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COMMUNICATION

Copper-catalyzed formylation of alkenyl C-H bonds with $BrCHCl_2$ used as a stoichiometric formylating reagent

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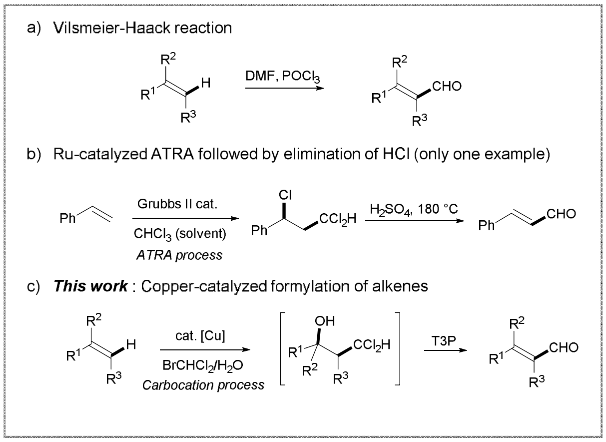
The first example of copper-catalyzed direct formylation of alkenyl C-H bonds for facile synthesis of α,β-unsaturated aldehydes has been developed. This transformation has demonstrated high reactivity, mild reaction conditions and broad substrate scope. $BrCHCl_2$ is expected to be developed as an effcient stoichimetric C1 bulding block in organic synthesis.

To develop novel methods for the synthesis of complex molecules in an efficient and expeditious manner still represents one kernel study and remains as a major challenge in organic synthesis. Accordingly, many novel strategies for quick construction of complex molecular skeleton have been developed and used for total synthesis of complex compounds.[1,2] Among all these strategies, domino reactions is emerging as an efficient key reaction to dominate the facile synthesis of key intermediates in the synthetic route. Of significant interest are cascade reactions that provide access to fundamental building blocks in a chemo-selective manner from readily available starting materials in a step-economical fashion.[3] As a key material used for cascade transformations, especially for organocatalyzed domino reactions, α,β-unsaturated aldehydes have offered a broad range of unconventional transformations to make complex molecules or key intermediates.[4] Thus, considerable efforts have been devoted to developing novel methods for facile synthesis of α,β-unsaturated aldehydes from readily available simple raw materials in efficient and quick ways.[5]

As produced on the large scale industrially and served as an important feedstock of petrochemical industry, simple alkenes have long been realized as one of the most widely used raw material for a great variety of organic transformations.[6] And thus, the direct formylation of simple alkenes thus offers the most economical and efficient method for facile construction of α,β-unsaturated aldehydes. Indeed, the constant exploration of Vilsmeier-Haack reaction has long been developed as a useful approach to introduce formyl group into alkenes.[7] On the other hand, using Grubbs II catalyst as the radical initiator succeeded in atom transfer radical addition (ATRA) of styrene, which affording the alkenyl aldehyde via the following elimination of hydrochloric acid under strong acid or stoichiometric amount of silver salts at high temperature.[8] Apart from these intersting progress, both known methods still suffered from the limited scope of alkenes and requirement of large amount of poisonous reagents ($POCl_3$ as precusor of Vilsmeier reagent or $CHCl_3$ as the solvent), which definitely hampered their practical application in organic synthesis. Herein, we reported a novel copper-catalyzed formylation of alkenyl C-H bonds for facile synthesis of α,β-unsaturated aldehydes, in which high reactivity, mild conditions and broad substrate scope have been demonstrated. The key to success is commercially available $BrCHCl_2$ was firstly used as a stoichiometric formylating reagent instead of $CHCl_3$, which was normally used as solvent in such reactions, and alkenyl aldehydes was then furnished by bifunctionalization of alkenes via a carbocation process and following dehydration.



Scheme 1 Facile synthesis of α,β-unsaturated aldehydes from alkenes.

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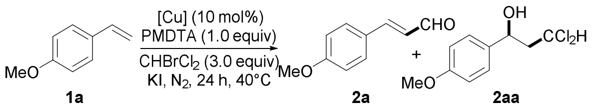
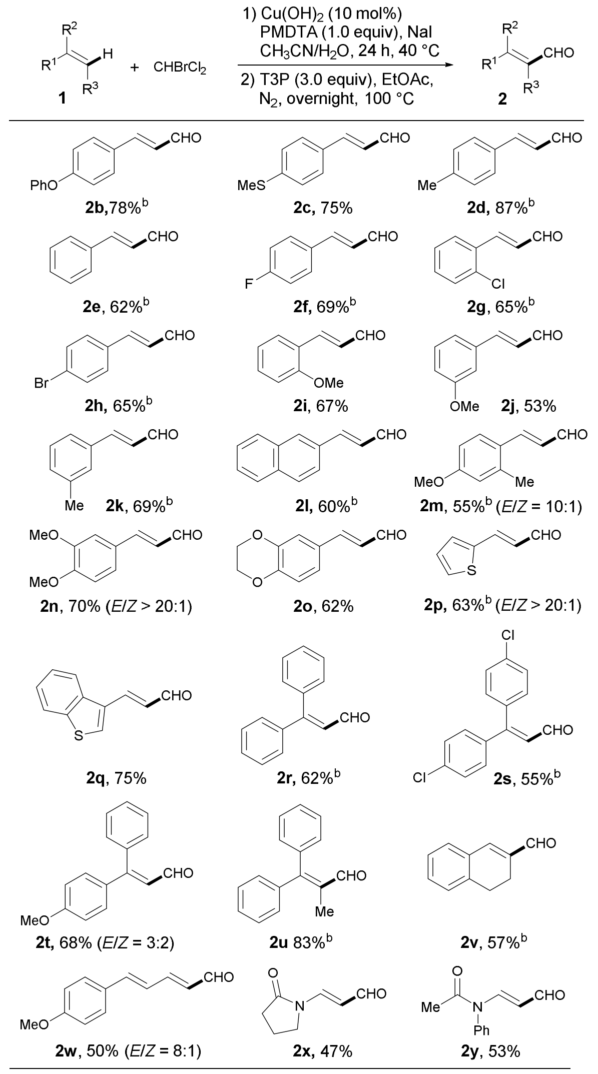
Table 1 Copper-catalyzed formylaion of styrene: optimization of conditions[a]



entry	[Cu]	Solvent (v/v)	Base	**2a/2aa** yield (%)[b]
1[c]	CuBr	CH_3CN	PMDTA	0
2	CuBr	CH_3CN	PMDTA	23/2
3	CuO	CH_3CN	PMDTA	0
4	$Cu(OH)_2$	CH_3CN	PMDTA	31/2
5	$Cu(OH)_2$	THF	PMDTA	0
6	$Cu(OH)_2$	H_2O	PMDTA	24/28
7	$Cu(OH)_2$	DMSO	PMDTA	5/57
8	$Cu(OH)_2$	CH_3CN/H_2O (1:1)	PMDTA	7/74 (80)[d]
9	$Cu(OH)_2$	CH_3CN/DMSO (4:1)	PMDTA	8/72
10	$Cu(OH)_2$	CH_3CN/H_2O (1:1)	/	0
11	$Cu(OH)_2$	CH_3CN/H_2O (1:1)	Et_3N	0
12	$Cu(OH)_2$	CH_3CN/H_2O (1:1)	TMEDA	0
13	$Cu(OH)_2$	CH_3CN/H_2O (1:1)	DMEDA	0
14[e]	$Cu(OH)_2$	CH_3CN/H_2O (1:1)	PMDTA	10/72 (82)[d]
15[f]	$Cu(OH)_2$	CH_3CN/H_2O (1:1)	PMDTA	9/85 (90)[d]

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), $CHBrCl_2$ (3.0 equiv), Cu Catalyst (10 mol%), PMDTA (1.0 equiv) and KI (1.0 equiv) in CH_3CN (1 mL) at 40 ˚C for 24 h. [b] Isolated yield by ^{1}HNMR analysis. [c] KI was not added. [d] The mixture of **2a**/**2aa** was dehydrated by T3P (1-Propanephosphonic acid cyclic anhydride 50% ethyl acetate). The yield in the parentheses was isolated yield of **2a**. [e] TBAI was used instead of KI [f] NaI was used instead of KI. PMDTA.; 1,1,4,7,7-pentamethyl-diethylenetriamin.

Table 2 Substrate scope[a]



[a] General conditions: **1** (0.2 mmol), $Cu(OH)_2$ (10 mol%), $CHBrCl_2$ (3.0 equiv), PMDTA (1.0 equiv) and NaI (1.0 equiv) in CH_3CN/H_2O (v:v = 1:1, 1 mL) at 40 ˚C for 24 h, then dehydrated by T3P (3.0 equiv.) in EtOAc at 100 °C; for **2x-y**, **1** (0.2 mmol), $Cu(hfacac)_2 \cdot xH_2O$ (10 mol%), $CHBrCl_2$ (3.0 equiv), PMDTA (1.0 equiv) and KI (1.0 equiv) in CH_3CN (1 mL) at 80 ˚C for 24 h, and aldehydes **2x-y** were obtained directly. Isolated yields were reported. [b] 80 ˚C.

Our initial investigation commenced with 4-methoxystrene (**1a**) as the pilot substrate, and bromodichloromethane as the stoichiometric formylating reagent in the presence of a catalytic amount of copper catalyst (10 mol%) and 1.0 equiv of PMDTA (1,1,4,7,7-pentamethyl-diethylenetriamin) in CH_3CN at 40 °C (Table 1). Unfortunately, none of the desired product **2a** was obtained when CuBr was used as the catalyst. Considering the halogen atom exchange may improve the reactivity of $CHBrCl_2$,[9] to our delight, the addition of 1.0 equiv of KI into the reaction system afforded **2a** successfully, albeit with a relatively low yield (23%, entry 2). Additionally, carefully examination of copper catalysts were next performed, which indicated $Cu(OH)_2$ gave the best result with 31% yield (entry 4). Meanwhile, further investigation of various solvents gave no improvement of yield and CH_3CN was still the best choice. While trace amount of bifunctionalized alcohol **2aa** was isolated as a byproduct, it was conjectured that water worked as the hydroxyl source for this bifunctional reaction. As we expected, up to 28% yield of **2aa** was obtained along with 24% yield of **2a** when water was used directly as the solvent. To further improve the yield, the co-solvent has been investigated and CH_3CN/H_2O (1/1) gave the dichloromethylated alcohol **2aa** in 74% yield along with the aldehyde **2a** in 7% yield. Actually, after simple work-up without purification and further dehydration with T3P, **2a** was finally furnished in 80% yield (Entry 8). Considering the key role of PMDTA played in this transformation,[10] other bases have also been screened instead of PMDTA, while giving none of the desired product **2a** (Table 1, entries 11-13). Notably, by the replacement of KI with NaI, the yield of **2a** was further improved to 90% after this two-step formylation of styrene (entry 15). Finally, control experiment indicated that none of the desired product was obtained without the addition of copper catalyst or base (For details, see the supporting information).

With the optimized conditions in hand, we next investigated the scope of alkenes (Table 2). Initially, the study of substituent effect on the aryl rings of styrene derivatives

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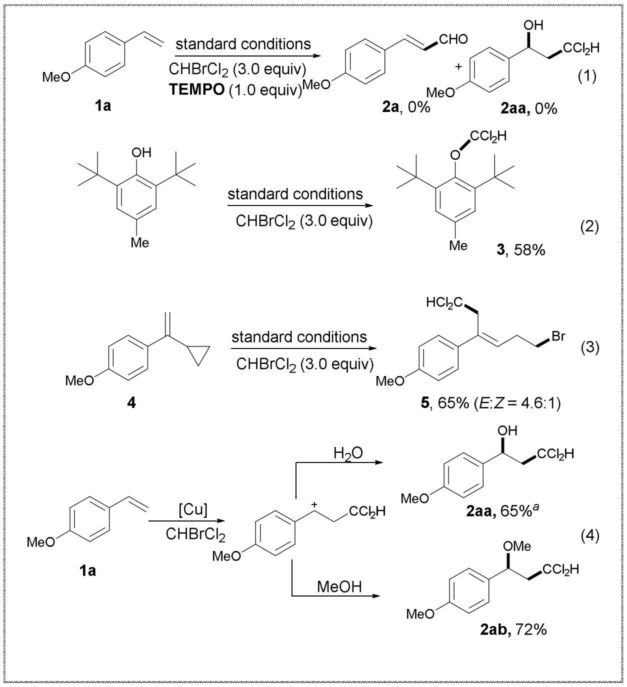
showed both electron-donating groups, such as 4-Methoxy, 4-Phenoxy, 4-Methyl and 4-Methylthio (**1a**-**d**), and weak electron-withdrawing (**1f**-**h**) groups, such as Fluorine, Chlorine, Bromine, were all compatible with this catalytic system and able to furnish the desired products in moderate to high yields. Not surprisingly, the substrates with electron-withdrawing groups installed on the aryl rings gave normally lower yields and required relatively higher reaction temperature (**2f**-**h**). Meanwhile, a variety of styrene derivatives with *ortho*-, *meta*-, as well as *para*-substituents were smoothly formylated to afford the corresponding α,β-unsaturated aldehydes **2i**-**k** in acceptable yields.

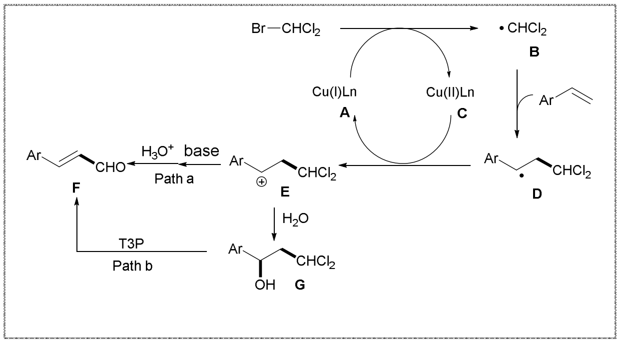
The ortho-chloro- and meta-methyl-substituted styrenes (**1g**, **1k**), styrene (**1e**) and 2-vinylnaphthalene (**1l**) also required a much higher temperature and gave moderate yields. Although the ortho- and meta-Methoxystyrene (**1i**-**j**) did not need high temperature, but the yields of reaction were only moderate. To our interests, heteroarene-derived styrene substrates, including 2-vinylthiophene **1p** and 3-vinylbenzothiophene **1q**, were also well tolerated in this novel transformation with synthetically useful yields (**2p**, 63%; **2q**, 75%). Just as expected, 1,1-diphenylethenes **1r**-**t**, normally worked as better radical trapper than styrene, generated the tri-substituted unsaturated aldehyde **2r**-**t** in relatively higher yields (Table 2, **2r**-**t**). Of note was that formylation of tri- substituted internal styrene **1u** also proceeded smoothly to give the corresponding tetra-substituted vinyl aldehyde with a pretty good yield (**2u**, 83%). Importantly, subjection of 1,2-dihydronaphthalene **1v** into the optimized conditions resulted in the formylation of C-H bond in cyclic double bonds successfully. It was also noteworthy that the conjugated alkene **1w** underwent the reaction efficiently, with an acceptable yield (**2w**, 50%) and a good *E/Z* selectivity (8:1). To our satisfaction, N-vinyl substrates could also been directly formylated at the end of terminal alkenes to afford β-aminoacrylaldehyde with moderated yields, by simply deviating the conditions to a combination of Cu(hfacac)$_2$ •xH$_2$O, KI and CH$_3$CN.

To gain some insights into the mechanism of this transformation, a series of control experiments were then performed accordingly. First, the reaction was completely quenched when 1.0 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the standard conditions. Meanwhile, subjection of 1.0 equivalent of butylated hydroxytoluene (BHT) into the standard conditions afforded the corresponding dichloromethyl adduct **3** in 58% yield. Both results indicated that this transformation may processed via a radical path. To further verify this speculation, the well known radical clock, 1-(1-cyclopropylvinyl)-4-methoxybenzene **4**, had been synthesized and added into this catalytic system, furnishing the cycle-opening product **5** in 65% yield, strengthening the surmise of the dichloromethyl radical (•CCl$_2$H) being involved in the catalytic cycle.

As alcohol **2aa** was isolated as the key intermediate along with vinyl aldehyde **2a** in the model reaction (Eq. 4, Scheme 2), a possible carbocation process was suggested to be involved in the catalytic cycle. Indeed, the replacement of H$_2$O with methanol as the cation scavenger afforded the corresponding bifunctional product **2ab** in 72% yield, which further verify this possibility.[11]



Scheme 2 Mechanistic studies. ^{a}For details of isolation of **2aa**, see the supporting information.



Scheme 3 Proposed mechanism.

On the basis of our preliminary results and previous reports,[12] a plausible mechanism involving a •CHCl$_2$ radical is proposed as shown in the Scheme 3. The copper salt is reduced to generate low-valent Cu complex, which can transfer a single electron to the CHBrCl$_2$ and then produce a free radical •CHCl$_2$ (**B**), Subsequently, The radical reacts with the styrene. The •CHCl$_2$ addition-compound **D** can be oxidized by high-valent Cu compelx to cationic intermediate **E**. At last, the high-valent Cu complex is reduced to low-valent Cu complex to complete the catalytic cycle. There are two possible pathways for the sequential transformation of cation **E** to vinyl aldehyde **F**: Path a, Deprotonation to regenerate C=C bond, and **F** is obtained by the following hydrolysis of dichloromethyl group to aldehyde. Path b, cation **E** is captured by H$_2$O to give the alcohol

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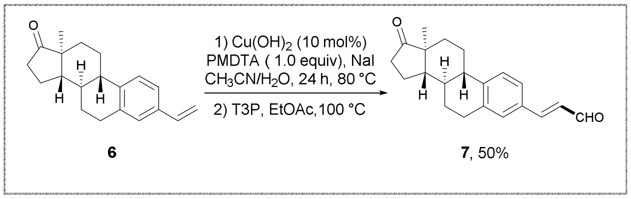

intermediate **G**, followed by dehydration with T3P and sequentially hydrolysis of dichloromethyl group to afford **F**.[13]

Scheme 4 Formylation of estrone derivative **6**.

To demonstrate the synthetic potential of this transformation, we had applied this two-step transformation to the late-stage formylation of complex biologically active molecules. As shown in Scheme 4, the estrone-derived aryl alkene **6**, which was synthesized from estrone in two steps, was transformed to the desired vinyl aldehyde **7** in 50% yield. This outcome clearly showed the great potential of this methodology as a facile strategy for the synthesis of various analogues or intermediates in drug discovery and screening.

Conclusions

In summary, we have developed a novel copper-catalyzed formylation of alkenyl C-H bonds for facile synthesis of α,β-unsaturated aldehydes. This transformation has demonstrated high reactivity, mild conditions and broad substrate scope. It is the utmost factor that commercially available $BrCHCl_2$ was used as a stoichiometric formylating reagent instead of $CHCl_3$, and mechanistic studies indicated that alkenyl aldehydes was furnished by bifunctionalization of alkenes via a carbocation process and following dehydration. Further application of this method for modification of bioactive molecules and $BrCHCl_2$ as an interesting C1 building block in organic synthesis are still underway in our laboratory.

Acknowledgment

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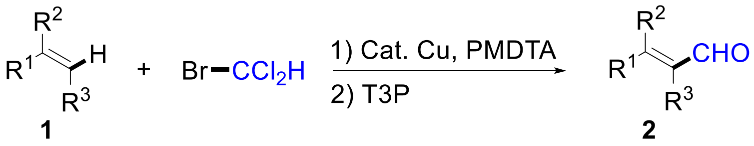

The first example of copper-catalyzed formylation of alkenyl C-H bonds with $BrCHCl_2$ used as a stoichiometric formylating reagent for facile synthesis of α,β-unsaturated aldehydes has been developed.