesized from simpler arenes/heteroarenes in multi-step reactions; (ii) halogenated arene/heteroarenes as aryl electrophiles; and (iii) expensive palladium as catalyst. “The next phase of research in cross-coupling chemistry will have to solve the above problems in order to develop more efficient processes, and there are currently three ways in which cross-coupling chemistry can ‘evolve’, which are summarized in Scheme 2,” said Professor Kenichiro Itami, an expert in this area of chemistry from Nagoya University (Japan).

Very recently, Professor Itami and co-workers Kei Muto and Dr. Junichiro Yamaguchi successfully developed a nickel-catalyzed C–H/C–O coupling of heteroarenes with phenol derivatives. “What was our key to success?” asked Professor Itami. “The pivotal moment was when my student Kei Muto developed an entirely new catalyst, nickel 1,2-bis(dicyclohexylphosphino)ethane (dcype), at the end of his struggle,” said Professor Itami. In 2009, his research group had already reported a nickel-catalyzed direct coupling of heteroarenes with aryl halides (C–H/C–X coupling: *Org. Lett.* **2009**, *11*,

1733; *Chem. Eur. J.* **2011**, *17*, 10113), which received attention because simple heteroarenes (evolution strategy #1 in Scheme 2) and an inexpensive nickel catalyst (evolution strategy #3) were used. However, the requirement of aryl halides as aryl electrophiles was still problematic at the time (evolution strategy #2). “Now, with the strategy we published in this

1. Aryl nucleophile: toward direct C–H functionalization

2. Aryl electrophile: searching for non-halogen aryl source

3. Metal catalyst: toward more ubiquitous and inexpensive metal

Scheme 2 Possible modes of ‘evolution’ in metal-catalyzed biaryl coupling

JACS paper, it is possible to couple phenol derivatives (C–H/C–O coupling), which is advantageous because many phenols are commercially available and inexpensive. This represents yet another step in the evolution of biaryl coupling,” said Professor Itami.

Although dcype is a commercially available ligand, it had never been used in conjunction with nickel. “Using the Ni/dcype catalyst under the influence of Cs_2CO_3 in dioxane at 120 °C, heteroaromatics (azoles) were successfully coupled with phenol derivatives in good or excellent yields,” explained Professor Itami. “Among the various reaction parameters that were modified in the screening process, the ligand effect was the most dramatic: dcype would enable the reaction, and other ligands would not,” he said.

Based on these findings, the Japanese researchers examined the direct arylation of various 1,3-azoles with phenol

derivatives (Scheme 3). “As for the azole coupling partner, benzoxazoles, oxazoles, benzothiazoles and thiazoles are effective; the phenol coupling partner can be substituted phenols, naphthols and pyridols, as their pivalate or triflate derivatives” said Professor Itami. “Concise syntheses of oxazole alkaloids, texamine, and unguenenazole were achieved, as well as the late-stage functionalization of bioactive structures such as estrone and quinine,” he continued.

The Itami group has thus discovered the first nickel-catalyzed C–H/C–O coupling reaction of azoles with phenol derivatives, and they believe that a range of catalytic C–O bond transformations of phenol derivatives with $\text{Ni}(\text{cod})_2$ /dcype should be possible. Furthermore, they wish to develop a second-generation catalyst with an even broader scope in order to continue the evolution of cross-coupling chemistry. ■

Scheme 3 Representative examples of C–H/C–O biaryl coupling catalyzed by a Ni-dcype system

Matteo Zanda

About the authors

From left: Prof. K. Itami, K. Muto, Dr. J. Yamaguchi

Kenichiro Itami was born in Pittsburgh (USA) in 1971 and raised in Tokyo (Japan). Educated in chemistry at Kyoto University (Japan) under the guidance of Professor Yoshihiko Ito, he received his Ph.D. in 1998. From 1997 to 1998, he was a predoctoral researcher in the group of Professor J.-E. Bäckvall at Uppsala University (Sweden). In the fall of 1998, he began his academic career at Kyoto University (Japan) as an Assistant Professor (with Professor Jun-ichi Yoshida). He moved to Nagoya University (Japan) to become an Associate Professor (with Professor Ryoji Noyori) in 2005, and was promoted to Full Professor in 2008. Representative awards include the Novartis-MIT Lectureship Award (2012), Nozoe Memorial Award for

Young Organic Chemists (2011), Merck-Banyu Lectureship Award (2008), the Minister Award for Distinguished Young Scientists (2006), the Mitsui Chemicals Catalysis Science Award of Encouragement (2005), the Chemical Society of Japan Award for Young Chemists (2005), and the Thieme Chemistry Journals Award (2004). Representative projects include (1) ideal chemical synthesis through C–H bond transformation, (2) rapid synthesis of pharmaceutically relevant molecules and natural products, (3) synthesis and properties of optoelectronic materials, and (4) controlled bottom-up synthesis of structurally uniform nanocarbons such as carbon nanotubes, graphenes, and fullerenes.

Junichiro Yamaguchi was born in Chofu, Tokyo (Japan) in 1979. He received his Ph.D. in 2007 from the Tokyo University of Science (Japan) under the supervision of Professor Yujiro Hayashi. From 2007 to 2008, he was a postdoctoral fellow in the group of Professor P. S. Baran at The Scripps Research Institute (USA) (JSPS postdoctoral fellowships for research abroad). In 2008, he became an Assistant Professor at Nagoya University working with Professor Kenichiro Itami. His research interests include the total synthesis of natural products and the innovation of synthetic methods.

Kei Muto was born in Okazaki, Aichi (Japan). He received his B.Sc. degree from Nagoya University (Japan) in 2011 under the supervision of Professor Kenichiro Itami. He is currently an M.Sc. student in the group of Professor Itami.

Young Career Focus: Professor Sylvain Canesi (Université du Québec à Montréal, Canada)

■ **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 Professor Sylvain Canesi, Université du Québec à Montréal, Canada.

BIOGRAPHICAL SKETCH

Prof. S. Canesi

Sylvain Canesi is a Professor of Organic Chemistry at the Université du Québec à Montréal (Canada). He was born in 1977 and raised on the beautiful Mediterranean island named Corsica (France). He obtained his BSc in chemistry in 1998 at the University of Corsica in Corte. Subsequently, he moved to Lyon to obtain an advanced degree in chemistry from the Ecole Supérieure de

Chimie, Physique et Electronique de Lyon (France) in 2001 and went on to become a graduate student in the group of Professor Marco A. Ciufolini. There, he carried out the total synthesis of (–)-cylindricine, a natural azaspiranic marine compound, and obtained his PhD in 2004. After postdoctoral studies in the group of Professor Pierre Deslongchamps in Sherbrooke (Quebec, Canada), where he worked on the synthesis of a paclitaxel macrocyclic model, he accepted, in the fall of 2006, a faculty position at the Université du Québec à Montréal. The research interests of his laboratory focus on the development of new synthetic methods and their rapid applications in total synthesis. This research aims to further develop novel, efficient, and environmentally benign methodologies devised for metal-free reactions and to apply such techniques to the rapid total or formal synthesis of natural products. Professor Canesi and his research have been recognized by support from Boehringer Ingelheim Ltd (Laval, Canada) awarded in 2009, a young Canadian investigator award, and a Thieme Chemistry Journal Award in 2011.

INTERVIEW

SYNFORM | Professor Canesi, what is the focus of your current research activity?

Professor Canesi | The central theme of our research is what may be termed ‘aromatic ring umpolung’. Electron-rich aromatic compounds, such as phenols and their derivatives, are involved in different biosyntheses of natural products. These compounds normally react as nucleophiles (electrophilic substitution); however, an oxidative activation mediated by a hypervalent iodine reagent, an environmentally benign reagent, can transform these aromatics into very reactive electrophilic species, which may be intercepted with appropriate carbon-based nucleophiles. This method provides new strategic opportunities in synthetic chemistry, performed by a dearomatizing avenue enabling the transformation of stable aromatic unsaturations into more reactive scaffolds as highly functionalized intermediates that can be readily used as an advanced precursor in the synthesis of natural products.

SYNFORM | When did you get interested in synthesis?

Professor Canesi | I have to admit that I have a very classical answer to this question: I became interested in synthesis at university. I have always considered organic chemistry as a puzzle, a strategic game such as chess, and I was fascinated by the different possibilities offered by organic synthesis. I find the possibility of redesigning a simple architecture into a very complex one, like a modern alchemist, enthralling. It is fascinating to transform simple petroleum derivatives into a bioactive compound, especially if we consider that the petroleum itself was derived from former complex organic substances; thus, synthesis would be a kind of ‘renaissance’. During my studies, I had very competent teachers who transferred to me their passion for this science, starting with my former thesis director Professor Ciufolini. I am very grateful to each of them for that.

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

Professor Canesi | On a general point of view – if we look at what Nature is able to do in synthesis – it appears obvious

that we still have a lot to accomplish in the future. We are at the very beginning of an era in synthesis and there are many opportunities and challenges for all researchers involved in synthesis. The recent recession has not been kind to chemistry these last few years; indeed, several important pharmaceutical and other companies have had serious economic problems. This situation does not appear sustainable as there are new diseases and pathologies appearing with the ageing population. With the rise in the entitlement age, our society will be required to generate new cures and leads. In this aim, we need to educate a next generation of competent chemists and to develop efficient synthetic methodologies as a pharmaceutical tool. We have to be grateful to our predecessors who did so much with little means. All these pioneers contributed to the foundation of our current knowledge in synthesis and gave their names in legacy to efficient transformations. We still have so much to discover in synthesis, it is just the beginning.

SYNFORM | Your research group is active in the areas of (1) total synthesis of natural compounds and (2) development of novel synthetic methodology. Could you tell us more about your research and its aims?

Professor Canesi | Our research focuses on the oxidative dearomatization of electron-rich aromatic systems mediated by hypervalent iodine reagents. It should be stressed that

such oxidative processes involving hypervalent iodine reagents, or other oxidizing agents enabling the reversal of reactivity, are well detailed in the literature by several leading groups. Formally, this strategy allows extending several well-known reactions in aliphatic chemistry to aromatic chemistry. Our contribution in this area mainly focuses on oxidative carbon–carbon bond-forming reactions and validating the generated core by using it as an advanced key intermediate in a concise total or formal synthesis of a natural product.

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

Professor Canesi | Our favorite contribution so far is the extension of aliphatic transpositions to aromatic systems. Such a process has allowed us to produce compact, highly functionalized and substituted scaffolds in one step and decent yields, from very simple and inexpensive starting materials, in a stereoselective pathway. We have developed oxidative extensions of the Prins–pinacol tandem process, the Wagner–Meerwein transformation involving a 1,2-alkyl shift, and an unprecedented 1,3-alkyl shift process. These methodologies have been applied in the synthesis of natural compounds, such as a (–)-platensimycin or acetylaspidoalbidine.

Matteo Zanda

COMING SOON ►► COMING SOON ►►

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April 18, 2012***In the next issues:****SYNSTORIES ■ ■ ■ ■ ■****■ Radical Addition of Alkyl Halides to Formaldehyde in the Presence of Cyanoborohydride as a Radical Mediator***(Focus on an article from the current literature)***■ A Highly Diastereo- and Enantioselective Reaction for Constructing Functionalized Cyclohexanes: Six Contiguous Stereocenters in One Step***(Focus on an article from the current literature)***FURTHER HIGHLIGHTS + + + +****SYNTHESIS****Review on: Transition-Metal-Catalyzed Functionalization of Propargylic Alcohols and their Derivatives***(by E. B. Bauer)***SYNLETT****Account on: Silicon-Bridged Biaryls: Molecular Design, New Synthesis, and Luminescence Control***(by M. Shimizu, T. Hiyama)***SYNFACTS****Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Synthesis of LY2784544](#)****CONTACT + + + +**

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