SYNSTORIES

- Oxidative Hydration of Alkynes: A Modular Connection Tool

- New Palladium(II)-Catalyzed Aerobic Oxidative Carbocyclizations

- A General Synthesis of syn-Deoxypolypropionates by Rhodium-Catalyzed Enantioselective Desymmetrization of meso-3,5-Dimethyl Glutaric Anhydride

- “Cycloaddition–Fluorination” Strategy for the Synthesis of Monofluorinated Carbocycles
Dear readers,

The 234th American Chemical Society (ACS) National Meeting & Exposition held in Boston on August 19–23, 2007 was, as usual, a huge event, featuring several thousands of communications, including oral presentations and posters, with a very high average level of quality. A number of outstanding speakers, including Nobel prize winners, and events, such as the Arthur C. Cope Awards as well as the Tetrahedron Prize Symposia, a very rich program of parallel sessions (perhaps even too many...), and an extremely rich exposition gave to the many attendees from all over the world a great opportunity to gather together and be exposed to the newest trends in the field of chemical sciences, and beyond. Every time I attend an ACS Meeting I have the feeling that if something is not presented there, then it probably doesn’t exist... Particularly impressive to me was the high level of the many presentations offered by young people, namely graduate students and postdocs, that certainly warrant a brilliant future to chemistry. The work of two of them, namely Jessica Raushel (and Professor V. Fokin) from the The Scripps Research Institute (USA) and Julio Piera (together with Professor J.-E. Bäckvall) from the University of Stockholm (Sweden), is presented in two SYNSTORY articles. Two more SYNSTORIES complete this issue. One is focused on a work published by Professor Tomislav Rovis (Colorado State University, USA), that was recently selected as a Synfact of the Month, on a new methodology in enantioselective synthesis. The other one deals with a new strategy for the selective preparation of organofluorine compounds, which was recently developed by Dr. Veronique Gouverneur and her group from Oxford University (UK).

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM

CONTACT

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
Organic azides and alkynes offer a unique window of reactivity, which can be useful in addressing the current challenges faced by chemists working in the fields of diversity-oriented synthesis of functional small molecules, chemical biology, and materials science. Owing to their chemical inertness, both are virtually ‘silent’ under most common synthetic and physiological conditions, and can be introduced in the synthetic scaffolds through standard transformations or in biomolecules of interest at genetic and post-translational levels. Products of their traceless union, 1,2,3-triazoles are among the most hydrolytically and oxidatively stable heterocycles. Furthermore, due to the high activation barrier of the reaction, azides and alkynes remain invisible to each other until the reaction between them is triggered by an appropriate catalyst.

The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC), which regiospecifically leads to 1,4-disubstituted 1,2,3-triazoles, has enjoyed numerous applications. It has enabled the discovery of novel bioactive compounds, ligands for transition metals, new materials, and bioconjugates, underscoring its exceptionally broad scope and fidelity. In an oral communication at the recent ACS meeting in Boston, fifth-year graduate student Jessica Raushel from The Scripps Research Institute in La Jolla, California (USA), with the postdoctoral fellows Dr. Suresh M. Pitram, Dr. Michael P. Cassidy and Associate Professor Valery V. Fokin as co-authors, reported new perspectives and applications of this chemistry. “While alkyl and aryl azides readily produce the expected 1,2,3-triazole products,” explained Jessica Raushel, “the reactions of sulfonyl azides proceed via a different pathway, forming reactive ketenimine intermediates with concomitant loss of a molecule of dinitrogen. The ketenimine intermediate then readily undergoes reactions with nucleophiles. Under aqueous conditions,” she continued, "N-acyl sulfonamides are readily formed. Thus, the copper-catalyzed reaction of sulfonyl azides with alkynes represents the formal oxidative hydration of a triple bond, expanding the scope of the CuAAC by shunting it in a distinctly different mechanistic pathway.” The modularity of the reaction (in effect, it is a three-component coupling which involves sulfonyl azides, terminal alkynes, and a nucleophile) makes it ideal for the synthesis of diverse libraries of N-acyl sulfonamides, amides, and imidates, which can be further functionalized if the appropriate reactive handles are present in the starting materials.

“The modular reaction sequence on the next page illustrates the incorporation of five separate modules,” concluded Jessica. “All reactions proceed in good to excellent yield and are experimentally simple, often requiring no purification step beyond filtration.”
About the authors. Jessica Raushel received a B.Sc. degree in chemistry from Texas A&M University (USA) in 2003. In the fall of 2003, she entered the graduate program at The Scripps Research Institute and joined the group of Professors K. Barry Sharpless and Valery V. Fokin. Currently, Ms. Raushel is a 5th-year graduate student. Valery V. Fokin received his Diploma in chemistry in 1993 from the University of Nizhny Novgorod (Russia) and his Ph.D. degree in 1998 from the University of Southern California (USA). After a postdoctoral stint in the group of Professor K. Barry Sharpless at The Scripps Research Institute in La Jolla, California, he was appointed Assistant (2000) and then Associate (2006) Professor in the chemistry department at Scripps. His research is centered on understanding chemical reactivity and its applications in chemistry, biology, and materials science.
Oxidation reactions are of fundamental importance in nature and selective aerobic oxidations of organic molecules are of key interest in modern organic chemistry. In the past decades there has been an increasing demand to develop catalytic processes where the terminal oxidant is molecular oxygen. The advantages of using molecular oxygen as oxidant are obvious not only from an environmental point of view but also for economical reasons. However, there is usually a high energy barrier for the direct reoxidation of the reduced form of the metal. This problem can be circumvented by mimicking biological oxidations, where large jumps in oxidation potentials are avoided by the use of several coupled redox catalysts as electron-transfer mediators (ETMs). In a biomimetic approach inspired by the aerobic chain, a metal catalyst would be used instead of NADH, a quinone in place of ubiquinone, and an oxygen-activating metal macrocycle would substitute cytochrome c in the transfer of electrons from the substrate to oxygen. At present there is a lack of efficient oxidative C–C bond-forming reactions with molecular oxygen as the oxidant since these reactions are often associated with the formation of radicals, leading to side products from auto-oxidation.

Now, Professor J.-E. Bäckvall, Dr. J. Piera and co-workers at Stockholm University (Sweden) have developed a novel aerobic oxidative carbocyclization of allene-substituted olefins and conjugated dienes via a multi-step electron transfer involving three redox systems: Pd(II)/Pd(0)–BQ/HQ–Fe(Pc)(ox)/Fe(Pc)(red), where Fe(Pc) is iron phthalocyanine. This system allows the use of a catalytic amount of Pd(II), BQ and Fe(Pc), and O₂ as the oxidant. The only stoichiometric waste product is water. In both transformations, a new C–C bond is obtained using the triple catalytic system.

“We had used similar triple-coupled catalytic systems previously in our group to perform 1,4-oxidation of dienes, oxidation of terminal alkenes, allylic oxidation, oxidation of alcohols, and oxidation of amines, but never for oxidation with formation of a C–C bond,” said Professor Bäckvall.

“We had our doubts when we started the project with the allene-substituted olefins, because the non-aerobic version of the reaction with benzoquinone as the stoichiometric oxidant (J. Am. Chem. Soc. 2003, 125, 6056) worked well only in aprotic solvents,” Dr. Piera explained. “In all previous quinone-mediated palladium-catalyzed aerobic oxidations, a protic
solvent had been required. However, we finally found that the present aerobic oxidation works efficiently in aprotic solvents such as toluene.

In most aerobic oxidations with C–C bond formation, catalytic loadings of 5–10 mol% of Pd are required except for a few cases; in the present reactions low catalyst loadings of 1 mol% are enough to obtain an efficient oxidation.

“There are other systems where Pd(0) is reoxidized to Pd(II) directly by O$_2$,” said Dr. Piera. “To show that the triple catalytic system was necessary for an efficient aerobic oxidation, the background reactions of the system were investigated. We therefore carried out the reaction (i) without $p$-benzoquinone and (ii) without iron(II) phthalocyanine.” In both experiments, the reaction was unselective and the desired oxidation product was obtained only in moderate yield together with substantial amounts of side products. “When both BQ and Fe(Pc) were omitted, the yield of the desired product became very low,” said Dr. Piera. “It is clear that the triple catalytic system is required for this reaction to proceed in a selective manner.”

To increase the synthetic utility of the aerobic oxidation of allene-substituted olefins, the Fe(Pc) was attached to a polystyrene resin. Use of the immobilized phthalocyanine resulted in a slightly slower oxidation. It was possible to adjust the conditions to obtain the desired product in almost quantitative yield and it was demonstrated that the immobilized catalyst could be recycled five times without any detectable loss of activity. “The development of new methodologies that employ environmentally friendly oxidants such as molecular oxygen is one of the most important goals in oxidation chemistry today,” continued Dr. Piera. “Although there are systems where Pd(0) is directly oxidized by molecular oxygen, this approach fails in some cases due to unfavored electron transfer between Pd(0) and O$_2$. Thus, for many Pd-catalyzed aerobic oxidations the use of co-catalysts as electron-transfer mediators is required in order to obtain high selectivity and high efficiency of the reaction. The two oxidations presented are good examples of such a coupled catalytic system in which two palladium-catalyzed aerobic oxidations leading to C–C bond formation were developed,” he concluded. “We believe that the use of co-catalysts as electron-transfer mediators is an important complement to the simple systems with direct reoxidation of Pd(0) by O$_2$ and this considerably extends the use of O$_2$ as oxidant in catalytic oxidation reactions.”

About the authors. Julio Piera was born in Valencia (Spain) in 1974. He studied pharmacy at the Universidad de Valencia. He obtained his Licenciade Thesis in 2001 and received his Ph.D. from Valencia University in 2004 under the guidance of Professor Fustero. Subsequently he joined the group of Professor Bäckvall at Stockholm University as a postdoctoral fellow. His research is focused on organometallic catalysis.

Jan-Erling Bäckvall was born in Malung (Sweden) in 1947. He received his Ph.D. from the Royal Institute of Technology, Stockholm, in 1975 under the guidance of Professor B. Åkermark. After postdoctoral work (1975–1976) with Professor K. Barry Sharpless at the Massachusetts Institute of Technology, he joined the faculty at the Royal Institute of Technology. He was appointed Professor of Organic Chemistry at Uppsala University in 1986. In 1997 he moved to Stockholm University where he is currently Professor of Organic Chemistry. He is a member of the Royal Swedish Academy of Sciences and the Finnish Academy of Science and Letters. His current research interests include transition-metal-catalyzed organic transformations, biomimetic oxidations, and enzyme chemistry.
“Cycloaddition–Fluorination” Strategy for the Synthesis of Monofluorinated Carbocycles

Angew. Chem. Int. Ed. 2007, 46, 5106–5110

In spite of the recent progress in methodology of stereoselective fluorination, certain commonplace organic structural motifs do exist for which the efficient preparation of fluorinated analogues remains challenging. One example of such a motif is the six-membered, non-aromatic carbocycle. A popular method for the expedient preparation of nonfluorinated, substituted carbocycles is the Diels–Alder reaction. The high regio- and diastereoselectivities of this reaction are well known and numerous enantioselective variants have been documented. In pursuit of a general strategy for the enantioselective synthesis of fluorinated six-membered carbocycles, it is therefore tempting to resort to this cycloaddition starting from fluorinated reactants (eq. 1, 2). However, fluorinated reactants are in general much less reactive than their nonfluorinated counterparts. The endo/exo selectivities are also less favorable using fluorinated dienes or dienophiles. These drawbacks have hampered the utility of the Diels–Alder reaction in the synthesis of monofluorinated carbocycles.

Now, Dr. Veronique Gouverneur and co-workers from the University of Oxford (UK) put forward a “cycloaddition–fluorination” strategy towards monofluorinated carbocycles that would harness the numerous advantages afforded by the Diels–Alder reaction and circumvent the problems associated with the use of fluorinated building blocks (eq. 3). Key to this approach is an allylsilane, which the Gouverneur group has identified as a suitable substrate for electrophilic fluorination giving allylic fluorides as products. “The success of this two-step approach hinges on the preparation of enantioenriched cycloadducts containing an allylsilane via a Diels–Alder reaction of silylated dienes, and the high levels of selectivity for the fluorination step,” said Dr. Gouverneur. “In our communication we showed that enantioenriched silylated cycloadducts could be obtained by using a chiral auxiliary or catalyst for the Diels–Alder step. Additionally, the fluorination selectivity is found to be dependent on the substitution pattern of the silylated cycloadduct with diastereomeric ratios up to >20:1. The full potential of this highly convergent sequence is elegantly demonstrated by the short synthesis of a six-membered carbocycle featuring five contiguous ring stereocenters, of which one is fluorinated, with a high enantiomeric excess in just two steps including a catalytic asymmetric cycloaddition.”
Another appeal of this sequence is the practicality of the fluorination step, which is easily performed by adding Selectfluor, the fluorinating reagent, to a solution of the substrate in acetonitrile at room temperature. “The fluorination reactions were all complete within four hours, with only the desired fluorinated products detectable in the crude reaction mixtures,” concluded Dr. Gouverneur. “We believe that our work offers a novel method for the convergent synthesis of mono-fluorinated carbocycles that can potentially accommodate a wide array of functional groups and substituents as one of the key steps is a modular Diels–Alder reaction. The study also provides an ideal platform to examine the sense and level of stereocontrol of fluorination as the substitution pattern of the substrates varies. Further investigations include the application of this novel methodology towards fluorinated heterocycles and biologically relevant molecules.”

According to Professor Günter Haufe, an expert in organo-fluorine chemistry at the University of Münster (Germany): “The past decade has seen remarkable progress in the asymmetric synthesis of organofluorine compounds. However, a more or less general strategy for the construction of fluorine-substituted centers of chirality is still missing. The paper by Gouverneur et al. does not change this situation. The authors chose another strategy starting with catalytic diastereo- and enantioselective Diels–Alder reactions to form chiral allylsilanes. Subsequently, a substituent-directed diastereoselective, electrophilic fluorodesilylation by an SN2 mechanism leads to alkylfluorides with up to >98% ee after deprotection of the chiral auxiliary, still present from the initial cycloaddition.” In a response to Professor Haufe’s comment, Dr. Gouverneur says that “Clearly, all researchers interested in fluorine chemistry would greatly benefit from a general strategy for the asymmetric construction of C–F bonds and many efforts have been invested towards this goal. Notably, the asymmetric α-fluorination of carbonyl derivatives has been met with important success. The asymmetric fluorination of poorly activated substrates has received less attention. Within this context, our objective was to develop a highly concise and stereoselective synthesis of six-membered fluorinated carbocycles with multiple stereocenters, one of them being fluorinated. The novelty of our approach relies on a sequential cycloaddition–fluorodesilylation, a strategy which makes the most of the advantageous features of the powerful Diels–Alder reaction. By introducing the fluorine substituent after the cycloaddition event, we circumvent the difficulties associated with the preparation and reactivity of fluorinated dienes or dienophiles. Having defined how the structural features of the adduct influence the stereochemical outcome of the fluorination,” she concluded, “we are now further investigating the exact mechanism of the fluorodesilylation process [SN2] and applying this strategy to key heterocyclic drug-like targets.”
around the development of new tactical approaches towards fluorinated molecules to address long-standing problems in the synthesis of fluorinated analogues of natural products, pharmaceutical drugs and molecular probes for PET imaging.

Since her appointment in Oxford, she also holds a tutorial fellowship at Merton College Oxford where she teaches organic chemistry. Veronique’s research was recently recognized with the AstraZeneca Award for Organic Chemistry 2005. In 2006, she was conferred the title of Reader in Chemistry. She is a member of the Editorial Board of the RSC journal Organic and Biomolecular Chemistry and is the UK representative of EUCHEM’s organic chemistry division. **Yu-hong Lam** was born in Hong Kong. He obtained his MChem degree at the University of Oxford (UK), with his final year devoted to research in fluoroorganic chemistry in the Gouverneur group. For his doctoral thesis, he is now working on synthetic routes to access selectively fluorinated cyclic compounds. His work is funded by the Croucher Foundation (Hong Kong), the Overseas Research Student Award (UK) and a GlaxoSmithKline studentship.

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**A General Synthesis of syn-Deoxypolypropionates by Rhodium-Catalyzed Enantioselective Desymmetrization of meso-3,5-Dimethyl Glutaric Anhydride**


Cyclic meso anhydrides offer the potential for desymmetrization reactions which would thus define multiple stereocenters in a single transformation. This strategy has been used to great effect by asymmetric alcoholysis to make succinic and glutaric acid half-esters in enantioenriched form. “Since we began our independent work in 2000,” explained Professor Tomislav Rovis from the Colorado State University (USA), “we have been interested in using carbon nucleophiles to effect the desymmetrization of meso anhydrides, which would provide a keto-acid product and thus increase the synthetic utility of this approach.” In previous work, Professor Rovis and his group have demonstrated that various Ni(0) sources will affect the alkylative cross-coupling of cyclic anhydrides with organozinc species (*J. Am. Chem. Soc.* **2002**, *124*, 174; *J. Am. Chem. Soc.* **2005**, *127*, 247). “We have also shown,” he continued, “that chiral palladium and rhodium...”
catalysts allow for the enantioselective desymmetrization of succinic anhydrides with aryl nucleophiles to afford 1,4-keto acids (J. Am. Chem. Soc. 2004, 126, 10248; Angew. Chem. Int. Ed. 2007, 46, 4514)."

The above conditions proved inferior for desymmetrizing glutaric anhydrides. Professor Rovis and his team were interested in developing an asymmetric alkylation protocol for the readily available 3,5-dimethyl glutaric anhydride, which would generate syn-deoxypolypropionate fragments that are common to many natural products.

"A number of elegant methods for the synthesis of syn-deoxypolypropionates have been reported," said Professor Rovis, "but most of them rely on iterative sequences to define the methyl stereocenters. We discovered that a Rh(I) phosphinoxazoline catalyst is highly efficient in adding Me₂Zn to dimethyl glutaric anhydride. More surprising was the discovery that Et₂Zn also worked, as, historically, Rh(I) alkyl complexes bearing β-hydrogens are prone to β-hydride elimination. A wide range of nucleophiles, including those prepared in situ, participate with good yields and excellent
enantioselectivities, thus greatly extending the scope of this reaction.”

The use of a zinc homoenolate nucleophile provided some insight into the mechanism of this reaction. “Conducting the reaction at a higher concentration provided straight $n$-alkylation,” explained Professor Rovis. “Conversely, at lower concentrations a large proportion of iso-alkylation is observed. Ligand change from tert-butyl PHOX to iso-propyl PHOX results in exclusive formation of the iso-alkylation product. This suggests that the alkyl Rh intermediate is formed prior to anhydride involvement and that steric properties of the ligand are partially responsible for stabilizing the $n$-alkyl Rh intermediate and preventing $\beta$-hydride elimination.”

“We have developed a system that allows for the synthesis of 1,5-keto acids and definition of at least two stereocenters from relatively trivial starting materials,” concluded Professor Rovis. “This catalytic system may potentially help in solving one of the major drawbacks in rhodium(I) catalysis: the propensity of alkyl groups to $\beta$-hydride elimination.”

According to Dr. Alan C. Spivey from the Imperial College London (UK), “Tom has developed an elegant approach to a structural motif that is widespread in polypropionate metabolites with interesting biological function. Although various synthetic approaches to related fragments have been developed previously, his is notable for its brevity and potential scalability, although the relatively high loading level (5 mol%) of expensive Rh catalyst currently required to ensure high yields would require optimization for a process scale. The uptake of the method,” continued Dr. Spivey, “will probably hinge on the versatility with which the desymmetrized fragments can be ‘stitched’ into target structures. In this regard, further research directed towards compatibility with sp$^2$ (alkenyl)/sp (alkynyl) nucleophiles would significantly extend the attractiveness of the approach as they would enable subsequent hydrometallation/metallometallation/oxidation protocols which would provide a ready entry to adjacent contiguous functionality often found in polypropionates. Of course, a diastereocomplementary process to provide the anti-deoxypolypropionate motif would be nice but would require something mechanistically ingenious if the meso-desymmetrization tactic was to be retained!” In a reply, Professor Rovis pointed out that “Catalyst loading with Rh, as with many other metals, is always an issue. In that respect, we have recently shown that catalyst loading may be reduced to 0.5 mol% Rh dimer with no loss in yield or enantiomeric excess. Of course, some optimization may need to be carried out on a case-by-case basis, but we believe the chemistry is robust enough to allow for that. Vinyl and alkylnl nucleophiles currently do not work with this protocol,” he concluded, “but they are the subject of active investigations in our group and we hope to report on that in the near future.”

About the authors. Tomislav Rovis obtained a B.Sc. degree from the University of Toronto (Canada) in 1990 and a Ph.D. under the guidance of Professor Mark Lautens at the same institution in 1998. Following a two-year stint as an NSERC Postdoctoral Fellow at Harvard University with Professor David Evans, he joined the faculty at Colorado State University (2000). His group’s achievements have been recognized with a number of awards including a Lilly grantee, an Amgen Young Investigator, a GSK Scholar, an Alfred P. Sloan Fellow and a Monfort Professor. He is currently Associate Professor of Organic Chemistry at Colorado State University. Matthew Cook obtained an MChem degree from the University of Sheffield (UK) in 2001 and a Ph.D. from the University of Bristol (UK) with Professor Timothy Gallagher in 2005. He is currently an American Heart Association Postdoctoral Fellow in the Rovis laboratory at Colorado State University.
SYNFORM

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SYNSTORIES

- One-Pot Entry to Enantioenriched Piperidines through a Novel Tandem Aza-Ene-Type Reaction/Cyclization Cascade (Focus on an article from the current literature)
- New Hypervalent Iodine Reagents for Organic Synthesis (Focus on an article from the current literature)
- A Synthetic Lectin Analogue for Biomimetic Disaccharide Recognition (Focus on an article from the current literature)
- Chiral Tetraaminophosphonium Salt Mediated Asymmetric Direct Henry Reaction (Focus on a Synfact of the Month)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: Oxidative Amidation of Phenols through the Use of Hypervalent Iodine Reagents: Development and Applications (by M. A. Ciufolini et al.)

SYNLETT
Account on: New Reactions in Fullerene Chemistry (by N. Martin et al.)

SYNFACTS
Synfact of the Month in category “Metal-Mediated Synthesis”: Cobalt-Catalyzed Reductive Coupling of Activated Alkenes with Alkynes

CONTACT
Matteo Zanda,
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy,
e-mail: Synform@chem.polimi.it, fax: +39 02 23993080

Editor
Matteo Zanda, C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Synform@chem.polimi.it
Fax: +39 02 23993080

Editorial Office
Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
Scientific Editor: Selena Boothroyd, selena.boothroyd@thieme.de, phone: +49 711 8931 776
Assistant Scientific Editor: Christiane Kemper, christiane.kemper@thieme.de, phone: +49 711 8931 778
Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
Production Assistant: Helene Deufel, helene.deufel@thieme.de, phone: +49 711 8931 744
Marketing: Thomas Krimmer, thomas.krimmer@thieme.de, phone: +49 711 8931 777
Postal Address: SYNTHESIS-SYNLETT/SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
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