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Synthesis and anti-inflammatory evaluation of *N*-sulfonyl anthranilic acids via Ir(III)-catalyzed C–H amidation of benzoic acids

Sang Hoon Han [a,c], Hyo Sun Suh [a,c], Hyeim Jo [a], Yongguk Oh [a], Neeraj Kumar Mishra [a], Sangil Han [a], Hyung Sik Kim [a], Young Hoon Jung [a,b], Byung Mu Lee [a,*], In Su Kim [a,*]

[a] School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea
[b] Biocenter, Gyeonggido Business & Science Accelerator (GBSA), Suwon 16229, Republic of Korea

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ABSTRACT

The iridium(III)-catalyzed *ortho*-C–H amidation of benzoic acids with sulfonyl azides is described. These transformations allow the facile generation of *N*-sulfonyl anthranilic acids, which are known as crucial scaffolds found in biologically active molecules. In addition, all synthetic products were evaluated for in vitro anti-inflammatory activity against interleukin-1β (IL-1β) and cyclooxygenase-2 (COX-2) with lipopolysaccharide (LPS)-induced RAW264.7 cells. Notably, compounds **4c** and **4d**, generated from *p*-OMe- and *p*-Br-sulfonyl azides, were found to display potent anti-inflammatory property stronger than that of well-known NSAIDs ibuprofen.

Anthranilic acid (2-aminobenzoic acid) scaffolds have been recognized as ubiquitous frameworks found in a large number of natural and synthetic products for the treatment of inflammatory disorders.[1] For instance, mefenamic acid, meclofenamates and tranilast have been used as non-steroidal anti-inflammatory drugs (NSAIDs) in pharmacological therapy (Fig. 1).[2] In addition, oscarellin and natural anthranilic derivative display potent anti-inflammatory activity through the inhibition of TNF-α and IL-6 production in activated macrophages.[3] Moreover, this class of compounds has attracted considerable attention by virtue of their diverse and interesting biological activities, i.e. antibacterial activity, antidiabetic activity, and antifungal activity.[4] In fact, the biological properties of these molecules are closely related with aryl motifs tethered with amine functionality, but vary depending on the nature and position of substituents on aryl rings. Consequently, a variety of *N*-aryl anthranilic acid derivatives has been synthesized and evaluated for clinical applications.

With recent advances in catalytic C–H functionalization, direct C–N bond formation reaction represents a valuable pursuit with profound synthetic potentials for the establishment of nitrogen-containing molecules.[5] For the installation of amine functionality, various amine surrogates such as *N*-carboxylates, *N*-tosylates, organic azides, dioxazolones and anthranils have been explored for C–H amination reactions.[6] In particular, organic azides have been widely employed in the catalytic C–H amination reactions of sp^2 and sp^3 C–H bonds. For example, Chang and coworkers first described a beautiful work on direct *N*-arylation of arenes through the redox-neutral Rh(III)-catalyzed C–H amination reactions using sulfonyl, aryl, and alkyl azides as amine surrogates.[6f,g] In addition, the directing group-assisted C–H amidation reactions of various (hetero)arenes with sulfonyl and acyl azides under Ir(III) catalysis have been reported (Scheme 1).[7] Notably, Chang et al. demonstrated the Ir(III)-catalyzed C–H amidation reaction of benzoic acid derivatives followed by subsequent Pd(II)-catalyzed protodecarboxylation introducing *meta*- and *para*-substituted *N*-sulfonyl anilines.[8] Recently, our group presented the Ru(II)-catalyzed site-selective C–H amination reactions of xanthones and chromones with sulfonyl azides to deliver anticancer 1-aminoxanthones and 5-aminochromones.[9] In continuation to our recent works on the synthesis of biologically active compounds via transition-metal-catalyzed C–H functionalization,[10] we herein disclose the Ir(III) Cp*-catalyzed direct amidation of benzoic acids with sulfonyl azides to afford anthranilic acids. All synthetic compounds were evaluated for anti-inflammatory activity against interleukin-1β (IL-1β) and cyclooxygenase-2 (COX-2) with lipopolysaccharide (LPS)-induced RAW264.7 cells,[11] and were found to display promising anti-inflammatory effect competitive with well-known NSAIDs drug ibuprofen. Particularly noteworthy was the resulting

* Corresponding authors.
E-mail addresses: bmlee@skku.edu (B.M. Lee), insukim@skku.edu (I.S. Kim).
[c] These authors equally contributed.

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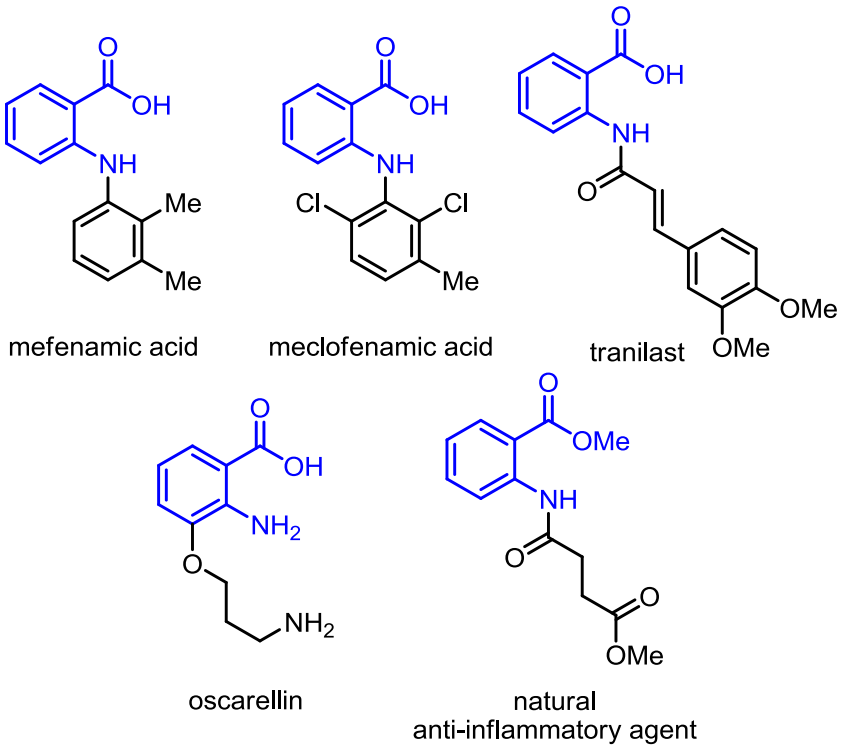
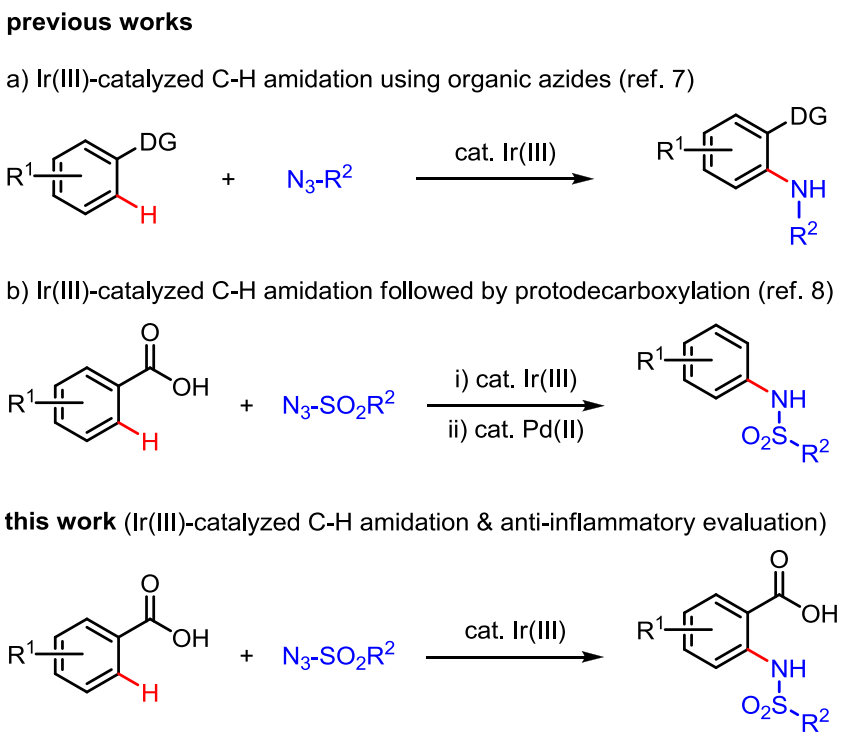


Fig. 1. Selected examples of bioactive anthranilic acids.



Scheme 1. Ir(III)-catalyzed C–H amidation reactions using organic azides.

framework containing sulfonamide groups at the *ortho*-position of benzoic acids, which represents a biologically important scaffold found in various synthetic molecules.[12]

Our optimization was initiated by investigating the coupling reaction of 2-methoxybenzoic acid (**1a**) with 4-methylbenzenesulfonyl azide (**2a**), as shown in Table 1. Surprisingly, Rh(III) and Ru(II) catalysts were found to be ineffective in this transformation (Table 1, entries 1 and 2). To our delight, a cationic Ir(III) complex derived from $[IrCp^*Cl_2]_2$ and $AgSbF_6$ was found to promote the coupling reaction between **1a** and **2a** to deliver *ortho*-sulfonamidated