

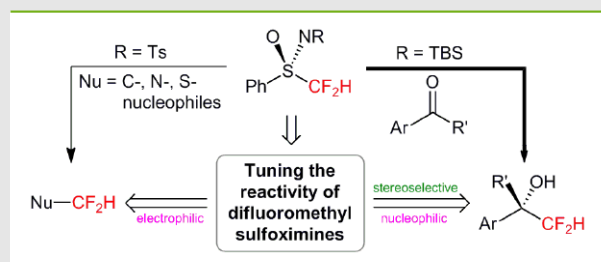
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2013/08

SYNSTORIES ■ ■ ■ ■

■ Chiral Fluorinated Sulfoximines as New Fluoroalkylating Agents



■ Synthesis of 1,5-Disubstituted 3-Amino-1*H*-1,2,4-triazoles from 1,3,4-Oxadiazolium Hexafluorophosphates

■ Copper(II) Triflate Catalyzed *tert*-Butylation of Anilines

■ Hydrocupration of Terminal Alkynes: A Key Step in New Catalytic Routes for Alkyne Hydrofunctionalization

CONTACT ++++

Your opinion about SYNFORM is welcome, please correspond if you like:
marketing@thieme-chemistry.com



Dear readers,

the 245th ACS National Meeting & Exposition, April 7–11, 2013, was held in New Orleans (Louisiana, USA). In line with my previous experience with ACS meetings, it was a massive chemistry experience and a great

opportunity to meet colleagues from all over the world and catch up with the most exciting and recent developments and trends in chemistry. Many think that ACS meetings are just too large and hectic, and although I tend to agree with that, I always take home a lot of excitement, new ideas and extra motivation. I confess that I really enjoy ACS meetings and I think they are a fantastic and unique experience, which I definitely recommend to young researchers. Not everything is ideal of course, for example the cost of most ACS Hotels is, in my opinion, exceedingly high, almost prohibitive. However, I am always impressed by the nearly perfect organization of these huge meetings, for example ca. 15,000 delegates gathered in New Orleans, a city that only eight years ago was struck by the disaster of Hurricane Katrina and today is amazingly back on track, vibrant and multicultural as one would expect from “The Big Easy”. In this special issue of **SYNFORM** we selected four communications (out of several thousand!!!), where we tried to emphasize the excellent work of younger up-and-coming researchers. The first **SYNSTORY** comes from the industry, and specifically from Genentech Inc. (USA) where Dr. B. Wong developed a new synthetic strategy for preparing 3-amino-1,2,4-triazoles. The second originates from the brilliant work developed by Professor J. Hu (P. R. of China) in the area of stereoselective organofluorine chemistry. The third **SYNSTORY** reports on a novel strategy for the efficient tert-butylation of anilines, a notoriously challenging reaction, developed by Dr. J. W. Cran (USA). Last but not least, a very interesting approach to alkyne hydrofunctionalization, which was very effectively communicated in New Orleans by postgraduate student R. Rucker from the group of Professor G. Lalic (USA). May I define all this “Creole-Cajun chemistry”?

Enjoy your tasty reading!

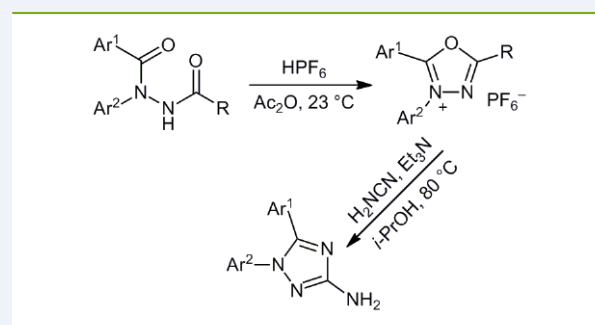
Matteo Zanda

Editor of **SYNFORM**

IN THIS ISSUE

SYNSTORIES ■ ■ ■ ■

Synthesis of 1,5-Disubstituted 3-Amino-1H-1,2,4-triazoles from 1,3,4-Oxadiazolium HexafluorophosphatesA94



Chiral Fluorinated Sulfoximines as New Fluoroalkylating Agents.....A97

Copper(II) Triflate Catalyzed tert-Butylation of Anilines.....A100

Hydrocupration of Terminal Alkynes: A Key Step in New Catalytic Routes for Alkyne Hydrofunctionalization.....A103

COMING SOONA106

CONTACT + + + +

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

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

Synthesis of 1,5-Disubstituted 3-Amino-1*H*-1,2,4-triazoles from 1,3,4-Oxadiazolium Hexafluorophosphates

Selected presentation (ORGN-878) from the 245th ACS National Meeting & Exposition, New Orleans (USA), April 7–11, 2013

■ In recent years, there has been a surprisingly high number of incidents, both in academic and industrial labs, resulting in serious injuries or even death. A certain lack of safety awareness persists in the synthetic organic chemistry community, especially in academia where most reactions are performed on a relatively small scale. However, in industry – especially in process research and development – safety is of paramount importance as reactions are often conducted on a much larger scale, thus, the severity of any incident would be much higher. Haiming Zhang, Brian Wong and their team at Genentech, Inc. (South San Francisco, USA) explained that safety assessment of reactions is very common before scaling up. “Developing safe reactions to mitigate the potential risk should be the responsibility of all chemists,” said Mr. Wong. Recently the group at Genentech became interested in developing a synthetic protocol for 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles. “The 3-amino-1*H*-1,2,4-triazole motif is very useful as it has found a wide array of applications in herbicides, anti-inflammatory agents, and anti-cancer therapies,” explained Mr. Wong.

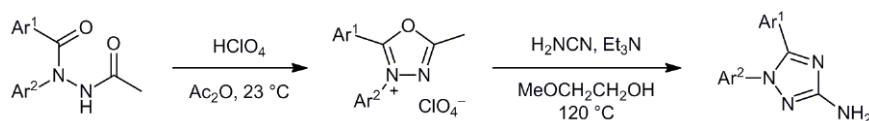
Szilágyi previously reported a synthesis of 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles through the reaction of 1,3,4-oxadiazolium perchlorates with cyanamide in 2-methoxyethanol (methyl cellosolve) at 120 °C (É. Bozó, G. Szilágyi, J. Janáky *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 583). Unfortunately, the use of perchloric acid and perchlorate salts raises serious safety concerns due to their explosive nature and shock sensitivity, making them poorly suited for large-scale synthesis.

Dr. Zhang said: “For our aminotriazole synthesis, safety and scalability are two of our main objectives.” He continued: “Our approach was to replace the hazardous perchloric acid in generating 1,3,4-oxadiazolium salts, thus minimizing the safety concerns of Szilágyi’s original synthesis. We began the salt formation using *N*’-acetyl-4-methyl-*N*-(*p*-tolyl)benzohydrazide as the model substrate.” A screening of acids including HPF₆, HBF₄, TfOH, MsOH, H₂SO₄, HCl and TFA showed that HPF₆ and TfOH are two of the best acids to convert *N*’-acetyl-4-methyl-*N*-(*p*-tolyl)benzohydrazide into the corresponding 1,3,4-oxadiazolium salts (74% for HPF₆ and 81% for TfOH). HPF₆ was eventually selected due to its easier handling compared to TfOH.

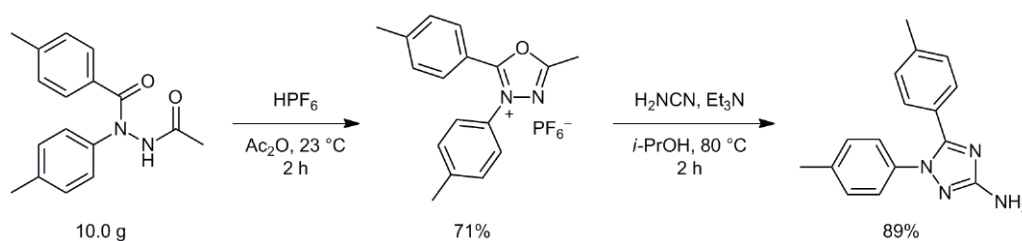
2,3-Bis(*p*-tolyl)-1,3,4-oxadiazolium hexafluorophosphate was readily converted into the corresponding 3-amino-1*H*-1,2,4-triazole in 77% yield (at 1 mmol scale) by reacting with cyanamide in the presence of triethylamine as a base. The toxic solvent 2-methoxyethanol was replaced with a much greener solvent, namely 2-propanol, and the reaction was conducted at a lower temperature, i.e. at 80 °C. “This reaction was proven scalable as we demonstrated both the salt and aminotriazole formation on a 10 g scale,” explained Dr. Zhang.

In addition, a variety of electronically and sterically diverse *N*’-acyl-*N*-acyl-*N*-arylhydrazides undergo the transformation, thus generating various 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles in good yields.

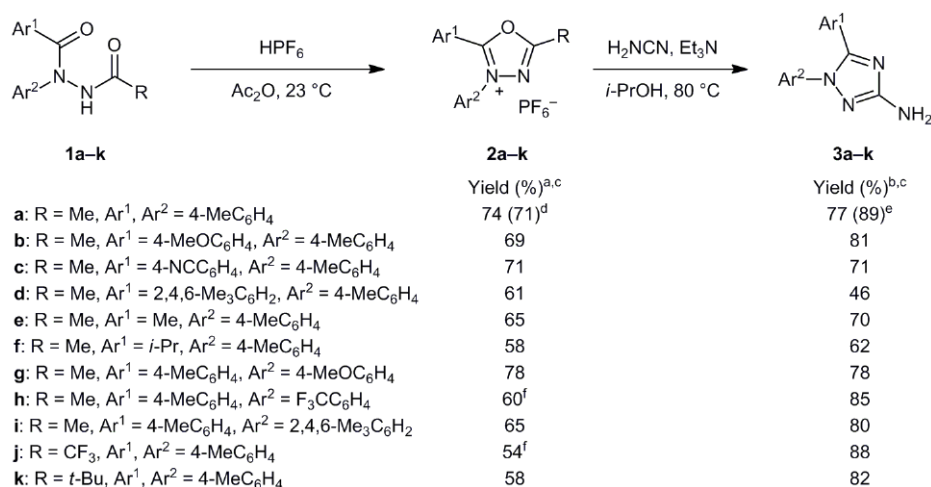
Dr. Zhang emphasized the importance of team work for the successful development of this new methodology. “I conceived the idea, achieved proof-of-concept of the chemistry



Scheme 1 Szilágyi’s synthesis of 3-amino-1*H*-1,2,4-triazoles



Scheme 2 Safe and scalable synthesis of 1,5-bis(p-tolyl)-3-amino-1H-1,2,4-triazole



^a Reaction conditions: **1** (0.50 g), HPF₆ (1.1 equiv), and Ac₂O (2.5 mL), 23 °C. The salt was isolated by adding MTBE (6.0 mL) and filtration.

^b Reaction conditions: **2** (1.0 mmol), cyanamide (3.0 equiv), Et₃N (3.0 equiv), and *i*-PrOH (2.0 mL), 80 °C, 2 h.

^c Isolated yield.

^d The yield in parenthesis was obtained by performing the reaction with **1a** at 10.0 g (35.4 mmol) scale.

^e The yield in parenthesis was obtained by performing the reaction with **2a** at 10.0 g (24.4 mmol) scale. Product **3a** was isolated by workup and crystallization.

^f The reaction was performed at 23 °C for 2 h and then 50 °C for 20 h.

Scheme 3 Improved synthesis of 1,5-disubstituted 3-amino-1H-1,2,4-triazoles

and subsequently assembled the team,” said Dr. Zhang. “Brian Wong performed most of the experiments. Andreas Stumpf, Diane Carrera and Chunang Gu worked on the starting substrate synthesis, mechanistic studies, and compound characterization. It’s a unique format of team work in industry as all of us have other commitments, so none of us can be fully devoted to a synthetic methodology project like this,” he continued. “In many cases, each chemist takes certain specific responsibility and the team thereby is able to finish the project quickly.”

Dr. Zhang concluded: “It’s still too early to call, but we certainly hope that the aminotriazole compounds we prepared will be added to our medicinal chemistry screening deck and

our safe synthesis of aminotriazoles will be applied to the process development of Genentech’s drug candidates.”

Matteo Zanda

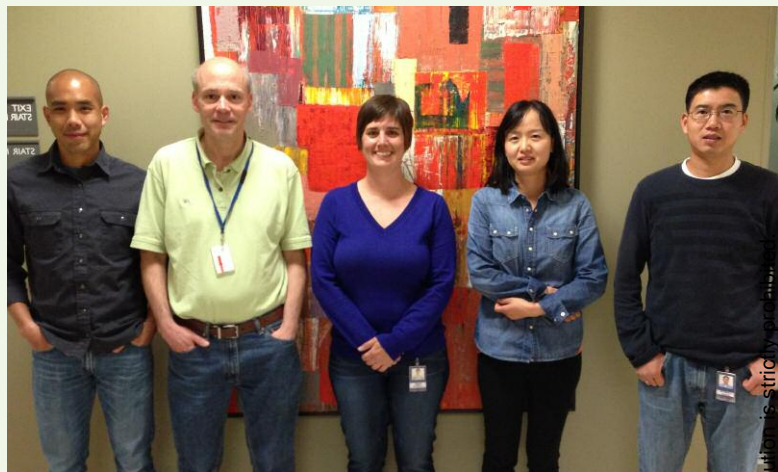
About the authors

Brian Wong received his B.S. in chemistry from the University of Wisconsin-Madison (USA) in 2000. He then spent two years as an associate scientist at Tetrionics Inc. in Madison, WI (USA) before moving into the Process Chemistry group at Array Biopharma in Boulder, CO (USA). In 2007, he joined the Small Molecule Process Chemistry group at Genentech as a research associate.

Andreas Stumpf obtained his Ph.D. degree from the University of Regensburg (Germany) in 1993 under the supervision of Professor Henry Brunner. After postdoctoral research in South Korea and the USA, he worked as a process chemist at Purdue Pharma and Scios (A Johnson & Johnson Company) before joining the Process Chemistry group at Genentech in 2006.

Diane Carrera did her graduate study with Professor David MacMillan at Caltech, Pasadena, CA (USA) after obtaining her B.S. degree from Stanford University (USA). She joined the Small Molecule Process Chemistry group as an associate scientist after receiving her Ph.D. degree in 2009.

Chunang Gu obtained her Ph.D. degree in Toxicology from the University of California, Riverside (USA). Before joining Genentech's Small Molecule Analytical Chemistry group in 2010, she worked at ThermoFisher Scientific for four years as a senior application scientist.



From left: B. Wong, Dr. A. Stumpf, Dr. D. Carrera, Dr. C. Gu, Dr. H. Zhang

Haiming Zhang obtained his Ph.D. degree in 2003 from Iowa State University (USA) under the direction of Professor Richard Larock. He then did two years of postdoctoral research with Professor Brian Stoltz at Caltech, Pasadena, CA (USA). He joined Genentech's Small Molecule Process Chemistry group in 2010 after five years of process research at Lexicon Pharmaceuticals.

Chiral Fluorinated Sulfoximines as New Fluoroalkylating Agents

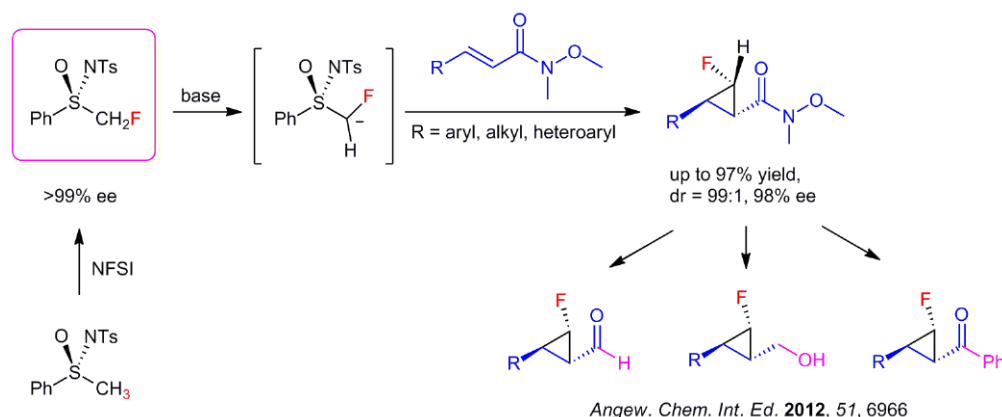
Selected presentation (FLUO-7) from the 245th ACS National Meeting & Exposition, New Orleans (USA), April 7–11, 2013

The selective incorporation of fluorine atoms or fluorinated moieties into organic molecules has become a ‘hot’ research topic in modern organic chemistry. Among various methods available for synthesizing the fluorinated compounds, fluoroalkylation represents one of the most streamlined and perfectly adapted approaches. However, unlike nucleophilic perfluoroalkylation, which can be easily realized with various perfluoroalkylating agents such as TMSCF_3 (Ruppert–Prakash reagent), the direct nucleophilic transfer of di- and mono-fluorinated C-1 moieties is much more difficult due to the lack of general and efficient reagents. To address this issue, recent efforts in Professor Jinbo Hu’s research group at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS, P. R. of China) have been devoted to the development of fluoroalkylating agents containing removable activation groups, as well as their efficient application in selective fluoroalkylations.¹ Professor Hu said: “Fluorine and sulfur have a good marriage, and many fluorination and fluoroalkylation reactions are achieved with sulfur-based reagents (such as DAST and the Umemoto reagent). In previous work, we and others have discovered that fluorinated organosulfur compounds, including tri-, di-, and monofluorinated sulfides, sulfoxides, sulfoniums, and sulfones, can be used as efficient fluoroalkylating agents.”² Sulfoximines, which were discovered incidentally by biochemists during an action of nitrogen trichloride on proteins in the 1940s, have been widely used in organic synthesis because of their physiological and diverse chemical properties.³ Surprisingly, less attention had been paid to the application of α -fluoro sulfoximines in fluoroalkyl transfer reactions until the publication of the account on selective fluoroalkylations with fluorinated sulfones, sulfoxides, and sulfides.² Since 2008, *N,N*-dimethyl α -fluoromethyl sulfoximinium salts (by research groups led by Shibata^{4,5} and Prakash⁶), *N*-tosyl racemic α -fluoro sulfoximines (by Hu’s group^{7–9}), and other α -fluoro sulfoximines (by Magnier’s group¹⁰) have been exploited for fluoroalkylation reactions. Inspired by recent developments in the synthesis of chiral fluorinated molecules, they envisioned several conceptually new chiral fluoroalkylation reagent controlled diastereoselective and enantioselective nucleophilic reactions by taking advantage of the stereogenic center of sulfur in sulfoximines.^{11,12}

“As the chemistry of fluorinated molecules is often distinct from that of their non-fluorinated counterparts, two major challenges to achieve a successful asymmetric fluoroalkylation lie in the modulation of the reactivity of the fluorinated sulfoximines and the control of the stereoselectivity of the reaction,” Professor Hu explained. In their previous investigation, Dr. Wei Zhang, now a research scientist at SIOC, identified that the carbanion of $\text{PhSO}(\text{NTs})\text{CF}_2\text{H}$ is highly unstable and readily undergoes α -elimination of *N*-tosyl (Ts) benzene-sulfonamide anion to afford difluorocarbene ($:\text{CF}_2$).⁷ Indeed, $\text{PhSO}(\text{NTs})\text{CF}_2\text{H}$ had been exploited as an electrophilic difluoromethylation reagent by Dr. Zhang during his graduate studies.⁷ Dr. Zhang also found that, while the nucleophilic reactions of monofluorinated sulfoximines $\text{PhSO}(\text{NTs})\text{CHFR}$ with nitrones could afford the monofluoroalkenes with high *Z/E*-selectivity,⁸ their reactions with ketones gave the monofluoroepoxides with nearly 50:50 diastereoselectivity.⁹

Xiao Shen, now a fifth-year Ph.D. candidate at SIOC, conducted the first high-yielding, highly diastereoselective, as well as highly enantioselective monofluorocyclopropanation through a Michael addition-induced ring closure (MIRC) reaction between (*R*)- $\text{PhSO}(\text{NTs})\text{CH}_2\text{F}$, which is probably the first enantiopure monofluoromethylenating reagent, and a variety of structurally diverse α,β -unsaturated Weinreb amides (see Scheme 1).¹¹ This reaction is also suitable for the construction of fluorinated quaternary stereogenic carbon centers using the enantiopure sulfoximine bearing a tertiary fluorinated carbon center. Professor Hu said: “This finding is based on Dr. Wei Zhang’s initial attempt on the diastereoselective MIRC reaction using the similar racemic monofluorinated sulfoximines and chalcones, in which either low yields or poor diastereoselectivities of the desired products were obtained.” Owing to the important application of monofluorinated cyclopropanes in life sciences, Professor André B. Charette and co-workers from the Université de Montréal (Canada) described Professor Hu and co-workers’ reaction as a major contribution in a very recent publication on enantioselective Simmons–Smith monofluorocyclopropanation.¹³

Xiao Shen also discovered the first stereoselective difluoromethylation of ketones using the newly developed *N*-tert-butyltrimethylsilyl (TBS)-substituted difluoromethyl sulfoximine (*R*)- $\text{PhSO}(\text{NTBS})\text{CF}_2\text{H}$ via a step-by-step reaction (see



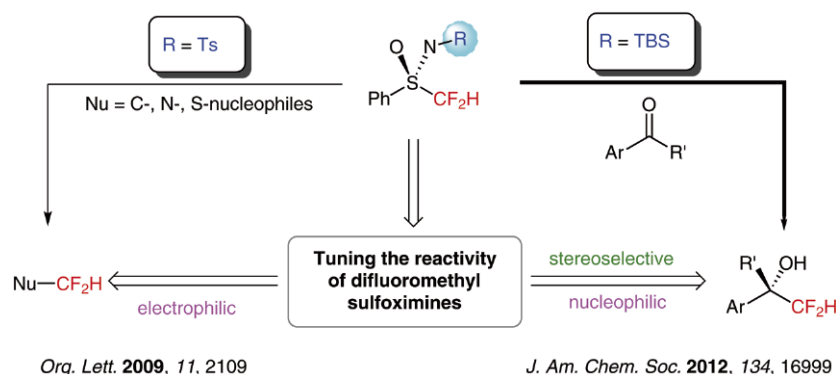
Scheme 1

Scheme 2).¹² Professor Hu explained: “In comparison with the aforementioned $\text{PhSO}(\text{NTs})\text{CF}_2\text{H}$, which failed to react with carbonyl compounds, the changing of the N-substituent from electron-withdrawing Ts to electron-donating TBS switches the reactivity of the difluoromethyl sulfoximine from electrophilic to nucleophilic.” The major diastereomer of the adduct can be isolated and further converted into the corresponding difluoromethyl alcohol of high enantiopurity after reductive removal of the sulfoximine moiety. Although this protocol can also be applied to aldehydes, its primary virtue is the facile preparation of α -difluoromethylated tertiary alcohols, which are otherwise difficult to prepare.

The group is now working on the asymmetric fluoroalkylation of several other electrophiles to expand the synthetic application of the concept. Professor Hu predicted: “Further structure modification of the fluorinated sulfoximines by

either altering the number of fluorine atoms on the carbon atom or changing the substituents on the sulfur atom will offer more opportunities for the discovery of new and interesting chiral fluoroalkylating agents and reactions.”

Matteo Zanda

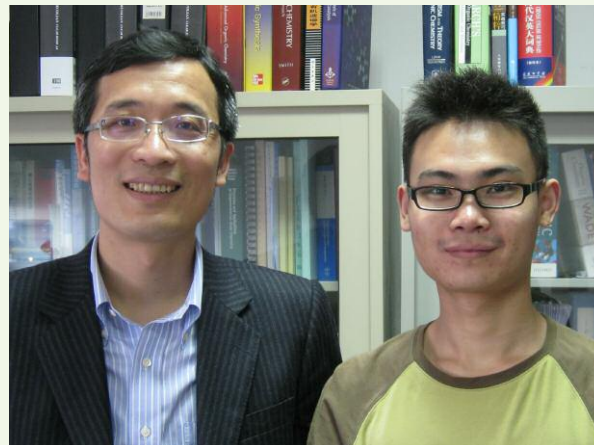


Scheme 2

REFERENCES

- (1) C. Ni, J. Hu *Synlett* **2011**, 770.
- (2) G. K. S. Prakash, J. Hu *Acc. Chem. Res.* **2007**, *40*, 921.
- (3) M. Reggelin, C. Zur *Synthesis* **2000**, 1.
- (4) S. Noritake, N. Shibata, S. Nakamura, T. Toru, M. Shiro *Eur. J. Org. Chem.* **2008**, 3465.
- (5) Y. Nomura, E. Tokunaga, N. Shibata *Angew. Chem. Int. Ed.* **2011**, *50*, 1885.
- (6) G. K. S. Prakash, Z. Zhang, F. Wang, C. Ni, G. A. Olah *J. Fluorine Chem.* **2011**, *132*, 792.
- (7) W. Zhang, F. Wang, J. Hu *Org. Lett.* **2009**, *11*, 2109.
- (8) W. Zhang, W. Huang, J. Hu *Angew. Chem. Int. Ed.* **2009**, *48*, 9858.
- (9) W. Zhang, J. Hu *Adv. Synth. Catal.* **2010**, *352*, 2799.
- (10) For a review, see: Y. Macé, E. Magnier *Eur. J. Org. Chem.* **2012**, 2479.
- (11) X. Shen, W. Zhang, L. Zhang, T. Luo, X. Wan, Y. Gu, J. Hu *Angew. Chem. Int. Ed.* **2012**, *51*, 6966.
- (12) X. Shen, W. Zhang, C. Ni, Y. Gu, J. Hu *J. Am. Chem. Soc.* **2012**, *134*, 16999.
- (13) L.-P. B. Beaulieu, J. F. Schneider, A. B. Charette *J. Am. Chem. Soc.* **2013**, *135*, 7819.

About the authors



From left: Prof. J. Hu, X. Shen

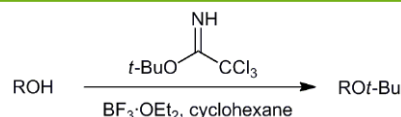
Jinbo Hu was born in Zhejiang (P. R. of China) in 1973. He obtained his B.S. (1994) and M.S. (1997) degrees at Hangzhou University and Chinese Academy of Sciences (P. R. of China), respectively. He did his Ph.D. work during 1997–2002 at the University of Southern California (USC), Los Angeles (USA) with Professors G. K. S. Prakash and G. A. Olah. After his postdoctoral work at USC with Professors Prakash and Olah, he accepted a Research Professorship at Shanghai Institute of Organic Chemistry (SIOC), CAS in early 2005. He is the recipient of the Royal Chemical Society Fluorine Prize (2009), Chen Jia-Gen Science Prize for Young Scholars (2012), and the Chinese Academy of Sciences Young Scientist Award (2012). His research interests are in selective fluorination methodologies and fluorinated materials.

Xiao Shen was born in Shandong (P. R. of China) in 1987. After he obtained his B.S. degree from Shandong Normal University (P. R. of China) in 2008, he entered SIOC as a graduate student. Currently, he is studying for his Ph.D. degree under the guidance of Professor J. Hu. His thesis work focuses on the investigation of new fluorinated sulfoximine and sulfone reagents and their reactions by tackling the 'negative fluorine effect'.

Copper(II) Triflate Catalyzed *tert*-Butylation of Anilines

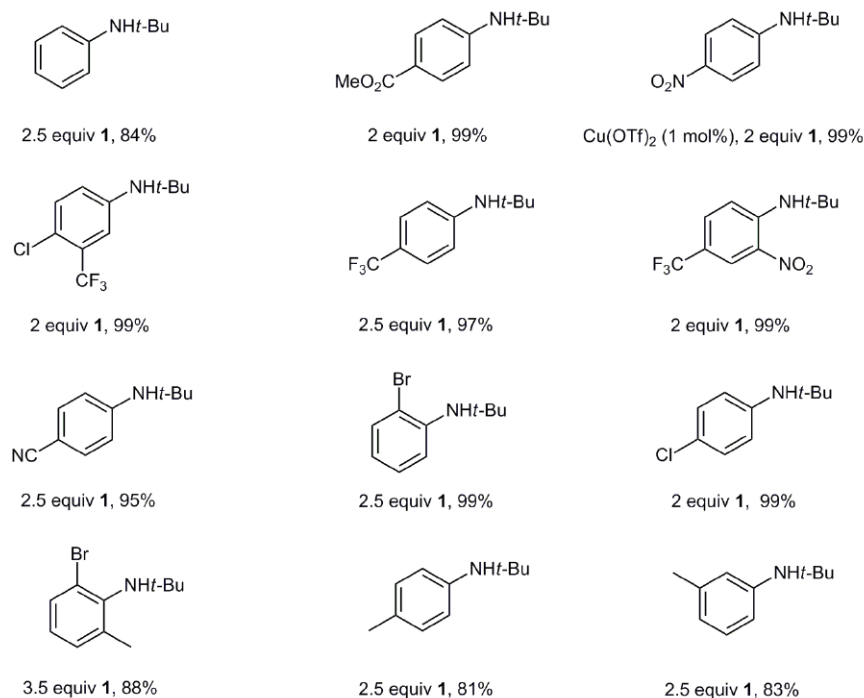
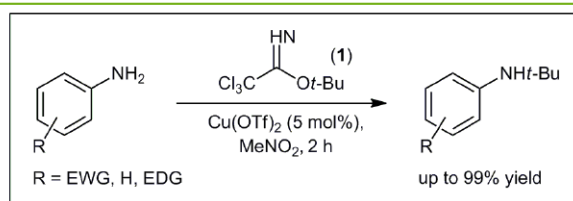
Selected presentation (ORGN-803) from the 245th ACS National Meeting & Exposition, New Orleans (USA), April 7–11, 2013

■ *tert*-Butyl anilines are useful compounds that find numerous applications as pharmaceuticals, agrochemicals, dyes, additives and plastics components. However, their synthesis is not simple, particularly because of the lower reactivity of anilines relative to more nucleophilic aliphatic amines and the bulky nature of the *tert*-butyl group. The research group of Dr. John W. Cran, a Visiting Professor at Florida State University (Tallahassee, USA), has recently been investigating how to make hindered aromatic amines, as part of a larger ongoing project. Dr. Cran said: “We were motivated to carry out this work because the *tert*-butylation of anilines is a reaction that has traditionally been difficult to accomplish, requiring the use of harsh reaction conditions and long reaction times, and



Scheme 1 *tert*-Butylation of alcohols and carboxylic acids according to Jackson et al. (*Tetrahedron Lett.* **1988**, 29, 2483)

often delivering only poor to moderate yields.”¹ To date, an efficient and mild general method has not been developed. Moreover, anilines constitute a fundamental building block in organic chemistry and there is a continuing need for general procedures for their functionalization, including alkylation.

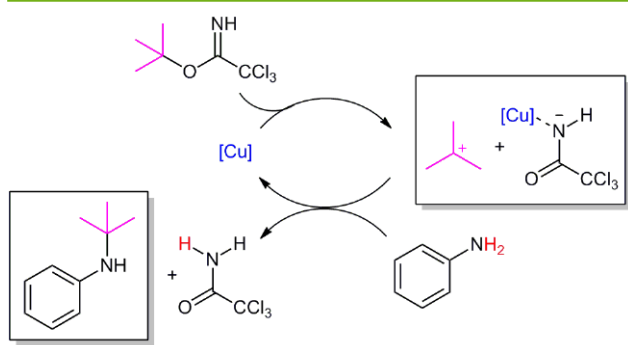


Scheme 2 The novel *tert*-butylation of anilines

It had previously been reported that *tert*-butyl trichloroacetimidate was an effective *tert*-butylating agent for alcohols and carboxylic acids in the presence of $\text{BF}_3 \cdot \text{OEt}_2$.² While alkyl amines are much more basic and therefore prone to quenching a reactive Lewis acid catalyst, anilines are considerably less basic as a result of conjugation of the nitrogen lone pair with the adjacent aromatic system. Dr. Cran said: “We conjectured that the lowered basicity of anilines would reduce their affinity for coordination to the Lewis acid catalyst sufficiently to allow competitive coordination of *tert*-butyl trichloroacetimidate, which should then undergo decomposition to release a *tert*-butyl cation to be captured by the aniline.”

After screening a variety of Lewis acids and conditions they found that copper-based catalysts had the desired reactivity, being very effective for a wide range of substrates.

At this point, the Florida-based scientists hypothesized that the copper species initially coordinated to *tert*-butyl trichloroacetimidate, catalyzing its decomposition and releasing the *tert*-butyl cation which could then be captured by the aniline, which may or may not be already coordinated to the catalyst. They found that at least two equivalents of the *tert*-butylating agent were usually needed, presumably due to the *tert*-butyl cation undergoing competitive proton elimination to give isobutene.



Scheme 3 Mechanistic rationale

Dr. Cran said: “Our current studies are focusing on further expanding the substrate scope with regard to anilines, and further looking at other functional groups which might be efficiently alkylated. To help do this we are studying the mechanism both experimentally and computationally.” Dr. Dinesh Vidhani, who is a co-author of this work, added: “We have previously had success developing a new methodology by adopting a multidisciplinary approach towards metal-catalyzed reactions. A greater understanding of reaction mechanisms through mechanistic and computational studies can act

as a guide for helping us to extend and develop new methods.” Dr. Cran concluded: “And in this current project we are applying this principle to help guide its further development, and we hope the revealed mechanistic details will enable us to further expand the reaction methodology and open up new avenues of research.” ■

Matteo Zanda

REFERENCES

- (1) (a) J. R. Gage, J. M. Wagner *J. Org. Chem.* **1995**, *60*, 2613. (b) M. Ishiguro, T. Kitahara, I. Tomino JP06271513, **1994**. (c) W. J. Hickinbottom *J. Chem. Soc.* **1933**, 946. (d) H. Yamamoto, K. Maruoka *J. Org. Chem.* **1980**, *45*, 2739. (e) J. C. Anderson, J. W. Cran, N. P. King *Tetrahedron Lett.* **2002**, *43*, 3849.
- (2) A. Armstrong, I. Brackenridge, R. F. W. Jackson, J. M. Kirk *Tetrahedron Lett.* **1988**, *29*, 2483.

About the authors



Dr. J. W. Cran

John Cran studied chemistry for his undergraduate degree at the University of Sheffield (UK) before completing a Ph.D. in organic and organometallic chemistry at the University of Nottingham (UK) under the supervision of Professor James C. Anderson. John was subsequently awarded a Postdoctoral Scholarship for three years working with Professor Marie E. Krafft, before moving on to become an Assistant Scientist and then Associate Scientist at Florida State University (Tallahassee, USA) in the same group. His research interests are mainly focused on the area of new methods' development, particularly employing transition-metal catalysts and mechanistic studies.

>>



Prof. D. Maiti

Dinesh Vidhani received his Ph.D. degree in synthetic organic chemistry from the Florida State University (USA) in 2010, where he carried out research on gold(I)-catalyzed cascade cyclizations, gold(I)-catalyzed [3,3]-rearrangements and tin-mediated selective reductions of aromatic enones under the supervision of Professor Marie E. Krafft. During his graduate years, he was awarded an MDS

(Molecular Design and Synthesis) fellowship with Professor Marie E. Krafft for four years. He continued as a Postdoctoral Research Associate for Professor Krafft and diversified his expertise into physical-organic and computational chemistry. Presently, he is devoted to multidisciplinary research on Rh(I)-catalyzed stereoselective transformations which encompasses developing a method and studying and rationalizing the mechanism using computational techniques.

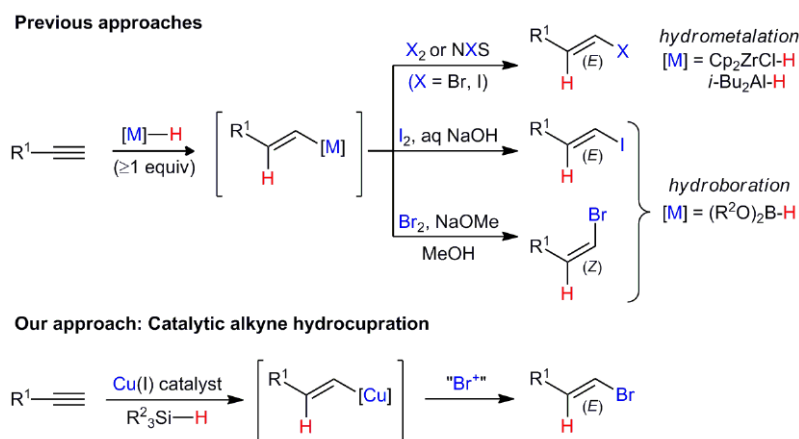
Hydrocupration of Terminal Alkynes: A Key Step in New Catalytic Routes for Alkyne Hydrofunctionalization

Selected presentation (ORGN-443) from the 245th ACS National Meeting & Exposition, New Orleans (USA), April 7–11, 2013

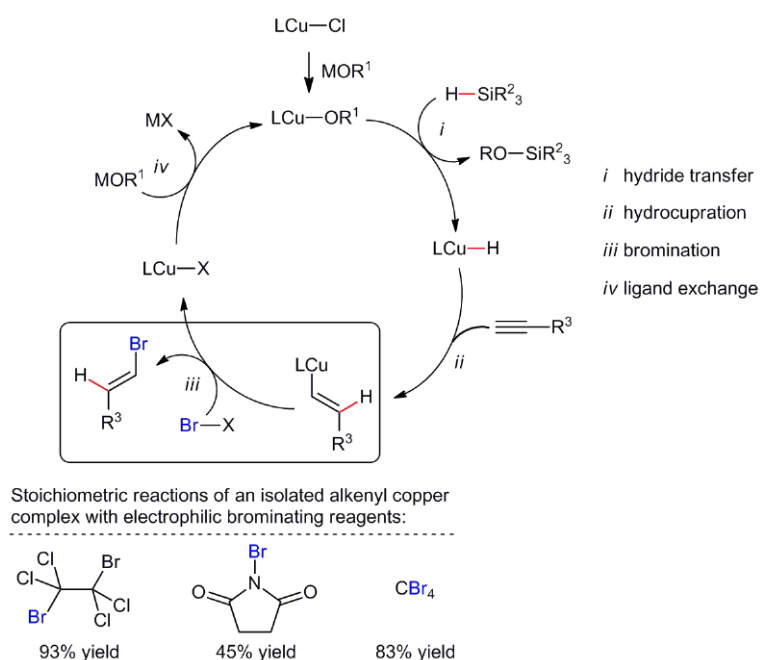
■ Haloalkenes are widely used in many types of synthetic transformations, including transition-metal-catalyzed cross-coupling reactions. Despite the ubiquity of haloalkenes in organic synthesis, most procedures for their preparation still rely on stoichiometric hydrometalation of alkynes. Typically, exposure of an alkyne to a super-stoichiometric amount of metal hydride, such as bis(cyclopentadienyl)zirconium(IV) chloride hydride (also known as Schwartz's reagent) or di(isobutyl)aluminum hydride (abbreviated as DIBAL-H), generates an alkenyl metal intermediate, which then undergoes reaction in the presence of an electrophilic halide source to produce an (*E*)-haloalkene in moderate to excellent yields. In a related transformation, either (*E*)-iodo- or (*Z*)-bromoalkenes can be obtained by alkyne hydroboration and further transformation of the resulting alkenyl borane intermediate. While alkyne hydrometalation and hydroboration are the standard protocols used for preparing haloalkenes, both methods possess limitations. For example, the chemoselectivity of alkyne hydrometalation using DIBAL-H, a strong reducing reagent, is limited. More chemoselective hydrometalating reagents, such as Schwartz's reagent or organoboranes, are available; however, these must be used in stoichiometric amounts and can be expensive on a large scale.

Recently, Professor Gojko Lalic and graduate students Richard Rucker and Mycah R. Uehling at the University of Washington, Seattle (USA), together with others,¹⁻⁴ developed an approach to catalytic alkyne hydrofunctionalization through alkyne hydrocupration and subsequent electrophilic functionalization of the alkenyl copper intermediate. Richard Rucker, who gave an excellent oral presentation at the recent ACS Meeting in New Orleans (USA), said: "In the course of these studies, we observed that the alkenyl copper intermediate obtained from alkyne hydrocupration has similar reactivity to the alkenyl metal intermediates obtained from stoichiometric alkyne hydrometalation. A key advantage afforded by alkyne hydrocupration, however, is that the reactive metal intermediate can be prepared catalytically using inexpensive silanes as hydride sources. In light of this observation, we sought to develop a catalytic method for hydrobromination of alkynes." Such an approach is anticipated to offer several benefits, including enhanced chemoselectivity, greater efficiency, and lower cost.

Richard Rucker continued: "In our initial experiments, we established the feasibility of the elementary steps of our proposed catalytic cycle, including the electrophilic bromination of an alkenyl copper intermediate by several easily handled



Scheme 1 (top) Stoichiometric alkyne hydrometalation or hydroboration and subsequent electrophilic halogenation; (bottom) copper-catalyzed hydrocupration and subsequent electrophilic bromination



Scheme 2 Proposed catalytic cycle for catalytic alkyne hydrobromination; (inset) proof of feasibility of step iii demonstrated through stoichiometric reactions of an isolated alkenyl copper complex with an electrophilic brominating reagent



Scheme 3 The approach is used to demonstrate the catalytic hydrobromination of 5-phenylpent-1-yne

and crystalline brominating reagents. However, our initial attempts at catalytic reactions were unsuccessful.” Fortunately, the Seattle-based researchers observed that a slow addition of the brominating reagent resulted in the catalytic synthesis of (*E*)-bromoalkenes from terminal alkynes. After further optimization of reaction parameters, they arrived at conditions that could effect this transformation at room temperature in less than 30 minutes.

Their preliminary results using a variety of functionalized terminal alkynes suggest that catalytic hydrobromination is more chemoselective than methods using stoichiometric hydrometalation. Although the scope remains to be fully explored, the authors believe that terminal alkynes bearing aryl halide, aryl nitrile, aryl ether, TIPS ether, and even aryl ester or ketone functionalities are all suitable substrates for the

reaction. “With all substrates, only the (*E*)-alkenyl bromides were produced with no evidence of bromoalkyne formation, which is commonly observed when existing methods are used,” confirmed Mycah Uehling.

“In summary, we have developed a procedure for catalytic alkyne hydrobromination through hydrocupration and subsequent electrophilic bromination. We anticipate that this method will be a useful alternative to alkyne hydrometalation and hydroboration reactions for the synthesis of (*E*)-bromoalkenes from terminal alkynes,” concluded Richard Rucker. ■

Matteo Zanda

Matteo Zanda

REFERENCES

- (1) T. Fujihara, T. Xu, K. Semba, J. Terao, Y. Tsuji *Angew. Chem. Int. Ed.* **2011**, *50*, 523.
- (2) K. Semba, T. Fujihara, T. Xu, J. Terao, Y. Tsuji *Adv. Synth. Catal.* **2012**, *354*, 1542.
- (3) A. M. Whittaker, G. Lalic *Org. Lett.* **2013**, *15*, 1112.
- (4) K. Semba, T. Fujihara, J. Terao, Y. Tsuji *Chem. Eur. J.* **2012**, *18*, 4179.

About the authors



From left: graduate students R. Rucker, M. R. Uehling

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2013/09

is available from August 19, 2013

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Synthesis of Peptides Containing C-Terminal Methyl Esters Using Trityl Side-Chain Anchoring: Application to the Synthesis of α -Factor and α -Factor Analogues*(Focus on an article from the current literature)*

■ Enantioselective Ketone Hydroacylation Using Noyori's Transfer Hydrogenation Catalyst

(Focus on an article from the current literature)■ Ligand-Controlled β -Selective C(sp³)-H Arylation of *N*-Boc-Piperidines*(Focus on an article from the current literature)*

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Allylic Oxidations of Olefins to Enones

(by V. Weidmann, W. Maison)

SYNLETT

Account on: Enantioselective Cycloaddition Reactions of Ketenes Catalyzed by N-Heterocyclic Carbenes

(by X.-Y. Chen, S. Ye)

SYNFACTS

Synfact of the Month in category "Synthesis of Materials and Unnatural Products": *ortho*-C-H Activation Yields*Dibenzo[a,e]pentalenes*

CONTACT + + + +

Matteo Zanda,
NRP Chair in Medical Technologies
Institute of Medical Sciences
University of Aberdeen
Foresterhill, Aberdeen, AB25 2ZD, UK
and

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, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and

C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage
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
- Assistant Scientific Editor: Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768
- Senior Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Editor: Helene Deufel, helene.deufel@thieme.de, phone: +49 711 8931 929
- Production Editor: Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
- Marketing Manager: Julia Stötzner, julia.stoetznern@thieme.de, phone: +49 711 8931 771
- Postal Address: SYNTHESIS/SYNLETT/SYNEFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
- Homepage: www.thieme-chemistry.com

Publication Information

SYNFORM will be published 12 times in 2013 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNEFACTS.

Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to SYNTHESIS, SYNLETT and SYNEFACTS

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

To order: customerservice@thieme.com or use the Web site facilities at www.thieme-chemistry.com, phone: +1 212 760 0888

Order toll-free within the USA: +1 800 782 3488

Fax: +1 212 947 1112

Airfreight and mailing in the USA by Publications Expeditors Inc., 200 Meacham Ave., Elmont NY 11003. Periodicals postage paid at Jamaica NY 11431.

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.

To order: customerservice@thieme.de or use the Web site facilities at www.thieme-chemistry.com.

Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access

The online versions of SYNFORM as well SYNTHESIS, SYNLETT and SYNEFACTS are available through Thieme-connect (www.thieme-connect.com/ejournals) where you may also register for free trial accounts. For information on multi-site licenses and pricing for corporate customers as well as backfiles please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695

Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407

India: eproducts@thieme.in, phone +91 120 45 56 600

Japan: brhosoya@poplar.ocn.ne.jp, phone +81 3 3358 0692

Manuscript Submission to SYNTHESIS and SYNLETT

Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com. Use of the Word template helps to speed up the refereeing and production process.

Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.