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Swiss Science Concentrates

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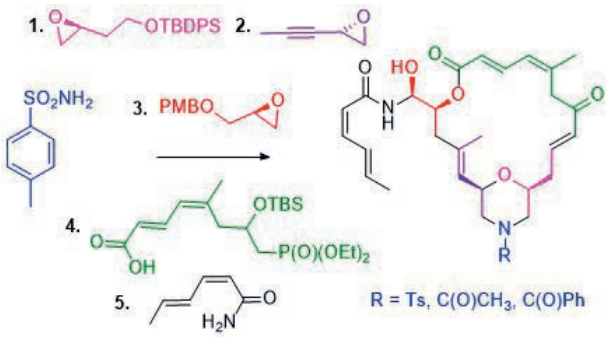
Short Abstracts of Interesting Recent Publications of Swiss Origin

Synthesis of Morpholine-Based Analogs of (–)-Zampanolide and Their Biological Activity

C. P. Bold, M. Gut, J. Schürmann, D. Lucena-Agell, J. Gertsch, J. F. Díaz, and K.-H. Altmann,* *Chem. Eur. J.*
doi: 10.1002/chem.202003996.
ETH Zurich

Natural products are a highly prolific source of biologically active leads for drug discovery and development. Among all natural products, those produced by marine organisms seem to possess the highest level of bioactivity. (–)-Zampanolide is a sponge-derived, marine macrolide which inhibits cancer cell growth at nanomolar concentrations through covalent binding to β-tubulin at the taxol site. To further explore structure-activity relationships and to improve the drug-likeness of zampanolide, the authors synthesized analogues containing a morpholine instead of the tetrahydropyran ring. The morpholine unit was assembled *via* two consecutive epoxide openings, and the macrocycle was efficiently closed by intramolecular Horner-Wadsworth-Emmons olefination. *N*-Acetyl and *N*-benzoyl analogues exhibited nanomolar antiproliferative activity against cancer cell lines, similar to the natural product. This work paves the way for the development of zampanolide analogues as new anticancer agents.

Authors' comments:
"After having overcome all synthetic challenges, it was gratifying to see that the proper substituent on nitrogen equipped these 'non-natural natural products' with activity similar to that of zampanolide."

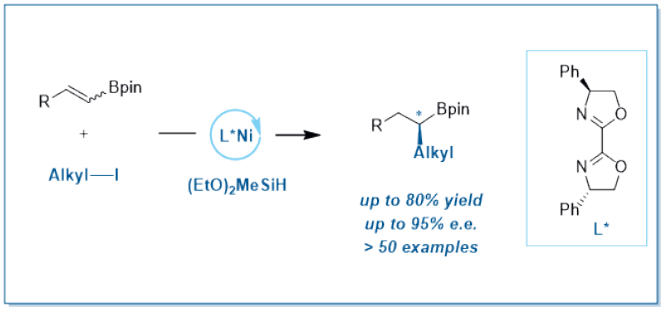


Enantioselective C(sp³)-C(sp³) Cross-Coupling of Non-Activated Alkyl Electrophiles via Nickel Hydride Catalysis

S. Bera, R. Mao, and X. Hu,* *Nat. Chem.* **2021**, *13*, 270–277.
Ecole polytechnique fédérale de Lausanne

The C(sp³)–C(sp³) cross-coupling of alkyl electrophiles poses a major challenge and enantioselective versions thereof are of high interest for the synthesis of bioactive molecules. The authors developed an enantioselective Ni–H-catalyzed cross-coupling between alkenyl boronates and alkyl iodides employing a chiral bis(oxazoline) ligand. The reaction delivers enantioenriched secondary alkyl boronates with high levels of reactivity, regio- and enantioselectivity, and shows a broad scope with respect to both coupling partners. The utility of this transformation was demonstrated through the functionalization of diverse active ingredients and the straightforward preparation of an intermediate in the synthesis of (*S*)-(+)-pregabalin. Preliminary mechanistic studies allowed the authors to propose a catalytic cycle involving Ni^{I}, Ni^{II} and Ni^{III} species. The presented methodology has a high potential for the synthesis of chiral complex molecules.

Authors' comments:
"Nickel hydride catalysis enables the use of readily available and stable olefins as pro-nucleophiles in enantioselective C(sp³)–C(sp³) cross-coupling, leading to a broad scope and high functional group tolerance."



Prepared by Shu-Min Guo, Anton Kudashev, Takeru Miyakoshi, Marco Zuccarello, and Olivier Baudoin*
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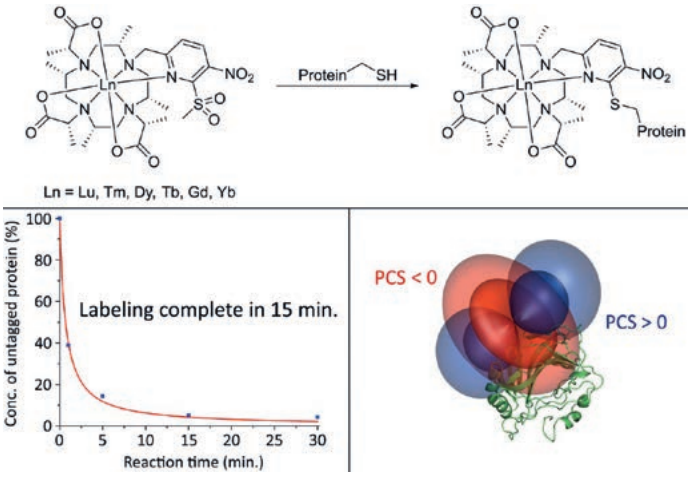
A Novel, Rationally Designed Lanthanoid Chelating Tag Delivers Large Paramagnetic Structural Restraints for Biomolecular NMR

D. Joss, F. Winter, and D. Häussinger,* *Chem. Commun*. **2020**, *56*, 12861–12864.
University of Basel

The rigid immobilization of lanthanoid chelating tags (LCTs) on biomacromolecules induces large paramagnetic effects, including pseudocontact shifts (PCS), residual dipolar couplings (RDC) and paramagnetic relaxation enhancement (PRE). These long-range effects provide unique and precise tools for the study of protein structures and dynamics by solution NMR. Conformational and positional invariant LCTs can provide accurate spatial information up to 200 Å and are therefore ideally suited to study protein interactions. The authors report a new, rationally designed LCT (Ln-M7-Nitro) containing an *ortho*-substituted pyridine activator that reacts rapidly and selectively with cysteine thiols. The LCT forms reduction-stable conjugates and induces very large PCS, RDC and PRE on both ubiquitin S57C and human carbonic anhydrase II S50C constructs under physiological conditions. The fast and clean ligation of the Ln-M7-Nitro LCT combined with its strong induced paramagnetic effects makes it an ideal structural probe for challenging applications.

Authors' comments:
"We are delighted to report a favourable combination of a highly rigid, methyl-substituted DOTA scaffold with a short and reduction-stable linker that shifts the limit of applications of paramagnetic probes in biomolecular NMR spectroscopy."



Regiodivergent Synthesis of Pyrazino-Indolines vs. Triazocines via α-Imino Carbenes Addition to Imidazolidines

A. Guarnieri-Ibáñez, A. de Aguirre, C. Besnard, A. I. Poblador-Bahamonde,* and J. Lacour,* *Chem. Sci.* **2021**, *12*, 1479-1485.
University of Geneva

N-Sulfonyl-1,2,3-triazoles are not only useful building blocks for various applications, but also precursors of α-imino carbenes under metal-catalyzed conditions. However, only a few studies have been reported on the reactivity of α-imino carbenes with aminals. The authors report the intramolecular reactivity of *N*-sulfonyl-1,2,3-triazoles with imidazolidines using $Rh_2(Piv)_4$ as the catalyst. Under optimized conditions, hexahydropyrazinoindoles, arising from formal [1,2]-Stevens rearrangement and Friedel-Crafts cyclization, were generated in good yield and moderate diastereoselectivity. A further treatment with TfOH led to tetrahydropyrazinoindoles. Interestingly, with unsymmetrically substituted imidazolidines, different products, namely 8-membered ring 1,3,6-triazocines, were observed. DFT calculations indicated a Curtin-Hammett behavior, with triazocines and pyrazinoindoles being the kinetic and thermodynamic products, respectively. This work further demonstrates the high potential of α-imino carbenes to generate a range of original nitrogen heterocycles.

Authors' comments:
"An enjoyable and effective synergy between experimental and computational approaches was key to explore and rationalize the reactivity. DFT computation of the Curtin-Hammett behaviour was particularly necessary to afford a detailed understanding of the divergent reaction pathways."