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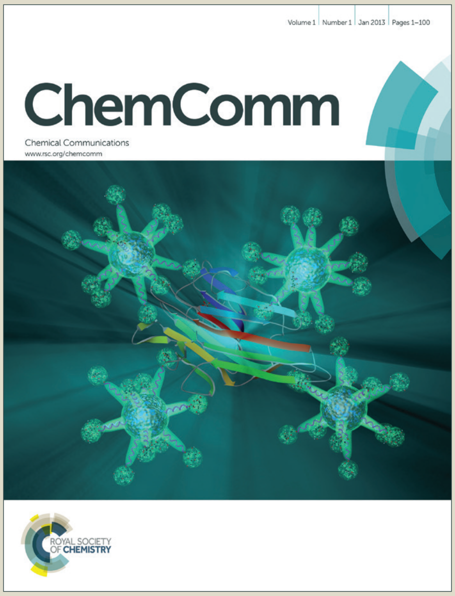

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ARTICLE TYPE

Catalytic amounts of CBr_4 Mediated Dehydrogenative Coupling of Isochromans with Aromatic Ketones

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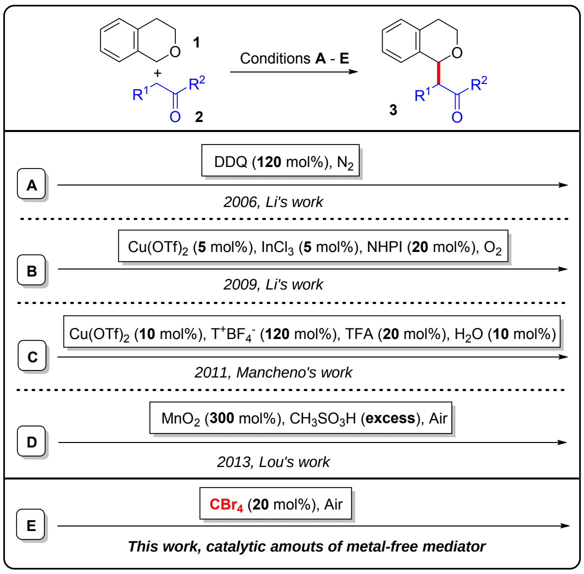
In the presence of catalytic amounts of CBr_4 (a metal-free mediator), an unexpected oxidative dehydrogenative coupling of isochromans with ketones occurred to construct new C^{sp3}-C^{sp3} bond. The reactions were performed under simple solvent-free aerobic conditions.

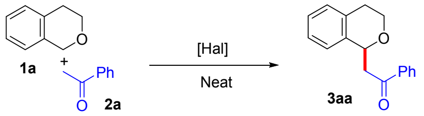
Carbon-carbon bond forming reactions are of fundamental interest and great significance in organic synthesis. In the past few years, oxidative dehydrogenative coupling, namely the direct coupling of two different C−H bonds, has gained significant attention since this strategy presented an atom-economic and concise way to construct complex molecules from simple starting materials.[1] Most of the oxidative dehydrogenative coupling reactions involve the activation of the sp^3 C-H bond adjacent to the nitrogen atom.[2] On the contrary, so far, much few catalyst systems have been developed to the activation of corresponding less reactive sp^3 C-H bonds next to an oxygen atom.[3,4] For example, through literature, there have been only four published cases involving the oxidative dehydrogenative coupling between isochromans and simple ketones until now.[4] This reaction was first reported by Li *et al* in 2006 using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 120 mol %) as the promoter under nitrogen atmosphere.[4a] They also developed another variant of the above reaction using $Cu(OTf)_2$ (5 mol %) and $InCl_3$ (5 mol %) as catalysts in the presence of *N*-hydroxyphthalimide (NHPI, 20 mol %) under oxygen atmosphere after three years.[4b] Recently, in 2011 and 2013, two similar approaches were developed respectively by Mancheño *et al* using $Cu(OTf)_2$ (10 mol %) as the catalyst and TEMPO oxoammonium salt ($T^+BF_4^-$, 120 mol %) as the oxidant[4c] and by Lou *et al* using manganese dioxide (MnO_2, 300 mol %) and methanesulfonic acid (CH_3SO_3H, large excess) as oxidation system under aerobic conditions[4d]. Although these examples have achieved notable progress in this area, metal complex involved catalyst systems and stoichiometric or more amounts of chemical oxidants were always necessary in these methods. Therefore, the development of a simple and efficient method only using catalytic amounts of metal-free mediator for this reaction is highly desired.

For many years, carbon tetrabromide (CBr_4) has been used for organic transformations occasionally.[5] In this paper, CBr_4 has been found for the first time to show good reactivity for cross-dehydrogenative coupling (CDC) reactions. We described a highly efficient oxidative dehydrogenative coupling reaction between isochromans and simple ketones mediated by catalytic amounts of CBr_4 without using any metal catalyst under air atmosphere. The use of catalytic amounts of very stable metal-free mediator instead of complex metal involved catalyst systems has many advantages such as low cost and easy handling.



Scheme 1. CDC Reaction of Isochromans with Ketones

Very recently, we discovered unprecedented auto-oxidative dehydrogenative coupling of glycine derivatives with indoles and auto-oxidative Povarov/aromatization tandem reaction of glycine derivatives with olefins.[6] The reactions were performed in the absence of any redox-active catalyst and any chemical oxidant under mild conditions and only organic solvents and atmosphere air were required. Encouraged by the above interesting results, we evaluated the auto-oxidative transformation using benzylic ethers as substrates because cyclic benzylic ethers, such as isochromans, are core units of a number of bioactive compounds and they are structurally interesting and pharmaceutically valuable.[7] However, the oxidation of corresponding less reactive C-H bonds next to an oxygen atom were not successful under these auto-oxidation reaction conditions. Our previous investigations revealed that dichloroethane (DCE) was crucial for the auto-oxidative coupling of glycine derivatives. This information enlightened us to screen other halogen-containing reagents. To begin this study, we chose isochroman **1a** and acetophenone **2a** as the model substrates to search for potential mediator and suitable reaction conditions. Surprisingly, C^{sp3}-C^{sp3} bond coupling compound **3aa** was produced in high yield (75 %) when 20 mol % of CBr_4 was used (**Table 1, entry 6**). Both increasing and decreasing CBr_4 loading resulted in lower yields (**Table 1, entries 10-12**). No improvement of the transformation were observed when pure oxygen gas was used instead of air (**Table 1, entry 13**). Further studies indicated that the yields decreased with lower or higher reaction temperature (**Table 1, entries 14-16**).

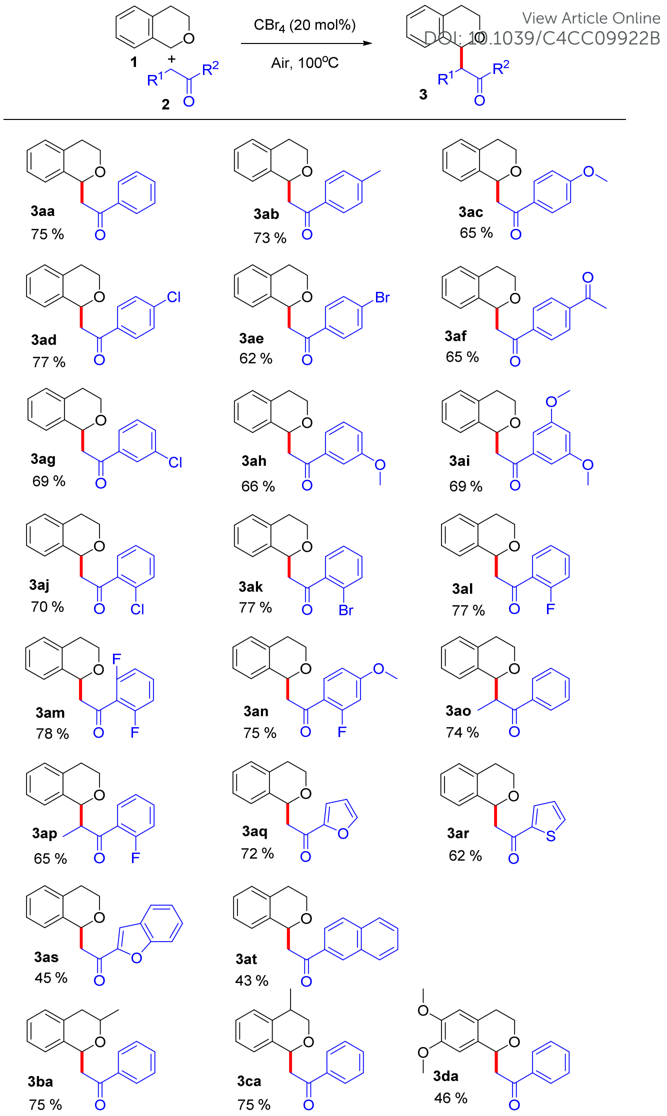


Entry	[Hal]	Loading	Atmosphere	Temperature	Yield [%]
1	DCE	20 mol%	Air	100 °C	0
2	DBE	20 mol%	Air	100 °C	9
3	NBS	20 mol%	Air	100 °C	38
4	NIS	20 mol%	Air	100 °C	40
5	DBDMH	20 mol%	Air	100 °C	33
6	CBr_4	20 mol%	Air	100 °C	75
7	$CHBr_3$	20 mol%	Air	100 °C	41
8	CH_2Br_2	20 mol%	Air	100 °C	8
9	Br_2	20 mol%	Air	100 °C	36
10	CBr_4	5 mol%	Air	100 °C	42
11	CBr_4	10 mol%	Air	100 °C	71
12	CBr_4	30 mol%	Air	100 °C	66
13	CBr_4	20 mol%	O_2	100 °C	65
14	CBr_4	20 mol%	Air	r.t.	50
15	CBr_4	20 mol%	Air	80 °C	66
16	CBr_4	20 mol%	Air	120 °C	71

[a] Reaction conditions: **1a** (1.5 mmol), **2a** (0.5 mmol), 48 h. [b] Yields of the isolated product. DCE = dichloroethane. DBE = dibromoethane. NBS = N-Bromosuccinimide. NIS = N-Iodosuccinimide. DBDMH = 1,3-dibromo-5,5-dimethylhydantoin.

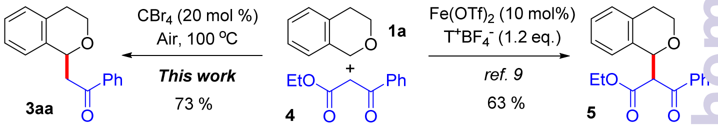
Table 1. Halogen-containing reagents mediated CDC reaction of isochroman with acetophenone[a,b]

Under the optimized conditions, we probed the scope and generality of both isochromans and ketones for this CBr_4 mediated dehydrogenative coupling (Table 2). Initially, we investigated different substituted aryl ketones. Various ketones (**Table 2, 3aa-3at**) with electron-donating groups or electron-withdrawing groups were all suitable substrates in this transformation. The ketones with *ortho* or *meta* substituents delivered the corresponding alkylated isochromans in good yields (**Table 2, 3ag-3an**), illustrating that steric hindrance played a poor role in the reaction. The preparation of halogen atoms bearing products makes this methodology more useful for further transformations (**Table 2, 3ad, 3ae, 3ag, 3aj-3an, 3ap**). Especially, bearing of fluorine atoms into organic compounds could produce meaningful changes in its chemical or pharmacological properties.[8] The procedure was also successfully applied for hetero aromatic ketones and polycyclic aromatic ketones (**Table 2, 3aq-3at**), and their corresponding products were obtained at good yields. Furthermore, we explored the different cyclic benzylic ethers. 3-Methylisochroman, 4-methylisochroman and 6,7-dimethoxyisochroman all gave the corresponding products in high yields. It is worth noting that, , unlike Mancheño group's previous report,[9] when *β*-keto ester **4** were used as carbon nucleophile instead of ketones, the decarboxylative alkylation of isochroman occurred under this CBr_4 promoted process. The corresponding decarboxylative coupling product **3aa** was obtained in high yield (**Scheme 2**).



[a] Standard reaction conditions: **1** (1.5 mmol), **2** (0.5 mmol), CBr_4 (0.1 mmol), neat, air, 100°C, 48 h. [b] Isolated Yields of the isolated products.

Table 2. CBr_4-Mediated CDC Reaction of Isochromans with ketones[a,b]



Scheme 2. CBr_4-Mediated Decarboxylative Alkylation of Isochromans

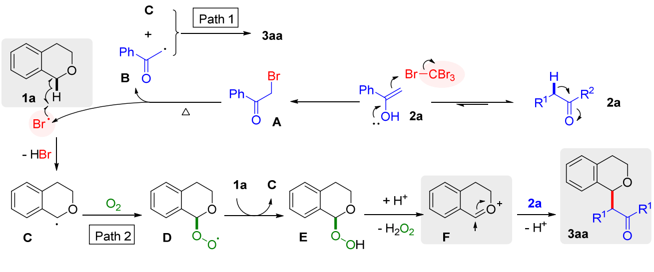
To investigate the mechanism of this transformation, some control experiments were carried out. First of all, the reaction of **1a** and **2a** under argon atmosphere were investigated (**Table 3, Entry 2**). The designed product **3aa** were achieved in 28 % yield. This result indicates that CBr_4 can initiate this oxidative coupling reaction without oxygen with lower efficiency. At the same time, the reaction of **1a** with **2a** under an argon atmosphere resulted in a significant drop in yield, thus indicating that oxygen is crucial for the reaction. Secondly, the reactions of **1a** and 2-bromo-1-phenylethan-1-one (**A**) in the presence of 0.2 equivalents of CBr_4 (**Table 3, Entry 3**) and in the absence of CBr_4 (**Table 3, Entry 4**) were investigated respectively. The designed product **3aa** was achieved in 55% and 10 % yields. These results indicate that compound **A** should be an important intermediate in this CBr_4 mediated process. Radical trapping experiment was also conducted by employing TEMPO as a radical scavenger. No designed product **3aa** was obtained in the standard reaction of **1a** with **2a** (**Table 3, Entry 5**). This result suggests that the present reaction includes a radical process.

Entry	Substrate[a]	Conditions	Yields (%)[b]
1	**1a, 2a**	CBr_4 (20 mol%), 100°C, **Air**	75
2	**1a, 2a**	CBr_4 (20 mol%), 100°C, **Ar**	28
3	**1a,** PhC(O)CH_2Br (**A**)	CBr_4 (20 mol%), 100°C, **Air**	55
4	**1a,** PhC(O)CH_2Br (**A**)	100°C, **Air**	10
5	**1a, 2a**	CBr_4 (20 mol%), 100°C, **TEMPO** (1 eq), **Air**	0

[a] **1a** (1.5 mmol), **2a** or **6** (0.5 mmol), 48 h. [b] Yields of the isolated products. **A** = 2-bromo-1-phenylethan-1-one. TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

Table 3. Control experiments.

Our proposed reaction mechanism for this catalytic amounts of CBr_4 induced C^{sp3}-C^{sp3} coupling is illustrated in **Scheme 3**. Acetophenone **1a** and CBr_4 initially react to form 2-bromo-1-phenylethan-1-one **A.** Then, a homolytic cleavage of C-Br bond occurs under heating conditions to form radical **B** and bromine radical. When the bromine radical is formed, it can abstract the hydrogen atom from isochroman **1a** to generate radical **C**, coupling of radical **B** and **C** results in the desired product **3aa** (**Path 1**). On the other path, radical **C** can react with dioxygen to provide the peroxide radical **D**. Peroxide radical **D** then abstracts the hydrogen atom from isochroman **1a** to form hydroperoxide **E** and radical **C**. Chain propagation continues until all isochroman **1a** are consumed. Benzoxy cation **F** is then formed through an acid catalyzed S_N1 type procedure from hydroperoxide **E**. Finally, benzoxy cation **F** can then be trapped with ketone **2a** to afford the desired product **3aa** (**Path 2**).



Scheme 3. Proposed Reaction Mechanism

Conclusions

In summary, we have demonstrated a novel CBr_4-mediated dehydrogenative coupling between cyclic benzyl ethers and ketones. The reactions were performed in simple solvent-free aerobic conditions. Only catalytic amounts of CBr_4 was used as a promoter. This work also presents a new way to initiate radical reaction. Further application of this CBr_4-mediated methodology will be reported in due course.

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