SYNSTORIES

- Cleavage of Carbon–Carbon Bonds through the Mild Release of Trifluoroacetate: Generation of α,α-Difluoroenolates for Aldol Reactions

- Catalytic Asymmetric Chloroamination Reaction of α,β-Unsaturated γ-Keto Esters and Chalcones

- Copper-Catalyzed Trifluoromethylation of Aryl- and Vinylboronic Acids with an Electrophilic Trifluoromethylating Reagent

CONTACT

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

This issue of SYNFORM features two SYNSTORIES on organofluorine chemistry, which remains a very important area of research. Fluorine-containing molecules often have very special and peculiar properties, sometimes superior to those of the parent unfluorinated compounds. Fluorinated chemicals find a number of extraordinarily important applications in drug discovery, materials science, and biomedical imaging, just to mention a few. However, only a handful of fluorinated compounds are natural, all of them containing a single fluorine atom and most of them being very simple molecules like fluoroacetic acid and its superior homologues. One enzyme is known to catalyze the formation of C–F fluorine bonds, but this fluorinase enzyme appears to be very specialized in terms of accepted substrates. This means that fluorine-containing compounds are almost exclusively man-made and obtained through chemical synthesis. Unfortunately, despite a remarkable progress in the field, many fluorinated molecules remain difficult to synthesize. Therefore, the development of novel methods to introduce fluorine atoms and fluorinated functions, like the trifluoromethyl group, in a user-friendly, efficient and economic manner remains a true priority for organic chemists. For this reason the work of Professors David A. Colby (USA) and Qilong Shen (P. R. of China) is extremely valuable, and likely to find important applications in the future. Another halogen, chlorine, is the protagonist of the third SYNSTORY, which reports on the elegant and highly efficient chloroamination reaction developed by the group of Professor Xiaoming Feng (P. R. of China).

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM
Catalytic asymmetric difunctionalization of olefins, such as dihydroxylation, aminohydroxylation, and diamination, has been a major area of research, since these reactions provide versatile building blocks which are difunctionalized in vicinal positions. In comparison with the strong progress achieved with dihydroxylation and aminohydroxylation reactions, the catalytic asymmetric electrophilic haloamination of olefins remained somewhat elusive until recent work by the group of Professor Xiaoming Feng from Sichuan University (Chengdu, P. R. of China), who accomplished the first catalytic asymmetric bromoamination reaction of chalcones with sulfonamide and N-bromosuccinimide (NBS) (Angew. Chem. Int. Ed. 2010, 49, 6160). Chiral scandium complexes of C2-symmetric N,N′-dioxide ligands, which were designed and developed in Professor Feng’s group, exhibited excellent efficiency and selectivity in the transformation. “Traditionally, difficult issues for this type of reaction, such as regioselectivity, racemization of the onium ion intermediate, and the enantioselectivity of the bromoamination reaction of chalcones, could be effectively addressed by our approach,” said Professor Feng. “Based on the exciting outcomes in the asymmetric bromoamination reaction, we envisioned that the replacement of the NBS electrophile with NCS (N-chlorosuccinimide) might efficiently extend the scope of our methodology to chloroamination products,” he continued. However, to their disappointment, only trace amount of the chloroaminated product was obtained using NCS/TsNH2 as the chlorine and nitrogen sources, even with a 400-fold increase in catalyst loading compared to that of the bromoamination reaction. “The catalytic asymmetric chloroamination reaction of C=C bonds seemed to be another tough challenge,” said Professor Feng. Recently, however, Professor Feng and his co-workers harnessed TsNCl/TsNH2 as a new effective system of reagents to perform the first catalytic asymmetric chloroamination reaction of α,β-unsaturated γ-keto esters and chalcones.

“We postulated that the main issues contributing to the low yield of the chloroamination reaction of olefins were the low reactivity of NCS to form the key bridged chloronium ion intermediate, as well as its instability,” said Professor Feng. “The method that we report in the JACS communication might provide some reaction engineering with a reactive chlorine source, and expand the scope of the method to other haloamination reactions.”

Yunfei Cai, a second-year graduate student in Professor Feng’s group, systematically screened a set of reaction conditions for the asymmetric chloroamination reaction. Careful investigation of the Cl− sources and tracing the origin of the proton in the final product allowed the identification of the conditions for accomplishing the highly efficient chloroamination reaction. Once again, the N,N′-dioxide–scandium(III) complex exhibited excellent stereorecognition capability in this reaction. “We hope to develop chiral N,N′-dioxide molecules into a type of privileged chiral ligand by achieving further insight into the mechanistic details and expanding their adaptability in new catalytic asymmetric reactions,” said Professor Feng confidently.
Concerning the future research prospects of difunctionalization of olefins, “the extension of the olefin substrates, in particular the use of simple unfunctionalized olefins, will be a big challenge,” he concluded.

Matteo Zanda

About the authors

Yunfei Cai was born in Chongqing (P. R. of China) in 1986. He received his B.S. degree from Sichuan University in 2009. He is currently a PhD student in the College of Chemistry, Sichuan University, under the supervision of Professor Xiaoming Feng. His research interests focus on transition-metal-catalyzed stereoselective synthesis.

Xiaoming Feng was born in 1964. He received his B.S. degree in 1985 and M.S. degree in 1988 from Lanzhou University (P. R. of China). Then he worked at Southwest Normal University (P. R. of China, 1988–1993) and became an Associate Professor in 1991. In 1996, he received his Ph.D. from the Chinese Academy of Sciences under the supervision of Professors Zhitang Huang and Yaozhong Jiang. He went to the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China, 1996–2000), and was appointed as a Professor in 1997. He did postdoctoral research at Colorado State University (USA, 1998–1999) with Professor Yian Shi. In 2000, he moved to Sichuan University as a Professor, focusing on the design of chiral catalysts, the development of new synthetic methods and the synthesis of bioactive compounds.
Incorporation of the trifluoromethyl group into drug-like molecules has become a powerful and widely employed tactic in the process of drug design, owing to the dramatic improvements of the compound’s binding selectivity, lipophilicity and metabolic stability that can be brought about by the CF₃ moiety. Consequently, the development of methods for the introduction of a trifluoromethyl group into an aromatic compound is of significant current interest. Recently, Professor Qilong Shen and graduate student Tianfei Liu from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) reported a new method for achieving this transformation based on the use of Togni’s reagent (Chem. Eur. J. 2006, 12, 2579). “Several trifluoromethylation reactions have been reported recently in the literature,” said Professor Shen. “For example, Professor Buchwald’s group at MIT developed the palladium-catalyzed trifluoromethylation of aryl chlorides using a sterically hindered phosphine as ligand (Science 2010, 328, 1679). Professor Yu’s group at Scripps reported on the palladium-catalyzed trifluoromethylation through C–H activation (J. Am. Chem. Soc. 2010, 132, 3648), Professor Amii at Gunma University of Japan on the copper-catalyzed trifluoromethylation of aryl iodides (Chem. Commun. 2009, 1909), and Professor Sanford at University of Michigan on the stoichiometric Pd(IV)-mediated trifluoromethylation of aromatic compounds (J. Am. Chem. Soc. 2010, 132, 2878),” he continued. “However, these methods either require the use of harsh reaction conditions or suffer from a limited substrate scope.” Professor Shen explained that his group is interested in developing synthetic methods with mild reaction conditions, yet with broad substrate scopes. “Inspired by the Chan–Lam coupling, which allows aryl carbon–heteroatom bond formation via an oxidative coupling of aryloboronic acids, stannanes or siloxanes under mild conditions (Tetrahedron Lett. 1998, 39, 2933; Tetrahedron Lett. 1998, 39, 2937; Tetrahedron Lett. 1998, 39, 2941), as well as by recent work by Professor Qing at Shanghai Institute of
Organic Chemistry and Professor Buchwald at MIT, who independently reported that arylboronic acids were easily converted into trifluoromethyl-substituted arenes under oxidative reaction conditions (Org. Lett. 2010, 12, 5060; J. Org. Chem. 2011, 76, 1174),” acknowledged Professor Shen, “we thought that developing a general method for the coupling of arylboronic acids with electrophilic ‘CF,’ might be possible.”

“I am lucky to have a brilliant student, Tianfei Liu, who has a magic hand,” said Professor Shen. “He was able to identify the reaction conditions within one month.” According to Professor Shen, it was revealed that a combination of CuI and phenanthroline is essential as active catalyst. “Using K₃CO₃ as the base is very important since reactions with other bases such as Na₂CO₃, Cs₂CO₃, K₃PO₄, CsOH·H₂O or KOH led to much lower yields or no detectable product,” said Professor Shen. “The reaction was not sensitive to water but very sensitive to oxygen. The reaction vessel was freeze-pump-thaw three times to get rid of trace amounts of oxygen. Otherwise, the yields would be much lower.” Initially, the researchers had some problems purifying the products even with preparative HPLC. “The reaction was then carefully examined,” said Professor Shen. “It was found that ArI and a biaryl compound were formed as side products in less than 5% yield. Later on, Tianfei discovered that a Kugelrohr distillation at reduced pressure is sufficient for isolating the pure trifluoromethyl arenes.”

“The cost of Togni’s reagent ($500/g from Aldrich) is the weak point of this methodology. We were able to synthesize the compound on a ten-gram scale at much lower cost,” said Professor Shen. “The future development of methods for the preparation of trifluoromethyl-substituted arenes with broad substrate scope, lower catalyst loading, milder reaction conditions, and using less expensive and more environmentally friendly trifluoromethylating agents is highly desirable,” he concluded.

Matteo Zanda
Organofluorine chemistry is becoming increasingly important due to the numerous exceptional properties of fluorine-containing molecules which find use in a number of fields, such as drug discovery, materials and nanoscience, energy and biomedical imaging. Although a great deal of progress has been achieved in the past 30 years, the development of novel selective and handy methodologies to incorporate fluorine and fluorinated functions into organic substrates remains an extremely important topic in organic synthesis. Recently, the group of Professor David A. Colby from Purdue University (West Lafayette, Indiana, USA) reported an extremely interesting new method to generate α,α-difluoroenoates for aldol reactions, which holds promise to become a very popular reaction in organofluorine chemistry.

“In my lab, we have been studying how to directly modify the structures of complex natural products, and an underlying objective is to remodel compounds into structural analogues by breaking carbon–carbon bonds selectively and then reassembling the core,” said Professor Colby. “Even though there are very few tools in a chemist’s toolbox to cleave bonds, an additional benefit emerges during the breaking of a bond: a reactive intermediate is formed. One of the primary methods in synthetic chemistry (and also biosynthesis) to break carbon–carbon bonds is decarboxylation,” he explained. “By thinking along these lines, we found an important article by Prager and Ogden (J. Org. Chem. 1968, 33, 2100) as we were exploring how to install a difluoromethylene group onto a key natural product.” According to Professor Colby, the studies in this paper demonstrate a unique carbon–carbon bond scission on hexafluoroacetone hydrate using basic conditions that liberate trifluoroacetate. “Intrigued by these experiments, which are largely lost in the literature, we aimed to modify the starting material, yet allow the bond fragmentation to occur. Although we envisioned the release of trifluoroacetate to be somewhat analogous to a decarboxylation, a manifold to new chemistry would be possible,” he said.

“We hypothesized that if one fluorine atom on hexafluoroacetone hydrate was exchanged with an alternative group that could stabilize an anion, a new reactive intermediate would be formed,” explained Professor Colby. “In this case, we replaced a fluorine atom with a carbonyl group and α,α-difluoroenoates are formed after the bond-breaking event. Other protocols to prepare difluoroenoates are very limited in scope and require harsh reaction conditions. Also, most strategies to add a difluoromethylene group to a molecule are confined to using a few commercially available building blocks.”

Cleavage of Carbon–Carbon Bonds through the Mild Release of Trifluoroacetate: Generation of α,α-Difluoroenoates for Aldol Reactions


Fragmentation of hexafluoroacetone hydrate

![Fragmentation of hexafluoroacetone hydrate](image)

Release of trifluoroacetate to generate α,α-difluoroenoates

![Release of trifluoroacetate to generate α,α-difluoroenoates](image)
After efficiently synthesizing the requisite highly α-fluorinated gem-diols in two steps from methyl ketones, Professor Colby said he and his co-workers Changho Han and Eun Hoo Kim were shocked to observe how quickly and efficiently the carbon–carbon bond cleavage occurred under mild basic conditions. “Specifically, by mixing the fluorinated starting material, an aldehyde, and LiBr in THF and following the addition of the Et3N, the resultant aldol reaction occurs almost instantaneously at room temperature,” said Professor Colby. “The process is so fast, that sometimes we had to cool the reaction mixture to –78 °C to control it. Even though many chemists are familiar with using LDA to form enolates at such low temperatures, using LiBr and Et3N to form enolates is quite unusual, yet considerably easier and safer,” he continued. Professor Colby explained that the aldol process with these difluoroenolates has a very broad scope and is compatible with many types of alkyl and aryl aldehydes. Also, sensitive functional groups, such as α-stereocenters and β-substituents, are very well tolerated. Another key benefit is that trifluoroacetate is released from the reaction and can be readily traced by 19F NMR spectroscopy.

“Overall, we have found that the release for trifluoroacetate is a powerful methodology to generate reactive intermediates and the scope of this reaction extends to intermediates that do not contain fluorine,” said Professor Colby. “We will soon report how this protocol can be easily applied to other types of reactive intermediates other than enolates. All in all, the release of trifluoroacetate has not been widely explored, and on a larger scale, only a minority of chemists are actively studying how to break bonds. We believe that this area is extremely ripe for the picking, and in the future, we will direct our enhanced knowledge of breaking bonds to the selective modification of complex structures and also to the generation of new types of reactive intermediates,” he concluded.
COMING SOON is available from July 20, 2011

SYNFORM 2011/08

In the next issues:

SYNSTORIES

- Synthesis of syn- and anti-1,4-Diols by Copper-Catalyzed Boration of Allylic Epoxides
  (Focus on an article from the current literature)

- 11-Step Enantioselective Synthesis of (−)-Lomaiviticin Aglycon
  (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Review on: Stereoselective Acetate Aldol Reactions from Metal Enolates
(by P. Römea, F. Urpi et al.)

SYNLETT

Account on: Asymmetric Organo-Catalyzed Direct Aldol Additions of Enolizable Aldehydes
(by U. Scheffler, R. Mahrwald)

SYNFACTS

Synfact of the Month in category “Organo- and Biocatalysis”:
Biosynthesis of Spinosyn A

CONTACT

Matteo Zanda,
NRP Chair in Medical Technologies
Institute of Medical Sciences
University of Aberdeen
Forresterhill, 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, Forresterhill, Aberdeen, AB25 2ZD, UK and C.N.R. – Istituto di Chimica del Riconoscimento Molecolare, Via Mancinelli, 7, 20131 Milano, Italy
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
» Scientific Editor: Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
» 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 Assistant: 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: Julia Stötzer, julia.stoetzner@thieme.de, phone: +49 711 8931 771
» Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
» Homepage: www.thieme-chemistry.com

Publication Information
SYNFORM will be published 12 times in 2011 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACTS.

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 SYNFACTS
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.
Order toll-free within the USA: +1 800 782 3488
Fax: +1 212 547 1112
Airfreight and mailing in the USA by Publications Expediters 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 via Thieme-connect
The online versions of SYNFORM as well SYNTHESIS, SYNLETT and SYNFACS are available through Thieme-connect (www.thiemec- 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: eaccess@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia, and Australia: products@thieme.de, phone: +49 711 8931 407

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., 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.

License of Copyright
The right of the author to be identified as the author of this work has been asserted in accordance with the Copyright, Designs and Patents Act 1988.