

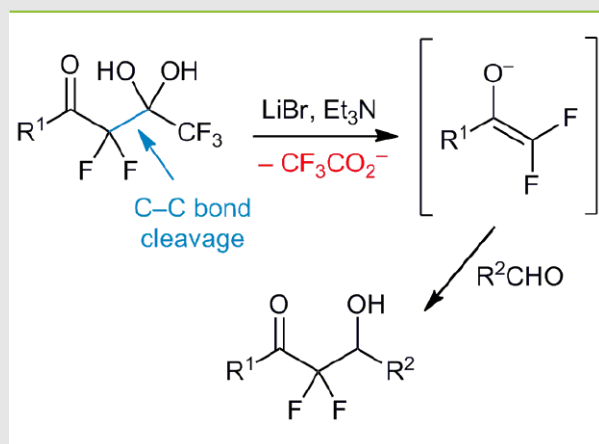
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/07

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**

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Your opinion about SYNFORM is welcome, please correspond if you like:
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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, some-

times 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

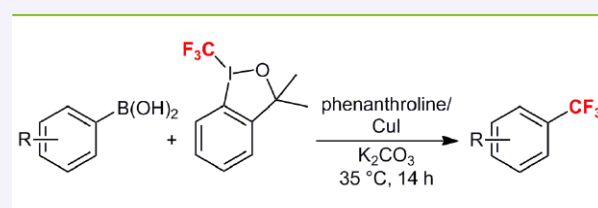
Editor of SYNFORM

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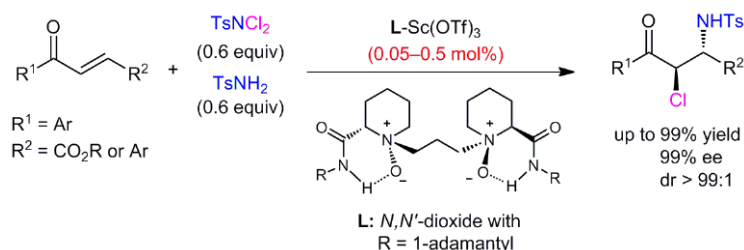
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If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

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

J. Am. Chem. Soc. **2011**, *133*, 5636–5639

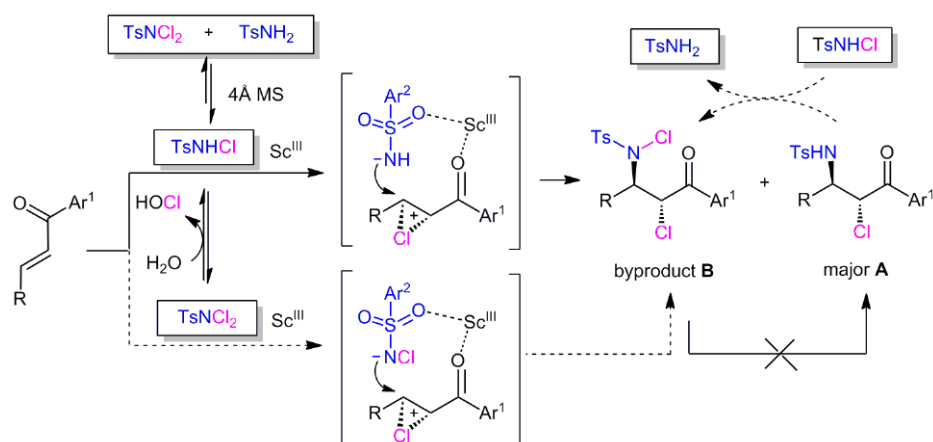


■ Catalytic asymmetric difunctionalization of olefins, such as dihydroxylation, aminohydroxylation, and diamination, has been a major area of research, since these reactions provide versatile building blocks which are difunctionalized in vicinal positions. In comparison with the strong progress achieved 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 C_2 -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 TsNCl₂/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



Y. Cai

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.



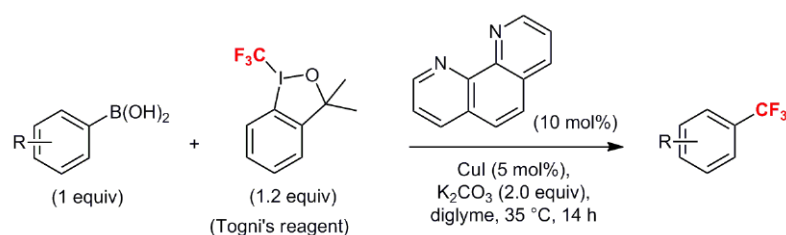
Prof. X. Feng

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

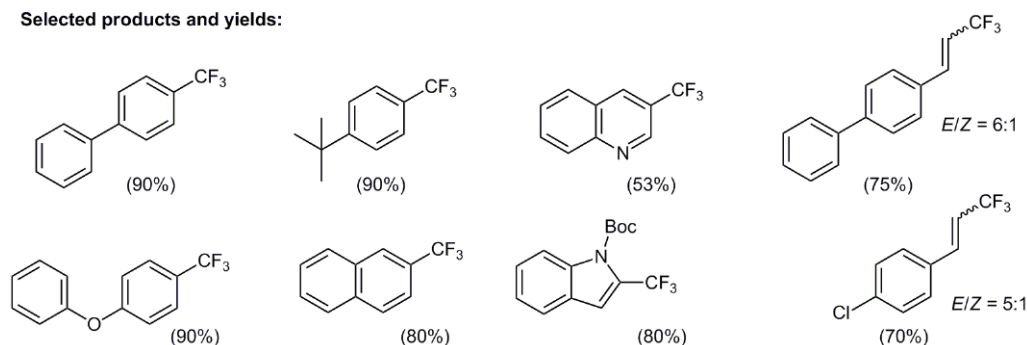
to the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China, 1996–2000), and was appointed as a Professor in 1997. He did postdoctoral research at Colorado State University (USA, 1998–1999) with Professor Yian Shi. In 2000, he moved to Sichuan University as a Professor, focusing on the design of chiral catalysts, the development of new synthetic methods and the synthesis of bioactive compounds.

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

Org. Lett. **2011**, *13*, 2342–2345



Selected products and yields:



■ 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 CF_3 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 arylboronic 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 ‘CF₃⁺’ 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 K₂CO₃ 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

About the authors



From left: Prof. Q. Shen, T. Liu

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

J. Am. Chem. Soc. **2011**, *133*, 5802–5805

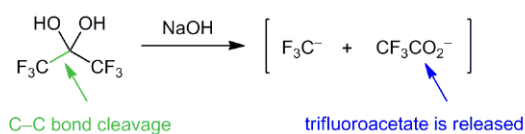
Organofluorine chemistry is becoming increasingly important due to the numerous exceptional properties of fluorine-containing molecules which find use in a number of fields, such as drug discovery, materials and nanoscience, energy and biomedical imaging. Although a great deal of progress has been achieved 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 -difluoroenolates 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 re-assembling 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 car-

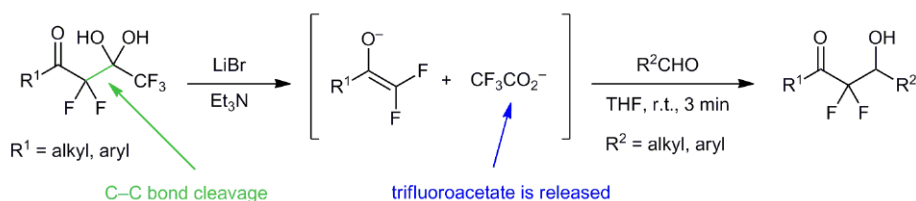
bon–carbon bonds is decarboxylation,” he explained. “By thinking along these lines, we found an important article by Prager and Ogden (*J. Org. Chem.* **1968**, *33*, 2100) as we were exploring how to install a difluoromethylene group onto a key natural product.” According to Professor Colby, the studies 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 -difluoroenolates are formed after the bond-breaking event. Other protocols to prepare difluoroenolates 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.”

Fragmentation of hexafluoroacetone hydrate



Release of trifluoroacetate to generate α,α -difluoroenolates

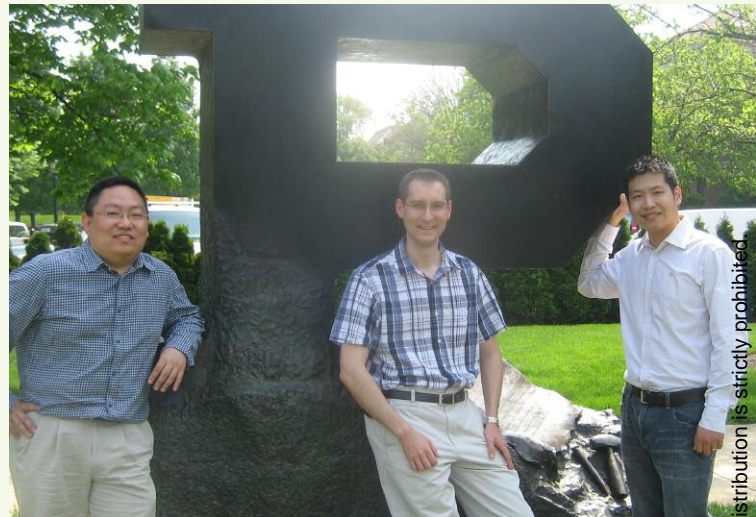


After efficiently synthesizing the requisite highly α -fluorinated *gem*-diols in two steps from methyl ketones, Professor Colby said he and his co-workers Changho Han and Eun Hoo Kim were shocked to observe how quickly and efficiently the carbon–carbon bond cleavage occurred under mild basic conditions. “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. ■

Matteo Zanda

About the authors



From left: Dr. E. H. Kim, Prof. D. Colby, C. Han

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SYNFORM 2011/08

is available from
July 20, 2011

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. Romea, F. Urpí 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](#)

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