

The ISHC Bulletin

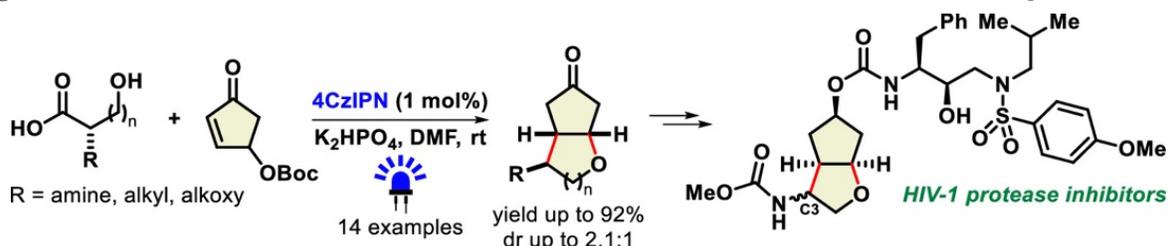
Recent Publications of ISHC Members

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Accessing HIV-1 Protease Inhibitors through Visible-Light-Mediated Sequential Photocatalytic Decarboxylative Radical Conjugate Addition–Elimination–Oxa-Michael Reactions

Tomislav Krolo, Aditya Bhattacharyya, and Oliver Reiser* (oliver.reiser@chemie.uni-regensburg.de)
Org. Lett. **2021**, *23*, 6283–6287.

DOI: 10.1021/acs.orglett.1c01964

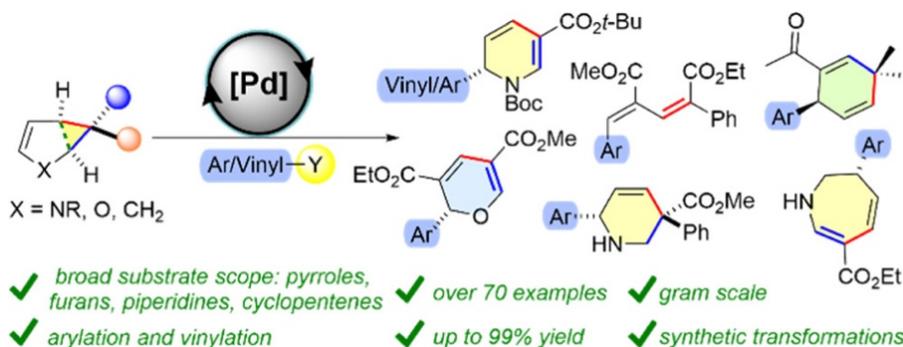


Abstract: A photocatalytic decarboxylative radical conjugate addition–elimination–oxa-Michael reaction of hydroxyalkylated carboxylic acids with cyclopentenones is developed to construct diverse cyclopentanonyl-fused functionalized 5–7 membered cyclic ethers. The stereoselective synthetic strategy is amenable to substructural variation, establishing a direct total synthetic route to two diastereomers of C3-amino cyclopentyltetrahydrofuran-derived potent HIV-1 protease inhibitors with low nanomolar IC_{50} values.

Heck-Type Coupling of Fused Bicyclic Vinylcyclopropanes: Synthesis of 1,2-Dihydropyridines, 2,3-Dihydro-1*H*-azepines, 1,4-Cyclohexadienes, and 2*H*-Pyrans

Nikolai Wurzer, Urszula Klimczak, Tobias Babl, Sebastian Fischer, Ricardo A. Angnes, Dominik Kreutzer, Aryaman Pattanaik, Julia Rehbein, and Oliver Reiser (oliver.reiser@chemie.uni-regensburg.de)
ACS Catal. **2021**, *11*, 12019–12028.

DOI: 10.1021/acscatal.1c02564



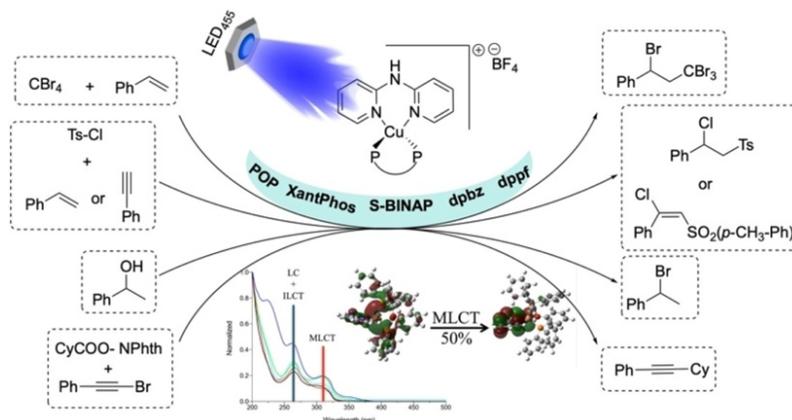
Abstract: Herein, we report a versatile approach for the endocyclic ring opening of bicyclic vinylcyclopropanes triggered by Heck arylations. The key step for this transformation is a β -C-elimination allowing the ring expansion of cyclopropanated pyrroles, piperidines, furans, as well as cyclopentadienes to grant access to the corresponding 1,2-dihydropyridines, 2*H*-pyrans, 2,3-dihydro-1*H*-azepines, and 1,4-cyclohexadienes, respectively. Additionally, *gem*-disubstituted cyclopropanated furans showed unexpected behavior by giving diastereoselectively asymmetrically substituted dienes. Mechanistic studies and theoretical calculations point toward a facile β -C-elimination with a concomitant shift of Pd along the cyclopropane moiety, which can successfully compete with the usual termination step of a Heck reaction *via* a *syn*- β -hydride elimination.

Phosphine Evaluation on a New Series of Heteroleptic Copper(I) Photocatalysts with dpa Ligand [Cu(dpa)(P,P)]BF₄

Marco A. Henriquez, Sebastian Engl, Pablo Jaque, Ivan A. Gonzalez, Mirco Natali, Oliver Reiser,* and Alan R. Cabrera* (oliver.reiser@chemie.uni-regensburg.de or arcabrer@uc.cl)

Eur. J. Inorg. Chem. **2021**, 4020–4029.

DOI: 10.1002/ejic.202100634



Abstract: Photocatalytic evaluation in three different reactions (ATRA, decarboxylative coupling, and Appel-type) was performed to five new heteroleptic Cu(I) complexes of the type [Cu(dpa)(P,P)]BF₄ based on dipyriddyamine (dpa) as *N,N* ligand and commercial diphosphines (POP, XantPhos, dpbz, dppf, S-BINAP) as *P,P* ancillary ligands. All complexes were structurally and electrochemical-optically characterised.

Catalyst-Free, Scalable Heterocyclic Flow Photocyclopropanation

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Green Chem. **2021**, *23*, 6366–6372.

DOI: 10.1039/d1gc01624e



Abstract: Industrial process development is driven by several factors, including safety, cost, robustness and environmental aspects. However, attempts to establish aryl diazo esters – which are highly valued in academic research for their reactivity as carbene precursors – in the chemical industry have been limited by their explosivity and toxicity. Their catalyst-free photolysis in continuous flow improves safety, sustainability and scalability compared to batch reactions. Herein, we report the continuous flow catalyst-free photocyclopropanation of heterocycles in up to grams per h productivity in a non-chlorinated, biodegradable solvent. Highly-functionalized cyclopropanated products are key intermediates in the synthesis of drugs and pharmaceutically-relevant compounds. Optimal conditions and process understanding were obtained by a Design of Experiments approach. In comparison with a large scale batch experiment, continuous flow conditions improved yield, productivity and process safety.

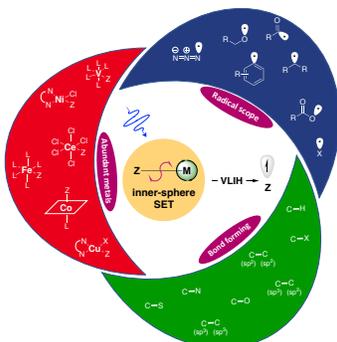
Visible-Light-Induced Homolysis of Earth-Abundant Metal-Substrate Complexes: A Complementary Activation Strategy in Photoredox Catalysis

Youssef Abderrazak, Aditya Bhattacharyya,* and Oliver Reiser* (aditya.bhattacharyya@chemie.uni-regensburg.de or oliver.reiser@chemie.uni-regensburg.de)

Angew. Chem. Int. Ed. **2021**, *60*, 21100–21115.

DOI: 10.1002/anie.202100270

10.1002/ange.202100270



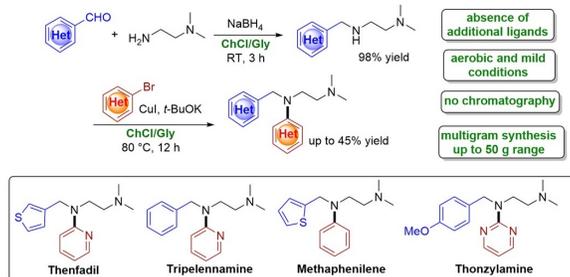
Abstract: The use of earth-abundant metal complexes in photoredox catalysis offers a complementary mode of activation for organic substrates through visible-light-induced homolysis (VLH) of metal–substrate bonds. This Minireview describes different electronic transitions that occur in photoexcited metal–substrate complexes as well as recent advancements and future prospects in this area.

Sustainable and Scalable Two-Step Synthesis of Thenfadil and Some Analogs in Deep Eutectic Solvents: From Laboratory to Industry

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ACS Sustainable Chem. Eng. **2022**, *10*, 4065–4072.

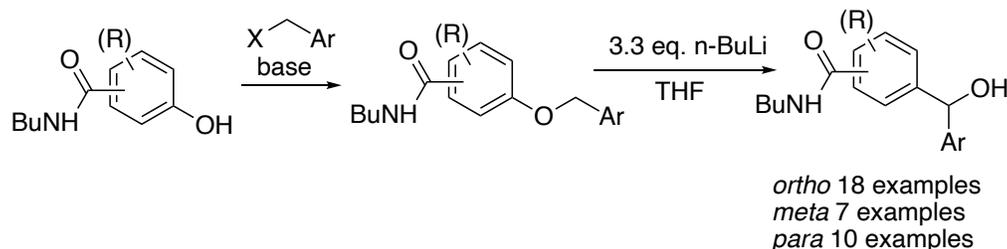
DOI: 10.1021/acssuschemeng.2c00417



Abstract: A sustainable two-step protocol was developed for the synthesis of the antihistamine drug Thenfadil by combining a reductive amination process with a Cu-catalyzed Ullmann-type C–N coupling reaction run in environmentally responsible deep eutectic solvents (DESs), constructed from biobased compounds. Under optimized conditions, both reactions proceed smoothly under aerobic conditions and in the absence of any additional ligand, with the desired active pharmaceutical ingredient isolated in an overall reaction yield of 39% with an effective suppression of the side products arising from competitive Cu-catalyzed C–O coupling reactions. A novel and simplified workup procedure has also been set up, which avoids the need for chromatographic purification, while allowing the recovery and the recycling of the unreacted intermediate secondary amine. The potential application and the robustness of the proposed methodology has been demonstrated (a) in scale-up studies up to 50 g of substrate in 0.5 kg of DES, taking place with no decrease in the reaction yield, and (b) in the synthesis of three other ethylenediamine derivatives (Thenfadil’s analogs) like tripelennamine, methaphenilene, and thonzylamine in 39%–44% overall yield. Typical metrics applied at First and Second Pass, according to the CHEM21 Metrics Toolkit, have been calculated as well for the whole synthetic procedure of Thenfadil and results compared with those of the classical procedure.

Access to Diarylmethanols by Wittig Rearrangement of *ortho*-, *meta*-, and *para*-Benzyloxy-*N*-Butylbenzamides

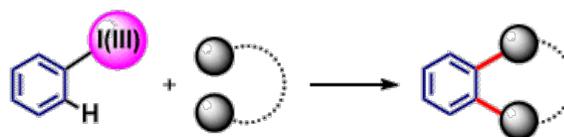
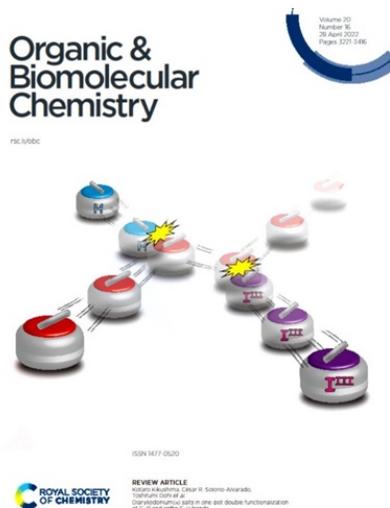
R. Alan Aitken,* Andrew D. Harper, Ryan A. Inwood, and Alexandra M. Z. Slawin (raa@st-and.ac.uk)
J. Org. Chem. **2022**, *87*, 4692–4701. DOI: 10.1021/acs.joc.1c03160



Abstract: The *N*-butyl amide group, CONHBu, has been found to be an effective promoter of the [1,2]-Wittig rearrangement of aryl benzyl ethers and thus allow the two-step synthesis of isomerically pure substituted diarylmethanols starting from simple hydroxybenzoic acid derivatives. The method is compatible with a wide range of functional groups including methyl, methoxy, and fluoro, although not with nitro and, unexpectedly, is applicable to *meta* as well as *ortho* and *para* isomeric series.

Diaryliodonium(III) Salts in One-Pot Double Functionalization of C–I^{III} and *ortho* C–H Bonds

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Org. Biomol. Chem. **2022**, *20*, 3231–3248. DOI: 10.1039/d1ob02501e



Double Functionalization of C–I(III) and *ortho* C–H bonds

Stepwise double functionalization

- Arylation/rearrangement sequence
- Arylation followed by electrophilic aromatic substitution
- [2 + 2 + 2] Cascade annulation via copper-catalyzed aryl C–N bond formation
- Sequential metal-catalyzed arylation reactions

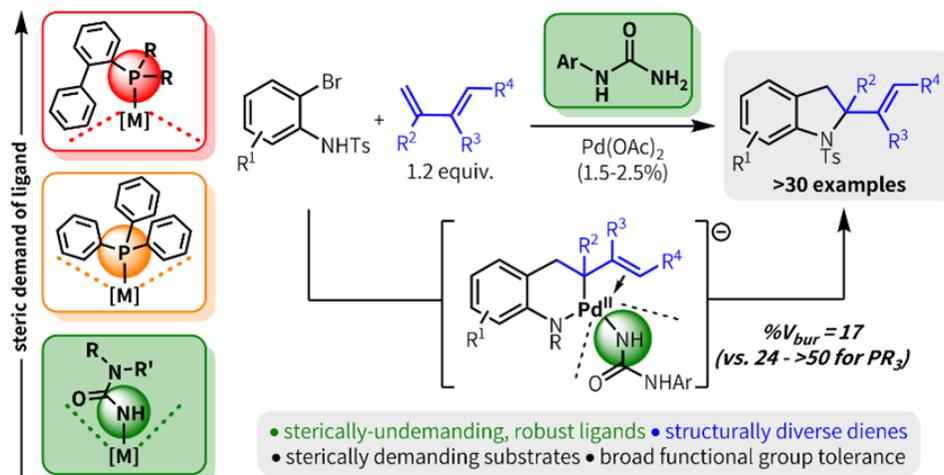
Double functionalization via aryne

Abstract: Since the 1950s, diaryliodonium(III) salts have been demonstrated to participate in various arylation reactions, forming aryl–heteroatom and aryl–carbon bonds. Incorporating the arylation step into sequential transformations would provide access to complex molecules in short steps. This focus review summarizes the double functionalization of carbon–iodine(III) and *ortho* carbon–hydrogen bonds using diaryliodonium(III) salts. This involves arylation/intramolecular rearrangement, arylation followed by electrophilic aromatic substitution, three-component [2 + 2 + 2] cascade annulation, sequential metal-catalyzed arylations, and double functionalization *via* aryne formation.

Pd-Catalyzed Heteroannulation Using *N*-Arylureas as a Sterically Undemanding Ligand Platform

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J. Am. Chem. Soc. **2022**, *144*, 6667–6673.

DOI: 10.1021/jacs.2c01019

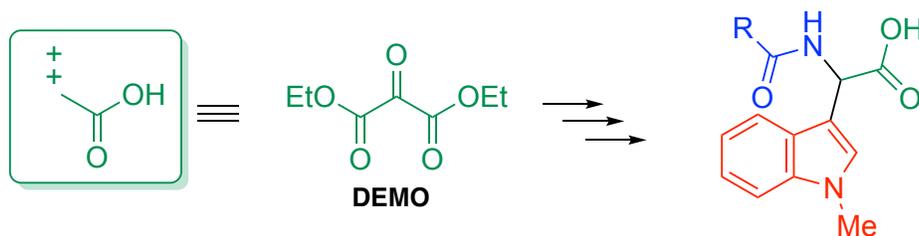


Abstract: We report the development of ureas as sterically undemanding pro-ligands for Pd catalysis. *N*-Arylureas outperform phosphine ligands for the Pd-catalyzed heteroannulation of *N*-tosyl-*o*-bromoanilines and 1,3-dienes, engaging diverse coupling partners for the preparation of 2-substituted indolines, including sterically demanding substrates that have not previously been tolerated. Experimental and computational studies on model Pd-urea and Pd-ureate complexes are consistent with monodentate binding through the nonsubstituted nitrogen, which is uncommon for metal-ureate complexes.

Development of a Synthetic Equivalent of α,α -Dicationic Acetic Acid Leading to Unnatural Amino Acid Derivatives *via* Tetrafunctionalized Methanes

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Org. Biomol. Chem. **2022**, *20*, 2282–2292.

DOI: 10.1039/d1ob02482e



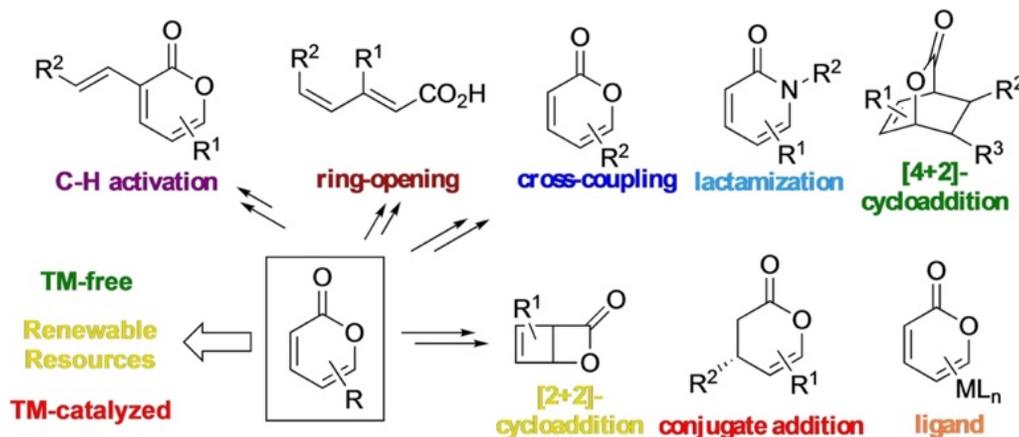
Abstract: Diethyl mesoxalate (DEMO) exhibits high electrophilicity and accepts the nucleophilic addition of a less nucleophilic acid amide to afford *N,O*-hemiacetal. However, our research showed that elimination of the amide moiety easily proceeded more easily than dehydration upon treatment with a base. This problem was overcome by reacting DEMO with an acid amide in the presence of acetic anhydride to efficiently obtain *N,O*-acetal. Acetic acid was eliminated leading to the formation of *N*-acylimine *in situ* upon treatment with the base. *N*-Acylimine is also electrophilic, accepting the second nucleophilic addition by pyrrole or indole to form α,α -disubstituted malonates. Subsequent hydrolysis followed by decarboxylation resulted in (α -indolyl- α -acylamino)acetic acids formation; homologs of tryptophan. Through this process, DEMO serves as a synthetic equivalent of α,α -dicationic acetic acid to facilitate nucleophilic introduction of the two substituents.

2-Pyrone – A Privileged Heterocycle and Widespread Motif in Nature

Daniel Dobler, Michael Leitner, Natalija Moor, and Oliver Reiser* (oliver.reiser@chemie.uni-regensburg.de)

Eur. J. Org. Chem. **2021**, 6180–6205.

DOI: 10.1002/ejoc.202101112



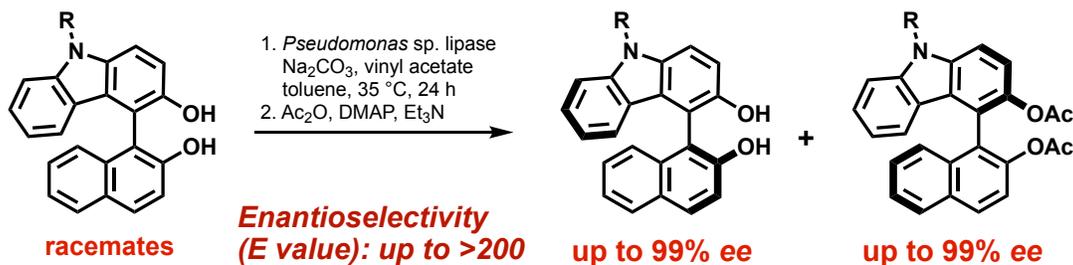
Abstract: This Review summarizes the syntheses and versatile reactions, such as cycloadditions, ring-openings and cross-couplings, of 2-pyrones and their conversion into biologically important compounds published over the last decade.

Lipase-Catalyzed Kinetic Resolution of C₁-Symmetric Heterocyclic Biaryl

Kengo Kasama, Yuya Hinami, Karin Mizuno, Satoshi Horino, Tomoya Nishio, Chiharu Yuki, Kyohei Kanomata, Gamal A. I. Moustafa, Harald Gröger, and Shuji Akai* (akai@phs.osaka-u.ac.jp)

Chem. Pharm. Bull. **2022**, 70, 391–399.

DOI: 10.1248/cpb.c22-00021



Abstract: The highly enantioselective lipase-catalyzed kinetic resolution (KR) of racemic C₁-symmetric biaryl compounds including heterocyclic moieties, such as carbazole and dibenzofuran, has been achieved for the first time. This enzymatic esterification was accelerated by the addition of disodium carbonate while maintaining its high enantioselectivities, and was particularly effective for biaryls having *N*-substituted carbazole moieties. Furthermore, mesoporous silica-supported oxovanadium-catalyzed cross-dehydrogenative coupling of 3-hydroxycarbazole and 2-naphthol was followed by the lipase-catalyzed KR in one pot to synthesize the optically active heterocyclic biaryl compounds with high optical purity.