

The ISHC Bulletin

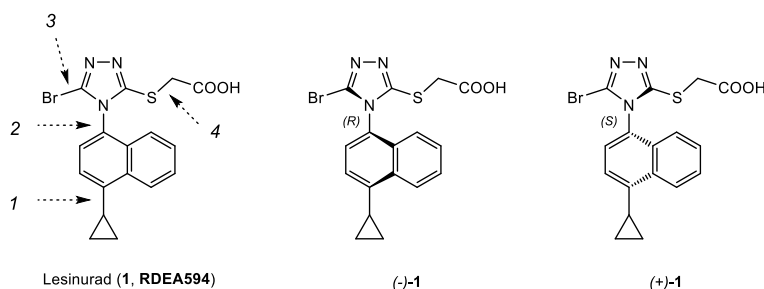
Recent Publications of ISHC Members

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Lesinurad – There are More Ways Than One of Synthesizing the Drug

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Heterocycles **2021**, 103, 129–143. *Special Issue for Prof. Yasuyuki Kita* DOI: 10.3987/REV-20-SR(K)4

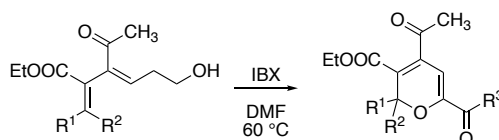


Abstract: Over the last several years significant efforts have been devoted, particularly in China, to develop new syntheses of Lesinurad. Virtually all key bonds in this molecule can now be created in more than a few different ways, often in a very high yield. Although almost all of the chemistry examples presented in this review come from patent applications and as such have not been subjected to rigorous peer review, they may serve well as an inspiration to organic chemists for solving analogous synthetic problems. However, the readers of this mini review are encouraged to pay particular attention to the very recent trends in using multicomponent reactions and flow chemistry to minimize the environmental impact and achieve high yields of API at the same time.

IBX Oxidations for the Synthesis of Substituted 2H-Pyrans

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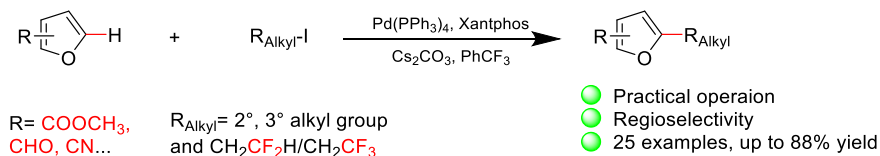
Abstract: Facile oxidation of highly substituted 3,5-hexadien-1-ols using 3-iodoxybenzoic acid (IBX) in DMSO has resulted in a one-pot preparation of 2,3,4,6-tetrasubstituted 2H-pyrans. Cycloisomerizations of the 1-oxatriene moiety, produced in the oxidation, spontaneously occur via a disrotatory oxa-electrocyclization. The 2H-pyran products of Table 1 feature three differentiated carbonyl substituents.

Regioselective Pd-Catalyzed α -Alkylation of Furans Using Alkyl Iodides

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RSC Adv. **2021**, 11, 13832–13838.

DOI: 10.1039/d1ra01522b

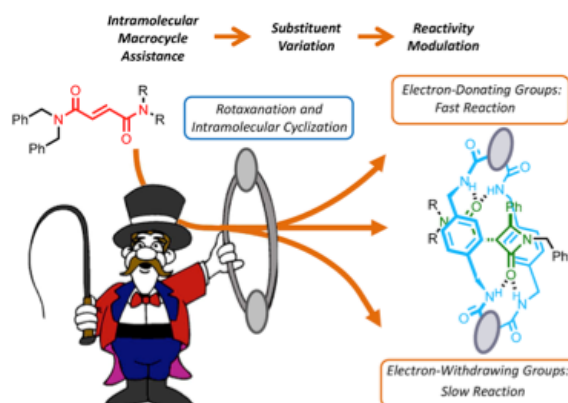


Abstract: Herein, direct alkylation of the C–H bond at the α -position of furans catalyzed by palladium catalyst is reported. This protocol targets α -alkylfurans, achieving moderate to good yields under very practical reaction conditions. With a broad scope of substrates and good functional group tolerance, this method will have promising utility in medicinal chemistry.

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/d0sc05757f

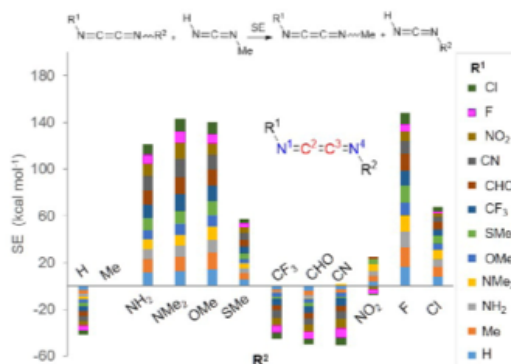


Abstract: A detailed mechanistic study of the diastereoselective CsOH-promoted cyclization of interlocked fumaramides to give β -lactams is described. The mechanistic analysis comprises the experimental evaluation of the structure-reactivity relationship for a wide range of fumaramide [2]rotaxanes (Hammett-plots), 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 amidate 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 adamantyl core speeds up the cyclization process in diadamantyl-derived rotaxanes.

Unmasking the Elusive 1,4-Diazabutatrienes: The Stabilizing Role of the *N*-Substituents

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Phys. Chem. Chem. Phys. **2021**, *23*, 6091–6097.

DOI: 10.1039/d1cp00274k



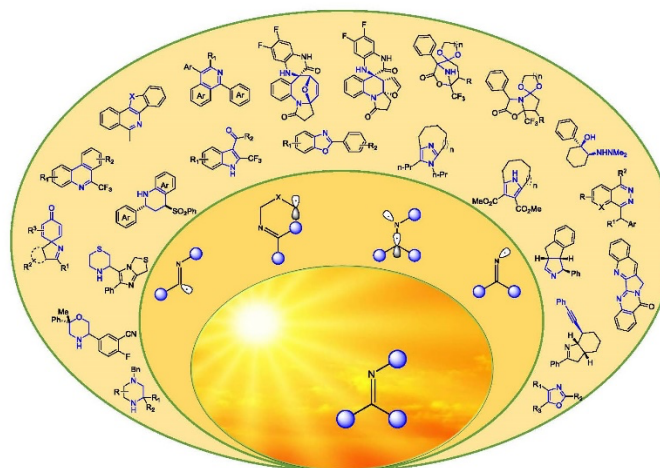
Abstract: The geometrical and electronic properties of a representative set of diversely-substituted 1,4-diazabutatrienes are analyzed by theoretical and statistical methods. The influence of the substituents on the stabilization of these exotic azacumulenes has been estimated through a homodesmotic reaction and compared with related heterocumulenes. The 1,4-diazabutatrienes are stabilized by π -donor or σ -acceptor substituents and, in some cases, by the combination of one donor with one acceptor substituents at both N termini, a fact that might be associated with the ideally linear geometry of the heterocumulenic core for keeping the optimal orbital overlapping between its atoms.

Photochemical Radical Cyclization Reactions with Imines, Hydrazones, Oximes and Related Compounds

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Chem. Soc. Rev. **2021**, *50*, 7418–7435.

DOI: 10.1039/D1CS00196E



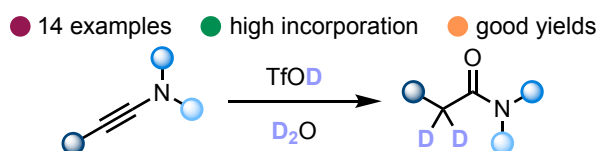
Abstract: Photochemical reactions are a key method to generate radical intermediates. Often under these conditions no toxic reagents are necessary. During recent years, photo-redox catalytic reactions considerably push this research domain. These reaction conditions are particularly mild and safe which enables the transformation of poly-functional substrates into complex products. The synthesis of heterocyclic compounds is particularly important since they play an important role in the research of biologically active products. In this review, photochemical radical cyclization reactions of imines and related compounds such as oximes, hydrazones and chloroimines are presented. Reaction mechanisms are discussed, and the structural diversity and complexity of the products are presented. Radical intermediates are mainly generated in two ways: (1) electronic excitation is achieved by light absorption of the substrates; and (2) the application of photoredox catalysis is now systematically studied for these reactions. Recently, excitation of charge transfer complexes has also been studied in this context from many perspectives.

Harnessing Ynamide Activation to Access Deuterated Carbonyls

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Tetrahedron **2021**, *90*, 132211 (1–4).

DOI: 10.1016/j.tet.2021.132211



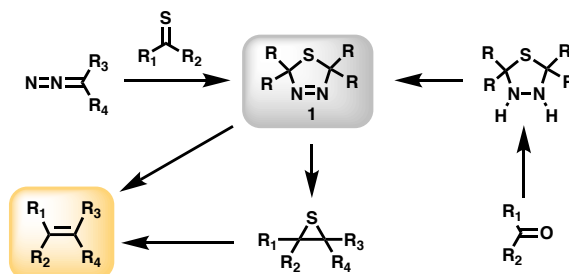
Abstract: We report a facile synthesis of α -bisdeuterated imides that hinges on the formation of highly electrophilic keteniminium ions by reaction of TfOD with ynamides, followed by nucleophilic trapping with D_2O . High yields and excellent levels of deuteration are observed throughout and the products can be easily formed on gram scale. Possible derivatization without deuterium erosion further highlights this method's synthetic utility for the formation of a wide range of isotopically labelled compounds.

Comprehensive Computational Investigation of the Barton–Kellogg Reaction for Both Alkyl and Aryl Systems

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J. Org. Chem. **2021**, 86, 7515–7528.

DOI: 10.1021/acs.joc.1c00506



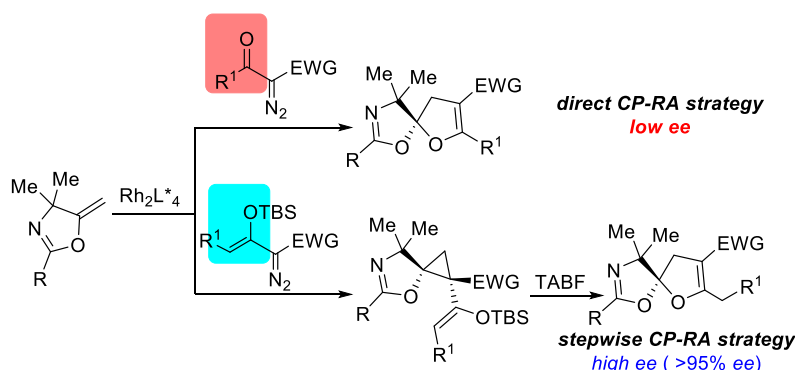
Abstract: The Barton–Kellogg reaction is recognized as one of the most efficient methods for the formation of sterically demanding double bonds, and has even been deployed to create molecular machines. In this report the course of the Barton–Kellogg reaction for both alkyl and aryl-substituted systems was investigated using high level DFT calculations, with the results being directly compared to available experimental data. Furthermore, correlation of unrestricted natural orbital eigenvalues with previous experimental models indicates that the dipole intermediates have low diradical character and are therefore considered to be closed-shell species. In addition, DLPNO-CCSD(T)// ω B97X-D was found to be a reliable method for estimating the feasibility of this reaction, and thus should assist practitioners in the selection of viable substrates for future synthetic campaigns.

Enantioselective Catalytic Cyclopropanation–Rearrangement Approach to Chiral Spiroketal

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Org. Lett. **2021**, 23, 3955–3959.

DOI: 10.1021/acs.orglett.1c01113



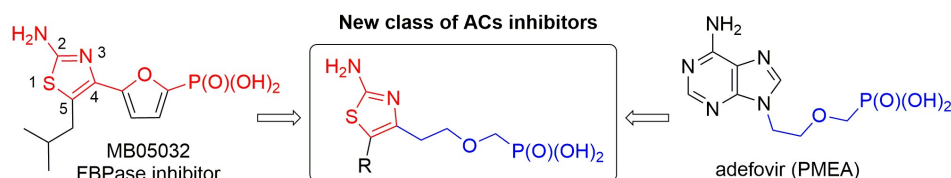
Abstract: A highly enantioselective synthesis of chiral heterobicyclic spiroketal is reported via a "one pot" cyclopropanation–rearrangement (CP–RA) cascade reaction that catalyzed by chiral Rh(II) catalyst and TBAF sequentially. Exocyclic vinyl substrates form spirocyclopropanes with TBS-protected enoldiazoacetates in excellent yields and enantioselectivities, when catalyzed by chiral dirhodium(II) carboxylates and, following desilylation with simultaneous rearrangement in the presence of TBAF, give (*S*)-spiroketals with high yields and excellent chirality retention (> 95% ee).

Acyclic Nucleoside Phosphonates with 2-Aminothiazole Base as Inhibitors of Bacterial and Mammalian Adenylate Cyclases

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Eur. J. Med. Chem. **2021**, 222, 113581 (1–8).

DOI: 10.1016/j.ejmech.2021.113581



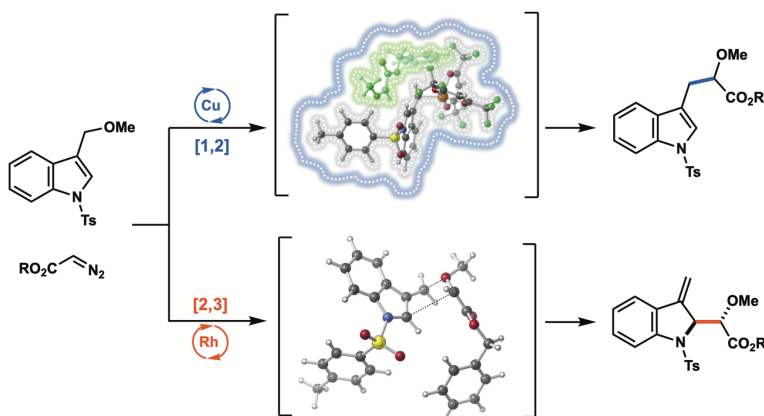
Abstract: A series of novel acyclic nucleoside phosphonates (ANPs) as potential adenylate cyclase inhibitors was synthesized where the adenine nucleobase of adefovir (PMEA) was replaced with a 5-substituted 2-aminothiazole moiety. The design was based on the structure of MB05032, a potent and selective inhibitor of fructose 1,6-bisphosphatase and a good mimic of adenosine monophosphate (AMP). From the series of eighteen novel ANPs, which were prepared as phosphoroamidate prodrugs, fourteen compounds were potent (single digit micromolar or submicromolar) inhibitors of *Bordetella pertussis* adenylate cyclase toxin (ACT), mostly without observed cytotoxicity in J774A.1 macrophage cells. Selected phosphono diphosphates (nucleoside triphosphate analogues) were potent inhibitors of ACT (IC_{50} as low as 37 nM) and *B. anthracis* edema factor (IC_{50} as low as 235 nM) in enzymatic assays. Furthermore, several ANPs were found to be selective mammalian AC1 inhibitors in HEK293 cell-based assays (although with some associated cytotoxicity) and one compound exhibited selective inhibition of mammalian AC2 (only 12% of remaining adenylate cyclase activity) but no observed cytotoxicity. The mammalian AC1 inhibitors may represent potential leads in development of agents for treatment of human inflammatory and neuropathic pain.

Catalyst-Controlled Regiodivergence in Rearrangements of Indole-Based Onium Ylides

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J. Am. Chem. Soc. **2021**, 143, 9016–9025.

DOI: 10.1021/jacs.1c00283



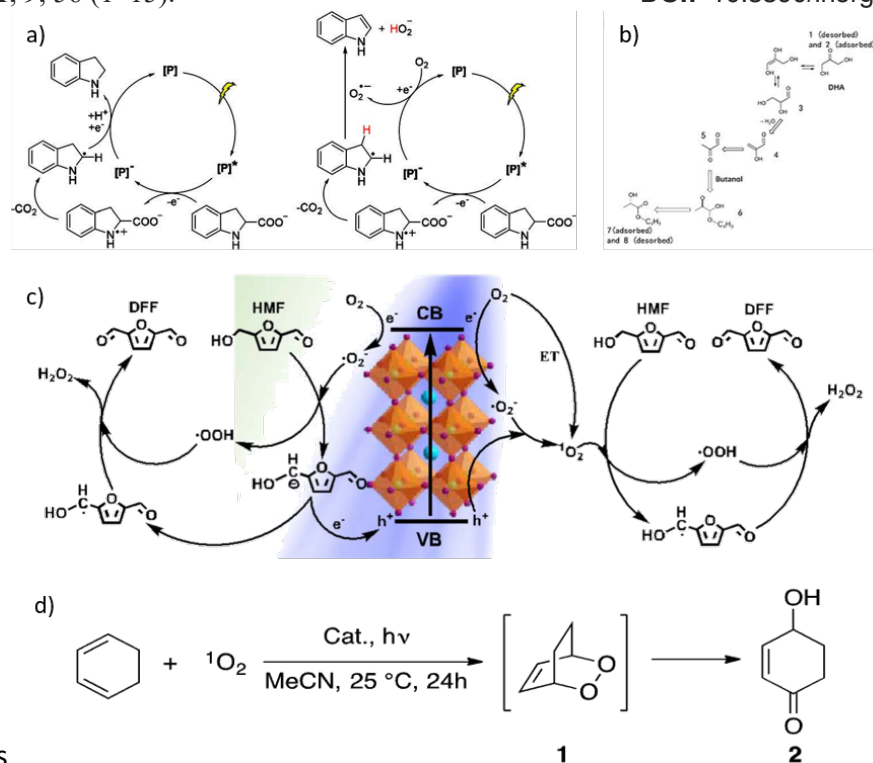
Abstract: We have developed catalyst-controlled regiodivergent rearrangements of onium-ylides derived from indole substrates. Oxonium ylides formed *in situ* from substituted indoles selectively undergo [2,3]- and [1,2]-rearrangements in the presence of a rhodium and a copper catalyst, respectively. The combined experimental and density functional theory (DFT) computational studies indicate divergent mechanistic pathways involving a metal-free ylide in the rhodium catalyzed reaction favoring [2,3]-rearrangement, and a metal-coordinated ion-pair in the copper catalyzed [1,2]-rearrangement that recombines in the solvent-cage. The application of our methodology was demonstrated in the first total synthesis of the indole alkaloid (±)-sorazolon B, which enabled the stereochemical reassignment of the natural product. Further functional group transformations of the rearrangement products to generate valuable synthetic intermediates were also demonstrated.

Application of Metal Halide Perovskites as Photocatalysts in Organic Reactions

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Inorganics **2021**, 9, 56 (1–15).

DOI: 10.3390/inorganics9070056



Abstract: This review summarizes the current status of the application of metal halide perovskites (MHPs) as photocatalysts in organic syntheses/transformations. It is shown that the optimal and unique electronic properties of MHPs can be advantageously used in several reaction types providing pros with respect to traditional photocatalysts. While still being at infancy, such field of application of MHPs as effective photocatalysts will for sure become a central research topic in the forthcoming years, thanks also to their rich structural and chemical tunability, which may provide tailored materials for most of the envisaged organic reactions.