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Unprecedented Construction of C=C Double Bonds via Ir-Catalyzed Dehydrogenative and Dehydrative Cross-Couplings

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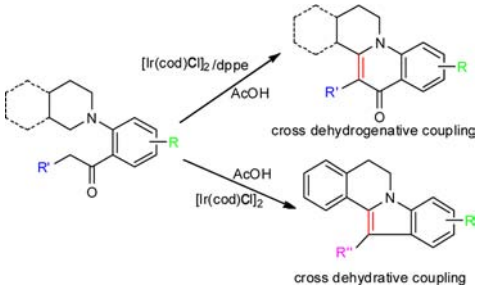
ABSTRACT



Unprecedented constructions of C=C double bonds have been achieved by Ir-catalyzed intramolecular dehydrogenative and dehydrative cross-coupling of tertiary amines and ketones. The reactions are proposed to proceed via an Ir-mediated C−H activation mechanism.

The construction of C−C bonds is the most important transformation in organic synthesis. Despite the numerous synthetic methods that have been developed, highly efficient and atom economical C−C bond formation reactions are still challenging goals.[1] In recent years, direct C−C bond formations via cross dehydrogenative couplings (CDCs) have exhibited great success.[2,3] However, almost all CDCs require sacrificial oxidants or H-acceptors. This drawback decreases the practicability and atom economy of CDCs. Oxidant-free or acceptorless CDCs are more attractive, and also more challenging. In these reactions, hydrogen gas is released as the only byproduct. So far only one successful case was reported. In 2010, Liang et al. developed a Pt-catalyzed intermolecular CDC reaction of tertiary amines and carbon nucleophiles in the absence of oxidants or H-acceptors.[4] To the best of our knowledge, the construction of C=C double bonds via an acceptorless

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(1) For reviews of ideal chemical synthesis, see: (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021. (b) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800. (c) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

(2) For reviews of CDC reactions, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (b) Li, Z.-P.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928–8933. (c) Li, C.-J.; Li, Z.-P. *Pure Appl. Chem.* **2006**, *78*, 935–945. (d) Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010**, *292*, 281–302. (e) Scheuermann, C. J. *Chem.—Asian J.* **2010**, *5*, 436–451. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (g) Zhang, M.; Zhang, A.-q. *J. Heterocycl. Chem.* **2012**, *49*, 721–725. (h) Yang, L.; Huang, H.-M. *Catal. Sci. Technol.* **2012**, *2*, 1099–1112.

(3) For selected recent examples of the construction of C−C bonds via CDC reactions, see: (a) Kuhl, N.; Hopkinson, M. N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8230–8234. (b) Shi, Z.-Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 9220–9222. (c) Qin, X.-R.; Feng, B.-Y.; Dong, J.-X.; Li, X.-Y.; Xue, Y.; Lan, J.-B.; You, J.-S. *J. Org. Chem.* **2012**, *77*, 7677–7683. (d) Bugaut, X.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7479–7481. (e) Alagiri, K.; Devadig, P.; Prabhu, K. R.; Prabhu. *Chem.—Eur. J.* **2012**, *18*, 5160–5164. (f) Zhang, J.-M.; Tiwari, B.; Xing, C.; Chen, X.-K.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 3649–3652. (g) Hu, H.-Y.; Liu, Y.; Zhong, H.; Zhu, Y.-L.; Wang, C.; Ji, M. *Chem.—Asian J.* **2012**, *7*, 884–888. (h) Wang, P.; Rao, H.-H.; Hua, R.-M.; Li, C.-J. *Org. Lett.* **2012**, *14*, 902–905. (i) Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2012**, *10*, 835–842. (j) Zhang, G.; Zhang, Y.-H.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429–10432.

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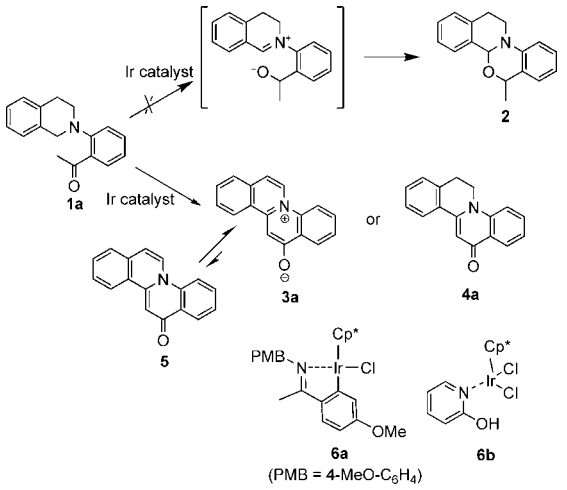
Scheme 1. Ir-Catalyzed CDC Reaction of **1a**



CDC has never been developed. Here, we report the efficient construction of C=C double bonds via an acceptorless CDC between four sp^3 C−H bonds of cyclic tertiary amines and carbonyl compounds. Direct functionalization of tertiary amines provided an efficient method for the synthesis of biologically important amines.[5] Ir-complexes have been found to be active catalysts for the dehydrogenation of alcohols and amines.[6] The formation of strong Ir−H bonds contributes to their excellent catalytic activities.

We speculated that the reaction of tetrahydroisoquinoline derivative **1a** in the presence of Ir-catalysts may provide N,O acetal **2** via an intramolecular hydride transfer and cascade acetalization (Scheme 1).[7] Initial reaction of **1a** in trifluoroethanol using $[Cp^*IrCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) as the catalyst did not provide the expected product **2**. Instead, zwitterionic product **3a** was isolated in substantial yield (Table 1, entry 1). Its structure was confirmed by NMR, MS, and IR spectral studies. Although **3a** can also exist in an equilibrium with its tautomer **5**, the IR spectrum indicated the absence of the carbonyl group and excluded this structure. The formation of an extensive conjugated system may strongly drive the equilibrium toward **3a**. Cyclometalated imido Ir(III) complex **6a** provided **3a** in a similar yield (Table 1, entry 2).[8] 2-Hydroxy pyridine Ir(III)-complex **6b** gave a slightly better yield (Table 1, entry 3).[9]

Table 1. Ir-Catalyzed CDC Reaction of **1a**[a]

			yield (%)[b]	
entry	catalyst	solvent	**3a**	**4a**
1	$[Cp^*IrCl_2]_2$	CF_3CH_2OH	24	5
2	**6a**	CF_3CH_2OH	25	–
3	**6b**	CF_3CH_2OH	30	–
4	$[Cp^*IrCl_2]_2$	AcOH	–	25
5	**6a**	AcOH	–	29
6	**6b**	AcOH	–	34

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (0.005 mmol), solvent (2 mL), refluxed for 24 h. [b] Isolated yield after column chromatography.

A number of reaction solvents were screened. Toluene, CH_2Cl_2, ether, THF, CH_3CN, ethanol, and methanol are not compatible with the transformation. The addition of H-acceptors such as norbornene and β-nitrostyrene did not exert a beneficial effect. On the contary they appeared to inhibit the reaction. Acetic acid was found to be a unique reaction solvent. Instead of product **3a**, another compound **4a** was obtained (Table 1, entries 4−6). It was identified as the CDC product, losing two molecules of hydrogen. Logically, **3a** can be generated by the further dehydrogenation of **4a**. However, the control test did not support this hypothesis. The result implies that 3,4-dehydrogenation occurs before the formation of the C1 double bond. The reaction solvent exerts the strong effect on this step.

To improve the yield of the reaction, an extensive screen of Ir and Rh complexes was carried out, and the results are summarized in Table 2. $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) was found to provide **4a** with a better yield. In addition, a new product **7a** was obtained in 26% yield (Table 2, entry 2). **7a** is generated via an interesting dehydrative coupling. By contrast, the $[Ir(cod)Cl]_2$-catalyzed reaction in trifluoroethanol provided **3a** in 29% yield and almost no product **4a**, and **7a** was obtained instead. Again, the reaction solvent showed a significant effect on the product distribution. Other Ir(I)-complexes, such as Ir(acac)(cod) (acac = acetylacetonate) and Ir(hfacac)(cod) (hfacac = hexafluoroacetylacetonate) provided **4a** in similar yields. However, no product **7a** was obtained (Table 2, entries 3 and 4). $[Rh(cod)Cl]_2$ is completely inefficient (Table 2, entry 5). Wilkinson's catalyst failed to catalyze the reaction (Table 2, entry 6).

The results suggest that $[Ir(cod)Cl]_2$ is a unique catalyst for this transformation. Furthermore, the effect of nitrogen and phosphine ligands was examined (Table 2, entries 7−14). The addition of 2-hydroxyl-pyridine increased the yield to 51% and completely inhibited the formation of product

(4) For acceptorless CDC reaction, see: (a) Shu, X.-Z.; Yang, Y.-F.; Xia, X.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2010**, *8*, 4077–4079.

(5) For reviews of direct functionalizations of tertiary amines, see: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069–1084. (b) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681–703. (c) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883.

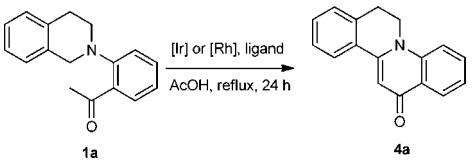
(6) For reviews of Ir-catalyzed dehydrogenation reactions, see: (a) Chio, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111*, 1761–1779. (b) Choi, J.; Goldman, A. S. *Top. Organomet. Chem.* **2011**, *34*, 139–168.

(7) For reviews of the "borrowing hydrogen" strategy, see: (a) Baehn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853–1864. (b) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *J. Chem. Soc., Dalton Trans.* **2009**, *38*, 753–762. (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681–703. (d) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555–1575. (e) Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7375–7378. (f) Neubert, L.; Michalik, D.; Bähn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239–12244.

(8) Wang, C.; Pettman, A.; Basca, J.; Xiao, J.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 7548–7552.

(9) (a) Yamaguchi, R.; Ikeda, C.; Takahashi, Y.; Fujita, K. *J. Am. Chem. Soc.* **2009**, *131*, 8410–8412. (b) Li, H.-X.; Jiang, J.-L.; Lu, G.; Huang, F.; Wang, Z.-X. *Organometallics* **2011**, *30*, 3131–3141.

Table 2. Screen of Metal Complexes and Ligands[a]



entry	metal complex	ligand	4a[b]
1	$(Cp^*IrCl_2)_2$	–	25
2[c]	$[Ir(cod)Cl]_2$	–	39
3	Ir(acac)(cod)	–	37
4	Ir(hfacac)(cod)	–	37
5	$[Rh(cod)Cl]_2$	–	trace
6	$Rh(Ph_3P)_3Cl$	–	trace
7	$[Ir(cod)Cl]_2$	2-hydroxyl-pyridine	51
8	$[Ir(cod)Cl]_2$	1,10-phenanthroline	46
9	$[Ir(cod)Cl]_2$	PPh_3	59
10	$[Ir(cod)Cl]_2$	BINAP	60
11	$[Ir(cod)Cl]_2$	DPPF	59
12	$[Ir(cod)Cl]_2$	DPPE	71
13	$[Ir(cod)Cl]_2$	DPPP	63
14	$[Ir(cod)Cl]_2$	DPPB	44
15[d]	$[Ir(cod)Cl]_2$	DPPE	trace

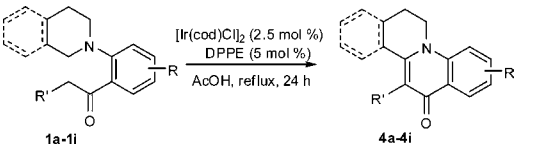
[a] Reaction conditions: **1a** (0.2 mmol), catalyst (0.005 mmol), ligand (0.01 mmol), solvent (2 mL), refluxed for 24 h. [b] Isolated yield after purification by flash-column chromatography. [c] Product **7a** was obtained in 26% yield. [d] Trifluoroethanol was used as the solvent.

7a (Table 2, entry 7). 1,10-Phenanthroline gave a lower yield (Table 2, entry 8), while PPh_3, BINAP, and DPPF [1,1′-bis(diphenylphosphino)ferrocene] provided improved yields (Table 2, entries 9−11). A better yield was achieved with DPPE [1,2-bis(diphenylphosphino)ethane] (Table 2, entry 12). DPPP [1,3-bis(diphenylphosphino)propane] and DPPB [1,4-bis(diphenylphosphino)butane] are less efficient than DPPE (Table 2, entries 13 and 14). The solvent acetic acid is critical for the success of this transformation, since $[Ir(cod)Cl]_2$/DPPE gave only a trace amount of **4a** in trifluoroethanol (Table 2, entry 15).

A variety of tetrahydroisoquinoline derivatives **1a**−**1j** were examined, and the results are summarized in Table 3. Substitution on both aryl groups could be tolerated very well (Table 3, entries 2−5). Thiophene derived substrate **1f** provided the product **4f** in moderate yield. Propiophenone derivative **1g** gave a lower yield. Piperidine derived substrate **1h** is also applicable, however, a low yield was obtained. In this case, only one molecule of hydrogen was eliminated (Table 3, entry 8). Morpholine derived substrate **1i** is unreactive (Table 3, entry 9). Oxime **1j** derived from **1a** reacted smoothly, and the corresponding CDC product **4j** was obtained in good yield (Table 3, entry 10).

The dehydrative coupling product **7a** and its analogs were reported to possess attractive biological activities.[10]

Table 3. Ir-Catalyzed CDC Reaction of Substrates **1a**−**1j**[a]



entry	substrate	product	yield (%)[b]
1	**1a**	**4a**	71
2[c]	**1b**	**4b**	72
3	**1c**	**4c**	67
4	**1d**	**4d**	70
5	**1e**	**4e**	63
6	**1f**	**4f**	51
7	**1g**	**4g**	48
8	**1h**	**4h**	32
9	**1i**	**4i**	0
10	**1j**	**4j**	72

[a] Reaction conditions: **1a**−**1j** (0.2 mmol), catalyst (0.005 mmol), ligand (0.01 mmol), acetic acid (2 mL), refluxed for 24 h. [b] Isolated yield after column chromatography. [c] DPPP was used in this case. DPPE provided lower yield (64%).

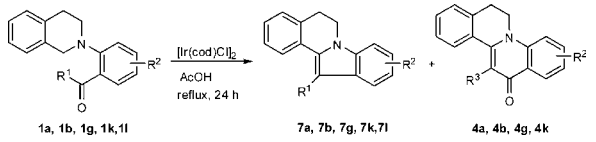
A preliminary investigation of this reaction was carried out, and the results are summarized in Table 4. The transformation was found to be quite sensitive to the substitution of the phenyl group. The 3-MeO substituted substrate **1b** gave only an 8% yield of **7b** together with CDC product **4b** (Table 4, entry 2). Propiophenone derived substrate **1g** provided **7g** in 24% yield (Table 4, entry 3). Benzophenone derived substrate **1l** afforded product **7l** in 50% yield.

(10) For the synthesis and biological activity of indolo[2,1-α]-isoquinolines, see: (a) Lötter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. A.; Otterlo, W. A. L. V.; Koning, C. B. D. *Tetrahedron* **2007**, *63*, 2263–2274. (b) Kraus, G. A.; Gupta, V.; Kohut, M.; Singh, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5539–5542. (c) Mahoney, S. J.; Fillion, E. *Chem.—Eur. J* **2012**, *18*, 68–71.

(11) For directing group assisted C−H activations, see: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (b) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977–1979. (c) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041–4047.

(12) See the Supporting Information for the tentative reaction pathway to product **3a**.

Table 4. Ir-Catalyzed Dehydrative Coupling[a]



				yield (%)[b]	
entry	R^1	R^2	R^3	**7**	**4**
1	Me	H	H	**7a**, 26	**4a**, 39
2	Me	3-OMe	H	**7b**, 8	**4b**, 43
3	Et	H	Me	**7g**, 12	**4g**, 27
4	Me	2-CF_3	H	**7k**, 20	**4k**, 50
5	Ph	H	–	**7l**, 50	–

[a] Reaction conditions: Substrate (0.2 mmol), catalyst (0.005 mmol), acetic acid (2 mL), refluxed for 24 h. [b] Isolated yield after column chromatography.

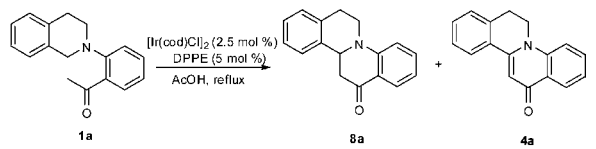
In this case, the competitive CDC was avoided, and thus a better yield could be achieved.

GC-TCD analysis of the gas components in the $[Ir(cod)Cl]_2$/DPPE catalyzed CDC of **1a** confirmed the existence of hydrogen gas. The fact suggests an acceptorless dehydrogenative process. On the other hand, the intermolecular CDC of *N*-phenyl-tetrahydroisoquinoline and acetophenone or acetone did not occur with the $[Ir(cod)Cl]_2$/DPPE catalyst.

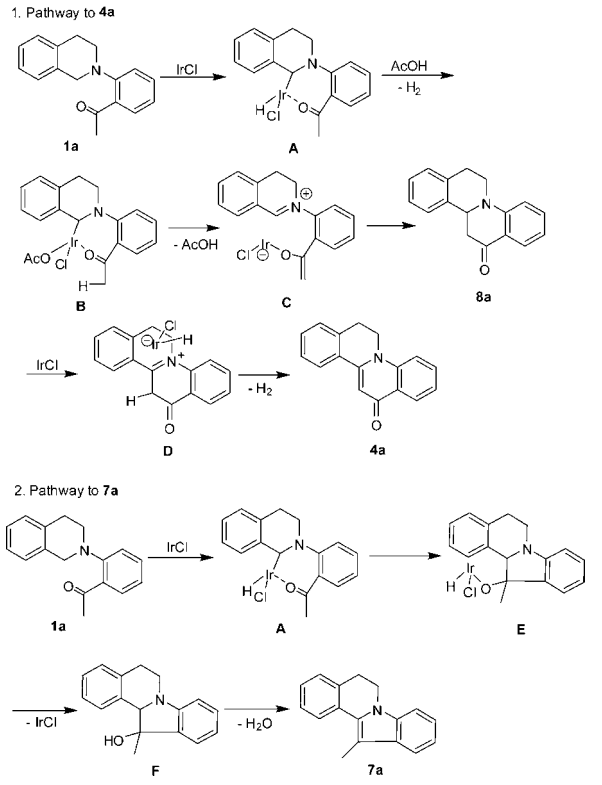
When the reaction of **1a** was stopped at 2, 4, and 8 h respectively, the analysis of the reaction mixture indicated the existence of partially dehydrogenated intermediate **8a**. The further transformation of **8a** to **4a** was observed after an extended reaction period (Scheme 2). The result demonstrates that **8a** is the primary product of the reaction and it is further dehydrogenated to give **4a**.

The tentative reaction pathway to product **4a** is outlined in Scheme 3. The carbonyl group works as a directing group for the oxidative insertion of Ir(I) into the C−H bond.[11] The protonation of intermediate **A** with acetic acid releases one molecule of hydrogen and generates intermediate **B**. After elimination of one molecule of acetic acid, iridium enolate **C** is formed. The subsequent intramolecular addition of iridium enolate to an iminium cation gives product **8a**. Then Ir-catalyzed abstraction of a hydride generates intermediate **D**, which eliminates a second molecule of hydrogen to provide product **4a**. On the other hand, the nucleophilic C1 of intermediate **A** can also attack

Scheme 2. Variation of Reaction Components with Time



Scheme 3. Tentative Reaction Pathways to Products **4a** and **7a**



the carbonyl group. The resulting intermediate **E** undergoes a reductive elimination to give intermediate **F**, which is readily dehydrated in acetic acid solvent to give product **7a**. Nitrogen and phosphine ligands can exert a strong effect on the selectivity for the two pathways.[12]

In conclusion, we have developed an intramolecular CDC reaction of tertiary amines and ketones. The construction of C=C double bonds was achieved with Ir-catalysts in the absence of oxidants or hydrogen acceptors. A number of tetrahydroisoquinoline derivatives were prepared in good yields. A unique cross dehydrative coupling reaction was also achieved to provide biologically important indolo[2,1-α]isoquinolines. The diversified reaction pathways could be realized via the change of the reaction solvent, ligands, and iridium complexes. The reactions are suggested to occur via a common Ir-mediated C−H activation step. The activation mechanism is potentially applicable for direct functionalization of various tertiary amines.

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Supporting Information Available. Experimental procedures, full spectroscopic data for all new products, and deuterium-labeling experiment data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.