

## The ISHC Bulletin

### Recent Publications of ISHC Members

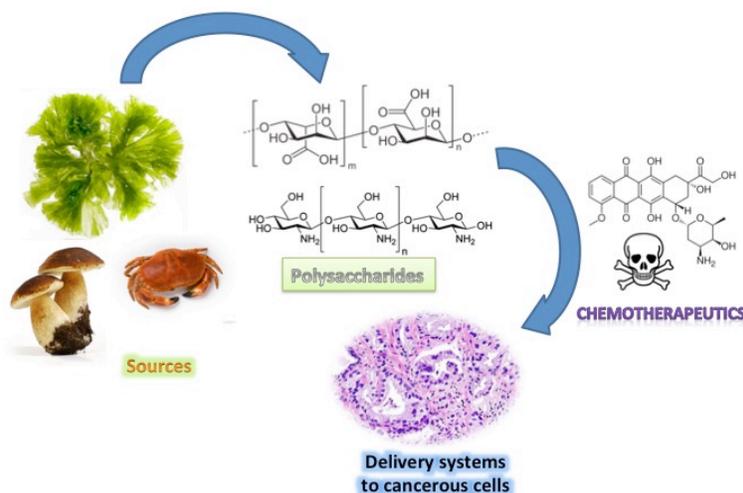
Issue 23; September 2018

#### Drug Delivery Systems for Chemotherapeutics through Selected Polysaccharidic Vehicles

Daniele Merli, Antonella Profumo, Paolo Quadrelli, Carla Renata Arciola and Livia Visai

*Curr. Org. Chem.* **2018**, *22*, 1157–1192.

DOI: 10.2174/1385272822666180122161444



**Abstract: Background:** The search for a drug delivery system is a highly desirable target when toxic drugs are considered (e.g. chemotherapeutics) or when the site of action of a drug is difficult to approach due to the pharmacokinetic profile of the chosen therapeutic agent.

**Objective:** Among the different delivery systems, those based on natural or semi-synthetic polysaccharides are very promising, due to their biocompatibility and biodegradability. Up to now, different polysaccharides are investigated, mainly based on chitosan, alginic acid, dextran and hyaluronic acid.

**Method:** These compounds are easily chemically modified, so that derivatives are able to form nanoparticles or micro vector by interaction with other chemicals (e.g. by ionotropic gelation). These delivery systems can be loaded with the drug of interest in a way that dramatically changes its pharmacokinetic profile, and further derivatization with molecules that selectively target the site of interest (e.g. neoplastic cells) is possible.

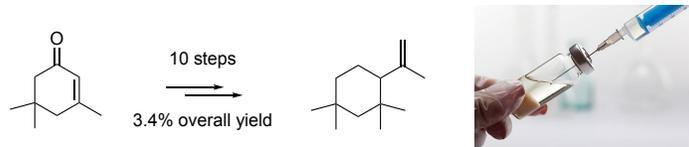
**Results and conclusion:** In this review, we describe the state of the art of polysaccharide-based biopolymeric drug delivery systems developed into the last ten years, with a particular attention to the most commonly used polysaccharides (dextran, chitosan, hyaluronic acid, alginic acid), the chemical derivatization procedures and the prospective use of the obtained vehicles in clinical medicine.

#### First Total Synthesis and Structural Confirmation of C13-Butylrubber Oligomers

Fabrizio Minicone, Robin Attrill, Michael Hodgson, Katherine Wheelhouse, and Adrian Dobbs

*Eur. J. Org. Chem.* **2018**, 3271–3275.

DOI: 10.1002/ejoc.201800496



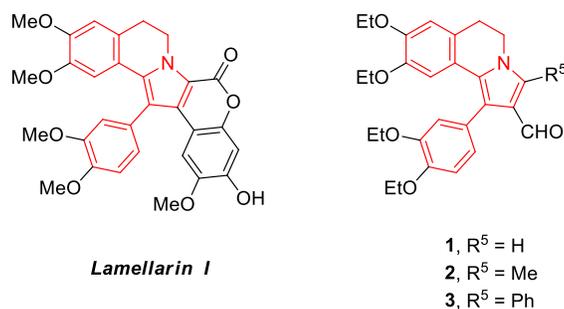
**Abstract:** The first total synthesis of an important C13 butyl rubber oligomer is reported. The structure of the oligomer, which is an important and potentially toxic extractable and leachable component of elastomeric closures, is confirmed by synthesis for the first time. The method described is scalable, making large quantities of the oligomer available for the first time for AMES toxicity studies. The challenging synthesis commences with isophorone and the key steps of the synthesis involve the development of highly novel dithioacetal chemistry, cuprate addition and Tebbe olefination.

## A New Class of 1-Aryl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline Derivatives as Reversers of P-Glycoprotein-Mediated Multidrug Resistance in Tumor Cells

Alisa A. Nevskaya, Maria D. Matveeva, Tatiana N. Borisova, Mauro Niso, Nicola A. Colabufo, Angelina Boccarelli, Rosa Purgatorio, Modesto de Candia, Saverio Cellamare, Leonid G. Voskressensky, and Cosimo D. Altomare

*ChemMedChem* **2018**, *13*, 1588–1596.

DOI: 10.1002/cmdc.201800177



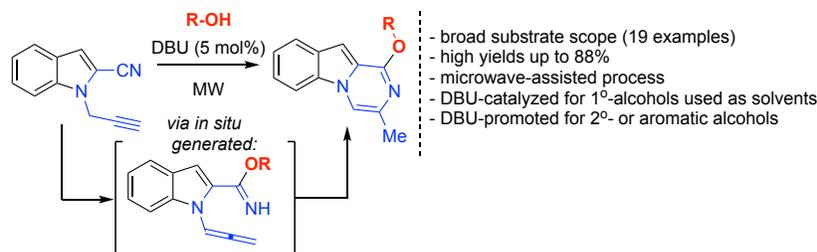
**Abstract:** A number of aza-heterocyclic compounds, which share the 5,6-dihydropyrrolo[2,1-*a*]isoquinoline (DHPIQ) scaffold with members of the lamellarin alkaloid family, were synthesized and evaluated for their ability to reverse in vitro multidrug resistance in cancer cells through inhibition of P-glycoprotein (P-gp) and/or multidrug-resistance-associated protein 1. Most of the investigated DHPIQ compounds proved to be selective P-gp modulators, and the most potent modulator, 8,9-diethoxy-1-(3,4-diethoxyphenyl)-3-(furan-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde, attained sub-micromolar inhibitory potency (IC<sub>50</sub>: 0.19 μm). Schiff bases prepared by the condensation of some 1-aryl-DHPIQ aldehydes with *p*-aminophenol also proved to be of some interest, and one of them, 4-((1-(4-fluorophenyl)-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-yl)methyleneamino)phenol, had an IC<sub>50</sub> value of 1.01 μm. In drug combination assays in multidrug-resistant cells, some DHPIQ compounds, at nontoxic concentrations, significantly increased the cytotoxicity of doxorubicin in a concentration-dependent manner. Studies of structure–activity relationships and investigation of the chemical stability of Schiff bases provided physicochemical information useful for molecular optimization of lamellarin-like cytotoxic drugs active toward chemoresistant tumors as well as nontoxic reversers of P-gp-mediated multidrug resistance in tumor cells.

## DBU-Catalyzed Alkyne–Imidate Cyclization toward 1-Alkoxyprazino[1,2-*a*]indole Synthesis

Alexey A. Festa, Rajesh R. Zalte, Nikita E. Golantsov, Alexey V. Varlamov, Erik V. Van der Eycken, and Leonid G. Voskressensky

*J. Org. Chem.* **2018**, *83*, 9305–9311.

DOI: 10.1021/acs.joc.8b01279



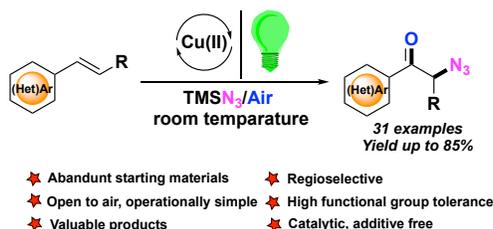
**Abstract:** 1-(Propargyl)indol-2-carbonitriles react with alcohols to afford 1-alkoxyprazino[1,2-*a*]indoles under DBU-catalyzed microwave-assisted conditions. The reaction scope includes a wide range of indoles, primary and secondary alcohols, and a thiol. The initial mechanistic study shows that the domino process presumably proceeds through an alkyne–allene rearrangement, imidate formation, and nucleophilic cyclization reaction sequence.

## Visible-Light-Accelerated Copper(II)-Catalyzed Regio- and Chemoselective Oxo-Azidation of Vinyl Arenes

Asik Hossain, Adiyala Vidyasagar, Christian Eichinger, Christian Lankes, Jenny Phan, Julia Rehbein, and Oliver Reiser

*Angew. Chem. Int. Ed.* **2018**, *57*, 8288–8292.

DOI: 10.1002/anie.2018001678



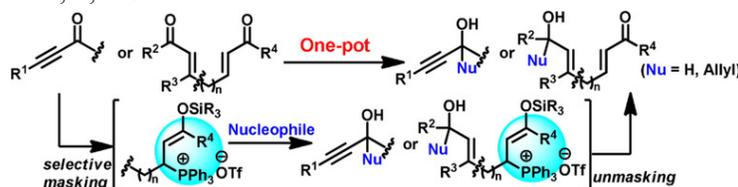
**Abstract:** The visible-light-accelerated oxo-azidation of vinyl arenes with trimethylsilylazide and molecular oxygen as stoichiometric oxidant was achieved. In contrast to photocatalysts based on iridium, ruthenium, or organic dyes, [Cu(dap)<sub>2</sub>]Cl or [Cu(dap)Cl]<sub>2</sub> were found to be unique for this transformation, which is attributed to their ability to interact with the substrates through ligand exchange and rebound mechanisms. Cu<sup>II</sup> is proposed as the catalytically active species, which upon coordinating azide will undergo light-accelerated homolysis to form Cu<sup>I</sup> and azide radicals. This activation principle (Cu<sup>II</sup>-X → Cu<sup>I</sup>+X) opens up new avenues for copper-based photocatalysis.

## Selective Transformation of β-Disubstituted Enones and Ynone in the Presence of β-Monosubstituted Enones

Kenta Morita, Reiya Ohta, Kei Watanabe, and Hiromichi Fujioka

*Asian J. Org. Chem.* **2018**, *7*, 829–835.

DOI: 10.1002/ajoc.201700711



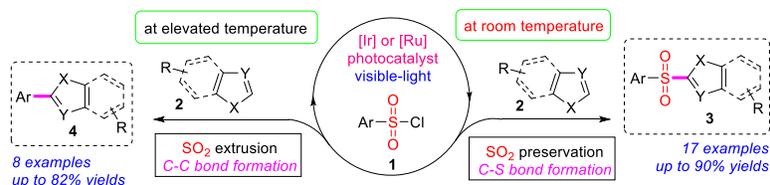
**Abstract:** A facile and selective transformation of ynones and β-disubstituted enones in the presence of β-monosubstituted enones is reported. Triphenylphosphine and trimethylsilyl triflate were used for protection in situ. This method can be used to differentiate two enones, or enones and ynones, to achieve selective one-pot reduction and allylation.

## Temperature Controlled Selective C–S or C–C Bond Formation: Photocatalytic Sulfonylation versus Arylation of Unactivated Heterocycles Utilizing Aryl Sulfonyl Chlorides

Santosh K. Pagire, Asik Hossain, and Oliver Reiser

*Org. Lett.* **2018**, *20*, 648–651.

DOI: 10.1021/acs.orglett.7b03790

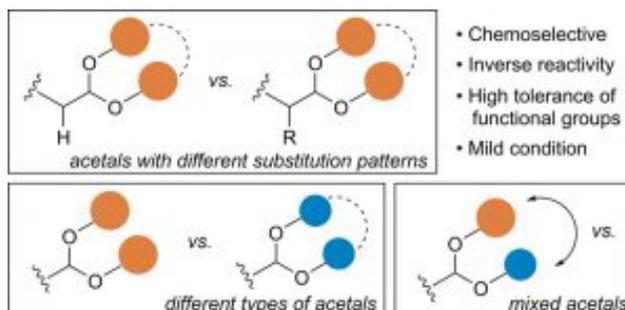


**Abstract:** A visible-light-induced photocatalytic method for the heterocyclic sulfonylation has been developed. The synthetic utility of this reaction is reflected by the direct use of commercially available sulfonyl chlorides and heterocycles under room temperature conditions. Complementarily, the photocatalytic arylation of heterocycles by sulfonyl chlorides via extrusion of SO<sub>2</sub> is feasible at elevated temperature conditions, thus allowing a switching between arylation or arylsulfonylation with excellent chemoselectivity.

## Highly Discriminative and Chemoselective Deprotection/Transformations of Acetals with the Combination of Trialkylsilyl Triflate/2,4,6-Collidine

Reiya Ohta, Nao Matsumoto, Yoshifumi Ueyama, Yuichi Kuboki, Hiroshi Aoyama, Kenichi Murai, Mitsuhiro Arisawa, Tomohiro Maegawa, and Hiromichi Fujioka  
*J. Org. Chem.* **2018**, *83*, 6432–6443.

DOI: 10.1021/acs.joc.8b00675

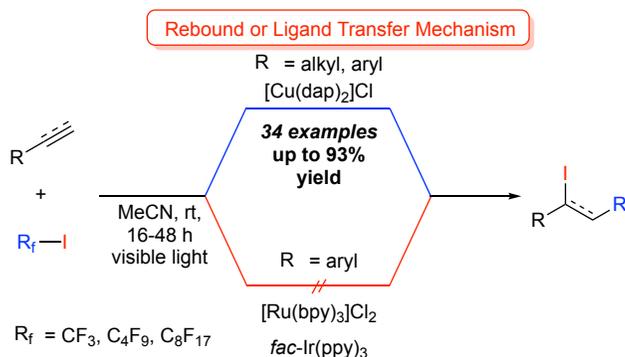


**Abstract:** Acetals are the most useful protecting groups for carbonyl functional groups. In addition to the role of protection, they can also be used as synthons of carbonyl functions. Previously, we developed a chemoselective deprotection and nucleophilic substitution of acetals from aldehydes in the presence of ketals. This article describes the highly discriminative and chemoselective transformations of acetals bearing different substitution patterns, different types of acetals, as well as mixed acetals. These reactions can achieve the transformations that cannot be attained by conventional methods, and their results strongly suggest the combination of  $R_3SiOTf/2,4,6$ -collidine to promote such unprecedented phenomena.

## The Different Faces of Photoredox Catalysts: Visible-Light-Mediated Atom Transfer Radical Addition (ATRA) Reactions of Perfluoroalkyl Iodides with Styrenes and Phenylacetylenes

Thomas Rawner, Eugen Lutsker, Christian A. Kaiser, and Oliver Reiser  
*ACS Catal.* **2018**, *8*, 3950–3956.

DOI: 10.1021/acscatal.8b00847



**Abstract:** A photoredox-catalyzed procedure for the iodoperfluoroalkylation of styrenes and phenylacetylenes using readily available copper phenanthroline catalyst is reported. In contrast to commonly employed  $[Ru(bpy)_3]Cl_2$ ,  $[Ru(phen)_3]Cl_2$  or *fac*- $Ir(ppy)_3$ ,  $[Cu(dap)_2]Cl$  is capable to convert styrenes to the corresponding perfluoroalkyl tagged ethyl benzenes, pointing towards an additional role of the copper catalyst beyond photoinduced electron transfer. An inner sphere catalytic cycle involving  $Cu(III)$  intermediates or ligand abstraction from a  $[CuI]^+$  intermediate is proposed.