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Recent Publications of ISHC Members

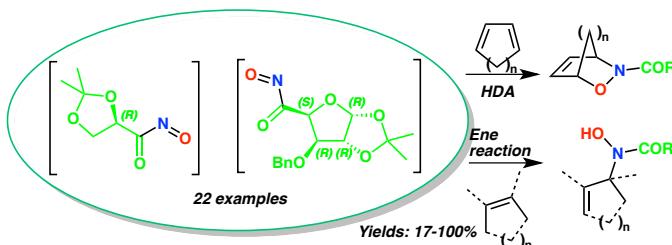
Issue 52; February 2021

Nitrosocarbonyl Carbohydrate Derivatives: Hetero Diels–Alder and Ene Reaction Products for Useful Organic Synthesis

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Synthesis **2021**, *53*, 574–586.

DOI: [10.1055/s-0040-1707276](https://doi.org/10.1055/s-0040-1707276)



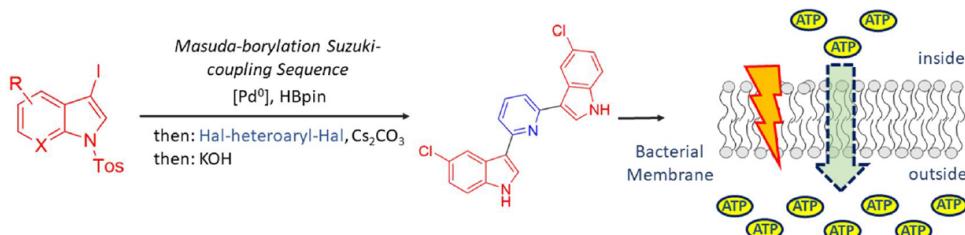
Abstract: The generation and trapping of two new nitrosocarbonyl intermediates bearing carbohydrate-based chiral substituents is achieved by the mild oxidation of the corresponding nitrile oxides with tertiary amine *N*-oxides. Their capture with suitable dienes and alkenes afforded the corresponding HDA cycloadducts and ene adducts from fair to excellent yields. The entire methodology looks highly promising by the easy conversion of aldoximes into hydroxymoyl halides, widening the access to nitrosocarbonyls, versatile tools in organic synthesis.

Nature-Inspired (di)Aazine-Bridged Bisindole Alkaloids with Potent Antibacterial *In Vitro* and *In Vivo* Efficacy against Methicillin-Resistant *Staphylococcus aureus*

Nidja Rehberg, Gereon A. Sommer, Daniel Drießen, Marco Kruppa, Emmanuel T. Adeniyi, Shang Chen, Lin Wang, Karina Wolf, Boris O. A. Tasch, Thomas R. Ioerger, Kui Zhu, Thomas J. J. Müller,* and Rainer Kalscheuer* (thomasjj.mueller@hhu.de or rainer.kalscheuer@hhu.de)

J. Med. Chem. **2020**, *63*, 12623–12641.

DOI: [10.1021/acs.jmedchem.0c00826](https://doi.org/10.1021/acs.jmedchem.0c00826)



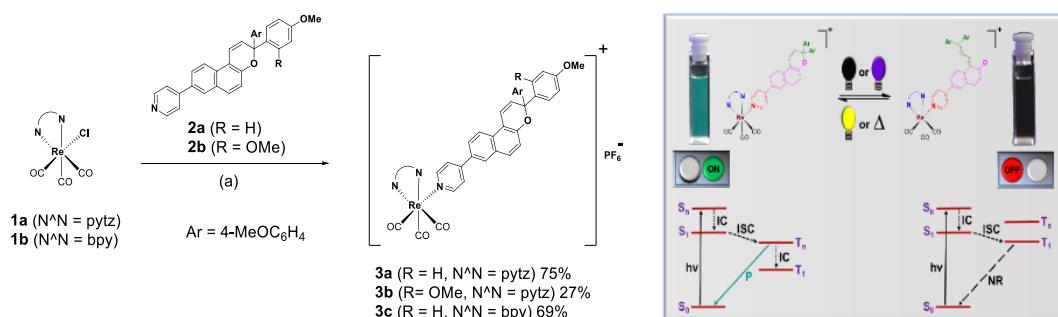
Abstract: Natural bisindole alkaloids such as Hyrtinadine A and Alocasin A, which are known to exhibit diverse bioactivities, provide promising chemical scaffolds for drug development. By optimizing the Masuda borylation–Suzuki coupling sequence, a library of various natural product-derived and non-natural (di)azine-bridged bisindoles was created. While unsubstituted bisindoles were devoid of antibacterial activity, 5,5'-dichloro derivatives were highly active against methicillin-resistant *Staphylococcus aureus* (MRSA) and further Gram-positive pathogens at minimal inhibitory concentrations ranging from 0.20 to 0.78 μ M. These compounds showed strong bactericidal killing effects but only moderate cytotoxicity against human cell lines. Furthermore, the two front-runner compounds **4j** and **4n** exhibited potent *in vivo* efficacy against MRSA in a mouse wound infection model. Although structurally related bisindoles were reported to specifically target pyruvate kinase in MRSA, antibacterial activity of **4j** and **4n** is independent of pyruvate kinase. Rather, these compounds lead to bacterial membrane permeabilization and cellular efflux of low molecular-weight molecules.

Quenching of the Phosphorescence of Thermally Reversible Photochromic Naphthopyran Re(I) Complexes Initiated by Either Visible or Ultraviolet Radiation

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Dalton Trans. **2021**, *50*, 830–834.

DOI: [10.1039/d0dt04220j](https://doi.org/10.1039/d0dt04220j)



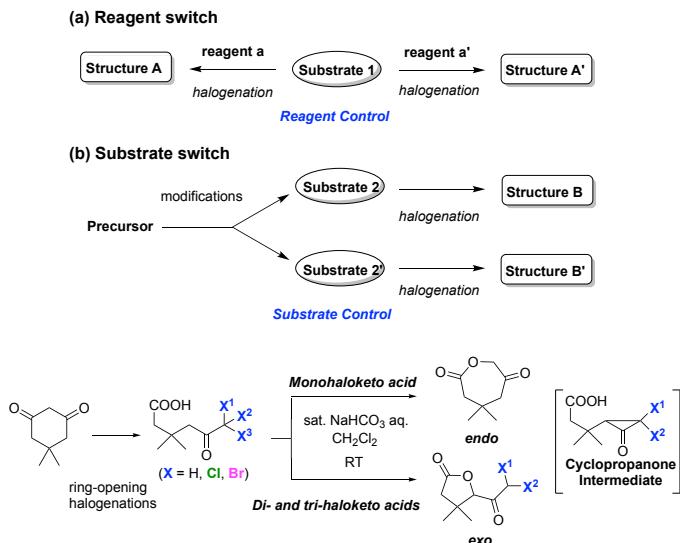
Abstract: Re(I) complexes bearing thermally reversible photochromic naphthopyran axial ligands undergo highly efficient, reversible phosphorescence quenching actuated by either visible or UV irradiation. The photoinduced quenching of the triplet metal-to-ligand charge-transfer (³MLCT) emission is interpreted based on changes in the relative energies of the excited states.

Halogen-Induced Controllable Cyclizations as Diverse Heterocycle Synthetic Strategy

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Molecules **2020**, *25*, 6007 (1–33).

DOI: [10.3390/molecules25246007](https://doi.org/10.3390/molecules25246007)



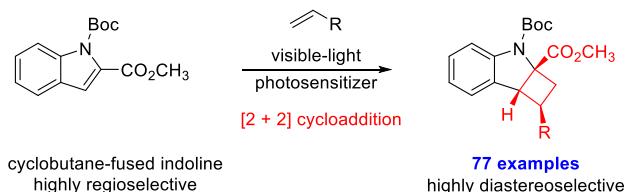
Abstract: Recently, cyclizations induced by halogen groups that allow the production of diverse targets and the structural reorganization of organic molecules have attracted significant attention from synthetic chemists. Electrophilic halogen atoms activate unsaturated and saturated hydrocarbon moieties by generating halonium intermediates, followed by the attack of carbon-containing, nitrogen-containing, oxygen-containing, and sulfur-containing nucleophiles to give highly functionalized carbocycles and heterocycles. New transformations of halogenated organic molecules that can control the formation and stereoselectivity of the products, according to the difference in the size and number of halogen atoms, have recently been discovered. These unique cyclizations may possibly be used as efficient synthetic strategies with future advances.

Photocatalytic Dearomative Intermolecular [2 + 2] Cycloaddition of Heterocycles for Building Molecular Complexity

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J. Org. Chem. **2021**, *86*, 1730–1747.

DOI: [10.1021/acs.joc.0c02547](https://doi.org/10.1021/acs.joc.0c02547)



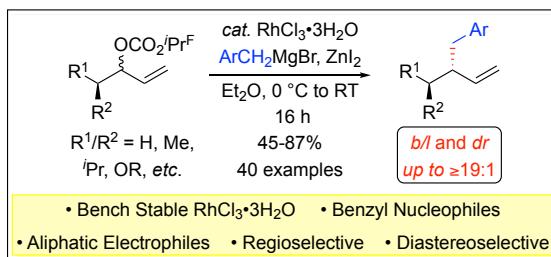
Abstract: Indole and indoline rings are important pharmacophoric scaffolds found in marketed drugs, agrochemicals, and biologically active molecules. The [2 + 2] cycloaddition reaction is a versatile strategy for constructing architecturally interesting, sp³-rich cyclobutane-fused scaffolds with potential applications in drug discovery programs. A general platform for visible-light mediated intermolecular [2 + 2] cycloaddition of indoles with alkenes has been realized. A substrate-based screening approach led to the discovery of tertbutyloxycarbonyl (Boc)-protected indole-2-carboxyesters as suitable motifs for the intermolecular [2 + 2] cycloaddition reaction. Significantly, the reaction proceeds in good yield with a wide variety of both activated and unactivated alkenes, including those containing free amines and alcohols, and the transformation exhibits excellent regio- and diastereoselectivity. Moreover, the scope of the indole substrate is very broad, extending to previously unexplored azaindole heterocycles that collectively afford fused cyclobutane containing scaffolds that offer unique properties with functional handles and vectors suitable for further derivatization. DFT computational studies provide insights into the mechanism of this [2 + 2] cycloaddition, which is initiated by a triplet-triplet energy transfer process. The photocatalytic reaction was successfully performed on a 100 g scale to provide the dihydroindole analog.

Regio- and Diastereoselective Rhodium-Catalyzed Allylic Substitution with Unstabilized Benzyl Nucleophiles

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DOI: [10.1002/anie.202008071](https://doi.org/10.1002/anie.202008071)

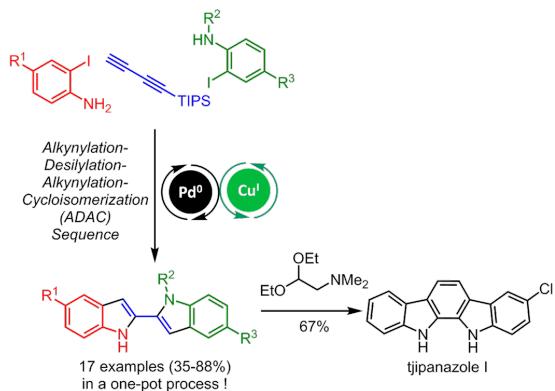


Abstract: We have developed a highly regio- and diastereoselective rhodium-catalyzed allylic substitution of challenging alkyl-substituted secondary allylic carbonates with benzylzinc reagents, which are prepared from widely available benzyl halides. This process utilizes rhodium(III) chloride as a commercially available, high-oxidation state and bench-stable pre-catalyst to provide a rare example of a regio- and diastereoselective allylic substitution in the absence of an exogenous ligand. This reaction tolerates electronically diverse benzylzinc nucleophiles and an array of functionalized and/or challenging aliphatic allylic electrophiles. Finally, the configurational fluxionality of the rhodium-allyl intermediate is exploited to develop a novel diastereoselective process for the construction of vicinal acyclic ternary/ternary stereogenic centers, in addition to a cyclic ternary/quaternary derivative.

Alkynylation-Desilylation-Alkynylation-Cycloisomerization (ADAC) Three-Component Synthesis of 2,2'-Biindolyls – Concise Synthesis of Tjipanazole I

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ChemCatChem **2021**, *13*, 217–220.

DOI: 10.1002/cctc.202001607



Abstract: A sequentially Pd/Cu-catalyzed alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) process in the sense of a consecutive three-component reaction using TIPS-butadiyne as a four carbon building block gives a rapid and efficient access to 2,2'-biindolyls in a one-pot fashion. This facile entry to unsymmetrically substituted title compounds has been employed in a concise two-step synthesis of the alga alkaloid tjipanazole I.

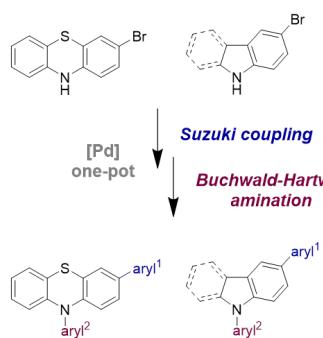
Concatenating Suzuki Arylation and Buchwald–Hartwig Amination by a Sequentially Pd-Catalyzed One-Pot Process—Consecutive Three-Component Synthesis of C,N-Diarylated Heterocycles

Laura Mayer, Regina Kohlbecher, and Thomas J. J. Müller* (thomasjj.mueller@hhu.de)

Chem. Eur. J. **2020**, *26*, 15130–15134.

DOI: 10.1002/chem.202003837

Sequentially Pd-catalyzed One-Pot Arylation-Amination Sequence



Abstract: The concatenation of Suzuki coupling and Buchwald–Hartwig amination in a consecutive multicomponent reaction opens a concise, modular and efficient one-pot approach to diversely functionalized heterocycles, as exemplified for 3,10-diaryl 10H-phenothiazines, 3,9-diaryl 9Hcarbazoles, and 1,5-diaryl 1H-indoles, in high yields starting from simple starting materials. Moreover, this one-pot reaction is a sequentially palladium-catalyzed process that does not require additional catalyst loading after the first coupling step.

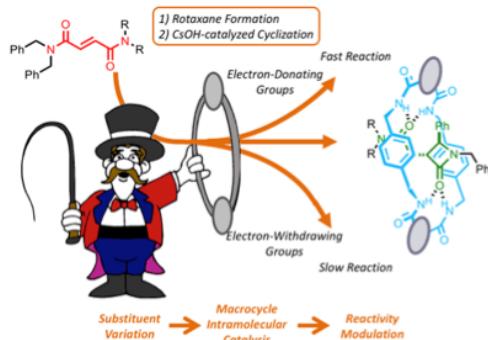
Cyclization of Interlocked Fumaramides into β -Lactams: Experimental and Computational Mechanistic Assessment of the Key Intercomponent Proton Transfer and the Stereocontrolling Active Pocket

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Chem. Sci. **2021**, *12*, 747–756.

DOI: 10.1039/DOSC05757F



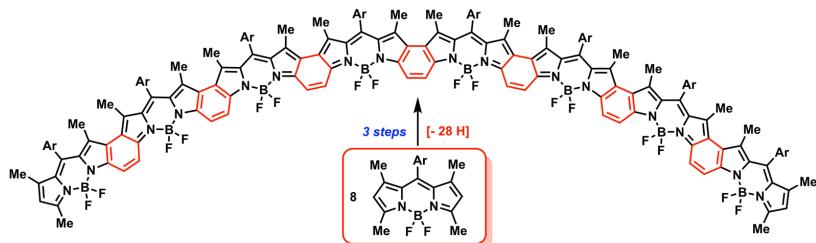
Abstract: A detailed mechanistic study of the diastereoselective CsOH-promoted cyclization of interlocked fumaramides to give β -lactams is described. The mechanistic analysis comprises the experimental evaluation of the structure-reactivity relationship for a wide range of fumaramide [2]rotaxanes (Hammett-plots), KIE studies with deuterium-labelled interlocked fumaramides and computational analysis of two alternative mechanistic pathways for the cyclization process. The obtained results confirm that: (a) the rate-determining step is the deprotonation of the *N*-benzyl group of the thread by the amide group of the macrocycle generated by the external base, (b) the polyamide macrocycle plays an important role not only as activating element but also as the stereodifferentiating factor responsible for the observed diastereoselection and (c) the higher flexibility of the adamantly core speeds up the cyclization process in diadamantyl-derived rotaxanes.

Extended Benzene-Fused Oligo-BODIPYs: In Three Steps to a Series of Large, Arc-Shaped, Near-Infrared Dyes

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DOI: 10.1002/anie.202012335



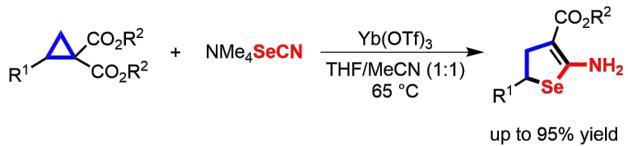
Abstract: We present a straightforward, three-step synthesis engaging an oligomerization and subsequent one-pot oxidation step to form fully conjugated, benzene-fused oligo-BODIPYs from simple BODIPY precursors. FeCl_3 serves as an efficient, bifunctional oxidant for a (multiple) cyclization/desaturation process, applied to ethylene-bridged dimeric, trimeric and oligomeric species to transform linking ethano units into stiff benzene fusions between unsubstituted β -positions of each BODIPY unit. The structural integrity was verified by X-ray crystallography, and all target compounds were studied in detail by photophysical, electrochemical and computational means. The main S_1 excited state gradually converges to a structure-specific excitation limit, displaying a strong shift of the absorption event from about 500 nm (BODIPY monomer) to 955 nm (octamer) with attenuation coefficients up to ca. $500\,000\,\text{M}^{-1}\,\text{cm}^{-1}$.

(3 + 2)-Cycloaddition of Donor–Acceptor Cyclopropanes with Selenocyanate: Synthesis of Dihydroselenophenes and Selenophenes

Anu Jacob, Peter G. Jones, and Daniel B. Werz* (d.werz@tu-braunschweig.de)

Org. Lett. **2020**, 22, 8720–8724.

DOI: [10.1021/acs.orglett.0c03329](https://doi.org/10.1021/acs.orglett.0c03329)



Abstract: We present a Lewis-acid-catalyzed (3 + 2)-cycloaddition of donor–acceptor cyclopropanes and selenocyanate (as its tetramethylammonium salt) for the synthesis of dihydroselenophenes. The transformation proceeded with moderate to excellent yields and showed a high functional group tolerance. Further oxidation using DDQ delivered selenophenes.