Issue 4; August 1, 2016

# The ISHC Bulletin

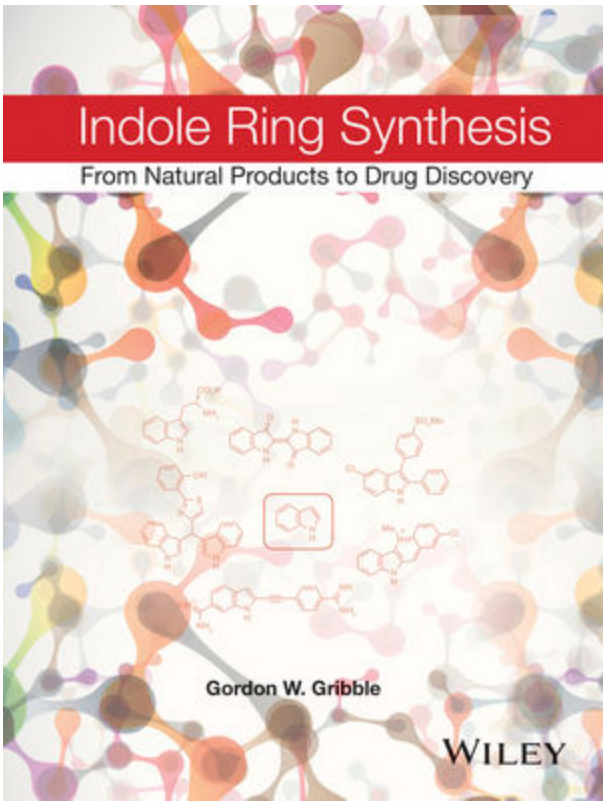
*Recent Publications of ISHC Members*

Issue 4; August 1, 2016

## *Indole Ring Synthesis – From Natural Products to Drug Discovery*

Gordon W. Gribble

Wiley, August **2016,** 704 pages. **ISBN**: 978-0-470-51218-0




**Abstract**: Of the myriad of heterocycles known to man, the indole ring stands foremost for its remarkably versatile chemistry, its enormous range of biological activities, and its ubiquity in the terrestrial and marine environments.

The indole ring continues to be discovered in natural products and to be employed in man-made pharmaceuticals and other materials. Given the enormous resurgence in indole ring synthesis over the past decade — highlighted by the power of transition metal catalysis — this authoritative guide addresses the need for a comprehensive presentation of the myriad of methods for constructing the indole ring, from the ancient to the modern, and from the obscure to the well-known.

Following presentation of the classic indole ring syntheses and many newer methods, coverage continues with indole ring syntheses via pyrroles, indolines, oxindoles, isatins, radical and photochemical reactions, aryne cycloadditions. This extensive volume concludes with the modern transition metal–catalyzed indole ring syntheses that utilize copper, palladium, rhodium, gold, ruthenium, platinum, and other metals to fashion the indole ring.

*Indole Ring Synthesis* is a comprehensive, authoritative and up-to-date guide to the synthesis of this important heterocycle for organic chemists, pharmaceutical researchers and those interested in the chemistry of natural products.

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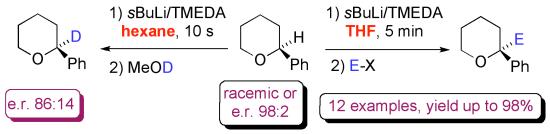
## Toward Customized Tetrahydropyran Derivatives through Regioselective α-Lithiation and Functionalization of 2-Phenylteetrahydropyran

Luciano Cicco, Valeria Addante, Andrea Temperini, Carsten Adam Donau, Konstantin Karaghiosoff, Filippo Maria Perna, Vito Capriati

*Eur. J. Org. Chem.* **2016**, 3157–3161. **DOI**: 10.1002/ejoc.201600365

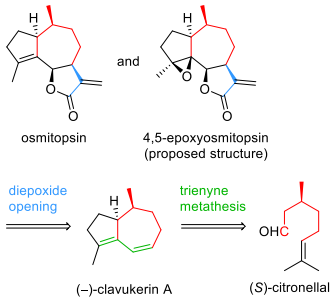



**Abstract**: In this contribution, the first direct and efficient functionalization of the preformed 2-phenyltetrahydropyran (2-PhTHP) nucleus by electrophilic interception of the corresponding α-lithiated derivative by employing *s*BuLi as the base and THF as the solvent at –78 °C was explored. The presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) proved to be critical to governing reaction feasibility both in polar and apolar solvents and for improving the yield of the reaction. Both carbon- and heteroatom-based halides were found to be competent electrophiles for this transformation, as well as aliphatic and aromatic aldehydes and ketones, isocyanates, and carboxylic acid derivatives. The combination of hexane/TMEDA lowered the rate of racemization of α-lithiated optically active 2-PhTHP, which thereby enabled calculation of its barrier to inversion at –78 °C.

## Enantioselective Synthesis of Guaianolides in the Osmitopsin Family by Domino Metathesis

André Barthel, Felix Kaden, Anne Jäger, Peter Metz

*Org. Lett.* **2016**, 3298–3301. **DOI**: 10.1021/acs.orglett.6b01619

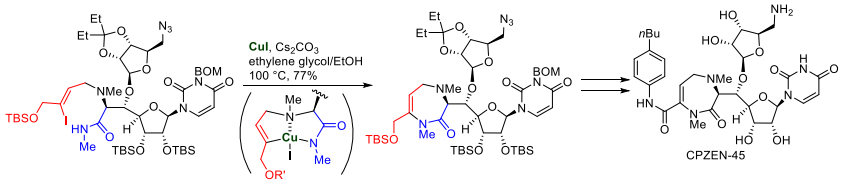



**Abstract**: Relay metathesis enabled an improved access from (*S*)-citronellal to the marine trisnorguaiane (–)-clavukerin A. This hydroazulene was applied as an advantageously functionalized building block for the asymmetric synthesis of the sesquiterpene lactone osmitopsin and the proposed structure of 4,5-epoxyosmitopsin using a chemo-, regio-, and diastereoselective diepoxide opening as the key step.

## Synthesis of CPZEN-45: Construction of the 1,4-Diazepin-2-one Core by the Cu-Catalyzed Intramolecular Amidation of a Vinyl Iodide

Hugh Nakamura, Takuma Yoshida, Chihiro Tsukano, Yoshiji Takemoto

*Org. Lett.* **2016**, *18*, 2300–2303. **DOI**: 10.1021/acs.orglett.6b00943




**Abstract**: CPZEN-45 was developed as an antibiotic against *Mycobacterium tuberculosis* by the chemical modification of caprazamycins. CPZEN-45 has been synthesized in this study by the Cu-catalyzed intramolecular amidation of a complex vinyl iodide precursor bearing uridine and sugar moieties with a secondary amide, allowing for the construction of its 1,4-diazepin-2-one core.

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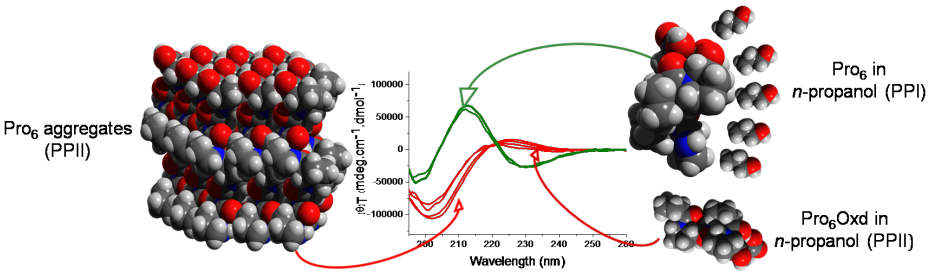
## Factors Affecting the Stabilization of Polyproline II Helices in a Hydrophobic Environment

Nicola Zanna, Lorenzo Milli, Benedetta Del Secco, Claudia Tomasini

*Org. Lett.* **2016**, *18*, 1662–1665. **DOI**: 10.1021/acs.orglett.6b00532

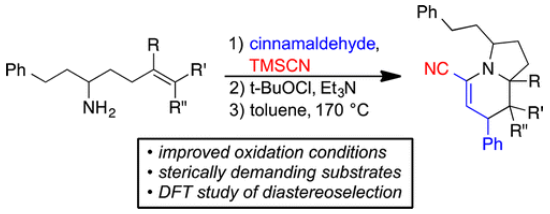



**Abstract**: Several parameters have a critical importance for the stabilization of either polyproline I (PPI) or polyproline II (PPII) helices in a hydrophobic environment. Among them, it was found out that the concentration is crucial as polyprolines at 3 mM concentration stably fold in PPII helices, that are organized in aggregates stable even after several days and are detectable by dynamic light scattering analysis. In more diluted concentration the same molecules stably fold in PPI helices, and no aggregates are found. In contrast, the introduction of a (4*S*,5*R*)-4-carboxy-5-methyloxazolidin-2-one (l-Oxd) moiety always inhibits the formation of the PPI helix, regardless of the l-Oxd position and the solution concentration.

## Stereoselection in Intramolecular Diels–Alder Reactions of 2-Cyano-1-azadienes: Indolizidine and Quinolizidine Synthesis

Gidget C. Tay, Nicholas Sizemore, Scott D. Rychnovsky

*Org. Lett.* **2016**, *18*, 3050–3053. **DOI**: 10.1021/acs.orglett.6b00881

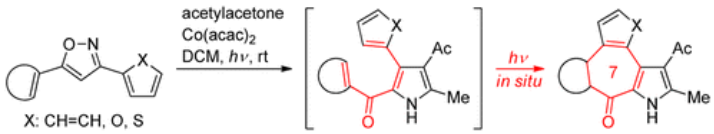



**Abstract**: Progress toward understanding the scope and diastereoselectivity of intramolecular Diels–Alder reactions using 2-cyano-1-azadienes is described herein. The resulting cyanoenamine products are underutilized intermediates in organic synthesis. Assembly of the Diels–Alder precursors was achieved using an improved imine condensation/oxidative cyanation protocol. By this method, several highly substituted indolizidine and quinolizidine architectures were constructed. Quantum mechanical DFT calculations at the B3LYP/6-31+G(d) level of theory were performed for these cyclizations and provide insights into the origins of the observed diastereoselectivities.

## A Light-Induced Vinylogous Nazarov-Type Cyclization

Stefan Pusch, Dieter Schollmeyer, Till Opatz

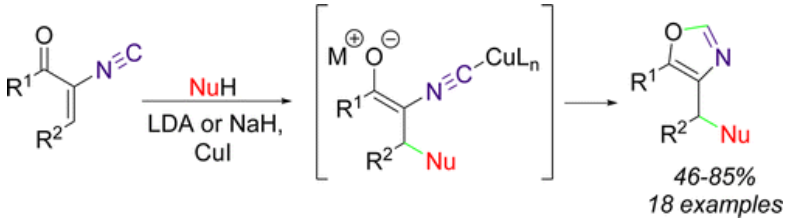
*Org. Lett.* **2016**, *18*, 3043–3045. **DOI**: 10.1021/acs.orglett.6b01449




**Abstract**: The first examples of a photochemically induced vinylogous Nazarov-type cyclization forming a cycloheptadienone core are described. The reaction can be included in a three-step cascade consisting of a photochemical isoxazole–azirine ring contraction, cobalt(II)-catalyzed ring expansion, and the photochemical cyclization. Furthermore, the first representative of the hitherto unknown 1-azatricyclo[2.2.0.0]hexanes has been identified as a side product of the azirine formation.

## Isocyano Enones: Addition–Cyclization Cascade to Oxazoles

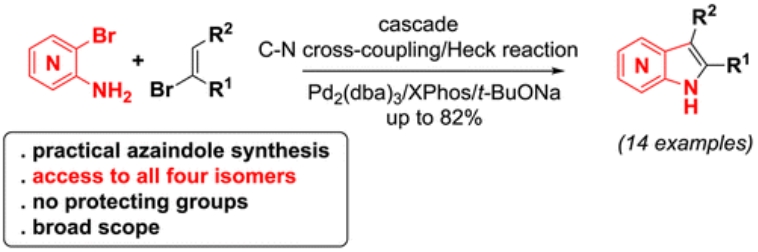
Allen Chao, J. Armando Lujan-Montelongo, Fraser F. Fleming
*Org. Lett.* **2016**, *18*, 3062–3065. **DOI**: 10.1021/acs.orglett.6b01147




**Abstract**: Copper iodide catalyzes the conjugate addition of organometallic and heteroatom nucleophiles to isocyano enones to afford oxazoles. A range of enolates, metalated nitriles, amines, and thiols undergo catalyzed conjugate addition to cyclic and acyclic oxoalkene isocyanides. Mechanistic studies suggest that copper complexation facilitates the nucleophilic attack on the isocyano enone to generate an enolate that cyclizes onto the isocyanide leading to a variety of substituted acyclic or ring-fused oxazoles.

## Synthesis of Substituted 4-, 5-, 6-, and 7-Azaindoles from Aminopyridines via a Cascade C–N Cross-Coupling/Heck Reaction

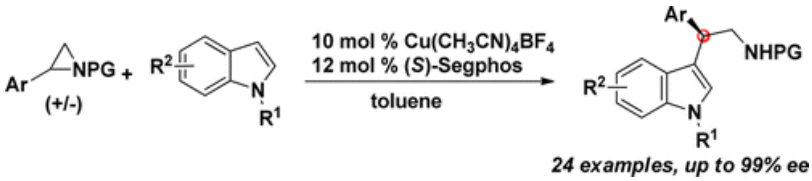
Marina J. D. Pires, Diogo L. Poeira, Sara I. Purificação , M. Manuel B. Marques
*Org. Lett.* **2016**, *18*, 3250–3253. **DOI**: 10.1021/acs.orglett.6b01500




**Abstract**: A practical palladium-catalyzed cascade C–N cross-coupling/Heck reaction of alkenyl bromides with amino-*o*-bromopyridines is described for a straightforward synthesis of substituted 4-, 5-, 6-, and 7-azaindoles using a $Pd_2(dba)_3$/XPhos/*t*-BuONa system. This procedure consists of the first cascade C–N cross-coupling/Heck approach toward all four azaindole isomers from available aminopyridines. The scope of the reaction was investigated and several alkenyl bromides were used, allowing access to different substituted azaindoles. This protocol was further explored for *N*-substituted amino-*o*-bromopyridines.

## Cu(I)-Catalyzed Enantioselective Friedel–Crafts Alkylation of Indoles with 2-Aryl-*N*-sulfonylaziridines as Alkylating Agents

Chen Ge, Ren-Rong Liu, Jian-Rong Gao, Yi-Xia Jia
*Org. Lett.* **2016**, *18*, 3122–3125. **DOI**: 10.1021/acs.orglett.6b01317




**Abstract**: A highly enantioselective Friedel–Crafts alkylation of indoles with *N*-sulfonylaziridines as alkylating agents has been developed by utilizing the complex of $Cu(CH_3CN)_4BF_4$/(*S*)-Segphos as a catalyst. A range of optically active tryptamine derivatives are obtained in good to excellent yields and enantioselectivities (up to >99% ee) via a kinetic resolution process.