

SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/02

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■ **New Approaches to Functionalize Glycine Derivatives via Direct C–C Bond Formation**

■ **Stereoretentive Halogenations and Azidations with Titanium(IV) Enabled by Chelating Leaving Groups**

■ **[4+2] Cycloadditions of *N*-Alkenyl Iminium Ions: Structurally Complex Heterocycles from a Three-Component Diels–Alder Reaction Sequence**

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Dear readers,

Recently, Professor Victor Snieckus from the University of Kingston (Ontario, Canada), who is a Regional Editor of *SYNLETT*, wrote in a letter to Chemical & Engineering News (2009, no. 2, 4) that “green chemistry

is defined as attempting to do chemistry the way Nature does chemistry” thus emphasizing “how incompetent we (especially organic chemists) ... are in the lab compared to Nature’s ways.” I think this definition captures very well the current level of chemistry, and particularly of organic chemistry, which remains way too far from the efficiency the World would need. However, organic chemists are working hard to meet that challenging goal. This is also well demonstrated by the high level of innovation and originality featured by the pieces of research highlighted in this issue of *SYNFORM*. Direct α -functionalization of amino acids and small peptides was achieved by the group of Professor C.-J. Li (Canada), while Professor S. D. Lepore (USA) found an amazingly simple and direct method to displace hydroxy groups by many nucleophiles in a stereoretentive manner. Finally, Professor S. G. Nelson (USA) developed a versatile new entry to nitrogen-containing heterocycles using *N*-alkenyl iminium ions as heterodienes in Diels–Alder-type reactions. We are still far from Mother Nature’s efficiency, but work is definitely in progress...

Enjoy your reading!!!

Matteo Zanda

Editor of *SYNFORM*

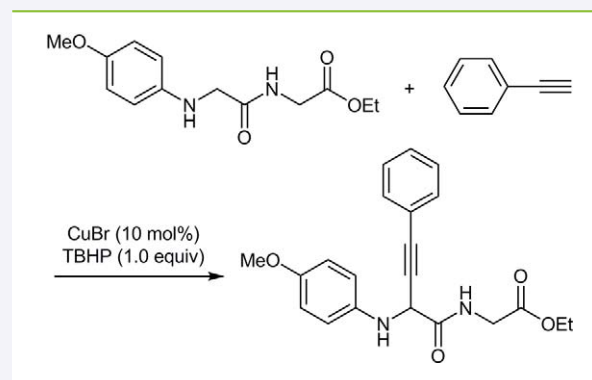
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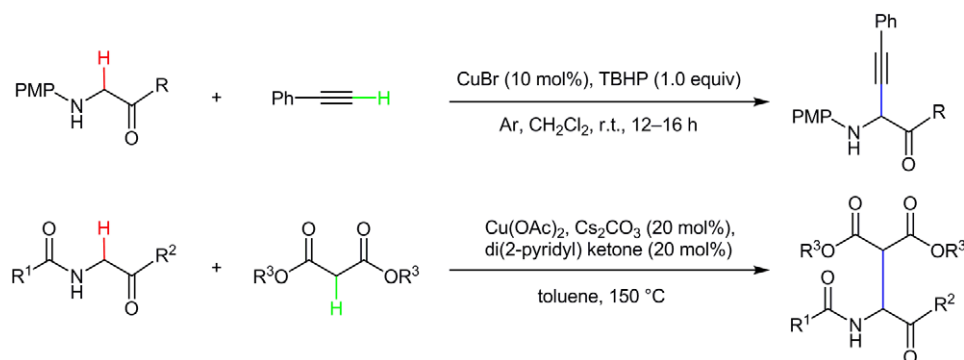
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New Approaches to Functionalize Glycine Derivatives via Direct C–C Bond Formation

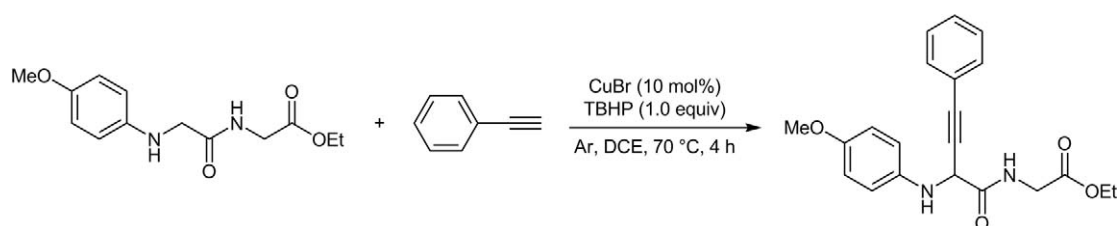
Angew. Chem. Int. Ed. **2008**, *47*, 7075–7078



■ Direct α -functionalization of α -amino acid derivatives with nucleophiles has recently attracted much interest in the field of organic chemistry due to the fact that α -amino acid derivatives can be used as nucleophiles by first letting them react with a stoichiometric amount of base. The carbanion thus formed will be able to undergo several reactions, such as substitutions with electrophiles, Claisen rearrangements, and transition-metal-catalyzed cross-coupling reactions.

Now, according to Professor Chao-Jun Li from the Chemistry Department of McGill University in Montreal (Canada), it is possible to achieve the direct α -functionalization of α -amino acid derivatives with nucleophiles using the cross-dehydrogenative-coupling (CDC) method. “The beginning of this project was, however, not as easy as it looks,” said Professor Li. “The substrates initially tested were simple secondary alkylamino acid derivatives. The problem associated with those simple secondary alkylamines is that various competing reactions can occur.”

“We envisaged that it would be possible to use a special secondary amine or amide that could control the regioselectivity of the reaction site and, once it was oxidized, the proposed imine-type intermediate would be stable enough to undergo further reactions,” said Professor Li. Bearing this idea in mind, a variety of secondary amine substrates were tested. Among them, *N*-acetyl glycine ester and *N*-*p*-methoxyphenyl (PMP) glycine amide were both effective in coupling with phenyl acetylene and malonate under their respective reaction conditions to afford the corresponding coupling products. Furthermore, it is also possible to apply this methodology towards short-chain peptide modifications, which are normally very difficult to carry out. It is worth mentioning that the *N*-PMP glycine amides are surprisingly much more effective in CDC reactions than the *N*-PMP glycine esters.



“We believe that this new concept will provide an important and complementary approach to access natural and non-natural α -amino acid derivatives and short-chain peptides. For modifications of short-chain peptides using the state-of-art enolate chemistry, scrambling and racemization of stereochemistry on other amino acid moieties might occur. The current CDC approach avoids the use of a base and allows selective

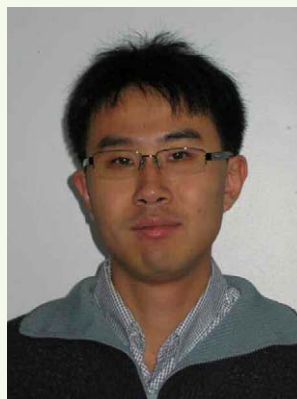
functionalization of the N-terminus carbon of the peptides under neutral conditions,” said Professor Li. “The current tasks for us are to expand the scope of nucleophiles and to explore a good system to achieve the enantioselective functionalization,” he concluded. ■

Matteo Zanda

About the authors

Chao-Jun Li was born in Henan (P. R. of China) in 1963. He received his B.Sc. degree from Zhengzhou University (1983), M.Sc. degree from the Chinese Academy of Sciences in Beijing (1988), and Ph.D. degree at McGill University (1992) (with T. H. Chan and D. N. Harpp). He spent 1992–1994 as an NSERC Postdoctoral Fellow with B. M. Trost at Stanford University (USA). He was an Assistant Professor (1994), Associate Professor (1998), and Full Professor (2000–2003) at Tulane University (USA) and a visiting faculty (with Robert G. Bergman) at the University of California at Berkeley (USA) in 2002. In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. His current research efforts are focused on developing innovative and fundamentally new organic reactions that will defy conventional reactivity and have high synthetic efficiency. His widely recognized research includes the development of Grignard-type reactions in water, transition-metal catalysis in air and water, alkyne–aldehyde–amine coupling (A^3 -coupling), asymmetric alkyne–aldehyde–amine coupling (AA^3 -coupling), and cross-dehydrogenative coupling (CDC) via the reactions of C–H bonds.

Liang Zhao was born in Zhengzhou (P. R. of China) in 1980. He received his B.Sc. degree from Zhengzhou University (2003). In 2004, he joined C.-J. Li's research group. He is currently a Ph.D. student at McGill University. His current research interest is C–H bond functionalizations.



L. Zhao



Prof. C.-J. Li

Stereoretentive Halogenations and Azidations with Titanium(IV) Enabled by Chelating Leaving Groups

Angew. Chem. Int. Ed. **2008**, *47*, 7511–7514

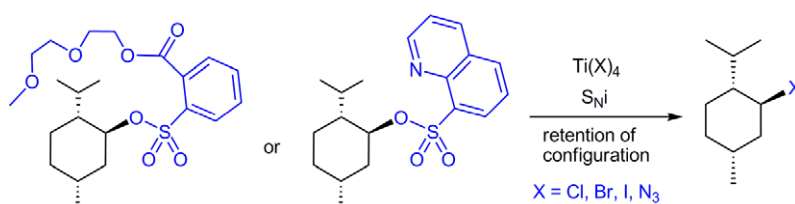
■ Having played a key role in such powerful reactions as the Mukaiyama aldol and the Nobel prize winning Sharpless epoxidation, titanium(IV) reveals its utility once again in a recent contribution from the group of Professor Salvatore D. Lepore from the Florida Atlantic University, Boca Raton (USA) on stereoretentive and chemoselective halogenations and azidations of hindered secondary sulfonates. “For the first time,” said Professor Lepore, “alcohols as their sulfonates can now be converted into azides with retention of configuration without having to resort to a double inversion technique. In addition, this method actually favors more hindered substrates and is thus complementary to S_N2 -based methods.”

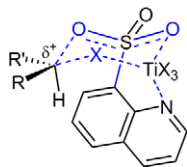
This new application for titanium(IV) was made possible by the use of aryl sulfonate based nucleophile-assisting leaving groups (NALGs) which were introduced by the Lepore group in 2005 (*J. Org. Chem.* **2005**, *70*, 8117). “NALGs may be defined as leaving groups which contain a chelating arm capable of stabilizing the transition state by chelating either a positively charged or a Lewis acidic metal center of a nucleophilic metal salt and thus enhance the rate and selectivity of nucleophilic substitution reactions,” explained Professor Lepore. “In our lab, aryl sulfonate based NALGs have been developed containing oligo-ether units as the chelating arm. The rate study of nucleophilic substitution reactions of NALGs sulfonate ester of alcohol with alkali metal halides in acetone has not only proved the concept of better reactivity of NALGs, but also provided evidence of a rare S_Ni mechanism. (For our recent review see *Tetrahedron* **2007**, *63*, 5103).”

One of the goals of the Lepore group with this new NALG technology was that it should do more than simply improve upon existing reactions. “We wanted to create a leaving group

that opened the door to new reactivity,” confirmed Professor Lepore. “Indeed, we became aware of the reactive potential of these new leaving groups in 2006 when we discovered a very rapid and completely stereoretentive chlorination of secondary hindered sulfonates at -78°C using TiCl_4 as a Lewis acid nucleophile (*J. Org. Chem.* **2006**, *71*, 3285). We noted that, while these leaving groups are very reactive towards selected reagents, they are completely stable to flash chromatography and can easily be stored,” he said. “Our continued studies of this reaction with other titanium(IV) species revealed that this transformation was of significantly broader scope. This is what led us to the work described in our 2008 *Angewandte* paper.”

“Our earlier NALGs contained mainly ether chelating units; however, we also found 8-quinoline sulfonate to be a phenomenal leaving group,” said Professor Lepore. “This nucleofuge gave excellent yields of substitution products with stereoretention, probably due to its increased conformational rigidity relative to our ether NALGs. Our nickname for this leaving group is ‘quisylate’, following the pattern of tosylate, mesylate and so on.” Although Professor Lepore and co-workers have not yet verified this computationally, they believe the most plausible mechanism to explain the observed results involves a six-membered transition state where titanium is coordinated to the quisylate aromatic nitrogen and one of the sulfonate oxygens. “In this model,” he said, “we expect a partial positive charge on the carbinol carbon in the transition state which may explain this reaction’s strong preference for secondary substrates. The front-side attack implicit in this cyclic transition state may also help in rationalizing the nearly exclusive retention of configuration observed in the substitution products.”



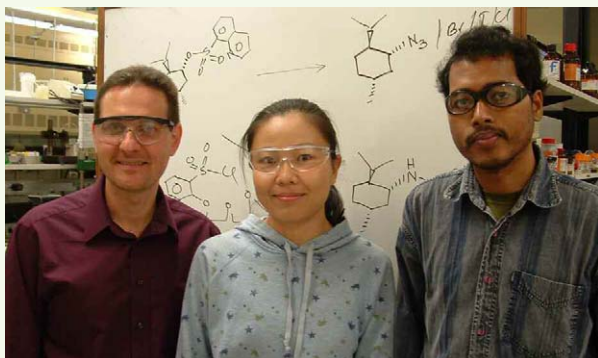


“This project also gave us the opportunity to design new reagents that might take full advantage of our chelating leaving groups,” said Professor Lepore. “For example, titanium(IV) azide, used in our stereoretentive azidation reactions with quinsylates, was never reported before, except in a crystallographic study. We sought to increase the Lewis acidity of this reagent and hence the reaction rate through the use of a mixed titanium(IV) reagent containing a non-transferable ligand with more electron-withdrawing capacity than azide.” According to Professor Lepore, graduate students Debo Mondal and Songye Li spent many months on this phase of the project, scanning numerous ligands and reaction conditions to produce

the optimal effect, especially with acyclic substrates which proved to be more problematic. The best results were achieved with $\text{TfOTi}(\text{N}_3)_3$, prepared by reacting trimethylsilyl triflate (1 equiv) with TiF_4 followed by the subsequent addition of TMSN_3 (3 equiv). “This new Lewis acid gave superior azidation results with quinsylate substrates,” said Professor Lepore. “The use of triflate to activate the azidation reagent may prove a useful and more general strategy in the development of future titanium(IV) reactions with NALGs involving reagents with diminished Lewis acidity.”

Professor Lepore believes this work not only describes an important new synthetic method but it also validates the idea that new nucleofugal entities can be designed to enable reactions not possible with currently available leaving groups. “Indeed,” he concluded, “we are beginning to extend the NALG/Ti(IV) concept to new reactions including stereoretentive carbon–carbon bond formation.” ■

Matteo Zanda



From left: Prof. S. D. Lepore, S. Li, D. Mondal

About the authors

Deboprosad (Debo) Mondal received his B.Sc. degree in chemistry from Calcutta University (India) in 2002 and his M.Sc. from the Indian Institute of Technology, Kanpur (India) in 2004. Currently, he is a fifth-year doctoral student in the Chemistry Department at Florida Atlantic University under the supervision of Professor Lepore. His research involves designing new leaving groups to solve critical problems in organic synthesis. He is also developing titanium(IV) reagents for stereoretentive halogenations, azidation and amide formation.

Songye Li received her B.Sc. and M.Sc. degrees in polymer science and engineering from Tianjin University (P. R. of China) in 2001 and 2004, respectively. Currently, she is a fourth-year doctoral student in the Chemistry Department at

Florida Atlantic University under the supervision of Professor Lepore. Her research involves developing new aryl sulfonate based NALGs with emphasis on their kinetic study and application to fluorination reactions for eventual application in positron emission tomography.

Salvatore D. Lepore was born in Philadelphia (USA) and received his B.Sc. in Chemical Engineering with honors in 1992 from the University of South Florida. He worked for one year as an engineer for an environmental consulting company before deciding to pursue graduate studies at Purdue University (USA). Salvatore received his doctoral degree in 1997 under the guidance of Merritt B. Andrus in the area of natural product total synthesis. He then spent three years as a postdoctoral fellow at Eli Lilly in Indianapolis (USA) under the direction of Michael R. Wiley. Salvatore's studies at Lilly focused on the development of new methods for solid-phase synthesis. In 2000, he joined the chemistry faculty at Florida Atlantic University as an Assistant Professor and was promoted to the Associate level in 2006. His current research efforts are in the development of new leaving groups with applications in radiotracer synthesis. He is also developing new asymmetric methods for the preparation of conjugated allenyl carbonyl compounds with applications in natural product total synthesis. Salvatore's research has been funded by a number of agencies including the ACS PFR, NIMH, NIGMS, NSF, and Florida Centers of Excellence program. In 2006, he received his university's Researcher of the Year award. His teaching excellence has been recognized by awards from a number of university and student organizations.

[4+2] Cycloadditions of *N*-Alkenyl Iminium Ions: Structurally Complex Heterocycles from a Three-Component Diels–Alder Reaction Sequence

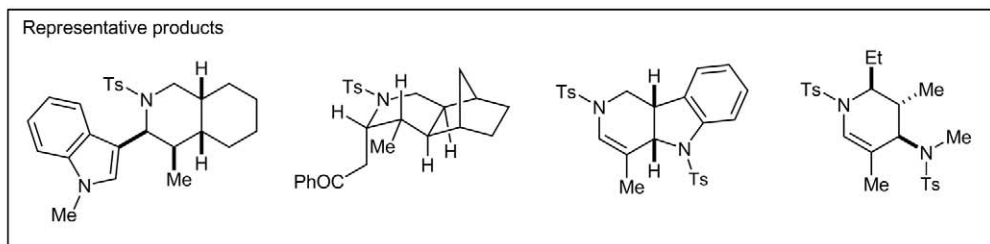
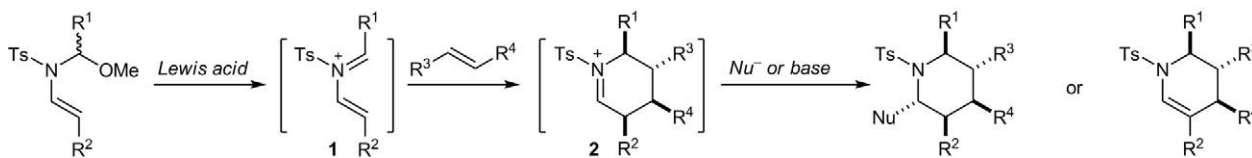
J. Am. Chem. Soc. **2008**, *130*, 9222–9223; *Synfacts* **2008**, 1039 (SYNFACT of the Month)

■ Nitrogen-containing heterocycles, including piperidine structural motifs, are ubiquitous substructures in a myriad of biologically active natural products and small-molecule pharmaceuticals. Accordingly, a wide range of target-directed and diversity-oriented synthesis activities are devoted to heterocycle synthesis. Recently, the group of Professor Scott G. Nelson from the University of Pittsburgh, Pennsylvania (USA) reported a novel approach to piperidine scaffolds based on a hetero-Diels–Alder reaction employing *N*-alkenyl iminium cations as heterodienes. “As part of our research in the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD),” said Professor Nelson, “we were interested in developing reactions capable of generating structurally complex and diverse heterocycles in a single operation from readily available reaction components.”

Professor Nelson indicated that the work was inspired by Heathcock’s investigations of related intermediates involved in the total synthesis of the *Daphniphyllum* alkaloids. The authors, therefore, focused on expanding existing hetero-Diels–Alder based approaches to heterocycle synthesis by developing cationic 2-azadienes **1** as conduits to three-component [4+2] cycloaddition reactions that would provide access to structurally and stereochemically diverse piperidine

derivatives (see Scheme). “The diene structure was central to a reaction design wherein the initial cycloaddition event would generate another reactive intermediate suitable for further, direct functionalization,” explained Professor Nelson. “Specifically, the putative *N*-alkenyl iminium ion-alkene [4+2] cycloadditions would generate tetrahydropyridinium ion cycloadducts **2**, allowing further functionalization through nucleophilic addition to the transposed iminium ion **2**. At the outset,” he continued, “it was unclear whether the *N*-alkenyl iminium ion dienes would be subject to the well-established mechanisms for *endo*, or *exo*, diastereoselection characterizing traditional Diels–Alder reactions. We were, therefore, gratified to discover that these processes could involve highly *endo*- or *exo*-selective cycloadditions and the mechanisms responsible for this diastereoselection.” The *N*-alkenyl iminium ions **1** emerged from these investigations as excellent substrates for these three-component [4+2] cycloaddition–iminium ion addition reactions that afford an efficient and versatile synthesis of highly substituted piperidine heterocycles.

According to Professor Nelson, “nitrogen-containing heterocycles are essential components of a vast array of chemotherapeutic agents. Moreover, nitrogen heterocycles continue to offer exceedingly attractive, challenging, and widely explored



targets for chemical synthesis. Therefore, reaction methodologies offering new or complementary strategies for accessing this important family of heterocycles have, traditionally, had considerable impact on chemists in both synthetic and medicinal chemistry laboratories. We hope," he concluded "that the *N*-alkenyl iminium ion cycloadditions find a productive place among these enabling reaction methodologies." ■

Matteo Zanda



From left: Prof. S. G. Nelson, N. Sarkar (A. Banerjee not pictured)

INFORMATION ++++

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(Focus on an article from the current literature)

■ **Synthesis of 3-Chlorofurans and 5-Chlorofuropyrimidine Nucleosides**
(Focus on an article from the current literature)

■ **Gold-Catalyzed Synthesis of Aromatic Azo Compounds from Anilines and Nitroaromatics**
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

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