

## The ISHC Bulletin

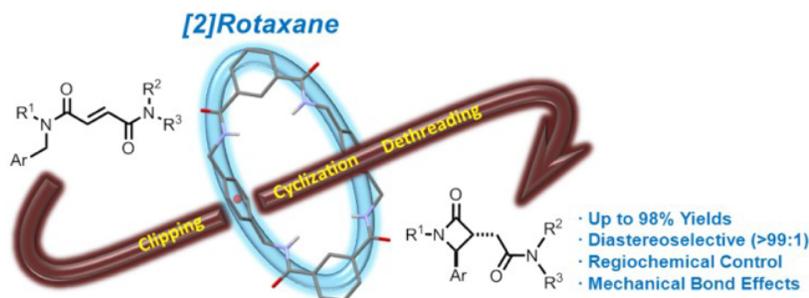
### Recent Publications of ISHC Members

Issue 6; October 2016

#### Stereocontrolled Synthesis of $\beta$ -Lactams within [2]Rotaxanes: Showcasing the Chemical Consequences of the Mechanical Bond

Alberto Martinez-Cuezva, Carmen Lopez-Leonardo, Delia Bautista, Mateo Alajarin, and Jose Berna  
*J. Am. Chem. Soc.* **2016**, *138*, 8726–8729.

DOI: 10.1021/jacs.6b05581

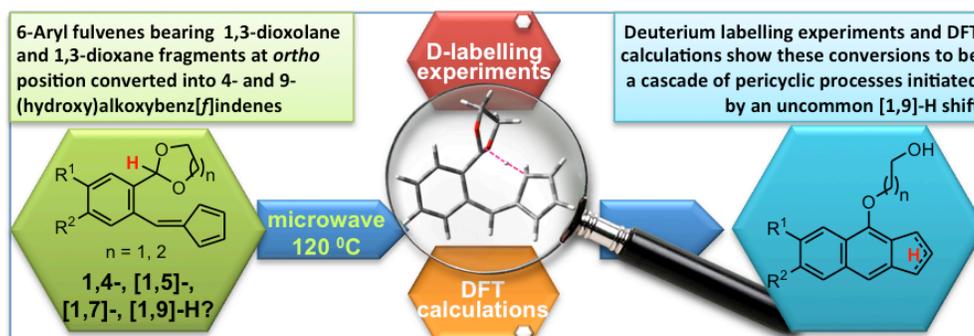


**ABSTRACT:** The intramolecular cyclization of *N*-benzylfumaramide [2]rotaxanes is described. The mechanical bond of these substrates activates this transformation to proceed in high yields and in a regio- and diastereoselective manner, giving interlocked 3,4-disubstituted *trans*-azetidin-2-ones. This activation effect markedly differs from the more common shielding protection of threaded functions by the macrocycle, in this case promoting an unusual and disfavored 4-*exo-trig* ring closure. Kinetic and synthetic studies allowed us to delineate an advantageous approach toward  $\beta$ -lactams based on a two-step, one-pot protocol: an intramolecular ring closure followed by a thermally induced dethreading step. The advantages of carrying out this cyclization in the confined space of a benzylic amide macrocycle are attributed to its anchimeric assistance.

#### Tandem Processes Promoted by a Hydrogen Shift in 6-Aryl-fulvenes Bearing Acetalic Units at *Ortho* Position: A Combined Experimental and Computational Study

Mateo Alajarin, Marta Marin-Luna, Pilar Sanchez-Andrada, Angel Vidal  
*Beilstein J. Org. Chem.* **2016**, *12*, 260–270.

DOI: 10.3762/bjoc.12.28



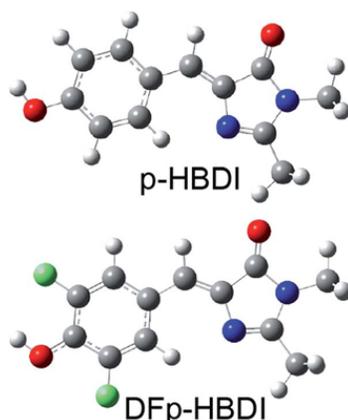
**ABSTRACT:** 6-Phenylfulvenes bearing (1,3-dioxolan or dioxan)-2-yl substituents at *ortho* position convert into mixtures of 4- and 9-(hydroxy)alkoxy-substituted benzofulvenes as result of cascade processes initiated by a thermally activated hydrogen shift. Structurally related fulvenes with non-cyclic acetalic units afforded mixtures of 4- and 9-alkoxybenzofulvenes under similar thermal conditions. Mechanistic paths promoted by an initial [1,4]-, [1,5]-, [1,7]- or [1,9]-H shift are conceivable for explaining these conversions. Deuterium labelling experiments exclude the [1,4]-hydride shift as the first step. A computational study scrutinized the reaction channels of these tandem conversions starting by [1,5]-, [1,7]- and [1,9]-H shifts, revealing that this first step is the rate-determining one and that the [1,9]-H shift is the one with the lowest energy barrier.

## Photoacid Behaviour in a Fluorinated Green Fluorescent Protein Chromophore: Ultrafast Formation of Anion and Zwitterion States

S. P. Laptanok, J. Conyard, P. C. B. Page, Y. Chan, S. Jaffrey, M. You, S. R. Meech

*Chem. Sci.* **2016**, *7*, 5747–5752.

DOI: 10.1039/C6SC02031C



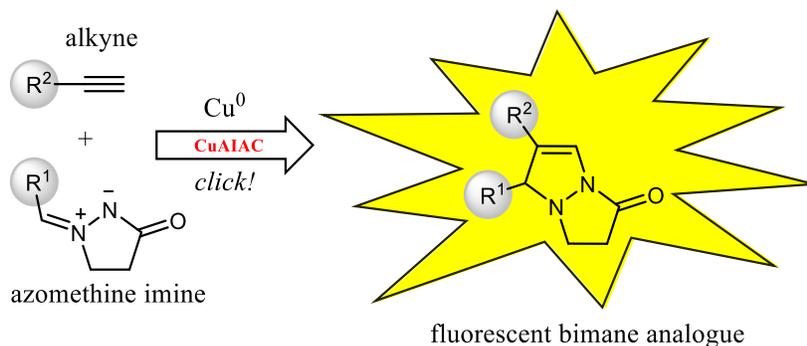
**Abstract:** The photophysics of the chromophore of the green fluorescent protein in *Aequorea victoria* (avGFP) are dominated by an excited state proton transfer reaction. In contrast the photophysics of the same chromophore in solution are dominated by radiationless decay, and photoacid behaviour is not observed. Here we show that modification of the  $pK_a$  of the chromophore by fluorination leads to an excited state proton transfer on an extremely fast (50 fs) time scale. Such a fast rate suggests a barrierless proton transfer and the existence of a pre-formed acceptor site in the aqueous solution, which is supported by solvent and deuterium isotope effects. In addition, at lower pH, photochemical formation of the elusive zwitterion of the GFP chromophore is observed by means of an equally fast excited state proton transfer from the cation. The significance of these results for understanding and modifying the properties of fluorescent proteins are discussed.

## “Click” Chemistry: Application of Copper Metal in Cu-Catalyzed Azomethine Imine–Alkyne Cycloadditions

Eva Pušavec Kirar, Uroš Grošelj, Giorgio Mirri, Franc Požgan, Gregor Strle, Bogdan Štefane, Vasko Jovanovski, Jurij Svete

*J. Org. Chem.* **2016**, *81*, 5988–5997.

DOI: 10.1021/acs.joc.6b00945

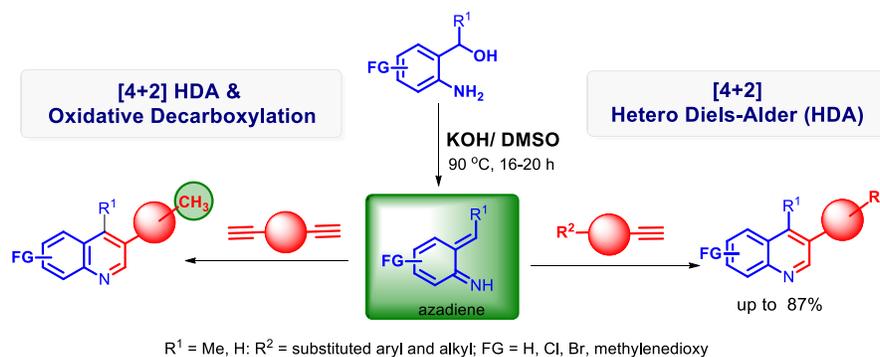


**Abstract:** A series of 16 copper metal-catalyzed CuAIAC reactions between four pyrazolidinone-1-azomethine imines and four terminal ynones gave the corresponding fluorescent cycloadducts as bimane analogues in very high yields. Applicability of CuAIAC was demonstrated by fluorescent labelling of functionalized polystyrene and by using Cu–C and Cu–Fe as catalysts. Experimental evidence, kinetic measurements and correlation between a clean catalyst surface and the reaction rate are in agreement with homotopic catalytic system with catalytic Cu<sup>I</sup>-acetylide formed from Cu<sup>0</sup> by 'in situ' oxidation. Availability of azomethine imines, mild reaction conditions, simple workup, and scalability make CuAIAC a viable supplement to CuAAC reaction in 'click' chemistry.

## Regioselective Synthesis of C-3-Functionalized Quinolines via Hetero-Diels–Alder Cycloaddition of Azadienes with Terminal Alkynes

Rakesh K. Saunthwal, Monika Patel and Akhilesh K. Verma  
*J. Org. Chem.* **2016**, *81*, 6563–6572.

DOI: 10.1021/acs.joc.6b01186



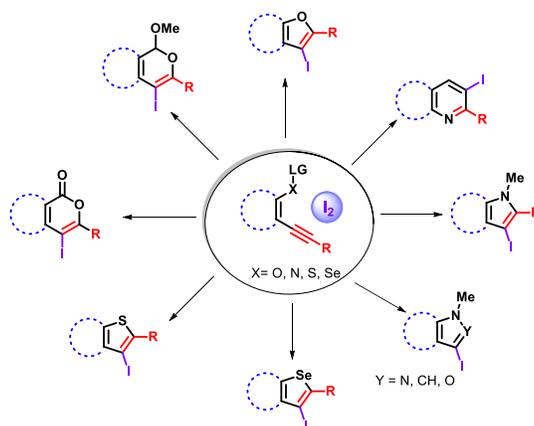
i. C-3 Selective, ii. Metal-free [4+2] HDA, iii. Protection-free, iv. Oxidative decarboxylation

**Abstract:** A highly efficient metal and protection-free approach for the regioselective synthesis of C-3 functionalized quinolines from azadienes (*in situ* generated from 2-aminobenzyl alcohol) and terminal alkynes through [4+2] cycloaddition has been developed. An unprecedented reaction of 2-aminobenzyl alcohol with 1,3- and 1,4-diethynylbenzene provided the C-3 tolyl-quinolines via [4+2] HDA and oxidative decarboxylation. The –NH<sub>2</sub> group directed mechanistic approach was well supported by the control experiments, deuterium labelling studies, and by isolating azadiene intermediate. The reactivity and selectivity of unprotected azadiene in metal-free base-assisted hetero diels alder (HDA) reaction is exploited to quickly assemble an important class of C-3 functionalized quinolines, which are difficult to access.

## Iodine-mediated Synthesis of Heterocycles via Electrophilic Cyclization of Alkynes

Trapti Aggarwal, Sonu Kumar and Akhilesh K. Verma  
*Org. Biomol. Chem.* **2016**, *14*, 7639–7653.

DOI: 10.1039/c6ob01054g

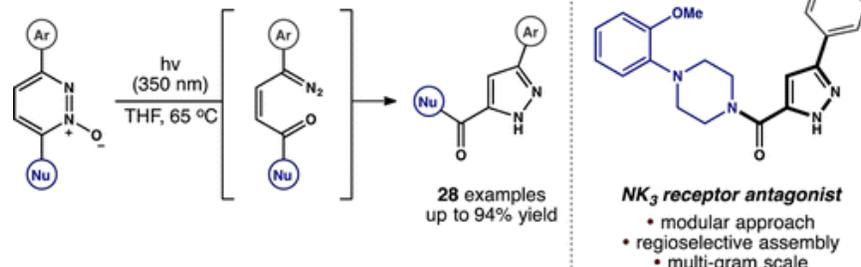


**Abstract:** Iodine has been recognized as an efficient, non-toxic, readily available and easy-to-handle electrophilic reagent to favour halocyclization reactions for the synthesis of novel iodofunctionalized heterocyclic molecules that serve as versatile intermediates in synthetic organic chemistry. This review presents numerous useful methodologies for the synthesis of O, N, S, and Se-heterocycles through electrophilic cyclization via the attack of an electrophile on the C(sp) bond of alkynes. The cyclization proceeds under mild reaction conditions and tolerates a wide variety of functional groups.

## Synthesis of Nitrogen Heterocycles via Photochemical Ring Opening of Pyridazine *N*-oxides

Maribel Portillo, Michael A. Maxwell and James H. Frederick  
*Org. Lett.* **2016**, *18*, 5142–5145.

DOI: 10.1021/acs/orglett.6b02562



**Abstract:** A photochemical method for the direct synthesis of 1H-pyrazoles from pyridazine *N*-oxides was developed. This chemistry features a regioselective approach to nonsymmetrically substituted pyridazine *N*-oxides. Herein, we highlight the first strategic use of photoinduced ring-opening reactions of 1,2-diazine *N*-oxides for the preparative synthesis of nitrogen heterocycles.

## Multicomponent Synthesis of 4-Arylidene-2-phenyl-5(4H)-oxazolones (Azlactones) Using a Mechanochemical Approach

Amin F. M. Fahmy, Amira A. El-Sayed and Magdy M. Hemdan  
*Chemistry Central Journal* **2016**, *10*:59 1–7.

DOI: 10.1186/s13065-016-0205-9



**Abstract:** We have developed a simple, efficient and ecofriendly strategy for facile synthesis of azlactones. The key advantages of this strategy, over conventional approach, include its simple, solvent free conditions, as well as its facile work-up, high yield economy and environmental friendliness. It is also successful in achieving three of the green chemistry objectives of a solvent free operation, high atom economy and step efficient. Thus, combining the features of both economic and environmental advantages. We introduced the yield economy [YE] as a metric to assess the conversion efficiency of grinding and conventional synthetic reactions of azlactones.