Synthetic Development of Key Intermediates and Active Pharmaceutical Ingredients (APIs)

We would like to express our sincere gratitude to all the contributors to this special issue. Distinguished researchers from academia and the pharmaceutical industry significantly enriched this compilation with their insightful articles.

This Special Issue consists of articles describing novel or practical synthesis of pharmaceuticals, including new chemical entities (NCEs), key or advanced intermediates of drugs, or active pharmaceutical ingredients (APIs). As a key feature of this Special Issue, several articles described new synthetic methodology for syntheses of pharmaceuticals, using cheap or safe reagents, environmentally friendly solvents e.g., water and alcohols, under transition metal-free conditions, electrochemical or photoredox catalytic conditions, or biocatalytic conditions. For example, Shi et al. reported a cross-coupling reaction of readily accessible acetals and commercially available Grignard reagents under transition-metal-free conditions in a synthesis of diarylmethyl alkyl ethers. In addition, a sequential difunctionalization of acetals led to a rapid synthesis of triarylmethanes and diarylalkanes. The reaction was believed to proceed through Lewis acid (magnesium)-mediated nucleophilic addition to acetals via oxocarbenium intermediates (Art ID: SS-2023-03-0141-OP). Chanda et al. developed a one-pot telescoped approach to an expedient synthesis of disubstituted benzimidazoles using a deep eutectic solvent (choline chloride/glycerol/H_2O) involving a sequential S_NAr reaction, nitro reduction, and intramolecular cyclization. This one-pot method satisfies several key criteria of green chemistry principles, which is a primary requirement in green and sustainable manufacturing of pharmaceuticals (Art ID: SS-2023-03-0135-ST). Wu and Chen et al. disclosed a synthesis of drug intermediates employing a key step of a Mizoroki-Heck reaction using a non-traditional catalytic membrane, palladium-loaded ceramic Pd-KH792-CM in a flow reactor (Art ID: SS-2023-05-0222-ST). Echeverria et al. developed a robust, scalable and telescoped synthesis of a chiral lactone 6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one, a key intermediate towards several pharmaceuticals. The key reactions included an organocatalyzed desymmetrization and a chemoselective reduction of a carboxylic acid in the presence of an ester (DOI: 10.1055/a-2217-0996). As nucleophiles, azauracils were unexplored in aza-Michael addition reactions. In a fifth example, Murarka et al. report a triethylamine-promoted 1,6-conjugate addition of azauracils to *para*-quinone methides, which furnished biologically relevant N_4-diarylmethane azauracils that were unknown in literature (Art ID: SS-2023-05-0215-OP). In another article, a continuous flow process was invented for PEGylation of two proteins that have potential for clinical applications in order to overcome the risks associated with traditional batch-mode PEGylation. This strategy can be applied in a wide variety of protein modifications and in gram-scale manufacturing of PEGylated bioconjugates without inducing appreciable aggregation (Art ID: SS-2023-02-0093-OP). Chen et al. reported a biocatalytic synthesis of enantiopure benzylic alcohols via asymmetric benzylic hydroxylation of structurally diverse aromatic compounds with cytochrome P450 monooxygenases (Art ID: SS-2023-02-0096-OP). The direct asymmetric hydroxylation of alkyl arenes has clear advantages over conventional methods such as catalytic asymmetric (transfer) hydrogenation that uses ketones or classical resolution of racemic benzylic alcohols: cheap and simple starting material, and step economy and waste reduction, especially transition metals.

Other articles in this Special Issue are exemplified with a novel synthetic process of a known drug, an improved synthesis of a reported route, a scalable and cost-effective synthesis, and a concise preparation of a complex pharmaceutical. For example, chemists at Pfizer herein disclosed a robust Pd-catalyzed Buchwald-Hartwig reaction to manufacture PF-06842874, a clinical candidate for the treatment of pulmonary arterial hypertension, on an 18-kilogram scale. Through process optimization, a Pd-phosphine complex was found to be an optimal catalyst together with NaO*t*-Bu base, which was essential for the reduction of impurity formation (Art ID: SS-2023-06-0254-OP). Swain et al. reported a one-pot synthesis of the antifungal drug tavaborole by employing a key step of borylation using bis(pinacoloto)diboron/4-phenylpyridine. The reaction was done in a flow reactor with an overall yield of 81% (Art ID: SS-2023-07-0318-OP). Scientists at Emcure Pharmaceuticals disclosed an improved synthesis of an advanced pyrrolidone derivative of (*S*)-(+)-vigabatrin, an antiseizure drug, by using a cheaper amino acid (*R*)-methionine from chiral pool and Meldrum's acid as a two-carbon homologating unit (Art ID: SS-2023-03-0128-ST). Ensitrelvir is a COVID-19 therapeutic drug. In another example, the efficiency and robustness of triazole introduction in Ensitrelvir synthesis was improved by the addition of LiCl to Et_3N base, which improved the selectivity of *N*-alkylation (Art ID: SS-2023-02-0088-OP). Pabbaraja and Singh et al. developed a continuous microflow synthesis of daclatasvir in an electro-flow reactor composed of patterned electrodeposited nickel met-

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al over a copper electrode. The multistep synthesis was 20-50 times faster than conventional batch reactions (Art ID: SS-2022-11-0518-ST). Ledipasvir is an antiviral drug used for the treatment of hepatitis C virus infection. In another article, an advanced intermediate of ledipasvir was prepared via a late-stage cyclopropanation and difluorination, which enabled a more efficient preparation of ledipasvir in only 8 steps with an overall 20% yield (Art ID: SS-2022-10-0494-ST).

We hope that this Special Issue will be of interest in academic research and for translational applications in the pharmaceutical industry.

Sincerely,

Joydev K. Laha and Jianrong Steve Zhou

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