

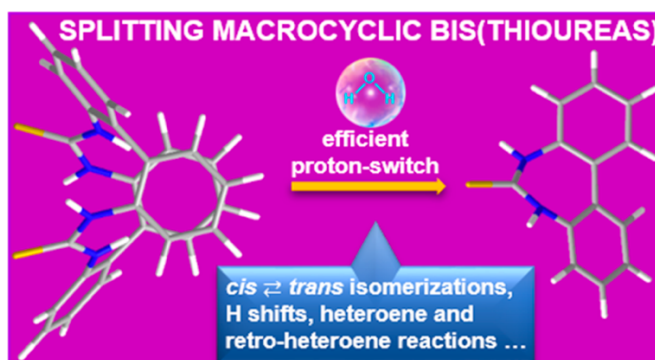
The ISHC Bulletin

Recent Publications of ISHC Members

Issue 27; January 2019

Exploring the Conversion of Macrocyclic 2,2'-Biaryl Bis(thioureas) into Cyclic Monothioureas: An Experimental and Computational Investigation

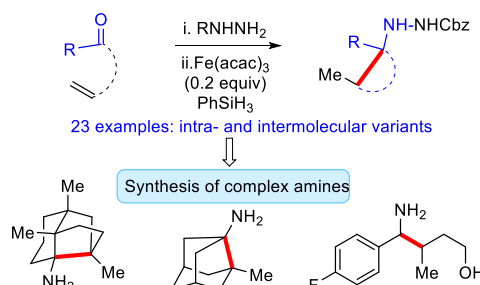
Mateo Alajarin, Carmen Lopez-Leonardo, Raul-Angel Orenes, Aurelia Pastor,* Pilar Sanchez-Andrada,* and Angel Vidal (aureliap@um.es or andrada@um.es)
J. Org. Chem. **2018**, 83, 14022–14035. DOI: 10.1021/acs.joc.8b02496



Abstract: Macrocyclic bis(thioureas) derived from 2,2'-biphenyl and binaphthyl skeletons have been synthesized by reaction of 2,2'-diaminobiaryl and 2,2'-bis(isothiocyanato)biaryl derivatives. The splitting of these bis(thioureas) into two units of the respective cyclic monothioureas has been monitored by NMR, shedding some light on the factors that control these processes. Additionally, a computational study revealed up to three mechanistic paths for the conversion of the 2,2'-biphenyl-derived bis(thiourea) into the corresponding monothiourea. The proposed mechanisms account for the participation of a molecule of water as an efficient proton-switch as well as for different classes of putative intermediates. The computational study also supports the ability of the thiourea group to participate in a plethora of processes, such as prototropic equilibria, sigmatropic shifts, heteroene and retro-heteroene reactions, and *cis* \rightleftharpoons *trans* isomerizations.

Hydrogen Atom Transfer (HAT)-Triggered Iron-Catalyzed Intra- and Intermolecular Coupling of Alkenes with Hydrazones: Access to Complex Amines

Mar Saladrigas, Guillem Loren, Josep Bonjoch,* and Ben Bradshaw* (benbradshaw@ub.edu or josep.bonjoch@ub.edu)
ACS Catal. **2018**, 8, 11699–11703. DOI: 10.1021/acscatal.8b03794



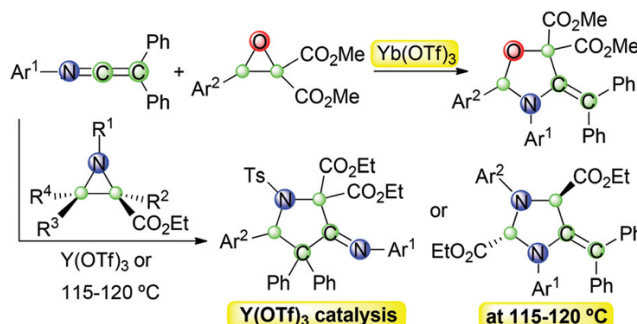
Abstract: A methodology for the coupling of alkenes with aldehyde- or ketone-derived Cbz-hydrazones to form a new C–C bond through a radical process is described. The sequence comprises an initial *in situ* generation of a putative iron hydride followed by a hydrogen atom transfer to an alkene, a coupling with a hydrazone, and a final reduction of the nitrogen-centered radical. Hydrogenation of the obtained hydrazines renders amines, including valuable *tert*-alkyl amines.

Accessing Polysubstituted Oxazolidines, Pyrrolidines and Imidazolidines by Regioselective [3 + 2] Annulations of Ketenimines with Donor–Acceptor Oxiranes and Aziridines

Mateo Alajarin, Daniel Bañón, Adrian Egea, Marta Marín-Luna, Raul-Angel Orenes, and Angel Vidal* (vidal@um.es)

Org. Chem. Front. **2018**, 5, 2020–2029.

DOI: 10.1039/c8qo00255j



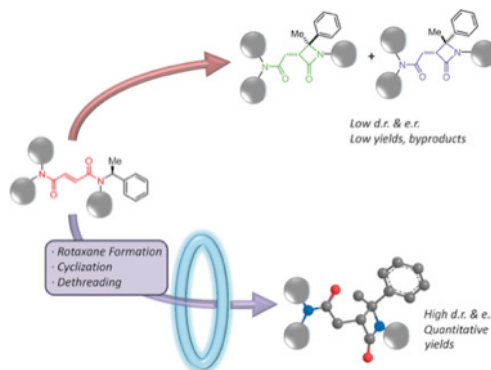
Abstract: Efficient [3 + 2] annulations of *N*-aryl-*C,C*-diphenyl ketenimines with metallo-carbonyl and metallo-azomethine ylides, generated via the respective $\text{Yb}(\text{OTf})_3$ and $\text{Y}(\text{OTf})_3$ promoted carbon–carbon bond heterolysis of donor–acceptor oxiranes and aziridines, have been accomplished. These reactions proceeded under mild conditions and supplied a general methodology for the regioselective construction of structurally complex oxazolidines and pyrrolidines. Moreover, heating neat mixtures of *N*-aryl-*C,C*-diphenyl ketenimines and diethyl aziridine-2,3-dicarboxylates led to imidazolidine derivatives. A computational study concluded in stepwise mechanisms for these [3 + 2] annulations, also shedding light on their regioselectivity, concerning which of the two cumulated double bonds of the ketenimine becomes involved in the reaction with the ylide.

Enantioselective Formation of 2-Azetidinones by Ring-Assisted Cyclization of Interlocked *N*-(α -Methyl)benzyl Fumaramides

Alberto Martinez-Cuezva,* Delia Bautista, Mateo Alajarin, and Jose Berna* (amcuezva@um.es or ppberna@um.es)

Angew. Chem. Int. Ed. **2018**, 57, 6563–6567.

DOI: 10.1002/anie.201803187



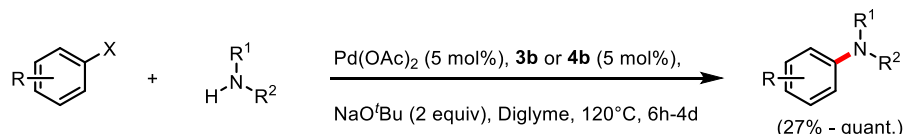
Abstract: The synthesis of optically active interlocked and non-interlocked 2-azetidinones by intramolecular cyclization of *N*-(α -methyl)benzyl fumaramide [2]rotaxanes is described. Two different strategies of asymmetric induction were tested in which the chiral group was located either proximal or distal to the reaction center of the thread. During these experiments, an interesting equilibration process inside the macrocyclic void occurred leading to the cyclization through the (α -methyl)benzyl carbon atom giving rise to β -lactams with a quaternary carbon atom in an enantio- and diastereocontrolled manner. This cyclization also proceeds in kinetically stable chiral pseudo[2]rotaxanes allowing further dethreading to provide enantioenriched 3,4-disubstituted trans-2-azetidinones. The stereochemical outcomes of the cyclizations inside and outside the macrocycle showed noticeable differences.

Biphenyl Sulfonic Acid Ligands for Catalytic C–N Cross Coupling of Aryl Halides with Anilines and Secondary Amines

Bärbel Wittel, Till Vogel, Heiko Scharl, Sven Nerdinger, Bernd Lehnemann, Andreas Meudt, and Victor Snieckus* (baderadm@chem.queensu.ca)

Bioorg. & Med. Chem. **2018**, 26, 4583–4593.

DOI: 10.1016/j.bmc.2018.07.028



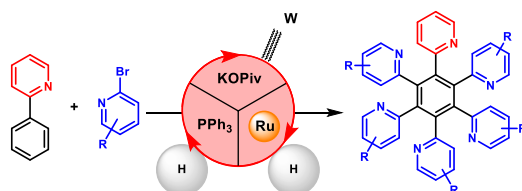
Abstract: The use of two biphenyl sulfonic acid ligands for the catalytic C–N cross coupling of aryl halides with anilines, 3-aminopyridine, and secondary amines is reported. Our results represent a significant improvement compared to state of the art methods especially with regards to the removal of palladium.

Ruthenium(II)-Catalyzed Microwave-Promoted Multiple C–H Activation in Synthesis of Hexa(heteroaryl)benzenes in Water

Miha Drev, Uroš Grošelj, Bine Ledinek, Franc Perdih, Jurij Svete, Bogdan Štefane, and Franc Požgan * (franc.pozgan@fkt.uni-lj.si)

Org. Lett. **2018**, 20, 5268–5273.

DOI: 10.1021/acs.orglett.8b02169



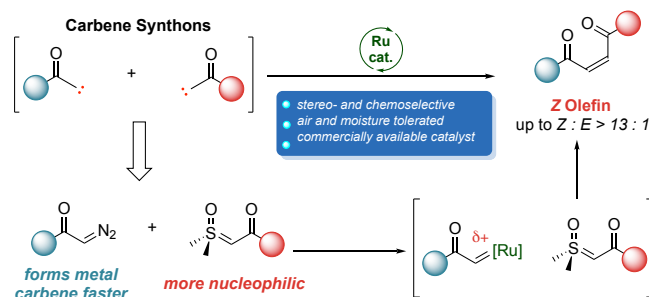
Abstract: A series of hexa(heteroaryl)benzenes were synthesized by the Ru(II)–carboxylate-catalyzed multiple C–H activation of benzenes carrying pyridyl, pyrimidyl, or pyrazolyl directing groups using *N*-heteroaryl bromides as coupling partners. The reactions proceeded with high selectivity under microwave irradiation in water. Iterative penta-arylation could be implemented *via* activation of C–H bonds of generated intermediates by cascade chelation assistance of *in situ* installed pyridyl groups. This strategy provides multidentate ligands for selective complexation of transition metals and potential building of photoredox systems.

A Catalytic Cross-Olefination of Diazo Compounds with Sulfoxonium Ylides

James D. Neuhaus, Adriano Bauer, Alexandre Pinto, and Nuno Maulide* (nuno.maulide@univie.ac.at)

Angew. Chem. Int. Ed. **2018**, 57, 16215–16218.

DOI: 10.1002/anie.201809934



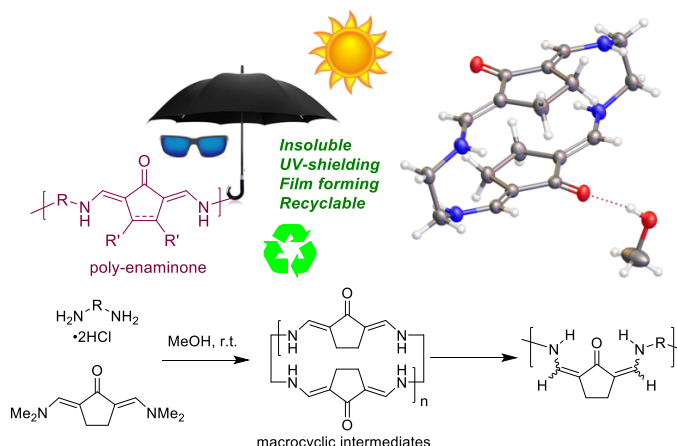
Abstract: A ruthenium-catalysed cross-olefination of diazo compounds and sulfoxonium ylides is presented. Our reaction design exploits the intrinsic difference in reactivity of diazo compounds and sulfoxonium ylides as both carbene precursors and nucleophiles, which results in a highly selective reaction.

Synthesis of Polyenaminones by Acid-Catalysed Amino-Enaminone ‘Click’ Polymerization

Urša Tomažin, Branko Alič, Anja Kristl, Aleš Ručigaj, Uroš Grošelj, Franc Požgan, Matjaž Krajnc, Bogdan Štefane, Urška Šebenik, Jurij Svete* (jurij.svete@fkkt.uni-lj.si)

Eur. Polymer J. **2018**, *108*, 603–616.

DOI: 10.1016/j.eurpolymj.2018.07.048



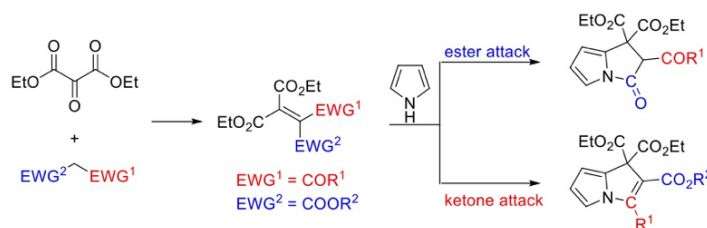
Abstract: A mild amino–enaminone ‘click’ polymerisation method for the preparation of polyenaminones by transamination of α,α' -bis-enaminocyclopentanones with diamines was developed. A series of 12 representative polymers were synthesised by acid-catalysed transamination of two bis-enaminones with six primary 1,2-, 1,3-, and 1,4-diamines. The method allows for combinatorial preparation of structurally diverse polyenaminones from easily available diamines and bis-enaminones. The reaction mechanism was studied by NMR and MS. It involves formation of open-chain and cyclic oligomers, which then undergo a step-wise polymerisation to furnish the title polymers with high average molecular weight ($M_w > 5.0 \times 10^4$ Da) and with spherical and porous microstructure. The obtained polymers were insoluble in most organic solvents, stable in diluted acids and bases, while degradable in concentrated hydrochloric acid at room temperature. They were thermally stable up to 200 °C and exhibited film-forming and UV-vis-shielding properties.

Unsymmetrical Tetra-Acceptor-Substituted Alkenes as Polyfunctionalized Building Blocks: A Divergent Synthesis of Densely Functionalized Pyrrolizines

Haruyasu Asahara,* Shu Kawakami, Kotaro Yoshioka, Shinki Tani, Kazuto Umez, and Nagatoshi Nishiwaki* (asahara@chem.eng.osaka-u.ac.jp or nishiwaki.nagatoshi@kochi-tech.ac.jp)

Bull. Chem. Soc. Jpn. **2018**, *91*, 1715–1723.

DOI: 10.1246/bcsj.20180213



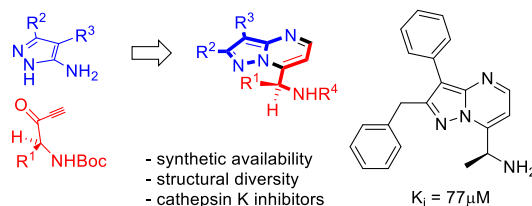
Abstract: Various tetra-acceptor-substituted alkenes possessing unsymmetrical substituents have been effectively synthesized from vicinal tricarboxyl compounds. The alkenes have polyfunctionality and high electron deficiency. In addition, they easily react with pyrroles to give divergent pyrrolizine derivatives via the conjugate addition of pyrroles followed by intramolecular cyclization. We successfully controlled the chemoselectivity of the intramolecular cyclization (ester/ketone attack) to afford a wide range of valuable pyrrolizine derivatives.

Synthesis and Biological Evaluation of 7-(Aminoalkyl)pyrazolo[1,5-*a*]pyrimidine Derivatives as Cathepsin K Inhibitors

Nejc Petek, Bogdan Štefane, Marko Novinec,* Jurij Svete* (jurij.svete@fkkt.uni-lj.si)

Bioorg. Chem. **2019**, *84*, 226–238.

DOI: 10.1016/j.bioorg.2018.11.029



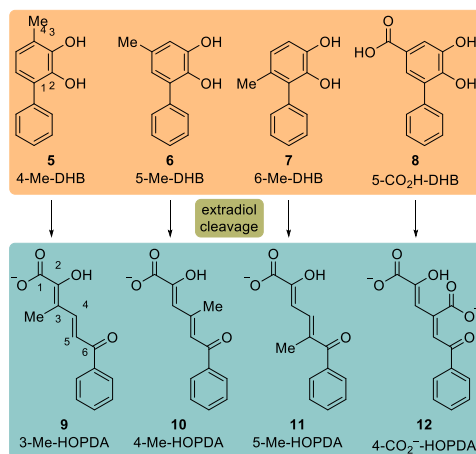
Abstract: A series of novel 7-aminoalkyl substituted pyrazolo[1,5-*a*]pyrimidine derivatives were synthesized and tested for inhibition of cathepsin K. The synthetic methodology comprises cyclization of 5-aminopyrazoles with *N*-Boc- α -amino acid-derived yrones followed by transformation of the ester and the Boc-amino functions. It allows for easy diversification of the pyrazolo[1,5-*a*]pyrimidine scaffold at various positions. Molecular docking studies with pyrazolo[1,5-*a*]pyrimidine derivatives were also performed to elucidate the binding mode in the active site of cathepsin K. The synthesized compounds exhibited moderate inhibition activity ($K_i \geq 77 \mu\text{M}$).

Bacterial Catabolism of Biphenyls: Synthesis and Evaluation of Analogues

Sven Nerdinger, Eugene Kuatsjah, Timothy E. Hurst, Inge Schlapp-Hackl, Volker Kahlenberg, Klaus Wurst, Lindsay D. Eltis,* and Victor Snieckus* (leltis@mail.ubc.ca or snieckus@chem.queensu.ca)

ChemBioChem **2018**, *19*, 1771–1778.

DOI: 10.1002/cbic.201800231



Abstract: A series of alkylated 2,3-dihydroxybiphenyls has been prepared on the gram scale by using an effective Directed *ortho* Metalation–Suzuki–Miyaura cross-coupling strategy. These compounds have been used to investigate the substrate specificity of the *meta*-cleavage dioxygenase BphC, a key enzyme in the microbial catabolism of biphenyl. Isolation and characterization of the *meta*-cleavage products will allow further study of related processes, including the catabolism of lignin-derived biphenyls.