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Highly Diastereoselective Metal-Free Catalytic Synthesis of Drug-Like Spiroimidazolidinone

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Abstract—A four-step procedure has been developed for the synthesis of (*S*)-3-isopropyl-1-[(*R*)-1-phenylethyl)-1,4-diazaspiro[4.5]decan-2-one with high diastereoselectivity (up to 95% *de*) from (*S*)-α-aminoisovaleric acid (L-valine). Quantum chemical computations of the synthesized compound have been performed using Gaussian 09 software package.

Keywords: spiroimidazolidinone, L-valine, catalysis, diastereoselectivity, DFT quantum chemical computations, B3LYP/6-31G(*d*).

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The design and synthesis of cyclic amides are a major perspective for the exploration and understanding of their applications [1]. Cyclic amides whose active centers contain amino acids with primary amino substructure are used as natural catalysts for the synthesis of carbohydrates [2, 3]. Chiral α-amino acids are fundamentally important structures in diverse applications [4]. A wide range of synthetic methods have been developed over the last decades to provide access to not only naturally occurring α-amino acids and their enantiomers [5, 6] but also to unnatural amino acid derivatives [7]. Amino acids and their derivatives such as amides (peptides) are widely used as organocatalysts [8–15]. A cyclic amide moiety, particularly imidazolidinone, is present in many biologically active natural products and pharmaceutically important compounds [16]. Examples are spiroimidazolones **A** [antagonist of human glucagon receptor (hGCGR)] [17] and **B** [BACE1 (β-secretase) inhibitor for the treatment of Alzheimer's disease] [18]. Diastereoisomeric imidazolidinones have been studied as a core unit of many pharmacological agents [19–22]. Chiral imidazolidinones **C** [23] and **D** [24] are successfully used in aminocatalysis, and imidazolidinone **E** is an analog of Sanger and Marfey reagents for analysis of D- and L-amino acids [25]. The imidazolidinone scaffold offers many opportunities for tuning and modification of steric requirements with regard to stereochemistry of a catalytic system like **F** [26] which has been tested as fragrance delivery system.

The construction of a quaternary stereogenic center in imidazolidinones seems to be a challenging problem, which is evidenced by increased interest from synthetic organic chemists over the last 10 years [27, 28]. Asymmetric synthetic strategies ranging from classical diastereoselective auxiliary-controlled methods to modern approaches involving enantioselective catalysis have been reported. These methods include allylic substitution [29], conjugate addition [30–32], and nucleophilic allylation [33, 34].

Therefore, search for efficient methodologies for the synthesis of imidazolidinone derivatives with specific biological activities has been undertaken [35]. The developed methods for the synthesis of imidazolidinones from chiral α-amino acids involve the use of amidophosphane precatalysts [36, 37]. Different reagents were utilized for the synthesis of disubstituted chiral *N*-aryl and *N*-alkylamines (including α- and β-amino acids) which can be further converted to differently functionalized imidazolidinones. The direct coupling reaction is one of the most common reactions for C–C and C–N bond formation [38–40].