CHIMIA

CHIMIA 2017, Volume 71
ISSN 0009-4293
www. chimia.ch
Supplementa to Issue 7-8/2017

SCS
Swiss Chemical
Society

SCS Fall Meeting 2017
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Session Organic Chemistry and Natural Products

August 21-22, 2017
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Azetidin-1-yl substituents to tune the photochemistry of photoactive molecules

G. Bassolino[1], P. Rivera-Fuentes[1]*

[1]Laboratorium für Organische Chemie, ETH Zürich, Vladimir-Prelog-Weg 1-5/10, 8093, Zürich

The ability to tune the photochemical evolution of a chromophore through structural modification is crucial to design photoresponsive materials for biological or chemical applications. There have been reports of remarkable increases in the fluorescence quantum yields of several dyes upon swapping a dialkylamino substituent for an azetidin-1-yl group (Figure 1a),[1,2] possibly arising from the inhibition of the formation of Twisted Intramolecular Charge Transfer (TICT) states (Figure 1b).[1,2] A photoprotecting group (PPG) is a chemical moiety that masks the activity of the compounds it is bound to, and that can be removed upon excitation with one or two photons.[3] 7-Dialkylamino-4-methyl-coumarin derivatives have been widely used as PPGs, even though the photorelease efficiencies (φ_{PA}) of the caged compounds tend to be moderate to low (usually below 20%).[3,4] We reasoned that the formation of a TICT state could be a competitive process for the photorelease reaction of 7-dialkylamino coumarins, and that substitution with an azetidin-1-yl group might prove beneficial. To test this hypothesis, we prepared a series of caged esters of 7-diethylamino (**1a-b**) and 7-azetidin-1-yl (**2a-b**) 4-methyl coumarin derivatives (Figure 1c) and measured their φ_{PA} (Figure 1d). The azetidin-1-yl substituted coumarins showed a higher φ_{PA} than the 7-diethylamino derivatives, with values comparable to julolidine-fused derivatives (**3a-b**), that cannot form a TICT state (Figure 1d). These results constitute a proof-of-principle demonstration of the feasibility to exploit the inhibition of TICT states formation by azetidines to enhance the quantum yield of photochemical processes that are in kinetic competition with TICT states formation. We are actively investigating other applications of this substitution, to broaden the scope even further.

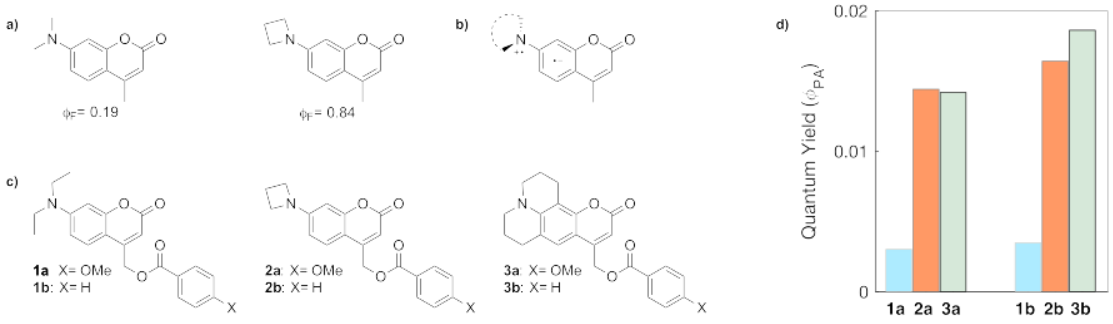

Figure 1. (a) Reported increase in fluorescence quantum yield (φ_F) for 7-(azetidin-1-yl)-4-methyl coumarin. (b) TICT state for a generic 7-dialkylamino-4-methyl coumarin. (c) Structures of the 4-methyl-coumarin benzoates studied. (d) Measured quantum yield of photorelease (φ_{PA}).

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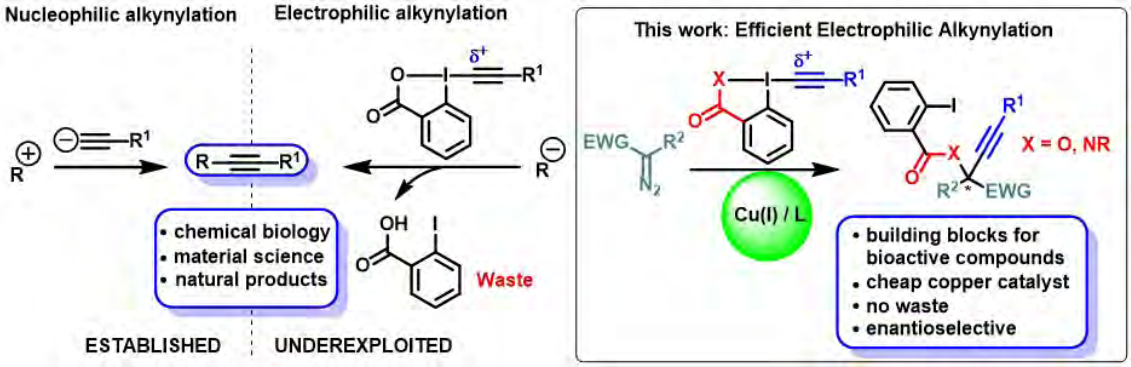
Copper-Catalyzed Electrophilic Alkyne Transfer: Accessing Important Building Blocks for Synthetic and Medicinal Chemistry by Reversing the Logic of Bond Disconnection

D. P. Hari[1], L. Schouwey[1], V. Barber[1], J. Waser[1]*

[1]EPF Lausanne

Alkynes are widely represented in biologically active natural products, materials, and medicines. Their use in cycloaddition reactions with azides ("Click Chemistry") has found widespread applications in the synthesis of nanomaterials, chemical biology, and drug delivery.[1a] Consequently, the efficient synthesis of structurally diverse alkynes is a prominent objective in chemical research. One of the most often used methods for the synthesis of alkynes consists in the addition of acetylenes anions on electrophilic positions of molecules. In contrast, the reversed polarity approach, -the addition of alkynes onto nucleophiles- has been less investigated, limiting the structural diversity and potential applications of this important class of compounds. In this context, hypervalent iodine reagents, a fascinating class of reagents based on iodine, have been used extensively for *electrophilic* alkynylations due to their exceptional reactivity.[1b,1c] However, alkynylations using hypervalent reagents generates one equivalent of a side-product, leading to waste generation. In 2016, our group developed an unprecedented copper-catalyzed reaction for the introduction of alkynes onto organic molecules, in which all the parts of the reagents are incorporated into the product.[2a] Key for success was the use of cyclic hypervalent iodine reagents –EthynylBenziodoXolones (EBX), now also commercially available- and diazo compounds as reactive small organic molecules. This reaction is highly practical and proceeds under mild conditions for a broad range of substrates. It uses a cheap base metal catalyst (copper), whereas other methods in the field are based on the use of expensive precious transition metals, such as rhodium or palladium. Herein, we will describe further important extensions of our work of high significance for synthetic and medicinal chemistry: 1) The development of an asymmetric reaction giving access to enantioenriched products.[2b] This is an important breakthrough, as the enantiomers of organic compounds have different bioactivities. 2) The introduction of a new hypervalent iodine reagent (EBZ) allowing us to synthesize alkyne-containing amino acids,[2c] which are key building blocks for the synthesis of bioactive compounds.



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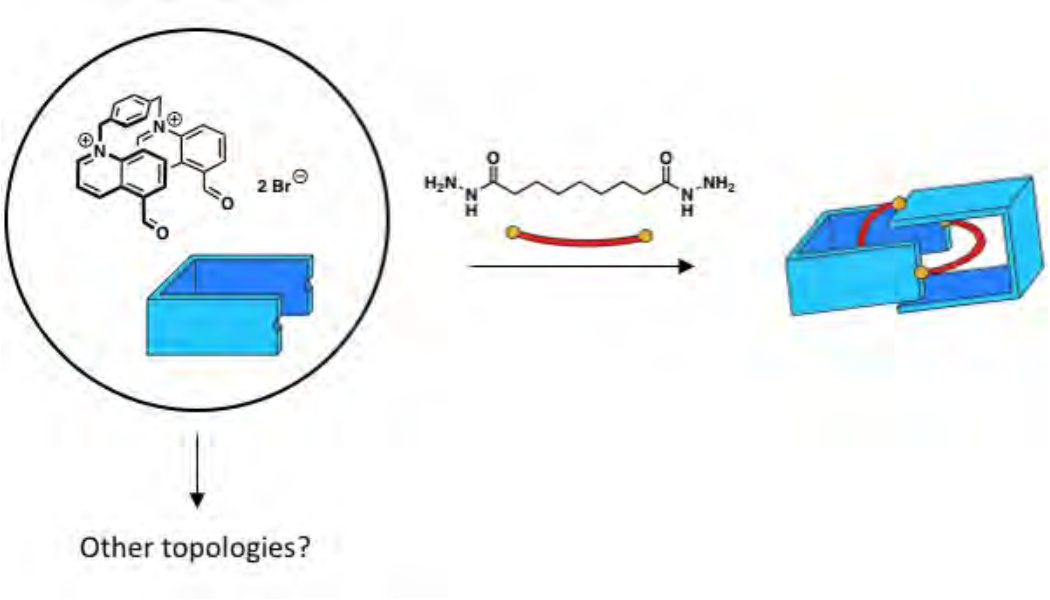
A synthetic strategy based on the hydrophobic effect to build molecular interlocked structures

F. B. Cougnon[1], K. Caprice[1]

[1]Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet 1211 Geneva, Switzerland

In spite of significant efforts spanned over the past 40 years, synthesising molecular links and knots more complex than [2]catenanes remains one of the biggest challenges of modern chemistry. Traditional approaches to build interlocked molecules consist in pre-organizing building blocks using metal templation, hydrogen-bonds or donor-acceptor pi-pi interactions.[1,2] The recent discovery of a trefoil knot by the Sanders group suggests that exploiting the hydrophobic effect could provide the basis of a powerful alternative strategy.[3] Inspired by this discovery, we hypothesised that hydrophobic building blocks could self-assemble in water into complex interlocked architectures depending on: 1) the size of the p-surface; 2) the amount of flexibility; and 3) the geometry of each parts. We present here a simple system where all these parameters can be varied with ease. The linkage between the building blocks is reversible (e.g. imine, hydrazine and oxime bonds). When the all these parameters are favourable, a mechanism of error-correction transforms trivial macrocycles into the thermodynamically more stable interlocked structure. We first proved the validity of our approach with the synthesis of a [2]catenane. We believe that the same system will soon allow us to build more complex topologies.



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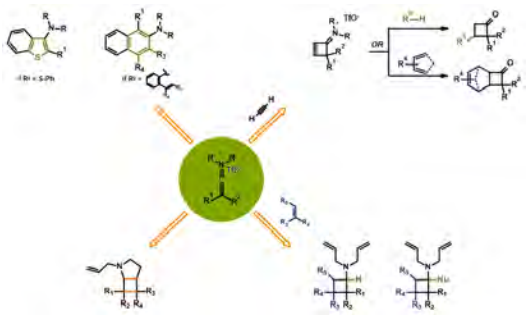
Keteniminium chemistry: a useful tool for the synthesis of small rings and aromatic derivatives

A. Kolleth[1], A. Lumbroso[1], S. Catak[2], S. Sulzer-Mossé[1], A. De Mesmaeker[1]*

[1]Syngenta Crop Protection AG, Switzerland, [2]Bogazici University, Department of Chemistry

Keteniminium salts possess different types of reactivities enabling the formation of versatile valuable skeletons. Highly substituted naphthylamines as well as 3-amino-benzothiophenes are indeed easily accessible and involve keteniminium salt intermediates reacting *via* a 6π-/10π or a 6π-electrocyclization respectively. But among all the reactions involving keteniminium salts, [2+2] cycloadditions have been by far the most studied; we recently developed a [2+2] cycloaddition with alkynes affording cyclobuteniminium salt adducts which were further elaborated by [4+2] cycloaddition or Michael addition reactions using various dienes or nucleophiles. Furthermore, we also reported a one-pot sequence to obtain aminocyclobutanes, relying on [2+2] cycloadditions with alkenes followed either by stereoselective reduction or nucleophilic addition. The use of easily removable *N*-allyl protecting groups increases the potential of this method to access, in a few steps, highly functionalized cyclobutaneamines-containing building blocks.



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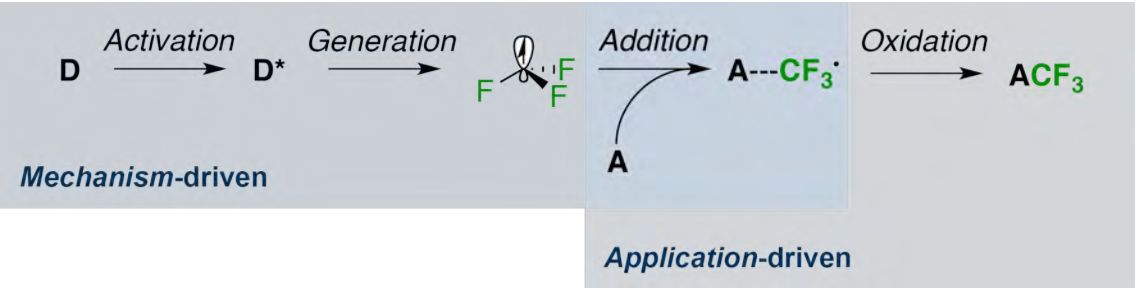
On the Generation and the Properties of the $F_3C^{\bullet}$ Radical

N. Santschi[1], B. J. Jelier[1], T. Nauser[1], D. Günther[1]*

[1]ETH Zürich, Department of Chemistry and Applied Biosciences, Vladimir-Prelog-Weg 1-5, 8093 Zürich.

"Introduction of the trifluoromethyl group into organic molecules can lead to drastic and desirable changes in chemical and physical properties" - Statements along this line regularly serve as motivation for application-driven research. However, within the framework of this approach, primarily the functionalized product is of interest and relatively little attention is being paid to the enabling underlying mechanistic scheme. For example, while the addition of the electrophilic (?) $F_3C^{\bullet}$ radical to arenes is undoubtedly an important process, it is most often depicted as an irreversible step - this constitutes a severe misconception.



Subject of the present contribution are the various facets of our mechanism-driven approach towards studying the generation of the trifluoromethyl radical and elucidating its properties. In this respect, it is important to realize that this reactive intermediate has to be accessed from a stable precursor *D* by a precursor-matched set of activating conditions, which then lead to an intermediate *D**. Subsequently, the latter will decay and release the species of interest. After addition of the trifluoromethyl radical to an acceptor *A*, a final single-electron oxidation will provide the stable product. In the context of this genreal mechanistic scheme, we will discuss:
(1) The limitations of oxidative and reductive activation strategies of commercially available $F_3C^{\bullet}$ precursors (trifluoroacetate, Langlois reagent and Togni's reagent) with primary radiolysis products ($H^{\bullet}$, $HO^{\bullet}$, e^{-}).[1]
(2) The additive-free, thermal activation of the hypervalent iodine-based Togni reagent as investigated by gas phase thermolysis in standard GC-MS equipment and the extension to a laboratory scale setup.[2]
(3) The degree of reversibility of $F_3C^{\bullet}$ addition to an aromatic model system and how this approach can be generalized to arrive at an experimental electrophilicity scale for radicals.[3]

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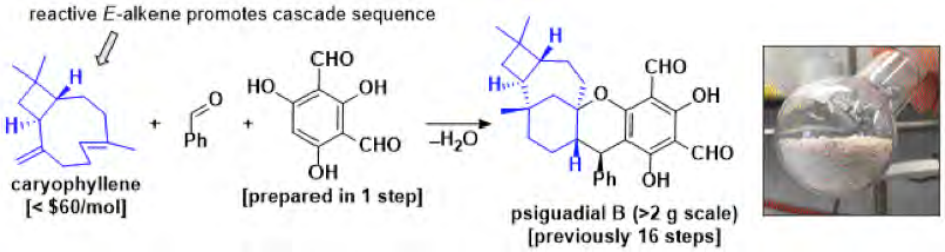
Gram–Scale Biomimetic Synthesis of Psiguadial B

C. Newton[1], D. Tran[1], M. Wodrich[1], N. Cramer[1]*

[1]EPF Lausanne

In recent years a growing number of synthetic chemists have begun to embrace the philosophies of efficient synthesis (e.g. atom, step, redox economy, etc.), indicative of a shift in focus away from purely the feasibility of a synthetic route, but rather towards considering the overall efficiency of a strategy.[1] Generally speaking, reactions that form multiple chemical bonds lead to a more rapid generation of structural complexity versus traditional stepwise approaches, ultimately resulting in improved syntheses.

Herein we present the first preparative synthesis of the complex meroterpenoid psiguadial B, a potent inhibitor of human hepatoma cell growth.[2] Psiguadial B was previously prepared in 16 steps, and in only milligram quantities, thus limiting further biological appraisal of the natural product.[3] Combined computational and experimental investigations from our research group suggest the biosynthesis of the natural product proceeds through a Michael addition between caryophyllene and a reactive *ortho*-quinone methide, followed by two sequential intramolecular cationic cyclization events. Through these considerations we have been able to develop a biomimetic synthesis of the psiguadial B via a three component coupling of caryophyllene, benzaldehyde and diformylphloroglucinol, enabling access to the molecule on gram-scale, and in only 2 steps.



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