

The ISHC Bulletin

Recent Publications of ISHC Members

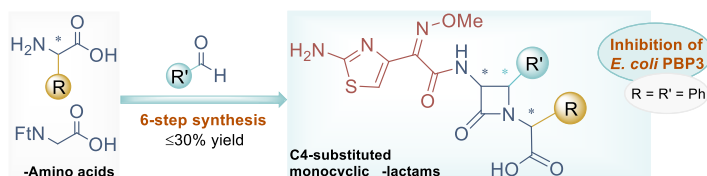
Issue 41; March 2020

Synthesis and Penicillin-Binding Protein Inhibitory Assessment of Dipeptidic 4-Phenyl- β -Lactams from α -Amino Acid-Derived Imines

Lena Decuyper, Marko Jukič, Izidor Sosič, Ana Maria Amoroso, Olivier Verlaine, Bernard Joris, Stanislav Gobec, and Matthias D'hooghe* (matthias.dhooghe@ugent.be)

Chem. Asian J. **2020**, *15*, 51–55.

DOI: 10.1002/asia.201901470



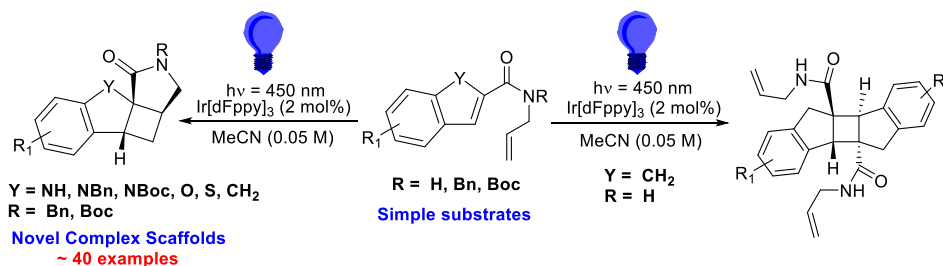
Abstract: Monocyclic β -lactams revive the research field on antibiotics, which are threatened by the emergence of resistant bacteria. A six-step synthetic route was developed, providing easy access to new 3-amino-1-carboxymethyl-4-phenyl- β -lactams, of which the penicillin-binding protein (PBP) inhibitory potency was demonstrated biochemically.

Synthesis of Cyclobutane-Fused Tetracyclic Scaffolds via Visible-Light Photocatalysis for Building Molecular Complexity

Martins S. Oderinde,* Edna Mao, Antonio Ramirez, Joseph Pawluczyk, Christine Jorge, Lyndon A. M. Cornelius, James Kempson, Muthalagu Vetrichelvan, Manivel Pitchai, Anuradha Gupta, Arun Kumar Gupta, Nicholas A. Meanwell, Arvind Mathur, and T. G. Murali Dhar* (martin.oderinde@bms.com or murali.dhar@bms.com)

J. Am. Chem. Soc. **2020**, *142*, 3094–3103.

DOI: 10.1021/jacs.9b12129



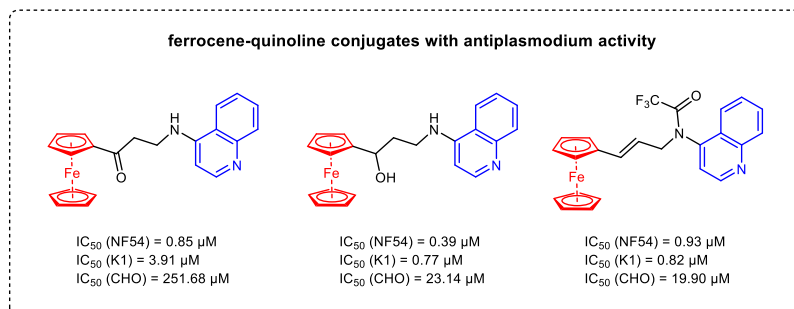
Abstract: We describe the synthesis through visible-light photocatalysis of novel functionalized tetracyclic scaffolds that incorporate a fused azabicyclo[3.2.0]heptan-2-one motif, which are structurally interesting cores with potential in natural product synthesis and drug discovery. The synthetic approach involves an intramolecular [2+2] cycloaddition with concomitant dearomatization of the heterocycle via an energy transfer process promoted by an iridium-based photosensitizer, to build a complex molecular architecture with three stereogenic centers from relatively simple, achiral precursors. These fused azabicyclo[3.2.0]heptan-2-one-based tetracycles were obtained in high yield (generally >99%) and with excellent diastereoselectivity (>99:1). The late-stage derivatization of a bromine-substituted, tetracyclic indoline derivative with alkyl groups, employing a mild Negishi C–C bond forming protocol as a means of increasing structural diversity, provides additional modularity that will enable the delivery of valuable building blocks for medicinal chemistry. DFT calculations were used to compute the T₁–S₀ free energy gap of the olefin-tethered precursors and also to predict their reactivities based on triplet state energy transfer and transition state energy feasibility.

Design and Synthesis of Novel Ferrocene-Quinoline Conjugates and Evaluation of Their Electrochemical and Antiplasmodium Properties

Aleksandra Minić,* Tim Van de Walle, Kristof Van Hecke, Jill Combrinck, Peter J. Smith, Kelly Chibale, and Matthias D'hooghe* (aleksandra.minic989@gmail.com or matthias.dhooghe@ugent.be)

Eur. J. Med. Chem. **2020**, *187*, 111963 (1–14).

DOI: 10.1016/j.ejmech.2019.111963



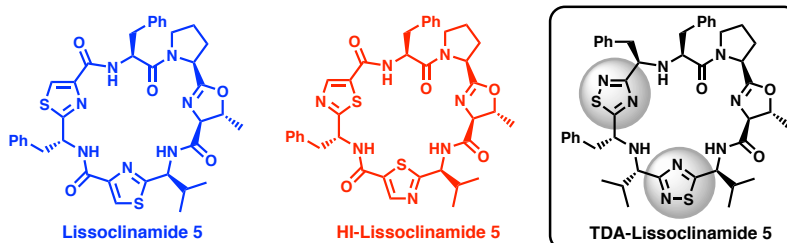
Abstract: The tropical disease malaria is responsible for more than 400,000 deaths annually, especially in Southeast Asia and Africa. Although the number of malaria cases is declining, there still is an urgent need for novel antimalarial agents. The emergence of hybrid antimalarial agents and the precedence set by the antimalarial drug ferroquine (FQ) prompted us to design new ferrocene-containing quinoline structures. Herein, we report the efficient synthesis of three different series of ferrocene-quinoline conjugates and a class of ferrocene-containing heterotricycles in good to high yields. For all twenty novel ferrocenyl derivatives, electrochemical properties were investigated using cyclic voltammetry and antiplasmodium evaluation against a chloroquine-susceptible NF54 strain of the human malaria parasite *Plasmodium falciparum* was conducted, pointing to three compounds showing submicromolar potency. Subsequently, cytotoxicity assays against a Chinese Hamster Ovarian cell line and evaluation against a chloroquine-resistant strain of *Plasmodium falciparum* for these three compounds revealed selective and promising antiplasmodium activity.

Contemplating 1,2,4-Thiadiazole-Inspired Cyclic Peptide Mimics: A Computational Investigation

Sida Xie, Paul V. Bernhardt, Lawrence R. Gahan,* and Craig M. Williams* (gahan@uq.edu.au or c.williams3@uq.edu.au)

Aust. J. Chem. **2019**, *72*, 894–899.

DOI: 10.1071/CH19248



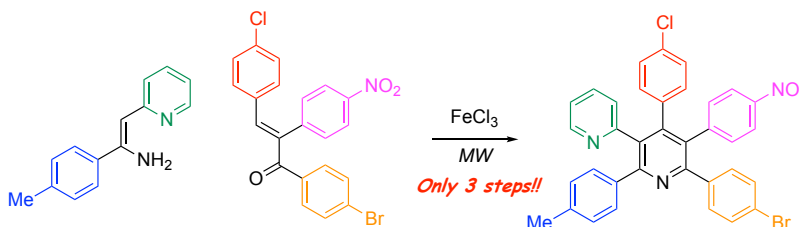
Abstract: We have previously described our interest in taking inspiration from the cavitand architectures revealed in the marine derived cyclic peptides lissoclinamide 5 and ascidiacyclamide. For decades chemists have compared these systems to macrocyclic ligands, and in turn as possible mediators of metal-ion transport via metal ion complexation. In continuation of our studies the current report details a computational study that was aimed at evaluating the stability, and potential for copper(II) ion binding to a new hypothetical system consisting of novel valine- and phenylalanine-derived 1,2,4-thiadiazole units in place of naturally occurring 4-carboxy-1,3-thiazole units found in lissoclinamide 5. The results suggest that one mimic, TDA-lissoclinamide, may be capable of forming two individual complexes 1) one with a single Cu(II) ion, and 2) one with two Cu(II) ions. Such observations set the stage for synthetic and experimental investigations.

Three Step Synthesis of Fully and Differently Arylated Pyridines

Mao Arita, Soichi Yokoyama, Haruyasu Asahara, and Nagatoshi Nishiwaki*
(nishiwaki.nagatoshi@kochi-tech.ac.jp)

Eur. J. Org. Chem. **2020**, 466–474.

DOI: 10.1002/ejoc.201901663



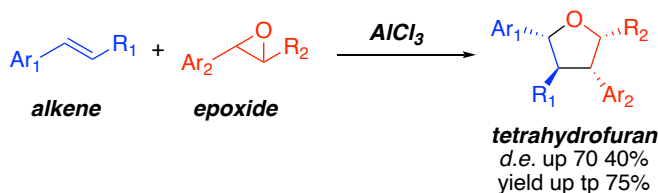
Abstract: Condensation of β -(2-pyridyl)enamine and α,β -unsaturated ketone in the presence of FeCl_3 under air afforded highly substituted pyridines. In this transformation, FeCl_3 acted as not only an acid catalyst but also an oxidant for the intermediate dihydropyridine. The substituents could be easily modified by altering the substrates to obtain tri- and tetraarylpiperidines including bipyridines and terpyridine. Synthesis of differently substituted pentaarylpiperidines was consequently achieved *via* only three steps from commercially available reagents with simple experimental manipulations.

Formal [3+2] Cycloaddition Reactions of Electron-Rich Aryl Epoxides with Alkenes Under Lewis Acid Catalysis Affording Tetrasubstituted Tetrahydrofurans

Víctor E. Macías-Villamizar, Luís Cuca-Suárez, Santiago Rodríguez, and Florenci V. González*
(fgonzale@uji.es)

Molecules **2020**, *25*, 692 (1–8).

DOI: 10.3390/molecules25030692



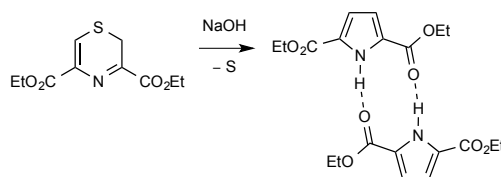
Abstract: We report on the regio- and stereoselective synthesis of tetrahydrofurans by reaction between epoxides and alkenes in the presence of a Lewis acid. This is an unprecedented formal [3 + 2] cycloaddition reaction between an epoxide and an alkene. The chemical reaction represents a very concise synthesis of tetrahydrofurans from accessible starting compounds.

Diethyl Pyrrole-2,5-Dicarboxylate

R. Alan Aitken,* Charles Bloomfield, Liam J. R. McGeachie, and Alexandra M. Z. Slawin
(raa@st-and.ac.uk)

Molbank **2020**, *2020*, M1117 (1–6).

DOI: 10.3390/M1117



X-ray structure

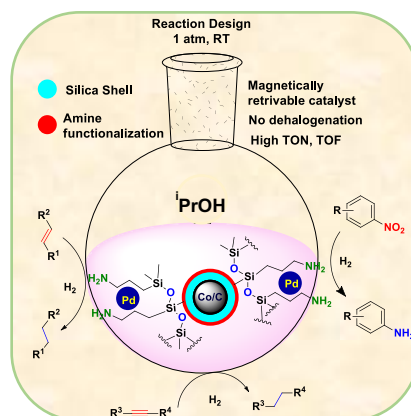
Abstract: The title compound was obtained in moderate yield by a new and unexpected base-induced ring contraction from a 1,4-thiazine precursor. Its X-ray structure showing hydrogen bonded dimers was compared with those of other crystallographically characterised 2-acylpyrroles.

Palladium Nanocatalysts Encapsulated on Porous Silica @ Magnetic Carbon-Coated Cobalt Nanoparticles for Sustainable Hydrogenation of Nitroarenes, Alkenes and Alkynes

Gunjan Purohit, Diwan S. Rawat,* and Oliver Reiser* (dsrawat@chemistry.du.ac.in or oliver.reiser@chemie.uni-regensburg.de)

ChemCatChem 2020, 12, 569–575.

DOI: 10.1002/cctc.201901371



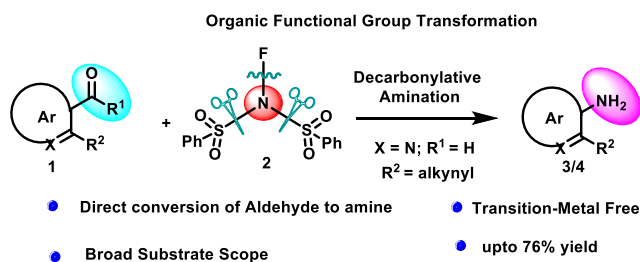
Abstract: Palladium nanoparticles were impregnated on porous silica shell carbon-coated cobalt nanoparticles, resulting in a magnetically retrievable material that was evaluated in the catalytic hydrogenation of nitroarenes, alkenes and alkynes. The prepared material was characterized by HR-XRD, HR-TEM, elemental mapping EDX, ICP-OES and XPS analyses, revealing highly dispersed palladium nanoparticles within the porous platform that could account for the high activity observed. Mild reaction conditions, easy retrievability of the catalyst with the aid of an external magnet, recycling in four runs with a total leaching of 19 ppm (1.2% of the initially employed Pd amount), and high stability makes this material attractive for sustainable and environmentally benign applications.

Triple-Bond Directed Csp²-N Bond Formation with *N*-Fluorobenzenesulfonimide as Aminating Source: One-Step Transformation of Aldehydes into Amines

Sushmita, Trapti Aggarwal, Norio Shibata, and Akhilesh K. Verma* (averma@acbr.du.ac.in)

Chem. Eur. J. 2019, 25, 16063–16067.

DOI: 10.1002/chem.201903495



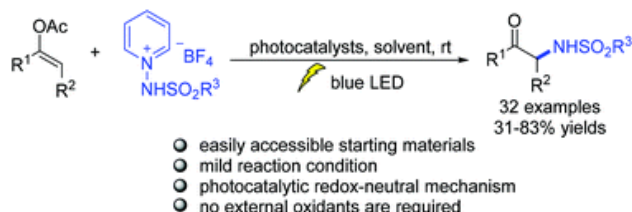
Abstract: A metal-free versatile triple bond directed approach for the decarbonylative C–H amination of *ortho*-alkynyl quinoline/pyridine aldehyde using *N*-fluorobenzenesulfonimide as nitrogen source under mild reaction conditions has been described. The designed reaction strategy was triggered by trapping of fluorine through base with subsequent attack of bis(phenylsulfonyl)-λ²-azane on carbonyl carbon of heterocycle which gradually converted to amine via Curtius type rearrangement. This protocol provides one-step approach for the conversion of aldehyde to amine in good yields. The synthesized amine compounds were successfully transformed into biologically important pyrroloquinolines/pyridines.

Visible-Light Promoted Sulfonamidation of Enol Acetates to α -Amino Ketones Based on Redox-Neutral Photocatalysis

Lin Wang, Pi Cheng,* Xinhao Wang, Wei Wang, Jianguo Zeng, Yun Liang, and Oliver Reiser
(picheng@hunau.edu.cn)

Org. Chem. Front. **2019**, *6*, 3771–3775.

DOI: 10.1039/c9qo01119f



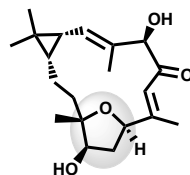
Abstract: A visible-light mediated photoredox-catalyzed sulfonamidation of enol acetates to α -amino ketones has been developed. Upon irradiation with a blue LED (λ 425 \pm 15 nm) in the presence of catalytic amounts of Ir(ppy)₃ (2 mol%), *N*-arylsulfonyl-1-aminopyridine salts were transformed into *N*-centered radical intermediates, which then underwent coupling with enol acetates to give α -sulfonylamino ketones in up to 83% yield. The process features mild and operationally simple reaction conditions and does not require an external oxidant.

EBC-342: A Novel Tetrahydrofuran Moiety Containing Casbane from the Australian Rainforest

Lidia A. Maslovskaya, Andrei I. Savchenko, Elizabeth H. Krenske, Sharon Chow, Victoria A. Gordon, Paul W. Reddell, Carly J. Pierce, Peter G. Parsons, Glen M. Boyle, and Craig M. Williams*
(c.williams3@uq.edu.au)

Eur. J. Org. Chem. **2020**, 1042–1045.

DOI: 10.1002/ejoc.202000017

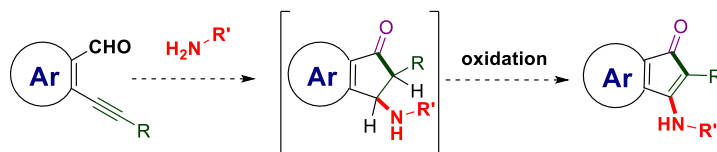


Abstract: *Croton insularis* – a small tree growing in eastern Australian rainforests, produces many casbane diterpenes. On this occasion a new casbane family member is reported, which contains a novel tetrahydrofuran ring (i.e., EBC-342). To confirm structure, along with relative and absolute stereochemistry, both DP4 and TD DFT CD computational methods were utilized.

Transition-Metal-Free Reverse Reactivity of (2-Alkynyl)-Arylaldimines: Assembly of Functionalized Amino-Indinones

Kapil Mohan Saini, Rakesh K. Saunthwal, Sushmita, and Akhilesh K. Verma* (averma@acbr.du.ac.in)
Chem. Eur. J. **2020**, *26*, 1017–1021.

DOI: 10.1002/chem.201904294



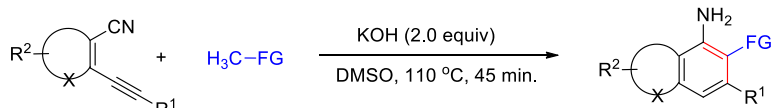
Abstract: Transition-metal-free regioselective synthesis of functionalized amino-indenones by the reaction of *ortho*-alkynylaldehydes with a broad range of primary amines *via* intramolecular cyclization has been described. The designed reaction proceeds *via* KOH-mediated Prins-type cyclization and DMSO-promoted oxidation of cyclopent-2-en-1-one system. The proposed mechanism and role of solvent were well supported by control experiments. For the first time, we have disclosed the reverse reactivity of (2-alkynyl)-arylaldimines in a super basic system.

Aza-Henry Reaction: Synthesis of Nitronaphthylamines from 2-(Alkynyl)benzonitriles

Shalini Verma, Manoj Kumar, and Akhilesh K. Verma* (averma@acbr.du.ac.in)

Org. Lett. **2020**, *22*, 130–134.

DOI: 10.1021/acs.orglett.9b04045



X = CH, N, O, S; R¹ = Aryl, alkyl, heteroaryl; R² = NO₂, F, CN, Aryl, alkyl, heteroaryl; FG = NO₂, CN, COPh

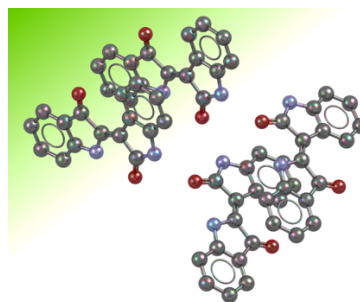
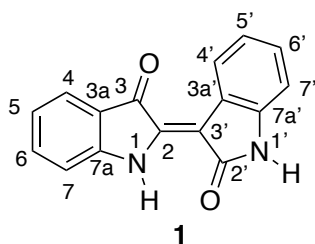
Abstract: A transition-metal-free approach for construction of nitronaphthylamines has been developed for the first time through aza-Henry, chemo- and regioselective annulation of 2-alkynylbenzonitriles with nitromethane. Additionally, the strategy provides an elegant, operationally simple and atom-economical route for the synthesis of nitroamino substituted heterocyclic scaffolds, featuring a range of sensitive functional groups. The reaction could also devise acetonitrile and acetophenone as nucleophile. The protocol has been successfully implemented for late stage modification of bioactive molecules.

A Theoretical and Spectroscopic (NMR and IR) Study of Indirubin in Solution and in the Solid State

Ibon Alkorta,* José Elguero, Christophe Dardonville, Felipe Reviriego, Dolores Santa María, Rosa M. Claramunt, Marta Marín-Luna (ibon@iqm.csic.es)

J. Phys. Org. Chem. **2020**, *33*, e4043 (1–11).

DOI: 10.1002/poc.4043



Abstract: The infrared spectrum of indirubin **1**, a natural product with several biomedical properties, in the solid state and the ¹H, ¹³C and ¹⁵N NMR spectra in DMSO-*d*₆ solution as well as the ¹³C and ¹⁵N CPMAS spectra have been recorded. Taking account of *E/Z* isomerism about the 2-3' bond and the oxo/hydroxy tautomerism, there are twenty six possible isomers and tautomers for indirubin. To explore both *E/Z* isomerism and oxo/hydroxy tautomerism different types of calculations (B3LYP, GIAO and GIPAW) have been carried out. Experimental and calculated values were compared yielding commensurate results.