

SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2010/02

SYNSTORIES ■ ■ ■ ■

■ Formation of *N*-Alkylpyrroles via Intermolecular Redox Amination

■ Asymmetric Histidine-Catalyzed Cross-Aldol Reactions of Enolizable Aldehydes

■ Solar Light-Driven Photocatalyzed Alkylations. Chemistry on the Window Ledge



CONTACT +++++

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Dear readers,

This winter is bringing lots of ice and snow in many parts of Europe, including the UK, where we are experiencing an unusually tough and freezing season. Does this mean that global heating is just a legend? Clearly not, as other places in the Northern Hemisphere are currently seeing weather that is unseasonably warm. What is definitely sure is that these days most of us need something hot to compensate the wintry conditions. What about some hot chemistry? If you think this would help, then you are in the right place because this issue of **SYNFORM** is full of very hot science! In the first **SYNSTORY**, for example, Professor Rainer Mahrwald (Germany) illustrates a new organocatalytic process allowing for the synthesis of stereodefined quaternary stereocenters from enolizable aldehydes. In the second **SYNSTORY** Professor Jon A. Tunge (USA) tells us more about his recent intermolecular redox amination leading to *N*-alkylpyrroles. Not enough to heat up? You can try with some sunlight from Italy, which, as explained by Professor Maurizio Fagnoni, can also be used to photocatalyze different alkylation reactions. And if, after reading all this, you still feel cold, you can always try with a hot drink but at least I hope you enjoyed the reading...

Matteo Zanda

Editor of SYNFORM

CONTACT ++++

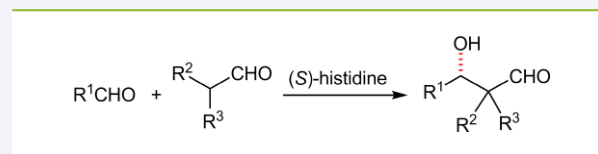
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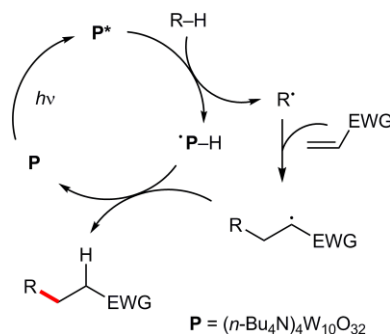
Solar Light-Driven Photocatalyzed Alkylations. Chemistry on the Window Ledge

Chem. Commun. **2009**, 7351–7353

■ Environmental concerns in organic synthesis are increasing and require a reconsideration of all the aspects of chemical processes. An ideal eco-friendly process must take place efficiently starting from non-toxic and cheap substrates, minimizing the amounts of additives, solvent (unless water is chosen) and external energy involved. A very interesting contribution to the development of “green chemistry” has been recently achieved by the group of Professor Maurizio Fagnoni from the University of Pavia (Italy), which authored a communication describing novel selective activations of C–H bonds driven by sunlight. “Photochemistry is an appealing alternative and light is a clean and powerful reagent that transforms molecules under mild conditions, avoiding the use of noxious or pollutant chemicals as activators, although energy for powering the lamps is required,” said Professor Fagnoni. “The ultimate ‘green’ source is obviously solar light, and its conversion into electrical power or into a fuel is indeed actively investigated. However, this has been rarely used in synthesis (*Photochem. Photobiol. Sci.* **2009**, *8*, 1499). This may be because of the spectral distribution over the UV-A and the visible part of the spectrum that results in a poor matching with the absorption of most organic compounds,” he continued, “as well as of the low intensity and discontinuous and inhomogeneous distribution depending on both weather and geographical conditions.” Professor Fagnoni explained that in Nature chlorophyll absorption allows for the formation of valuable organic compounds, suggesting that the use of a **photocatalyst** (a compound able to absorb the light and to activate transparent substrates that are otherwise unreactive: *Chem. Rev.* **2007**, *107*, 2725) is the best way to exploit sunlight.

“In recent years our research group has focused its attention on C–C bond formation by the use of decatungstate tetra-butylammonium salt (TBADT) as photocatalyst,” said Professor Fagnoni. This approach enables the C–H activation in simple aliphatic derivatives (such as alkanes, alcohols, ethers, aldehydes and amides) and the subsequent addition of the photogenerated radicals onto electron-poor olefins affords alkylated products in a 100% atom-economical process (see Scheme 1). “The reactions were initially carried out by using

UV lamps,” he continued, “but we reasoned that since TBADT absorbs all of the UVA, this would be a sensible candidate to test the usefulness of sunlight for synthesis.”



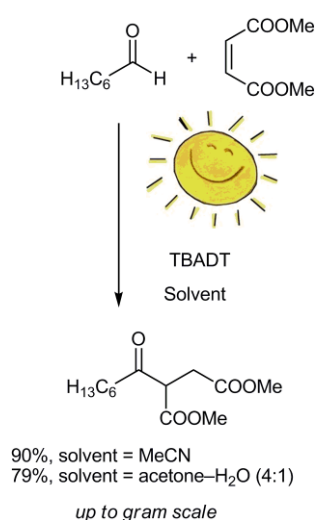
Scheme 1

“To our delight, these reactions were found to occur smoothly under solar irradiation indeed, in many cases with a better yield than when carried out by using artificial lamps, avoiding the emission of up to 100 grams of CO₂ per gram of product.”



Figure 1 Photocatalyzed reaction: the blue color demonstrates the presence of reduced catalyst $P\text{--}H$

Professor Fagnoni and his coworkers further explored the scale-up and the minimization of both the environmental and the economic costs of the method. The acylation of dimethyl maleate by heptanal (see Scheme 2) was well suited because of the use of equimolecular amounts of the reagents and the short irradiation time required. “We found that the reagents’ concentrations could be increased up to 0.5 M and a more economical and environmentally benign medium, such as an acetone–water (4:1, v/v) mixture, could be used in place of acetonitrile with no significant decrease in the product yield,” explained Professor Fagnoni. “This resulted in a dramatic improvement of the environmental index, as calculated by the EATOS method.”



Scheme 2

“Useful amounts of products were obtained by simply leaving a Pyrex vessel containing the reaction mixture in a sunny place, such as the window ledge of our laboratory: up to 10 grams in a few days for 1 dm² exposed surface, no stirring required,” he said. “The achievement of such **“chemistry on the window ledge”** suggests that photochemistry, and particularly photocatalysis, is an exceptionally versatile method, exactly because of its experimental simplicity which may give to it an ‘evolutionary’ advantage with respect to the more sophisticated methods typical of present-day organic synthesis. We may learn from living beings that have long made versatility and adaptability a key for their success, as in the well known rhyme by Eleanor Farjeon,” Professor Albini concluded. ■

Cats sleep anywhere, any table, any chair.

*Top of piano, **window ledge**, in the middle, on the edge.*

Open draw, empty shoe, anybody’s lap will do.

Fitted in a cardboard box, in the cupboard with your frocks.

Anywhere! They don’t care! Cats sleep anywhere.

Matteo Zanda



Figure 2 Cats seem to like photocatalysis...

About the authors



From left: Dr. S. Protti, Prof. M. Fagnoni, D. Ravelli, Prof. Angelo Albini

Angelo Albini completed his studies in chemistry in 1972, did postdoctoral work at the Max-Planck Institute for Radiation Chemistry in Mülheim an der Ruhr (Germany, 1973–1974) and joined the Faculty at Pavia in 1975, where he is currently Professor of Organic Chemistry, after a period at the University of Torino (Italy) and stays at the Universities of Western Ontario (Canada, 1976–1977) and Odense (Denmark, 1983). He is active in the field of organic and applied photochemistry, organic synthesis via radicals and ions, photoinitiated reactions, and mild synthetic procedures in the frame of the increasing interest for sustainable/green chemistry.

Maurizio Fagnoni graduated in Pavia in 1992 with a thesis on the synthetic applications of photo-SET reactions under the guidance of Professor Angelo Albini. He spent part of his PhD period at the University of Münster (Germany) working on the photochemistry of cyclopropylketones with Professor Jochen Mattay as the supervisor. He moved to the Istituto Ronzoni in Milan (Italy) where he worked on the synthesis of peptidomimetics and functionalized chitosans, and in 1998 returned to the University of Pavia where in 2008 he was appointed Associate Professor. His interest lies in the application of photochemistry to organic synthesis encompassing photocatalysis and phenyl cation chemistry.

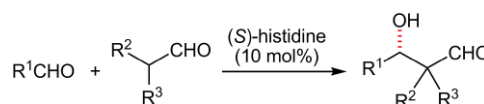
Stefano Protti studied chemistry at the University of Pavia, graduated in 2003 and completed his PhD in 2006 developing photochemical arylation reactions via phenyl cations. He then moved to LASIR laboratory in Lille (France), where he studied the photoreactivity of flavonoids. In 2007 he won the CINMPIS prize for the best PhD thesis in organic chemistry. In 2009 he spent a post-doctoral period at the iBitTec-S laboratory (CEA Saclay, France), where he studied photocatalyzed oxidation reactions. He is currently investigating eco-sustainable photochemistry at the University of Pavia.

Davide Ravelli obtained his Master degree from the University of Pavia in 2008. He is currently a PhD student at the University of Pavia (Professor Albini is the supervisor), and his research interests focus on decatungstate-photocatalyzed C–C bond-forming reactions. In 2009 he was awarded with a Federchimica prize for his thesis on photocatalysis.

Asymmetric Histidine-Catalyzed Cross-Aldol Reactions of Enolizable Aldehydes

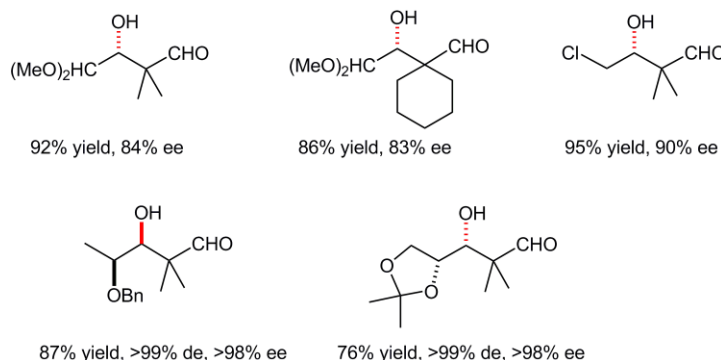
J. Am. Chem. Soc. **2009**, *131*, 16642–16643

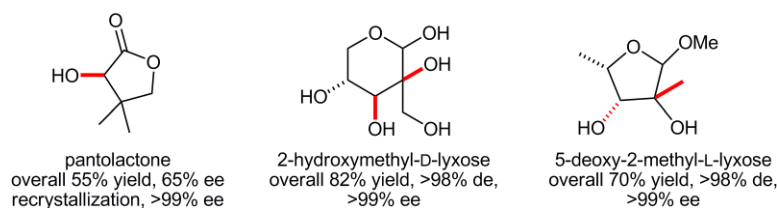
■ According to Dr. Rainer Mahrwald from the Humboldt University of Berlin (Germany), the direct asymmetric cross-aldol addition of two different enolizable aldehydes has been a challenge in organic chemistry since time immemorial. “With the exception of enzymatic catalysis (W.-D. Fessner, In *Modern Aldol Reactions*, Vol. 1; R. Mahrwald, Ed.; Wiley-VCH, **2004**, 201.), no reaction conditions have been found that both suppress side reactions and, at the same time, sufficiently discriminate between the different reactivities of the aldehydes,” explained Dr. Mahrwald. “For a successful execution of these transformations, enolizable aldehydes have to be differentiated strictly and selectively into two discrete components – a carbonyl component and an ene component,” he continued. “This goal is a topic in proline catalysis. Unfortunately, the required discrimination between two different enolizable aldehydes can be achieved only by syringe pump techniques. Thus, self-aldol additions of aldehydes can be suppressed,” said Dr. Mahrwald. “Moreover, α -branched enolizable aldehydes do not act as ene components in proline-catalyzed cross-aldol additions. Instead, they operate exclusively as carbonyl compounds (A. B. Northrup, D. W. C. MacMillan *J. Am. Chem. Soc.* **2002**, *124*, 6798; *Science* **2004**, *305*, 1752). As a result, the construction of quaternary centers is impossible under the conditions required by proline or proline-derivative catalysis.” Recently, the Mahrwald group disclosed a practical solution of this puzzling issue, based on a chemo-, diastereo- and enantioselective process catalyzed by L-histidine in water at room temperature.



“During our ongoing studies in the field of direct aldol additions we have discovered that histidine solves the above-mentioned problems,” confirmed Dr. Mahrwald. “Histidine is able to recognize enolizable aldehydes as ene or as carbonyl components without any additional techniques. Electron-rich aldehydes act as ene components whereas electron-deficient aldehydes act as carbonyl components,” he continued. “Based on this clear differentiation, we can predict the results of a direct aldol addition between two different enolizable aldehydes. In particular, electron-rich α -branched enolizable aldehydes tend to react as ene components in these transformations. Thus, we are able to demonstrate the construction of quaternary and stereogenic centers.”

This method represents a breakthrough in direct aldol additions, because an inexpensive and easy-to-handle catalyst can be used to produce aldol adducts in enantiopure form. “This method opens up the way for the synthesis of a wide range of functionalized β -hydroxy aldehydes,” agrees Dr. Mahrwald. “Furthermore, we have illustrated the application of the new method in shortcuts of existing total syntheses as well as completely new approaches to natural products.”





The authors are convinced of the enormous potential of this method. “We believe that the asymmetric direct aldol additions of structurally diverse and enolizable aldehydes using histidine as an organocatalyst do represent a useful integration of the known proline-catalyzed additions,” said Dr. Mahrwald. On top of that, the method also provides an enantioselective access to highly hydroxylated and defined configured polyketide structures, such as carbohydrates, as well as defined configured tertiary alcohols.

“Investigations into further substrates are currently underway, alongside experiments around iterative construction of acetate and propionate aldol structures using this new method,” concluded Dr. Mahrwald. ■

Matteo Zanda

About the authors



From left: Prof. R. Mahrwald, M. Markert, U. Scheffler

Rainer Mahrwald (born in 1950) studied chemistry at Martin-Luther University Halle (Germany) and subsequently joined the “Manfred von Ardenne” Research Institute in Dresden (Germany) where he led the synthetic group. He gained his doctorate under G. Wagner in Leipzig (Germany) in 1979 and went on to the Institute of Organic Chemistry at the Academy of Sciences in Berlin, where he remained

until 1990. Following a stay at the Philipps University in Marburg (Germany) with M. T. Reetz he qualified as a lecturer at the Humboldt University Berlin (Germany), where is now a private lecturer. Research in his group is focused on new concepts for asymmetric catalysis and methods development.

Morris Markert was born in 1977 in Nashville (USA). He received his Diploma degree from Humboldt University Berlin (Germany) in 2003 under the supervision of Dr. Rainer Mahrwald. He is currently carrying out his PhD thesis in the Mahrwald group at the Humboldt University Berlin.

Ulf Scheffler was born in 1980 in Rheda-Wiedenbrück (Germany). He received his Diploma degree from Humboldt University Berlin (Germany) in 2008 under the supervision of Dr. Rainer Mahrwald. He is currently carrying out his PhD studies under the supervision of Rainer Mahrwald at the Humboldt University Berlin.

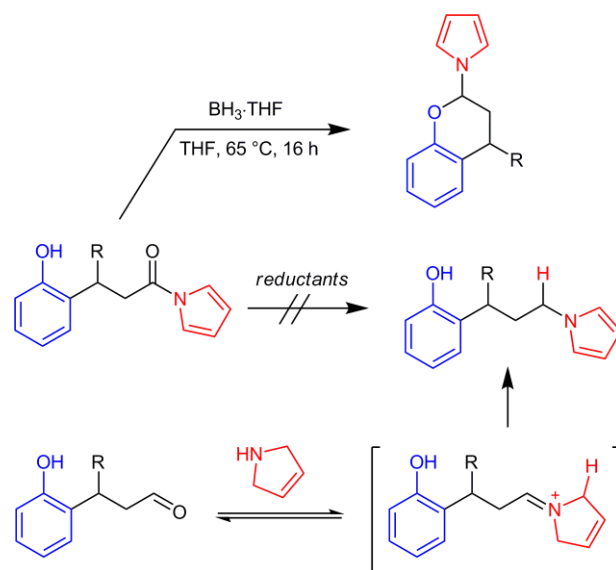
Formation of *N*-Alkylpyrroles via Intermolecular Redox Amination

J. Am. Chem. Soc. **2009**, *131*, 16626–16627

■ The development of environmentally friendly and economically sustainable methods is one of the current priorities in the area of organic synthesis. Catalysis offers an increasing number of potential solutions to a wide range of synthetic problems, but there is still a strong need for more efficient technologies characterized by high atom-economy and the use of non-hazardous chemicals and procedures. An important achievement was reported recently by the group of Professor Jon A. Tunge from the University of Kansas (Lawrence, USA), who developed an intermolecular redox amination process that produces a wide range of *N*-alkylpyrroles. The new method features excellent atom-economy, high yields and user-friendly experimental protocols.

“Our research has previously focused on the utilization of the inherent reactivity of organic molecules to obviate the need for high-energy organometallic reactants,” explained Professor Tunge. “In this new publication we described the utilization of H₂ embedded in 3-pyrrolines to effect the reduction of aldehydes and ketones via redox isomerization.” The idea originated from a chance confluence of two different research projects in Professor Tunge’s group. “In conjunction with the University of Kansas Center for Chemical Methodologies and Library Development we were trying to prepare a chemical library of pyrrole-substituted phenols,” he said. “Unfortunately, standard methods that were successful in analogous cases only resulted in reductive cyclization and failed to give the desired pyrroles (Scheme) (K. Li, J. A. Tunge *J. Org. Chem.* **2008**, *73*, 8651). At the same time, Professor Tunge had coincidentally identified a small amount of a pyrrole as a byproduct in a reaction of an aldehyde with 3-pyrroline. “Thus, it became apparent that the solution to our library synthesis was the condensation of pyrrolines with aldehydes,” he continued. “The hypothesis was that 3-pyrroline would condense with aldehydes to generate iminium ion intermediates. These intermediates are “redox-frustrated” with the pyrroline fragment wanting to be oxidized to the aromatic pyrrole and the iminium carbon wanting to be reduced to quench the charge (Scheme). These desires can both be satisfied by a simple redox isomerization.”

“Searching the literature revealed that Cook had observed a similar pyrrole product when 3-pyrroline was condensed with ketones under thermal conditions,” said Professor Tunge

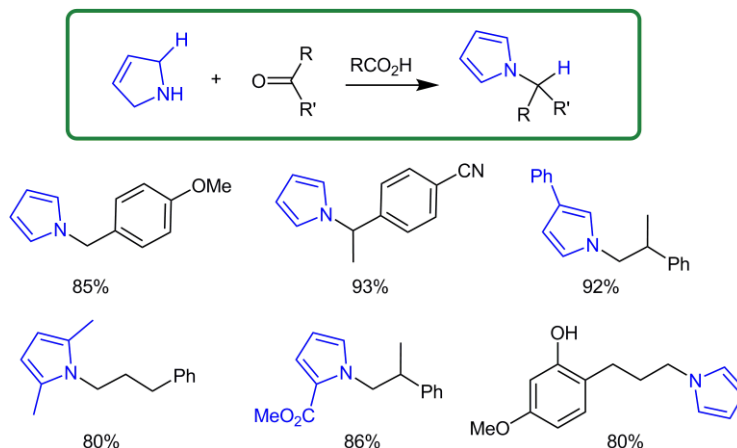


(A. G. Cook, K. A. Switek, K. A. Cutler, A. M. Witt *Lett. Org. Chem.* **2004**, *1*, 1). Unfortunately, this reaction involved harsh reaction conditions and was low-yielding. Thus, an undergraduate researcher in Tunge’s lab (Miranda Paley) was tasked with finding a catalyst for the reaction that would allow a variety of aldehydes and ketones to undergo the redox amination reaction. “She quickly discovered that mild Brønsted acids like MeCO₂H and PhCO₂H would catalyze the reaction to provide pyrroles in good to excellent yields,” said Professor Tunge. “Next, Dr. Nirmal Pahadi optimized the catalytic conditions and investigated the substrate scope.” The mild reaction conditions allow one to perform the redox amination on a variety of aldehydes and ketones (Figure). Moreover, differently substituted 3-pyrrolines are excellent partners for the redox amination reaction. “Most gratifyingly, the condensations with chromanols provided the pyrrole-substituted phenols that we needed for our chemical library preparation,” said Professor Tunge. “Ultimately, the reaction provides a wide variety of *N*-alkylpyrroles using aldehydes as alkylating agents, yet it avoids the strong reductants that are typically associated with reductive aminations. In addition, our reaction avoids the

strong bases that are typically required for alkylation of pyrroles and we can access many pyrroles that cannot be synthesized by the alkylation of pyrrole anions. We anticipate that

this method will be useful to medicinal chemists who routinely need to access pyrrole-based scaffolds as potential pharmaceuticals," he concluded. ■

Matteo Zanda



About the authors



Prof. J. A. Tunge

Jon A. Tunge was born in Yankton, South Dakota (USA) in 1973. He received a BS in Chemistry from the University of Idaho (USA) where he worked with Professor Ray von Wandruszka on the development of fluorescent probes for high explosives. From 1995–2000 he worked on developing asymmetric transformations of organozirconocenes under the direction of Professor Jack R. Norton. After

receiving his PhD from Columbia University (USA) in 2000, he moved to the University of Wisconsin-Madison (USA) to study the mechanisms of organometallic transformations under the guidance of Professor Charles P. Casey. In the fall of 2002, Dr. Tunge joined the Faculty at the University of Kansas where he has established a research program combining the topics of catalytic reaction development, combinatorial chemistry, and green synthetic chemistry.



Dr. N. Pahadi

Nirmal Pahadi is a native of Nepal. He received his BS in Chemistry from Tribhuvan University (Kathmandu, Nepal) in 1996. He moved to Japan, where he received his PhD under the direction of Professor Yoshinori Yamamoto at Tohoku University. After completing a JSPS postdoctoral fellowship under the direction of Professor Terada, Dr. Pahadi joined the group of Professor Tunge. He has been active

in developing palladium-catalyzed decarboxylative aminations as well as hydroaminations.

Miranda Paley (not pictured) received her BSc degree from Grinnell College (Grinnell, IA, USA) in 2009. She performed research in the Tunge lab as part of the National Science Foundation's Research Experiences for Undergraduates program.



Dr. R. Jana

Ranjan Jana is a native of India. He received his BS in Chemistry from Midnapur College (West Midnapur, India) in 2000. After attaining his PhD in Organic Chemistry from the Indian Association for the Cultivation of Science (Kolkata, India) under the direction of Professor Ranu, Dr. Jana moved to Israel for postdoctoral studies at Bar-Ilan University. He joined the group of Professor Tunge and the

University of Kansas Center for Environmentally Beneficial Catalysis in 2008. He has developed polymer-supported catalysts for continuous synthesis as well as decarboxylative couplings of coumarins.



Dr. S. Waetzig

Shelli Waetzig received her BSc (Magna Cum Laude) from Creighton University (Omaha, NE, USA) in 2004. She matriculated to the University of Kansas and joined the group of Professor Tunge at in 2005. Since that time, she has developed a variety of synthetic methods involving selenium catalysis as well as tandem catalytic decarboxylative coupling/sigmatropic rearrangement reactions. She

received her PhD with honors from the University of Kansas in 2008 and is currently working as an NIH postdoctoral fellow under the direction of Professor Keith Woerpel at the University of California-Irvine (USA).

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2010/03

is available from
February 18, 2010

In the next issues:

SYNSTORIES ■ ■ ■ ■

■ Radical Cyclization of α -Bromo Aluminum Acetals: An Easy Approach to γ -Lactols

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Synthesis of Cyclic Hydrazino α -Carboxylic Acids

(by C.-H. Küchenthal, W. Maison)

SYNLETT

Cluster on "Grignard Reagents" in issue 2/2010

SYNFACTS

Synfact of the Month in category "Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions": [Synthesis of Indanes by Enantioselective Direct Arylation](#)

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