Highly Efficient CuBr-Catalyzed Cross-Dehydrogenative Coupling (CDC) between Tetrahydroisoquinolines and Activated Methylene Compounds

Zhiping Li[a] and Chao-Jun Li*[a]

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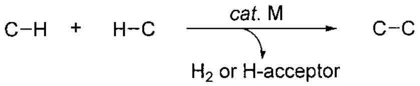
A novel and efficient C–C bond-formation method was developed: the cross-dehydrogenative coupling (CDC) reaction catalyzed by copper bromide in the presence of an oxidizing reagent, *t*BuOOH. The CDC reaction provides a simple and efficient catalytic method to construct β-amino diesters and β-dicyano amines by a combination of two different sp^3 C–H bonds followed by C–C bond formation.

Introduction

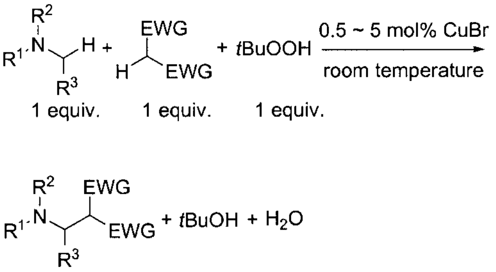
Pursuing efficient C–C bond formation reactions has been of cntinuous interest in chemistry, because they provide key steps in building more complex molecules from simple precursors. In this respect, transition metal catalyzed cross-coupling reactions of various reactive functional groups have shown to be powerful methods of constructing C–C bonds.[1]

Cross-dehydrogenative coupling (CDC) reaction, namely, the cross coupling of two different C–H bonds of pronucleophiles and proelectrophiles, will avoid the preparation of functional groups and thus make synthetic schemes shorter and more efficient (Scheme 1).[2] Therefore, the development of CDC reactions is highly desirable for the next generation of C–C bond formations. There has been excellent, but very limited, progress in this area.[3] However, from a practical point of view, highly efficient CDC reactions under mild reaction conditions are still greatly needed for synthesis. To realize CDC reactions, it is a prerequisite to activate the C–H bonds in both the pronuleophile and the proelectrophile in situ and selectively, while avoiding homocoupling.



Scheme 1. Cross-dehydrogenative coupling (CDC) for the formation of C–C bonds.

Tetrahydroisoquinoline derivatives are important structural features of natural products and pharmaceuticals; therefore, numerous studies on their synthesis have been developed.[4] We recently reported two new types of C–C bond formations to generate tetrahydroisoquinoline derivatives by CDC reactions: (i) sp^3 C–H and sp C–H coupling (CuBr-catalyzed alkynylation of sp^3 C–H bonds adjacent to a nitrogen atom)[3a,3b] and (ii) sp^3 C–H and sp^3 C–H coupling (an efficient catalytic method to construct β-nitro amines).[2] Herein, we report a highly efficient CDC reaction under mild reaction conditions to construct β-diester- and β-dicyano-substituted tetrahydroisoquinoline derivatives catalyzed by copper bromide in the presence of *t*BuOOH (TBHP) by a combined reaction of sp^3 C–H bonds in pronucleophiles and sp^3 C–H bonds of proelectrophiles followed by C–C bond formation (Scheme 2).



Scheme 2. CDC reaction between different sp^3 C–H bonds.

Results and Discussion

We began our study by examining various reaction conditions for the desired CDC reaction between tetrahydroisoquinoline derivative **1a** and dimethyl malonate (**2a**) (Table 1). Without any solvent, the reactions generated the desired products **3a** in good to excellent yields at room temperature (Entries 1–3). The yield increased to 90% when 3

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[a] Department of Chemistry, McGill University
801 Sherbrooke St. West, Montreal, Quebec H3A 2K6, Canada
Fax: +1-514-398-3797
E-mail: cj.li@McGill.ca

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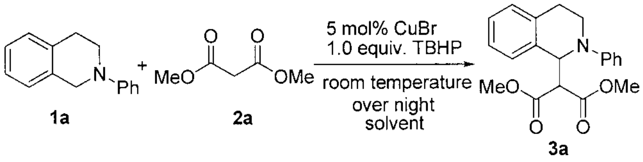
equiv. of dimethyl malonate were used (Entry 3 vs. 1). Increase of the temperature reduced the reaction time (Entry 4). Various solvents were also tested for the reaction. In polar solvents, the desired products were obtained with reasonable to good yields (Entries 5–11). However, with hexane as solvent, the product was obtained in less than 5% yield (Entry 12). Although a higher isolated yield was obtained when dimethyl malonate was in excess (Entries 2 and 3), we chose the conditions of the equimolar reaction of **1a** and **2a** (Entry 1), which is more "atom-economical" as our standard reaction conditions.

Table 1. Optimization of the reaction conditions.[a]

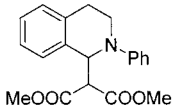
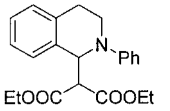
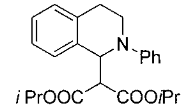
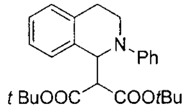
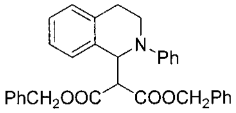
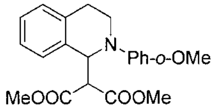
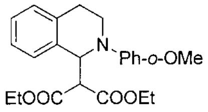
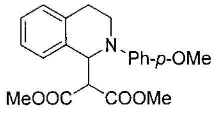
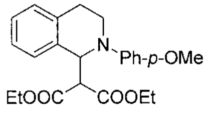


Entry	Solvent[b]	Conv. [%] of **1a**[c]	Yield [%] of **3a**[d]
1	no	95	80
2[e]	no	95	85
3[f]	no	95	90
4[g]	no	95	80
5	H_2O	70	20
6	THF	95	40
7	1,4-dioxane	100	50
8	DMSO	95	60
9	*t*BuOH	95	70
10	CH_2Cl_2	95	60
11	CH_3CN	100	40
12	Hexane	75	< 5

[a] Tetrahydroisoquinoline (0.1 mmol), dimethyl malonate (0.1 mmol), and *t*BuOOH (0.02 mL, 5–6 M in decane). [b] Solvent (0.5 mL) was used, if needed. [c] Determined by NMR spectroscopy from recovered **1a**. [d] Determined by NMR spectroscopy by using an internal standard. [e] Standard conditions, except that dimethyl malonate (0.2 mmol) was used. [f] Standard conditions, except that dimethyl malonate (0.3 mmol) was used. [g] Standard conditions, except that the reaction was carried out at 35 °C for 3 h.

Under the standard conditions, various β-amino diester derivatives were generated by this new methodology. Representative results obtained by the CDC reaction are summarized in Table 2. The reaction of 2-phenyltetrahydroisoquinoline with various dialkyl malonates gave the desired products in excellent yields (Entries 1, 3–6). For substituted 2-phenyltetrahydroisoquinoline, the expected products were also obtained with reasonable to good yields (Entries 7–10). To further improve the high efficiency of this new methodology, the reaction was carried out on a 1 mmol scale with 0.5 mol-% of CuBr as the catalyst. The progress of this reaction is clearly seen by the changes of the reaction mixture: the reaction starts with a clear solution, then changes to a red color solution gradually, and turns into a reddish solid after 53 h. The desired product **3a** was obtained in 72% isolated yield (Entry 2).

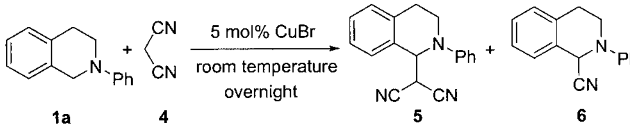
Table 2. CDC reaction of tetrahydroisoquinolines **1** with malonates **2**.[a]

Entry	Conv. [%] of **1**[b]	Product **3**	Yields [%] of **3**[c]
1 2[d]	95 95	 **(3a)**	74 72
3	95	 **(3b)**	65
4	95	 **(3c)**	82
5	100	 **(3d)**	78
6	95	 **(3e)**	70
7	100	 **(3f)**	71
8	100	 **(3g)**	56
9	95	 **(3h)**	70[e]
10	90	 **(3i)**	58

[a] Tetrahydroisoquinoline (0.1 mmol), malonate (0.1 mmol), and *t*BuOOH (0.02 mL, 5–6 M in decane). [b] Determined by NMR spectroscopy from recovered **1**. [c] Isolated yields. [d] CuBr (0.005 mmol, 0.5 mol-%), tetrahydroisoquinoline (1.0 mmol), malonate (1.0 mmol), *t*BuOOH (0.2 mL, 5–6 M in decane), reaction time 53 h. [e] Tetrahydroisoquinoline (0.1 mmol), malonate (0.2 mmol), and *t*BuOOH (0.02 mL, 5–6 M in decane).

Next, we investigated the synthesis of β-dicyano-substituted tetrahydroisoquinoline derivatives by using malononitrile as the pronucleophile under the standard reaction conditions. The results are listed in Table 3. The desired product **5** was obtained in 29% isolated yield (Entry 1). Surprisingly, α-cyano product **6**[5] was also obtained as one of the unexpected by-products. The yield of product **5** was increased to 46% along with 6% of **6** when 6 equiv. of malononitrile were used (Entry 2). More interestingly, if 2 equiv. of TBHP were used, product **5** was not observed by NMR spectroscopy and only compound **6** was obtained as the main product (Entry 3). This unexpected result is probably due to a certain oxidative degradation of malononitrile to cleave the C–CN bond by Cu^{II}[6] and to give the corresponding product **6**.

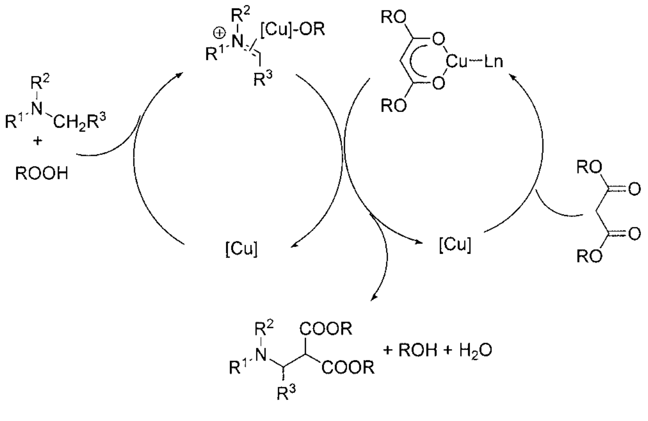
Table 3. CDC reaction of tetrahydroisoquinoline with malononitriles.[a]



Entry	4	TBHP	Conv. [%] of **1a**[b]	Yield [%] of **5**[c]	Yield [%] of **6**[c]
1	1 equiv.	1 equiv.	95	29	7
2	6 equiv.	1 equiv.	100	46	6
3	1 equiv.	2 equiv.	90	0	36

[a] Tetrahydroisoquinoline (0.1 mmol). [b] Determined by NMR spectroscopy from recovered **1a**. [c] Isolated yields based on tetrahydroisoquinoline.

A tentative mechanism for the formation of the β-diester derivatives is proposed in Scheme 3. Copper catalyzes the formation of an imine-type intermediate[7] (coordinated to the copper ion[8]) through H-abstraction of the sp^3 C–H group adjacent to the nitrogen atom. The copper catalyst also activates the malonate.[9] Subsequently, coupling of the two intermediates results in the desired product and regenerates the copper catalyst. Alternatively, it is possible that *tert*-butyl peroxide products are involved as intermediates[3b,10] which are further converted into the corresponding cross-coupling products with CuBr.



Scheme 3. Tentative mechanism for the CDC reaction of amine with malonate.

Conclusions

In conclusion, a new type of tetrahydroquinoline derivatives, β-diester and β-dicyano derivatives, were efficiently synthesized by a CDC reaction between two different sp^3 C–H bonds catalyzed by copper bromide under solventless conditions. This novel methodology provides the simplest way to construct such β-diester and β-dicyano derivatives. We also report here an unexpected C–CN bond cleavage under mild reaction conditions. The scope, mechanism, and synthetic application of this reaction are under investigation.

Experimental Section

Representative Procedure and Results: To a mixture of CuBr (0.7 mg, 0.005 mmol) and 2-phenyl-1,2,3,4-tetrahydroisoquinoline (209 mg, 1.0 mmol), dimethyl malonate (116 µL, 1.0 mmol) was added. Then *tert*-butyl hydroperoxide (0.20 mL, 5–6 M in decane) was added dropwise into the mixture under nitrogen at room temperature. The resulting mixture was stirred at room temperature for a certain time as mentioned in the tables. The resulting suspension was diluted with dichloromethane. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 5:1), and the fraction with an $R_f = 0.5$ was collected and concentrated to give the desired product **3a** in 72% isolated yield.

Dimethyl 2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)malonate (3a): IR (neat liquid): $\tilde{\nu}_{max}$ = 3065, 3022, 2959, 2911, 2843, 1765, 1754, 1740, 1596, 1577, 1504, 1476, 1450, 1436, 1386, 1344, 1307, 1273, 1232, 1199, 1162, 1136, 1111, 1019 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.21–7.15 (m, 3 H), 7.13–7.05 (m, 3 H), 6.96 (d, J = 8.1 Hz, 2 H), 6.73 (dd, J = 6.9, 6.9 Hz, 1 H), 5.69 (d, J = 9.3 Hz, 1 H), 3.94 (d, J = 9.3 Hz, 1 H), 3.72–3.56 (m, 2 H), 3.63 (s, 3 H), 3.52 (s, 3 H), 3.05 (ddd, J = 16.2, 8.7, 6.3 Hz, 1 H), 2.85 (dt, J = 16.2, 5.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 168.00, 167.13, 148.55, 135.47, 134.58, 128.92, 128.79, 127.45, 126.86, 125.85, 118.45, 115.03, 59.05, 58.12, 52.48, 52.47, 42.15, 26.06 ppm. MS (EI): m/z (%) = 339, 209, 208 (100), 193, 165, 128, 115, 104, 91, 77, 65, 51. HRMS: calcd. for $C_{20}H_{21}NO_4$ 339.1471; found: 339.1475.

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