Issue 31; May 2019

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Recent Publications of ISHC Members

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Gold-Catalyzed 1,2-Acyloxy Migration/Coupling Cascade of Propargyl Diazoacetates: Synthesis of Isomycin Derivatives

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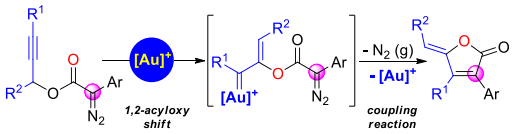
Org. Lett. **2019**, *21*, 1813–1817. **DOI:** 10.1021/acs.orglett.9b00392



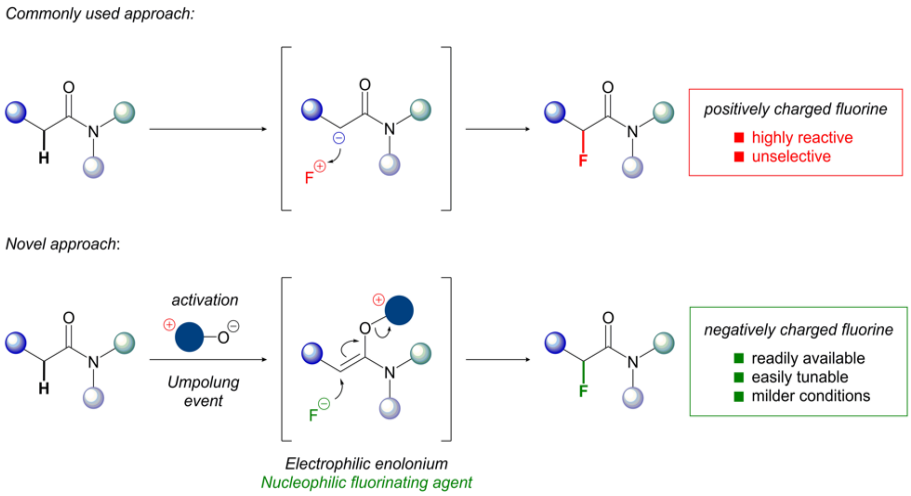
- Preferential 1,2-acyloxy shift of a propargyl ester with a diazo motif
- Novel cascade reaction, mild conditions & broad substrate scope
- Useful isomycin derivatives & amenable to gram-scale synthesis

Abstract: An efficient gold(I)-catalyzed carbocyclization reaction for the synthesis of isomycin derivatives from propargyl diazoacetates has been developed. The suggested cyclization pathway delineated the first example of a vinyl gold carbenoid species generated *in situ* from gold(I)-catalyzed 1,2-acyloxy migration and intercepted by a cross-coupling reaction with the remaining tethered diazo functionality. The use of protic additives was essential to regulating the reaction outcome by fine-tuning the catalytic preference of the gold(I)-complex.

α-Fluorination of Carbonyls with Nucleophilic Fluorine

Pauline Adler, Christopher J. Teskey, Daniel Kaiser, Marion Holy, Harald H. Sitte, and Nuno Maulide*
(nuno.maulide@univie.ac.at)

Nat. Chem. **2019**, *11*, 329–334. **DOI:** 10.1038/s41557-019-0215-z

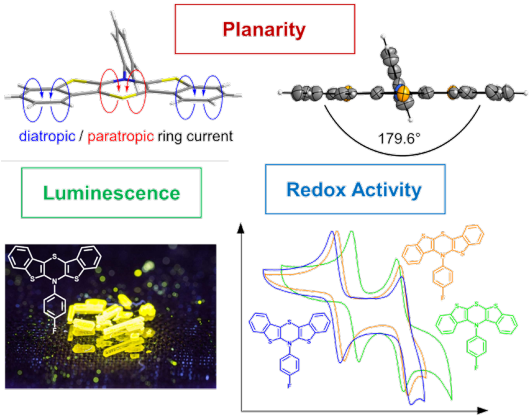


Abstract: There is significant interest from medicinal chemists in innovative methodologies that enable the synthesis of new fluorinated motifs. State-of-the-art syntheses of α-fluorinated carbonyl compounds invariably rely on electrophilic fluorinating agents, which can be strongly oxidizing and difficult to handle. Here we show that reversing the polarity of the enolate partner to that of an enolonium enables nucleophilic fluorinating agents to be used for direct chemoselective α-C–H-fluorination of amides. A fluorinated analogue of citalopram, a marketed antidepressant drug, is presented as an example of the preserved biological activity after fluorination.

Bis[1]benzothieno[1,4]thiazines: Planarity, Enhanced Redox Activity and Luminescence by Thieno-Expansion of Phenothiazine

Arno P. W. Schneeweis, Simone T. Hauer, Guido J. Reiss, and Thomas J. J. Müller* (thomasjj.mueller@hhu.de)

Chem. Eur. J. **2019**, *25*, 3582–3590. **DOI:** 10.1002/chem.201805085



Abstract: Twofold Buchwald–Hartwig aminations selectively furnish three regioisomers of bis[1]benzothieno-[1,4]thiazines; X-ray structure analyses and DFT calculations were corroborated for correlation of their electronic properties. All regioisomers outscore the parent compound phenothiazine with respect to a low-lying oxidation potential and reversible redox activity. The *anti-anti* bis[1]benzothieno[3,2-*b*:2′,3′-*e*][1,4]thiazines possess the lowest oxidation potentials in this series and displayed pronounced green luminescence in solution ($\Phi_F \approx 20$ %) and in the solid state. *Syn-anti* regioisomers were only weakly luminescent in solution, but showed aggregation-induced emission enhancement and solid-state luminescence. Most interestingly, X-ray structure analyses revealed that *anti-anti* derivatives have an amazingly coplanar structure of the pentacyclic anellated 1,4-thiazine system, emphasizing a structural similarity to heteroacenes. The calculated theoretical nucleus-independent chemical shifts additionally suggested that these 8π-electron core systems can be considered as the first electronically unbiased anellated 1,4-thiazines with antiaromatic character.

Synthetic Studies on Spirolides A and B.: Formation of the Upper Carbon Framework Based on a Lewis Acid Template-Catalyzed Diels–Alder Reaction

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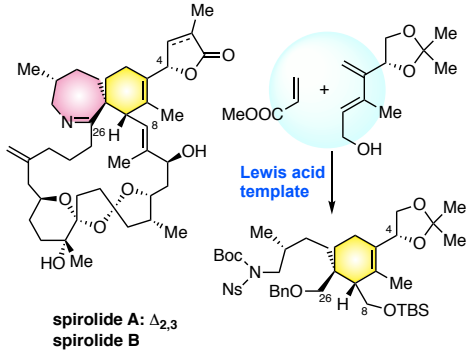
Chem. Eur. J. **2019**, *25*, 1543–1552. **DOI:** https://doi.org/10.1002/chem.201804977

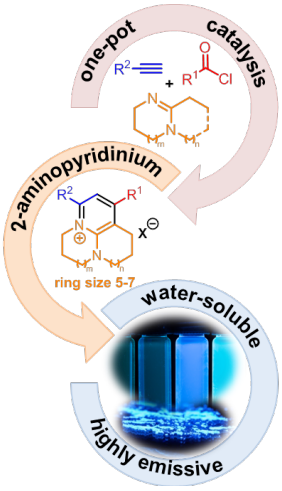


Abstract: The upper fragment of spirolides A and B, which are marine phycotoxins that exhibit strong antagonistic activities on nicotinic acetylcholine receptors, was constructed. The functionalized cyclohexene in spirolides was stereoselectively synthesized from the bicyclic lactone, which could be readily accessed by the Lewis acid template-catalyzed asymmetric Diels–Alder reaction of the pentadienol and methyl acrylate.

Synthesis of Water-Soluble Blue-Emissive Tricyclic 2-Amino-pyridinium Salts by Three-Component Coupling-(3+3)-Anellation

Olga Bakulina, Franziska K. Merkt, Tim-Oliver Knedel, Christoph Janaik, and Thomas J. J. Müller* (thomasjj.mueller@hhu.de)

Angew. Chem. Int. Ed. **2018**, *57*, 17240–17244. **DOI:** 10.1002/anie.201808665

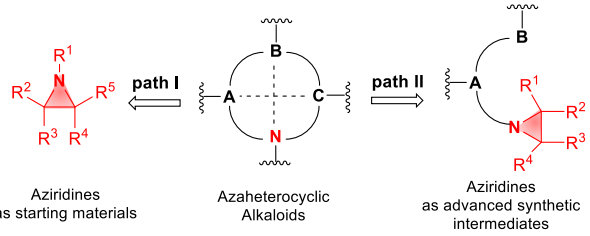


Abstract: The (3+3) anellation of alkynones and cyclic amidines is a novel and unexpected approach to intensively blue luminescent tricyclic 2-aminopyridinium salts with quantum yields Φ_F up to 63% in water. By implementation into a consecutive three-component reaction these title compounds are obtained rapidly and efficiently in a diversity-oriented fashion. Most interestingly, these bi- and tricyclic 2-aminopyridinium salts emit in dichloromethane and water solutions, making them interesting novel luminophore probes for bioanalytics, as well as in the solid state as blue emitters with tunable efficiency.

Deployment of Aziridines for the Synthesis of Alkaloids and Their Derivatives

Lingamurthy Macha, Matthias D'hooghe,* and Hyun-Joon Ha* (matthias.dhooghe@ugent.be or hjha@hufs.ac.kr)

Synthesis **2019**, *51*, 1491–1515. **DOI:** 10.1055/s-0037-1611715

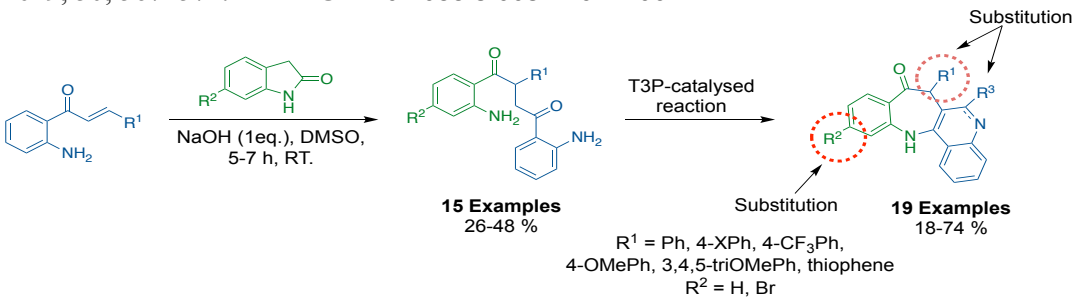


Abstract: Various (activated and non-activated) aziridines with diverse substitution patterns have been deployed successfully as starting materials for the synthesis of a wide variety of alkaloids via proper functionalization and aziridine ring transformation. Alternatively, the preparation and interception of reactive aziridine intermediates has been shown to constitute a suitable approach toward alkaloid synthesis as well. This review deals with aziridine-mediated syntheses of alkaloids, in which the aziridine is mobilized as either a substrate or an advanced synthetic intermediate.

A General Synthesis of 7-Phenyl-7,13-dihydro-8*H*-benzo[6,7]azepino[3,2-*c*]quinolin-8-ones

Jeremy C. Dobrowolski, Duyen H. T. Nguyen, Benjamin H. Fraser, Mohan Bhadbhade, David StC. Black, and Naresh Kumar* (n.kumar@unsw.edu.au)

Synlett **2019**, *30*, 567–572. **DOI:** 10.1055/s-0037-1612106

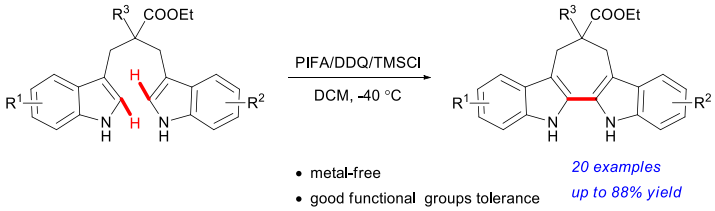


Abstract: Chemical compounds with the dibenzazepine moiety have found use in a range of areas, most prominently as drugs for the treatment of heart conditions, neuropsychiatric disorders, as well as in the search for novel structures for the treatment of cancer. However, access to azepine containing scaffolds with high degrees of substitution has remained a challenge and typically requires long synthesis strategies. The dihydrobenzo[6,7]azepino[3,2-*c*]quinolinones have remained largely unexplored with only a few examples in the literature showing the dihydrobenzazepine scaffold. We report a robust and simple synthetic pathway to access a novel series of 7-phenyl-7,13-dihydro-8*H*-benzo[6,7]azepino[3,2-*c*]quinolin-8-one derivatives via an initial addition-oxidation-ring cleavage cascade reaction under basic conditions in the presence of NaOH in DMSO. A subsequent T3P® in DMF catalysed cyclisation reaction gave the fused quinoline ring incorporating the one carbon unit from the DMF. Reaction with aldehydes or ketones with T3P® in ethyl acetate as the catalyst, gave the corresponding C6 substituted compounds. The key feature of this synthetic pathway is that it provides rapid access to a new class of heterocyclic compounds, namely benzo[6,7]azepino[3,2-*c*]quinolin-8-ones. A high level of substitution is possible around the core scaffold allowing for diverse functionalisation to be achieved. These derivatives possess moderate anti-cancer activity and have the potential for further development.

Convenient Synthesis of 6,7,12,13-Tetrahydro-5*H*-Cyclohepta[2,1-*b*:3,4-*b*′]diindole Derivatives Mediated by Hypervalent Iodine(III) Reagent

Lei Peng, Xiaofei Zhang,* and Chunhao Yang* (xiaofeizhang@simm.ac.cn or chyang@simm.ac.cn)

Molecules **2019**, *24*, 960 (1–13). **DOI:** 10.3390/molecules24050960

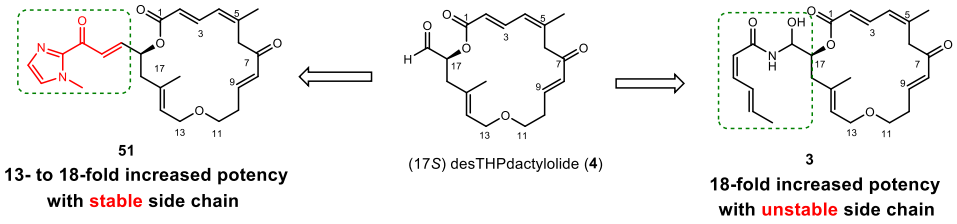


Abstract: Bisindolyl alkaloids represent a large family of natural and synthetic products that display various biological activities. Among the bisindole compounds, 6,7,12,13-tetrahydro-5*H*-cyclohepta[2,1-*b*:3,4-*b*′]diindoles have received little attention. Only two methods have been developed for the construction of the 6,7,12,13-tetrahydro-5*H*-cyclohepta[2,1-*b*:3,4-*b*′]diindole scaffold thus far, including the classical Fischer indole synthesis conducted by reacting indole-fused cycloheptanone and hydrazines, and the condensation reaction to build the seven-membered ring. Here, we report for the first time a new route to synthesize 6,7,12,13-tetrahydro-5*H*-cyclohepta[2,1-*b*:3,4-*b*′]diindoles through intramolecular oxidative coupling of 1,3-di(1*H*-indol-3-yl)propanes in the presence of PIFA, DDQ and TMSCl with moderate to excellent yields.

Synthesis and Antiproliferative Evaluation of New Zampanolide Mimics

Guanglin Chen, Manee Patanapongpibul, Ziran Jiang, Qiang Zhang, Shilong Zheng, Guangdi Wang, James D. White, and Qiao-Hong Chen* (qchen@csufresno.edu)

Org. Biomol. Chem. **2019**, *17*, 3830–3844. **DOI:** 10.1039/C9OB00556K

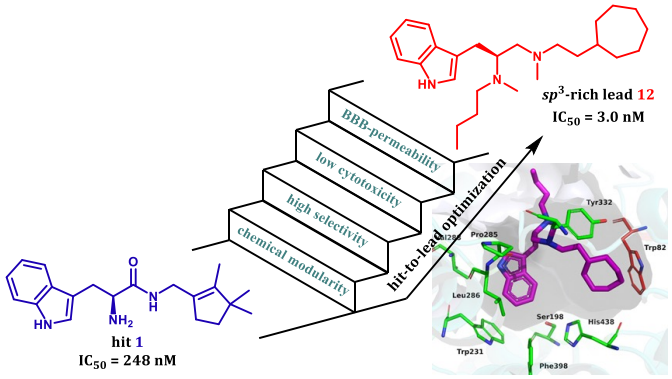


Abstract: (–)-Zampanolide is a marine microtubule-stabilizing macrolide that has been shown by *in vitro* experiments to be a promising anticancer lead compound. Through its unique covalent-binding with β-tubulin, zampanolide exhibits cytotoxic potency towards multi-drug resistant cancer cells that is superior to paclitaxel. However, the limited availability of zampanolide impedes its further *in vivo* evaluation as a viable drug candidate. Zampanolide is envisioned to become more drug-like if its chemically fragile side chain can be stabilized; hence, this project aims to develop mimics of zampanolide with a stable side chain using straightforward synthetic methods. To this end, twelve novel zampanolide mimics (**51**–**62**) with conjugated and planar side chains have been synthesized via a 24-step sequence for each mimic from commercially available 2-butyn-1-ol as starting material. A Horner–Wadsworth–Emmons reaction incorporates the α,β-unsaturated ketone side chain and also closes the core macrocycle. WST-1 cell proliferation assays in three docetaxel-sensitive and two docetaxel-resistant human prostate cancer cell models confirm that a suitably designed side chain can serve as a bioisostere for the *N*-acyl hemiaminal side chain in zampanolide. Mimic **52** with a 17*R* chiral center was identified as the optimal candidate with IC_{50} values of 0.29–0.46 μM against both docetaxel-sensitive (PC-3 and DU145) and docetaxel-resistant prostate cancer cell lines (PC-3/DTX and DU145/DTX). Zampanolide mimic **52** exhibited equivalent antiproliferative potency towards both docetaxel-sensitive and docetaxel-resistant cell lines, with relative resistance in the range of 0.9–1.6.

Tryptophan-derived Butyrylcholinesterase Inhibitors as Promising Leads Against Alzheimer's Disease

Anže Meden, Damijan Knez, Marko Jukič, Xavier Brazzolotto, Marija Gršič, Anja Pišlar, Abida Zahirović, Janko Kos, Florian Nachon, Jurij Svete, Stanislav Gobec,* and Uroš Grošelj* (stanislav.gobec@ffa.uni-lj.si or uros.groselj@fkkt.uni-lj.si)

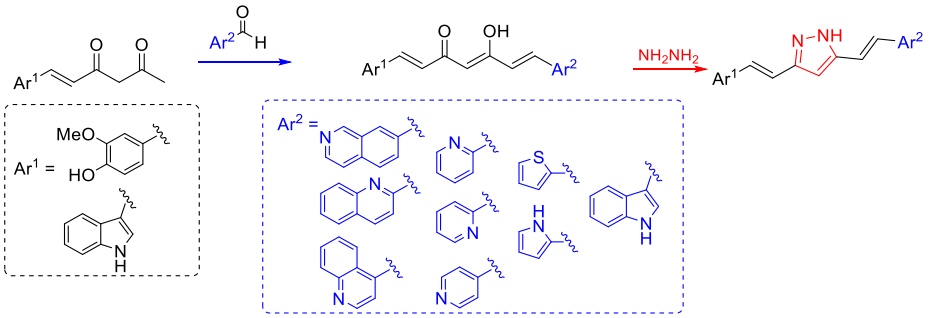
Chem. Commun. **2019**, *55*, 3765–3768. **DOI:** 10.1039/C9CC01330J



Abstract: Tryptophan-based selective nanomolar butyrylcholinesterase (BChE) inhibitors have been identified. They are defined according to their chemical modularity, novel binding mode revealed by five solved crystal structures with human BChE, low cytotoxicity, and predicted permeability of the blood-brain barrier. Altogether, these factors indicate their potential as unique lead compounds for symptomatic therapy against Alzheimer's disease.

Synthesis of Non-Symmetrical Nitrogen-Containing Curcuminoids in the Pursuit of New Anticancer Candidates

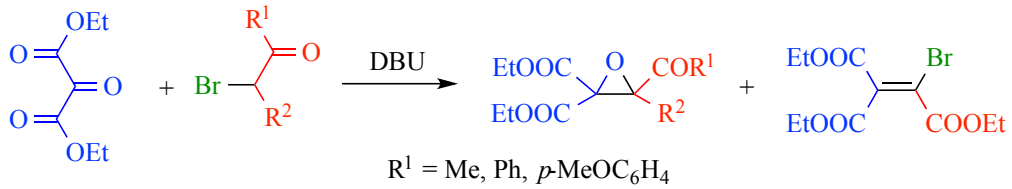
Atiruj Theppawong, Tim Van de Walle, Charlotte Grootaert, Kristof Van Hecke, Nathalie Catry, Tom Desmet, John Van Camp, and Matthias D'hooghe* (matthias.dhooghe@ugent.be)
ChemistryOpen **2019**, *8*, 236–247. **DOI:** 10.1002/open.201800287



Abstract: Curcumin is known to display pronounced anticancer effects and a variety of other biological activities. However, the low bioavailability and fast metabolism of this molecule present an issue of concern with respect to its medicinal applications. To address this issue, structural modifications of the curcumin scaffold can be envisioned as a strategy to improve both the solubility and stability of this chemical entity, without compromising its biological activities. Previous work in our group targeted the synthesis of symmetrical azaheteroaromatic curcuminoids, which showed better solubility and cytotoxicity profiles compared to curcumin. In continuation of that work, we now focused on the synthesis of non-symmetrical nitrogen-containing curcuminoids bearing both a phenolic and an azaheteroaromatic moiety. In that way, we aimed to combine good solubility, antioxidant potential and cytotoxic properties into one molecule. Some derivatives were selected for further chemical modification of their rather labile β-diketone scaffold to the corresponding pyrazole moiety. In this way, thirteen new non-symmetrical aza-aromatic curcuminoids and three pyrazole-based analogues were successfully synthesized in a yield of 11–69%. All newly synthesized analogues were evaluated for their antioxidant properties, reactive oxygen species (ROS) production, water solubility and anticancer activities. Several novel derivatives displayed good cytotoxicity profiles compared to curcumin, in combination with an improved water solubility and stability, and were thus identified as potential hit scaffolds for further optimization studies.

A Facile Synthesis of Oxiranes Possessing Three or Four Carbonyl Groups

Haruyasu Asahara,* Shuhei Kikuchi, Yuto Unno, Soichi Yokoyama, Kotaro Yoshioka, Shinki Tani, Kazuto Umezu, and Nagatoshi Nishiwaki* (nishiwaki.nagatoshi@kochi-tech.ac.jp)
Curr. Org. Chem. **2019**, *23*, 97–102. **DOI:** 10.2174/1385272823666190112103813



R^1 = Me, Ph, *p*-$MeOC_6H_4$
R^2 = H, COOEt

Abstract: Tri-carbonylated oxiranes were efficiently synthesized by condensing a vicinal tricarbonyl compound with α-bromoketones in the presence of a base. This protocol was applicable to α-bromo-β-keto esters to create tetra-carbonylated oxiranes, from which trifunctionalized bromoalkene was competitively formed. The ratio of these compounds was influenced by the solvent and reaction temperature.