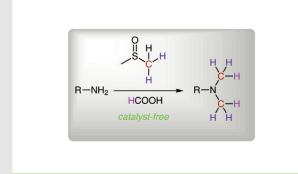


2014/03

SYNSTORIES 🔳 🔳 🔳

A General Method for the N-Methylation of Amines and Nitro Compounds with Dimethylsulfoxide



Catalytic Direct β-Arylation of Simple Ketones with Aryl lodides

Young Career Focus: Dr. Santosh J. Gharpure (Indian Institute of Technology Bombay, Mumbai, India)

Copper(I)-Catalyzed N-H Insertion in Water: A New Tool for Chemical Biology

CONTACT ++

Your opinion about SYNFORM is welcome, please correspond if you like: marketing@thieme-chemistry.com



SYNFORM



Dear Readers,

Once again, there is a lot of Asian chemistry in this issue of **SYNFORM**. The only notable exception is the first **SYNSTORY**, which further expands the potential of "click chemistry" by means of a very original tandem pro-

cess designed by D. Gillingham (Switzerland). The reaction starts with a copper(I)-catalyzed coupling between α -diazoesters and anilines, resulting in a N-H insertion leading to N-aryl-a-phenylglycines. When the N-aryl group carries an azide or alkyne substituent it is possible to perform the reaction in the presence of another terminal alkyne or azide, respectively, which leads to a sequential Huisgen cycloaddition. Since the whole process can be performed in water as solvent, this method can be used as an efficient bioconjugation strategy, as shown in the case of nucleic acids. The Asian chemistry parade starts with the impressively siteselective palladium-catalyzed β-arylation of un-functionalized ketones developed by G. Dong (P. R. of China). Next, the mechanistically intriguing and synthetically useful catalyst-free N-methylation reaction achieved by C. Wang (P. R. of China) by treating nitroarenes with formic acid/FeCl₂ followed by DMSO/formic acid gives the target N-methyl- or N,N-dimethylamines. The issue is completed by a Young Career Focus featuring Dr. S. J. Gharpure (India) who speaks about his work and aims in research.

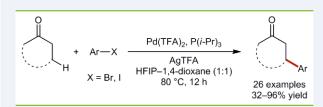
Enjoy your reading!

Matteo Zanda Editor of SYNFORM

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(Indian Institute of Technology Bombay, Mumbai,
India)

CONTACT ++++

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

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NEWS AND VIEWS IN NEWS AND VIEWS IN NEWS AND VIEWS

Copper(I)-Catalyzed N–H Insertion in Water: A New Tool for Chemical Biology

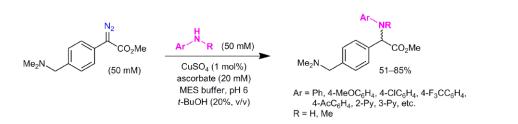
Chem. Sci. 2013, 4, 4401-4406

Methods for DNA and RNA tailoring are crucial for understanding their biological role as well as adapting them for diagnostic or therapeutic use. In most cases such modifications are done pre-synthetically, using modified building blocks (e.g., for solid-phase oligonucleotide synthesis) or post-synthetically by enzyme-catalyzed 3'-terminal transfer of the tagged nucleotide. The group of Professor Dr. Dennis Gillingham at the University of Basel (Switzerland) has been working towards the implementation of metal catalysis as a straightforward, efficient, and easy-to-use alternative for postsynthetic nucleic acid modification. Professor Gillingham said: "In this sense the CuAAC (copper-catalyzed alkyneazide cycloaddition) is a mainstay of nucleic acid chemical biology as it enables the facile introduction of a variety of functionally important tags and reporter groups into nucleic acids under mild conditions. Our initial concept, however, was to exploit the copper(I)-catalytic system for a different modification reaction, namely N-H insertion." An initial small screen study confirmed that copper(I) was indeed the best choice for a carbene-based N-H-insertion reaction amongst a number of transition-metal species.

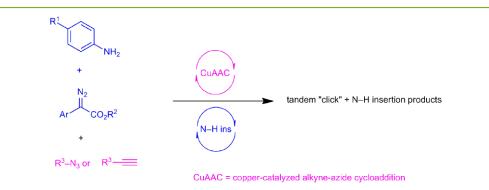
Nucleic acid conversion of up to 70% could be achieved in a matter of hours without the use of any special ligands or other additives. "Moreover, our optimized conditions converged with those for the CuAAC, and allowed us to carry out a tandem catalytic CuAAC/N-H insertion," continued Professor Gillingham. In other words, with properly engineered diazo compounds (precursors for the carbene-based N-Hinsertion) and appropriately tagged azides or alkynes, one can achieve efficient decoration of the target nucleic acid structures with the desired functionalities.

The efficacy of the copper(I)-catalyzed N-H-insertion reaction led the group to believe that it would be of value not only for nucleic acid functionalization, but also for applications with small molecules. In addition, the reaction can be carried out entirely in water - a readily available and easy-tohandle solvent. "To our delight the N-H-insertion with a number of aniline substrates in aqueous media turned out to be remarkably fast and efficient, yielding almost complete conversion of the substrates at reaction times ranging from minutes to a few hours," explained Professor Gillingham. He concluded: "The reaction also provides us with a tool for a strict selection of aromatic over aliphatic amines, as the latter proved to be completely unreactive under the conditions employed. We also showed that the copper-catalyzed N-Hinsertion works equally well alone or in combination with CuAAC, potentially making it a valuable tool for chemical library development in medicinal chemistry."

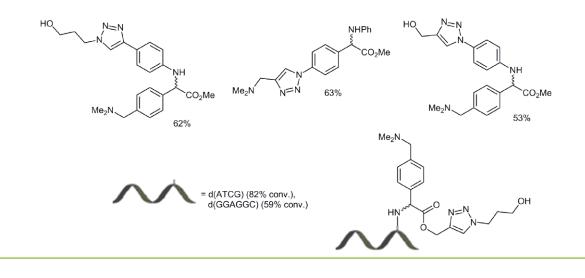
Matteo Zanda



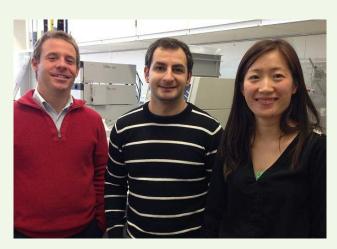
Reaction times: 15-60 min when Ar = Ph, 20 h when Ar = Py



Some tandem "click" + N–H insertion products obtained by this method:



About the authors



From left to right: Prof. Dr. D. Gillingham, K. Tishinov, N. Fei

Dennis Gillingham was born in Newfoundland (Canada). He studied at the Memorial University of Newfoundland, receiving a BSc in 2001. He then moved to Boston College (USA) for a PhD in organometallic catalysis, before joining the ETH Zürich (Switzerland) for post-doctoral work in enzymology. In November 2010 he took up his current position as an Assistant Professor at the University of Basel (Switzerland). His research interests are in new synthetic methods for chemical biology, with a particular focus on nucleic acids.

Kiril Tishinov was born in 1981 in Sofia (Bulgaria). He graduated from Sofia University with a BSc in molecular biology in 2004, and with an MSc degree in biophysical chemistry in 2008. He worked as a junior scientist at the Institute of Organic Chemistry in Sofia before starting his graduate studies at the University of Basel under the supervision of Professor Dr. Dennis Gillingham in 2011. He is currently working on catalytic synthetic strategies for DNA and RNA tailoring. This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

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Na Fei was born in Rizhao (P. R. of China). She received her Bachelor's degree in chemistry from Shandong Agricultural University (P. R. of China) in 2008. Later, she joined Shaozhong Wang's group at Nanjing University (P. R. of China) for her MSc studies. She started her PhD work in Professor Dr. Dennis Gillingham's group at the University of Basel in 2011, where she is developing new methods for the alkylation of nucleic acids.

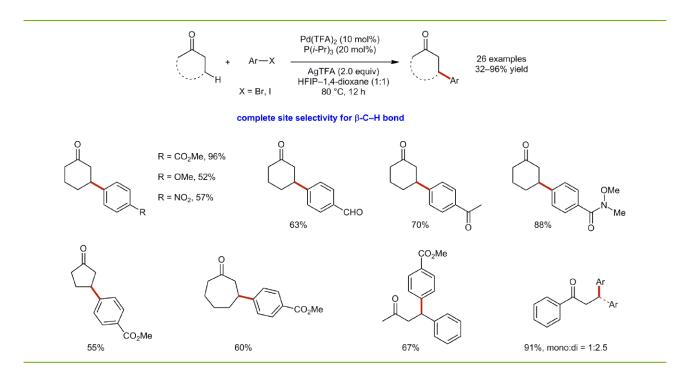
Catalytic Direct β -Arylation of Simple Ketones with Aryl lodides

J. Am. Chem. Soc. 2013, 135, 17747-17750

 \blacksquare β -Functionalization of saturated ketones is not a routine process in organic chemistry, as β-substituted ketones are normally prepared by Michael addition from α,β -unsaturated ketones or by using one of the many conceptually related variants of this textbook reaction. Recently, Professor Guangbin Dong's research group at The University of Texas at Austin (USA) reported a very useful β-arylation reaction of cyclic and acyclic ketones that expands the portfolio of methods available for the synthesis of β -aryl ketones. This project started when, after joining Professor Dong's research group, postgraduate student Zhongxing Huang raised the question about whether the direct β -arylation of ketones had been achieved previously. At that time, no such direct method was available. Professor Dong then conceived one idea on how to achieve that transformation and designed the experiments together with Zhongxing Huang, who then carried out all the experimental efforts by himself. Eventually, Zhongxing Huang and Professor Dong analyzed the data and wrote the manuscript together.

"One of the long-term goals of our group," explained Professor Dong, "is to control the **site-selectivity** of C–H functionalization using more common functional groups, such as ketones, halides or alcohols." He continued: "For this particular work, we hoped to use simple ketones to control which C–H bond would be converted into an aryl group. As we know, functionalization of carbonyl compounds represents a cornerstone of organic chemistry. Particularly, an avalanche of transformations has been achieved at the α -carbon, relying on the acidity of the α -C–H bonds. However, methods to functionalize unactivated β -C–H bonds have been generally underdeveloped."

Conventionally, β -aryl carbonyl motifs are reliably prepared via conjugate additions of aryl nucleophiles (e.g., aryl copper or aryl boron reagents) with α , β -unsaturated compounds (e.g., conjugated enones). However, the starting materials, conjugated enones and aryl nucleophiles, often come from the corresponding saturated ketones and aryl halides, which generally require several steps and redox processes. Professor



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Dong explained: "This method directly employs ketones and aryl halides as reactants, which increases efficiency and saves steps." He continued: "On the other hand, unlike conjugate additions, this method does not involve basic or nucleophilic conditions, thus, many sensitive functional groups (e.g., aldehydes, Weinreb amides, methyl ketones) are tolerated."

Professor Dong commented: "When we started this research, there was no direct method available for the β-arylation of ketones." Prior to this work, a number of Pd-catalyzed β-functionalizations of amides and esters had been developed; however, these methods are limited to linear nonketone/aldehyde substrates due to the requirement for metallocycle formation. Recently (March, 2013), MacMillan and co-workers developed a β-arylation reaction of ketones and aldehydes with electron-deficient aryl nitriles via photo-redox chemistry (*Science* **2013**, *339*, 1593). "Our method allows 1) simple (both cyclic and acyclic) ketones as substrates and 2) readily available (both electron-rich and electron-poor) aryl halides as the aryl source," said Professor Dong. "Thus, it complements the previous β-functionalization methods."

"We have demonstrated the application of this β -arylation methodology by synthesizing the intermediate of serotonin antagonists in this communication," remarked Professor Dong. "Actually, β -aryl ketones are common motifs found in many insecticides, drug candidates and other bioactive molecules." Professor Dong mentioned that a quick search for such substructures in Scifinder or Reaxys revealed hundreds of compounds that exhibit various bioactive properties. "Given that this direct β -arylation method has the potential to offer an efficient and straightforward approach to such moieties, we expect it will be widely applied in chemical and pharmaceutical industries," he said.

With regard to current or future prospects and developments, Professor Dong explained: "Firstly, we will try to fully understand the reaction mechanism (it could be far more complicated that we thought). In addition, from the reaction conditions the silver salt is the most costly component. Thus, one important direction for future development is to replace the silver salt with more economically viable promoters, such as main-group metal salts." He continued: "We believe reducing the cost of this reaction will render it more useful on a practical level. The substrate scope also needs to be further extended, such as 1) using aryl chlorides and triflates as the aryl source, and 2) optimizing the yields with the aldehydes and ketones having substituents at the C2 and C3 positions." Professor Dong concluded: "We also plan to apply this β-arylation to other carbonyl derivatives, such as esters, amides and cyanides, and, moreover, to develop enantioselective transformations."

Matteo Zanda



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From left to right: Z. Huang, Prof. G. Dong

Zhongxing Huang was born in Shanghai (P. R. of China) in 1990. He received his BSc degree in chemistry from Peking University (P. R. of China) in 2012 under the supervision of Professor Jianbo Wang and Yan Zhang. He is currently a PhD student in Professor Guangbin Dong's group at The University of Texas at Austin (USA).

Guangbin Dong received his B.S. degree from Peking University (P. R. of China) and completed his PhD in chemistry at Stanford University (USA) with Professor Barry M. Trost, where he was a Larry Yung Stanford Graduate Fellow. In 2009, he began to research with Professor Robert H. Grubbs at California Institute of Technology (USA), as a Camille and Henry Dreyfus Environmental Chemistry Fellow. In 2011, he joined the Department of Chemistry and Biochemistry at The University of Texas at Austin (USA) as an Assistant Professor and a CPRIT Scholar. His research interests lie at the development of powerful chemical tools for addressing questions of biological importance.

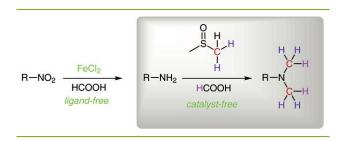


A General Method for the N-Methylation of Amines and Nitro Compounds with Dimethylsulfoxide

<u>Chem. Eur. J. 2013, 20, 58–63</u>

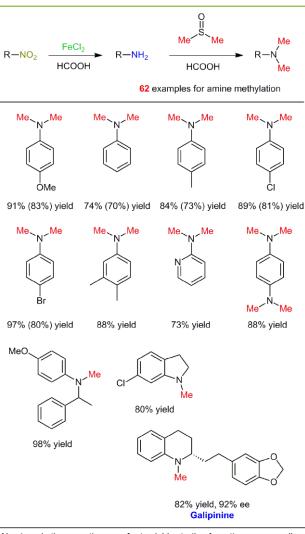
N-Methylation of amines is an important reaction in biological processes, as well as a general and ubiquitous transformation in organic synthesis. Many natural products, pharmaceuticals, and dyes, as well as bulk and fine chemicals, contain N-methylated amine moieties. These amines are generally prepared via N-methylation reactions of primary or secondary amines with methylating reagents, such as iodomethane and dimethyl sulfate. Alternatively, formaldehyde could be used in the presence of a reducing reagent (reductive N-methylation). One famous example is the Eschweiler-Clarke reaction, in which formaldehyde and formic acid are used for the methylation of amines. The limitations of these methods are that most of the methylating reagents are toxic or carcinogenic, and that the reactions have issues of chemoselectivity such as over-methylation or limited substrate scope. Although greener N-methylation methods are emerging, for example, using dimethyl carbonate, methanol or carbon dioxide, new reactions featuring simpler operational protocols, better environmental compatibility, and broader substrate scope are highly desirable.

Professor Chao Wang's newly formed group in the Department of Chemistry & Chemical Engineering at Shaanxi Normal University (P. R. of China) is interested in developing new and green methods for organic synthesis with the aid of molecular catalysis. Professors Wang and Xiao commented: "During our study aimed at greener amination reactions (*Chem. Commun.* **2013**, *49*, 5408; *Chem. Eur. J.* **2013**, *19*, 4021; *Green Chem.* **2013**, *15*, 2685), we serendipitously discovered that *p*-anisidine could be methylated by a dimethylsulfoxide (DMSO) solution of formic acid, requiring no other reagents."





The reaction turned out to be surprisingly general, with primary, secondary and heterocyclic amines all being N-methylated with moderate to excellent yields. Moreover, aromatic nitro compounds could also be one-pot-reduced to amines and N-methylated with good yields in an unprecedented way, using a cheap iron catalyst without employing any ligand (Scheme 2).



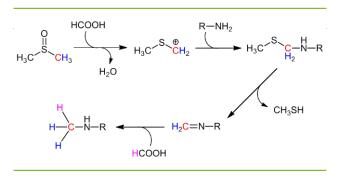
Numbers in the parantheses refer to yields starting from the corresponding nitro compounds.

Scheme 2

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The mechanism of this new transformation was studied in detail. "We initially thought that the reaction might proceed via the formation of a formamide followed by amide reduction, as formamide could be easily formed under the reaction conditions," said Professor Wang. "However, when ¹³C-labelled formic acid was used, we did not observe any ¹³C-labelled methyl groups in the newly formed *N*-methyl amine product. We then used various deuterium reagents to further probe the mechanism." The results clearly showed that out of the three hydrogens in the newly formed *N*-methyl group, two came from DMSO and one from formic acid. On the basis of these studies and known chemistry of DMSO, a mechanism was proposed as shown in Scheme 3. Further support for the mechanism was found in the trapping of the sulfonium intermediate with 1,3,5-trimethoxybenzene.



Scheme 3

Both molecules involved in the N-methylation could be derived from renewable resources. Indeed, DMSO is a cheap, relatively low-toxicity solvent widely used in organic synthesis and the pharmaceutical industry: it is a by-product of the wood industry through the Kraft process. Formic acid can be obtained from biomass feed stocks via acid dehydration of carbohydrates. Professors Wang and Xiao concluded: "Thus, this novel N-methylation reaction provides a green, practical method for the synthesis of *N*-methyl amines starting from either amines or nitro compounds, with the additional merit of being operationally simple and of using cheap reagents. The ease with which ¹³C and various levels of ²H isotopes could be introduced into the *N*-methyl amines may make the method particularly valuable for biological studies."



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About the authors



Chao Wang was born in Hunan (P. R. of China) in 1981. He received his BSc in chemistry from Hunan Normal University in 2004. He then moved on to an MSc in organic chemistry with Professor Yi Jiang at the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China). He obtained his PhD from the University of Liverpool (UK) in the group of Professor Jianliang Xiao

Prof. C. Wang

in 2011, and joined Shaanxi Normal University (P. R. of China) as an Associate Professor in the same year. He received the Chinese Government Award for Outstanding Self-financed Students Abroad 2010. His current research interests include deydrogenation reactions, selective transformation of biomass platform molecules with molecular catalysis, and green chemistry.



Jianliang Xiao received his B.Eng at the Northwest University in Xi'an (P. R. of China) in 1982. This was followed by an M.Eng with Professors Chi Wu and JunYu Wang at the Research Institute of Petroleum Processing in Beijing (P. R. of China) and a PhD in organometallic chemistry under Professor Martin Cowie at the University of Alberta (Canada). After a two-year postdoctoral appointment with Profes-

Prof. J. Xiao

sor Richard J. Puddephatt at the University of Western Ontario (Canada), he joined the ERATO Molecular Catalyst Project as a Researcher to learn homogeneous catalysis under 2001 Noble Laureate Professor Ryoji Noyori. In 1996, he took up a Principal Scientist position at the University of Liverpool (UK), becoming a Lecturer in the Chemistry Department in 1999. He was promoted to Professor in 2005 and is now Professor of Catalysis at the University of Liverpool. He was awarded the UK Prize for Process Chemistry Research (2008) and the Chang-Jiang Chair Professor by the Ministry of Education of China for collaborative research at Shaanxi Normal University. His research is concerned with the design, assembly and understanding of molecular architectures that act as catalysts for sustainable chemical synthesis.

Young Career Focus: Dr. Santosh J. Gharpure (Indian Institute of Technology Bombay, Mumbai, India)

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. Santosh J. Gharpure, Indian Institute of Technology (IIT) Bombay, Mumbai, India.

BIOGRAPHICAL SKETCH



Santosh J. Gharpure was born in Thane, Maharashtra (India) in 1974 and grew up in Kasa, Maharashtra (India). He received his B.Sc. degree from KET's V. G. Vaze College in Mumbai (India) in 1994. He joined the IIT Bombay, Mumbai (India) for an M.Sc. program during which he did his M.Sc. dissertation with Professor (Mrs.) S. V. Bhat. Subsequently, he joined the Indian Institute of

Dr. S. J. Gharpure

Science Bengaluru for a Ph.D. program under the guidance of the late Professor A. Srikrishna and graduated in 2001. His Ph.D. thesis focused on enantiospecific total synthesis of neopupukeananes belonging to the sesquiterpene class of natural products. From 2001–2004, Santosh was a Postdoctoral Fellow at Indiana University, Bloomington (USA) in the lab of Professor P. Andrew Evans. He developed bismuthmediated etherification reactions for the synthesis of cyclic ethers, which were used in the total synthesis of mucosin – a natural product belonging to the family of *anonaceous* acetogenins and a potent antitumor agent active against pancreatic cancer.

Upon his return from the USA, Santosh joined the Department of Chemistry, IIT Madras (India) as an Assistant Professor. In 2012, he moved to the Department of Chemistry, IIT Bombay, Mumbai as an Associate Professor. His research focuses on organic chemistry pertaining to natural and unnatural product synthesis and developing new synthetic methodologies.

Santosh is a recipient of the INSA Medal for Young Scientists awarded by the Indian National Science Academy, New Delhi. He was presented with the IIT Madras Young Faculty Recognition Award (YFRA) for his contribution in teaching and research in 2010. He received the B. M. Birla Science Prize in Chemistry for the year 2011. Recently, he was selected as one of the Thieme Chemistry Journal Awardees for the year 2013.

INTERVIEW

SYNFORM What is the focus of your current research activity?

Dr. Santosh J. Gharpure We are developing new methods for the stereoselective synthesis of natural and unnatural products bearing both oxa- and azacycles. One major focus of our research has been following a functional group based approach, i.e. using vinylogous carbonates and carbamates for constructing these heterocycles under a variety of conditions. In another direction, we are developing new strategies for the construction of 1,4-heterocycles using oxonium ion chemistry as well as transition-metal-mediated coupling reactions. We are exploiting o-quinone methides (o-QMs) for the stereoselective synthesis of benzopyrans. We have always aimed towards applying the developed methods in the synthesis of natural products. The other focus in our research is directed toward the synthesis of unnatural products. These are designer molecules such as oxa-bowls, which have aesthetically pleasing, symmetrical architectures with distinct concave and convex faces. In a collaborative program, we are using these as ligands in the synthesis of metal-organic frameworks or co-ordination polymers as well as in discrete molecular self-assembly.

SYNFORM When did you get interested in synthesis?

Dr. Santosh J. Gharpure After finishing high school, I chose to pursue science rather than opting for a course in engineering or medicine. It was in the final year of my B.Sc. during 'study circles' conducted by Professor Lakshmy Ravishankar that it became abundantly clear to me that I would like to pursue a career in organic synthesis. It was while doing the project work at IIT Bombay during M.Sc. days when I was clinched to the pursuit of organic synthesis. The training acquired during my Ph.D. at IISc and a postdoctoral stint at Indiana University gave further definitive shape to the pursuit. The interest and the passion in the subject increased manifold while teaching the bright students of IIT.

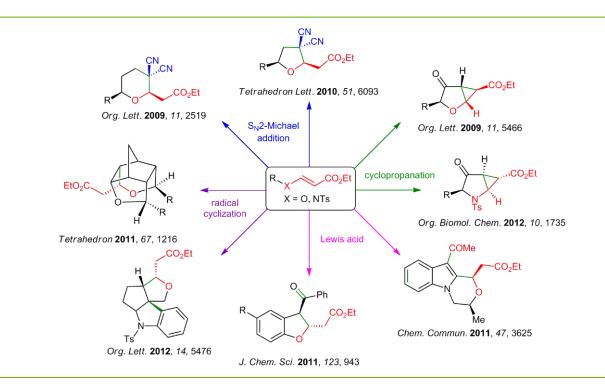
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SYNFORM What do you think about the modern role and prospects of organic synthesis?

Dr. Santosh J. Gharpure In the past century, organic synthesis largely focused on natural product synthesis. Method development was also pursued in parallel to solve related problems. Enormous progress has been made over the years and modern organic synthesis touches human life directly. It could be in the form of materials like polymers or organic electronics or life-saving medicines. And yet, there are many challenges - challenges in terms of making synthesis more efficient – higher yields, higher stereoselection and at the same time maintaining cognizance of environmental concerns. So the emphasis on developing green synthetic methods as well as tandem reactions factoring in atom economy and step economy has gained currency. New discoveries and innovations in organic synthesis will further help in solving problems at the frontiers of biology as well as materials chemistry.

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

Dr. Santosh J. Gharpure The main focus of our research has been the development of new methods for the synthesis of natural and unnatural products of biological relevance. We have used vinylogous functional groups, namely carbonates and carbamates, in the stereoselective synthesis of both oxa- and azacycles. The reactivity of vinylogous carbonates/carbamates was studied under a variety of conditions. Thus, our group has used radical cyclization to vinylogous carbonates/carbamates for the stereoselective synthesis of new oxa-cages as well as angular oxa- and azatriquinanes (Scheme 1). An efficient strategy for the synthesis of tetrahydrofurans, tetrahydropyrans, and benzoxepine derivatives has been developed employing a tandem S_N2-Michael addition to vinylogous carbonates. On the other hand, intramolecular cyclopropanation of vinylogous carbonates and carbamates using carbenes led to the oxygen- and nitrogenbearing donor-acceptor-substituted cyclopropanes (DACs), respectively. Vinylogous carbonates/carbamates were also found to show useful reactivity in the presence of Lewis acids undergoing intramolecular Pictet-Spengler as well as Prins-type cyclizations leading to N-fused oxazinoindoles, dihydrobenzofurans and dihydroindole derivatives. Apart from this, our group has developed an efficient method for the synthesis of flavans and isoflavans. The strategy relying

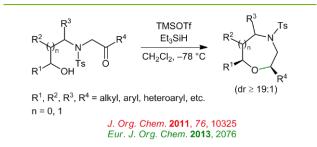


Scheme 1

on quinone methides has been used for the total synthesis of a variety of natural products of this family, like equal, 3'-hydroxyequal, vestitol and myristinin B/C.

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

Dr. Santosh J. Gharpure Typically, only the bond that is sandwiched between donor and acceptor of the DAC can be cleaved regioselectively. With our design of DACs possessing two acceptors and one donor on different carbon atoms, we were able to show that each of the cyclopropane bonds of substituted DACs can be cleaved with complete regiocontrol by judicious choice of the reaction conditions. Harnessing the reactivity of these DACs led to ready assembly of a diverse array of oxa- and azacycles as well as lactones.



Scheme 2

We have also developed a general strategy for the stereoselective construction of biologically important, diversely substituted 1,4-heterocycles like morpholines and oxazepanes through oxonium ion intermediates (Scheme 2).

Matteo Zanda

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2014/04 is available from March 18, 2014

In the next issues:

SYNSTORIES

a, β -Unsaturated Acyl Cyanides as New Bis-Electrophiles for Enantioselective Organocatalyzed Formal [3+3] Spiroannulation (*Focus on an article from the current literature*)

Total Synthesis and Anti-Hepatitis C Virus Activity of MA026 (Focus on an article from the current literature)

Rapid Assembly of Complex Cyclopentanes Employing Chiral, α,β-Unsaturated Acylammonium Intermediates (Focus on an article from the current literature)

FURTHER HIGHLIGHTS ++++

SYNTHESIS

Review on: Sequential Addition/Cyclization Processes of α,β -Ynones and α,β -Ynoates Containing Proximate Nucleophiles (by A. Arcadi et al.)

SYNLETT

Account on: The Design and Synthesis of Planar Chiral Ligands and Their Application to Asymmetric Catalysis (by W. Zhang et al.)

SYNFACTS

Synfact of the Month in category "Polymer-Supported Synthesis": <u>A Silicon Nanowire Array Stabilized Palladium-Nanoparticle</u> <u>Catalyst</u>

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