

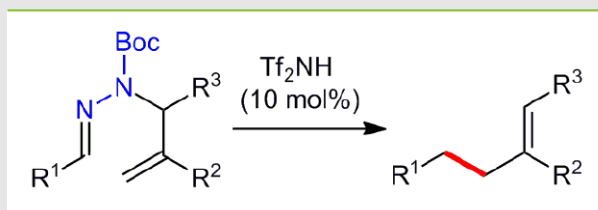
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2010/10

SYNSTORIES ■ ■ ■ ■

■ **Triflimide-Catalyzed Sigmatropic Rearrangement of *N*-Allylhydrazones**



■ **Cascade Cyclization to Produce a Series of Fused, Aromatic Molecules**

■ **SYNTHESIS/SYNLETT Advisory Board Focus: Dr. Klaus Ditrich (BASF, Germany)**

CONTACT +++++

Your opinion about SYNFORM is welcome, please correspond if you like:
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Dear readers,

This issue of **SYNFORM** covers two topics having pivotal importance in modern organic synthesis: the development of innovative and efficient synthetic methodology, and the synthesis of chemical structures having a potential use in emerging technological applications. There is increasing pressure mounting on synthetic chemists to discover and optimize more effective, environmentally compatible and economically sustainable methodologies to prepare target chemicals, whereas the impressive technological advances in areas like bio- and nanotechnology, medicine, electronics and materials science are driving the research on novel molecular entities. An interesting advance in the area of novel synthetic methodologies is covered in the first **SYNSTORY** dedicated to an efficient sigmatropic rearrangement leading to complex stereodefined organic frameworks from *N*-allylhydrazones, recently developed by Professor R. J. Thomson (USA). The second **SYNSTORY** details a novel strategy for the preparation of fused aromatic molecules, which are extremely important in the fabrication of a number of modern electronic devices, developed by Professor C. B. Gorman (USA). The issue is completed by an Editorial Advisory Board profile on Dr. K. Ditrich (Germany).

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

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

Triflimide-Catalyzed Sigmatropic Rearrangement of *N*-Allylhydrazones

Nat. Chem. **2010**, *2*, 294–297

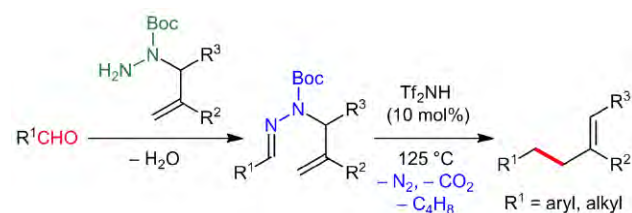
■ The Stevens reaction, first reported in 1973 (*J. Chem. Soc., Chem. Commun.* **1973**, 662), is a thermal [3,3]-sigmatropic rearrangement of aryl-aldehyde-derived *N*-allylhydrazones leading to the corresponding homoallyl-aryl compounds. Recently, the group of Professor Regan J. Thomson from Northwestern University (Evanston, USA) re-examined the Stevens reaction and found novel experimental conditions that greatly expand its scope, and make this process a very useful and practical C–C bond-forming reaction with totally new perspectives of applications in organic and total synthesis.

“I came across the 1973 paper by R. V. Stevens and co-workers,” explained Professor Thomson, “in which they described the thermal rearrangement of *N*-allylhydrazones, while I was a post-doc with Prof. David Evans. I was conducting a literature search on hydrazones and two things really struck me about this short one-page communication. The first was that this reaction represented a fascinating non-obvious formal two-step reductive allylation of aldehydes, that if harnessed could become a powerful fragment-coupling method for synthesis. The second thing that struck me,” he continued, “was that I had never seen this reaction before, and that a citation search revealed only a handful of citations since 1973 mostly dealing with reviews of heteroatom-substituted Cope rearrangements.

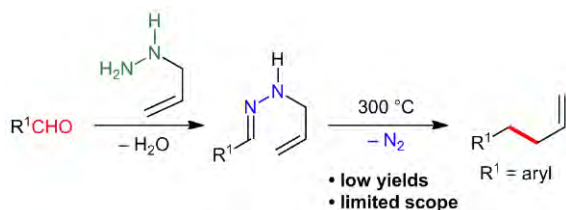
“The limited substrate scope, high temperatures, and low yields reported by Stevens and co-workers might explain this lack of further development and recognition. However,” said Professor Thomson, “given the great potential of this chemistry, when I started my independent career at Northwestern

University in 2006, I decided to initiate a research program centered on the development of *N*-allylhydrazones.”

Professor Thomson and his co-workers therefore decided to explore different experimental conditions for conducting the Stevens reaction. “Our first forays revolved around attempted Lewis acid catalysis in the hopes that such additives would lower the inherently high barrier for this reaction,” said Professor Thomson. “Results were not encouraging, but Devon Mundal (then a first-year graduate student) found that stoichiometric copper(II) chloride induced a novel tandem carbon–carbon, carbon–chlorine bond-forming rearrangement that proceeded at room temperature (*J. Am. Chem. Soc.* **2008**, *130*, 1148). While this chlorination chemistry and a subsequent one-pot diene synthesis (*Org. Lett.* **2009**, *11*, 465) utilizing *N*-allylhydrazones were important for the research program, we decided to refocus fully on our original goal. To this end, Devon tested a variety of metal triflates and found that 20 mol% of hafnium(IV) triflate catalyzed the reaction at 125 °C.” Triflic acid alone was more effective than the metal triflate, and after further investigations into Brønsted acids, the researchers found that 10 mol% triflimide in diglyme at 125 °C produced the best yields across a range of substrates.

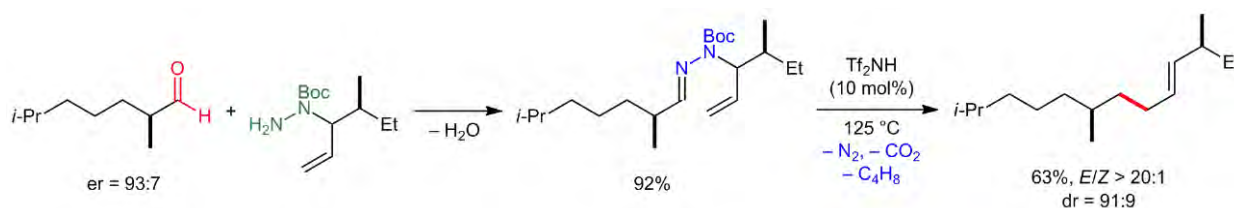


Triflimide-catalyzed, ‘traceless’ bond construction of *N*-allylhydrazones



The original reaction as reported by Stevens and co-workers

“The reaction proved to be tolerant to a wide range of both aromatic and aliphatic aldehyde-derived hydrazones,” said Professor Thomson, “which was gratifying since our prior reactions were limited to arylhydrazones. Stereocenters are tolerated on both fragments, which bodes well for future applications in natural product synthesis.”



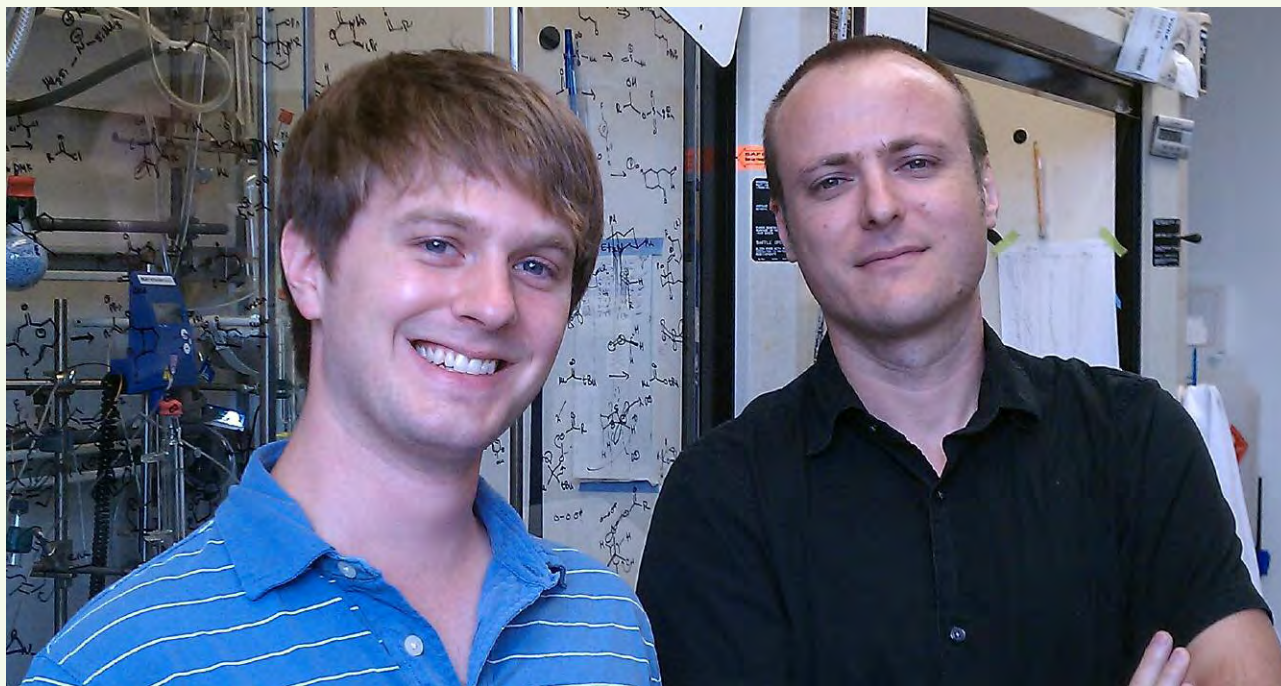
The two-step condensation–rearrangement method for fragment coupling: potential for complex molecule synthesis

“While we have termed this reaction a ‘traceless’ bond construction, since the two functional groups that allow for fragment union are lost in the subsequent rearrangement,” explained Professor Thomson, “we consider that the long-term use of this reaction is as a powerful fragment-coupling method.” In effect, the synthesis of a hydrazone is one of the most straightforward reactions (a ‘click’ reaction as originally defined by Sharpless) that can allow for a high-yielding union of two complex molecules. “The addition of a catalyst to the hydrazone would then allow for a traceless rearrangement,

forging the more challenging carbon–carbon bond,” said Professor Thomson. “Current limitations to our triflimide system are the still relatively high reaction temperatures required (125 °C) and the strongly acidic conditions that militate against the use of an acid-sensitive functionality. Resolving these limitations, and developing an enantioselective variant of the rearrangement represent current focuses of this research in my laboratory,” he concluded. ■

Matteo Zanda

About the authors



From left to right: D. A. Mundal, Prof. R. J. Thomson (co-author C. T. Avetta, Jr. not pictured)

Cascade Cyclization to Produce a Series of Fused, Aromatic Molecules

Org. Lett. **2010**, *12*, 2146–2148; *Synfacts* **2010**, 763 (*Synfact* of the Month)

■ Novel methods for the synthesis of fused aromatic molecules are of paramount importance in modern material science, particularly for the fabrication of organic thin-layer devices, which are key components of electronic circuits, solar cells, light sensors, memory cells and light-emitting diodes such as full-color, video-rate, flexible, all plastic displays. The group of Professor Christopher B. Gorman from North Carolina State University (Raleigh, USA) has recently described a very interesting approach to monoaza-acenes, which constitute a specific and promising class of these compounds.

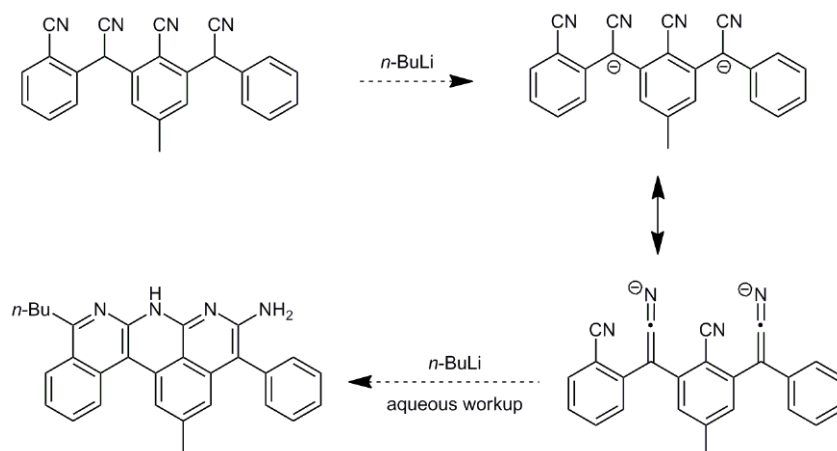
“Completely fused, aromatic molecules have the propensity to stack well in the solid state and because they have small HOMO–LUMO gaps due to their extended conjugation,” explained Professor Gorman. “Routes to them, however, often involve stepwise ring closings that are inefficient. Our group wondered whether a cascade cyclization was possible – reminiscent of the ‘zip’ synthesis of steroids and many ensuing cascade or domino cyclization reactions.” According to Professor Gorman, the cyclization of poly(acrylonitrile) at elevated temperatures provided further inspiration to the researchers. “Poly(acrylonitrile), however, requires further reaction to aromatize, and this aromatization is not clean,” he continued. “We hypothesized that oligomers composed of *ortho*-cyano

diphenyl acetonitrile units could cyclize and aromatize via a CH-to-NH tautomerization.”

Simple calculations performed by Professor Gorman and his co-workers showed that the tautomerization was thermodynamically favorable. “In the presence of an anion, it is also kinetically feasible,” he said. “No intermediates with benzylic CH units in them were ever observed upon cyclization. The *n*-butyllithium-initiated cyclization is also highly regioselective. We speculate that the anion is responsible for both the kinetic feasibility and the regioselectivity. Deprotonation of the relatively acidic, benzylic carbon promotes the tautomerization and also would make a less nucleophilic, delocalized anion that would be less reactive,” concluded Professor Gorman.

All products were emissive, and showed interesting photo-physical properties. Future work will show whether these compounds are suitable for applications in materials science. ■

Matteo Zanda



About the authors

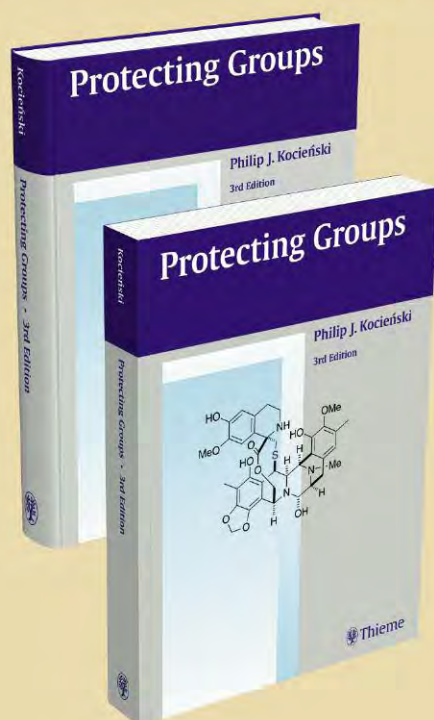


Prof. C. B. Gorman

Christopher B. Gorman received his B.A. in chemistry and computer science from Drew University (USA) in 1987 and his Ph.D. in chemistry from the California Institute of Technology (USA) in 1991, working under Professor Robert Grubbs. He then did postdoctoral work at the NASA Jet Propulsion Laboratory (USA) with Dr. Seth Marder and at Harvard University (USA) with Professor George Whitesides. He is now Professor of Chemistry at North Carolina State University. His research interests are in the design and synthesis of new materials with interesting and useful electronic properties at nanometer-length scales.

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INFORMATION ++++



Do you already have your Protecting Groups?

"... it is well organized, covers useful information, and is eminently readable – an excellent combination."

P. DeShong, University of Maryland, USA,
J. AM. CHEM. SOC., 2006

"... by far the best book on protection groups ..."

T. Laird, Scientific Update, UK, Organic
Process Research & Development, 2005

SYNTHESIS/SYNLETT Advisory Board Focus: Dr. Klaus Ditrich (BASF, Germany)

■ **Background and Purpose.** *SYNFORM* will from time to time portrait *SYNTHESIS/SYNLETT* Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this issue, we present Dr. Klaus Ditrich from BASF in Germany.

BIOGRAPHICAL SKETCH



Dr. K. Ditrich

Klaus Ditrich was born in Rhina (Germany) in 1956. He studied chemistry at the University of Marburg where he joined Prof. R. W. Hoffmann's group for a diploma thesis (oxidation of metal organic compounds) and a PhD thesis in the field of natural product synthesis (total synthesis of macrolide antibiotics). After having received his PhD in 1986, he joined BASF SE in 1987, starting his

career in the field of agrochemicals research. In 1992 he moved to the research unit for fine chemicals & biocatalysis, working in the field of asymmetric catalysis and enzymatic reactions. Since 1995 he is responsible for the process development for the production of optically active amines. In 1996 he received the "BASF Innovations Award" and in 2008 the "Siegfried Gold Medal" for innovations in process chemistry. Since 2002 he is also a lecturer at the University of Freiburg (Germany) where he was appointed as an honorary professor (2006).

INTERVIEW

SYNFORM | *Dr. Ditrich, which are your main current research interests?*

K. Ditrich | Application of chemo-enzymatic reactions to the efficient synthesis of optically active intermediates.

SYNFORM | *What is your most important scientific achievement to date?*

K. Ditrich | It is the development of a production process allowing the efficient synthesis of enantiopure amines on a commercial scale.

SYNFORM | *Can you mention discoveries in the area of organic chemistry, which you consider to be particularly important?*

K. Ditrich | In my opinion the developments in the area of olefin metathesis are most important. Within a short period of time it was clearly demonstrated that this methodology is an enormously valuable enrichment of the organic chemist's toolbox.

With respect to more recent research, I think that Michael Krische's work in the area of C–C bond formation via catalytic hydrogenation is a very promising concept which will find many applications in synthetic organic chemistry.

SYNFORM | *Do you have hobbies, besides chemistry?*

K. Ditrich | Hiking, biking, and gardening. ■

Matteo Zanda

COMING SOON ►► COMING SOON ►►

SYNFORM 2010/11 is available from November 22, 2010

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Synergistic Organocatalysis in the Kinetic Resolution of Secondary Thiols

(Focus on an article from the current literature)

■ Professor Max Malacria

(Focus on a SYNTHESIS/SYNLETT Advisory Board Member)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Syntheses of Galbulimima Alkaloids

(by U. Rinner)

SYNLETT

Account on: Ruthenium Porphyrin Catalyzed Carbenoid Transfer Reactions

(by C.-M. Che)

SYNFACTS

Synfact of the Month in category "Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions": [Pd-Catalyzed Asymmetric Cross-Coupling of Allyl Carbonates and Allyl Boronates](#)

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Erratum

Synform

Matteo Zanda *Synform* **2010/10**, A86.

The PDF version of this issue did contain wrong page numbers. The starting page of the current version has been corrected to A86.