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Original article

Iridium-catalyzed direct *ortho*-C–H amidation of benzoic acids with sulfonylazides

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ABSTRACT

A mild and efficient iridium-catalyzed *ortho*-C–H amidation with sulfonyl azides by weakly coordinating carboxylic acid was demonstrated, which provided a novel approach to anthranilic acid derivatives.

1. Introduction

C–N bond construction has been one of the most important research topic in organic synthesis, accompanied by the development of Ullmann reaction [1,2] and Buchwald–Hartwig amination [3,4]. However, their high cost and environmental toxicity, such as stoichiometric amounts of halogen salt as by-product, prevent the large-scale syntheses in industrial applications. Recently, the direct C–H bond functionalization has been more facility, straightforward and environment friendly protocols to construct carbon–carbon [5] and carbon–heteroatom bonds [6–8]. However, most of transition-metal-catalyzed C–H amination reactions require stoichiometric external oxidants and the harsh reaction conditions. Organic azides, which is an environmental amino source and also as an internal oxidant *via* N–N_2 bond cleavage, would be key to develop an efficient C–H amination and the sole byproduct is molecular nitrogen (N_2) [9,10]. Recently, Chang reported elegant works on azides as nitrogen source for transition-metal-catalyzed direct C–H amidations [11–21]. Miura [22], Daugulis [23] and Yu [24–31] have independently achieved direct *ortho*-C–H amidation of benzoic acids. Along with our continuing efforts to explore novel C–N bond formations [7], we herein independently reported an iridium-catalyzed carboxylic acid-directed C–H aminations with sulfonyl azides as amino sources, which afforded sulfonamide and anthranilic acid derivatives [32]. Notably, the products obtained from this protocol as an important structural units widely exist in pharmaceutical molecules and natural products, such as the potent inhibitor of methionine aminopeptidase-2 (MetAP-2) (Fig. 1, left), and sulfonamide derivatives with efficiently anti-inflammatory and aldose reductase inhibitory activities (Fig. 1, right) [33,34].

2. Experimental

To a screw capped vial with a spinvane triangular-shaped Teflon stir bar were added benzoic acids (**1**, 0.20 mmol), azide (**2**, 0.20 mmol), $[IrCp^*Cl_2]_2$ (3.2 mg, 4 mol%), $AgNTf_2$ (6.2 mg, 8 mol%), Li_2CO_3 (2.2 mg, 15 mol%), AcOH(1.8 mg, 15 mol%) and 1,2-dichloroethane (2.0 mL) under N_2 atmosphere. The reaction mixture was stirred in a pre-heated oil bath at the indicating temperature for 12 h. Then, the reaction mixture was cooled to room temperature in case of heating, filtered through a pad of celite and then washed with CH_2Cl_2

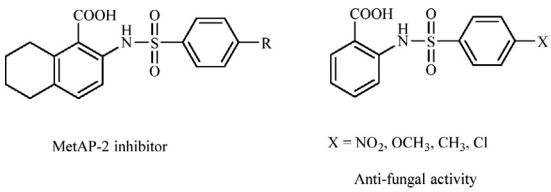

Fig. 1. Examples illustrating the importance of 2-sulfonylamido benzoic acids.

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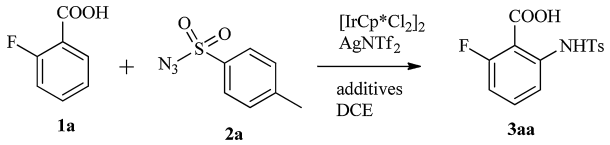
Table 1
Optimization of various reaction parameters.[a]



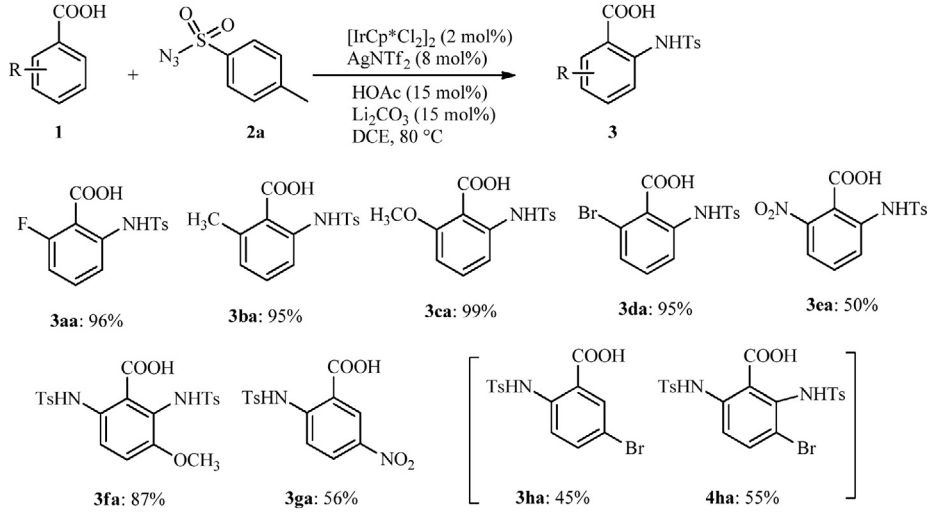
Entry	Catalyst	Silver salt	Additive	Solvent	T (°C)	**3aa** (%)
1	–	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	80	0
2	$[IrCp^*Cl_2]_2$	–	$HOAc + Li_2CO_3$	DCE	80	0
3	$[IrCp^*Cl_2]_2$	$AgNTf_2$	–	DCE	80	0
4	$[IrCp^*Cl_2]_2$	$AgNTf_2$	NaOAc	DCE	50	39
5	$[IrCp^*Cl_2]_2$	$AgNTf_2$	Li_2CO_3	DCE	50	22
6	$[IrCp^*Cl_2]_2$	$AgNTf_2$	LiOAc	DCE	50	60
7	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	50	68
8	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	THF	50	10
9	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	1,4-Dioxane	50	25
10	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DMA	50	0
11	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	*t*-AmylOH	50	0
12	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	Acetonitrile	50	0
13	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	25	15
14	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	60	80
15	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	70	85
16	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	80	95
17[b]	$[IrCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	80	72
18	$[IrCp^*Cl_2]_2$	$AgNO_3$	$HOAc + Li_2CO_3$	DCE	80	20
19	$[IrCp^*Cl_2]_2$	$AgBF_4$	$HOAc + Li_2CO_3$	DCE	80	5
20	$[IrCp^*Cl_2]_2$	Ag_2CO_3	$HOAc + Li_2CO_3$	DCE	80	50
21	$[IrCp^*Cl_2]_2$	Ag_2O	$HOAc + Li_2CO_3$	DCE	80	41
22	$[IrCp^*Cl_2]_2$	$AgCF_3SO_4$	$HOAc + Li_2CO_3$	DCE	80	56
23	$[RhCp^*Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	80	0
24	$[Ru(p\text{-cymene})Cl_2]_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	80	0
25	$Pd(OAc)_2$	$AgNTf_2$	$HOAc + Li_2CO_3$	DCE	80	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $[IrCp^*Cl_2]_2$ (2 mol%), $AgNTf_2$ (8 mol%), additives (15 mol%), solvent (2 mL), 12 h, isolated yields.
[b] $[IrCp^*Cl_2]_2$ (1 mol%), $AgNTf_2$ (4 mol%).

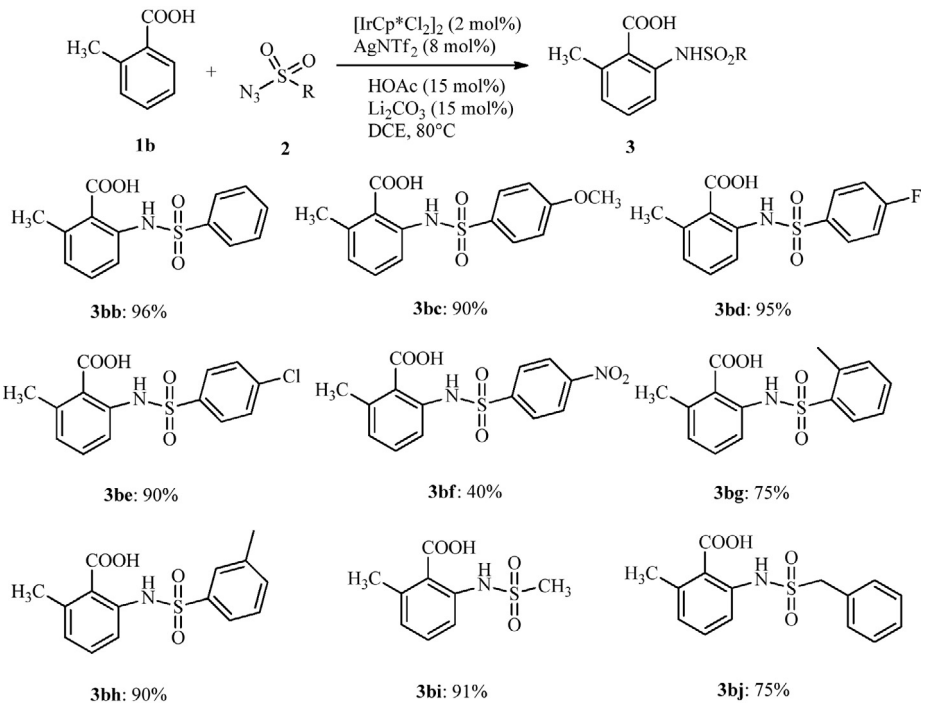
(5 mL × 3). The solvents were removed in vacuo, and the residue was purified by column chromatography on silica gel (PE/EtOAc/HCOOH = 30:1:0.1–25:5:0.1, v/v/v) to give the target product **3**.

3. Results and discussion

At the outset of our studies, the model reaction of 2-fluorobenzoic acid (**1a**) with *para*-methylphenylsulfonyl azide (**2a**) in the presence of $[IrCp^*Cl_2]_2$ was chosen to screen the reaction parameters (Table 1). The reaction did not proceed in the absence of $AgNTf_2$ or Ir(III) catalyst (entries 1–2). To our delight, LiOAc (15 mol%), NaOAc (15 mol%) or LiOAc (15 mol%) could evidently promote this amidation. HOAc and Li_2CO_3 as co-additives make the yield increase to 68% (entries 3–7). The solvent also played a crucial role. Among the solvents tested (DCE, THF, 1,4-dioxane, DMA, *t*-AmylOH and acetonitrile), DCE was proved to be the best for this transformation (entries 7–12). It is noteworthy that reaction temperature was critical for this transformation as well. Lower reaction temperatures resulted in decreasing reactivity. The yields were gradually improved to 95% by continuous increasing to 80 °C (entries 6, 13–16). Notably, this catalytic system also provided satisfactory yields even with a lower loading of iridium catalyst (1 mol%) (entry 17).



Scheme 1. Amidation of benzoic acids (**1**) with TsN_3 (**2a**).



Scheme 2. Amidation of benzoic acid (**1b**) with sulfonyl azides (**2**).

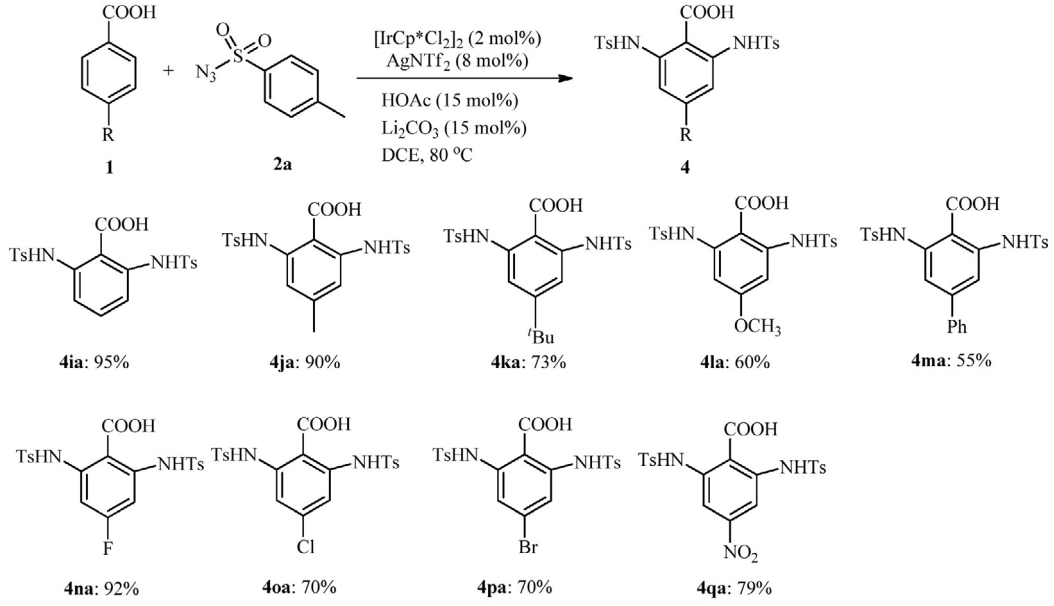
Furthermore, we examined various silver salt, $AgNTf_2$ was proved to be the best (entries 18–22). In addition, no conversion was observed with $[RhCp^*Cl_2]_2$, $[Ru(p\text{-cymene})Cl_2]_2$ or $Pd(OAc)_2$ as catalyst (entries 23–25).

3.1. Amidation of benzoic acids with TsN_3

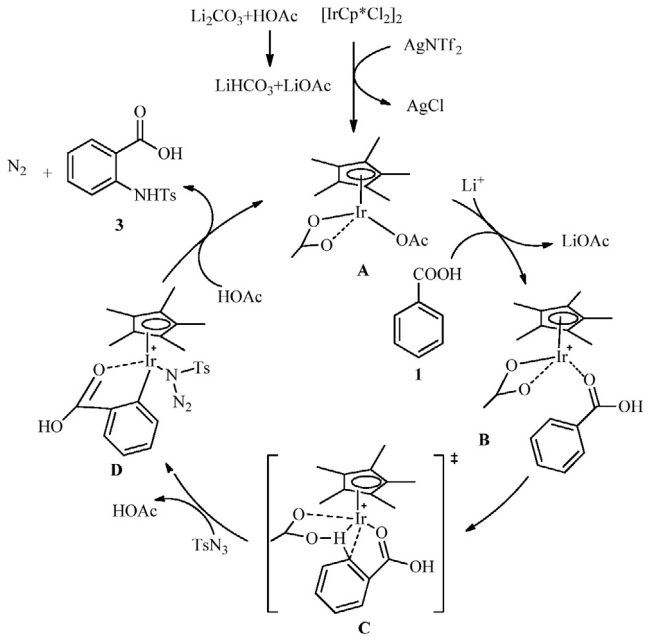
With the optimal reaction conditions in hand, we firstly investigated various *ortho*-benzoic acids **1** with *para*-methylphenylsulfonyl azide (**2a**) (Scheme 1). Benzoic acids with weakly electron-withdrawing and electron-donating groups at *ortho* position could be smoothly converted to the target products in excellent yields (**3aa–3da**, Scheme 1). Deficient sulfonyl azide, such as 2-nitrobenzoic acids (**3ea**), behaved less active. For *meta*-substituted benzoic acids, there are two different C–H bonds could be aminated. The electron-donating substituents (OMe) promoted the reaction producing the di-amidation products (**3fa**). For *meta*-nitrobenzoic acid only gave *mono*-amidated product because of its lower activity (**3ga**). *meta*-Bromobenzoic acid (**1h**) could generated isolatable mono- and di-amidation products **3ha** and **4ha** in totally excellent yield.

3.2. Amidation of benzoic acid with sulfonyl azides

The scope of sulfonyl azides **2** was then examined in the amidation of 2-methylbenzoic acid (**1b**) (Scheme 2). Various



Scheme 3. Amidation of *para*-benzoic acids (**1**) with TsN_3 (**2a**).



Scheme 4. Proposed reaction mechanism.

functional groups, such as F, Cl and NO_2, were well tolerated under the standard reaction conditions. Benzenesulfonyl azide (**2b**) resulted in the target product **3bb** in excellent yield. For *para*-substituted benzenesulfonyl azides, electron-donating substituents (**3ba**, **3bc**) promoted the reaction much more rapidly than the electron-withdrawing groups (**3bd**, **2bf**). Methyl substituent at *ortho*-position of the arene ring (**3bg**) led to a much lower yield than the *meta*-methyl benzenesulfonyl azide (**3bh**) due to the steric hindrance. Moreover, alkane sulfonyl azides **3bi** and **3bj** were readily amidated under the standard reaction conditions.

3.3. Amidation of para-benzoic acids with TsN_3

Next, we explored the generality and scope of *para*-substituted benzoic acids. As shown in Scheme 3 **(1j–1q)**, di-amidated products, rather than mono-amidation, were consistently obtained in high yields under the standard reaction conditions, which are complementary to previous directed *ortho*-amidation reactions. Benzoic acids (**4i**) resulted in the target product **4ia** in 95% yield. Electron-donating benzoic acid such as –Me, –^{t}Bu, –OCH_3 and –Ph (**4j, 4k, 4l** and **4m**) provided 90%, 73%, 60%, 55%, respectively. In addition, benzoic acids bearing the halogen groups, such as, –F, –Cl, –Br (**4n**, **4o**, **4p**) and strong electron-withdrawing group –NO_2 (**1q**) at the *para* position performed smoothly as well, delivering the desired products **4na**, **4oa**, **4pa, 4qa** in 92%, 70%, 70% and 79% yields, respectively. Good tolerance of large scope functional group made this reaction particularly attractive for increasing the molecular complexity by various chemical transformations.

3.4. Proposed reaction mechanism

According to the literatures [11,12], a plausible mechanistic pathway for this Ir(III)-catalyzed amidation reaction was proposed in Scheme 4. Initially, a combination of AcOH and Li_2CO_3 in situ generated lithium acetate and lithium bicarbonate. Then, acetate ion and $AgNTf_2$ prompted neutral dimeric iridium precursor to convert into its monomeric **A**, which dissociated the acetate ligand and combined with benzoic acid to form species **B**. Subsequently, iridium species induced C–H activation, leading to the formation of 5- or 6-membered metacyclic intermediate **C** and coordination of the azide to **C** formed the intermediate **D**. Finally, the desired amidated product **3** was generated with the formation of C–N bond and the release of N_2.

4. Conclusion

In summary, we have developed an iridium-catalyzed direct C–H amidation of weakly coordinating benzoic acids with sulfonyl azides. The protocol exhibited a broad substrate scope and proceeded under mild conditions with excellent functional group tolerance. Carboxylic acids are more available compared to other traditional coupling reagents and easy to save, the process of carboxylic acid-directed C–H amination herein has a great significance on synthetic organic products and medicinal intermediates.

Acknowledgment

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2015.08.009.

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