Tentative Outline

Special Thematic Issue for Current Organic Chemistry

Title of thematic issue: 'Late-stage functionalization of (hetero)arenes'

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Aims & Scope:

The aim of this special issue should be to discuss some of the most recent results in the late-stage diversification of (hetero)arenes, with a particular attention toward the preparation of families of pharmacologically active compounds and new organic materials.

Keywords:
Heteroarenes, CH functionalization, Heck coupling, alkynylation, alkylation, arylation, cross-dehydrogenative coupling, selanylation, fluorination, metal-free coupling

Subtopics along with Contributing authors and abstract

The subtopics to be covered within this issue are listed below:

Title no. 1: Pd-catalyzed intermolecular dehydrogenative Heck reactions of six membered heteroarenes

- **Author's name:** Jacques Muzart
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- **Email address:** jacques.muzart@univ-reims.fr
- **Abstract:** The Pd-mediated cross-coupling of (hetero)arenes with alkenes may be an effective method for the formation of a C–C bond from two C–H bonds. Discovered by Fujiwara and co-workers in 1967, this reaction led to a number of reports that we firstly highlighted in 2011 (review with references till June 2010) and for which, we retained the name "dehydrogenative Heck reaction". The DHR of six-membered heteroarenes, has been the subject of intensive research over the last ten years. The present review is limited to these dehydrogenative Heck reactions published since 2010, underlining the progress of the procedures.
- **Keywords:** palladium, heteroarenes, dehydrogenative cross-couplings, C–H activation.

Title no. 2: Late-stage Alkylation of (Hetero)arenes Using N-acyloxy phthalimides

- **Author's name:** Sandip Murarka
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- **Abstract:** Synthetic methods enabling late-stage modification of (hetero)arenes holds tremendous importance in pharmaceutical industry, agrochemistry and drug discovery. Accordingly, efficient, functional group tolerant and selective late-stage alkylation of valuable molecular entities is of enormous significance and well acknowledged in medicinal chemistry. Radical alkylation of heteroarenes employing carboxylic acids as the alkyl radical precursor represents one of the most direct ways of C-H functionalizations. Recently, the field has undergone a revolutionary development especially with regard to the generation of alkyl radicals under much milder conditions. In this regard *N*-(acyloxy)phthalimides (NHPI esters) have emerged as a suitable precursor of a diverse set of alkyl radicals under reductive decarboxylative conditions allowing formal C-H alkylation of (hetero)arenes. Since 2017, NHPI esters have been employed in the visible-light driven or electrochemical alkylation of a range of simple heteroarenes and as well as of heteroarenes that are

embedded in complex molecules. This review delineates all these discoveries and provides readers a comprehensive overview of this rapidly expanding field with selected examples and mechanistic discussions.

- **Keywords:** Late-stage Functionalization, N-acyloxypthalimides, Radicals, Alkylation, Heterocycles, Redox-active esters.

Title no. 3: Late-stage Functionalization of (hetero)arenes through Cross Dehydrogenative Coupling

- **Author's name:** Biswajit Panda
- **Affiliation:** Department of Chemistry, City College, Kolkata, West Bengal, India.
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- **Abstract:** Late stage functionalization (LSF) through transformations of X–H (X = C, N) bonds in a direct approach allows the synthetic chemists to speed up the diversification of natural products, drug molecules, agrochemicals and enabling rapid access to biologically active molecules without following the traditional step-wise synthetic strategy. LSF does not only allow tapping of the hitherto unexplored chemical space but also provides the synthetic sequence simpler, atom economical and cost-effective. In this regard, the recent decade has witnessed several reports on the emergence of cross-dehydrogenative coupling (CDC) of two different nonfunctionalized C–H bonds under oxidative conditions represents state-of-the-art C–C bond formation technology and imparts immense applications in the late stage functionalization of unactivated C–H bonds of heterocycles.
- **Keywords:** to be provided.

Title no. 4: (Regioselective) Alkynylation of heteroarenes

- **Author's name:** Fabio Bellina
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- **Abstract:** The functionalization of a Csp2-H bond of an heteroarene with an alkyne represent one of the most attractive procedure for the late-stage functionalization of the aromatic core. The aim of this review is to cover the literature of regioselective alkynylation protocols involving the direct C-H functionalization of heteroarenes starting from terminal acetylenes
- **Keywords:** CH activation, dehydrogenative coupling, inverse Sonogashira coupling, regioselectivity, heteroarenes, palladium catalyst

Title no. 5: Recent advances in transition metal-free late-stage N-H and C-H arylation of Heteroarenes using diaryliodonium salts

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- **Abstract:** Transition metal-free direct arylation of C–H or N-H bonds is one of the key emerging methodologies that is currently attracting tremendous attention. Diaryliodonium salts serve as a stepping stone on the way towards alternative environmentally friendly and straightforward pathways for the construction of C-C and C-heteroatom bonds. In this review, we emphasize on the recent synthetic advances of late-stage C(sp2)-N and C(sp2)-C(sp2) bond-forming reactions under metal-free conditions using diaryliodonium salts as arylating reagent and its applications to the synthesis of new arylated bioactive heterocyclic compounds.
- **Keywords:** diaryliodonium salts; arylation; heteroarenes; metal-free; eco-friendly

Title no. 6: Regioselective C–H selanylation of heteroarenes under metal-free conditions

- **Author's name:** Ricardo Frederico Schumacher, Roberta Cargnelutti

- **Affiliation:** Departamento de Química, Universidade Federal de Santa Maria, Brazil
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- **Abstract:** Selenium-containing heteroarenes consist in a synthetically valuable family of compounds that found applications in many different areas, such as organic synthesis, medicinal chemistry, supramolecular chemistry and optoelectronic devices construction. Over the past decade many advances have been achieved to the synthesis of these substances, and this review aims to cover a literature survey of the direct selanylation of heteroarenes under metal-free conditions, which represents one of most powerful synthetic strategies for the preparation of those target molecules. The construction of new C-Se bonds through selective C-H functionalization reactions has become useful and atom-economical. The widespread adoption of metal-free approaches has emerged as a versatile, sustainable and safe access to these organoselenium compounds. Among the features of these new protocols are the use of mild oxidants and halogen-based catalysts, alternative solvents and reagents as well as photo-induced reactions.
- **Keywords:** C-H selanylation, Iodine-catalyzed reaction, Photocatalysis, Mild oxidants, Diorganyl Diselenides, Heteroarenes

Title no. 7: F-based small groups tuning heteroarenes properties: medicinal chemistry rationale and synthetic methods

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- **Affiliation:** CHIESI FARMACEUTICI S.p.A., Largo Belloli, 10/A - 43122 Parma (Italy).
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- **Abstract:** The use of F-based decorations in drug discovery started from the development of fluorocorticoids and fluorochinolones (1950s and 1980s respectively) and it resulted in about 20% of approved drugs on the Market containing fluorine. From a medicinal chemistry perspective, the installation of F-based small groups (e.g. -CF3, -CF2H, -OCF3, -OCF2H, SCF3) necessarily impact on physicochemical, pharmacokinetics, pharmacodynamics and toxicological properties. Accordingly, a huge interest on this topic is constantly arising in the medicinal chemistry community. Focusing on heteroarenes, the synthetic access to these substitutions is guaranteed by a number of effective reactions particularly exploiting the C-H activation, including Minisci-type reaction, photochemistry or electrochemistry. The aim of this work is to analyze the rational in using these groups in medicinal chemistry and to highlight the current available synthetic toolbox for their introduction on heterorenes at late stage of the functionalization process.
- **Keywords:** Late stage functionalization, LSF, Fluorine, CH activation, heteroarenes, F-based small groups, medicinal chemistry, phys-chem properties

Schedule:

- Final manuscripts due: January 31, 2021.

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