Access to α-Chiral Olefin via Nickel-Catalyzed Enantioconvergent Cross-Coupling between α-Bromostyrenes and Secondary Grignard Reagents

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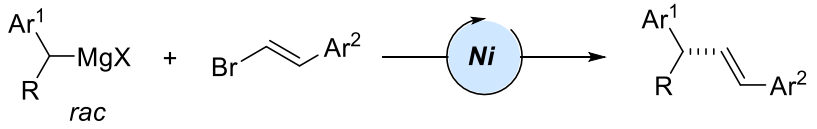
Owing to the prevalence of α-chiral olefins in biologically active compounds, access to this motif has attracted continuous attention.[1] In recent years, significant efforts have been placed on the development of direct methods to forge potentially stereolabile tertiary benzylic/allylic stereocenters via Csp^2–Csp^3 bond-forming strategies.[2] Among other examples, this includes several Ni-catalyzed enantioselective reductive cross-coupling reactions,[3] photo-induced Ni-catalyzed Csp^3–H benzylic alkenylations,[4] and an enantioselective dual [Cu/Pd]-catalyzed hydroalkenylation of olefins.[5]



>25 examples
44–91% yield
61:39–95:5 *er*

While the Ni-catalyzed cross-coupling between vinyl bromide and rapidly epimerizing benzylic Grignard reagents is well-documented,[2,6] the corresponding reaction using α-bromostyrenes has not reached the same level of achievement.[3,6] We report herein our efforts in this direction with the identification of a general and highly enantioselective nickel catalyst supported by a chiral (P,N) ligand. Rarely explored secondary benzylic Grignard reagents were evaluated as electrophiles and showed excellent reactivity and enantioselectivity in most cases. The protocol is operationally simple, and applicable to a broad range of substrates.

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A Gold-Catalysed [3,3]-Sigmatropic Rearrangement of *ortho*-Alkynyl-*S*,*S*-Diarylsulfilimines

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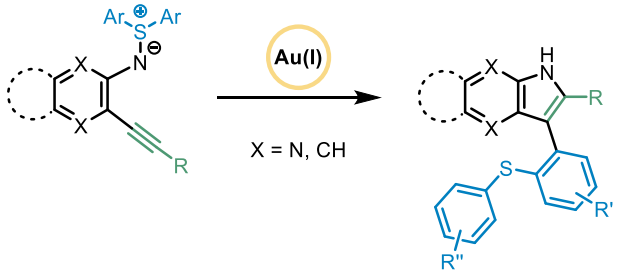
Some examples of gold-catalysed sulfonium [3,3]-sigmatropic rearrangements have been explored, most of them involving oxygen-bound sulfonium cations.[1] We now present the first gold-catalysed sulfonium [3,3]-sigmatropic rearrangement based on a nitrogen-bound sulfonium cation, derived from *ortho*-alkynyl-*S*,*S*-diarylsulfilimines.[2]



This methodology gives facile access to highly functionalised 5*H*-pyrrolo[2,3-*b*]pyrazines, substituted with a diaryl sulfide moiety at the C-7 position. The reaction is characterised by mild reaction conditions, a high functional group tolerance and excellent yields. Furthermore, the use of sulfilimines as nitrene transfer reagents in gold catalysis is broadened. While there have been many examples of sulfilimines being used as intermolecular nitrene transfer reagents in conjunction with ynamides in the recent years,[3] this constitutes the first example of a sulfilimine-derived intramolecular nitrene transfer to alkynes. Therefore, the nitrene transfer is no longer limited to activated alkynes, a significant expansion of the scope. We provide experimental mechanistic evidence that suggests the reaction to proceed intramolecularly, most likely involving a [3,3]-sigmatropic rearrangement instead of the formation of an α-imino gold carbene.[2]

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Interrupted Polonovski strategy for the functionalization of amino acids and peptides

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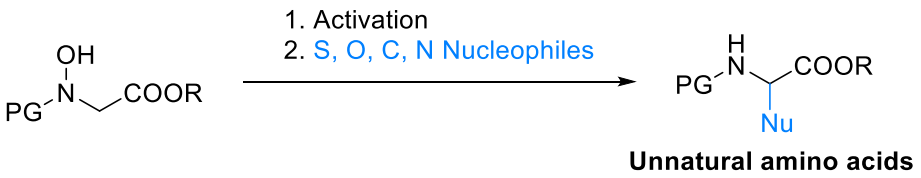
Non proteinogenic α amino-acids are an important class of compounds in biologically active products. However, their synthesis still often requires toxic reagents or strongly oxidative or basic conditions. We report here the α functionalization, under mild basic conditions, of carbamate-protected hydroxylamine glycine substrates, employed as imine surrogates[1], in an interrupted Polonovski reaction to modify the backbone of the amino acids. The addition of S, N, O and C nucleophiles was achieved in a one-pot procedure.



Unnatural amino acids

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Synthesis and Reactivity of a Terminal 1-Alkynyl Triazene

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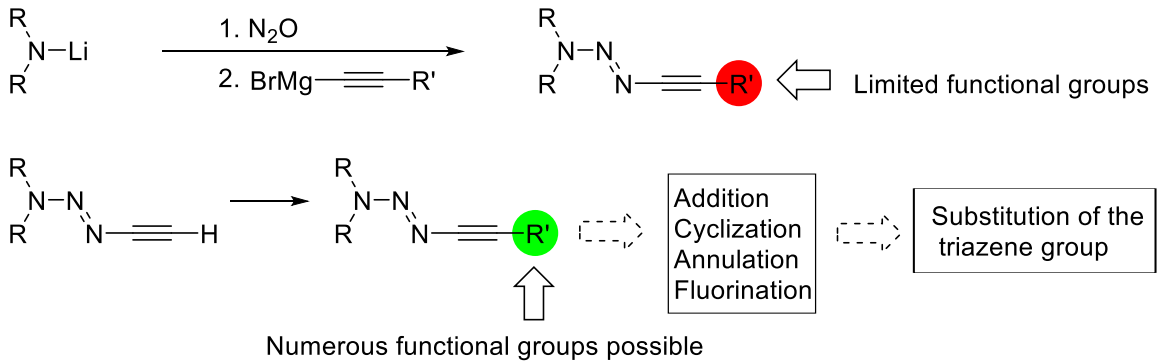
1-Alkynyl triazenes have emerged as highly versatile reagents in organic synthesis.[1] The electron-donating character of the triazene group activates the triple bond, resulting in ynamide-like reactivity. 1-Alkynyl triazenes can be employed as suitable substrates for a variety of reactions, including cycloadditions, annulations, rearrangements, and 1,2-additions, as well as fluorination reactions. A distinct advantage of using 1-alkynyl triazenes in these transformations is the possibility for further derivatizations of the products. Under acidic conditions, the triazene function can be substituted by a variety of nucleophiles, facilitating divergent product modifications.[1]

Thus far, 1-alkynyl triazenes have been accessible only by one synthetic route, namely, the coupling of lithium amides with first nitrous oxide (N_2O) and then an alkynyl Grignard reagent.[2] The utilization of strongly basic and nucleophilic reagents severely restricts the functional groups, which can be employed. We have now developed a procedure for the synthesis of a terminal 1-alkynyl triazene.[3] The easy-to-access compound enables the preparation of 1-alkynyl triazenes with a range of functional groups including esters, alcohols, cyanides, phosphonates, and amides. The availability of functionalized 1-alkynyl triazenes makes this class of compounds attractive for applications in organic synthesis. The terminal 1-alkynyl triazene can also be used for the synthesis of di- and triynes and for the preparation of (hetero)aromatic triazenes via transition-metal-catalyzed cyclization reactions.[3]



Scheme 1. Versatile reactivity of terminal 1-alkynyl triazene

The authors greatly appreciate the financial support from EPFL as well as the facility/equipment available within EPFL.

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Advancing the Synthesis of Lipid-Linked Oligosaccharides as Probes for Investigating *N*-Glycosylation Machinery

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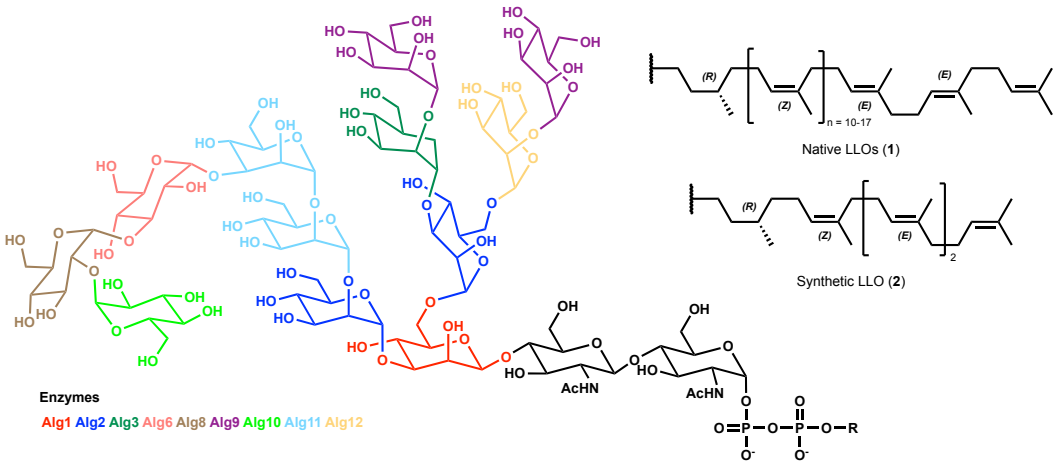
Lipid-linked oligosaccharides (LLOs) play important roles in *N*-protein glycosylation, a vital post-translational modification that enables a wide range of *N*-glycan structures. In eukaryotes, this biological process is regulated by various enzymes, including ALG (asparagine-linked glycosylation) and OST (oligosaccharyltransferase), which utilize LLOs as substrates. However, the native LLOs (**1**) are challenging to obtain through chemical synthesis, and their limited water solubility hampers the study of *N*-glycosylation enzymes. To address these challenges, our laboratory has developed simplified LLOs precursors, which are converted to synthetic LLOs through enzymatic synthesis (e.g., **2**), and are used as chemical probes to investigate these enzymes.[1–4]

Extending on this work, we aim to explore the minimal LLO structure that enzymes can utilize as a substrate in eukaryotic cell *N*-glycosylation machinery. Additionally, we are optimizing the synthetic steps involved in LLO preparation. This optimization not only facilitates the production of analogues but also ensures a continuous supply of LLOs, crucial for sustaining enzymatic studies.



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Synthesis of Porphyrin-based Molecular Photocatalysts for Carbon Dioxide Reduction

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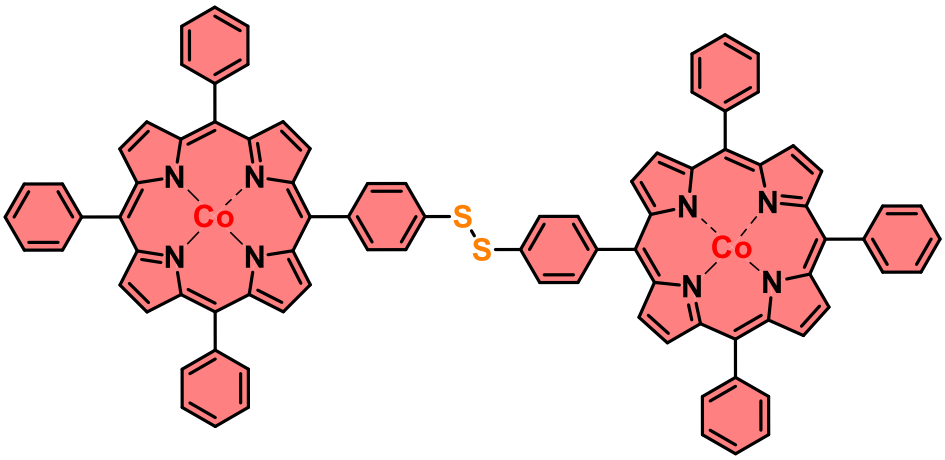
Porphyrins are ubiquitous macrocyclic pigments and referred as the ‘‘pigments of life’’. The term porphyrin actually derives from the Greek word for ‘‘purple’’ (porphyra). Porphyrins constitute a unique structural class of compounds and play pivotal role in vital phenomena such as photosynthesis and respiration). Recently, there are intense research occurs on the photocatalytic applications of porphyrins.[1-5] Our group have involved in the rational design and synthesis of promising porphyrins derivatives, where Co ion was used as the central metal ion and phenyl based bulk groups were used to provide sufficient solubility and steric hindrance.



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Synthesis of Nonacethrene derivatives with the goal to obtain a magnetic photoswitch

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In this project we aim to design a new all organic chiral magnetic photoswitch. The target compound is called nonacethrene and is the bigger homolog of cethrene, a chiroptical diradicaloid photoswitch. Pristine cethrene is too reactive but functionalization with two methyl groups in the fjord region leads to dimethylcethrene, which can be switched between an open and a closed form via light but does not possess an electron paramagnetic resonance (EPR) signal at room temperature. By expanding the π-backbone and therefore lowering the singlet-triplet gap, nonacethrene is EPR active. Nonacethrene undergoes an unwanted cascade reaction and dimethylnonacethrene is not reactive enough to act as a photoswitch. The adjustment of the steric bulk in the fjord region with only one methyl group represents an opportunity for further optimization to achieve bistability and is a viable strategy to realize a magnetic photoswitch operating at ambient temperature.

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Photoinduced intramolecular cyclization via a Norrish I reaction

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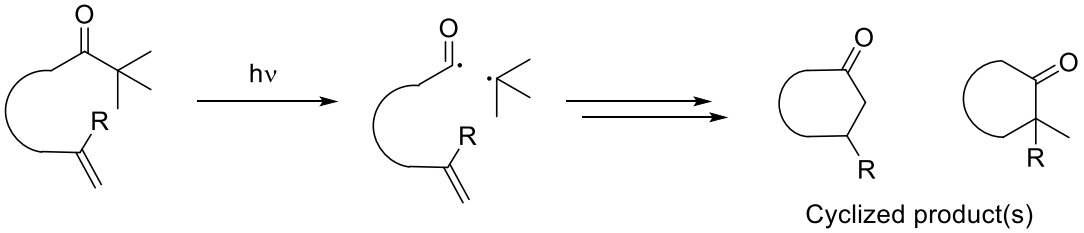
In the last decades, photochemistry has gained more importance in organic synthesis, with the wish to develop greener and more sustainable chemistry. Applying this chemistry to the synthesis of natural products leads to new possibilities in terms of transformations and bond formation. In this project, the idea is to use a photochemical reaction, the Norrish type I, to afford cores bearing multiple rings via an intramolecular cascade reaction. Norrish reactions were described for the first time by Norrish in 1932[1] and were widely studied, and as well applied in the synthesis of natural products.[2] Nevertheless, it was, to the best of our knowledge, never used to form multi-ring systems via an intramolecular cascade reaction. In this work, the focus stands in the study of short chain irradiations. By performing several modifications on the substrates, as well as screening different conditions, the change in the ratio between desired products and Paternó-Büchi products could be observed, leading toward desired cycles.



Looking at those results, achieving the desired cyclization on longer chains could lead to the formation of cores using a simple irradiation. Those could further be used in the synthesis of natural products and the development of new pathways.

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Further Investigations on Excited State Potential Energy Surfaces: Can the Hammond Postulate be Applied to Photochemical Reactions?

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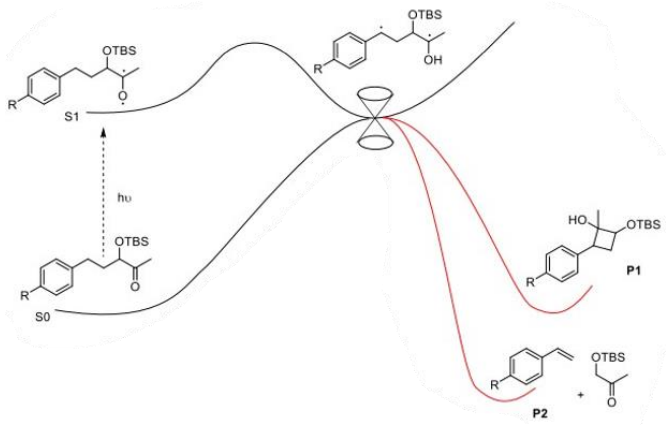
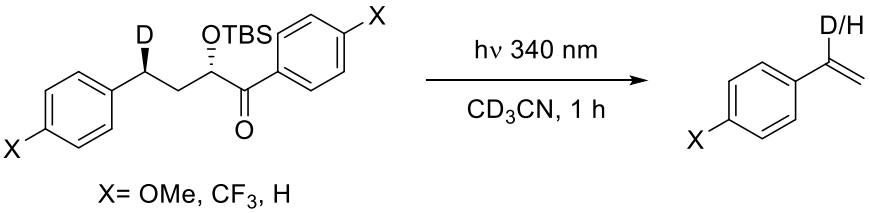
The goal of this project is to investigate the location of the conical intersection between S_0 and S_1 Potential Energy Surfaces (PES) using the Norrish-Yang type II reaction. A conical intersection of two or more potential energy surfaces is the set of molecular configurations points where the PES are degenerate. Studies on CIs have become an essential topic for understanding reaction mechanisms in photochemistry, as important as transition states in thermal chemistry. For this purpose, methylketones photosubstrates were synthesized to favor the singlet pathway. As depicted on **Scheme 1**, we hypothesized that CIs are normally close to the products formation in a photochemical reaction and we propose to use the ratio of fragmented against cyclized NYII products to locate this CI.



Scheme 1. Locating a CI with a NYII reaction

Having the methylketones in hand, they were submitted to light excitation.[1,2] The excited carbonyl moiety abstracted one of the two diastereotopic benzylic hydrogen atoms forming a [1,4]-biradical. By altering the substituents on *para* position of the aromating ring, the benzylic radicals will either be stabilized or destabilized. This will influence the fragmented *vs* cyclized ratio.

In parallel, further studies are made with the γ–deuterated arylketones previously studied in our group (**Scheme 2**).[3,4] These photosubstrates are investigated now in two sets of experiments, once with triplet sensitizer (benzophenone), once with an excess of triplet quencher (piperylene) to probe the spin state of the reaction.



Scheme 2. γ-deuterated arylketones to be studied in a NYII reaction

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Astrocyte–specific targeting and kinase inhibition of the TNFR1 pathway

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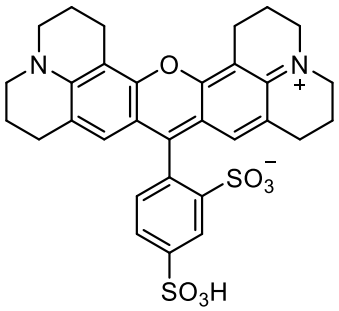
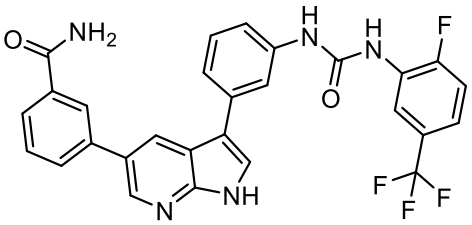
Astrocytes, the most abundant subtype of glial cell, have important roles in metabolic support of the neurons i.e. regulation of blood flow, detoxification and clearance of the synapses.[1] Additionally, astrocytes are active players in synaptic functions by releasing gliotransmitters as the cytokine TNFα. Therefore, the consequences of disruption of astrocytic supportive functions or gliotransmission could play a significant role in human neuronal diseases. TNFα transforms astrocytes into a neurotoxic phenotype and elevated levels of TNF are found in several human brain diseases including Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis, trauma and stroke.[2]



(1)



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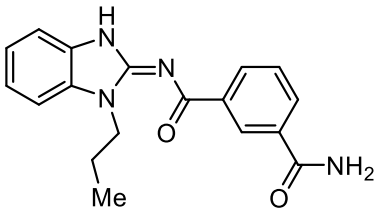

(3)

In this context, we aim to specifically inhibit upstream and downstream kinases of the TNFR1 pathway in astrocytes to gain insight in their function and for further physiological studies. Astrocytes can be specifically labelled by sulforhodamine 101 **(1)** via the thyroid hormone transporter OATP1C1.[3] Here we report the design, synthesis and cellular activity of linked sulforhodamines connected to RIPK1 **(2)** and TAK1 **(3)** inhibitors via cleavable and non-cleavable linkers.

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Hydroperfluoroalkylation of unactivated alkenes

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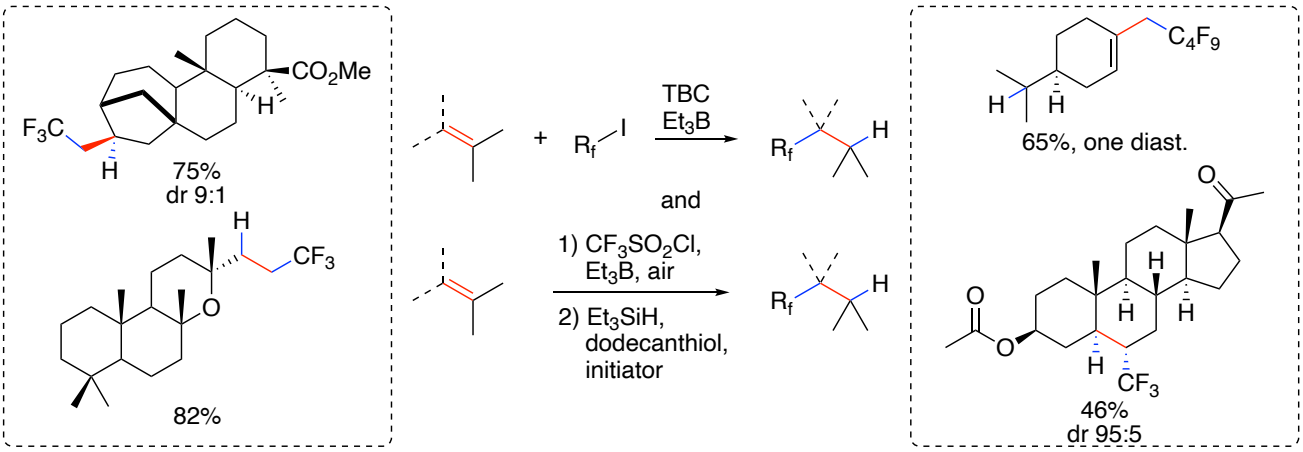
Recent advances in fluorination methods bring a huge impact on research areas such as medicinal chemistry, agrochemistry and material science.[1] Trifluoromethyl groups are known for their ability to increase the lipophilicity of the molecules while retaining their biological activity.[2,3] Classical strategies to access fluorinated substrates include iodoperfluoroalkylation, utilization of fluorinated sulfones and sulfonyl chlorides.[4] The hydroalkylation method developed in our group[5] has been extended to perfluoroalkylation of unactivated alkenes.



Scheme 1. Radical mediated hydroperfluoroalkylations and structures of some modified natural products.

The introduction of perfluorinated alkyl chains into a wide range of substrates was achieved with iodoperfluoroalkanes. The trifluoromethylation was conveniently achieved in two steps using trifluoromethanesulfonyl chloride as the source of CF_3 radical, followed by the dechlorination step adopted from polarity-reversal catalysis (PRC) method by Roberts et. al.[6,7] Under the applied reaction conditions, a diversity of functional groups can be tolerated and olefin-containing natural products can be readily derivatised.

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Synthesis of Steroidal-Nitroxide Hybrids for the Treatment of Chronic Inflammatory Disease

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Prevalence of chronic inflammatory conditions is increasing exponentially and presently represents over 50% of deaths annually worldwide, fuelling the need to explore novel treatments. Owing to their potent anti-inflammatory effects, glucocorticoids (GCs) are first-in-class treatment against the symptoms of inflammatory conditions, however they along with other anti-inflammatory agents do not address the probable underlying cause of oxidative stress.[1] Furthermore administered GCs not only exhibit a lower therapeutic efficacy due to oxidative stress, but they themselves can also induce it.[2-3]

This research aims to address these issues by using pharmacophore hybridisation strategy to design and synthesize novel steroidal hybrid drugs that incorporate an antioxidant nitroxide moiety. To date, several first generation steroidal-nitroxide hybrid molecules featuring either a cleavable or non-cleavable linker have been synthesized and investigation into their biological activity both *in vitro* and *in vivo* is ongoing.

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Deuterated quinoline derivatives in information storage

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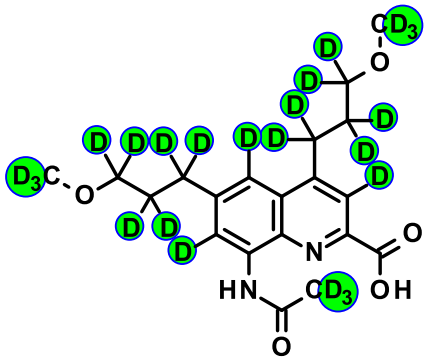
Information storage on the molecular level can be achieved not only by macromolecules (like DNA, RNA, proteins), but by coding small molecules. When creating a coded library of small molecules, the most important and indispensable property of the code is that it must unambiguously identify the individual library members. The code can be the physical position in a well-plate, a chemical tag or an optical or radio chip. Alternatively, the code can be directly incorporated into each library member by using isotope ratio encoding. Here we present our approach using deuterium labelled quinoline derivatives.



The basic principle is that each member is coded by a specific mixture of deuterated isotopologues (molecules with the same chemical formula but containing different isotopes). The mixing ratios must be set to provide a unique mass fingerprint for each member, which can be unambiguously distinguished by current MS techniques. We designed a quinoline derivative, where deuteration is possible up to the D24 isotopologue. Our initial calculations showed that using the mixtures of the 25 isotopologues, several thousand unique mass fingerprints can be created. To validate the approach, the synthesis of these isotopologues is ongoing. The mixtures generating the most similar MS spectra will be prepared to see if they can be unambiguously distinguished.

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Development of NHC-Cu complexes for asymmetric hydroboration

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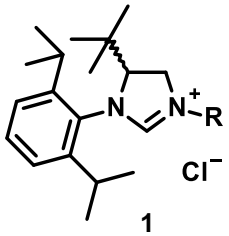
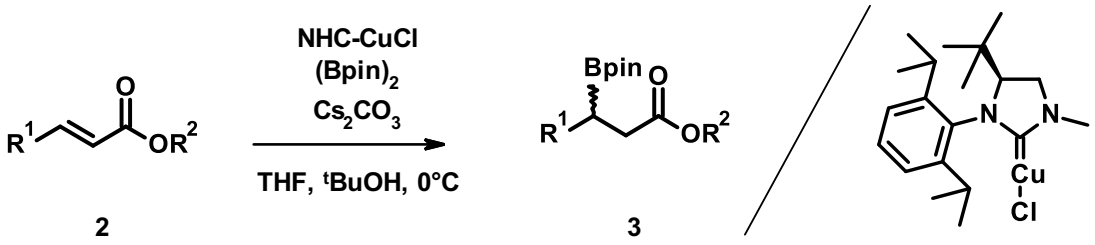
The use of selective catalysts plays a very important role in nowadays modern synthesis and in green chemistry. Our research group has a years of experience in the development of asymmetric NHC scaffolds and came up with a unique synthetic rout which allows us to synthesize a great variety of enantiomer or diastereomer pure imidazolinium salts, that serves as carbene precursors(**1**). [1]



1

One of our newer projects is the development of a Cu-NHC based catalyst library for enantioselective hydroboration of α,β unsaturated esters. After choosing the most suitable catalyst(**4**) and optimizing the reaction conditions we were able to synthesize several boronic-esters(**3**) with up to 98ee% and 95% yield.



2 **3** **Up to 95% yield and 98ee%** **4**

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Synthesis and Catalytic Applications of Hetero-Bimetallic Nickelates

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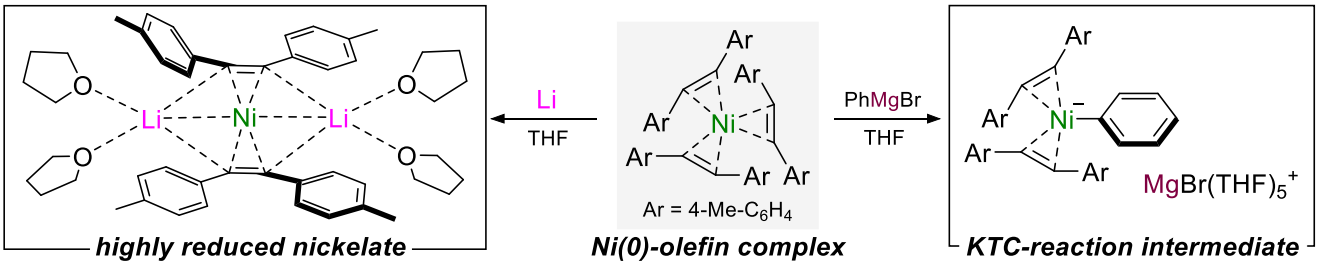
Nickel olefin complexes were first reported in the 1960s by Wilke[1] and they continue to serve as ubiquitous and versatile Ni(0) sources with widespread use as reagents or as catalysts. The treatment of Ni(0) olefin complexes with polar organometallics can give rise to heterobimetallic nickelates, which have recently been shown to be key intermediates in challenging organic transformations, such as the cross-coupling of aryl ethers.[2]



In this work, we will present our mechanistic investigations into the Kumada-Tamao-Corriu (KTC) cross-coupling reaction using simple Ni(0)-olefin catalysts, without the use of auxiliary ligands. Under these "ligand-free" conditions, the reaction relies on the formation of electron-rich heterobimetallic nickelates, several of which have been isolated and characterised by solution and solid-state techniques. Furthermore, the structure and reactivity of highly reduced nickelates, derived directly from the treatment of Ni(0)-olefins with alkali metals (Li, Na and K) will be discussed. Their highly reducing nature allows challenging catalytic transformations, such as the reductive coupling of unactivated olefins.[3]

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Taming Triangulene: Taking Control over π-Radical Dimerization

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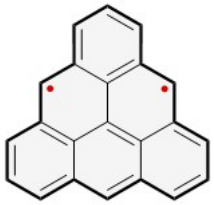
The synthesis of persistent triangulene, the most iconic member of the open-shell nanographene family, represented a challenge for over half a century, due to the high reactivity of this diradical and therefore high likeliness to polymerize. We now show that we can be in full control over triangulene's reactivity and use π-radical cascade reactions as a step-economic synthetic tool for making complex graphene-based carbon nanostructures.

Radical reactions are among the fastest and most efficient, but it is difficult to control and direct their selectivity. To demonstrate that such control is possible, we investigated dimerization of triangulene. We found that by strategic placement of substituents, we can block some positions from reacting, and thus control the selectivity and the reaction outcome. This new synthetic approach opens up opportunities to access new tailor-made materials and changes the current paradigm that π-radical reactivity is undesired.

triangulene:
in control of its reactivity



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