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Iridium(III)-Catalyzed One-Pot Access to 1,2-Disubstituted Benzimidazoles Starting from Imidamides and Sulfonyl Azides

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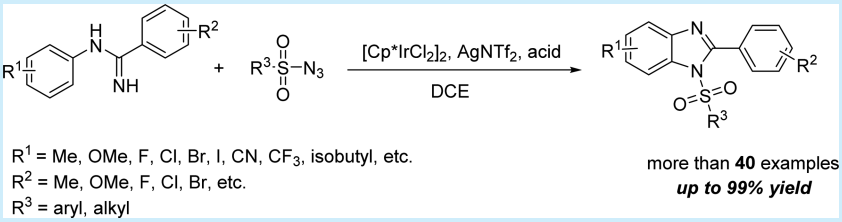
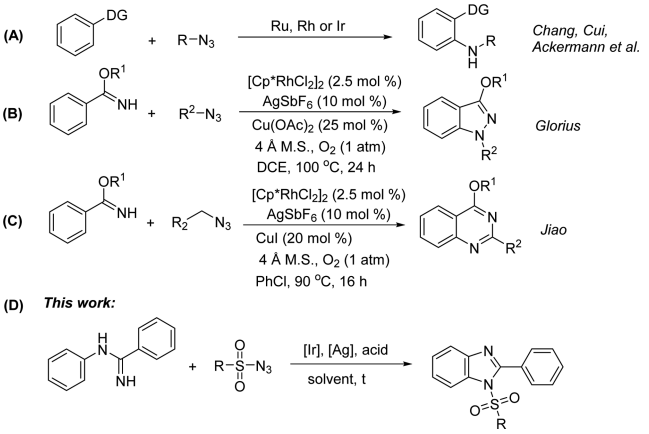
Supporting Information



ABSTRACT: A novel Ir-catalyzed annulation of imidamides with sulfonyl azides has been developed. 1,2-Disubstituted benzimidazoles could be easily obtained in up to 99% yield for more than 40 examples. The products further streamline the synthesis of molecules that are important building blocks for organic synthesis and drug discovery. This strategy features high regioselectivity, efficiency, good tolerance of functional groups, and mild reaction conditions.

Transition-metal-catalyzed C−N bond formation has been one of the major research topics in organic synthesis because of the ubiquity of C−N bonds in natural products, synthetic intermediates, pharmaceuticals, and functional materials.[1] Ullmann and Goldberg have developed Cu-mediated C−N cross-coupling of aryl halides with amines, which has been proven as a powerful pathway to build C−N bonds.[2] Palladium-catalyzed amination with the help of a suitable ligand as developed independently by Buchwald and Hartwig is an alternative procedure.[3] Recently, significant advances in direct C−H amination/amidation reactions have been achieved. However, harsh conditions or/and stoichiometric external oxidants are required for most procedures.[4] To avoid the external oxidants, preactivated amino precursors have been employed as reagents;[5] this requires an additional step to prepare the amine reagent, and stoichiometric byproducts are still unavoidable. Organic azide has been developed as an elegant amino source and internal oxidant by $N-N_2$ bond cleavage to effectively solve these limitations.[6] Chang, Ackermann, Jiao, and our group have extensively studied Rh-, Ru-, and Ir-catalyzed directed amination/amidation reactions under mild reaction conditions with various chelating groups (path A, Scheme 1),[6] such as amide,[7] *N*-phenylamide,[7] ketoxime,[8] hydrazine,[9] ketone,[10] carboxylic acid,[11] aldehyde,[12] nitrone,[13] *N*-oxide,[14] and other heterocycles, including pyridine,[15] pyrazol,[15a] imidazole,[16] oxazole,[9] pyrrolidinone,[9] and carbamate[9]. However, most of these directing groups were not easily removed or modified. This shortcoming can be attenuated if the chelating groups can be converted into the desired functional groups in the final products. Following this strategy, construction of azacycles using organic azide as the nitrogen source has received attention.[17] Glorius' group recently developed a novel synthesis of 1,3-substituted

Scheme 1. Transition-Metal-Catalyzed C−H Amination Using Organic Azides



indazoles from easily available arylimidates and sulfonyl azides via Rh(III)/Cu-catalyzed C−H activation/cyclization (path B, Scheme 1).[17a] Subsequently, the Jiao group reported the Rh(III)/Cu-catalyzed C−H annulation of arylimidates and benzyl azides to synthesize quinazolines (path C, Scheme 1).[17b] Benzimidazole is a valuable heterocyclic scaffold and displays various biological activities. In particular, 1,2-disubstituted benzimidazoles widely exist in natural products and pharmaceuticals.[18] Herein we report a convenient, efficient, and straightforward approach to synthesize 1,2-disubstituted

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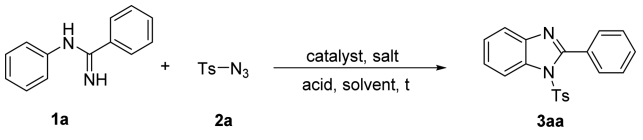
benzimidazoles via Ir(III)-catalyzed C−H activation of *N*-phenylbenzimidamides with organic azides (path D, Scheme 1).

This study commenced with the reaction of *N*-phenylbenzimidamide (**1a**) with TsN_3 (**2a**) catalyzed by $[Cp^*IrCl_2]_2$ (Table 1). The desired benzimidazole **3aa** was obtained in 32%

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

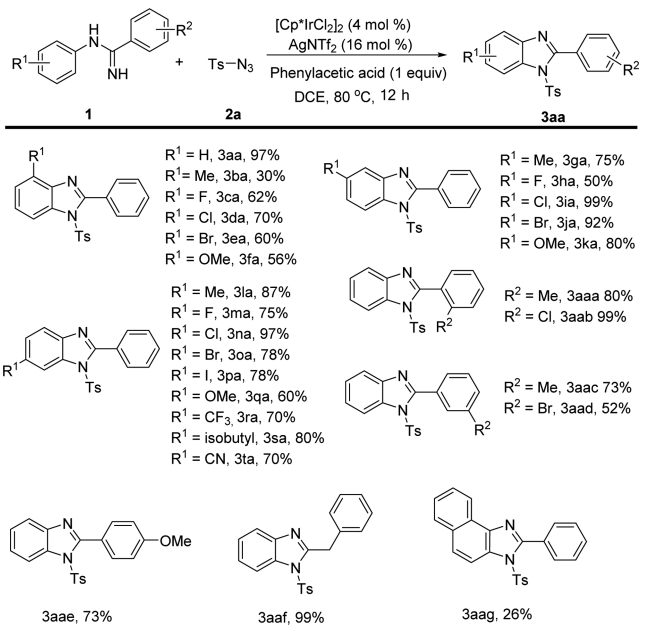
entry	catalyst	salt	acid (equiv)	solvent	yield (%)[b]
1	$[Cp^*IrCl_2]_2$	$AgNTf_2$	–	DCE	32
2	$[Cp^*IrCl_2]_2$	$AgNTf_2$	HOAc (0.5)	DCE	45
3	$[Cp^*IrCl_2]_2$	$AgNTf_2$	HOAc (1.0)	DCE	61
4	$[Cp^*IrCl_2]_2$	$AgNTf_2$	HOAc (1.0)	dioxane	26
5	$[Cp^*IrCl_2]_2$	$AgNTf_2$	HOAc (1.0)	toluene	28
6	$[Cp^*IrCl_2]_2$	$AgNTf_2$	PivOH (1.0)	DCE	54
7	$[Cp^*IrCl_2]_2$	$AgNTf_2$	benzoic acid (1.0)	DCE	35
8	$[Cp^*IrCl_2]_2$	$AgNTf_2$	phenylacetic acid (1.0)	DCE	80
9[c]	$[Cp^*IrCl_2]_2$	$AgNTf_2$	phenylacetic acid (1.0)	DCE	97
10[c]	$[Cp^*IrCl_2]_2$	$AgSbF_6$	phenylacetic acid (1.0)	DCE	87
11[c]	$[Cp^*IrCl_2]_2$	AgOAc	phenylacetic acid (1.0)	DCE	54
12[c]	$[Cp^*IrCl_2]_2$	NaOAc	phenylacetic acid (1.0)	DCE	45
13[d]	$[Cp^*IrCl_2]_2$	$AgNTf_2$	phenylacetic acid (1.0)	DCE	62
14[c]	–	$AgNTf_2$	phenylacetic acid (1.0)	DCE	N.R.
15[c]	$[Cp^*RhCl_2]_2$	$AgNTf_2$	phenylacetic acid (1.0)	DCE	N.R.
16[c]	$[Cp^*CoCl_2]_2$	$AgNTf_2$	phenylacetic acid (1.0)	DCE	N.R.
17[c]	[Ru(*p*-cymene)$Cl_2]_2$	$AgNTf_2$	phenylacetic acid (1.0)	DCE	18

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (1.5 equiv), $[Cp^*IrCl_2]_2$ (2.5 mol %), salt (10 mol %), acid, solvent (2 mL), 80 °C, 12 h, under air. [b]Isolated yields. N.R. = no reaction. [c]$[Cp^*IrCl_2]_2$ (4 mol %), salt (16 mol %). [d]$[Cp^*IrCl_2]_2$ (4 mol %), 70 °C.

yield (entry 1). Addition of HOAc (0.5 equiv) resulted in a higher yield of 45% (entry 2), which encouraged us to further increase the amount of HOAc. Product **3aa** was isolated in 61% yield when the amount of HOAc was increased to 1 equiv (entry 3). Subsequently, screening of solvents revealed that 1,2-DCE was optimal (entries 4−5). We then examined various acids. Phenylacetic acid was the most efficient (entries 6−8). To our delight, benzimidazole **3aa** was isolated in 97% yield when the loading of $[Cp^*IrCl_2]_2$ was increased to 4 mol % (entry 9). Among various salts tested, $AgNTf_2$ gave the best yield (entries 9−12). Temperature also has a great impact on this reaction, as **1a** showed low reactivity at 70 °C (entry 13). Control experiments revealed that no reaction occurred when the $[Cp^*IrCl_2]_2$ catalyst was omitted, which revealed the metal catalyst to be essential for this transformation (entry 14). Meanwhile, no desired conversion was observed using $[Cp^*RhCl_2]_2$ or $[Cp^*CoCl_2]_2$ as a catalyst (entries 15 and 16). A trace amount of **3aa** was detected when [Ru(*p*-cymene)$Cl_2]_2$ was used as the catalyst (entry 17). Finally, the optimized reaction conditions were identified as follows: $[Cp^*IrCl_2]_2$ (4 mol %), $AgNTf_2$ (16 mol %), and phenylacetic acid (1 equiv) in DCE at 80 °C for 12 h under air.

With the optimized reaction conditions in hand, we next explored the generality and scope of the reaction of *N*-phenylbenzimidamides with **2a** (Scheme 2). To our delight,

Scheme 2. Ir(III)-Catalyzed Synthesis of *N*-Tosyl Benzimidazoles from *N*-Phenylbenzimidamides[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.5 equiv), $[Cp^*IrCl_2]_2$ (4 mol %), $AgNTf_2$ (16 mol %), phenylacetic acid (1 equiv), DCE (2 mL), 80 °C, 12 h, under air. [b]Isolated yields are shown.

various *N*-phenylbenzimidamides containing electron-donating or electron-withdrawing groups or halogens worked well under the optimized reaction conditions, leading to the functionalized benzimidazoles. A methyl substituent at the ortho position of the benzene ring (**3ba**) led to a lower yield than for the *m*- and *p*-methyl-substituted *N*-phenylbenzimidamides (**3ga, 3la**), perhaps because of steric hindrance. A broad range of functional groups were also tolerated at the para position. The desired products were obtained in good to excellent yields (**3la−ta**). For instance, *N*-phenylbenzimidamides bearing fluoro (**3ma**), chloro (**3na**), bromo (**3oa**), iodo (**3pa**), methoxy (**3qa**), trifluoromethyl (**3ra**), isopropyl (**3sa**), and cyano (**3ta**) groups reacted smoothly with **2a**. These results indicated that the electronic properties of the *N*-phenylbenzimidamide had no apparent effect on the reaction. Meta-substituted *N*-phenylbenzimidamides gave the desired products in moderate to excellent yields with high regioselectivity, where C−H functionalization occurred at the less hindered site (**3ga−ka**). The steric effect of a 2-substituted benzene ring had no significant influence on the reactivity (**3aaa** vs **3aac**). 2-Diphenylacetimidamide also worked well, affording the corresponding product **3aaf** in 99% yield. *N*-Naphthylbenzimidamide was a suitable substrate, giving the corresponding benzimidazole **3aag** in 26% yield through selective reaction at the 2-position rather than the 8-position.

Next, we investigated the scope of sulfonyl azides **2** in the sulfamidation of **1a** under the optimized conditions (Scheme 3). It was found that a broad range of functional groups could

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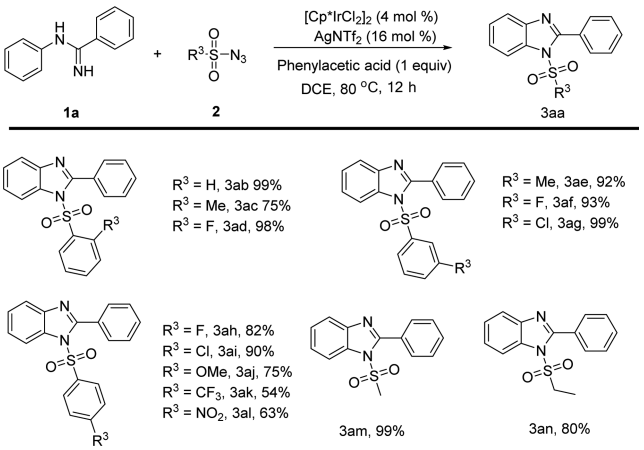
Scheme 3. Ir(III)-Catalyzed Synthesis of *N*-Sulfonyl Benzimidazoles with Sulfonyl Azides[a,b]



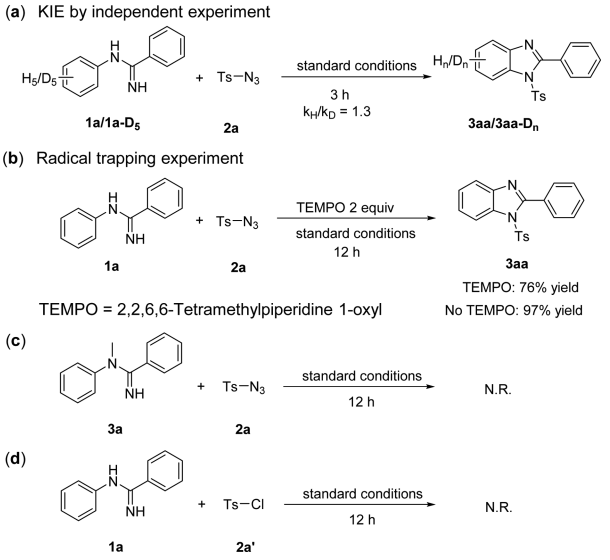
[a]Reaction conditions: **1a** (0.2 mmol), **2** (1.5 equiv), $[Cp^*IrCl_2]_2$ (4 mol %), $AgNTf_2$ (16 mol %), phenylacetic acid (1 equiv), DCE (2 mL), 80 °C, 12 h, under air. [b]Isolated yields are shown.

be tolerated. The arenesulfonyl azide with an *o*-methyl group (**3ac**) exhibited slightly decreased reactivity, presumably due to steric hindrance. Aromatic rings substituted with halogens worked well, providing the desired products in excellent yields (**3ah** and **3ai**). Moderate yields were obtained with 4-trifluoromethylbenzenesulfonyl azide and 4-nitrobenzenesulfonyl azide (**3ak** and **3al**). In addition, alkylsulfonyl azides worked well (**3am** and **3an**). No target products were obtained when aryl azides, benzyl azide, $TMSN_3$, and benzoyl azides were used as the substrates under the standard conditions. Compared with methods in the literature,[19] the current reaction provides easier, more straightforward, and more step-economical access to various 1,2-disubstituted benzimidazole derivatives with important biological and pharmacological activities.[18]

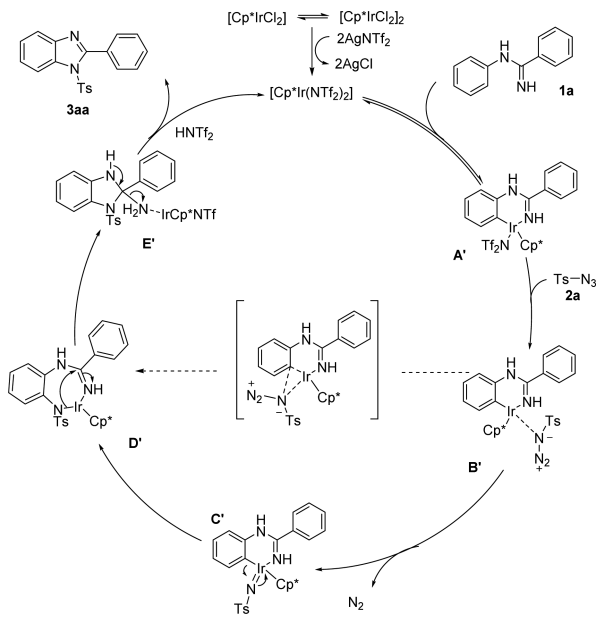
To shed light on the reaction mechanism of this cyclization process, a series of experiments were performed. To further probe the C−H activation process, the kinetic isotope effect was determined by running two parallel reactions using **1a** and **1a-D5** under the standard reaction conditions and terminating them after 3 h. A k_H/k_D value of 1.3 was obtained on the basis of the product yields of **3aa** and **3aa-D$_n$**, indicating that C−H bond cleavage is likely not involved in the turnover-limiting step (Scheme 4a). To our surprise, H/D exchange of **1a-D5** at the ortho position (the 4-position of the benzimidazole) was observed (with 26% H) according to the ^{1}H NMR spectra (see the Supporting Information), suggesting reversible C−H activation. Furthermore, a radical trapping experiment was carried out using TEMPO as the radical trap under the standard reaction conditions (Scheme 4b). The reaction was not obviously inhibited, suggesting that a radical process could be ruled out. In addition, no desired product was attained when *N*-methyl-*N*-phenylbenzimidamide (**3a**) was used as a substrate (Scheme 4c), which indicated the requirement of a free N−H group in the benzimidamide. Moreover, a control reaction between **1a** and TsCl did not deliver the target product (Scheme 4d), which proved that the nitrogen attached to Ts in **3aa** is from **2a** rather than **1a**.

According to these observations and literature precedents,[20,21] a plausible reaction mechanism is given in Scheme 5. First, the active catalyst, $[Cp^*Ir(NTf_2)]_2$, is generated

Scheme 4. Mechanism Studies



Scheme 5. Plausible Mechanism



through anion exchange. Coordination of **1a** to the catalyst and subsequent cyclometalation generates iridacyclic intermediate **A′**. Coordination of TsN_3 followed by elimination of nitrogen gives iridium carbene species **C′**. The Ir−Ar bond is proposed to undergo migratory insertion into the carbene unit to generate intermediate **D′**. The Ir−N(TsN_3) bond then undergoes migratory insertion into the C=N bond to afford amide species **E′**. The product **3aa** is eventually formed from **E′** by elimination of the active Ir(III) catalyst and one molecule of NH_3 from **E′** upon protonolysis and intramolecular protonolysis, which was proven by the reaction shown in Scheme 4c.

In conclusion, we have developed an efficient synthetic route to access 1,2-disubstituted benzimidazoles via Ir(III)-catalyzed C−H activation/annulation of readily available *N*-phenylbenzimidamides by coupling with sulfonyl azides. Good functional group tolerance, high atom efficiency, and moderate to high yields under relatively mild conditions make this protocol useful in preparing various substituted benzimidazole

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derivatives. Further mechanistic studies and other novel transformations of imidamides are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02028.

General procedures, relevant NMR spectra, and catalytic experiments (PDF)

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Notes

The authors declare no competing financial interest.

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