Issue 58; August 2021

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Recent Publications of ISHC Members

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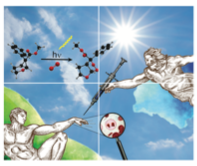
Visible-Light Mediated Oxidative Ring Expansion of Anellated Cyclopropanes to Fused Endoperoxides with Antimalarial Activity

Simon Budde, Felix Goerdeler, Johannes Floß, Peter Kreitmeier, Elliot F. Hicks, Oren Moscovitz, Peter H. Seeberger, Huw M. L. Davies, and Oliver Reiser* (oliver.reiser@chemie.uni-regensburg.de)

Org. Chem. Front. **2020**, *7*, 1789–1795. **DOI:** 10.1039/D0QO00168F



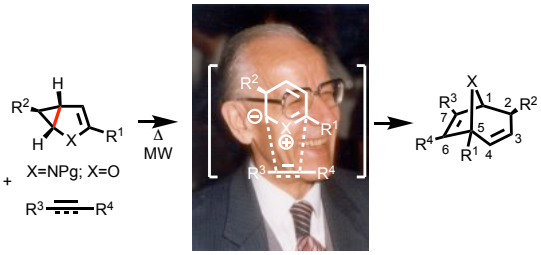
Abstract: A visible light mediated ring expansion of readily available carbo- and heterocyclic anellated cyclopropanes by molecular oxygen at ambient pressure has been developed. Tolerating a variety of functional groups, the reaction yields fused 1,2-dioxolanes, which were tested for antimalarial activity given their close analogy to the active principle of approved drugs such as artemisinin.

Stereoselective Synthesis of Tropanes via a 6π-Electrocyclic Ring-Opening/Huisgen [3+2]-Cycloaddition Cascade of Monocyclopropanated Heterocycles

Carina M. Sonnleitner, Saerom Park, Robert Eckl, Thomas Ertl, and Oliver Reiser* (oliver.reiser@chemie.uni-regensburg.de)

Angew. Chem. Int. Ed. **2020**, *59*, 18110–18115. **DOI:** IE: 10.1002/anie.202006030

Angew. Chem. **2020**, *132*, 18266–18271. GE: 10.1002/ange.202006030

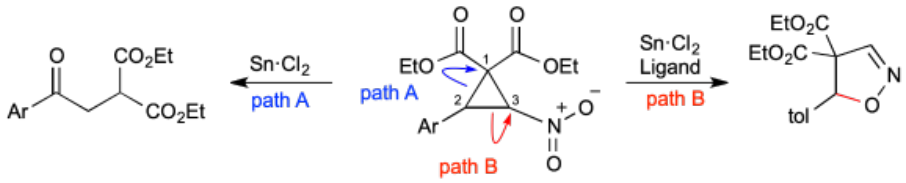


Abstract: The synthesis of tropanes via a microwave-assisted, stereoselective 6π-electrocyclic ring-opening/Huisgen [3+2]-cycloaddition cascade of cyclopropanated pyrrole and furan derivatives with electron-deficient dipolarophiles is demonstrated. Starting from furans or pyrroles, 8-aza- and 8-oxabicyclo[3.2.1]octanes are accessible in two steps in dia- and enantioselective pure form, being versatile building blocks for the synthesis of pharmaceutically relevant targets, especially for new cocaine analogues bearing various substituents at the C-6/C-7 positions of the tropane ring system. Moreover, the 2-azabicyclo[2.2.2]octane core (isoquinuclidines), being prominently represented in many natural and pharmaceutical products, is accessible via this approach.

Regiodivergent Ring Opening Reactions of 2-Arylated 3-Nitrocyclopropane-1,1-Dicarboxylates Leading to Polyfunctionalized Dipoles

Haruyasu Asahara,* Rikiya Kamidate, and Nagatoshi Nishiwaki* (asahara@phs.osaka-u.ac.jp or nishiwaki.nagataoshi@kochi-tech.ac.jp)

Heterocycles **2021**, *103*, 379–391. *Special Issue for Prof. Yasuyuki Kita* **DOI:** 10.3987/COM-20-S(K)21



Abstract: Two kinds of Lewis acid induced ring-opening reactions of 2-aryl-3-nitrocyclopropane-1,1-dicarboxylates proceeded to afford 5-aryl-2-isoxazolines and γ-keto acid derivatives, respectively. Different ring-opening modes could be controlled by choosing the ligand or solvent.

Synthesis of Lactone-Fused Cyclopropanes by Ring Contractive α-Ketol Rearrangement of Ketal-Fused Cyclobutanones

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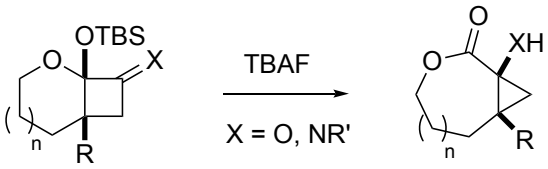
Heterocycles **2021**, *103*, 177–182. *Special Issue for Prof. Yasuyuki Kita* **DOI:** 10.3987/COM-20-S(K)6



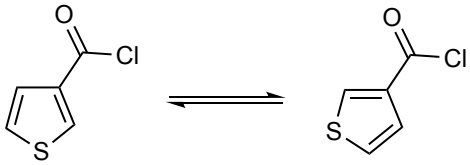
ring contractive α-ketol rearrangement

Abstract: Ring contraction of cyclic silyl ketal-fused cyclobutanones into lactone-fused cyclopropanes under desilylative conditions is described. The reaction affords 1-hydroxy- and 1-amino-1-cyclopropanecarboxylic acid derivatives from cyclobutanone substrates and their imine congeners, respectively.

Thiophene-3-carbonyl Chloride

R. Alan Aitken*and Alexandra M. Z. Slawin (raa@st-and.ac.uk)

Molbank **2021**, *2021*, M1254 (1–4). **DOI:** 10.3390/M1254



X-ray structure

Abstract: The X-ray structure of the title compound has been determined for the first time. It shows the ring flip disorder common among thiophene-3-carbonyl derivatives and the occurrence of this phenomenon in the structures of such compounds is discussed.

Copper Makes the Difference: Visible Light-Mediated Atom Transfer Radical Addition Reactions of Iodoform with Olefins

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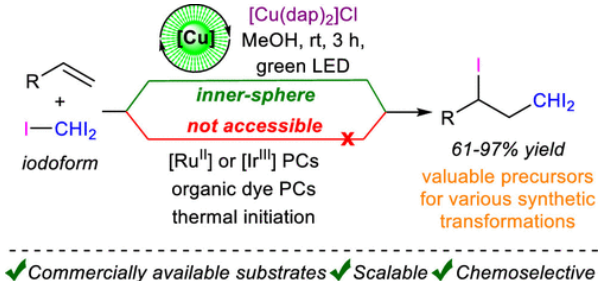
ACS Catal. **2020**, *10*, 9899–9906. **DOI:** 10.1021/acscatal.0c02984

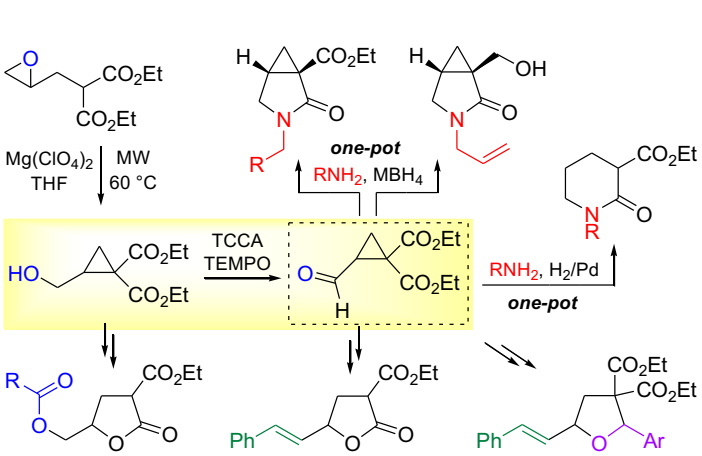


Abstract: Herein, we report a visible light-mediated copper-catalyzed protocol enabling the highly economic, vicinal difunctionalization of olefins utilizing the readily available bulk chemical iodoform. This protocol is characterized by high yields under environmentally benign reaction conditions and allows the regioselective and chemoselective functionalization of activated double bonds. Besides the synthetic utility of the shown transformation, this study undergirds the exclusive role of copper in photoredox catalysis as the title transformation is not possible via the most commonly employed ruthenium, iridium, or organic dye-based photocatalysts owing to the ability of copper to stabilize and interact with radical intermediates in its coordination sphere. Furthermore, the protocol can be smoothly scaled to gram quantities of the product, which offers manifold possibilities for further transformations, for example, heterocycle synthesis or intramolecular cyclopropanation.

Functionalized Cyclopropanes as Versatile Intermediates for the Diversity-Oriented Synthesis of γ-Lactones, γ-Lactams and δ-Lactams

Adrielle P. Maximiano, Giovana S. Ramos, Marcelo V. Marques, Marcus M. Sá* (marcus.sa@ufsc.br)

Synthesis **2021**, *53*, 2408–2421. **DOI:** 10.1055/a-1389-1203

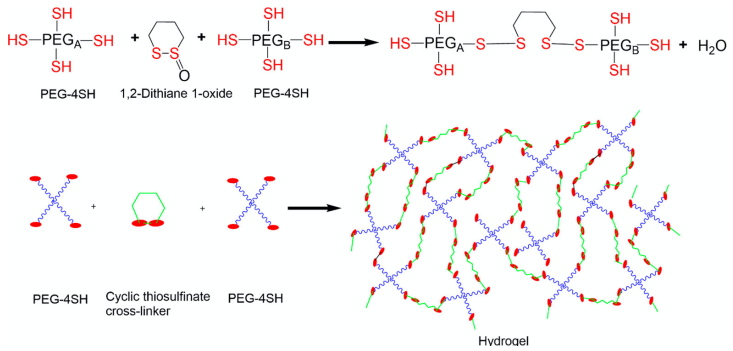


Abstract: A two-step procedure for the preparation of cyclopropanecarboxaldehyde-1,1-diester from a γ,δ-epoxyester and its synthetic versatility are described herein. The epoxide ring-opening/cyclopropanation process occurs in the presence of $Mg(ClO_4)_2$ under heating, resulting in cyclopropanemethanol-1,1-diester in 65% yield. A mild TEMPO-mediated oxidation of this substrate readily generated the corresponding aldehyde in 75% yield, which was applied in the one-pot synthesis of four cyclopropylidene γ-lactams and three δ-lactams. In addition, vinyl cyclopropanes were obtained through the Wittig reaction of the aldehyde with phosphonium salts and used as precursors for tetrahydrofurans.

Cyclic Thiosulfinates as a Novel Class of Disulfide Cleavable Cross-Linkers for Rapid Hydrogel Synthesis

Krishna C. Aluri, Md Amin Hossain, Ninad Kanetkar, Brandon C. Miller, Matthew G. Dowgiallo, Durgalakshmi Sivasankar, Matthew R. Sullivan, Roman Manetsch, Tania Konry, Adam Ekenseair, and Jeffrey N. Agar* (j.agar@northeastern.edu)

Bioconjugate Chem. **2021**, *32*, 584–594. **DOI:** 10.1021/acs.bioconjchem.1c00049

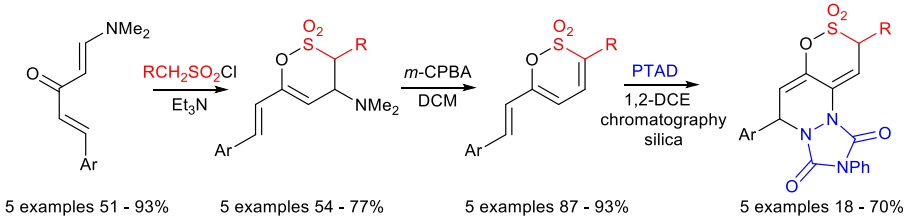


Abstract: We recently reported that cyclic thiosulfinates are cysteine selective cross-linkers that avoid the "dead-end" modifications that contribute to other cross-linkers' toxicity. In this study, we generalize the chemistry of cyclic thiosulfinates to that of thiol selective cross-linking and apply them to the synthesis of hydrogels. Thiol-functionalized four-arm poly(ethylene glycol) and hyaluronic acid monomers were cross-linked with 1,2-dithiane-1-oxide to form disulfide cross-linked hydrogels within seconds. The synthesized hydrogel could be reduced with physiological concentrations of glutathione, which modulated hydrogel mechanical properties and degradation kinetics. Bovine serum albumin protein was successfully encapsulated in hydrogel, and diffusion-mediated release was demonstrated in vitro. Hep G2 cells grew in the presence of preformed hydrogel and during hydrogel synthesis, demonstrating acceptable cytotoxicity. We encapsulated cells within a hydrogel and demonstrated cell growth and recovery up to 10 days, with and without cell adhesion peptides. In summary, we report cyclic thiosulfinates as a novel class of cross-linkers for the facile synthesis of biodegradable hydrogels.

Synthesis, C–H Bond Functionalisation and Cycloadditions of 6-Styryl-1,2-oxathiine 2,2-Dioxides

Christopher D. Gabbutt, B. Mark Heron,* Thomas Lilly, Ochola W. Ogwang, and Dimitrios Zonidis* (m.heron@hud.ac.uk or dimitrios.zonidis@hud.ac.uk)

Org. Biomol. Chem. **2021**, *19*, 6431–6446. **DOI:** 10.1039/d1Ob01125a

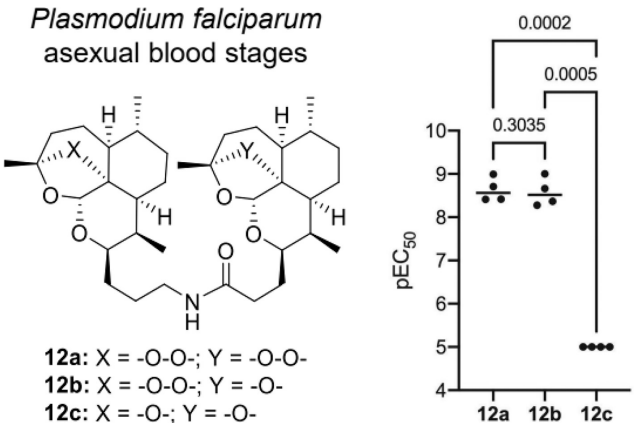


Abstract: A series of 6-styryl-1,2-oxathiine 2,2-dioxides have been efficiently obtained by a two-step protocol from readily available (1*E*,4*E*)-1-(dimethylamino)-5-arylpenta-1,4-dien-3-ones involving a regioselective sulfene addition and subsequent Cope elimination. Pd-mediated direct C–H bond functionalisation of the 6-styryl-1,2-oxathiine 2,2-dioxides and a wider selection of 5,6-diaryl substituted 1,2-oxathiine 2,2-dioxides proceeded smoothly to afford C-3 (hetero)aryl substituted analogues and the results are contrasted with those of a complementary bromination – Suzuki cross-coupling sequence. Whilst the cycloaddition of benzyne, derived from *in situ* fluoride initiated decomposition of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, to the substituted 1,2-oxathiine 2,2-dioxides resulted in low yields of substituted naphthalenes, the addition of 4-phenyl-1,2,4-triazoline-3,5-dione to the 6-styryl-1,2-oxathiine 2,2-dioxides afforded novel 5,9-dihydro-1*H*-[1,2]oxathiino[5,6-*c*][1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione 8,8-dioxides through a silica-mediated isomerisation of the initial [4+2] adducts.

Synthesis of Mono- and Bisperoxide-Bridged Artemisinin Dimers to Elucidate the Contribution of Dimerization to Antimalarial Activity

Cynthia L. Lichorowic, Yingzhao Zhao, Steven P. Maher, Vivian Padín-Irizarry, Victoria C. Mendiola, Sagan T. de Castro, Jacob A. Worden, Debora Casandra, Dennis E. Kyle, and Roman Manetsch* (r.manetsch@northeastern.edu)

ACS Infect. Dis. **2021**, *7*, 2013–2024. **DOI:** 10.1021/acsinfecdis.1c00066

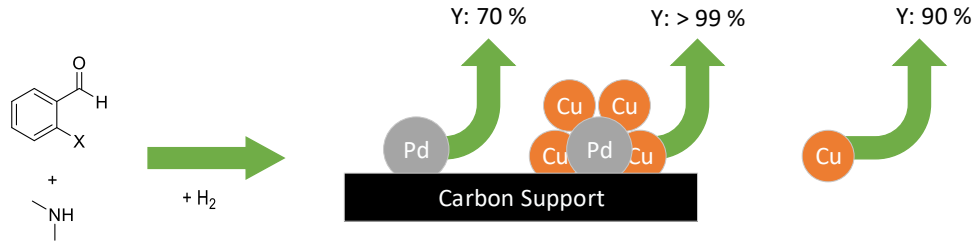


Abstract: During the past decade, artemisinin as an antimalarial has been in the spotlight, in part due to the Nobel Prize in Physiology or Medicine awarded to Tu Youyou. While many studies have been completed detailing the significant increase in activity resulting from the dimerization of natural product artemisinin, activity increases unaccounted for by the peroxide bridge have yet to be researched. Here we outline the synthesis and testing for antimalarial activity of artemisinin dimers in which the peroxide bridge in one-half of the dimer is reduced, resulting in a dimer with one active and one deactivated artemisinin moiety.

Heterogeneous Catalyzed Chemoselective Reductive Amination of Halogenated Aromatic Aldehydes

Kim N. R. Demoleijn,* Alberto Villa, Marcello Marelli, Laura Prati, Kristof Moonen, and Christian V. Stevens* (kimdumoleijn@eastman.com or chris.stevens@ugent.be)

ChemCatChem **2021**, *13*, 3021–3026. **DOI:** 10.1002/cctc202100334

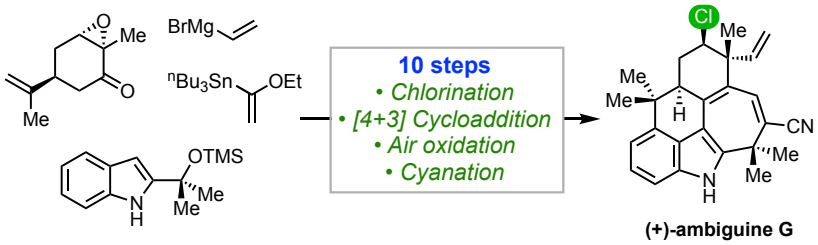


Abstract: The chemoselective conversion of a specific functional group in a multifunctional substrate is of great importance in the chemical industry to obtain cost efficient, sustainable and waste free processes. This work focuses on the chemoselective amination of halogenated aromatic aldehydes with dimethyl amine towards halogenated aromatic amines, a raw material used in the production of for example agrochemical active ingredients. It was found that by combining palladium, a metal known for dehalogenation reactions, and copper, known for its direct hydrogenation of aldehydes to alcohols, in one heterogeneous bimetallic catalyst, a synergistic effect is obtained. By depositing copper onto a palladium on carbon catalyst with a Cu/Pd ratio of at least 1:1, the yield could be increased from 66% (Pd/C) to 98% (PdCu/C). Moreover, this highly active and stable catalyst also showed suppressed dehalogenation side-reactions in several other chemical conversions such as hydrogenation of nitro functional groups and hydrogenation of aldehydes.

Total Synthesis of the Chlorinated Pentacyclic Indole Alkaloid (+)-Ambiguine G

Lingbowei Hu and Viresh H. Rawal* (vrawal@uchicago.edu)

J. Am. Chem. Soc. **2021**, *143*, 10872–10875. **DOI:** 10.1021/jacs.1c05762

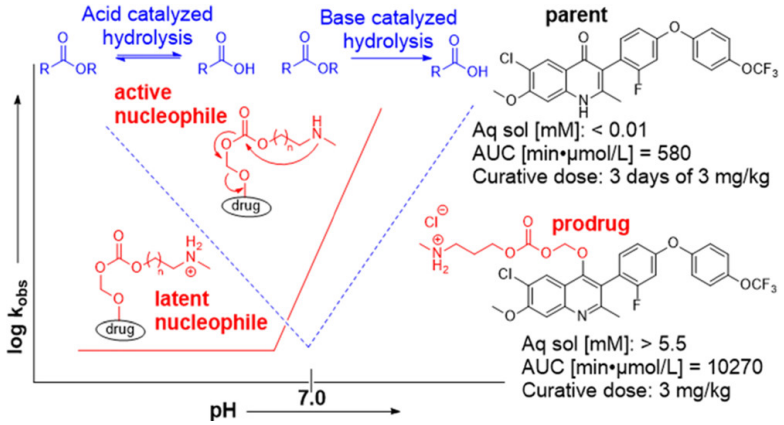


Abstract: We report the total synthesis of (+)-ambiguine G, the first member of the chlorinated pentacyclic ambiguines to yield to chemical synthesis. The synthesis is accomplished through a convergent strategy that proceeds in 10 steps from (*S*)-carvone oxide. Pivotal to the concise route is the successful realization of a [4+3] cycloaddition that conjoins two easily synthesized components of the carbon framework of the natural product. Also featured in the synthesis is the efficient, diastereoselective construction of a key vinylated chloro ketone and the unprecedented, one-pot reduction–elimination–oxidation sequence that transforms an enone to an advanced hydroxylated-diene intermediate.

Aminoalkoxycarbonyloxymethyl Ether Prodrugs with a pH-Triggered Release Mechanism: A Case Study Improving the Solubility, Bioavailability, and Efficacy of Antimalarial 4(1*H*)-Quinolones with Single Dose Cures

Andrii Monastyrskyi, Fabian Brockmeyer, Alexis N. LaCrue, Yingzhao Zhao, Steven P. Maher, Jordany R. Maignan, Vivian Padin-Irizarry, Yana I. Sakhno, Prakash T. Parvatkar, Ami H. Asakawa, Lili Huang, Debora Casandra, Sherwin Mashkouri, Dennis E. Kyle, and Roman Manetsch* (r.manetsch@northeastern.edu)

J. Med. Chem. **2021**, *64*, 6581–6595. **DOI:** 10.1021/acs.jmedchem.0c01104



Abstract: Preclinical and clinical development of numerous small molecules is prevented by their poor aqueous solubility, limited absorption, and oral bioavailability. Herein, we disclose a general prodrug approach that converts promising lead compounds into aminoalkoxycarbonyloxymethyl (amino AOCOM) ether-substituted analogues that display significantly improved aqueous solubility and enhanced oral bioavailability, restoring key requirements typical for drug candidate profiles. The prodrug is completely independent of biotransformations and animal-independent because it becomes an active compound via a pH-triggered intramolecular cyclization–elimination reaction. As a proof-of-concept, the utility of this novel amino AOCOM ether prodrug approach was demonstrated on an antimalarial compound series representing a variety of antimalarial 4(1*H*)- quinolones, which entered and failed preclinical development over the last decade. With the amino AOCOM ether prodrug moiety, the 3-aryl-4(1*H*)-quinolone preclinical candidate was shown to provide single-dose cures in a rodent malaria model at an oral dose of 3 mg/kg, without the use of an advanced formulation technique.