

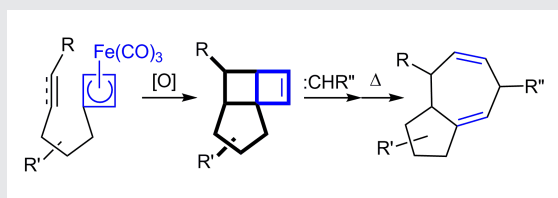
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2007 / 03

## SYNSTORIES ■ ■ ■ ■

■ **Stereoselective Approach to Natural Products by Intramolecular Cyclobutadiene Cycloaddition/Cyclopropanation/Thermal Rearrangement**



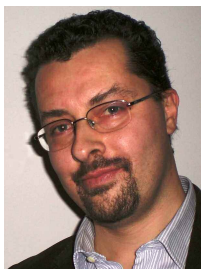
■ **Direct Strecker Reaction of Ketones and Fluorinated Ketones for the Preparation of  $\alpha$ -Aminonitriles and their Fluorinated Analogues**

■ **Functionalized Cyclopentenones through a Novel Gold(I)-Catalyzed Cyclization of Enynes**

■ **Regioselective One-Pot Protection of Carbohydrates**

**CONTACT + + + +**

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Dear readers,

This issue of **SYNFORM** presents four **SYNSTORIES** focused on new exciting scientific advances in the realm of organic synthesis. Professor G. K. Surya Prakash and Nobel Laureate Professor George Olah (USA) tell us more about their new gallium(III)-catalyzed Strecker reaction of ketones. A new gold(I)-catalyzed process developed by the group of Dr. Fabien Gagosz (France) is covered in the second **SYNSTORY**, within the frame of a Cluster on "Gold Chemistry in Organic Synthesis" published by **SYN-LETT** in issue 11/2007. Professor Marc Snapper (USA) elaborates on his newest exciting synthetic methodology that can be applied to the total synthesis of complex natural cyclic molecules. Finally, Professor Shang-Cheng Hung (Taiwan) and his powerful new methodology for the regio-selective protection of carbohydrates are the protagonists of the fourth **SYNSTORY**. With these features, scientific excitement is guaranteed!

Let me end this brief editorial with a thought for Professor Charles Mioskowski, who left us on June 2<sup>nd</sup> 2007. I had the privilege of spending one year (1999) as a postdoctoral fellow in his group in Strasbourg. I will always remember his enthusiasm and creativity in research, his friendly character, and his unmistakable voice from the "salle café" ironically asking "Do you want green tea, Matteo?", as he already knew my overwhelming preference for coffee. He is a great loss to the chemical community, as a chemist, as a respected colleague and as a friend. Ciao, Miko

Matteo Zanda

Editor of **SYNFORM**

**CONTACT ++++**

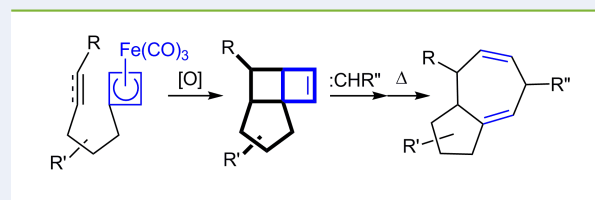
If you have any questions or wish to send feedback, please write to Matteo Zanda at:  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

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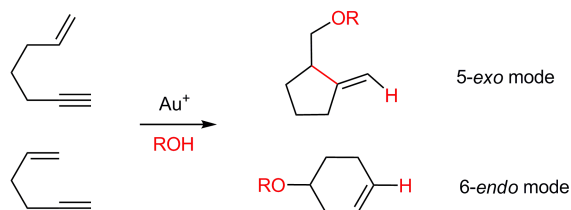
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## NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

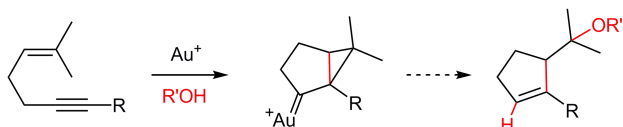
# Functionalized Cyclopentenenes through a Novel Gold(I)-Catalyzed Cyclization of Enynes

*Angew. Chem. Int. Ed.* **2007**, *46*, 1141–1144

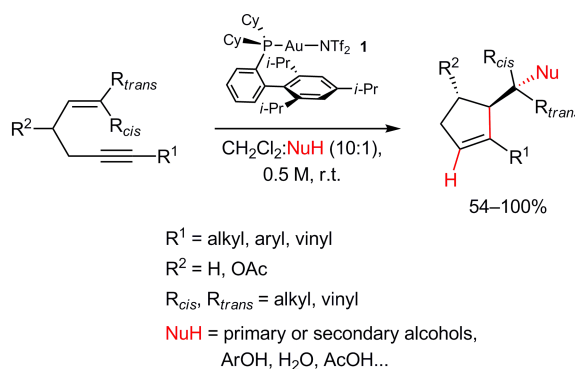
■ Gold complexes have emerged as efficient and mild catalysts for the activation of alkynes towards addition by a variety of nucleophiles. The potential of these catalysts has been demonstrated recently by Dr. Fabien Gagosz and coworkers from the Ecole Polytechnique of Palaiseau (France) who described the hydroxy- and alkoxy-cyclization of enynes, leading to the formation of carbocycles through the creation of two new C–C and C–O bonds.



“Motivated by the frequent occurrence of cyclopentene units in the structures of natural products,” explained Dr. Gagosz, “we reasoned that a well-defined substitution pattern of the alkene and alkyne moieties in a 1,5-enyne might favor a 5-endo cyclization process. The resulting cyclopropyl gold carbene could then be trapped by an oxygenated nucleophile present in the reaction medium.”



Among the catalysts tested, the air-stable gold(I) catalyst **1**, that belongs to a family of catalysts previously reported by Dr. Gagosz (*Org. Lett.* **2005**, *7*, 4133–4136), was the most efficient in mediating the cyclization and allowed for the formation of a variety of functionalized cyclopentenenes in good yields.



According to Dr. Gagosz “this transformation possesses many advantages:

- the mild conditions employed (room temperature, open flask),
- the low catalyst loading (1 mol%),
- the stereospecific formation of two adjacent asymmetric centers,
- the wide range of compatible oxygenated nucleophiles (from alcohols and water to carboxylic acids), and
- the reduced amount (2 equiv) of the oxygenated nucleophile.”



From left: Mr. F. Istrate, Dr. F. Gagosz

“We now plan to use this new strategy for the rapid and stereoselective formation of cyclopentenones,” he concluded, “which could then serve as intermediates in the synthesis of polycyclic natural products. We are also focusing on the use of carbon-based nucleophiles which might allow the creation of a second intermolecular C–C bond.”

According to Dr. Antonio M. Echavarren, an expert in this area of chemistry, from the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain), cationic gold(I) complexes are known to be the most active catalysts for the reac-

tions of 1,6-enynes with alcohols or water. “The recent work of Gagosz et al.,” said Dr. Echavarren, “extends this reaction to 1,5-enynes, a type of substrate that reacts exclusively by the 5-*endo-dig* pathway. It is very interesting that the alternative opening of the gold intermediate to form the corresponding cyclohexene was not observed, although Zhang and Kozmin (*J. Am. Chem. Soc.* **2005**, *127*, 6962–6963) have found both types of ring opening in the gold(III)-catalyzed intramolecular alkoxycyclization of 1,5-enynes bearing hydroxyl groups as terminal alkene substituents.” ■

Matteo Zanda

## Stereoselective Approach to Natural Products by Intramolecular Cyclobutadiene Cycloaddition/Cyclopropanation/Thermal Rearrangement

*J. Am. Chem. Soc.* **2007**, *129*, 486–487

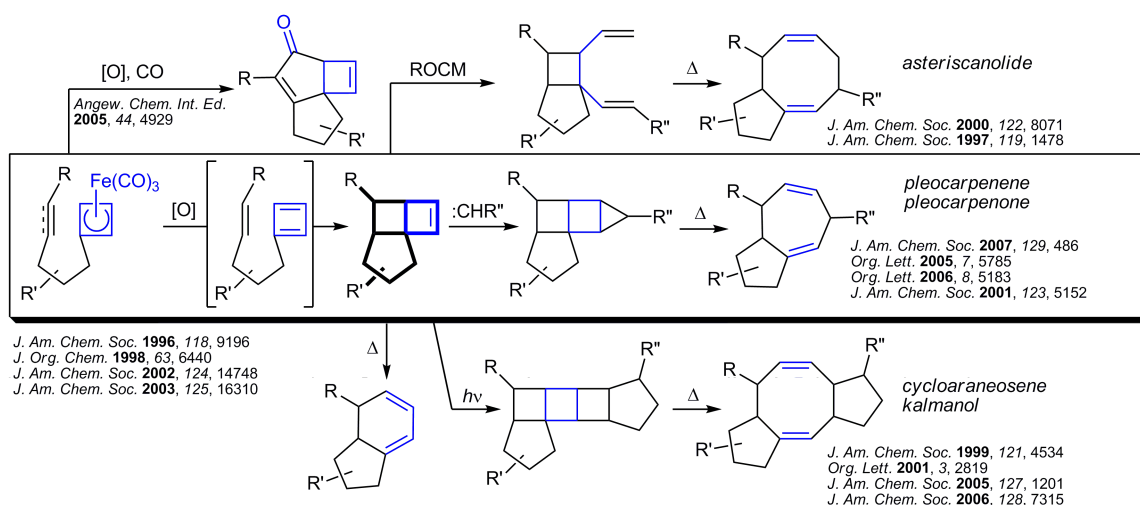
■ As evidenced by the landmark syntheses of vitamin B<sub>12</sub>, palytoxin, and brevetoxin B, chemists, given the appropriate resources, can match nature’s ability to construct molecules of incredible structural complexity. In terms of cost and practicality, however, we still fall far short of achieving nature’s efficiency. For example, while all are notable achievements, none of the laboratory syntheses of paclitaxel are considered practical and economical routes to this important anticancer drug. Unfortunately, chemists still lack the tools (i.e. reactions) to build complex products in a fashion that is economically competitive with nature. For this reason, the development of new reactions (and strategies on how to use these transformations) remains an important research objective.

Recently, Professor Marc L. Snapper and coworkers from the Department of Chemistry of Boston College, Massachusetts (USA), reported a new important synthetic methodology for the construction of the framework of natural polycyclic systems from strained cyclobutadienes.

“Over the past 10 years, Snapper has explored the synthetic utility of iron cyclobutadienyl complexes, building on the pioneering work of Pettit, who prepared the parent complex

and showed that oxidation leads to a highly reactive cyclobutadiene, and Grubbs, who showed that alkenes tethered to the complex undergo cycloaddition reactions upon oxidation to produce highly strained products,” commented Mark Lautens, Professor of Organic Synthesis at the University of Toronto (Canada) and Regional Editor of **SYNTHESIS**. “Snapper’s contributions can be viewed as bringing an organometallic curiosity into the realm of being a useful synthetic procedure and a clever strategy to consider when designing complex molecules.”

“We found that a wide variety of highly functionalized cyclobutenes can be prepared rapidly through intramolecular cycloadditions of cyclobutadiene,” said Prof. Snapper. “We also imagined that further functionalization of these highly strained cyclobutenes could offer a novel and efficient strategy for generating several classes of compounds containing medium-sized rings. For example, Holly Deak and coworkers found that cyclopropanation of these cyclobutenes, followed by a selective fragmentation, offered a new entry to bicyclo[5.3.0]decane ring systems, such as those found in pleocarpene and pleocarpene. Moreover, we noted that this



*New synthetic opportunities afforded through intramolecular cycloadditions of cyclobutadiene*

strategy generates the target ring system with functionality in all the right places to access a wide range of terpenoid natural products.”

While there may be biomedical interest in pleocarpenene, this possibility was not Professor Snapper’s main motivation for targeting its synthesis. “We wanted to develop the utility of the cyclobutadiene cycloaddition methodology by examining its strategic use in synthesis. We anticipated that this application would both highlight the strengths of the strategy and, perhaps, uncover some of its weaknesses that could benefit from further development. Moreover, we would be remiss to undersell the importance of student training in pursuing these synthetic objectives. Given the need in the chemical and pharmaceutical industry for those that can identify and solve a wide range of problems, navigating and charting the first application of a new methodology toward the first total syntheses of these natural products represents, at least, a challenging training ground for developing the important and transportable skill of problem solving.”

In these regards, the synthesis was a success. “We found that our initial methodology was weak in its ability to prepare sufficient quantities of the cyclobutadiene cycloadduct in an enantiomerically controlled fashion,” continued Prof. Snapper. “Modifications to the early steps in the synthesis addressed this shortcoming. We also noted that the previously reported Simmons–Smith cyclopropanations of the cyclobutadiene cycloadducts were not going to provide the functionality required for our targets. To address this problem, Michael Williams spent significant time on developing a high-yielding copper-catalyzed diastereoselective cyclopropanation of the cyclobutene substrates.” In addition, while the

thermal fragmentation of the functionalized substrate proceeded as planned, including inversion of the stereochemistry at one of the ring fusion centers, a new appreciation of the challenges of post-fragmentation functionalization of the cycloheptadiene substrate was achieved. “In particular, identifying conditions for the selective reduction of the diene, without concurrent hydrogenolysis of the tertiary allylic alcohol, required optimization,” he added. “Notwithstanding these synthetic challenges, this first application of the synthetic methodology did allow us to achieve the first syntheses of these targets, thus hopefully raising the awareness of the utility of this new strategy within the greater synthetic organic community, while also providing an outstanding training experience for the coworkers involved.”

“The exercise also taught us there is still significant room for improvement in our strategy,” concluded Prof. Snapper. “Our reliance on protecting-group chemistry, for example, is still unacceptable. As we approach new synthetic targets and continue to test and build our methodology, we will also work to address these shortcomings. Ideally, we would like to achieve a synthetic efficiency that would make even nature envious.”

According to Prof. Lautens, “The efficiency of the thermal processes (76%) is remarkable, given the temperature and functional groups in the starting material, and benefited from the addition of DBU to prevent acid-catalyzed side reactions. Overall the sequence gets high marks for novelty and being a ‘non-obvious’ strategy. The primary drawbacks of this and other routes based on metal complexes are that it is stoichiometric in metal and, while iron is not expensive, iron carbo-



nyl species can be toxic. One other issue is that it may be difficult to prepare very large quantities of the starting materials, which are made under photochemical conditions. On the plus side, the high facial selectivity in the fused intermediates is very attractive when stereocontrol is required," concluded Prof. Lautens.

*About the authors.* **Michael Williams** received his undergraduate training at the University of Illinois, Urbana-Champaign, graduating in 2001. Currently, he is completing his PhD studies at Boston College before joining Schering Plough in Cambridge, Massachusetts this summer. **Holly Deak** completed her BSc at Lehigh University, followed by her PhD at Boston College. She has been employed as a medicinal chemist at Amgen (Cambridge, Massachusetts) since 2003. **Marc Snapper** completed his graduate training at Stanford University and his postdoctoral studies at Harvard University. Snapper's independent career started as an Assistant Professor at Boston College in 1993. Since 1999,



From left: M. Williams, Dr. H. Deak, Prof. M. Snapper

Marc Snapper has been a Professor of Chemistry at the same university. ■

Matteo Zanda

## Direct Strecker Reaction of Ketones and Fluorinated Ketones for the Preparation of $\alpha$ -Aminonitriles and their Fluorinated Analogues

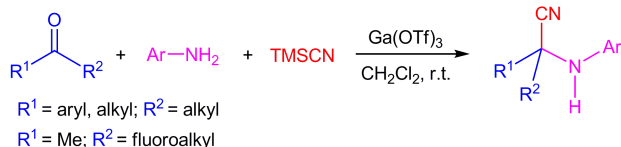
*Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 3703–3706

■ One of the most important multicomponent reactions connected with the origin of life on earth is the Strecker reaction to synthesize  $\alpha$ -amino acids via the formation of  $\alpha$ -aminonitriles. However, successful three-component Strecker reactions using ketones and fluorinated ketones are rare. Fluorinated amino acids are becoming increasingly important in pharmaceutical and other biological applications, such as the development of anticancer drugs for attenuating tumor growth, and drugs for controlling blood pressure and allergies. They have been widely used in biological tracers, as mechanistic probes, enzyme inhibitors, and in many medical applications, and also as a valuable tool for the screening of protein dynamics by  $^{19}\text{F}$  NMR spectroscopic studies. Due to the specific properties of the fluorine atom, such as its small

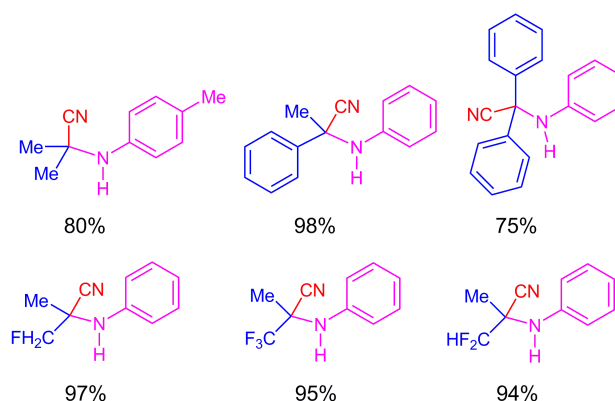
size, high electronegativity, and lipophilicity, as well as the strength of the C–F bond, the introduction of a fluorine atom into many biologically active molecules can bring about remarkable and profound changes in their physical, chemical and biological behavior.

Reactions involving common Lewis acid catalysts generally require water-free conditions and large amounts of the catalyst. Recent studies show that gallium(III) trifluoromethanesulfonate [ $\text{Ga}(\text{OTf})_3$ , gallium triflate] acts as an effective but mild and nonhydrolyzable Lewis acid catalyst for many organic synthetic transformations. This catalyst can be easily recovered from the reaction mixture and reused, showing its significant potential as a safe and environmentally friendly catalyst.

The Strecker reaction with aldehydes has been studied extensively with a variety of catalysts including a number of metal triflates. However, the reactions are not feasible for ketones. Efficient, clean and direct three-component Strecker reactions using ketones are difficult. Quite often these reactions have to be carried out stepwise (preparation of imines first, followed by cyanide addition) or under high-pressure conditions (see, e.g.: G. Jenner et al. *Tetrahedron Lett.* **2003**, *44*, 447–449). Direct Strecker reactions using aromatic ketones and aromatic amines have been repeatedly cited in the literature as a **challenge**. Now, Professor G. K. Surya Prakash, Prof. George A. Olah and coworkers from the Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles (USA) have reported the synthesis of both fluorinated and nonfluorinated  $\alpha$ -aminonitriles from the corresponding ketones and amines with TMSCN using a catalytic amount (5 mol%) of gallium triflate as a catalyst in dichloromethane. “These reactions are fast and clean, requiring no further purification in most of the cases,” explained Professor Prakash.



“Other metal triflate catalysts and various solvent systems have been also screened for their catalytic activity and the results showed that **gallium triflate/dichloromethane** is the most effective catalyst–solvent system,” he continued. “Previous attempts involved acetonitrile and toluene as solvents, which are, however, not suitable for the Lewis acid



catalyzed direct Strecker reaction of ketones due to their interaction with the catalyst. Use of dichloromethane minimizes such interaction, resulting in enhanced catalytic activity of the catalyst towards ketones and providing a suitable environment for the reaction.”

Extension of this methodology using mono-, di- and trifluoromethylated ketones provides the corresponding fluorinated  $\alpha$ -aminonitriles in high yield and purity. “One of the significant aspects of this methodology is that we can incorporate a monofluoro-, difluoro- or trifluoromethyl moiety in the  $\alpha$ -aminonitrile product by simply varying the nature of the fluorinated ketones,” added Professor Prakash.

Another major advantage of this procedure is that no further purification is needed in most cases, thus avoiding tedious chromatography and loss of products during purification. The products are obtained in very high yield and purity.

According to Professor Prakash “Various metal triflates show good catalytic activity. However, gallium(III) triflate is



From left: C. Do, Dr. T. Mathew, Prof. G. A. Olah, H. Vaghoo, Prof. G. K. S. Prakash, Dr. C. Panja

the preferred catalyst in the series due to its nonhydrolyzable and reusable nature as additional advantages. It provides an efficient alternate route for the existing high-pressure and stepwise methodologies for the Strecker reaction of ketones. Furthermore, it is a convenient general reaction for the synthesis of mono-, di- and trifluoromethylated amino acids via the formation of the corresponding aminonitrile intermediates." Attempts to find a suitable chiral catalyst for a general and direct Strecker reaction of ketones with high stereoselectivity are now underway. "This might become a promising step towards the development of a very facile direct asymmetric Strecker reaction of ketones," Professor Prakash added.

"In contrast to numerous examples of the Strecker reactions with aldehydes, the direct Strecker reactions of aromat-

ic ketones and aromatic amines are still difficult and challenging in current organic synthesis," commented Professor Keiji Maruoka from the Department of Chemistry of Kyoto University (Japan). "Very recently, Prakash and Olah worked out the solution to this problem. Their success depends heavily on the choice of a proper catalyst and solvent system, i.e., gallium triflate in dichloromethane by using trimethylsilyl cyanide as a cyanide source. This system is also applicable to fluorinated ketone substrates. The next step is undoubtedly the realization of an asymmetric version, and the key issue is the design of a certain chiral metal triflate," concluded Professor Maruoka. ■

Matteo Zanda

## Regioselective One-Pot Protection of Carbohydrates

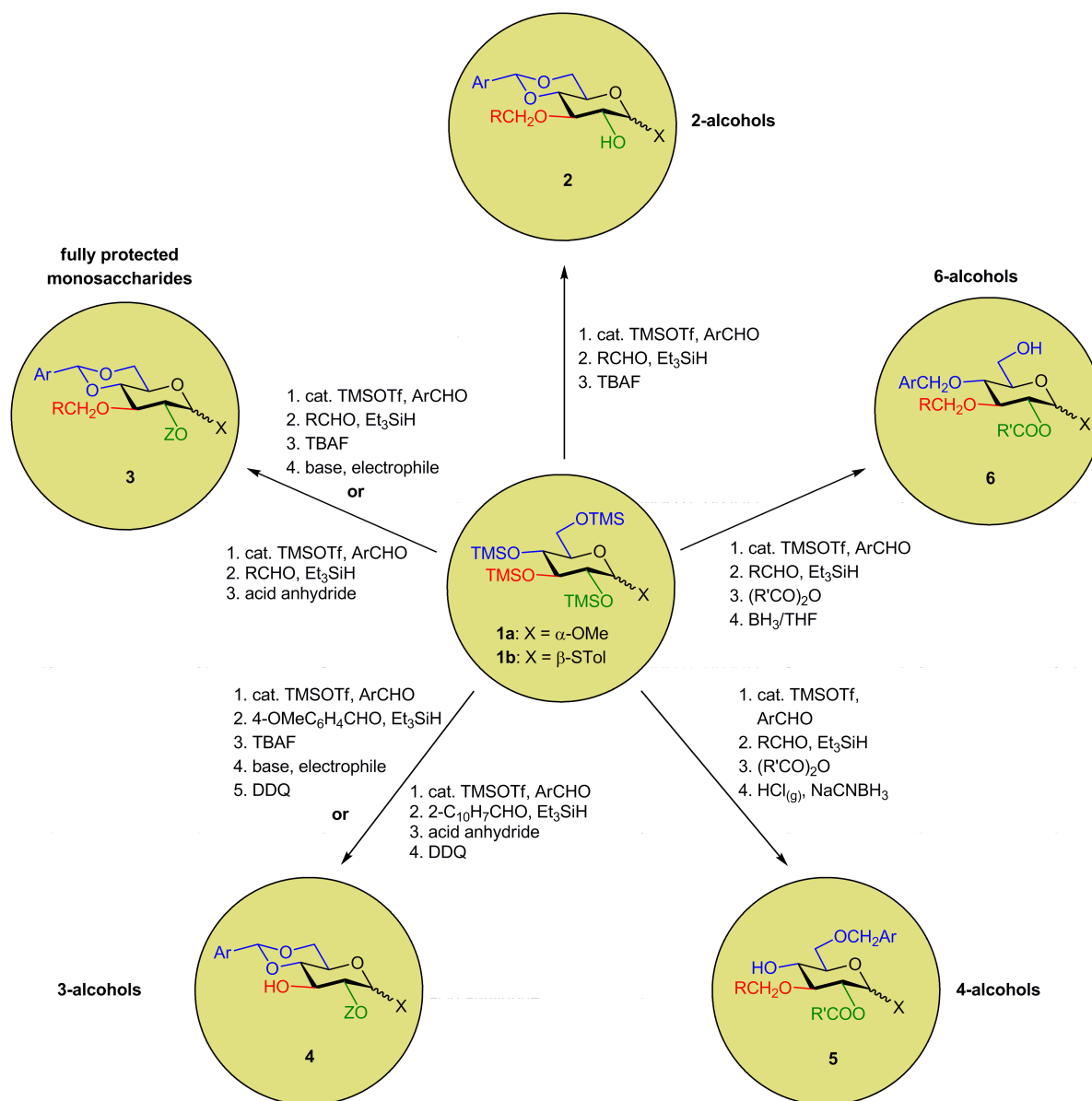
*Nature* 2007, 446, 896–899

■ Carbohydrates are involved in numerous important life processes. Structurally, they are present in micro-heterogeneous forms in nature and are much more diverse and complex than proteins and nucleic acids. The chemical synthesis of carbohydrates is thus immensely important to the realization of structurally well-defined and functionally endowed oligosaccharides and glycoconjugates. However, the high complexity which enables them to participate in diverse biological domains also renders their synthesis difficult. In the assembly of sugar-biopolymers, it is necessary to control regioselectivity of glycosylation so that only a specific hydroxyl group is coupled with the donor sugar in a stereoselective manner, producing either the  $\alpha$ - or the  $\beta$ -anomer. Consequently, the regioselective differentiation of each hydroxyl group present on a sugar unit is the first and foremost problem.

Since its advent, carbohydrate synthesis has always been concerned with two main challenges: regioselective protection of individual hydroxyl groups of sugar polyols, and stereoselective construction of glycosidic bonds. The former, which exists as a prerequisite of the latter, has been appropriated much less concern and thus remained an arduous

affair, requiring multi-step protocols and intermittent tedious purifications. This is a result of all secondary hydroxyl groups showing comparable reactivity under various reaction conditions. Now, Professor Shang-Cheng Hung and coworkers from the Department of Chemistry of the National Tsing-Hua University (Taiwan) have established a straightforward one-pot method for the combinatorial, regioselective, orthogonal protection of sugar polyols employing a single catalyst, TMSOTf. The 2,3,4,6-tetra-*O*-trimethylsilylated hexopyranosides bearing an anomeric group (**1a**:  $\alpha$ -OMe or **1b**:  $\beta$ -STol) can be transformed into a whole set of differentially protected 2-alcohols **2**, 3-alcohols **4**, 4-alcohols **5**, 6-alcohols **6**, and fully protected monosaccharides **3** in a sequential one-pot manner. "Using this novel method, we prepared hundreds of building blocks starting from D-glucopyranoside," explained Professor Hung. "It is expected that the protocol is equally applicable to other sugars as well, according to the preliminary results of our studies in D-mannosides, D-galactosides, and 2-deoxy-2-azido-D-glucosides. These monosaccharide syntheses can be efficiently coupled using a sequential one-pot glycosylation method to obtain the desired oligosaccharides





in a rapid manner. This is verified by an expedient synthesis of  $\beta$ -1,6-glucans and an influenza virus-binding trisaccharide library."

This innovative one-pot protection in conjunction with one-pot glycosylation is of vital importance to decrease both the time and labor involved in oligosaccharide synthesis. "Applications of this breakthrough 'one-pot' combination to prepare various glycosaminoglycans and other biologically significant oligosaccharides are under extensive investigation," concluded Professor Hung.

According to Professor Philip Kociński from the School

of Chemistry of the University of Leeds (UK), an expert of protecting groups and Editorial Board member of **SYNTHESIS**, "The synthesis of even a modestly complex molecule without the aid of protecting groups is sufficiently rare to warrant fanfare and swagger. For most classes of polyfunctional molecules, the dependency on protecting groups remains and progress will require efficiency and selectivity of protecting-group manipulations. Oligosaccharides are especially demanding targets whose monosaccharide precursors typically require protracted multistep synthetic sequences," he continued. "Hung and co-workers have shown that by judicious



From left: Prof. S.-C. Hung, Dr. C.-C. Wang, Dr. S. S. Kulkarni

choice of reagents and conditions, up to five separate protecting-group manipulations can be performed sequentially in one pot to access a wide range of variously protected monosaccharides starting from cheap and readily available precursors. Their protocols exploit the efficiency and high selectivity of two known reactions—the Noyori acetalization and the Hatakeyama–Nishizawa reductive etherification. The scope of their procedures is impressive: over 150 monosaccharide donors and acceptors were prepared in good overall yield. No new protecting groups were invented and no new strategies emerged. The Hung group's contribution was tactical in the conflation of multiple known steps into a single streamlined operation with the attendant gain in efficiency and abbreviation," concluded Professor Kociński.

*About the corresponding author:* **Shang-Cheng Hung** obtained his PhD from the National Tsing Hua University of Taiwan in 1992. After a two-year military service, he spent

one year with Professor Andrew Streitwieser as a postdoctoral fellow at the University of California, Berkeley. In 1995, he moved for three years to the Scripps Research Institute for his second postdoctoral appointment, in the research group of Professor Chi-Huey Wong. He was recruited back to Taiwan as an Assistant Research Fellow at the Institute of Chemistry, Academia Sinica in 1998 and was promoted to the rank of Associate Research Fellow in 2002. In 2005, he moved to the Department of Chemistry, National Tsing Hua University, as an Associate Professor and was promoted to Full Professor in 2006. His research interests focus on the preparation of heparin/heparan sulfate oligosaccharides and the development of new one-pot protection and one-pot glycosylation strategies for carbohydrate synthesis. He is the recipient of several awards, including the Mr. Tayou Wu Memorial Award (2003) and the Distinguished Research Award (2004) from the National Science Council, Taiwan. ■

**Matteo Zanda**

COMING SOON ► ► COMING SOON ► ►

# SYNFORM 2007/04 IS AVAILABLE FROM AUGUST 22, 2007

In the next issues:

THE INSIDE STORY ► ► ► ►

## ► The Impact of REACH (Registration, Evaluation and Authorization of Chemicals) on the Chemical Enterprise

Interviewee: Dr. Geert Dancet, Head of Unit "REACH" at DG ENTREPRISE and INDUSTRY of the European Commission

Interviewers: Dr. S. Russell, Senior Director, American Chemistry Council (USA);

Dr. M. Kayser, Head of REACH Implementation and the Department of Product Safety, BASF (Germany)

## SYNSTORIES ■ ■ ■ ■ ■

### ■ Assigning the Configuration of Cryptochiral Small Molecules

(Focus on article from the current literature)

### ■ Total Synthesis of (±)-Merrilactone A via Catalytic Nazarov Cyclization

(Focus on Synfact of the Month)

## FURTHER HIGHLIGHTS + + + + +

### SYNTHESIS

Special Issue dedicated to Professor Paul Wender on the occasion of his 60th birthday in August

### SYNLETT

Cluster on "Gold in Organic Synthesis" in issue 11/2007

### SYNFACTS

Synfact of the Month in category "Organo- and Biocatalysis":  
[Enantioselective Reduction of Activated Olefins Using 'Old Yellow Enzymes'](#)

## CONTACT + + + + +

Matteo Zanda,  
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,  
Via Mancinelli, 7, 20131 Milano, Italy,  
e-mail: [Synform@chem.polimi.it](mailto: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](mailto:Synform@chem.polimi.it)

Fax: +39 02 23993080

### Editorial Office

- Managing Editor: Susanne Haak,  
[susanne.haak@thieme.de](mailto:susanne.haak@thieme.de), phone: +49 711 8931 786
- Scientific Editor: Selena Boothroyd,  
[selena.boothroyd@thieme.de](mailto:selena.boothroyd@thieme.de), phone: +49 711 8931 776
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- Production Assistant: Helene Deufel,  
[helene.deufel@thieme.de](mailto:helene.deufel@thieme.de), phone: +49 711 8931 929
- Editorial Assistant: Sabine Heller,  
[sabine.heller@thieme.de](mailto:sabine.heller@thieme.de), phone: +49 711 8931 744
- Marketing: Thomas Krimmer,  
[thomas.krimmer@thieme.de](mailto:thomas.krimmer@thieme.de), phone: +49 711 8931 772
- Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office,  
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