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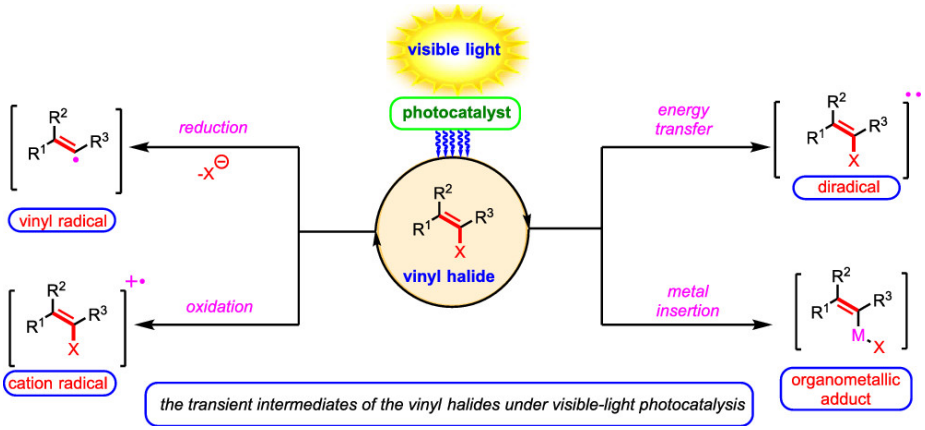
Shining Visible Light on Vinyl Halides: Expanding the Horizons of Photocatalysis

Santosh K. Pagire, Thomas Föll, and Oliver Reiser* (oliver.reiser@chemie.uni-regensburg.de)

Acc. Chem. Res. **2020**, *53*, 782–791. **DOI:** 10.1021/acs.accounts.9b00615

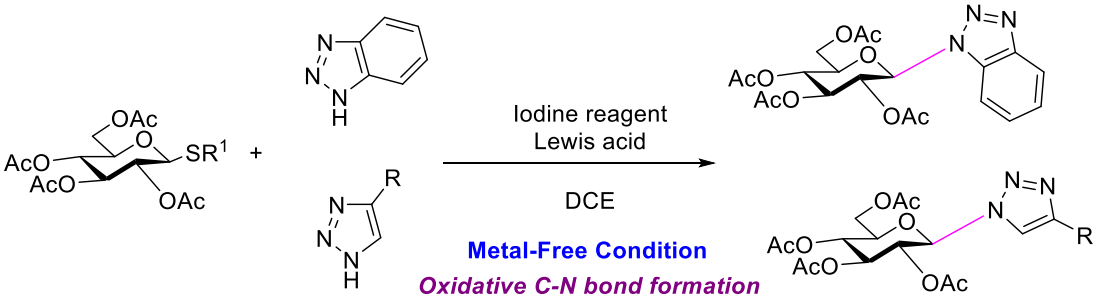


Abstract: In this Account, we discuss the various strategies of photoredox processes involving vinyl halides, classifying the material into four categories: (a) formation of a vinyl radical upon receipt of an electron from the photocatalyst, (b) formation of a radical cation after donation of an electron to the photocatalyst, (c) energy transfer corresponding to diradical formation upon triplet–triplet sensitization, and (d) dual transition metal and photocatalysis employing vinyl halides as precursors. While in the first three approaches the activation of vinyl halides is part of the photochemical step, the fourth one involves the interaction of a photochemically generated radical with a vinylnickel(II) halide obtained in turn by the oxidative addition of nickel(0) to the vinyl halide. Therefore, we highlight these important developments for conceptual comparison to the direct activation of vinyl halides by light, but they are not covered in depth in this Account.

N-Glycosylation Reaction of *Thio*-Glycoside Using Hypervalent Iodine(III) Reagent

Koji Morimoto, Kana Yanase, Takumi Ikeda, Chihiro Uchikawa, Yasuyuki Kita,* and Tetsuya Kajimoto* (kita@ph.ritumei.ac.jp or kajimoto@fc.ritsumei.ac.jp)

Heterocycles **2020**, *101*, 621–630. **DOI:** 10.3987/COM-19-S(F)53

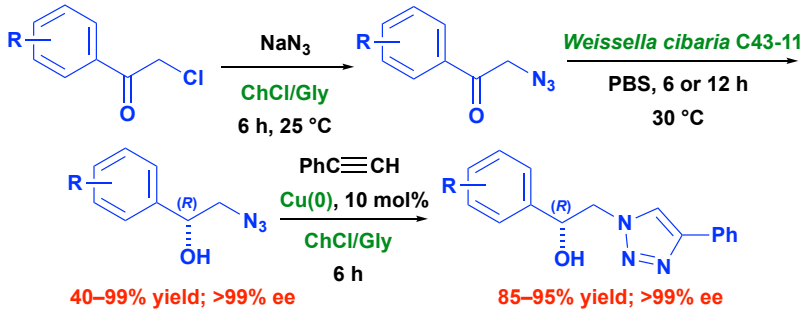


Abstract: We have developed a straightforward and efficient method for the synthesis of glycosyl azoles using hypervalent iodine(III) reagent. In this reaction, when 1,2,3-benzotriazole was used, the *N*1 selective glycosylation reaction proceeded. This protocol offers a rapid approach to glycosyl azoles along with the achievement of a remarkable structural diversity.

Sustainable Chemo-Enzymatic Preparation of Enantiopure (*R*)-β-Hydroxy-1,2,3-triazoles *via* Lactic Acid Bacteria-mediated Bioreduction of Aromatic Ketones and a Heterogeneous "Click" Cycloaddition Reaction in Deep Eutectic Solvents

Paola Vitale,* Francesco Lavolpe, Francesca Valerio,* Mariaelena Di Biase, Filippo Maria Perna, Eugenia Messina, Gennaro Agrimi, Isabella Pisano, and Vito Capriati* (paola.vitale@uniba.it or vito.capriati@uniba.it)

React. Chem. Eng. **2020**, *5*, 859–864. **DOI:** 10.1039/d0re00067a

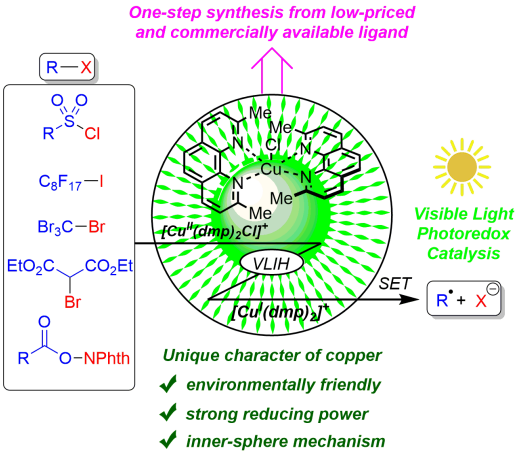


Abstract: Enantiomerically pure (*R*)-β-hydroxy-1,2,3-triazole derivatives, which are important β-blocker analogues, have been synthesized by exploiting an unusual Prelog enantioselective reduction of aromatic azido ketones by whole cells of lactic acid bacterium (*Weissella cibaria* C43-11) and a "click" cycloaddition reaction carried out in deep eutectic solvents, under heterogeneous and aerobic conditions at room temperature.

Making Copper Photocatalysis Even More Robust and Economic: Photoredox Catalysis with $[Cu^{II}(dmp)_2Cl]Cl$

Sebastian Engl and Oliver Reiser* (oliver.reiser@chemie.uni-regensburg.de)

Eur. J. Org. Chem. **2020**, 1523–1533. **DOI:** 10.1002/ejoc.201900839

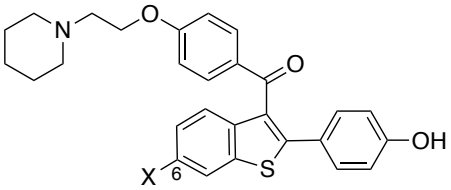


Abstract: The Cu(II)-complex $[Cu^{II}(dmp)_2Cl]Cl$ (dmp = 2,9-dimethyl-1,10-phenanthroline) is evaluated as an oxidation stable precursor for visible-light-mediated Cu(I)-photoredox catalysis, being efficient and considerably more cost-effective compared to previously established copper(I) photocatalysts. Its performance and efficiency are demonstrated within a broad scope of atom transfer radical addition (ATRA) reactions, allowing the 1,2-difunctionalization of alkenes, as well as for decarboxylative coupling and an Appel reaction. Moreover, the utility of the complex is shown by various gram-scale functionalizations of styrene, thus suggesting $[Cu^{II}(dmp)_2Cl]Cl$ to be a low-priced alternative precatalyst for processes run on scale. Furthermore, this study provides UV-vis evidence on the mechanism for the visible light activation of Cu(II) complexes.

6′-Methoxy Raloxifene-Analog Enhances Mouse Bone Properties with Reduced Estrogen Receptor Binding

Katherine M. Powell, Alexa P. Brown, Cayla G. Skaggs, Alexis N. Pulliam, Alycia G. Berman, Padmini Deosthale, Lilian I. Plotkin, Matthew R. Allen, David R. Williams, and Joseph M. Wallace* (jmwalla@iupui.edu)

Bone Reports **2020**, *12*, 100246 (1–9). **DOI:** 10.1016/j.bonr.2020.100246



1 (X = OH)
2 (X = OCH_3) (RAL-A)

Figure 1. Structures of RAL (**1**) and RAL-A (**2**). RAL possesses a 6-hydroxy substituent, while RAL-A possess a 6-methoxy substituent.

Abstract: Raloxifene (RAL) is an FDA-approved drug used to treat osteoporosis in postmenopausal women. RAL suppresses bone loss primarily through its role as a selective estrogen receptor modulator (SERM). This hormonal estrogen therapy promotes unintended side effects, such as hot flashes and increased thrombosis risk, and prevents the drug from being used in some patient populations at-risk for fracture, including children with bone disorders. It has recently been demonstrated that RAL can have significant positive effects on overall bone mechanical properties by binding to collagen and increasing bone tissue hydration in a cell-independent manner. A Raloxifene-Analog (RAL-A) was synthesized by replacing the 6-hydroxyl substituent with 6-methoxy in effort to reduce the compound's binding affinity for estrogen receptors (ER) while maintaining its collagen-binding ability. It was hypothesized that RAL-A would improve the mechanical integrity of bone in a manner similar to RAL, but with reduced estrogen receptor binding. Molecular assessment showed that while RAL-A did reduce ER binding, downstream ER signaling was not completely abolished. In-vitro, RAL-A performed similarly to RAL and had an identical concentration threshold on osteocyte cell proliferation, differentiation, and function. To assess treatment effect in-vivo, wildtype (WT) and heterozygous (OIM+/–) female mice from the Osteogenesis Imperfecta (OI) murine model were treated with either RAL or RAL-A from 8 weeks to 16 weeks of age. There was an untreated control group for each genotype as well. Bone microarchitecture was assessed using microCT, and mechanical behavior was assessed using 3-point bending. Results indicate that both compounds produced analogous gains in tibial trabecular and cortical microarchitecture. While WT mechanical properties were not drastically altered with either treatment, OIM+/– mechanical properties were significantly enhanced, most notably, in post-yield properties including bone toughness. This proof-of-concept study shows promising results and warrants the exploration of additional analog iterations to further reduce ER binding and improve fracture resistance.

The Solid-State Structures of Cyclic NH Carboximides

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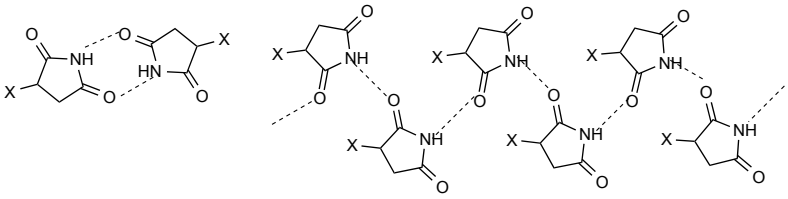
Crystals **2020**, *10*, 606 (1–48). **DOI:** 10.3390/cryst10070606

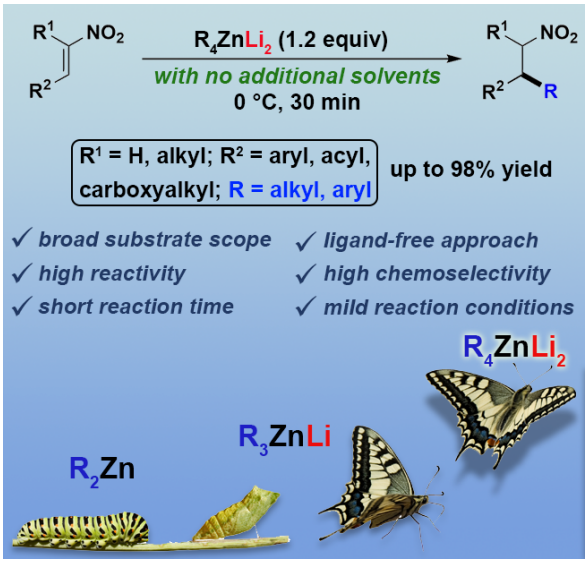


Abstract: The patterns adopted in the solid-state structures of over 300 cyclic NH carboximides as determined by X-ray diffraction are reviewed. While the analysis shows that the majority of these fit into just a few common patterns, a significant number exhibit more complex and interesting patterns involving the other functional groups present in addition to the cyclic imide.

Boosting Conjugate Addition to Nitroolefins Using Lithium Tetraorganozincates: Synthetic Strategies and Structural Insights

Marzia Dell'Aera, Filippo Maria Perna, Paola Vitale, Angela Altomare, Alessandro Palmieri, Lewis C. H. Maddock, Leonie J. Bole, Alan R. Kennedy, Eva Hevia,* and Vito Capriati* (eva.hevia@dcb.unibe.ch or vito.capriati@uniba.it)

Chem. Eur. J. **2020**, *26*, 8742–8748. **DOI:** 10.1002/chem.202001294

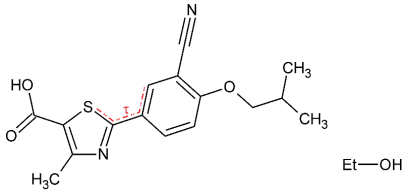


Abstract: We report the first transition metal catalyst- and ligand-free conjugate addition of lithium tetraorganozincates (R_4ZnLi_2) to nitroolefins. Displaying enhanced nucleophility combined with unique chemoselectivity and functional group tolerance, homoleptic aliphatic and aromatic R_4ZnLi_2 provide access to valuable nitroalkanes in up to 98% yield under mild conditions (0 °C) and short reaction time (30 min). This is particularly remarkable when employing β-nitroacrylates and β-nitroenones, where despite the presence of other electrophilic groups, selective 1,4 addition to the C=C is preferred. Structural and spectroscopic studies confirmed the formation of tetraorganozincate species in solution, the nature of which has been a long debated issue, and allowed to unveil the key role played by donor additives on the aggregation and structure of these reagents. Thus, while chelating *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and (*R,R*)-*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane (TMCDA) favour the formation of contacted-ion pair zincates, macrocyclic Lewis donor 12-crown-4 triggers an immediate disproportionation process of Et_4ZnLi_2 into equimolar amounts of solvent-separated Et_3ZnLi and EtLi.

Febuxostat Ethanol Monosolvate

Thomas Gelbrich,* Volker Kahlenberg, Verena Adamer, Sven Nerdinger, and Ulrich J. Griesser (thomas.gelbrich@uibk.ac.at)

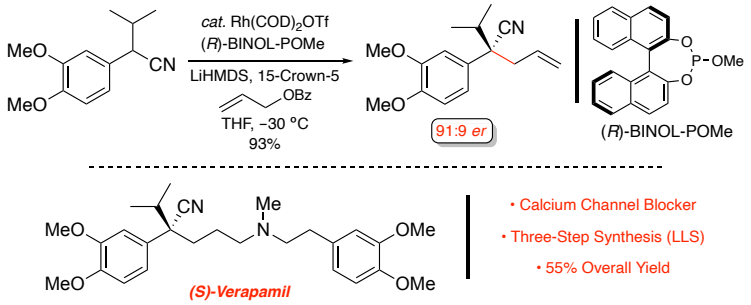
Acta Cryst. **2020**, *E76* 816–819. **DOI:** 10.1107/S2056989020006076



Abstract: The title compound, 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid ethanol monosolvate, $C_{16}H_{16}N_2O_3S{\cdot}C_2H_6O$, (I), displays intermolecular O—H···O and O—H···N bonds in which the carboxyl group of the febuxostat molecule and the hydroxyl group of the ethanol molecule serve as hydrogen-bond donor sites. These interactions result in a helical hydrogen-bonded chain structure. The title structure is isostructural with a previously reported methanol analogue.

A Concise and Modular Three-Step Synthesis of (*S*)-Verapamil using an Enantioselective Rhodium-Catalyzed Allylic Alkylation Reaction

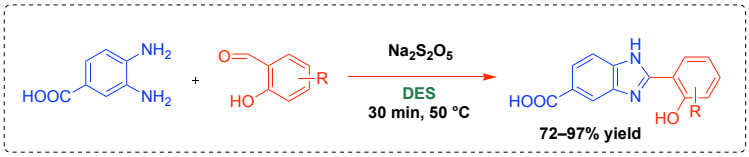
Mai-Jan Tom, Ben W. H. Turnbull, and P. Andrew Evans* (andrew.evans@chem.queensu.ca)
Synthesis **2020**, *52*, 2185–2189. **DOI:** 10.1055/s-0040-1707390

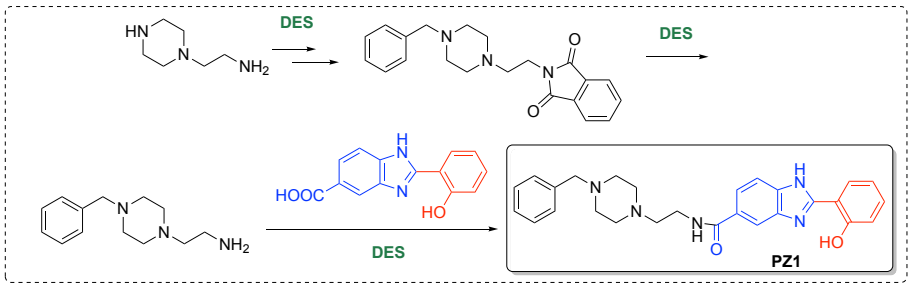


Abstract: A concise and modular three-step asymmetric synthesis of the calcium channel blocker (*S*)-verapamil is described. This approach employs an enantioselective rhodium-catalyzed allylic alkylation reaction between an α-isopropyl substituted benzylic nitrile and allyl benzoate to construct the challenging acyclic quaternary stereocenter. The terminal olefin then serves as a convenient synthetic handle for a hydroamination to introduce the phenethylamine moiety, furnishing (*S*)-verapamil in 3-steps and 55% overall yield, thus providing the most efficient synthesis of this important pharmaceutical reported to date. Furthermore, given the modular nature of the synthesis, it can be readily modified to prepare structurally related bioactive agents.

Deep Eutectic Solvents as Effective Reaction Media for the Synthesis of 2-Hydroxyphenylbenzimidazole-based Scaffolds en Route to Donepezil-Like Compounds

Luca Piemontese,* Roberta Sergio, Federica Rinaldo, Leonardo Brunetti, Filippo M. Perna, M. Amélia Santos, and Vito Capriati* (luca.piemontese@uniba.it or vito.capriati@uniba.it)
Molecules **2020**, *25*, 574 (1–14). **DOI:** 10.3390/molecules25030574

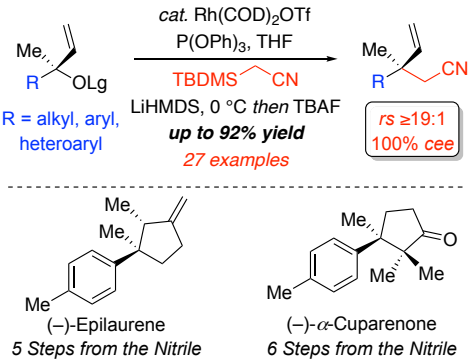




Abstract: An unsubstituted 2-hydroxyphenylbenzimidazole has recently been included as a scaffold in a series of hybrids (including the hit compound PZ1) based on the framework of the acetylcholinesterase (AChE) inhibitor Donepezil, which is a new promising multi-target ligand in Alzheimer's disease (AD) treatment. Building upon these findings, we have now designed and completed the whole synthesis of PZ1 in the so-called deep eutectic solvents (DESs), which have emerged as an unconventional class of bio-renewable reaction media in green synthesis. Under optimized reaction conditions, the preparation of a series of 2-hydroxyphenylbenzimidazole-based nuclei has also been perfected in DESs, and comparison with other routes which employ toxic and volatile organic solvents (VOCs) provided. The functionalization of the aromatic ring can have implications on some important biological properties of the described derivatives and will be the subject of future studies of structure-activity relationships (SARs).

Regioselective and Stereospecific Rhodium-Catalyzed Allylic Cyanomethylation with an Acetonitrile Equivalent: Construction of Acyclic β-Quaternary Stereogenic Nitriles

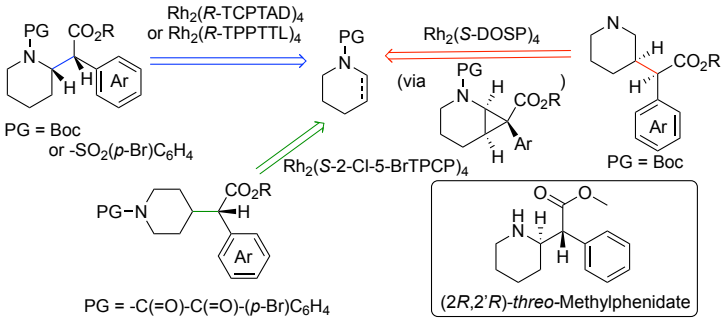
Mai-Jan Tom and P. Andrew Evans* (andrew.evans@chem.queensu.ca)
J. Am. Chem. Soc. **2020**, *142*, 11957–11961. **DOI:** 10.1021/jacs.0c02316



Abstract: A highly regioselective and stereospecific rhodium-catalyzed cyanomethylation of tertiary allylic carbonates for the construction of acyclic β-quaternary stereogenic nitriles is described. This protocol represents the first example of a metal-catalyzed allylic substitution reaction using a triorganosilyl-stabilized acetonitrile anion, which permits access to several carbonyl derivatives that are challenging to prepare using conventional pronucleophiles. The synthetic utility of the stereospecific cyanomethylation is further exemplified through the construction of the intermediate utilized in the total synthesis of both (+)-epilaurene and (+)–α-cuparenone.

Functionalization of Piperidine Derivatives for the Site-Selective and Stereoselective Synthesis of Positional Analogues of Methylphenidate

Wenbin Liu, Tobias Babl, Alexander Röther, Oliver Reiser,* and Huw M. L. Davies* (oliver.reiser@chemie.uni-regensburg.de or hmdavie@emory.edu)
Chem. Eur. J. **2020**, *26*, 4236–4241. **DOI:** 10.1002/chem.201905773



Abstract: Rhodium-catalyzed C–H insertions and cyclopropanations of donor/acceptor carbenes have been used for the synthesis of positional analogs of methylphenidate. The site selectivity is controlled by the catalyst and the amine protecting group. C–H functionalization of *N*-Boc-piperidine using Rh_2(*R*-TCPTAD)$_4$, or *N*-brosyl-piperidine using Rh_2(*R*-TPPTTL)$_4$ generated 2-substitited analogs. In contrast, when *N*-α-aryloxoacetyl-piperidines were used in combination with Rh_2(*S*-2-Cl-5-BrTPCP)$_4$, the C–H functionalization produced 4-substituted analogs. Finally, the 3-substituted analogs were prepared indirectly by cyclopropanation of *N*-Boc-tetrahydropyridine followed by reductive regio- and stereoselective ring-opening of the cyclopropanes.