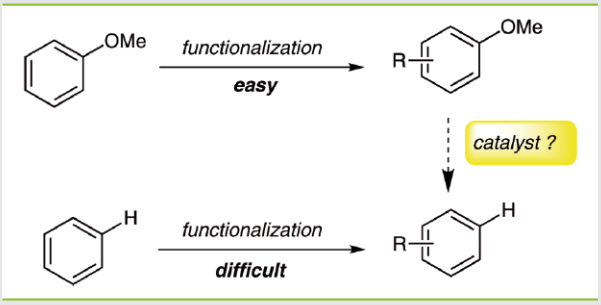
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/04

SYNSTORIES

Ni-Catalyzed Reduction of Inert C–O Bonds: A New Strategy for Using Aryl Ethers as Easily Removable Directing Groups



Visible-Light-Mediated Conversion of Alcohols to Halides

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Dear readers,

This issue of **SYNFORM** features two **SYNSTORIES** which share a common theme: the use of metals as catalysts for breaking C–O bonds. In the first **SYNSTORY**, Dr. R. Martin (Spain) describes how his group was able to develop a process allowing for the Ni-catalyzed reduction of a methoxy group in aryl methyl ethers. The methodology is particularly important because a methoxy group can be thereby used as a removable activating group in the synthesis of a broad range of aromatic compounds. The second **SYNSTORY** reports on a novel reaction discovered by Professor C. Stephenson (USA), which allows for the conversion of primary and secondary alcohols to the corresponding halides. This photoredox process features a conceptually new activation of the C–O bond by visible light, mediated by a ruthenium(II) catalyst. The methodology holds promise for future developments which might impose this reaction as an alternative to the Mitsunobu reaction.

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

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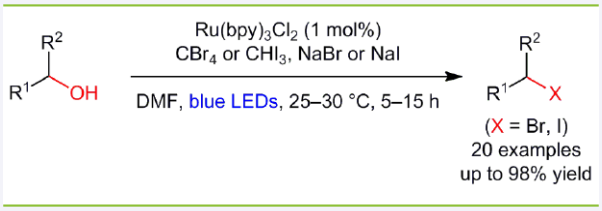

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CONTACT ++++

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NEWS AND VIEWS NEWS AND VIEWS NEWS AND VIEWS

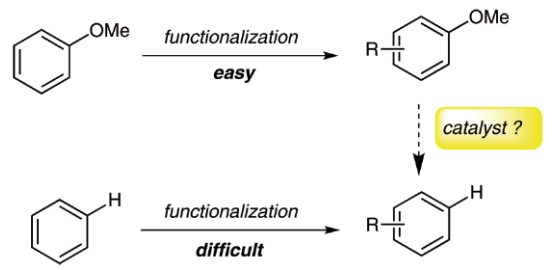
Ni-Catalyzed Reduction of Inert C–O Bonds: A New Strategy for Using Aryl Ethers as Easily Removable Directing Groups

J. Am. Chem. Soc. **2010**, *132*, 17352–17353

Methyl aryl ethers are highly ubiquitous in nature. The importance of such motifs, however, is primarily associated with their unique role as directing groups, allowing a number of interesting transformations including *ortho*-metalation, electrophilic aromatic substitution or Friedel–Crafts-type reactions, among many others. However, once their task has been accomplished, directing groups should be easily removed, which is often not the case. Recently, the group of Dr. Rubén Martín from the Institute of Chemical Research of Catalonia (ICIQ, Tarragona, Spain) described an effective method to fully exploit the potential of the methoxy group as a removable directing group in organic synthesis.

"Directing groups are generally very difficult to cleave under mild reaction conditions," said Dr. Martín. "An illustrative example is the elegant C–H bond activation protocols recently reported in the literature based upon the ability of pyridine, oxazoline, pyrazole or anilide motifs to act as directing groups; although by no doubt very powerful methods, these procedures are not yet synthetically attractive, as the cleavage of such groups still constitutes a tremendous challenge." According to Dr. Martín, the same concept applies when using the methyl aryl ether motif. "We decided to venture into this area of expertise by developing a metal-catalyzed reductive cleavage of inert C–OMe bonds," he said. "Among all the inert C–O bonds, the C–OMe bond is beyond doubt the most difficult to activate. Indeed, only a limited number of C–C or C–N bond-forming reactions have been reported when coupling C–OMe bonds." Dr. Martín and the article's co-author, Dr. Paula Álvarez-Bercedo, anticipated that a reductive cleavage of C–OMe bonds would be very valuable for both pharmaceutical and academic laboratories, thus constituting a new strategy for using methyl aryl ethers as easily removable directing groups. "If successful, such a protocol would represent an alternative for arene functionalization, as electronically unbiased arenes are certainly very difficult to functionalize when using common synthetic organic techniques (Scheme 1)," confirmed Dr. Martín.

"We certainly had to face a tremendous challenge as inert C–OMe bonds have bond strengths in the range of 90–105 kcal · mol^{-1}. In other words, this can be translated with the difficulty of achieving oxidative addition of C–OMe bonds to metal complexes," said Dr. Martín. "Our inspiration came from the seminal work of Wenkert (*J. Am. Chem. Soc.* **1979**, *101*, 2246) when cleaving strong bonds by employing nickel complexes, a concept that has been recently revisited in the excellent work of Shi (*Angew. Chem. Int. Ed.* **2010**, *49*, 4566) and Chatani (*Angew. Chem. Int. Ed.* **2010**, *49*, 2929). We hypothesized that a judicious choice of the supporting ligand as well as the hydride source would be critical for achieving success. As quoted by Julius Caesar, *"nothing is so difficult that it cannot be easily accomplished with careful planning"*. Indeed, after extensive screening, Dr. Martín and his co-worker discovered that the use of Cy_3P and tetramethyldisiloxane (TMDSO) as the hydride source provided the best results. The protocol turned out to be widely tolerant of functional groups as silyl groups, esters, amides, acetals, amines and heterocycles remained intact (Scheme 2). "Not surprisingly, naphthalene backbones were much more reactive than anisole derivatives, likely due to the intermediacy of η^2-arene or Meisenheimer-type complexes," explained Dr. Martín. "The presence of a directing group in an *ortho*-position, such as pyridine or oxazoline, among others, allowed us to cleave the C–OMe in anisole derivatives, possibly one of the most important accomplishments of our publication. We believe that the presence of a directing group could facilitate the oxidative addition of the corresponding *ortho*-C–O bond to the catalytically active Ni(0) species," he said.



Scheme 1 *Aryl ethers as temporary protecting groups*

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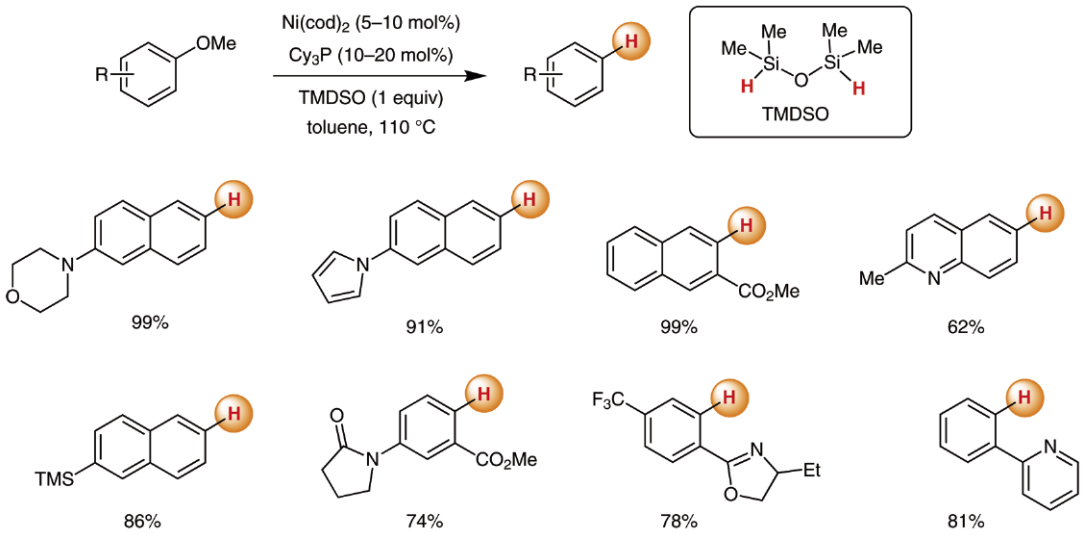
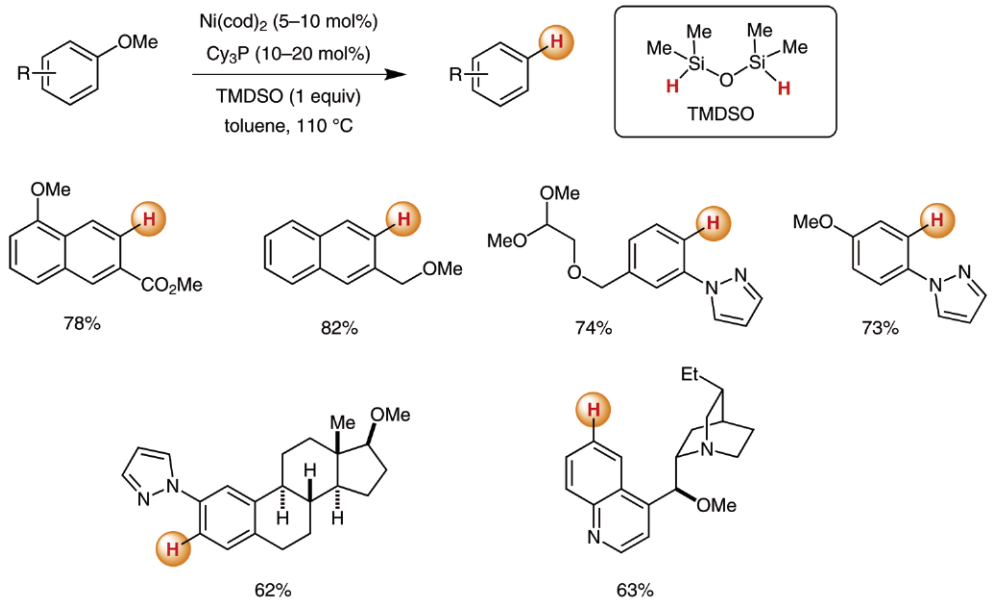


Scheme 2



Scheme 3

"Even more interestingly, our protocol allowed for site selectivity, as C–OMe bonds could be reductively cleaved in the presence of other C–OMe bonds, likely due to subtle steric as well as electronic differences," continued Dr. Martín. "Importantly, the protocol can be used for natural product diversity, as highly complex molecules such as estradiol or quinine-type derivatives were used in good yields (Scheme 3)."

"We are still far from understanding the mechanism of this intriguing transformation; our current hypothesis, supported by deuterium-labeling experiments, is based upon a σ-bond metathesis of the Si–H bond with the initially formed oxidative addition species," said Dr. Martín. "Indeed, our current efforts are focused primarily on the identification and isolation of the putative reactive intermediates, hoping to shed light into the mechanism. In my honest opinion," he concluded, "these mechanistic experiments will undoubtedly be the foundation for future developments of other related processes."

Matteo Zanda

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About the authors

Dr. R. Martín

Rubén Martín was born in 1976. He received his PhD in 2003 at the Universitat de Barcelona (Spain) with Professor Antoni Riera. After two postdoctoral stages at the Max-Planck-Institut für Kohlenforschung with Professor Alois Fürstner and at the Massachusetts Institute of Technology with Professor Stephen L. Buchwald, he initiated his independent career in 2008 at the Institute of Chemical Research of Catalonia (ICIQ). He has recently received the Young Investigator Award by the RSEQ (2010) and the Thieme Chemistry Journal Award (2011). His interests are focused primarily on the metal-catalyzed activation of inert chemical bonds.

Dr. P. Álvarez-Bercedo

Paula Álvarez-Bercedo was born in Santander (Spain). After a short stage at the University of Cambridge (UK), she received her MSc in chemistry at the Universidad de Oviedo (Spain). In 2008, she received her PhD at Jaume I University (Spain) working with Professor Miguel Carda. In 2009, she did a postdoctoral stage at the Institute of Chemical Research of Catalonia (ICIQ) with Dr. Rubén Martín. Since July 2010, she is a project researcher at Esteve-ICIQ Joint Unit (Tarragona, Spain).

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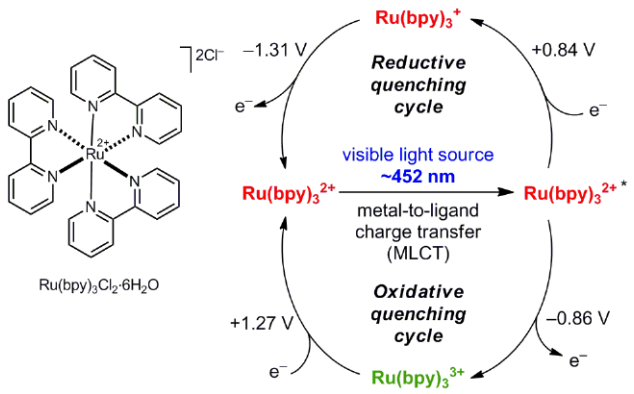
Visible-Light-Mediated Conversion of Alcohols into Halides

Nat. Chem. **2011**, *3*, 140–145

One of the biggest challenges of modern organic synthesis consists in developing selective and efficient reactions where the production of co-products and waste is minimized, and the process relies on the use of recyclable and environmentally sustainable sources of energy. One further significant step in that direction was recently accomplished by the group of Professor Corey Stephenson from Boston University (Massachusetts, USA) who reported an elegant process whereby alcohols can be converted into halides (bromides and iodides) simply by visible-light irradiation.

"Our group is particularly interested in exploring new reactivity concepts in the area of photoredox catalysis," said Professor Stephenson. "We became interested in this area when we sought a solution to a problem encountered in an alkaloid synthesis project under investigation in the group. Specifically, we were able to utilize the reductive quenching pathway (Scheme 1) of $Ru(bpy)_3Cl_2$ to generate the desired radical which provided our malonate couple products in excellent chemical yield. Perhaps most impressive to us was the broad substrate scope and functional group compatibility which we have observed," he continued. "At this stage, we decided to take full advantage of the redox properties of $Ru(bpy)_3Cl_2$ in utilizing the oxidative quenching pathway, hoping to gain similar functional group compatibility. This pathway would provide access to the strong oxidative potential of Ru^{3+} (+1.27 V vs. SCE), generated via the oxidative quenching of the excited state, to further expand the scope of photocatalysis and its application in organic synthesis."



Scheme 1 *Photoredox paradigm for $Ru(bpy)_3Cl_2$*

Professor Stephenson recalls that while Chunhui Dai, one of the article's co-authors, was examining another photocatalytic oxidation reaction in late December 2009, she observed a byproduct which corresponded to the conversion of an alcohol into the corresponding formate ester. She and her colleague, Dr. Jagan Narayanam, surmised that this product was formed via the hydrolysis of an in situ generated Vilsmeier–Haack intermediate. "We immediately noted the potential to leverage this discovery as a catalytic method for activating carbon–oxygen bonds towards nucleophilic displacement, a ubiquitous transformation in organic chemistry," said Professor Stephenson. "Fortunately, further optimization revealed that simple visible light irradiation of polyhalomethanes (CBr_4 or CHI_3) in the presence of $Ru(bpy)_3Cl_2$ in DMF was sufficient to convert primary and secondary alcohols into the corresponding bromide or iodide," he continued. Professor Stephenson explained that in comparison with traditional methods to conduct this transformation, in particular the Appel reaction (Denton and co-workers reported a catalytic variant of the Appel reaction which uses substoichiometric quantities of triphenylphosphine oxide to convert alcohols into chlorides. See: R. M. Denton, J. An, B. Adeniran *Chem. Commun.* **2010**, *46*, 3025), this innovative catalytic method avoids the stoichiometric generation of phosphine oxide waste by acting as an electron shuttle for the redox reaction. "The reagents are all commercially available and easily handled on the bench; the apparatus is easy to set up and inexpensive (in contrast to traditional photochemical apparatus); and the subsequent purification is simple, which make this phosphine-free halogenation method potentially viable on large scale," he confirmed. "Although it is not necessary, the reaction conversion and yield was improved if an external halide source (like NaBr or NaI) was added. High functional group tolerance was observed." Furthermore, as explained by Professor Stephenson, the reaction can be carried out in the presence of ethers, esters, carbamates, alkenes (including trisubstituted alkene and *cis*-allylic alcohol), alkynes, and electron-rich aromatics. Acid-sensitive functional groups such as *tert*-butyl carbamates and silyl ethers were also tolerated if 2,6-lutidine was added.

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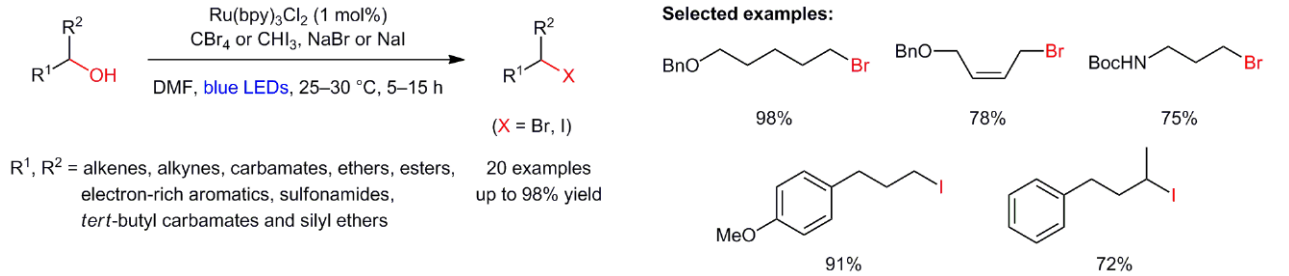
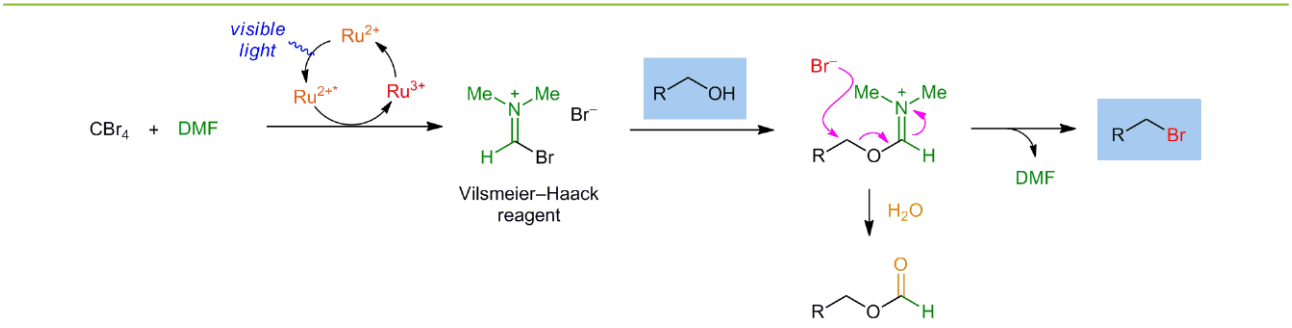


Scheme 2 *Visible-light-mediated conversion of alcohols into halides*

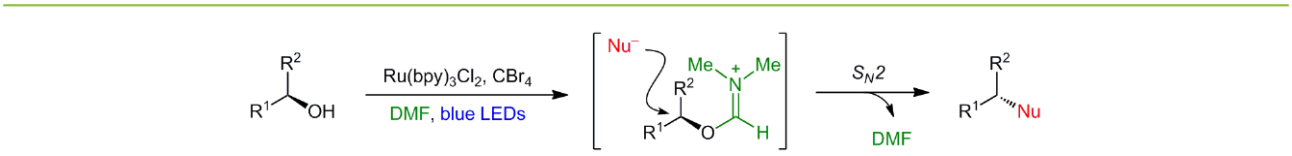


Scheme 3 *Proposed mechanism via oxidative quenching of Ru(bpy)$_3$Cl$_2$*

The mechanism of this transformation starts from irradiation of the Ru^{2+} complex by visible light to its excited state Ru^{2+*}, which reduces the C–Br bond in CBr_4 to form a $\cdot CBr_3$ radical and Br^-. The electron-deficient radical then combines with DMF and the resultant intermediate is quickly oxidized by Ru^{3+} to ultimately generate a reactive species such as the Vilsmeier–Haack reagent. The alcohol is then activated by this reagent to form the penultimate intermediate in the halide-forming reaction. "The reaction proved to be efficient on primary and acyclic secondary alcohols," said Professor Stephenson, "however, cyclic secondary alcohols failed to give the corresponding halides, but provided the corresponding formate ester instead. On closer examination," he continued, "this intermediate could also be isolated from reactions of primary and acyclic secondary alcohols, providing valuable mechanistic information." Professor Stephenson said that one drawback of this transformation in its current form was the racemization observed when subjecting chiral secondary acyclic alcohols to the reaction conditions as a result of a degenerate displacement of bromide by bromide. "This limitation of this method remains as a current challenge to our group," he said.

"Irrespective of these challenges, we strongly believe that C–O bond activation using photoredox catalysis would provide a waste-free alternative for the well-known Mitsunobu reaction," said Professor Stephenson. "Currently, our group is working on the direct nucleophilic substitution of alcohols using photoredox catalysis. In addition, this method may also be useful for the activation of acids for the formation of esters, amides, lactones and lactams," he concluded.

Matteo Zanda



Scheme 4 *Future directions: A general catalytic method for C–O bond activation towards nucleophilic displacement*

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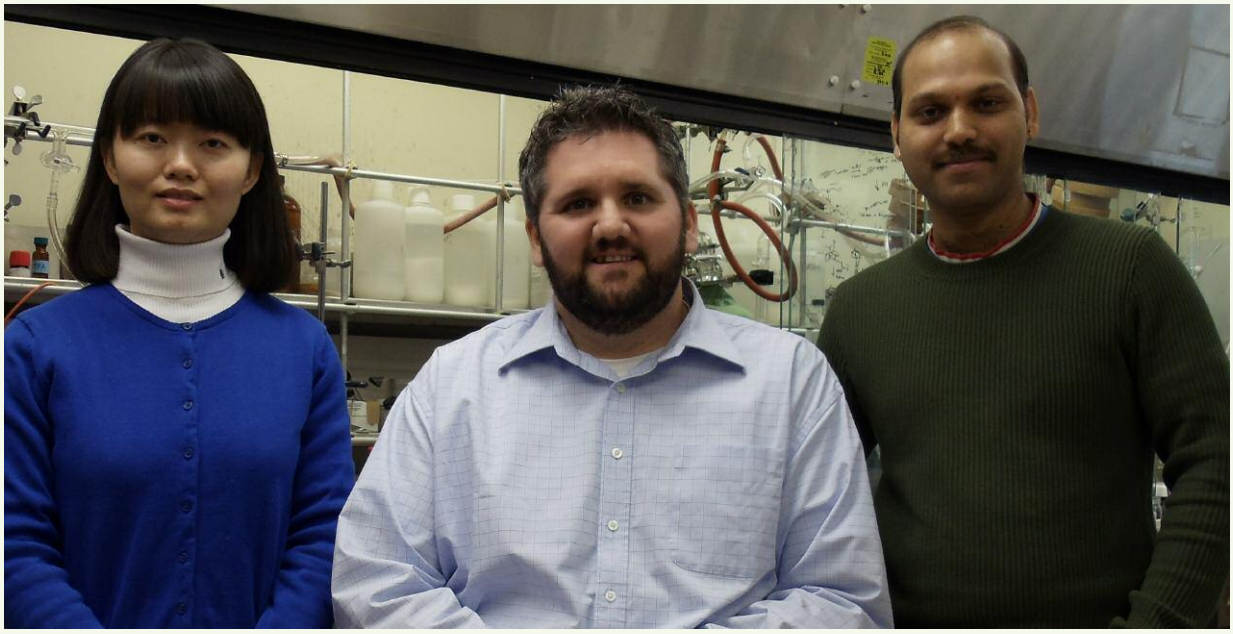

From left: C. Dai, Prof. C Stephenson, Dr. J. Narayanam

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(Focus on an article from the current literature)

One-Pot Azidochlorination of Glycals
(Focus on an article from the current literature)

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SYNTHESIS

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(by T. R. Ramadhar, R. A. Batey)

SYNLETT

Account on: Synthesis of Trifluoromethylated and *gem*-Difluoromethylenated Biologically Interesting Compounds from Fluorine-Containing Synthons
(by F.-L. Qing, F. Zheng)

SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": Synthesis of (+)-Lyconadin A

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