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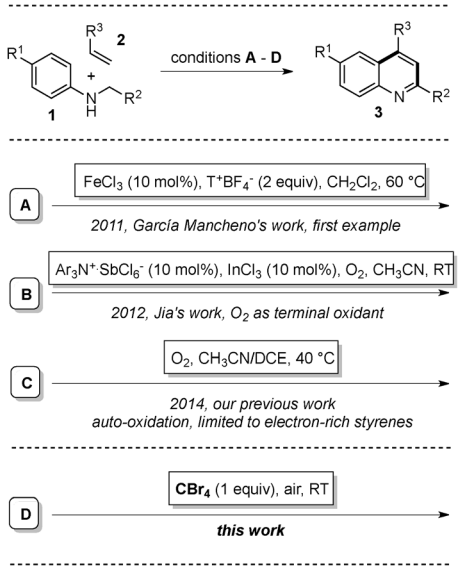
Synthetic Methods

CBr_4-Mediated Cross-Dehydrogenative Coupling Reaction of Amines

Congde Huo,* Haisheng Xie, Mingxia Wu, Xiaodong Jia, Xicun Wang, Fengjuan Chen, and Jing Tang[a]

Abstract: A novel CBr_4-mediated dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes, leading to complex quinoline derivatives, and a CBr_4-mediated dehydrogenative C–H functionalization of *N*-aryl tetrahydroisoquinolines with nucleophiles to form C–C and C–P bonds are reported. The reactions were performed under very simple and mild reaction conditions; only CBr_4 was used as a promoter. A plausible mechanism involving a radical process is proposed.

The imino Diels–Alder reaction was first discovered by Povarov in the 1960s.[1] It consists of a formal [4+2] cycloaddition reaction of imines derived from aromatic amines with electron-rich alkenes to give tetrahydroquinolines. Since the pioneering study reported by Li in 2008,[2] the oxidative dehydrogenative coupling of glycine derivatives has gained significant attention. This reaction relies on the oxidation of the secondary amine substrates to generate reactive imine intermediates.[3] A one-pot oxidative Povarov/aromatization tandem reaction of glycine derivatives with alkenes was first reported by García Mancheño et al. in 2011 (Scheme 1, A).[4] A series of substituted quinolines were synthesized by using $FeCl_3$ as the catalyst and a 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) oxoammonium salt as the oxidant. In 2012, Jia et al. developed the same tandem process under the catalysis of radical cation salts in the presence of $InCl_3$ under O_2 atmosphere (Scheme 1, B).[5] In the same year, a similar approach between glycine derivatives and alkynes was developed by Hu et al. by using $FeCl_3$ as the catalyst and $(t\text{BuO})_2$ as the oxidant.[6] Although these examples represent notable progress in this area, metal reagents and complex catalyst systems were always required. Very recently, we discovered an unprecedented auto-oxidation coupling of glycine derivatives (Scheme 1, C).[7] The reaction was performed in the absence of any redox-active catalyst and chemical oxidant under mild conditions; only organic solvents and an air atmosphere were required. However, under these autoxidation conditions, the dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes was limited to highly electron-rich alkenes. The quinoline products obtained by this tandem reaction are important structures that can be found in a number of biologically significant natural products and synthetic drugs.[8] Therefore, the development of a more practical and metal-free method under simpler reaction conditions is still highly desired.



Scheme 1. Dehydrogenative Povarov/aromatization tandem reaction.

Carbon tetrabromide (CBr_4) has been used for several organic transformations;[9] for example, it catalyzes the deprotection of trialkylsilyl esters and β-(trimethylsilyl)ethoxymethyl ethers,[9a,b] esterifications,[9c] the formation of C–S bonds,[9d] the acetalization of aldehydes,[9e] the tetrahydropyranylation of alcohols,[9e] and the Friedel–Crafts alkylation of indoles with carbonyl compounds.[9f] In this Communication, CBr_4 has been found to show good reactivity in cross-dehydrogenative coupling (CDC) reactions.[10] Herein, we describe a novel, metal-free CBr_4-mediated dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes. Furthermore, we also developed an efficient CBr_4-promoted dehydrogenative C–H functionalization of *N*-aryl tetrahydroisoquinolines.[11–13] To the best of our knowledge, no CBr_4-mediated CDC reaction of amines has been described yet. The use of CBr_4 instead of complex catalyst systems involving metals has many advantages, such as the low cost and easy handling.

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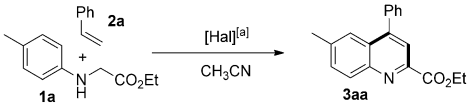
Recently, we observed the auto-oxidative coupling of glycine derivatives in acetonitrile (CH_3CN) and dichloroethane (DCE) as mixed reaction solvents. Further investigations revealed that DCE was crucial for this auto-oxidative progress.[7] This information encouraged us to test other halogen-containing reagents. Initially, glycine ester **1a** and styrene **2a** were chosen as model substrates. Interestingly, ethyl 6-methyl-4-phenylquinoline-2-carboxylate (**3aa**) was produced in 55% yield when 1.0 equivalent of CBr_4 was used under air atmosphere (Table 1, entry 5). The most surprising finding was that the efficiency of this transformation was promoted when the reaction was carried out in an argon-filled Schlenk tube with an air balloon on the branch pipe (Table 1, entry 6, see the Supporting Information for experimental device). We believe the reason is that the formation of the side product ethyl 2-oxo-2-(*p*-tolylamino)acetate[7] from self-oxidation can be avoided under these decreased oxygen concentration conditions. Further studies indicated that the yields decreased with lower CBr_4 loadings (Table 1, entries 9 and 10). In addition, both increasing and decreasing the temperature resulted in lower yields (Table 1, entries 11–13). The effect of different solvents was also surveyed, the best choice still being CH_3CN. All together it was discovered that 1.0 equivalent of CBr_4 in CH_3CN at room temperature were the optimized reaction conditions (81%, Table 1, entry 6).

Table 1. Dehydrogenative Povarov/aromatization tandem reaction of **1a** with **2a** promoted by halogen-containing reagents.



Entry	[Hal]	Atmosphere	Loading [equiv]	Temp.	Yield [%][b]
1	DCE	open flask	37.0[c]	RT	51
2	DCE	open flask	1.0	RT	0
3	DBE	open flask	1.0	RT	0
4	NBS	open flask	1.0	RT	trace
5	CBr_4	open flask	1.0	RT	55
6	CBr_4	Ar + air balloon	1.0	RT	81
7	CBr_4	vacuum line	1.0	RT	0
8	CBr_4	Ar + air balloon	1.5	RT	80
9	CBr_4	Ar + air balloon	0.5	RT	45
10	CBr_4	Ar + air balloon	0.2	RT	22
11	CBr_4	Ar + air balloon	1.0	40 °C	74
12	CBr_4	Ar + air balloon	1.0	60 °C	61
13	CBr_4	Ar + air balloon	1.0	0 °C	trace

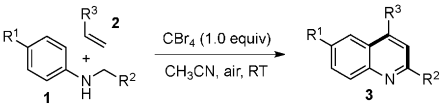
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (20 equiv), CH_3CN (30 mL), 16 h. [b] Yields of the isolated products. [c] DCE as a co-solvent. DCE = dichloroethane. DBE = dibromoethane. NBS = *N*-bromosuccinimide.

Under the optimized conditions given above, the scope of the glycine derivatives **1** was investigated. Various glycine esters (Table 2, A) and glycine amides (Table 2, B) could be smoothly transformed into the desired products. In addition, a short peptide (**1k**) was also tolerated in this transformation, generating **3ka** in 84% yield (Table 2, F). The scope of this CBr_4-induced anaerobic CDC reaction leading to substituted quinolines was further expanded to a range of substituted styrenes (Table 2, D, E and F). The results demonstrate that styrenes with electron-donating or electron-withdrawing groups on the phenyl ring are suitable substrates in this transformation. It is worth noting that when indene was used, complex polycyclic quinolines were obtained (Table 2, C). To evaluate the practicability of our method, the reaction of **1a** with **2a** was performed on a 20 mmol scale in a single batch; no obvious loss of yield was observed (78% yield).

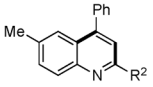
To develop a more general and useful method, we subsequently turned our attention to investigating the dehydrogenative coupling reaction of tertiary amines under the CBr_4-induced conditions. First, the sp^3–sp^2 C–H coupling between *N*-aryl tetrahydroisoquinolines and indoles was successfully performed.[11] Different *N*-aryl tetrahydroisoquinolines (Table 3, A) and indoles with electron-donating or electron-withdrawing groups (Table 3, B) all worked well under the present reaction conditions. The coupling reaction between two sp^3 C–H bonds is a very attractive but challenging area. CBr_4 was also demonstrated to be an efficient promoter for the dehydrogenative Mannich reaction of *N*-aryl tetrahydroisoquinolines and non-activated ketones under mild conditions (Table 3, C).[12] The combination of *N*-aryl tetrahydroisoquinolines and phosphites could also give the corresponding C–P coupling products (Table 3, D).[13]

To probe the mechanism of this transformation, some control experiments were carried out. Firstly, the reaction of **1a** in the absence of styrene (**2**) under the standard reaction conditions was investigated. Imine **7a** and its dimer **8a** were ob-

Table 2. CBr_4-mediated CDC reaction of glycine derivatives with alkenes.[a,b]

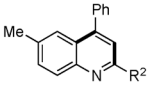


A



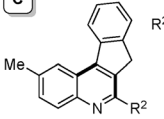
R^2 = CO_2Et **3aa** (81 %); CO_2Me **3ba** (80 %); CO_2nBu **3ca** (75 %); CO_2tBu **3da** (78 %); CO_2Allyl **3ea** (74 %)

B[c]



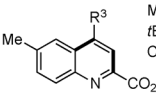
R^2 = C(O)NHEt **3fa** (80 %); C(O)NHMe **3ga** (79 %); C(O)NH*n*Bu **3ha** (72 %); C(O)NH*t*Bu **3ia** (68 %); C(O)NHBn **3ja** (75 %)

C



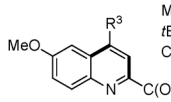
R^2 = CO_2Et **3af** (76 %); C(O)NHMe **3gf** (75 %)[c]; $C(O)NHCH_2CO_2Et$ **3kf** (78 %)

D



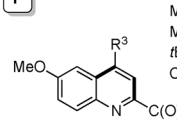
R^3 = C_6H_5 **3aa** (81 %); Me-C_6H_4 **3ab** (76 %); MeO-C_6H_4 **3ac** (78 %); *t*Bu-C_6H_4 **3ad** (72 %); Cl-C_6H_4 **3ae** (74 %)

E[c]



R^3 = C_6H_5 **3ga** (79 %); Me-C_6H_4 **3gb** (79 %); MeO-C_6H_4 **3gc** (80 %); *t*Bu-C_6H_4 **3gd** (76 %); Cl-C_6H_4 **3ge** (77 %)

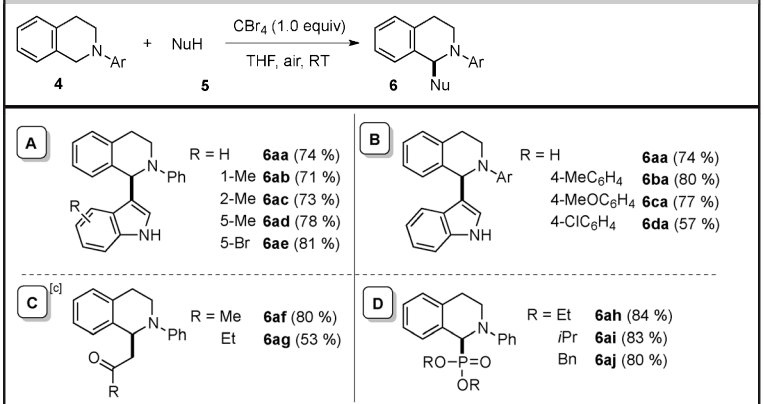
F



R^3 = C_6H_5 **3ka** (84 %); Me-C_6H_4 **3kb** (74 %); MeO-C_6H_4 **3kc** (78 %); *t*Bu-C_6H_4 **3kd** (80 %); Cl-C_6H_4 **3ke** (68 %)

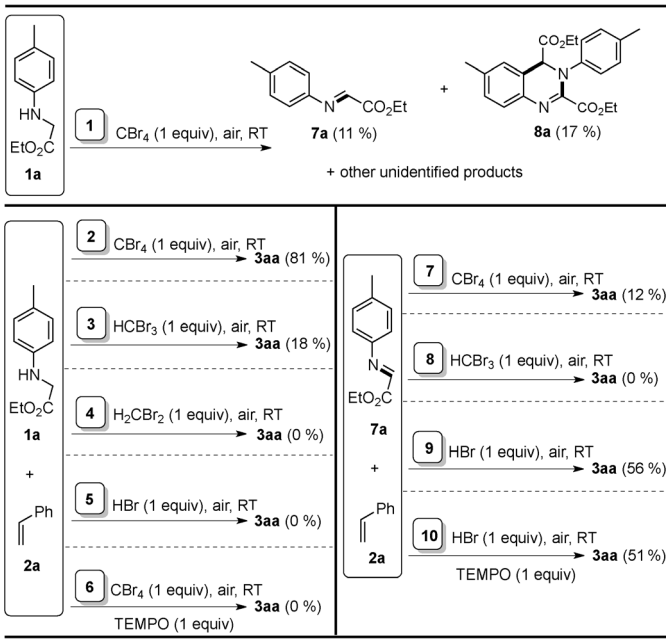
[a] Standard reaction conditions: **1** (1.0 mmol), **2** (20 equiv), CBr_4 (1.0 equiv), CH_3CN (30 mL), air, RT, 16 h. [b] Yields of the isolated products. [c] 60 °C.

Table 3. CBr_4-mediated CDC reaction of *N*-aryl tetrahydroisoquinolines with nucleophiles.[a,b]



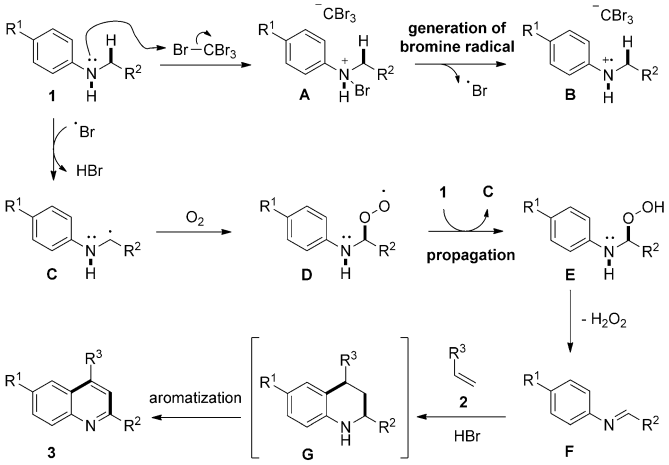
[a] Standard reaction conditions: **4** (1.0 mmol), **5** (1.5 equiv), CBr_4 (1.0 equiv), THF (40 mL), air, RT, 48 h. [b] Yields of the isolated products. [c] Ketone as the solvent, 60 °C.

tained in a low yield (Scheme 2, rxn. 1). This result indicates that the imine is involved as an intermediate in this CBr_4-mediated process. Secondly, the reaction of **1a** and **2a** in the presence of 1.0 equivalent of CBr_4 (Scheme 2, rxn. 2), $HCBr_3$ (Scheme 2, rxn. 3), H_2CBr_2 (Scheme 2, rxn. 4), or HBr (Scheme 2, rxn. 5) was investigated. The desired product **3aa** was obtained in a very low yield in reaction 3 and not obtained in reactions 4 and 5. These results indicate that CBr_4 is crucial for this transformation and that only one bromine atom in CBr_4 is active for this transformation. Furthermore, the reaction of imine **7a** and styrene **2a** in the presence of 1.0 equivalent of CBr_4 (Scheme 2, rxn. 7), $HCBr_3$ (Scheme 2, rxn. 8), or HBr (Scheme 2, rxn. 9) was investigated. When CBr_4 was used, the desired product **3aa** was detected, albeit in only 12% yield (rxn. 7), which is much lower than that of the model reaction (81%, Scheme 2, rxn. 2). However, when HBr was used, the desired product **3aa** was obtained in a higher yield (56%, Scheme 2, rxn. 9). These results indicate that the in situ generated HBr is important for the subsequent [4+2] cycloaddition process. In addition, radical trapping experiments were conducted by employing TEMPO as a radical scavenger. No product was obtained in the standard reaction of **1a** with **2a** (Scheme 2, rxn. 6), but no inhibition was observed in the reaction of **7a** with **2a** (Scheme 2, rxn. 10). These results suggest that the oxidation step of the imine generation in the present reaction includes a radical process.



Scheme 2. Control experiments.

Although the mechanism of this transformation is not fully clarified yet, a plausible mechanism based on the results described above is depicted in Scheme 3. Secondary amine **1** and CBr_4 initially react to form intermediate **A.** Then, a homolytic cleavage of the weak N–Br bond occurs to form the radical cation intermediate **B** and a bromine radical. Next, after abstraction of a hydrogen atom by the Br radical, the radical intermediate **C** is formed. Intermediate **C** can react with dioxygen to provide the peroxide radical **D**, which then abstracts a hydrogen atom from substrate **1** to form the hydroperoxide **E** and radical **C**. Chain propagation continues until all substrate **1** is consumed. Subsequently, a Povarov reaction and the following aromatization result in the desired product **3**.



Scheme 3. Proposed mechanism.

In summary, we have demonstrated a novel CBr_4-mediated dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes, leading to complex quinoline derivatives, and a CBr_4-mediated dehydrogenative C–H functionalization of *N*-aryl tetrahydroisoquinolines with nucleophiles to form C–C and C–P bonds. The starting materials and the promoter are commercial available or easily prepared. This

method is highly efficient and has a broad substrate scope. The reactions were performed under very simple and mild reaction conditions; only CBr_4 was used as a promoter. This work also presents a new way to initiate radical reactions under mild reaction conditions. Further applications of these CBr_4-mediated methodologies will be reported shortly.

Experimental Section

General procedure for the CBr_4-mediated CDC reaction of glycine derivatives with alkenes

Glycine derivatives (**1**, 1.0 mmol), alkenes (**1**, 20 mmol), and CBr_4 (1.0 mmol) were dissolved in CH_3CN (30 mL). The reactions were performed in an argon-filled Schlenk tube with an air balloon on the branch pipe at ambient temperature and completed within 16 h. The products were isolated by column chromatographic separation.

General procedure for the CBr_4-mediated CDC reaction of *N*-aryl tetrahydroisoquinolines with nucleophiles

N-Aryl tetrahydroisoquinolines (**4**, 1.0 mmol), nucleophiles (**5**, 1.5 mmol), and CBr_4 (1.0 mmol) were dissolved in THF (40 mL). The reactions were performed in an argon-filled Schlenk tube with an oxygen balloon on the branch pipe at ambient temperature and completed within 48 h. The products were isolated by column chromatographic separation.

Acknowledgements

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Keywords: alkenes · carbon tetrabromide · dehydrogenation · glycine derivatives · quinolines · tetrahydroisoquinolines

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