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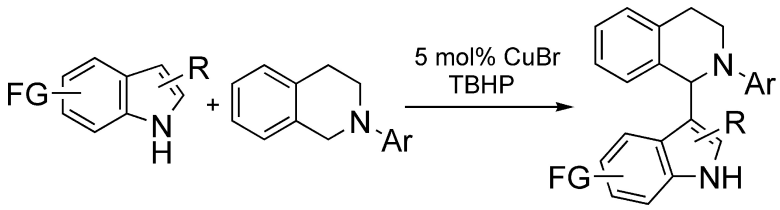

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CuBr-Catalyzed Direct Indolation of Tetrahydroisoquinolines via Cross-Dehydrogenative Coupling between sp^3 C−H and sp^2 C−H Bonds

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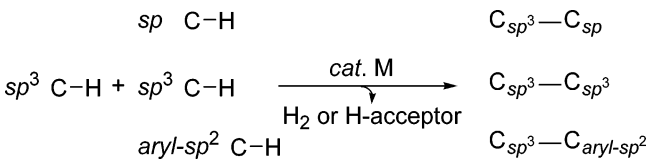
With the emergence of the concepts of "atom economy"[1] and "green chemistry",[2] transition metal-catalyzed C−H bond activation as well as direct use of unactivated C−H bond and subsequent C−C bond formations have attracted much interest in recent years *by providing an alternative to traditional functional group organic chemistry*. Directed toward such challenging goals, our attentions are focused on cross-dehydrogenative coupling (CDC) methodologies to construct molecules by directly using C−H bonds.[3] Recently, we reported two types of CDC reactions: sp^3 C−H with sp C−H[3B(a),(b)] and sp^3 C−H with sp^3 C−H [3A(a)] (Scheme 1). Herein, we report a new type of CDC reactions, combining sp^3 C−H with aryl-sp^2 C−H and leading to direct indolation of tetrahydroisoquinolines.[4]

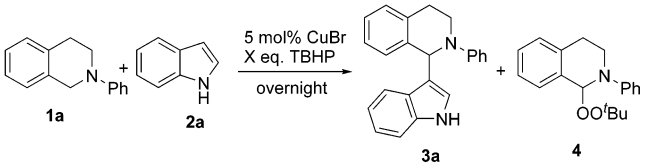
Scheme 1. Cross-Dehydrogenative Coupling for the Formation of C−C Bonds



Compounds containing heteroatoms, such as nitrogen, widely exist in nature. The syntheses of these compounds have attracted much attention in industrial and academic research due to their biological and pharmaceutical properties. Tetrahydroisoquinolines[5] and indoles[6] are common substructures in natural products. To synthesize and/or introduce these simple structures to complex molecules[7] *would not only have* significant potential biological *applications* but also *represent a significant contribution* to synthetic methodologies.

With the CDC methodology in mind, our study plan *centered on connecting* tetrahydroisoquinolines with indoles via the most direct way and under mild reaction conditions. There are two general methods to synthesize indolyl tetrahydroisoquinolines: (1) the reactions of indoles with cotarnine[8] and (2) the reactions of *N*-imidolylcycloimmonium salts with indoles, and then catalytic hydrogenation gives indolyl tetrahydroisoquinolines.[9] However, *there are limitations for both methods. For the first one, the natural tautomeric pseudobase, cotarnine, was used as the precursor and needs several steps to synthesize.*[10] *For the second one, a relatively long synthetic scheme has to be taken*. The limitations of methods for synthesizing such compounds heavily impede their biological studies.[11] To address this challenge, our attention focused on finding efficient methods for the synthesis of such alkaloids. To use free (NH) indoles directly would eliminate the protection−deprotection process in the introduction of these structures.[12] We envisioned two big challenges in this plan: (1) *Can the relatively reactive N−H bonds in indoles tolerate the reaction conditions without protection?* and (2) Can we introduce indoles with functional groups, which can be used for further transformations, into tetrahydroisoquinolines? To our delight, the desired product was obtained with free (NH) indoles (Table 1, entry 1). While optimizing the reaction conditions, we discovered that the reaction was not sensitive to moisture and air. Even when the reaction was performed in air and water, the desired product was obtained with a reasonable yield (Table 1, entry 8). Interestingly, when a large excess of water was used, only peroxide compound **4** was obtained and product **3a** was not observed (Table 1, entry 9). If an excess amount of only one of the three reagents (**1a**, **2a**, and TBHP) was used, the yields of desired product **3a** were not satisfactory (Table 1, entries 2, 4, 6). The yields of desired product **3a** were lower at room temperature than at 50 °C (Table 1, entries 1 and 2). The best reaction condition is using a slight excess amount of **2a** and TBHP under 50 °C (Table 1, entry 10).

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	*T* (°C)	**2a** (equiv)	TBHP (equiv)	conv. of **1a** (%)[b]	**3a** (%)[b]	**4** (%)[b]
1	neat	22	1.0	1.0	90	45	<5
2	neat	22	2.0	1.0	85	40	trace
3	neat	50	1.0	1.0	90	75	N.D.[c]
4	neat	50	1.0	1.25	95	70	N.D.[c]
5	*t*-BuOH	50	1.0	1.0	90	30	trace
6[d]	neat	50	1.0	1.0	90	60	N.D.[c]
7	neat	50	1.5	1.5	100	60	N.D.[c]
8	H_2O/PhMe (0.5 mL/0.1 mL)	50	1.2	1.3	100	50	N.D.[c]
9	H_2O/PhMe (2.0 mL/1.0 mL)	50	1.2	1.3	100	N.D.[c]	70
10	neat	50	1.2	1.3	100	85	N.D.[c]

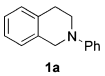
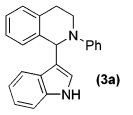
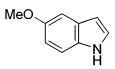
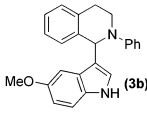
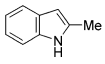
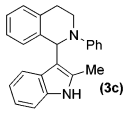
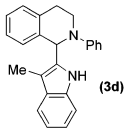
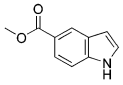
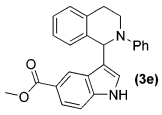
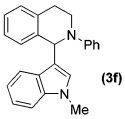
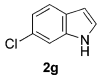
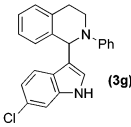
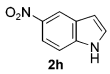
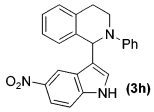
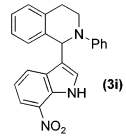
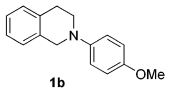
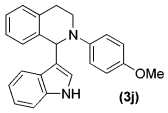
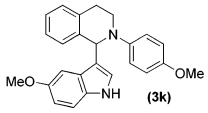
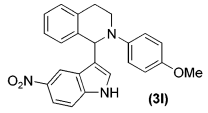
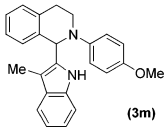
[a] Tetrahydroisoquinoline (0.1 mmol) was used; unless otherwise noted; ^{t}BuOOH (5−6 M in decane). [b] Detected by NMR using an internal standard. [c] Not detected by NMR. [d] Tetrahydroisoquinoline (0.15 mmol) was used.

Under the optimized reaction conditions, various indoles were used to react with tetrahydroisoquinolines, and representative results are listed in Table 2. The desired products were formed in good to excellent yields.[13] The reactions selectively occur at the C3 position of indoles if both C2 and C3 positions of indoles are unoccupied. When the C3 position of indoles is substituted, the C2 products are obtained (Table 2, entries 4 and 13). Indoles with electron-withdrawing groups or electron-donating groups on C5, C6, and C7 also worked well with tetrahydroisoquinolines under the present reaction conditions (Table 2, entries 2, 5, 7−9, 11, and 12).

For the mechanism of this formation of indolyl tetrahydroisoquinolines, the first step is most likely the formation of an imine-type intermediate[14] (coordinated to copper[15]) through H-abstraction

10.1021/ja0516054 CCC: $30.25

Table 2. CDC Reaction of Indoles with Tetrahydroisoquinolines[a]

entry	1	2	product	yield (%)[b]
1	 **1a**	 **2a**	 **(3a)**	86 (79)
2	**1a**	 **2b**	 **(3b)**	89 (57)
3	**1a**	 **2c**	 **(3c)**	80 (61)
4	**1a**	 **2d**	 **(3d)**	81 (77)
5	**1a**	 **2e**	 **(3e)**	77 (63)
6	**1a**	 **2f**	 **(3f)**	58 (44)
7	**1a**	 **2g**	 **(3g)**	89 (73)
8	**1a**	 **2h**	 **(3h)**	(85)
9	**1a**	 **2i**	 **(3i)**	64 (50)
10	 **1b**	**2a**	 **(3j)**	95 (71)
11	**1b**	**2b**	 **(3k)**	98 (65)
12	**1b**	**2h**	 **(3l)**	78 (50)
13	**1b**	**2d**	 **(3m)**	95 (49)

[a] Tetrahydroisoquinolines (0.1 mmol), indoles (0.12 mmol), CuBr (0.005 mmol, 5 mol %), and ^{t}BuOOH (0.13 mmol, 5−6 M in decane). [b] NMR yields are based on tetrahydroisoquinolines and determined by NMR using an internal standard; isolated yields are given in parentheses.

of the sp^3 C−H adjacent to nitrogen catalyzed by CuBr. Then the reaction is followed by an in situ Friedel−Crafts-type reaction to give the final products. However, it is also possible that the *tert*-butyl peroxide product **4** is involved as an intermediate[3B(b),16] and is further converted into the corresponding cross-coupling product.

In summary, indolyl tetrahydroisoquinoline derivatives were efficiently synthesized via a CDC reaction between sp^3 C−H bonds and sp^2 C−H bonds catalyzed by copper bromide. This novel methodology not only provides the simplest way to construct indolyl tetrahydroisoquinolines but also opens a new way to construct and study more complex alkaloids. The advantages of this method include: (1) relatively mild reaction conditions, (2) use of free (NH) indoles, (3) *tolerance of* various functional groups, (4) high *regioselectivity*, and (5) *use of a relatively* cheap metal, copper, as catalyst. The scope, mechanism, and synthetic application of this reaction are under investigation.

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Supporting Information Available: Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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