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**Issue 79 July 2023**

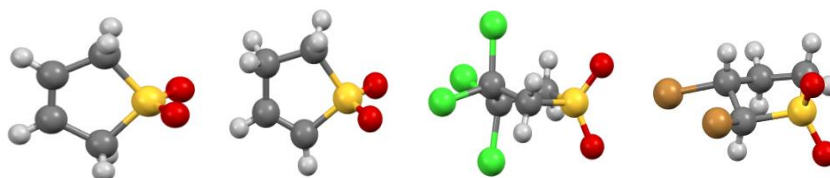
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**The X-ray Structures of 2- and 3-Sulfolene and Two Halogenated Derivatives**

R. Alan Aitken, Alexandra M. Z. Slawin and Dheiryra K. Sonecha

*J. Chem. Crystallogr.* **2023**, *53*, 431–437. DOI: 10.1007/s10870-023-00982-4

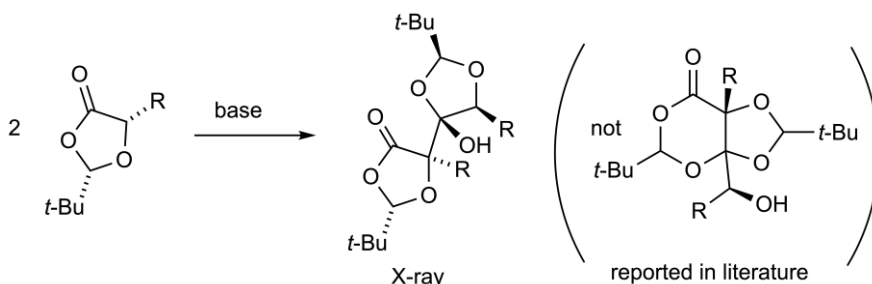


The structures of the isomeric 2,5-dihydrothiophene 1,1-dioxide [orthorhombic,  $a = 11.340(2)$ ,  $b = 7.0887(15)$ ,  $c = 6.2811(13)$ , space group  $Pnma$ ] and 2,3-dihydrothiophene 1,1-dioxide [orthorhombic,  $a = 6.3903(13)$ ,  $b = 7.2783(16)$ ,  $c = 11.075(2)$ , space group  $Pnma$ ] have been determined and show perfectly planar rings with the expected bond lengths and angles. In contrast, the halogenated derivatives 3,3,4,4-tetrachlorotetrahydrothiophene 1,1-dioxide [monoclinic,  $a = 11.8716(8)$ ,  $b = 6.5579(4)$ ,  $c = 11.4802(8)$ .,  $\beta = 97.705(17)$ , space group  $P2_1/c$ ] and 2,3-dibromotetrahydrothiophene 1,1-dioxide [orthorhombic,  $a = 5.2502(3)$ ,  $b = 11.3561(6)$ ,  $c = 24.9802(17)$ ., space group  $Pbca$ ] both show twisted conformations. The degree of planarity is compared with that in the structures of comparable 5-membered ring cyclic sulfones and C–H...O hydrogen bonding patterns are discussed for all four structures.

**(2*S*,2'*S*,4*R*,5*S*,5'*R*)-2,2'-Di-*tert*-butyl-4-hydroxy-5,5'-dimethyl-4,5'-bi(1,3-dioxolanyl)-4'-one**

R. Alan Aitken, Lynn A. Power and Alexandra M. Z. Slawin

*Molbank.* **2023**, *2023*, M1699 (1–5). DOI: 10.3390/M1699

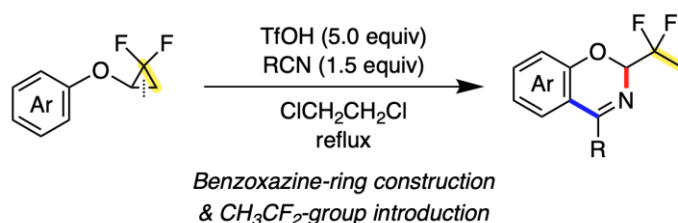


The product formed by base-induced dimerisation of (2*S*,5*S*)-2-*tert*-butyl-5-methyl-1,3-dioxolan-4-one is shown by X-ray diffraction to be the title compound and not the isomeric fused-ring 1,3-dioxolane/1,3-dioxane-4-one structure proposed by previous workers. The analogous compound derived from (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-1,3-dioxolan-4-one has also been obtained and characterised.

## Synthesis of 2-Difluoroethylated 2*H*-1,3-Benzoxazines via Proton-Mediated Ring Opening/Interrupted Ritter Reaction of 1,1-Difluorocyclopropanes

Kohei Fuchibe,\* Taro Matsuo, and Junji Ichikawa\*

*Org. Lett.* **2023**, 25, 4276–4280. DOI: 10.1021/acs.orglett.3c01277

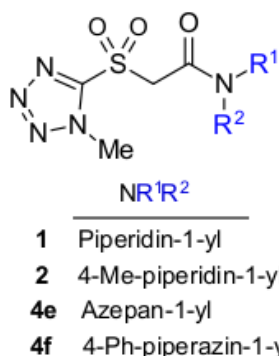


2-(1,1-Difluoroethyl)-2*H*-1,3-benzoxazines were synthesized by (i) the regioselective ring opening of 1,1-difluorocyclopropanes bearing an aryloxy group and (ii) the Ritter reaction followed by a Friedel–Crafts-type ring closure. When 2-aryloxy-1,1-difluorocyclopropanes were treated with triflic acid, the C–C bond distal to the CF<sub>2</sub> moiety was cleaved regioselectively via protonation to generate the corresponding oxocarbenium ions. These intermediates readily underwent nucleophilic attack by nitriles, followed by a carbocationic cyclization to afford the 2-difluoroethylated benzoxazines.

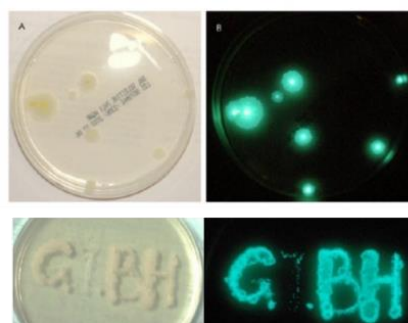
## Synthesis and biological evaluation of 2-(Tetrazol-5-yl)sulfonylacetamides as inhibitors of *Mycobacterium tuberculosis* and *Mycobacterium marinum*

Robin Henches, Théo Ozga, Yamin Gao, Zhengchao Tu, Tianyu Zhang, Craig L. Francis

*Bioorg. Med. Chem. Lett.* **2023**, 92, 129391. <https://doi.org/10.1016/j.bmcl.2023.129391>



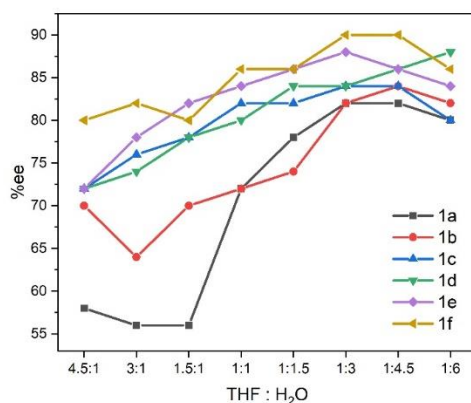
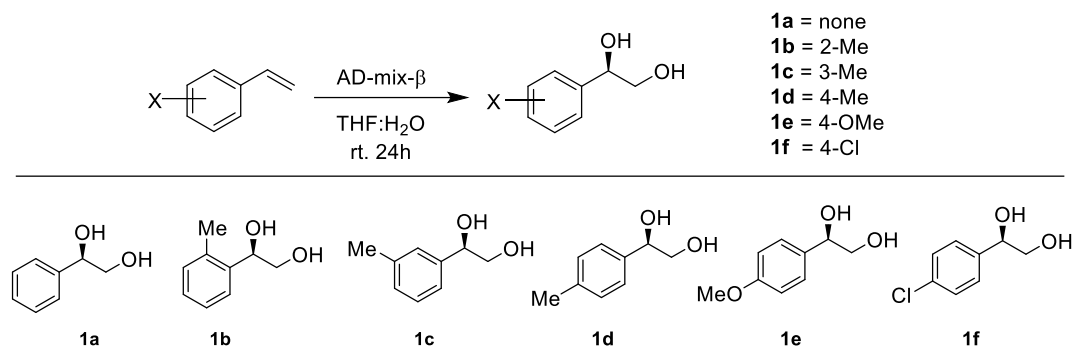
Compound	MIC (µg/mL)
<b>1</b>	1.56
<b>2</b>	1.56
<b>4e</b>	1.25
<b>4f</b>	1.25



A series of 2-(tetrazol-5-yl)sulfonylacetamide derivatives were synthesized and evaluated for their *in vitro* inhibitory activity against *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium marinum* (Mm). The most active compounds exhibited *in vitro* MIC<sub>90</sub> values of 1.25 µg/mL against Mtb, but they were less effective against Mm (MIC<sub>90</sub> ≥ 10 µg/mL). Despite the most active compounds having favourable physicochemical properties and one of them having a half-life of ~3 h when incubated with mouse liver microsomes, two representative highly active compounds showed strong chemical reactivity to cysteine derivatives, as surrogate *in vivo* sulfur-centred nucleophiles, indicating excessive electrophilicity, and therefore, likely indiscriminate chemical reactivity *in vivo*, representing an unacceptably high risk of general toxicity, and low likelihood of being therapeutically effective.

## Aggregation-Induced Catalysis (AIC): Asymmetric Catalysis with Chiral Aggregates

Yao Tang, Yu Wang, Qingkai Yuan, Sai Zhang, Jia-Yin Wang, Shengzhou Jin, Ting Xu, Junyi Pan, Kazimierz Surowiec and Guigen Li\*  
*Research*, 2023, 2023, article 0163, <https://doi.org/10.34133/research.0163>

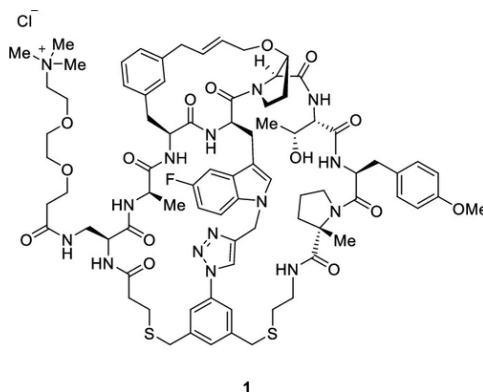


Curve of enhancement in aggregation-induced catalysis of styrenes from AD-mix- $\beta$   
(For the opposite control on Diels-Alder reaction and aggregates' determination, see the paper)

So far, there have been four methods to control chirality including the use of chiral auxiliaries, reagents, solvents, and catalysts documented in literature and textbooks. Among them, asymmetric catalysts are normally divided into homogeneous and heterogeneous catalysis. In this report, we present a new type of asymmetric control – asymmetric catalysis via chiral aggregates which would not belong to the above categories. This new strategy is represented by catalytic asymmetric dihydroxylation reaction (AD) of olefins in which chiral ligands are aggregated by taking advantage of typical AIE systems containing THF and H<sub>2</sub>O co-solvents. It was proven the chiral induction can be enhanced from er of 78:22 to 97:3 simply by changing the ratios of these two co-solvents. The formation of chiral aggregates of AD ligands, (DHQD)<sub>2</sub>PHAL and (DHQ)<sub>2</sub>PHAL, has been proven by AIE (aggregation-induced emission) and a new analytical tool – AIP (aggregation-induced polarization) established by our lab. In the meanwhile, chiral aggregates were found to be formed either by adding NaCl into THF/H<sub>2</sub>O systems or by increasing concentrations of chiral ligands. The present strategy also showed promising reverse control of enantioselectivity in the Diels-Alder reaction. This work is anticipated to be extended broadly to general catalysis, especially to asymmetric catalysis in the future.

## Synthesis of a Complex and Highly Potent PCSK9 Inhibitor

Jeffrey T. Kuethe, Joshua Lee, David Thaisrivongs, Nobuyoshi Yasuda, Scott R. Pollack, Joseph Leone, Jimmy DaSilva, Mirlinda Biba, Fuh-Rong Tsay, Erik L. Regalado, Ji Qi, Hongming Li, Guilherme Dal Poggetto, Ryan Cohen  
*Org. Lett.* 2023, 25, 27, 5001–5005 <https://doi.org/10.1021/acs.orglett.3c01635>

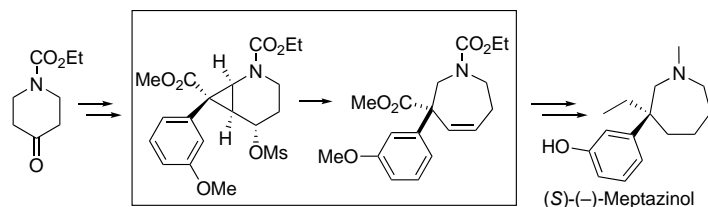


The solution-based gram-scale synthesis of complex and highly potent proprotein convertase subtilisin-like/kexin type 9 (PCSK9) inhibitor **1** is presented. Construction of Northern fragment **2**, followed by stepwise installation of Eastern **3**, Southern **4**, and Western **5** fragments, provided macrocyclic precursor **19**. This intermediate was cross-linked via an intramolecular azide–alkyne click reaction, which preceded macrolactamization to afford the core framework of compound **1**. Finally, coupling with poly(ethylene glycol) side-chain-based **6** gave the PCSK9 inhibitor **1**.

## Asymmetric Total Synthesis of Meptazinol

T. Babl, O. Reiser

*J. Org. Chem.* 2022, 87, 6410–6417; doi: [10.1021/acs.joc.2c00272](https://doi.org/10.1021/acs.joc.2c00272)

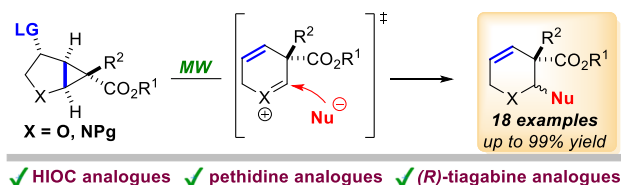


The first enantioselective synthesis of (*S*)-meptazinol in 14 steps from commercially available ethyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate, being widely used in racemic form for pain treatment, and, en route, the formal synthesis of two anti-Alzheimer's agents are reported. A novel ring expansion of 2-azabicyclo[4.1.0]heptanes, readily available via the stereoselective cyclopropanation of 1,2,3,4-tetrahydropyridine-4-ols, provides an effective entry to 3,3-disubstituted azepanes that represent the core for a variety of approved drugs.

## Stereoselective Synthesis of Biologically Relevant Tetrahydropyridines and Dihydro-2H-pyrans via Ring-Expansion of Monocyclopropanated Heterocycles

R. Eckl, S. Fischer, C. M. Sonnleitner, D. Schmidhuber, J. Rehbein, O. Reiser\*

*ACS Org. Inorg. Au* **2022**, 2, 169-174; doi: [10.1021/acsorginorgau.1c00042](https://doi.org/10.1021/acsorginorgau.1c00042)

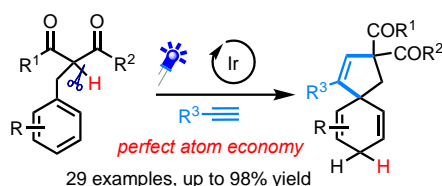


A stereoselective, scalable, and metal-free ring-expansion of monocyclopropanated pyrroles and furans has been developed, leading to value-added highly functionalized tetrahydropyridine and dihydro-2H-pyran derivatives. Featuring a cyclopropylcarbinyl cation rearrangement as the key step, the selective cleavage of the unactivated endocyclic cyclopropane C–C bond is achieved. Targeted transformations of the thus obtained six-membered heterocycles give access to versatile building blocks with relevance for drug synthesis.

## Thermoneutral synthesis of spiro-1,4-cyclohexadienes by visible-light-driven dearomatization of benzylmalonates

Q-Q. Zhao, J. Rehbein, O. Reiser

*Green Chem.* **2022**, 24, 2772-2776; doi: [10.1039/D1GC04686A](https://doi.org/10.1039/D1GC04686A)

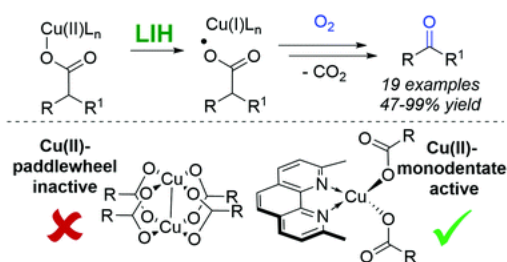


A visible-light-driven dearomatization of unactivated arenes with perfect atom economy to access spiro-1,4-cyclohexadienes is disclosed. Calculations suggest that the overall process is approximately thermoneutral, showcasing the special opportunities of light-driven processes to develop sustainable transformations that defy thermodynamic requirements.

## Copper(II)-photocatalyzed decarboxylative oxygenation of carboxylic acids

A. Reichle, H. Sterzel, P. Kreitmeier, R. Fayad, F. N Castellano\*, J. Rehbein\*, O. Reiser

*Chem. Commun.* **2022**, 58, 4456-4459; doi: [10.1039/D2CC00570K](https://doi.org/10.1039/D2CC00570K)

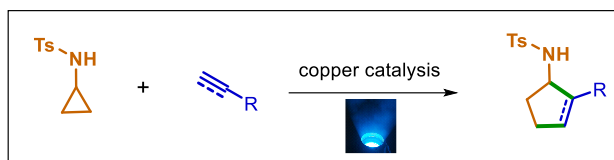


Showcasing the concept of light-induced homolysis for the generation of radicals, the Cu<sup>II</sup>-photocatalyzed decarboxylative oxygenation of carboxylic acids with molecular oxygen as the terminal oxidant is described. Two Cu<sup>II</sup>-carboxylate complexes with different coordination geometries were synthesized and characterized by X-ray analysis, correlating their structure with their ability to initiate light-induced decarboxylations.

## Visible-Light-Accelerated Copper-Catalyzed [3 + 2] Cycloaddition of *N*-Tosylcyclopropylamines with Alkynes/Alkenes

M. Kumar, S. Verma, V. Mishra, O. Reiser\*, A.K. Verma

*J. Org. Chem.* **2022**, *87*, 6262-6272; doi: [10.1021/acs.joc.2c00491](https://doi.org/10.1021/acs.joc.2c00491)



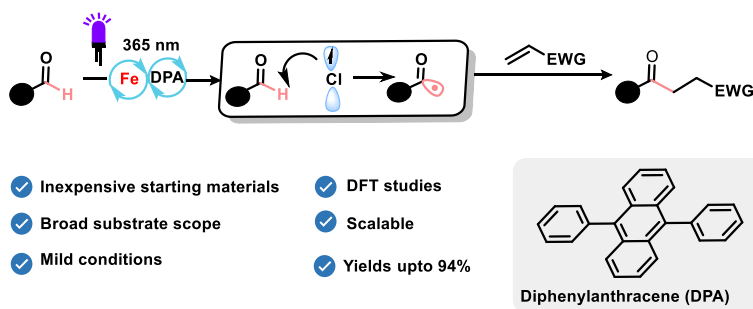
- Successful with alkenes and alkynes
- Ligand, base and additive free
- Copper catalysis

Copper-catalyzed [3 + 2] cycloadditions of *N*-tosylcyclopropylamine with alkynes and alkenes have been accomplished under visible light irradiation. The developed approach is compatible with a range of functionalities and allows the synthesis of diversified aminated cyclopentene and cyclopentane derivatives being relevant for drug synthesis. The protocol is operationally simple and economically affordable as it does not require any ligand, base, or additives. As the key step, the one-electron oxidation of the *N*-tosyl moiety by visible light-induced homolysis of a transient Cu(II)-tosylamide complex is proposed, providing a facile entry for *N*-centered radicals.

## Iron(III)-Light-Induced Homolysis: A Dual Photocatalytic Approach for the Hydroacylation of Alkenes Using Acyl Radicals via Direct HAT from Aldehydes

A. Chinchole, M. A. Henriquez, D. Cortes-Arriagada, A. R. Cabrera, O. Reiser

*ACS Catal.* **2022**, *12*, 13549-13555; doi: [10.1021/acscatal.2c03315](https://doi.org/10.1021/acscatal.2c03315)

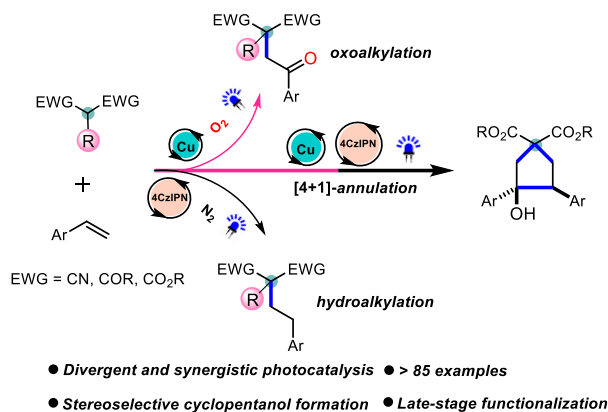


A dual photocatalytic protocol was developed to generate acyl radicals from readily available aldehydes via hydrogen atom transfer (HAT). Synergistic cooperation, being supported by DFT studies, between earth-abundant iron(III)chloride and 9,10-diphenylanthracene (DPA) to activate the aldehyde for a HAT step proved to be an efficient, economic, and green route for the hydroacylation of electron-deficient alkenes under UV-light irradiation with broad functional group compatibility. This methodology can be conveniently scaled up and applied to produce valuable materials from renewable feedstock chemicals.

## Divergent and Synergistic Photocatalysis: Hydro- and Oxoalkylation of Vinyl Arenes for the Stereoselective Synthesis of Cyclopentanols via a Formal [4+1]-Annulation of 1,3-Dicarbonyls

N. Katty, Q.-Q. Zhao, T. Mandal, O. Reiser

*ACS Catal.* **2022**, *12*, 14398-14407; doi: [10.1021/acscatal.2c04736](https://doi.org/10.1021/acscatal.2c04736)

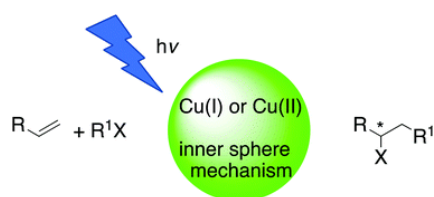


The controllable divergent reactivity of 1,3-dicarbonyls is described, which enables the efficient hydro- and oxoalkylation of vinyl arenes. Both reaction pathways are initiated through the formation of polarity-reversed C-centered-radical intermediates at the active methylene center of 1,3-dicarbonyls via direct photocatalytic C–H bond transformations. The oxoalkylation of alkenes is achieved under aerobic conditions via a Cu(II)-photomediated rebound mechanism, while the corresponding hydroalkylation becomes possible under a nitrogen atmosphere by the combination of 4CzIPN and a Brønsted base. The breadth of these divergent protocols is demonstrated in the late-stage modification of drugs and natural products and by the transformation of the products to a variety of heterocycles such as pyridines, pyrroles, or furans. Moreover, the two catalytic modes can be combined synergistically for the stereoselective construction of cyclopentanol derivatives in a formal [4+1]-annulation process.

## Copper-photocatalyzed ATRA reactions: concepts, applications, and opportunities

S. Engl, O. Reiser

*Chem. Soc. Rev.* **2022**, *51*, 5287-5299; doi: [10.1039/d2cs00303a](https://doi.org/10.1039/d2cs00303a)

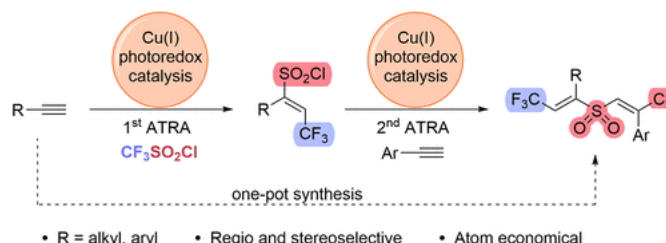


Atom transfer radical addition (ATRA) reactions are linchpin transformations in synthetic chemistry enabling the atom-economic difunctionalization of alkenes. Thereby a rich chemical space can be accessed through smart combinations of simple starting materials. Originally, these reactions required toxic and hazardous radical initiators or harsh thermal activation and thus, the recent resurgence and dramatic evolution of photocatalysis appeared as an attractive complement to catalyze such transformations in a mild and energy-efficient manner. Initially, this technique relied primarily on complexes of precious metals, such as ruthenium or iridium, to absorb visible light. Hence, copper photocatalysis rapidly developed into a powerful alternative, not just from an economic point of view. Originally considered to be disadvantageous as a pathway for deactivation by quenching their excited state, the dynamic nature of Cu-complexes enables them to undergo facile ligand exchange and thus opens up special opportunities for transformations utilizing their inner-coordination sphere. Moreover, the ability of Cu(II), representing a persistent radical, to capture incipient radicals offers the possibility to access heretofore elusive two-component, but also three-component, ATRA reactions, not feasible with ruthenium or iridium catalysts. In this regard, the idea of using Cu(I)-substrate assemblies as active photocatalysts is an emerging field to achieve such 3-component coupling reactions even under enantioselective control, which is reflected by an increasing number of reports being covered in this review.

## Copper- and Photoredox-Catalyzed Cascade to Trifluoromethylated Divinyl Sulfones

N. Petek, H. Brodник, O. Reiser\*, B. Štefane

*J. Org. Chem.* **2023**, *88*, 6538-6547; doi: [10.1021/acs.joc.2c02422](https://doi.org/10.1021/acs.joc.2c02422)



A Cu(I)-photoredox-catalyzed trifluoromethylchlorosulfonylation reaction of terminal alkynes under visible light conditions was developed, giving rise to trifluoromethyl-substituted vinylsulfonyl chlorides, which can subsequently be coupled to a second alkyne under photocatalytic conditions. The transformation proceeds with high regio- and stereoselectivity and can be applied to aliphatic and aromatic alkynes with various functional groups. Trifluoromethyl-substituted divinyl sulfones prepared by this protocol can be readily used as synthetically valuable intermediates as demonstrated with various postmodification examples.

## Cu(I)-photocatalyzed Bromonitroalkylation of Olefins: New Evidence for Highly Efficient Inner Sphere Pathways

A. Reichle, M. Koch, H. Sterzel, L.-J. Großkopf, J. Floss, J. Rehbein\*, O. Reiser

*Angew. Chem. Int. Ed.* **2023**, *62*, e202219086; doi: [10.1002/anie.202219086](https://doi.org/10.1002/anie.202219086)

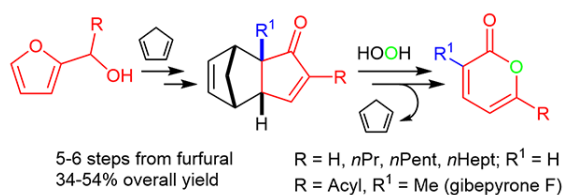


Photocatalytic bromonitroalkylations of activated and unactivated olefins with broad scope become possible in the presence of Cu<sup>I</sup>-photocatalysts. The key to success for this transformation is the highly efficient interaction of Cu<sup>II</sup> with radical intermediates, which can even outperform a highly favorable cyclization of a transient to a persistent radical.

## Synthesis of 2-Pyrones from Renewable Resources

D. Dobler, M. Leitner, P. Kreitmeier, O. Reiser

*Synthesis* **2023**, *55*, 2304-2310; doi: <https://doi.org/10.1055/a-2085-4089>



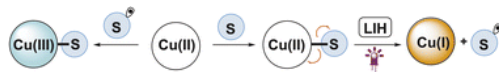
An atom-economic reaction sequence on a multigram scale for synthesizing 2-pyrone was developed starting from furfuryl alcohol, a renewable resource made from bran or bagasse, utilizing a large-scale thermal rearrangement of cyclopentadienone epoxide as the key step. Additionally, 6-substituted 2-pyrone natural product derivatives are readily accessible by this approach.



## Light-induced homolysis of copper(ii)-complexes – a perspective for photocatalysis

A. Reichle, O. Reiser

*Chem. Sci.* **2023**, *14*, 4449-4462; doi: [10.1039/D3SC00388D](https://doi.org/10.1039/D3SC00388D)

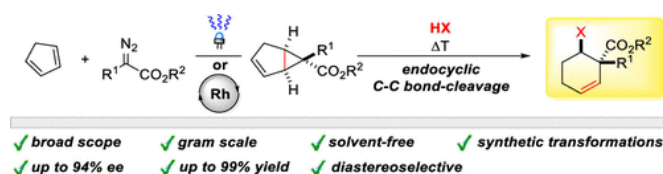


Over the past decade, photocatalysis has developed into a powerful strategy for the selective functionalization of molecules through radical intermediates. Besides the well-established iridium- or ruthenium-based photocatalysts, which ideally fulfill the requirements for a photocatalyst, such as long excited-state lifetimes and photostability, the shift towards earth-abundant metal-based photocatalysts has so far been less explored. The concept of light-induced homolysis (LIH) for generating radicals has recently gained significant interest as a new platform for inducing photoreactions with earth-abundant 3d-metal complexes despite only having excited-state lifetimes in the low nanosecond range or even below. Cu(II)-complexes play a prominent role in exploiting this concept, which will be discussed by showcasing recent developments in organic synthesis with a view to identifying the future prospects of this growing field.

## Stereoselective Synthesis of Highly Functionalized Cyclohexenes via Strong-Acid-Mediated Endocyclic C–C Bond Cleavage of Monocyclopropanated Cyclopentadienes

S. Fischer, T.-T. H. Nguyen, A. Ratzenboeck, H. M. L. Davies\*, O. Reiser

*Org. Lett.* **2023**, *25*, 4411-4415; doi: [10.1021/acs.orglett.3c00935](https://doi.org/10.1021/acs.orglett.3c00935)



A stereoselective, solvent- and metal-free endocyclic C–C bond cleavage of monocyclopropanated cyclopentadienes mediated by strong acids was developed, leading to highly functionalized six-membered carbocycles with high stereocontrol. The critical step for this ring-expansion is the formation of a cyclopropyl carbocation that undergoes endocyclic ring opening via an  $SN_2'$ -type attack of various nucleophiles. Subsequent synthetic transformations show the versatility of the resulting cyclohexenes for the synthesis of new compounds with nonconventional substitution patterns.