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Efficient Construction of C=N Double Bonds *via* Acceptorless Dehydrogenative Coupling

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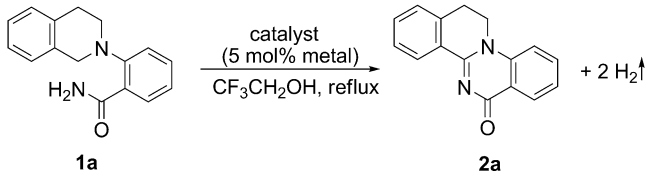
Abstract: The efficient construction of C=N double bonds has been achieved by the Ir-catalyzed intramolecular acceptorless dehydrogenative cross-coupling of tertiary amines and amides. An iridium/2-hydroxypyridine complex was identified as the highly efficient catalyst. A number of quinazolinone derivatives was prepared in excellent yields. An iridium-mediated C–H activation mechanism is proposed. This finding provides an unprecedented strategy for the direct imidation of sp^3 C–H bonds.

Keywords: C–H functionalization; C=N double bond; dehydrogenative coupling; imidation; iridium complexes

Nitrogen heterocycles are most important structural units in natural products and synthetic drugs. Thus, tremendous efforts have been made to develop synthetic methods towards nitrogen heterocycles.[1] Recently the direct C–H amidation has proven to be an efficient strategy for the synthesis of various amines and nitrogen heterocycles.[2] Most of these reactions proceed *via* nitrene intermediates,[3] however, limited substrate scope and low chemoselectivity were frequently observed. In addition, the formation of nitrene intermediates generally involves hypervalent iodine reagents or other oxidants, so that oxidation-sensitive functional groups are not tolerated. In recent years, the cross dehydrogenative coupling (CDC) reaction has emerged as a powerful tool for organic synthesis.[4] The direct construction of C–N bonds *via* CDC has been successfully developed.[5] However, these CDC reactions generally require sacrificial oxidants or H-acceptors. The acceptorless CDC reaction *via* release of hydrogen gas is more attractive from the view points of atom economy and green chemistry.[6] Zhou et al. reported the synthesis of cyclic amidines *via* the acceptorless dehydrogenation of alcohols and 2-aminobenzamides.[7] Liang et al. developed an intermolecular acceptorless CDC reaction of tertiary amines and ketones. The formation of C–C bonds was also achieved.[8] Recently we reported an intramolecular CDC reaction of tertiary amines and ketones. The construction of C=C double bonds was achieved with iridium-diphosphine catalysts in the absence of oxidants or hydrogen acceptors.[9] To the best of our knowledge, the construction of C–N bonds *via* acceptorless CDC reactions has never been reported. As a continuous effort to develop new methods for the direct functionalization of α-C–H bonds of amines, we extended the strategy to amide derivatives. In this paper, we report the highly efficient construction of C=N double bonds *via* iridium-catalyzed acceptorless dehydrogenative coupling of tertiary amines and amides.

Iridium complexes are found to be efficient catalysts for the catalytic dehydrogenations.[9] Initially, we examined the reaction of tetrahydroisoquinoline-derived benzamide **1a** in the presence of $[Cp^*IrCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl). To our delight, quinazolinone **2a** was obtained in good yield. TCD-GC analysis indicated the release of hydrogen gas during the reaction. Furthermore, a number of transition metal catalysts was screened and the results are summarized in Table 1. $[Ir(cod)Cl]_2$(cod=1,5-cyclooctadiene) provided a similar yield, however, the reaction was significantly slower (Table 1, entry 2). Ir(cod)(acac) (acac = acetylacetonate) and Ir(cod)-(hfacac) (hfacac = hexafluoroacetylacetonate) showed low catalytic activity (Table 1, entries 3 and 4). $[Cp^*RhCl_2]_2$ was found to be completely inefficient (Table 1, entry 5). Several ruthenium complexes are also poor catalysts (Table 1, entries 6–8). $Pd(OAc)_2$ provided **2a** in low yield (Table 1, entry 9) and the deposition of Pd(0) particles was observed. The re-

Table 1. Screen of catalysts.[a]



Entry	Catalyst	Time [h]	Yield [%][b]
1	$[Cp^*IrCl_2]_2$	2	86
2	$[Ir(cod)Cl]_2$	12	89
3	Ir(cod)(acac)	12	6
4	Ir(cod)(hfacac)	12	18
5	$[Cp^*RhCl_2]_2$	12	-
6	$Ru(cod)Cl_2$	12	8
7	$RuCl_2(PPh_3)_2$	12	-
8	$RuCl_3$	12	<5
9[c]	$Pd(AcO)_2$	12	34
10	$Pd(PPh_3)_2Cl_2$	12	-
11[d]	$PtCl_2$	12	20

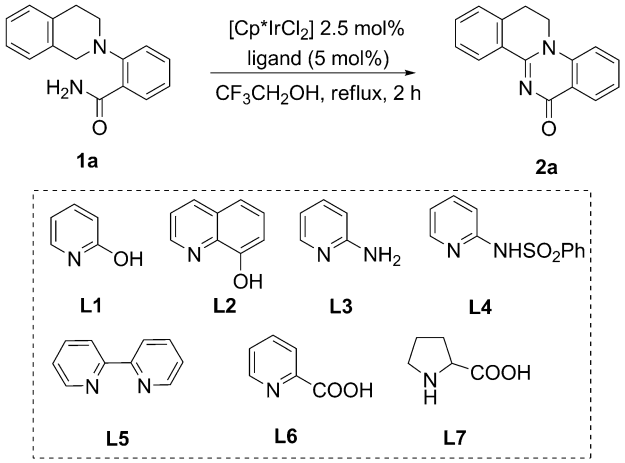
[a] *Conditions*: **1a** (0.2 mmol), catalyst (5 mol% metal), trifluoroethanol (2 mL), argon atmosphere, 100 °C, 12 h.
[b] The yields were determined by ^1H NMR using dimethyl terephthalate as the internal standard.
[c] Silvery metal particles were observed.
[d] 5 Å molecular sieves were added.

duction of $Pd(OAc)_2$ by **1a** may account for this phenomena. $Pd(PPh_3)_2Cl_2$ did not show catalytic activity in this reaction (Table 1, entry 10). $PtCl_2$ in combination with 5 Å molecular sieves gave **2a** in low yield (Table 1, entry 11).[10]

To improve the yield, a series of nitrogen ligands was screened and the results are summarized in Table 2. The addition of 2-hydroxypyridine (**L1**) led to excellent yield (Table 2, entry 1). Fujita, Wang and co-workers suggested that **L1** can assist Ir-catalyzed dehydrogenation by tautomerization.[11] In contrast, 8-hydroxyquinoline and 2-aminopyridine significantly decreased the yields (Table 2, entries 2 and 3). 2-Sulfamidopyridine provided **2a** in good yield (Table 2, entry 4). 2,2′-Bipyridine and picolinic acid completely inhibited the reaction (Table 2, entries 5 and 6). Proline is an efficient ligand and a good yield could be obtained (Table 2, entry 7). The reaction could also be carried out under an air atmosphere and a similar yield was obtained (Table 2, entry 8). The decrease of the $[Cp^*IrCl_2]_2$ loading to 1 mol% and 0.1 mol% resulted in lower yields (94% and 87%, respectively) (Table 2, entries 9 and 10).

The reaction solvent exerted a strong effect on the reaction. Trifluoroethanol was identified as the best solvent. Lower yields were obtained in acetic acid and ethanol (47% and 22%, respectively). Other solvents such as toluene, dichloroethane, isopropyl alcohol, DMF, and acetone are not compatible with the transformation.

Table 2. Effect of nitrogen ligands.[a]

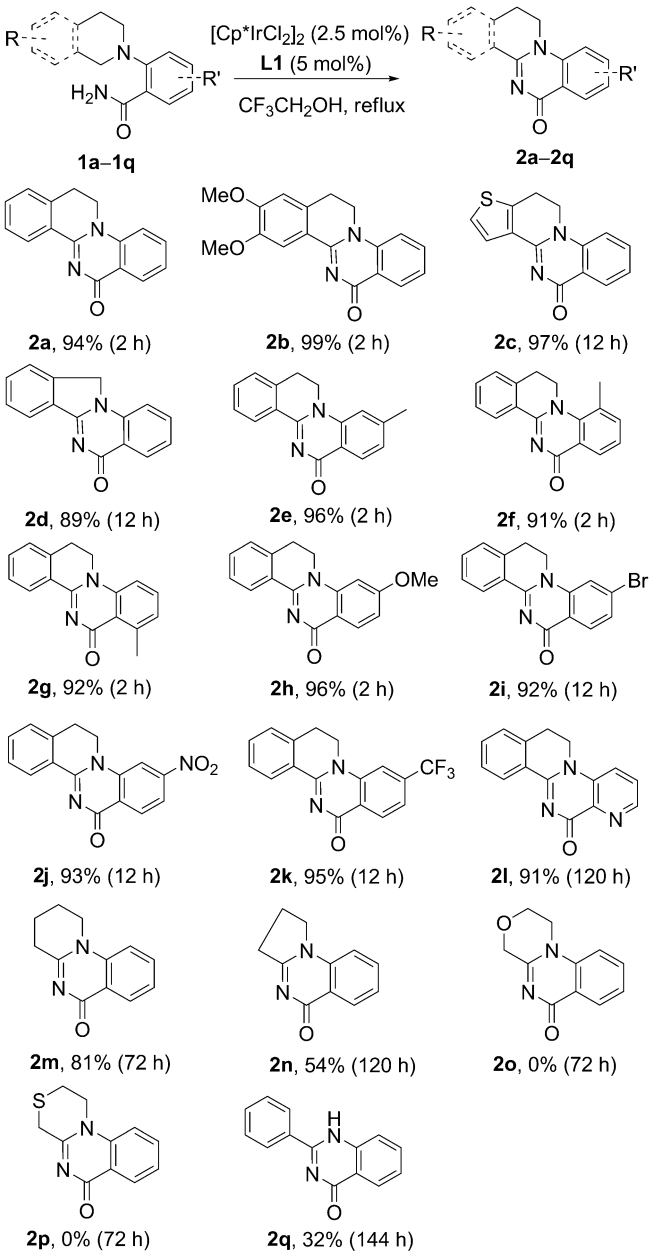


Entry	Ligand	Yield [%][b]
1	**L1**	99
2	**L2**	26
3	**L3**	21
4	**L4**	89
5	**L5**	–
6	**L6**	–
7	**L7**	91
8[c]	**L1**	98
9[d]	**L1**	94
10[e]	**L1**	87

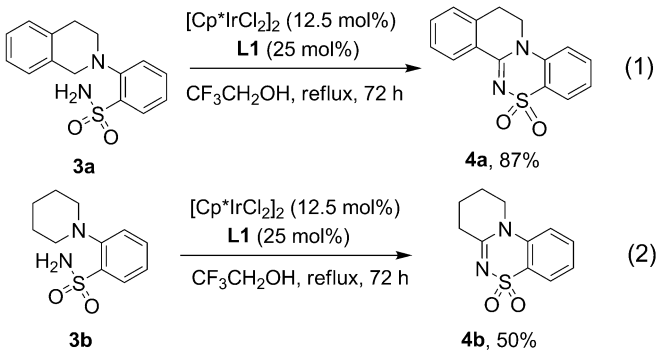
[a] *Conditions*: **1a** (0.2 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%), ligand (5 mol%), trifluoroethanol (2 mL), argon atmosphere, 100 °C, 2 h.
[b] The yields were determined by ^1H NMR using dimethyl terephthalate as the internal standard.
[c] The reaction was carried out under an air atmosphere.
[d] $[Cp^*IrCl_2]_2$ (1 mol%) and **L1** (2 mol%) were used.
[e] $[Cp^*IrCl_2]_2$ (0.1 mol%) and **L1** (0.2 mol%) were used.

A variety of 2-aminobenzamide derivatives was examined and the results are summarized in Scheme 1. The benzamides with 2-tetrahydroisoquinolinyl (**1a**, **1b**), 2-thieno[3,2-*c*]piperidinyl (**1c**) and 2-(isoindolin-2-yl) (**1d**) groups provided the expected products in excellent yields. 2-Tetrahydroisoquinolinylbenzamides (**1e–1k**) are also suitable substrates and excellent yields were generally obtained. 2-Tetrahydroisoquinolinylpicolinamide (**1l**) afforded an excellent yield after an extended reaction time. A good yield was also obtained for 2-piperidinylbenzamide (**1m**). A lower yield was observed for 2-pyrrolidinylbenzamide (**1n**). 2-Morpholinylbenzamide (**1o**) and 2-thiomorpholinylbenzamide (**1p**) are unreactive. The lower electronic density of these two nitrogen heterocycles appears to inhibit the reaction. 2-(Benzylamino)benzamide (**1q**) afforded the product **2q** in a low yield.

2-Tetrahydroisoquinolinyl-benzenesulfonamide (**3a**) is also applicable [Scheme 2, Eq. (1)]. The product **4a** was obtained in good yield when a higher catalyst



Scheme 1. Dehydrogenative coupling of 2-aminobenzamide derivatives.



Scheme 2. Dehydrogenative coupling of 2-aminobenzenesulfonamides.

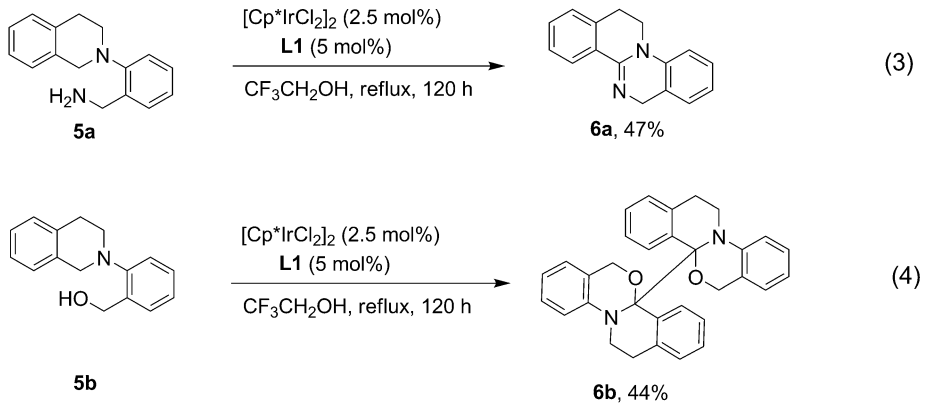
loading (12.5 mol%) was used. 2-(Piperidin-1-yl)benzenesulfonamide (**3b**) afforded the corresponding product **4b** in moderate yield [Scheme 2, Eq. (2)].

Under the optimal reaction conditions, 2-tetrahydroisoquinolinylbenzylamine (**5a**) provided the expected product **6a** in low yield [Scheme 3, Eq. (3)]. Interestingly, the reaction of 2-tetrahydroisoquinolinylbenzyl alcohol (**5b**) gave a dimer product **6b** in low yield [Scheme 3, Eq. (4)].

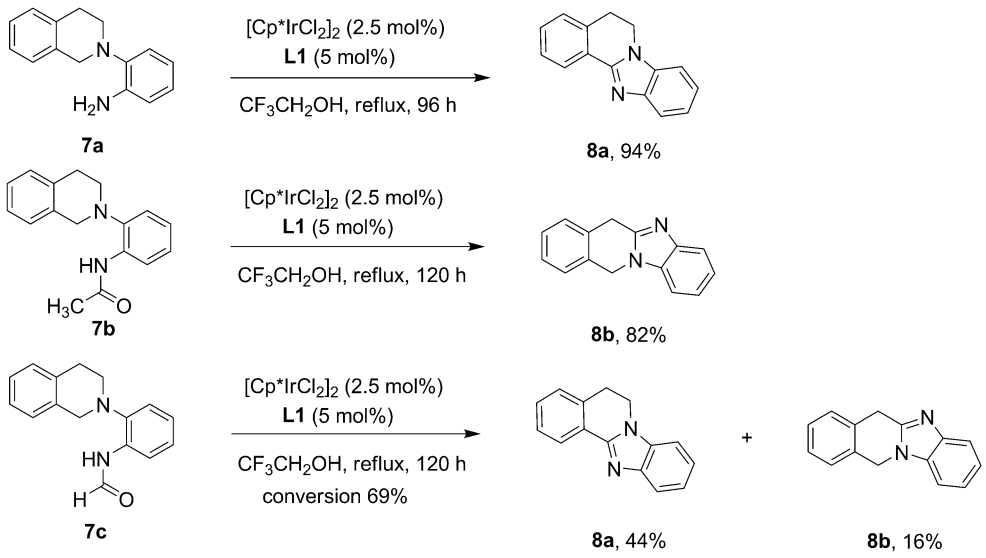
To further illustrate the scope of the reaction, the dehydrogenative coupling of 2-[3,4-dihydroisoquinolin-2(1*H*)-yl]aniline derivatives (**7a**–**7c**) was investigated (Scheme 4). 2-[3,4-Dihydroisoquinolin-2(1*H*)-yl]-aniline (**7a**) gave imidazole derivative **8a** in excellent yield. However, the acetamide derivative **7b** provided an abnormal product **8b** in good yield. On the other hand, the reaction of the formamide derivative **7c** afforded a mixture of **8a** (44% yield) and **8b** (16% yield). The steric hindrance of the amide group appears to affect the regioselectivity of the dehydrogenative coupling. In addition, the deacylation process also occurred in these transformations.

The dehydrogenative coupling of **1a** was found to be reversible under an elevated pressure of hydrogen gas. When the dehydrogenative reaction of **1a** was completed as indicated by TLC analysis, the reaction mixture was charged with 10 atm hydrogen gas and stirred at 60 °C for 12 h. The regeneration of **1a** was observed with 35% yield (Scheme 5). The result suggests that iridium catalyst also promotes the hydrogenation of amidine **2a** under an elevated pressure of hydrogen gas.

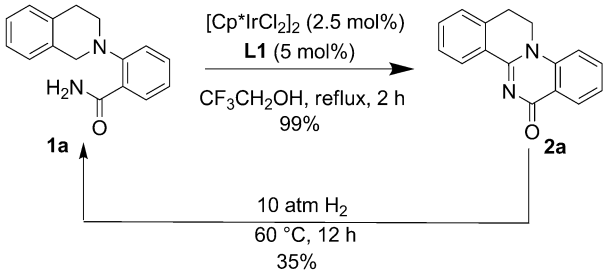
We explored the intermolecular dehydrogenative coupling of *N*-phenyltetrahydrogenisoquinoline and benzamide, however, no reaction was observed. Because $[Ir(cod)Cl]_2$ also promotes the reaction efficiently (Table 1, entry 2), $[Cp^*IrCl_2]_2$ may be reduced *in situ* by **1a** to a catalytically active Ir(I) species. A tentative reaction mechanism is proposed (Scheme 6). The amide group coordinates with Ir(I) catalyst and assists a C–H insertion process.[12] The intermediate **A** releases one molecule of hydrogen gas to give **B**. The reductive elimination leads to intermediate **C**. A hydride transfer provides an Ir–H species and iminium intermediate **D**. The release of a second molecule of hydrogen gas provides the product **2a**. Although the formation of an iminium species is also possible in the first step, the amide group-assisted C–H insertion should be more favorable due to the avoidance of charge separation. The intermediate **C** was never observed in the reaction. The fast dehydrogenation of **C** may account for this result.



Scheme 3. Dehydrogenative coupling of 2-tetrahydroisoquinolinylbenzylamine and 2-tetrahydroisoquinolinylbenzyl alcohol.



Scheme 4. Dehydrogenative coupling of 2-[3,4-dihydroisoquinolin-2(1*H*)-yl]aniline derivatives.



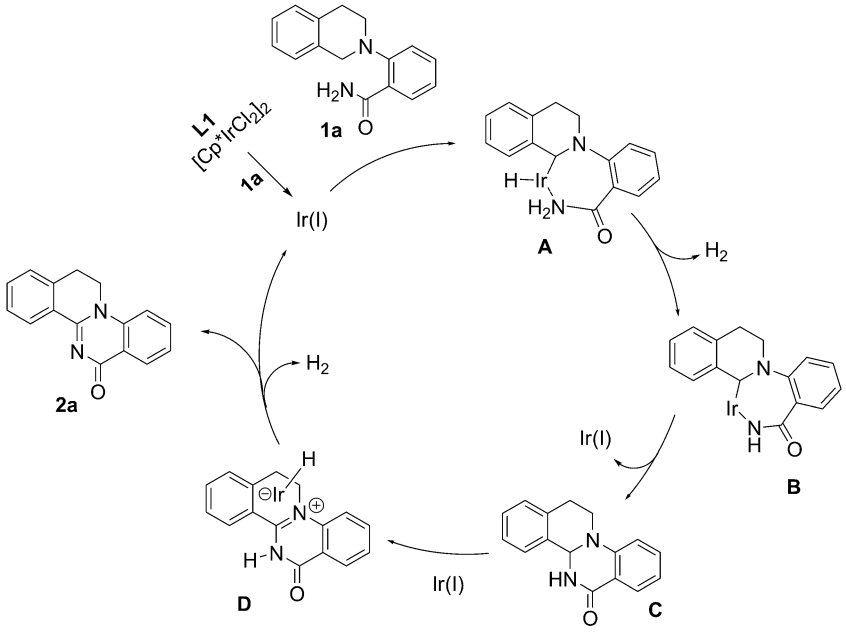
Scheme 5. Reversibility of dehydrogenative coupling of **1a**.

In conclusion, we have developed an intramolecular acceptorless dehydrogenative coupling of tertiary amines and amides. An iridium/2-hydroxypyridine complex was identified as the highly efficient catalyst. A number of quinazolinone derivatives was prepared in excellent yields. An iridium-mediated C–H activation mechanism is suggested. This finding provides an unprecedented strategy for the direct imidation of sp^3 C–H bonds.

Experimental Section

General Procedure for the Dehydrogenative Coupling

Under an argon atmosphere, $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol) and 2-hydroxypyridine (1.0 mg, 0.01 mmol) were stirred in dichloromethane (1 mL) at room temperature for 30 min. After the solvent had been removed under vacuum, **1a** (50.5 mg, 0.2 mmol) in trifluoroethanol (2 mL) was added. The reaction mixture was stirred at 100 °C for 2 h. The solvent was removed under vacuum and the residue was purified by flash column chromatography over silica gel to give the product **2a** as a white solid; yield: 46.7 mg (94%); mp 264.7–266.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.59 (d, $J = 7.9$ Hz, 1H), 8.43 (d, $J = 7.9$ Hz, 1H), 7.76 (t, $J =$



Scheme 6. Proposed reaction mechanism.

7.2 Hz, 1H), 7.60–7.40 (m, 4H), 7.30 (d, $J=7.4$ Hz, 1H), 4.37 (t, $J=6.6$ Hz, 2H), 3.28 (t, $J=6.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=169.3$, 155.0, 140.7, 135.7, 133.7, 132.7, 129.6, 129.1, 128.9, 127.8, 126.9, 125.8, 120.4, 113.8, 43.3, 27.1; IR (KBr): $\nu=3070$, 2949, 1634, 1601, 1521, 1486, 1454, 1415, 1350, 1118, 1035, 891, 754, 691 cm^{-1}; HR-MS (ESI): $m/z=249.1025$, calculated for $C_{16}H_{13}N_2O$ $(M+H)^+$: 249.1022.

Acknowledgements

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