

# The ISHC Bulletin

## Recent Publications of ISHC Members

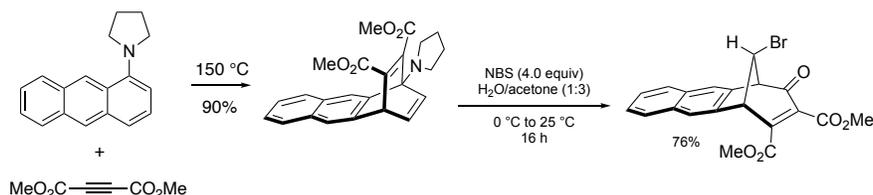
Issue 59; September 2021

### Diels–Alder Reactions and Electrophilic Substitutions with Atypical Regioselectivity Enable Functionalization of Terminal Rings of Anthracene

Vinh Ngoc Huynh, Michael Leitner, Aditya Bhattacharyya, Lisa Uhlstein, Peter Kreitmeier, Patrick Sakrausky, Julia Rehbein,\* and Oliver Reiser\* ([julia.rehbein@chemie.uni-regensburg.de](mailto:julia.rehbein@chemie.uni-regensburg.de) or [oliver.reiser@chemie.uni-regensburg.de](mailto:oliver.reiser@chemie.uni-regensburg.de))

*Commun. Chem.* **2020**, *3*, 158 (1–9).

DOI: 10.1038/s42004-020-00407-9



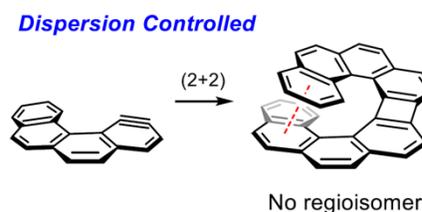
**Abstract:** Reversing the regioselectivity of the renowned Diels-Alder reaction by overriding the usual thermodynamic and kinetic governing factors has always been a formidable challenge to synthetic organic chemists. We, herein, report a 1,4-selective [4 + 2]-cycloaddition strategy of 9,10-unsubstituted anthracenes by installing electron-donating substituents on the terminal rings which is heretofore unprecedented to the best of our knowledge.

### Could London Dispersion Force Control Regioselective (2 + 2) Cyclodimerizations of Benzenes? YES: Application to the Synthesis of Helical Biphenylenes

Takashi Ikawa,\* Yuta Yamamoto, Akito Heguri, Yutaka Fukumoto, Tomonari Murakami, Akira Takagi, Yuto Masuda, Kenzo Yahata, Hiroshi Aoyama, Yasuteru Shigeta, Hiroaki Tokiwa,\* and Shuji Akai\* ([ikawa-ta@gifu-pu.ac.jp](mailto:ikawa-ta@gifu-pu.ac.jp) or [htokiwa@yahoo.co.jp](mailto:htokiwa@yahoo.co.jp) or [akai@phs.osaka-u.ac.jp](mailto:akai@phs.osaka-u.ac.jp))

*J. Am. Chem. Soc.* **2021**, *143*, 10853–10859.

DOI: 10.1021/jacs.1c05434



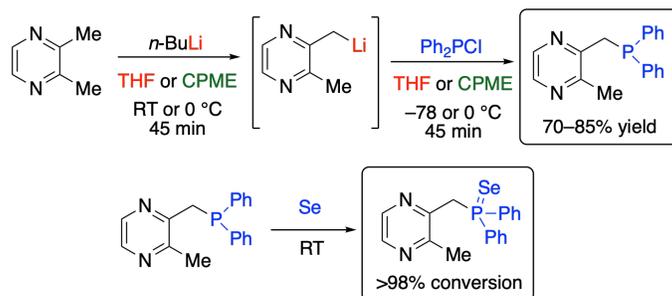
**Abstract:** In recent years, London dispersion interactions, which are the attractive component of the van der Waals potential, have been found to play an important role in controlling the regio- and/or stereoselectivity of various reactions. Particularly, the dispersion interactions between substrates and catalysts (or ligands) are dominant in various selective catalyses. In contrast, repulsive steric interactions, rather than the attractive dispersion interactions, between bulky substituents are predominant in most of the noncatalytic reactions. Herein, we demonstrate the first example of London dispersion-controlled noncatalytic (2 + 2) cyclodimerization of substituted benzenes to selectively afford proximal biphenylenes in high yields and regioselectivities, depending on the extent of dispersion interactions in the substituents. This method can be applied for the synthesis of novel helical biphenylenes, which would be fascinating for chemist as these compounds are potential skeletons for ligands, catalysts, and medicines.

## 2-Diphenylphosphinomethyl-3-methylpyrazine

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*Molbank* **2021**, 2021, M1267 (1–7).

DOI: 10.3390/M1267



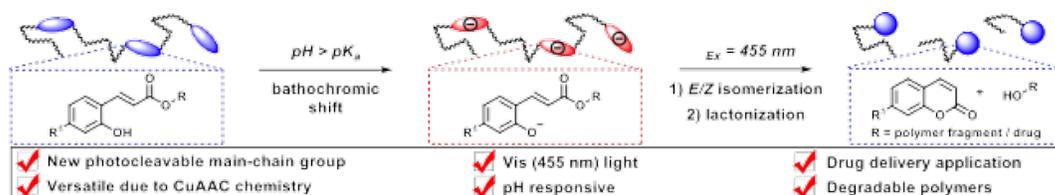
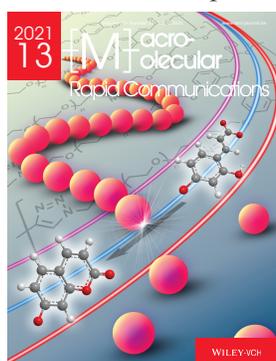
**Abstract:** The lateral metalation-electrophilic trapping reaction of alkyl-substituted pyrazines has always been challenging and poorly regioselective, with the corresponding derivatives often being isolated in moderate yield. In this contribution, we first report on the preparation of an unsymmetrically substituted pyrazine, that is 2-diphenylphosphinomethyl-3-methylpyrazine, by subjecting to metalation with *n*-BuLi the commercially available 2,3-dimethylpyrazine, followed by interception of the putative lithiated benzyl-type intermediate with Ph<sub>2</sub>PCl. Such a functionalization has been successfully carried out in the absence of additional ligands, working either in THF at –78 °C or in a more environmentally friendly solvent like cyclopentyl methyl ether at 0 °C, with the desired phosphine derivative being isolated in 70–85% yield. The newly synthesized adduct has been fully characterized by means of multinuclear magnetic resonance spectroscopic techniques, and also by preparing a selenium derivative, which furnished single crystals that were suitable for X-ray analysis.

## A pH-Triggered Polymer Degradation or Drug Delivery System by Light-Mediated *Cis/Trans* Isomerization of *o*-Hydroxy Cinnamates

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*Macromol. Rapid Commun.* **2021**, 42, 2100213 (1–6).

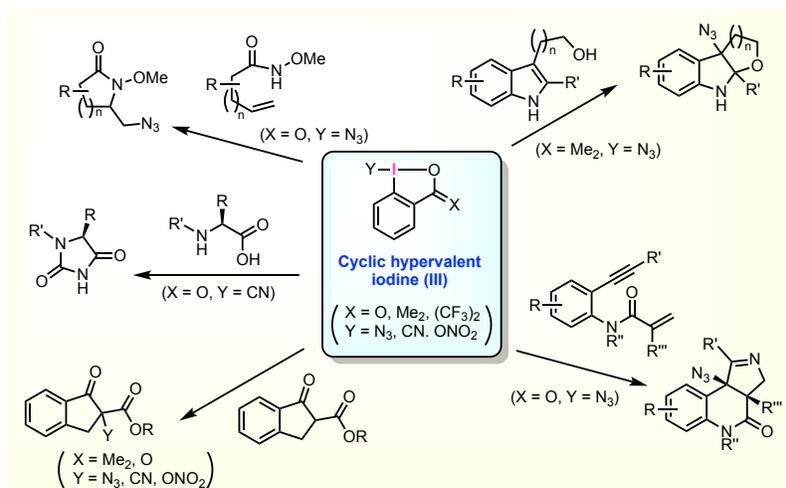
DOI: 10.1002/marc.202100213



**Abstract:** Coumarins can be rapidly synthesized from *trans-ortho*-hydroxycinnamates under visible light irradiation in the absence of a photocatalyst based on a bathochromic shift of its absorption from the UV to the visible light region under basic conditions. This methodology is applied for the preparation of dual pH- and photo-responsive polymers with potential for degradable polymer and drug delivery applications.

## Azido, Cyano, and Nitrate Cyclic Hypervalent Iodine(III) Reagents in Heterocycle Synthesis

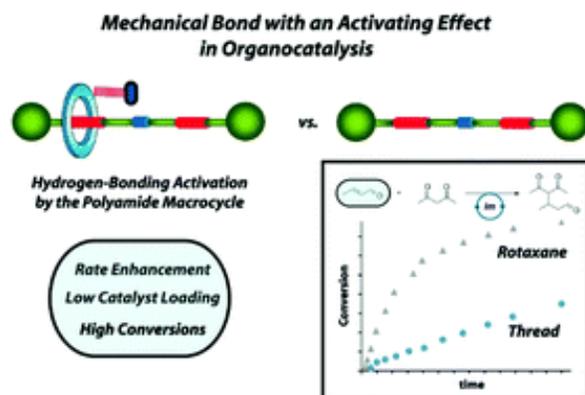
Naoko Takenaga,\* Hideyasu China, Ravi Kumar, and Toshifumi Dohi\* ([ntakenag@meijo-u.ac.jp](mailto:ntakenag@meijo-u.ac.jp))  
*Heterocycles* **2021**, *103*, 144–164. *Special Issue for Prof. Yasuyuki Kita* DOI: 10.3987/REV-20-SR(K)5



**Abstract:** In recent years, synthetic applications of cyclic hypervalent iodine reagents have undergone significant developments. Among them, benziodoxol(on)es containing azido, cyano, and nitrate ligands have been found to be useful synthetic tools for the preparation of functionalized heterocyclic compounds. This review aims to summarize recent synthetic applications of benziodoxol(on)es as effective heteroatom-introducing reagents.

## Mechanical Bonding Activation in Rotaxane-Based Organocatalysts

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*Org. Chem. Front.* **2021**, *8*, 4202–4210. DOI: 10.1039/d1qo00789k



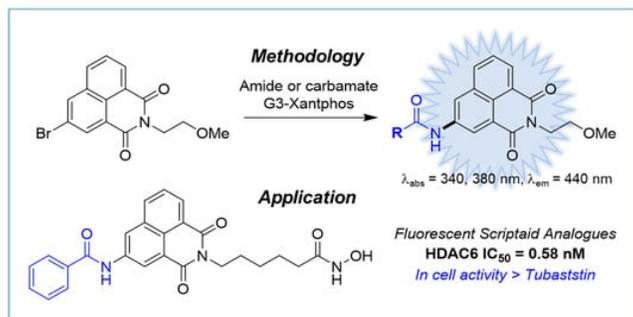
**Abstract:** We report herein the enhanced efficiency as organocatalysts of a series of succinamide-based hydrogenbonded [2]rotaxanes functionalized with an acyclic secondary amine as the catalytically active site. We also evaluated their catalytic activity, compared with that of their non-interlocked threads, in an iminium-type process between crotonaldehyde and acetylacetone. The presence of an interlocked polyamide macrocycle notably increased the catalytic activity of the entwined organocatalysts. The mechanized catalysts rapidly form a reactive iminium intermediate with the aldehyde, increasing its population. The hydrogen-bonding interaction established between the macrocycle and the electrophile has been proposed as one of the reasons for the rapid formation and stabilization of this key intermediate.

## Direct Amidation to Access 3-Amido-1,8-Naphthalimides Including Fluorescent Scriptaid Analogues as HDAC Inhibitors

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*Cells* **2021**, *10*, 1505 (1–10).

DOI: 10.3390/cells10061505

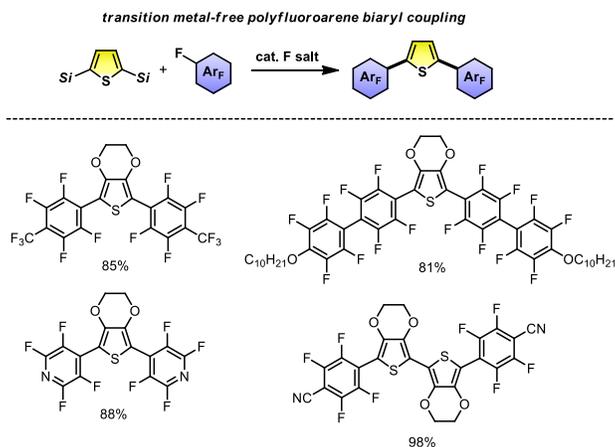


**Abstract:** Methodology to access fluorescent 3-amido-1,8-naphthalimides using direct Buchwald–Hartwig amidation is described. The protocol was successfully used to couple a number of substrates (including an alkylamide, an arylamide, a lactam and a carbamate) to 3-bromo-1,8-naphthalimide in good yield. To further exemplify the approach, a set of scriptaid analogues with amide substituents at the 3-position were prepared. The new compounds were more potent than scriptaid at a number of histone deacetylase (HDAC) isoforms including HDAC6. Activity was further confirmed in a whole cell tubulin deacetylation assay where the inhibitors were more active than the established HDAC6 selective inhibitor Tubastatin. The optical properties of these new, highly active, compounds make them amenable to cellular imaging studies and theranostic applications.

## Polyfluoroarene-Capped Thiophene Derivatives via Fluoride-Catalyzed Nucleophilic Aromatic Substitution

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*Heterocycles* **2021**, *103*, 878–892. *Special Issue for Prof. Yasuyuki Kita* DOI: 10.3987/COM-20-S(K)54



**Abstract:** Arylthiophene derivatives are potential components of functional materials, including organic electronics. Herein, we describe a nucleophilic aromatic substitution reaction of polyfluoroarenes using silylthiophenes as nucleophiles in the presence of a catalytic amount of a fluoride salt. Various polyfluoroarene-capped thiophene derivatives were synthesized via double arylation under transition metal-free conditions. A fluoride ion activates a silylthiophene to trigger a nucleophilic aromatic substitution, subsequently affording the coupling product along with elimination of the fluoride ion, which serves as a promoter of the catalytic reaction.

## Catalyst-Free Visible-Light-Mediated Iodoamination of Olefins and Synthetic Applications

Sebastian Engl and Oliver Reiser\* ([oliver.reiser@chemie.uniregensburg.de](mailto:oliver.reiser@chemie.uniregensburg.de))

*Org. Lett.* **2021**, *23*, 5581–5586.

DOI: 10.1021/acs.orglett.1c02035



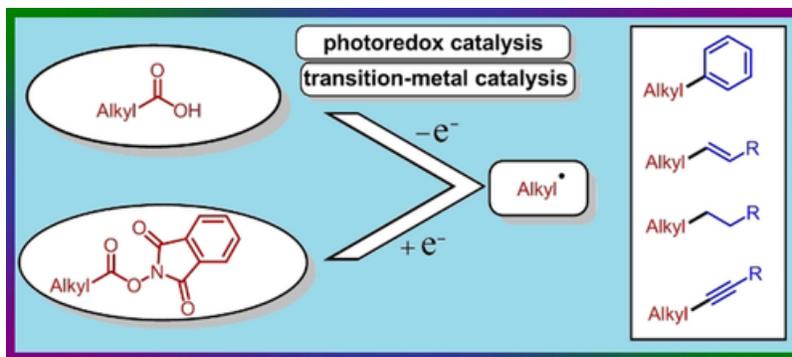
**Abstract:** Herein we report a catalyst- and metal-free visible-light-mediated protocol enabling the iodoamination of miscellaneous olefins. This protocol is characterized by high yields under environmentally benign reaction conditions utilizing commercially available substrates and a green and biodegradable solvent. Furthermore, the protocol allows for late-stage functionalization of bioactive molecules and can be scaled to gram quantities of product, which offers manifold possibilities for further transformations, including morpholine, piperidine, pyrrolidine, and aziridine synthesis.

## Utilization of C(sp<sup>3</sup>)-Carboxylic Acids and Their Redox-Active Esters in Decarboxylative Carbon–Carbon Bond Formation

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*Adv. Synth. Catal.* **2021**, *363*, 3693–3736.

DOI: 10.1002/adsc.202100314



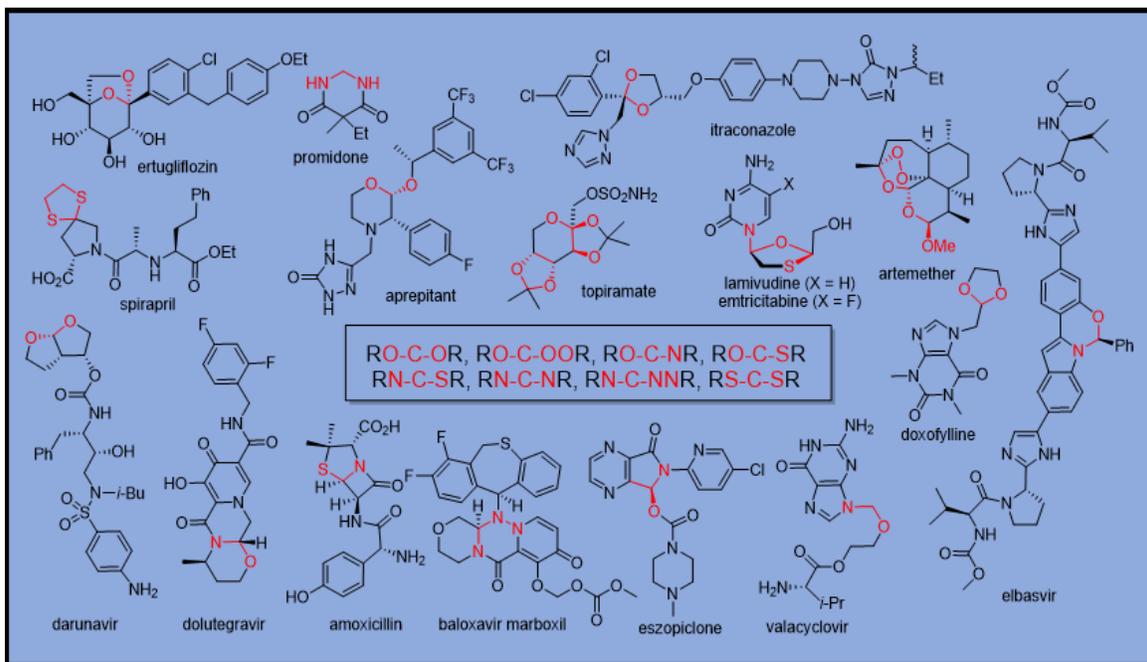
**Abstract:** Over the last several years, radical-mediated decarboxylative cross-coupling reactions employing alkyl carboxylic acids have emerged as a powerful tool for the regiospecific construction of carbon-carbon bonds. Under thermal or photocatalytic conditions, a wide variety of C(sp<sup>3</sup>)-carboxylic acids and their redox-active esters undergo decarboxylative C–C bond formation with suitable reactant partners, leading to complex chemical scaffolds with wide-ranging applications. This synthetic strategy has several advantages over the more conventional organometallic reagents, including abundant starting material availability and high functional group tolerance associated with the mild reaction conditions. This review article highlights recent developments in the functionalization of  $\alpha$ -heteroatom-substituted carboxylic acids as well as the more challenging unactivated acids, with representative examples discussed against the backdrop of insightful comments on reaction mechanisms. In addition, examples of the synthesis of natural products, drug molecules, and the late-stage modification of bioactive molecules employing this non-traditional C–C bond formation strategy are included. This review has been categorized into three main sections that are organized around the type of C–C bond being forged: C(sp<sup>3</sup>)–C(sp<sup>2</sup>), C(sp<sup>3</sup>)–C(sp<sup>3</sup>), and C(sp<sup>3</sup>)–C(sp). Further, the reactions of carboxylic acids and their redox-active esters have been organized separately in each section.

## Geminal Diheteroatomic Motifs: Some Applications of Acetals, Ketals, and Their Sulfur and Nitrogen Homologues in Medicinal Chemistry and Drug Design

Yong-Jin Wu\* and Nicholas A. Meanwell\* ([yong-jin.wu@bms.com](mailto:yong-jin.wu@bms.com) or [nicholas.meanwell@bms.com](mailto:nicholas.meanwell@bms.com))

*J. Med. Chem.* **2021**, *64*, 9786–9874.

DOI: 10.1021/acs.jmedchem.1c00790



**Abstract:** Acetals and ketals and their nitrogen and sulfur homologues are often considered to be unconventional and potentially problematic scaffolding elements or pharmacophores for the design of orally bioavailable drugs. This opinion is largely a function of the perception that such motifs might be chemically unstable under the acidic conditions of the stomach and upper gastrointestinal tract. However, even simple acetals and ketals, including acyclic molecules, can be sufficiently robust under acidic conditions to be fashioned into orally bioavailable drugs, and these structural elements are embedded in many effective therapeutic agents. The chemical stability of molecules incorporating geminal diheteroatomic motifs can be modulated by physicochemical design principles that include the judicious deployment of proximal electron-withdrawing substituents and conformational restriction. In this Perspective, we exemplify geminal diheteroatomic motifs that have been utilized in the discovery of orally bioavailable drugs or drug candidates against the backdrop of understanding their potential for chemical lability.