

SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

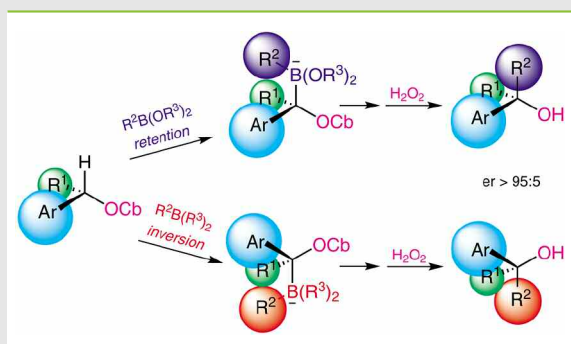
2009/03

SYNSTORIES

■ Gold-Catalyzed Synthesis of Aromatic Azo Compounds from Anilines and Nitroaromatics

■ Synthesis of 3-Chlorofurans and 5-Chlorofuropyrimidine Nucleosides Using a Pool Sanitizer as a Chlorocyclization Reagent

■ Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols



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

this issue features three **SYNSTORIES** which highlight important advances in the art of synthesis. The first article reports on an industrially important transformation, the synthesis of aromatic azo compounds, that is now

possible through a direct oxidation from anilines which in turn can be obtained by reduction of the corresponding nitroaromatics using the same gold catalyst. This striking achievement is due to the work of Professor Avelino Corma and his group from the University of Valencia (Spain). The second **SYNSTORY** covers a novel methodology for the synthesis of important compounds like halogenated heterocycles, based on the use of a rather peculiar and inexpensive reagent like a pool sanitizer (trichloroisocyanuric acid) developed by Professor Roman Dembinski and co-workers (USA). The third **SYNSTORY** reports on a conceptually innovative, exciting methodology for converting, in a stereo-controlled manner, chiral secondary alcohols into tertiary alcohols using boron reagents, as described in the original *Nature* report by Professor Varinder K. Aggarwal (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

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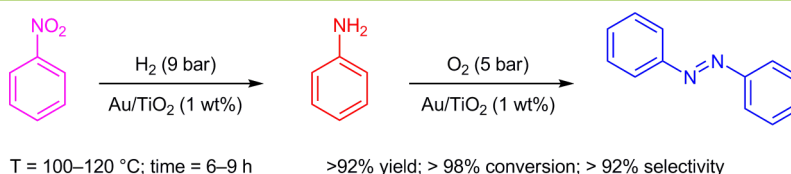
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Gold-Catalyzed Synthesis of Aromatic Azo Compounds from Anilines and Nitroaromatics

Science **2008**, *322*, 1661–1664



■ Organic chemistry is doing an outstanding job in creating new highly complex molecules. Meanwhile, it has been responsible, in conjunction with catalysis and chemical engineering, for many manufactured products that improve both the quality and length of our lives. However, when one reviews industrial processes involving the production of chemicals, one sees that there are still cases where dangerous and/or sacrificial stoichiometric reactants are being used. Now, the group of Professor Avelino Corma from the University of Valencia (Spain) has developed a novel technology allowing for the direct oxidation of anilines and nitroaromatics to azo compounds, in high yields and selectivities, by exploiting a novel gold catalyst.

“We have concentrated part of our research efforts on the development of solid catalysts which allow the design of alternative chemical routes that avoid the use of dangerous reactants and substitute stoichiometric by catalytic processes,” explained Professor Corma. “Following this, we introduced a new catalyst system (Sn-Beta and Sn-MCM-41) that allows us to synthesize lactones using H_2O_2 as oxidant instead of the classical organic peracids (*Nature* **2001**, *412*, 423), to use solid acids or bases instead of mineral or organic acids and bases for a large number of reactions (*Chem. Rev.* **1997**, *97*, 2373; *Advances in Catalysis*, Vol. 49; B. C. Gates, H. Knozinger, Eds.; Academic Press, **2006**, 239–302; *Catal. Rev. - Sci. Eng.* **2004**, *46*, 369), to prepare metal catalysts for the chemoselective reduction of substituted aromatic compounds using H_2 as reactant (*Science* **2006**, *313*, 332), and now to synthesize aromatic azo compounds from anilines and from nitroaromatics in a one-pot reaction. These types of catalysts based on gold and on platinum decorated with titanium oxide open new possibilities for the processes described above.”

In the case of azo compounds, the catalytic process discovered by Professor Corma and his co-workers avoids the use

of lead tetraacetate or stoichiometric amounts of nitrite salts. “Furthermore,” confirmed Professor Corma, “the fact that the same gold-supported catalyst allows us to carry out selectively the reduction of substituted nitroaromatics to the corresponding anilines and the oxidation of the anilines formed to the azo compounds has opened the possibility for a cleaner, more intensive one-pot process. We are hoping that industry will be interested in this new system and will study the economic and practical viability.” This work on the catalytic synthesis of azo compounds followed, rationally, previous work by Professor Corma’s research group on the reduction of substituted nitroaromatics, since a mechanistic study showed that the azo compounds are potential intermediates, at least through one of the routes for producing anilines from nitroaromatics. “We are already finding that these catalysts and the already reported processes allow the opening of new routes for synthesizing additional products of commercial interest through cascade-type reactions,” concluded Professor Corma. ■

Matteo Zanda



Prof. A. Corma and co-workers discussing the progress of the work

Synthesis of 3-Chlorofurans and 5-Chlorofuropyrimidine Nucleosides Using a Pool Sanitizer as a Chlorocyclization Reagent

Eur. J. Org. Chem. **2008**, 3449–3452; *Synfacts* **2008**, 1145 (*Synfact* of the Month)

■ The development of simple and inexpensive procedures for the preparation of complex building blocks, like halogenated heterocycles and their derivatives, continues to be an important area of research. Recently, Professor Roman Dembinski and his co-workers Dr. Adam Sniady and Marco S. Morreale from the Oakland University (Rochester, USA), together with Professor Craig A. Wheeler from the Eastern Illinois University (Charleston, USA), described a novel electrophilic halocyclization reaction that represents an efficient and potent methodology leading to functionalized heterocycles by a tandem cycloisomerization–halogenation processes. The electrophilic component serves as both cycloisomerization catalyst and halogen donor, thus creating a very effective process from the standpoint of material economy. “Despite the fact that useful compounds like iodo, bromo, thio, seleno, and telluro derivatives can be produced relatively easily with the use of halogen or pseudohalogen reagents,” said Professor Dembinski, “chlorocyclization reactions remain little explored due, in part, to the diminished electrophilic character of chlorine compared to iodine or bromine.”

“After initial screening,” continued Professor Dembinski, “we succeeded in a chlorocyclization reaction using trichloro-*s*-triazinetriene (TCCA, or trichloroisocyanuric acid). Although inexpensive, it is seldom used in laboratories, mainly due to its dual oxidation/chlorination activity or lack of chlorination

selectivity. Adam and Marco were able to find reaction conditions that include slow reagent addition via a syringe pump at ambient temperature. Such a procedure practically eliminated the formation of overchlorination products.” TCCA uses all its chlorine atoms (thus featuring an effective halogen economy) in the reactions yielding 3-chlorofurans or 5-chlorofuropyrimidine nucleosides. “We realized that this reagent is sold commercially for swimming pool/spa treatments,” said Professor Dembinski. “Dr. Wayne Meyer (Chemtura, USA) supplied us with the BioGuard SmartSticks,” he continued. “We noticed that the TCCA contents sold in a chemicals catalogue almost match those of a pool care system. However, we had to grind the sticks to provide better homogeneity of the reaction. We also used boronic acids from a wide palette generously provided by Frontier Scientific (USA), a manufacturer of a variety of specialty boron compounds.”

The appeal of aryl/heteroaryl chlorides produced by this novel methodology can be attributed to their versatility as reaction precursors in cross-coupling processes, and their lower costs as compared to iodides, bromides, or triflates. “Even so, the relatively few examples of arylation reactions employing heteroaryl chlorides reported have been largely limited to the position α to a heteroatom (predominantly nitrogen),” noticed Professor Dembinski. “Heteroaryl chlorides are readily available by direct chlorination of aromatic compounds; however, such reactions are frequently restricted to activated positions or are less selective compared to the other halogens and lead to difficult-to-separate multiple products. We believe that this novel methodology provides a useful alternative entry to these interesting chloro heterocycles and may further advance the development of chlorocyclization reactions.”

In a commentary to this work, Victor Snieckus, a Professor of Organic Chemistry from Queen’s University, Kingston, Ontario (Canada) and an Editor of *Synlett* and *Synfacts*, said: “The report by Dembinski and co-workers was chosen unanimously to abstract as *Synfact* of the Month by our group against some serious competition. In our *Synfacts* abstract’s commentary,” continued Professor Snieckus, “we noted that it is a simple and convenient procedure for the synthesis of

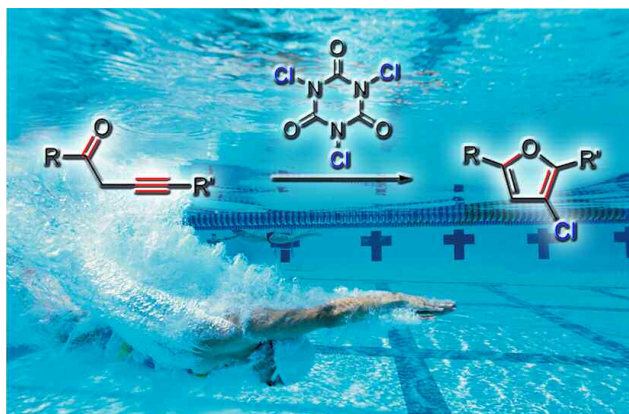


Illustration by Tomasz Sniady

3-chlorofurans in excellent preparative yields, that it uses inexpensive and readily available (we no doubt will think of the authors' source when we, in Canada, see the replacement of snow by water in the swimming pools) chlorination/oxidation reagent, that it uses easily accessible starting materials, and that it achieves a difficult substitution pattern for furans.

The somewhat limited substrate scope investigated is ameliorated by intelligently chosen examples and the application to furopyrimidine nucleosides which are potent antiviral agents," concluded Professor Snieckus. ■

Matteo Zanda



From left: Prof. R. Dembinski, M. S. Morreale, Dr. A. Sniady



(Photos by Andrea Eis)

Prof. K. A. Wheeler

About the authors

Adam Sniady obtained his M.Sc. in chemistry from the Technical University of Łódź (Poland). In 2008 he graduated with a Ph.D. (advisor Roman Dembinski) from Oakland University (USA). His thesis focused on developing new synthetic methodologies, including electrophilic cyclizations, and the synthesis of modified nucleosides. Currently he is a postdoctoral associate with Prof. Timothy Jamison at the Massachusetts Institute of Technology (USA).

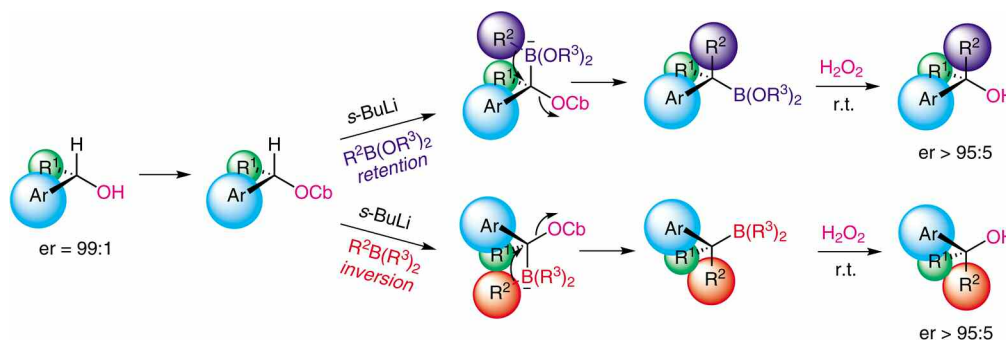
Marco S. Morreale obtained his B.A. in chemistry from Wayne State University (USA) in 1999. He entered the graduate program in chemistry at Oakland University in 2004. Under the direction of Roman Dembinski, he is currently investigating cyclization strategies for the synthesis of substituted furans and other heterocycles, and their reactivity.

Kraig A. Wheeler received his bachelor's degree in chemistry at the University of Minnesota (USA) in 1987 (Margaret Etter) and a Ph.D. from Brandeis University (USA) in 1992 (Bruce Foxman). After postdoctoral studies at the University of Texas at Austin (USA) (Ray Davis and Jim Whitesell) he moved on to a career in academia. Currently he serves as an Associate Professor at Eastern Illinois University (USA) where his research interests include chemical crystallography, molecular recognition of quasiracemate materials, and molecular-shape-directed supramolecular assemblies.

Roman Dembinski was educated (Ph.D.) at the Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Łódź (Poland) (undergraduate studies at the Technical University of Łódź). He then joined the group of J. A. Gladysz at the University of Utah (USA) as a research associate. Since 1999 he has held a faculty appointment at Oakland University. His scientific interests include synthetic organic, fluororous, medicinal, and organometallic chemistry.

Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols

Nature **2008**, 456, 778–782



Conversion of secondary alcohols into tertiary alcohols, essentially by removing a proton and adding the R² group, but of course it is more complicated than that!

■ A straightforward and enantiodivergent reaction allowing for the preparation of tertiary alcohols in both optical forms starting from a single enantiopure secondary alcohol was a sort of dream reaction for organic chemists. Now such a process has become reality thanks to the work of Professor Varinder K. Aggarwal and his group from the University of Bristol (UK). This striking methodology, which has a broad scope as it can be used for the synthesis of both cyclic and acyclic tertiary carbinols, is based on the formation of an intermediate carbon–boron bond from a metalated *N,N*-diisopropyl carbamate (Cb) alcohol derivative. This key process can take place with retention or inversion of configuration, depending on the nature of the boron reagent (see the scheme above). The carbamoyloxy function (OCb) is then displaced, with inversion of configuration, by the incoming R² function, originally bound to the boron atom. The carbon–boron bond is then oxidatively cleaved with retention of configuration by action of hydrogen peroxide, and transformed into the final carbon–oxygen bond.

“Basically, we have a conceptually new way of making quaternary centres via tertiary boronic esters,” said Professor Aggarwal. “The conversion into tertiary alcohols illustrates this, but there are competing technologies for such compounds, such as the work by Walsh (*J. Am. Chem. Soc.* **2005**, *127*, 16416) and Yus (*Tetrahedron: Asymmetry* **2005**, *16*, 3341). Our work, though, provides a non-intuitive and different disconnection with more readily available reagents. Further-

more,” continued Professor Aggarwal, “the power in the chemistry will come from the other transformations that are open to the tertiary boronic esters, for example, conversion into amines and all-carbon quaternary stereogenic centres. This will be the subject of forthcoming papers.” Pharmaceuticals and agrochemicals sometimes contain (one of) tertiary alcohols, C-tertiary amines or all-carbon quaternary stereogenic centres. “Our new method provides a reliable route to this important class of compounds. By having a new and different synthesis it opens the door to the synthesis of many more compounds of this sort and so enables the testing of such compounds much more easily. Although such compounds have not found widespread application in the past, this could, in part, be due to their poor availability. It is to some extent the chicken and egg question,” concluded Professor Aggarwal. ■

Matteo Zanda

About the authors

Varinder K. Aggarwal was born in Kalianpur in North India in 1961 and immigrated to the United Kingdom in 1963. He received his B.A. (1983) and Ph.D. (1986) from Cambridge University, the latter under the guidance of Dr. Stuart Warren.

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He was subsequently awarded a Harkness fellowship to carry out post-doctoral work with Professor Gilbert Stork at Columbia University (USA) from 1986–1988. He returned to a lectureship at Bath University (UK) and in 1991 moved to Sheffield University (UK), where in 1997, he was promoted to Professor of

Organic Chemistry. In 2000, he moved to the University of Bristol to take up the Chair of Synthetic Chemistry. He is the recipient of the AstraZeneca Award, Pfizer Award, GlaxoWellcome Award, Novartis Lectureship, RSC Hickinbottom Fellowship, Nuffield Fellowship, RSC Corday Morgan Medal and the Liebig's Lecturship (Germany), 1999/2000 (inaugural), RSC Green Chemistry Award (2004), Zeneca Senior Academic Award (2004), RSC Reaction Mechanism Award (2004), Royal Society Wolfson Merit Award (2006), RSC/GDCh-Alexander Todd–Hans Krebs Lectureship (2007), RSC Tilden Lecturer (2007), and an EPSRC Senior Research Fellowship (2007).

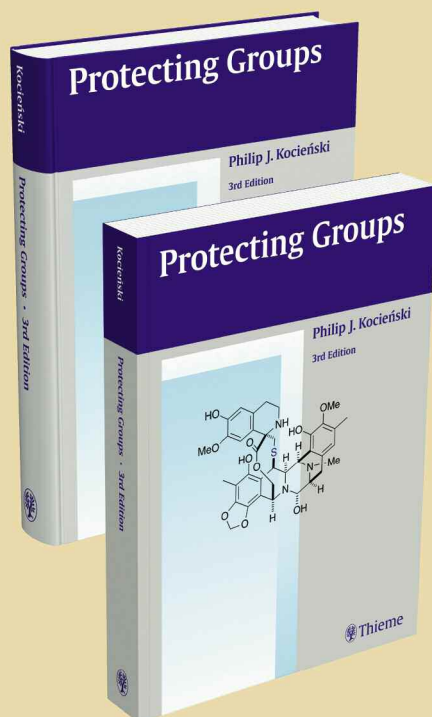


Rosalind M. French was born in Taplow (UK). She received her M.Sc. from Oxford University (UK) in 2006 under the supervision of Dr. Veronique Gouverneur. In 2006 she commenced her Ph.D. studies in the group of Professor Aggarwal at Bristol University and is currently working on the lithiation/borylation reactions of secondary benzyl carbamates.

Jake Stymiest was a PDRA from Alberta (Canada) (Ph.D. with Professor John C. Vederas), and a postdoctoral fellow with Professor Aggarwal from 2005–2007 in Bristol. Currently he is a Senior Research Chemist for Purdue Pharma (USA), working at the Coventry site in Rhode Island (USA).

Viktor Bagutski is a PDRA from Göttingen (Germany) (Ph.D. with Professor Armin de Meijere) and is currently in his final year with Professor Aggarwal.

INFORMATION ++++



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SYNFORM 2009/04

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In the next issues:

SYNSTORIES ■ ■ ■ ■

■ A Diels–Alder Approach to Benzannulated [5,6]-Spiroketal

(Focus on an article from the current literature)

■ Manganese-Catalyzed Cross-Coupling Reaction Between Aryl Grignard Reagents and Alkenyl Halides

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Michael Additions to Activated Vinylphosphonates

(by T. Janecki)

SYNLETT

Account on: Synthetic Efforts towards the Synthesis of the Complex Diterpene Providencin

(by J. Mulzer)

SYNFACTS

Synfact of the Month in category "Metal-Mediated Synthesis":

Efficient Co-Catalyzed Coupling of Aryl Grignard Reagents with Alkyl Bromides

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