Synthetic Methods

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Highly Efficient Cross-Dehydrogenative-Coupling between Ethers and Active Methylene Compounds**

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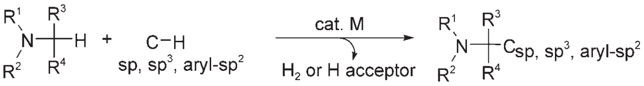
Transition-metal-catalyzed C−H bond activation and subsequent C−C bond formation provide an alternative to traditional functional-group organic chemistry.[1] With the aim of seeking novel and highly efficient synthetic approaches,[2] our group recently focused on developing cross-dehydrogenative-coupling (CDC) methodologies to construct molecules by directly utilizing C−H bonds. We recently reported three types of CDC reactions (Scheme 1)[3] in which the presence of an adjacent nitrogen atom was essential. However, the synthesis of oxygen-containing compounds such as epoxides and ethers are of great interest in industrial and academic research, because these compounds are not only important structural units in many natural products and biologically active compounds,[4] but also highly versatile building blocks in synthetic organic chemistry.[5] Therefore, in an effort to functionalize the C−H bond of ethers and related oxygen-containing compounds directly,[6] we report herein a new type of CDC reaction under mild conditions to construct β-diester ethers catalyzed by a combination of indium[7] and copper[8] catalysts in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). This reaction combines a C(sp^3)−H bond adjacent to an oxygen atom with a C(sp^3)−H bond in pronucleophiles, leading to a new C−C bond (Scheme 2).



Scheme 1. Cross-dehydrogenative-coupling (CDC) of amines to form C−C bonds.

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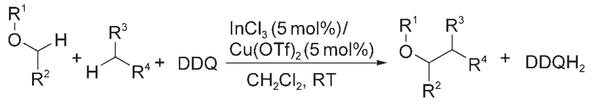
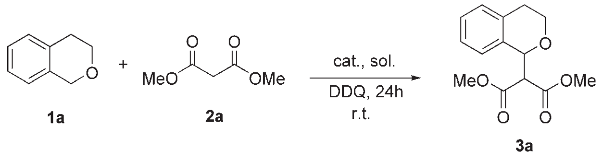


Scheme 2. Cross-dehydrogenative-coupling (CDC) of ethers to form C–C bonds. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; Tf = trifluoromethanesulfonyl.

Various transition metals were initially examined as potential catalysts for the desired CDC reaction between isochroman[9] and dimethyl malonate (Table 1). A combination of InCl$_3$ and Cu(OTf)$_2$ provided the best results. No desired product was observed without these catalysts. To improve the yield, we examined various ratios of isochroman, dimethyl malonate, and DDQ. The best yield was obtained when isochroman/malonate/DDQ = 1:1.2:1–1.2. When the amount of DDQ was increased to more than 1.5 equivalents, the yield decreased dramatically. The reaction did not proceed in the absence of DDQ. It was also found that the suitable solvents for this reaction are CH$_2$Cl$_2$, 1,2-dichloroethane (DCE), and MeNO$_2$. The desired product was not detected when the reaction was performed in THF or H$_2$O. There was no evident difference when the reaction was performed in dry CH$_2$Cl$_2$ or CH$_2$Cl$_2$ without drying.

Table 1: Optimization of reaction conditions.[a]

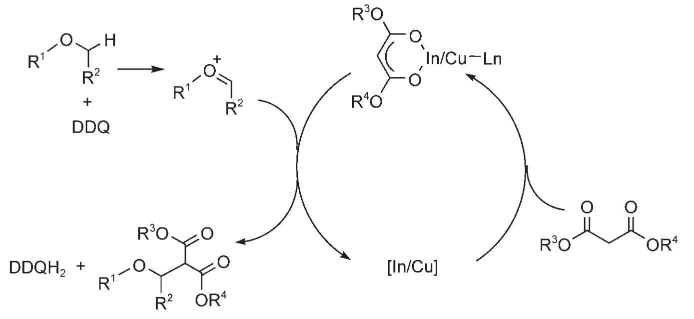


Entry	Catalyst	Solvent	Conversion (**1a**) [%][b]	Yield (**3a**) [%][b]
1	InCl$_3$[c]	CH$_2$Cl$_2$	96	72
2	In(OAc)$_3$[c]	CH$_2$Cl$_2$	100	n.d.[d]
3	In(OTf)$_3$[c]	CH$_2$Cl$_2$	94	76
4	In(NO$_3$)$_3$[c]	CH$_2$Cl$_2$	100	n.d.[d]
5	In(OH)$_3$[c]	CH$_2$Cl$_2$	100	n.d.[d]
6	Cu(OTf)$_2$[c]	CH$_2$Cl$_2$	93	69
7	Cu(OTf)[c]	CH$_2$Cl$_2$	94	50
8	InCl$_3$/Cu(OTf)$_2$ (5 mol%/5 mol%)	CH$_2$Cl$_2$	92	77
9	InCl$_3$/Cu(OTf)$_2$ (10 mol%/5 mol%)	CH$_2$Cl$_2$	95	74
10	InCl$_3$/Cu(OTf)$_2$ (5 mol%/10 mol%)	CH$_2$Cl$_2$	95	77
11	InCl$_3$/Cu(OTf)[e]	CH$_2$Cl$_2$	96	71
12	InCl$_3$/Cu(OTf)$_2$[e]	DCE	96	76
13	InCl$_3$/Cu(OTf)$_2$[e]	MeNO$_2$	82	66
14	InCl$_3$/Cu(OTf)$_2$[e]	THF	0	n.d.[d]
15	InCl$_3$/Cu(OTf)$_2$[e]	H$_2$O	68	n.d.[d]
16	InCl$_3$/Cu(OTf)$_2$[e]	PhMe	80	43
17	InCl$_3$/Cu(OTf)$_2$[e]	MeCN	68	44

[a] Isochroman (0.5 mmol), dimethyl malonate (0.6 mmol), DDQ (0.6 mmol), solvent (2–3 mL). [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Catalyst: 10 mol%. [d] Not detected by ^{1}H NMR spectroscopy. [e] In/Cu (5 mol%/5 mol%).

Several active methylene compounds were then used in the reaction with isochroman derivatives, phthalan, and benzyl methyl ether under the optimized reaction conditions (Table 2). Isochroman and its derivatives were found to be more reactive than phthalan and benzyl methyl ether. A large amount of benzyl methyl ether remained unchanged after the reaction. No desired product was isolated when benzyl phenyl ether was treated with dimethyl malonate, which could be due to the increased steric effect of the bulky phenyl group in the ether. Notably, benzoylnitromethane was also reactive with isochroman. 2,4-Pentanedione and β-ketone esters also reacted effectively with isochroman; however, they generated a rather complicated mixture that is still under investigation.

A likely mechanism of this CDC reaction is shown in Scheme 3. The first step involves a hydride abstraction from the benzylic position of isochroman to generate a cationic species.[10] The malonate is activated by the In/Cu catalyst.[11] Subsequently, the coupling of the two intermediates results in the desired product and regenerates the catalyst. However, it is also possible that the lactol compound is involved as an intermediate and is further converted into the corresponding cross-coupling product. Alternatively, In^{III} may activate DDQ through coordination with its carbonyl oxygen atom, which increases the oxidizing power of DDQ.[12]



Scheme 3. Possible mechanism for the CDC reaction of ether with malonate.

In summary, the first highly efficient cross-dehydrogenative-coupling reaction between a C(sp^3)–H bond adjacent to an oxygen atom and a C(sp^3)–H bond of a pronucleophile, catalyzed by In/Cu, has been developed to generate a C–C bond. This methodology not only provides the simplest way to construct isochroman derivatives and β-ether diesters, but also opens a new way to build and study more complex oxygen-containing natural products. The advantages of this method include: 1) relatively mild reaction conditions; 2) tolerance of various functional groups; 3) direct use of simple ethers as starting materials; 4) high regioselectivity; and 5) direct use of relatively cheap metals, indium and copper, as catalysts. The scope, mechanism, and synthetic application of this reaction are currently under investigation.

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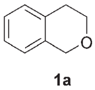
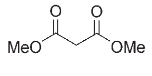
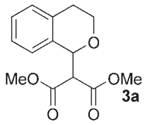
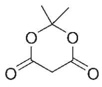
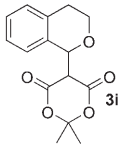
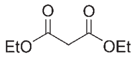
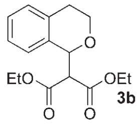
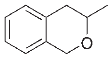
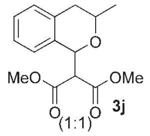
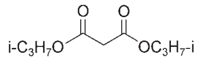
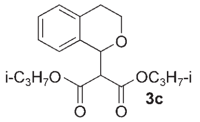
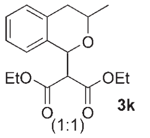
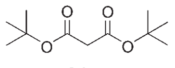
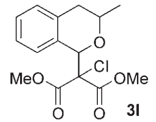
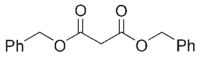
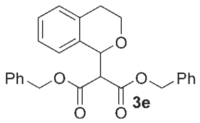
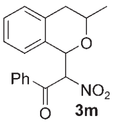
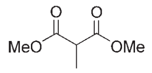
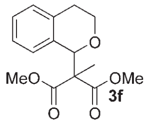
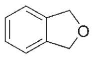
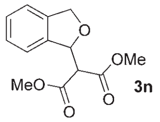
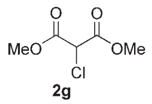
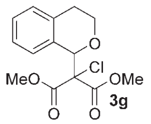
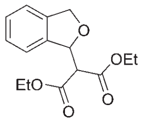
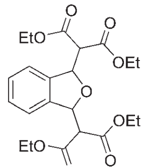
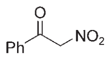
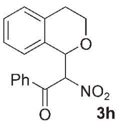
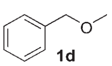
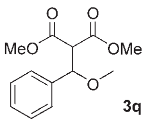
Keywords: C–C coupling · C–H activation · copper · homogeneous catalysis · indium

Table 2: CDC reaction of ethers with active methylene compounds.[a]

Entry	1	2	Product	Yield [%][b]	Entry	1	2	Product	Yield [%][b]
1	 **1a**	 **2a**	 **3a**	71	9	**1a**	 **2i**	 **3i**	65
2	**1a**	 **2b**	 **3b**	66	10	 **1b**	**2a**	 **3j** (1:1)	60
3	**1a**	 **2c**	 **3c**	63	11	**1b**	**2b**	 **3k** (1:1)	57
4	**1a**	 **2d**	decomp.		12	**1b**	**2g**	 **3l** (1:0.7)	40
5	**1a**	 **2e**	 **3e**	65	13	**1b**	**2h**	 **3m** (1:0.5:1.5:1)	65
6	**1a**	 **2f**	 **3f**	53	14[c]	 **1c**	**2a**	 **3n**	48
7	**1a**	 **2g**	 **3g**	64	15[d]	**1c**	**2b**	 **3o** 13% +  (1.5:1) **3p** 15%	
8	**1a**	 **2h**	 **3h** (2.5:1)	72	16	 **1d**	**2a**	 **3q**	17

[a] Diethyl ether (0.5 mmol), active methylene compound (0.6 mmol), $InCl_3/Cu(OTf)_2$ (5 mol%/5 mol%), DDQ (0.6 mmol); all reactions were run for 24–36 h. [b] Yields of isolated products based on ethers. [c] Phthalan (0.2 mmol), dimethyl malonate (0.4 mmol), DDQ (0.2 mmol). [d] Phthalan (0.2 mmol), diethyl malonate (0.4 mmol), DDQ (0.24 mmol).

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