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COMMUNICATION

Synthesis of Benzimidazoles *via* Iridium-catalyzed Acceptorless Dehydrogenative Coupling

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Iridium-catalyzed acceptorless dehydrogenative coupling of tertiary amines and arylamines has been developed. A number of benzimidazoles were prepared in good yields. An iridium-mediated C-H activation mechanism is suggested. This finding represents a novel stragety for the synthesis of benzimidazoles.

Benzimidazole derivatives possess a wide variety of biological activities[1], including anti-bacterial, antivirus, anticancer, antifungal, antiulcer, and antihypertensive. Many benzimidazole drugs went to the market such as Albendazole, Omeprazole, Tiabendazole, Mizolastine and Telmisartan (Figure 1). A number of synthetic methods of benzimidazoles have been developed.[2-3] The general methods include the condensation of 1,2-phenylenediamine with aldehydes, carboxylic acids or their derivatives (nitriles, orthoesters), the transition metal-catalyzed C−N coupling of *N*-(2-haloaryl) amidines, and the intramolecular oxidative C−N couplings of arylamidine. In 2014, Long and co-workers reported an attractive synthesis of benzimidazoles from *N*-benzyl/alkyl-1,2-phenylenediamines *via* the TEMPO−air promoted oxidative C-N coupling.[3d] In recent years, cross dehydrogenative coupling (CDC) has emerged as a new strategy for the construction of C−N bonds.[4-5] Generally, CDC reactions require the presence of stoichiometric amount of oxidants or hydrogen acceptors. Acceptorless CDC reactions, which are completed with the release of hydrogen gas, have proven to be more challenge. So far, only few successful examples were reported.[6] Recently we developed two iridium-catalyzed acceptorless CDC reactions of tertiary amines with ketones and amides.[7] The C-C and C-N double bonds could be generated respectively. As a continuous effort, herein we report an acceptorless CDC reaction of tertiary amines and arylamines. The reaction provided a series of benzimidazoles in good yields under mild reaction conditions.

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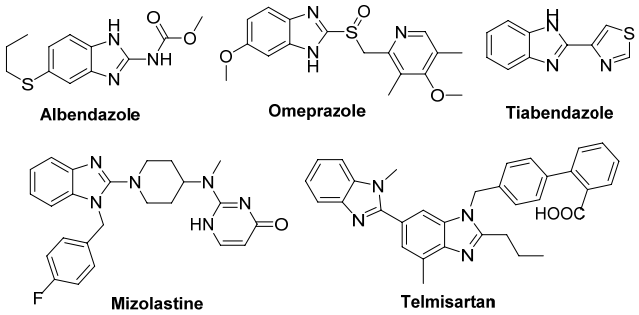
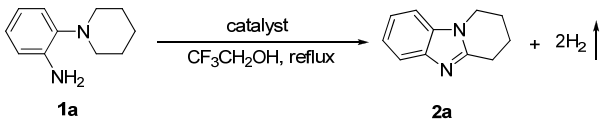


Figure 1 Marketed drugs with benzimidazole scafford.

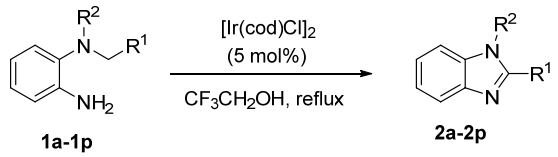
Table 1 Optimization of reaction conditions[a]

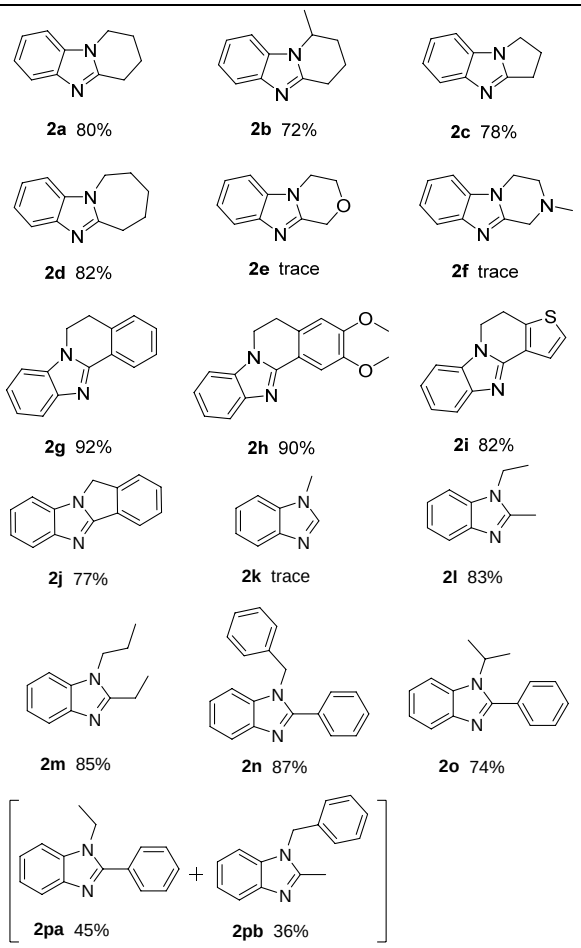


Entry	Catalyst	Yield [b] (%)
1	$[Cp^*IrCl_2]_2$	62
2	$[Ir(cod)Cl]_2$	82
3	$[Ir(coe)_2Cl]_2$	57
4	$[Ir(cod)OMe]_2$	41
5	Ir(cod)acac [c]	55
6	$IrCl_3$	-
7	$[Cp^*RhCl_2]_2$	-
8	$PtCl_2$ [d]	9
9	$[Ir(cod)Cl]_2$ [e]	33

[a] Conditions: **1a** (0.2 mmol), catalyst (5 mol% metal), trifluoroethanol (2 mL), argon atmosphere, 80 °C, 72 h. [b] The yields were determined by ^{1}H NMR using dimethyl terephthalate as the internal standard. [c] 10 mol% catalyst was used. [d] 5Å Molecular sieves was added. [e] Hexafluoroisopropanol was used instead of trifluoroethanol.

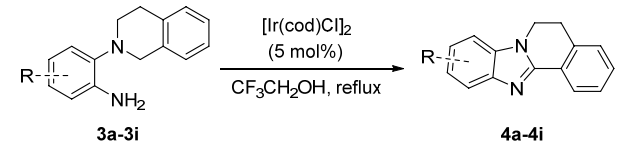
Table 2 Dehydrogenative coupling of substrates **1a**-**1p** [a,b]

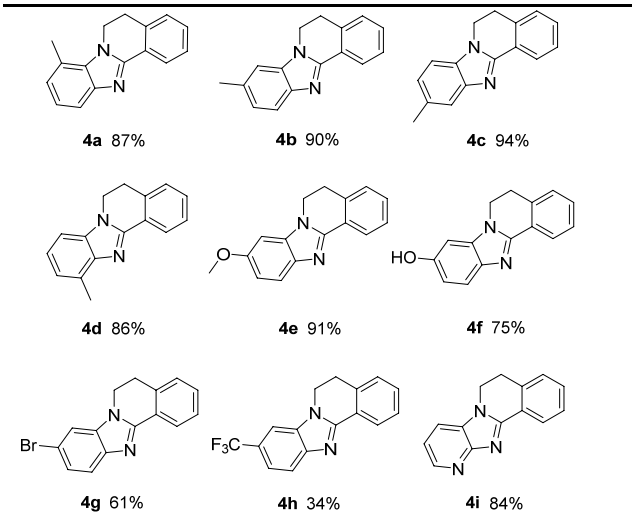




[a] Conditions: **1a-1p** (0.2 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), trifluoroethanol (2.0 mL), argon atmosphere, 80 °C, 72 h. [b] Isolated yields.

Table 3 Dehydrogenative coupling of substrates **3a-3i** [a,b]





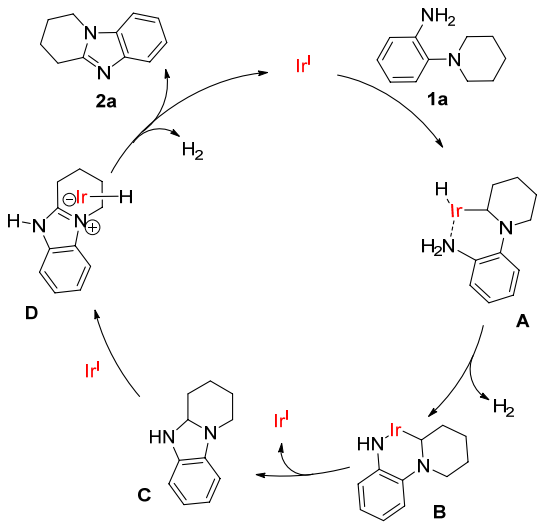
[a] Conditions: **3a-3i** (0.2 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), trifluoroethanol (2.0 mL), argon atmosphere, 80 °C, 72 h. [b] Isolated yields.

We chose 2-(piperidin-1-yl)aniline **1a** as the model substrate. A number of iridium catalysts were examined and the results are summarized in Table 1. $[Cp^*IrCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) gave a moderated yield of benzimidazole **2a** (Table 1, entry 1). $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) afforded **2a** in a better yield (Table 1, entry 2). $[Ir(coe)_2Cl]_2$ (coe = cyclooctene), $[Ir(cod)OMe]_2$ and Ir(cod)acac gave inferior yields (Table 1, entries 3-5). $IrCl_3$ is completely inefficient, probably due to its poor solubility in trifluoroethanol (Table 1, entry 6). $[Cp^*RhCl_2]_2$ did not show any catalytic activity (Table 1, entry 7). $PtCl_2$ in combination with 5Å molecular sieves provided **2a** in 9% yield (Table 1, entry 8).[6a] A series of nitrogen ligands were screened to improve the yield, however detrimental effect was observed.[8] The use of trifluoroethanol as the reaction solvent is important. The reaction did not occur in usual organic solvents (such as DMF, AcOH, toluene, $CHCl_3$, etc.). Lower yield was obtained in hexafluoroisopropanol (Table 1, entry 9). The emitted gas from the reaction of **1a** catalyzed by $[Ir(cod)Cl]_2$ was collected via the water-repulsion method. GC-TCD analysis of the gas components confirmed the existence of hydrogen gas. The result approves an acceptorless dehydrogenative process.

The substrate scope of this reaction was explored and the results are summarized in Table 2. The reaction of 2-methylpiperidine, pyrrolidine and azepane derivatives (**1b-1d**) provided the products (**2b-2d**) in good yields. However, 2-morpholinoaniline (**1e**) and 2-(4-methylpiperazin-1-yl)aniline (**1f**) are unreactive. The lower electronic density of these nitrogen heterocycles may inhibit the reaction. The anilines with 2-tetrahydroisoquinolinyl (**1g**-**1h**), 2-thieno[3,2-c]piperidinyl (**1i**) and 2-(isoindolin-2-yl) (**1j**) are suitable substrates. Good yields were generally obtained. *N,N*-Dimethylamino aniline (**1k**) is unreactive, however the reaction of *N,N*-diethylamino, *N,N*-dipropylamino, and *N,N*-dibenzylamino anilines (**1l-1n**) provided benzimidazole products in good yields. Again, the results demonstrate that the reaction is highly sensitive to the electronic density of α-carbon of tertiary amine. *N*-Isopropyl-*N*-benzyl-amino aniline (**1o**) gave **2o** as the major product, but *N*-ethyl-*N*-benzyl-amino aniline (**1p**) gave a mixture of benzimidazoles **2pa** and **2pb**. The steric hindrance seems to exert significant effect on the regioselectivity of the reaction.

The effect of the substitution at the phenyl ring of aniline was investigated and the results are summarized in Table 3. The

reaction of 3-, 4-, 5- and 6-methyl derivatives (**3a-3d**) afforded the benzimidazole products in good yields. The steric hindrance of the methyl group had a slight impact on the reaction. 4-Methoxyl and 4-hydroxyl substituted substrates (**3e-3f**) gave the products in good yields. Lower yield was obtained for the 4-bromo substituted substrate **3g**. The introduction of electron-withdrawing trifluoromethyl groups led to a poor yield. Pyridin-2-amine derivative (**3i**) is applicable and the expected product **4i** was obtained in a good yield.



Scheme 1 Proposed Reaction Mechanism

A tentative reaction mechanism is proposed (Scheme 1). The C-H insertion assisted by the coordination of the amino group with Ir(I) catalyst generates the intermediate **A**. After the release of one molecule of hydrogen gas, the Ir(III) intermediate **B** is formed. The reductive elimination leads to the dihydro-benzimidazole **C**. The Ir-catalyzed hydride transfer provides iminium intermediate **D**. After the release of second molecule of hydrogen gas, benzimidazole **2a** is obtained.[9]

In summary, we have developed an acceptorless dehydrogenative coupling of tertiary amines and arylamines. A number of benzimidazoles were prepared in good yields. An iridium-mediated C-H activation mechanism is suggested. The reaction provides a new strategy for the synthesis of benzimidazole derivatives from 2-(*N,N*-dialkylamino)-anilines.

Acknowledgements

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