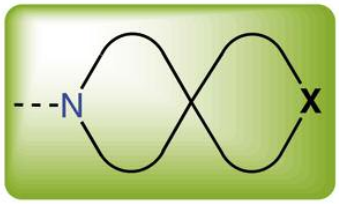
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/12

SYNSTORIES



X = O, NMe, S, SO_2, CH_2

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

Thieme

Dear readers,

This last 2012 issue of ***SYNFORM*** carries a remarkable novelty: a *FEATURED* ***SYNSTORY***. "Featured SynStories" are non-peer-reviewed articles authored by scientists working for private companies and describing the research activity conducted within the company. These articles are not meant to be an advertisement about the company itself, but rather a useful tool for informing our readership about the excellent research developed in the private sector. This information, which is not always easily accessible, is meant to facilitate interactions between these companies and the broader scientific community, which includes both academics and scientists working in an industrial environment. We will strive to maintain a high scientific level in these "Featured SynStories", hoping to provide a useful service to the entire scientific community.

The first *FEATURED* ***SYNSTORY***, authored by SpiroChem's Dr. Thomas Fessard (Switzerland), provides an interesting insight into spirocyclic compounds and their potential in drug discovery. More in line with ***SYNFORM***'s tradition, but definitely not less interesting, are the two ***SYNSTORY*** articles reporting on: (1) a novel metal-free strategy for introducing an SCF_3 group on the terminal alkyne position, developed by Professor F. L. Qing (P. R. of China) and (2) the iron-catalyzed carboxylation of styrenes with CO_2, recently reported by Dr. S. Thomas (UK).

Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

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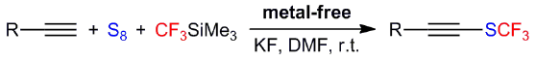

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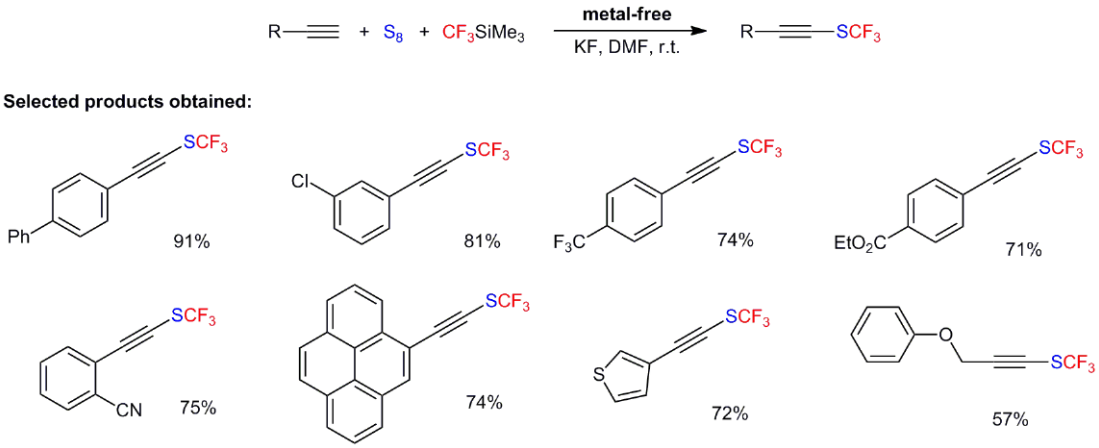
Metal-Free Oxidative Trifluoromethylthiolation of Terminal Alkynes with CF_3SiMe_3 and Elemental Sulfur

J. Am. Chem. Soc. **2012**, *134*, 12454–12457



The introduction of fluorine in organic molecules continues to represent a key area of research in chemical sciences, owing to the exceptional properties of fluoroorganics and their widespread applications in the fields of pharmaceutical science, materials science and energy. The trifluoromethylthio (SCF_3) group is especially prominent in the pharmaceutical and agrochemical industries. Thus, the development of mild and efficient synthetic methods for the introduction of the SCF_3 group into organic compounds has become the subject of intensive research. In stark contrast to the tremendous progress that has been made in the development of transition-metal-mediated/catalyzed trifluoromethylation reactions, the analogous transformation to incorporate the SCF_3 group into organic molecules remains underdeveloped. Recently, the group of Professor Feng-Ling Qing from the Shanghai Institute of Organic Chemistry and Donghua University (People's Republic of China), including PhD student Chao Chen and Dr. Lingling Chu, reported the first transition-metal-free oxidative trifluoromethylthiolation of terminal alkynes with CF_3SiMe_3 and elemental sulfur. This reaction leads to the formation of a series of C(sp)-SCF_3 bonds under mild, transition-metal-free conditions.

"This work is inspired by our recent contributions to copper-mediated/catalyzed oxidative trifluoromethylation protocols using the Ruppert–Prakash reagent (CF_3SiMe_3), allowing direct and efficient constructions of carbon–CF_3 bonds (e.g., *J. Am. Chem. Soc.* **2010**, *132*, 7262; *Org. Lett.* **2010**, *12*, 5060; *J. Am. Chem. Soc.* **2012**, *134*, 1298; *J. Org. Chem.* **2012**, *77*, 1251; *Org. Lett.* **2012**, *14*, 2106)," said Professor Qing. "We hypothesized that a similar oxidative trifluoromethylthiolation system might allow the formation of a carbon–SCF_3 bond. Indeed, earlier this year we successfully developed a Cu-catalyzed oxidative trifluoromethylthiolation of arylboronic acids with CF_3SiMe_3 and elemental sulfur (*Angew. Chem. Int. Ed.* **2012**, *51*, 2492)." This provides a convenient method that is complementary to the Pd- or Ni-catalyzed cross-coupling reactions of aryl halides with $AgSCF_3$ or [NMe4][SCF_3], independently developed by Professor Buchwald at MIT and Professor Vicic at University of Hawaii (*Angew. Chem. Int. Ed.* **2011**, *50*, 7312; *J. Am. Chem. Soc.* **2011**, *134*, 183). Professor Qing said: "On the basis of that work, we wondered whether the construction of C(sp)–CF_3 bonds could be achieved through a similar oxidative trifluoromethylthiolation of terminal alkynes."

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"We began our studies by evaluating the established Cu-mediated oxidative trifluoromethylation of terminal alkynes as a platform for constructing C(sp)–SCF_3 bonds," he continued. "The biggest challenge we met in the reaction evaluation was to inhibit the formation of trifluoromethylated side products. Initial trials by switching the catalysts and ligands were unsuccessful, and we finally found that no formation of the trifluoromethylated by-products was observed in the presence of a catalytic amount of a copper salt." Surprisingly, the researchers subsequently found that a higher yield of the desired trifluoromethylthiolated product was obtained in the absence of copper catalysts and ligands. Compared to the previously reported transition-metal-catalyzed trifluoromethylthiolation reactions, this transition-metal-free method is very attractive, especially for pharmaceutical applications.

"Interestingly, with careful control of the reaction conditions, we discovered that oxygen is not required for this oxidative transformation, as the desired product was still formed with excellent efficiency when the reaction was conducted in an argon atmosphere," remarked Professor Qing. "We surmised that elemental sulfur might be the real oxidant for facilitation of the desired oxidative cross-coupling, and GC-MS analysis of the reaction mixture indicated that elemental sulfur acted as the stoichiometric oxidant in the current reactions, further confirming our hypothesis." Professor Qing concluded: "However, the detailed mechanism of this oxidative trifluoromethylthiolation reaction remains to be elucidated."

Matteo Zanda

About the authors

From left: C. Chen, Prof. F.-L. Qing, Dr. L. Chu

Feng-Ling Qing received his PhD in 1990 from the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences under the supervision of Professor Chang-Ming Hu. He was promoted to an Associate Professor at the SIOC in 1992. From 1992–1995, he was a postdoctoral fellow at Wyeth Research (Pearl River, New York). He returned to the SIOC in 1995 and became a full Professor in 1997. Since 2001, he has been CheungKong Professor at Donghua University. He is currently a member of the Editorial Board of Journal of Fluorine Chemistry. His research interests include the synthesis and applications of fluorine-containing building blocks, fluorinated bioactive compounds, and fluorinated functional polymers.

Chao Chen was born in 1988 in Shandong (China). He received his BSc degree in 2009 from Qufu Normal University. He is currently a PhD student at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Professor Feng-Ling Qing.

Lingling Chu was born in 1985 in Anhui (China). She received her BSc degree in 2007 from Hefei University of Technology. In 2012, she received her PhD in organic chemistry from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Professor Feng-Ling Qing. Her doctoral research focused on the development of new synthetic methodologies for the introduction of the trifluoromethyl group (CF_3) into organic molecules.

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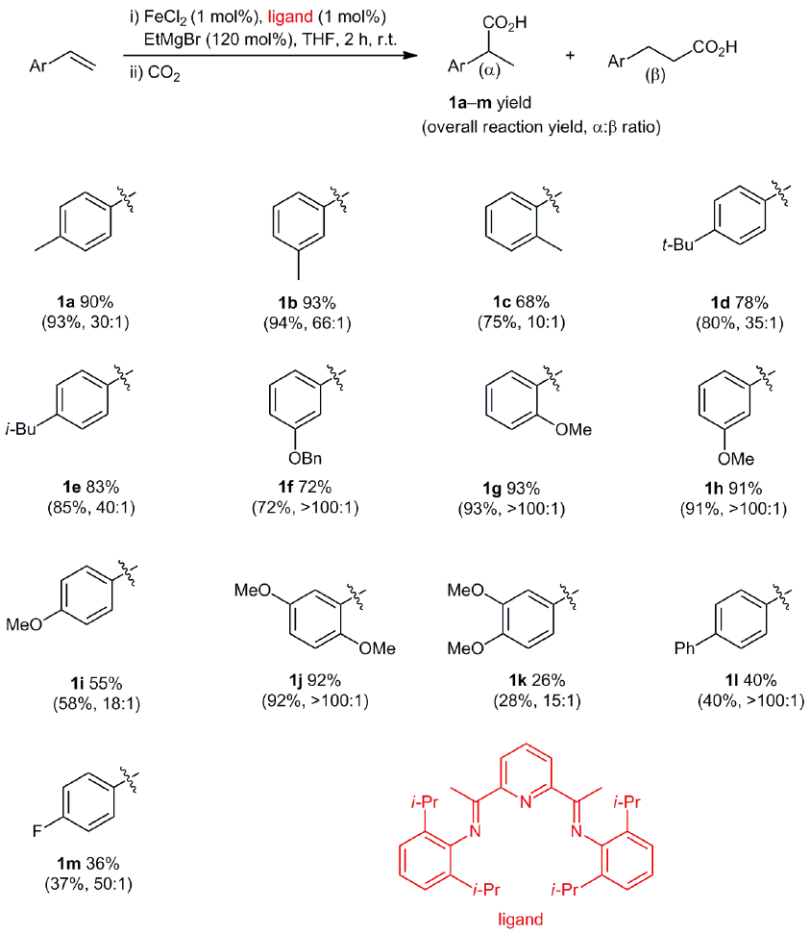
Iron-Catalyzed, Highly Regioselective Synthesis of α-Aryl Carboxylic Acids from Styrene Derivatives and CO_2

J. Am. Chem. Soc. **2012**, *134*, 11900–11903

The Thomas group at The University of Edinburgh (UK) is in its infancy, having only started independent research in the last couple of years and consisting of just four members (including two PhD students and one post-doc). "The research in our group is focused on the use of non-precious metals to replace and expand upon the reactivity of traditionally used 2nd and 3rd row transition metals," explained Dr. Thomas. "In particular, we aim to develop synthetic methodologies that can be used by non-experts. We therefore try to use inexpensive, non-toxic, environmentally benign and readily available reagents under reaction conditions that do not require specialized techniques or equipment."

Mark Greenhalgh is Dr. Thomas' first PhD student working on iron catalysis. "Mark joined the Bristol Chemical Synthesis DTC program after completing his MChem at The University of Sheffield (UK) and this *JACS* paper is the work of Mark's first year of study," said Dr. Thomas, who credited Mark's ability, dedication and attention to detail for the relatively quick publication of this paper.

"One of our primary research areas is iron catalysis. Recently we have focused on iron-catalyzed cross-coupling reactions, olefin hydrogenations and reductive cross-coupling reactions (for a combination of both the previous reactions, see: *Chem. Commun.* **2012**, *48*, 1580)," said Dr. Thomas.



Scheme 1 *Iron-catalyzed hydrocarboxylation of styrene derivatives: scope and limitations*

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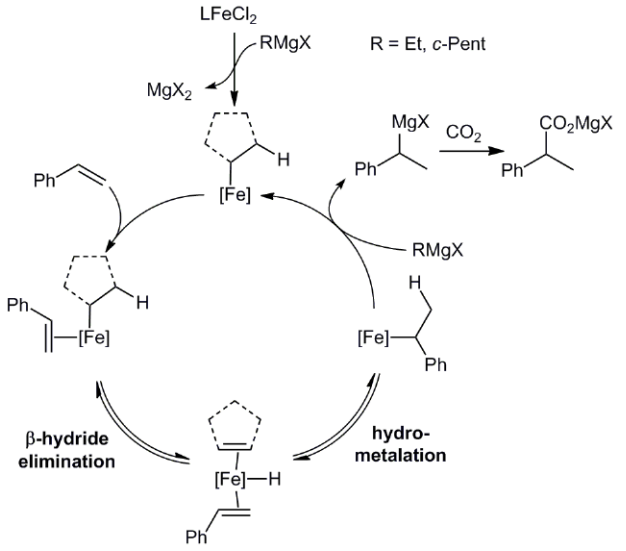
"Within this, the use of iron(II/III) pre-catalysts is key as they are 'bench-stable' and can be handled in air/moisture. By reducing the pre-catalysts in situ, the reaction protocol is greatly simplified as the highly reactive low-valent iron catalyst does not need to be manipulated." As described by Bogdanović, the reaction of iron(II) salts with Grignard reagents bearing β-hydrogens results in reduction of the iron center to give a low-valent, highly reactive, 'inorganic Grignard' species (*Angew. Chem. Int. Ed.* **2000**, *24*, 4610). The proposed reduction pathway involves the formation of transient low-valent iron hydride species (produced by β-hydride elimination of the alkylated iron center). Dr. Thomas said: "In this work, we sought to develop a methodology where we could exploit such a species directly for alkene functionalization beyond hydrogenation."

He continued: "Thus, we envisaged that the iron hydride could react with an alkene in a hydrometalation process to give an organometallic reagent which could react with CO_2 to give a carboxylic acid. This reaction would give the products of hydrocarboxylation and provide an iron-catalyzed alternative for hydroformylation/hydroxycarbonylation. Our key aims at the outset of the project were: <5 mol% bench-stable catalyst, >10:1 regioselectivity (branched/linear), commercially available reagents, 0–60 °C reaction temperature, <4 hour reaction time (including work-up), atmospheric pressure of CO_2."

"We were delighted to find that a range of styrene derivatives were efficiently hydrocarboxylated in the reaction to give carboxylic acids with excellent regioselectivity and in good to excellent yield," explained Dr. Thomas. "We demonstrated that a catalyst loading as low as 0.1 mol% was effective. In addition, the substrate scope provided complementary reactivity to the methodologies reported by Rovis (*J. Am. Chem. Soc.* **2008**, *130*, 14936) and Hayashi and Shirakawa (*J. Am. Chem. Soc.* **2012**, *134*, 272)."

"The methodology proved to be very robust," said Dr. Thomas. The iron(II) pre-catalyst was formed in situ, and then reduced to the active species by the addition of a Grignard reagent (which also acted as a stoichiometric hydride source). "Although a 1:1 ratio of iron(II) chloride to ligand was reported, in reality a range of stoichiometries were just as effective, meaning that pre-complexation and isolation of the pre-catalyst was not necessary," he explained. The addition of a large excess of ethylmagnesium bromide also did not hinder the reaction, although accordingly more propanoic acid would be formed from the direct addition of the Grignard reagent to carbon dioxide.

"The economical and practical aspects of the methodology were extended as we found that hydrated iron(II) chloride



Scheme 2 *Proposed mechanism for the iron-catalyzed hydrocarboxylation of alkenes*

($FeCl_2 \cdot 4H_2O$) was equally active in the reaction, presumably with the excess Grignard reagent acting as a drying agent," said Dr. Thomas. "Iron salts are also non-toxic and environmentally benign and so we expect that the methodology could be applied in pharmaceutical chemistry. An immediately obvious example would be the synthesis of the profen-class of pharmaceuticals (for example ibuprofen from the paper), which all possess an α-aryl carboxylic acid moiety. We are currently working at extending the practical aspects of the methodology in terms of functional group tolerance and reaction scale-up."

Dr. Thomas concluded: "We have already conducted a number of experiments in an attempt to elucidate the mechanism (some of which were discussed in the manuscript); however, there are still a number of questions we wish to address. In particular, we want to better understand the origin of regioselectivity in the reaction, and we would also like to obtain evidence for some of the proposed intermediate species. With this insight we may be able to further develop this, and other lines of research in the group."

Matteo Zanda

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About the authors

Dr. S. P. Thomas

Stephen Thomas was born in Toronto (Canada) and moved to the South West of the UK at a young age. After completing his MChem at Cardiff University (UK) working with Professor Nick Tomkinson, he moved to Churchill College, Cambridge University (UK) in 2007 for a PhD, working with Dr. Stuart Warren. Postdoctoral work with Professor Andreas Pfaltz at the University of Basel (Switzerland) was soon followed by an appointment as a Lecturer at the University of Bristol (UK). In 2012, Stephen and his group moved to the University of Edinburgh. His research interests are based on organometallic catalysis, synthetic methodology and mechanism, with a focus on the use of non-precious metals to replace and expand upon the reactivity of traditionally used 2nd and 3rd row transition metals.

M. D. Greenhalgh

Mark Greenhalgh was born in Great Ayton in North Yorkshire (UK) in 1987. He studied chemistry at The University of Sheffield with a year's study in Wollongong (Australia) and obtained a Masters in Chemistry in 2010. He then moved to the University of Bristol for his doctorate studies at the Bristol Chemical Synthesis Doctoral Training Centre. In 2011, he began his PhD studies with Dr. Stephen Thomas, and moved with him to The University of Edinburgh to complete his studies.

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Featured SynStory: Spirocycles in Drug Discovery

Background and Purpose. *FEATURED SYNSTORIES* report non-peer-reviewed scientific information about research activities conducted by a private company. Other potential authors from the private sector are welcome to get in touch with ***SYNFORM*** for writing similar articles. Contributions of this type clearly focus on scientific content and have no advertisement character.

In an increasingly competitive environment, pharmaceutical companies are seeking new tools to accelerate their drug discovery programs, explore new chemical space domains and secure novel intellectual property in order to fill their pipelines and stay ahead of competitors. In this context, novel molecular fragments that provide beneficial properties to drug candidates, either in terms of physico-chemical properties (solubility, lipophilicity) or pharmaco-kinetic properties (stability) are of particular interest for the industry.

Spirocyclic modules have recently attracted the interest of academic and industry researchers alike. New 'improved' building blocks have been generated and are finding their place in the toolbox of medicinal chemists working in drug discovery to replace or complement the existing set of common building blocks, while new spirocyclic scaffolds are designed to explore new structural conformations to feed screening libraries. The approaches to the design, synthesis and use of new spirocyclic building blocks could be classified into two main categories: bio-isosteres and novel exploratory scaffolds.

The Bio-isosteric Approach

A number of spirocyclic building blocks have been developed to offer a straightforward alternative to their parent heterocycles commonly used in medicinal chemistry.

Found on the periphery of drug candidates, heterocycles such as morpholines, piperidines or thiomorpholines are used to modulate efficacy as well as physico-chemical and pharmaco-kinetic properties. But they also constitute soft spots that can be metabolized (Figure 1). Carreira and co-workers have reported the effect of spirocyclization on a number of parameters such as lipophilicity, solubility and stability, showing that spirocyclic isosteres usually improve solubility and stability.[1–4]

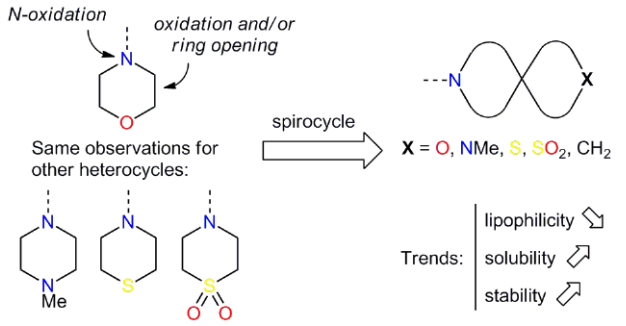

Figure 1 *Modulation of ADME properties with spirocycles*

A number of these spirocyclic versions of 'peripheral' groups are now commercially available and used in drug discovery programs.

Similarly, N,N-heterocycles such as piperazines or diazepane fragments are often used as spacers or scaffolds and found in many drug candidates from early stage to the market. This has led medicinal chemists looking for alternatives to design and synthesize a full set of bis-azaspiroalkanes that can be used to test the effect of structural features such as exit vector orientation. The resulting spirocyclic fragments offer two handles for attachment of substituents as their parent structure but are usually more rigid and offer a large range of possible dihedral angles between exit vectors (Figure 2).

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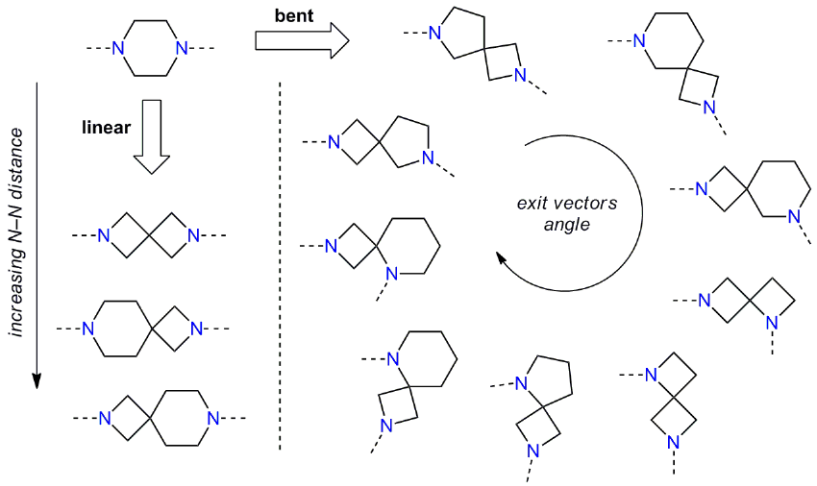

Figure 2 *Diazaspiroalkane modules*

The Exploratory Approach

More recently, new spirocyclic modules have been designed to increase chemical complexity and diversity in order to explore new chemical space domains. These include examples such as angular modules or benzofused spirocycles that conveniently bear extra exit vectors and handles for further functionalization (Figure 3).[5–10] Due to the novelty and also the rigidity of these examples, they are ideal candidates for chemical space exploration and can be used as scaffolds in the preparation of libraries of products. The introduction of stereogenic centers also provides an opportunity for developing three-dimensional molecules, an opportunity for medicinal chemists to 'escape from flatland'.[11]

These fragments are not necessarily designed to match any pre-defined alignment of vectors or become isosteres of known scaffolds, but rather find their usefulness in the creativity and novelty that will allow access to unexplored structures/spaces.

In conclusion, spirocyclic fragments are attracting much interest and are being incorporated into numerous drug discovery programs. Although we lack the history to define general trends and benefits over more traditional non-spiro building blocks, they have demonstrated advantageous properties in a number of research programs in terms of physicochemical or metabolic properties as well as intellectual property. If it is too early to say that they are superior to older fragments, they definitely deserve their place in the toolbox of medicinal chemists.

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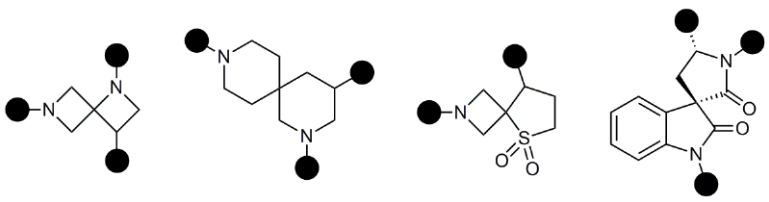

Figure 3 *Some recent spirocyclic modules*

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Dr. T. C. Fessard

Thomas C. Fessard holds a PhD in chemistry. After several appointments in academia and biotech companies, he has co-founded SpiroChem AG, a spin-off of the Swiss Federal Institute of Technology (ETH) in Zürich (Switzerland). SpiroChem designs and commercializes novel high-value-added building blocks to help the pharmaceutical and agrochemical industries accelerate their Research & Development programs and expand chemical diversity.
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SYNSTORIES

Iron-Catalyzed Asymmetric Oxyamination of Olefins
(Focus on an article from the current literature)

The Synthesis of η-1,2,3,4,5,6-Hexafluorocyclohexane (Benzene Hexafluoride) from Benzene
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

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Review on: Strategies for Spiroketal Synthesis Based on Transition-Metal Catalysis
(by J. A. Palmes, A. Aponick)

SYNLETT

Account on: Palladium-Catalyzed Cyanation of Nonactivated Alkynes; Development of Cyanopalladation and Its Application to Cyclization and Cycloaddition Reactions
(by S. Arai, A. Nishida)

SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": Synthesis of (–)-205B

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