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ARTICLE TYPE

Cu/Ag-catalyzed double decarboxylative cross-coupling reaction between cinnamic acids and aliphatic acids in aqueous solution

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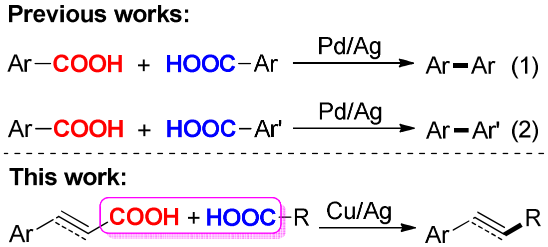
A novel double decarboxylative cross-coupling catalyzed by copper and silver has been developed. This method provides a practical approach for the flexible synthesis of alkenes and alkynes from the readily affordable substrates.

Carbon-carbon bond formation by transition-metal-catalyzed decarboxylative cross-couplings has emerged as an attractive and important method due to its efficiency, convenience and environmentally benign properties.[1] The method does not use sensitive reagents and is easy to handle. Goossen,[2] Larrosa,[3] Su,[4] Becht,[5] and others[6] have reported that arene carboxylic acids could be coupled with a range of substrates, such as aryl halides, aryl triflates (mesylates), diaryliodonium salts and unactivated arenes. Myers and others have shown Heck type couplings of benzoic acids with various olefins through decarboxylative method.[7,4b-c] In addition, other studies such as alkynylation,[8,6f] acylation,[9,2c,6j] esterification[10,2b-c] and decarboxylation reaction[11,3b] have also been investigated in this area. Despite of the significant advances, these processes still suffer from some drawbacks, such as high temperature and the need of stoichiometric amount of copper or silver salts. On the other hand, the substrates are mainly focused on arene carboxylic acids, which restricts their potential application. Therefore, the development of decarboxylative couplings that are capable of coupling alkynyl and alkyl carboxylic acids in a catalytic manner is of considerable interest. Recently, Liu[12] and Mao[13] reported decarboxylative couplings of cinnamic acids with alcohols and methyl arenes respectively. Li[14] reported decarboxylative alkynylation and fluorination of aliphatic acids under mild conditions. These works greatly advanced the chemistry of decarboxylative coupling. Nevertheless, the double decarboxylative cross-coupling has received much less attention in this field. Larrosa reported the first example of homocoupling between aromatic carboxylic acids in 2010.[15] Afterwards, Tan and Su extended this method to the cross-coupling of two different aryl carboxylic acids (Scheme 1, eqn(1-2)).[16] Herein, we describe the first Cu/Ag-catalyzed double decarboxylative cross-couplings of vinyl or alkynyl carboxylic acids with alkyl carboxylic acids.



Scheme 1 Double decarboxylative cross-couplings.

Optimization of the reaction conditions was carried out using (*E*)-cinnamic acid (**1a**) with pivalic acid (**2a**) as the model substrates. We were pleased to found that the reaction could proceed in aqueous solution with the presence of a catalytic amount of $Cu(OAc)_2$ or $CuSO_4$, affording the desired product **3aa** in moderate yields (Table 1, entries 1-3). CuO and CuI were evaluated but resulted in low yields using 10% catalyst loading under the same conditions (Table 1, entries 4-5). CuCl was ineffective to initiate the decarboxylative coupling (Table 1, entry 6). To our delight, Cu powder displayed good catalytic activity in this transformation with about 70% product yield (Table 1, entries 7-9). Good yield was also obtained using 5% Cu powder as catalyst when the temperature was lowered to 90°C (Table 1, entry 10). It was found that temperature has great influence on the reaction, only 44% yield was obtained when we performed the reaction at 65℃ and no product was detected at RT (Table 1, entries 11-12). In addition, no reaction occurred in the absence of either Cu or $AgNO_3$, it showed that both of the metals were essential for this transformation (Table 1, entries 13-14). Slightly lower product yield was obtained when $AgBF_4$ was used as catalyst instead of $AgNO_3$ (Table 1, entry 15). We also performed the reaction in Acetone/H_2O (1:1), the result was not good as that we obtained in CH_3CN/H_2O (1:1) (Table 1, entry 10).

With the optimal conditions in hand, the scope of the substrates was examined. As shown in Table 2, the cinnamic acids with weak electron-withdrawing group could be coupled with pivalic acid via double decarboxylative processes to give the cross-coupled products in good yields (Table 2, **3ba-3ea**),

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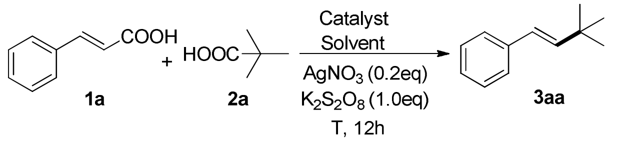
whereas the yield dropped to 29% when (*E*)-4-fluorocinnamic acid was used (Table 2, **3fa**). For (*E*)-4-methylcinnamic acid, it gave the corresponding product in 36% yield. Unfortunately, the use of (*E*)-4-methoxycinnamic acid did not furnish any of the alkenylation product, it only produced the 4-methoxybenzaldehyde in 82% yield (Table 2, **3ja**, see ESI). (*E*)-3-(naphthalen-2-yl)acrylic acid could also afford the desired product in 40% yield (Table 2, **3ha**). Various aliphatic acids were then tested, the double decarboxylative couplings proceeded smoothly for both secondary and tertiary alkyl acids. For example, product **3ic** was furnished in 96% yield when 2-(9*H*-fluoren-9-ylidene)acetic acid coupled with 2-ethylhexanoic acid. Other secondary alkyl acids such as cyclobutanecarboxylic acid and 2-ethylbutanoic acid also coupled smoothly to afford the products in high yields (Table 2, **3ae**, **3be** and **3af**). In addition, satisfactory yields were observed for the more congested tertiary carboxylic acids although the efficacy was slightly lowered to compare with the secondary congeners (Table 2, **3ad** and **3bd**). Similarly, carboxylic acid containing free hydroxyl group, for example, 3-hydroxy-1-adamantanecarboxylic acid was efficiently transformed into the desired product **3ak** in 76% yield while hydroxy group remained intact. Moreover, the functionalized aliphatic acids, such as **2i**, **2j** and **2l** could also participate in the transformation affording moderately high yields except for **2h** (Table 2, **3ai**, **3aj**, **3ak** and **3ah**). It is noteworthy that 2,2-dimethylpentanedioic acid (**2j**) coupled exclusively with the tertiary carboxyl group with the primary carboxyl group remained intact which could be further functionalized. Strangely, the primary carboxylic acids failed to give the desired products. The reasons were unclear at this stage and deserve further clarification. However, *N*-phthaloylglycine (**2g**) and 2-(4-chlorophenoxy)acetic acid (**2l**) could generate the desired products **3ag** and **3al** in moderate yields under the above experimental conditions (Table 2, **3ag**- and **3al**). Gemfibrozil is an oral drug used to lower lipid levels. As an application of this protocol, Gemfibrozil could also be modified to its alkenylation product **3em** in 20% yield (eqn (3)).

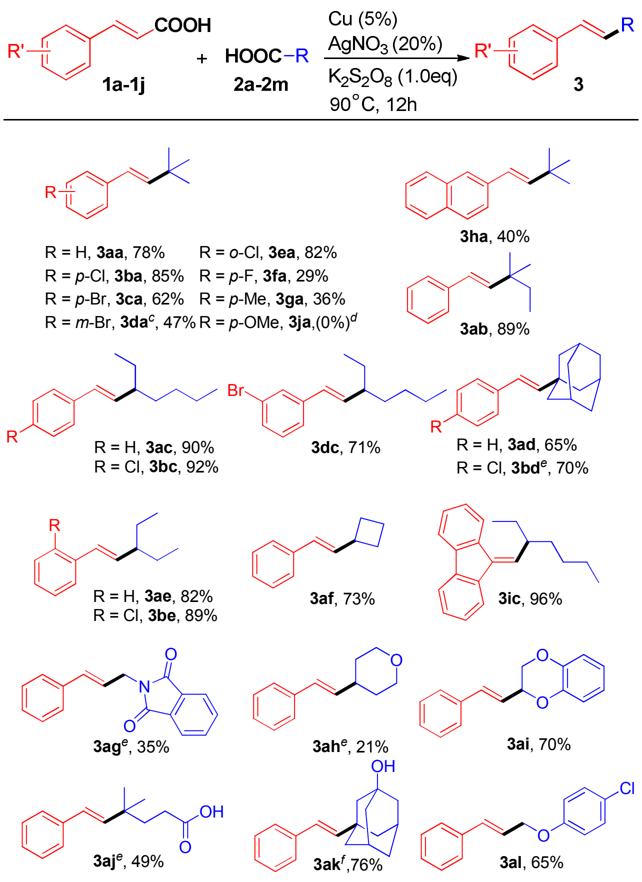
Table 1 Optimization of reaction conditions[a]



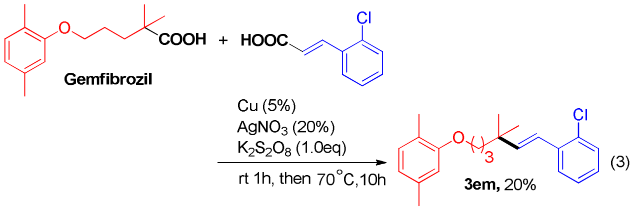
Entry	Catalyst (mol%)	T(℃)	Solvent	Yield (%)[b]
1	$Cu(OAc)_2$ (5)	110	CH_3CN/H_2O (1:1)	62
2	$Cu(OAc)_2$ (10)	110	CH_3CN/H_2O (1:1)	67
3	$CuSO_4$ (5)	110	CH_3CN/H_2O (1:1)	55
4	CuO (10)	110	CH_3CN/H_2O (1:1)	26
5	CuI (10)	110	CH_3CN/H_2O (1:1)	30
6	CuCl (10)	110	CH_3CN/H_2O (1:1)	n.d
7	Cu (10)	110	CH_3CN/H_2O (1:1)	74
8	Cu (10)	100	CH_3CN/H_2O (1:1)	71
9	Cu (5)	110	CH_3CN/H_2O (1:1)	68
10	Cu (5)	90	CH_3CN/H_2O (1:1)	78(50[c])
11	Cu (5)	65	CH_3CN/H_2O (1:1)	44
12	Cu (5)	16(rt)	CH_3CN/H_2O (1:1)	n.d
13	Cu (0)	90	CH_3CN/H_2O (1:1)	n.d
14	Cu (5)	90	CH_3CN/H_2O (1:1)	n.d[d]
15	Cu (5)	90	CH_3CN/H_2O (1:1)	67[e]

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), $K_2S_2O_8$ (1.0 mmol), CH_3CN (3 mL), H_2O (3 mL), under air atmosphere, 12 h, 90℃. [b] Isolated yield. [c] Acetone/H_2O (1:1) as solvent. [d] Without $AgNO_3$. [e] 20% $AgBF_4$ as catalyst.

Table 2 Cu/Ag-catalyzed double decarboxylative cross-coupling of cinnamic acids with aliphatic acids[a,b]



[a] Reaction conditions: cinnamic acids (1.0 mmol), alphatic acids (1.5 mmol), Cu (5 mol%), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (1.0 mmol), CH_3CN (3 mL), H_2O (3 mL), 90 ℃, 12 h. [b] Isolated yield. [c] At 70℃. [d] See ESI. [e] RT 1 h, then 70℃, 10 h. [f] 90℃, 5 h.



(3)

Having demonstrated the reactivity of cinnamic acids, we

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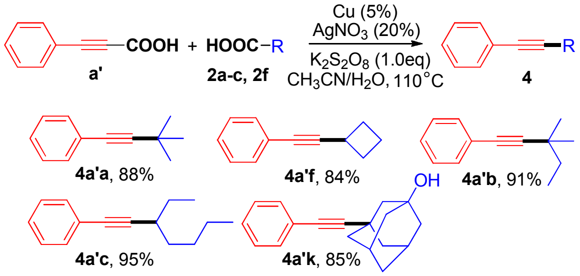
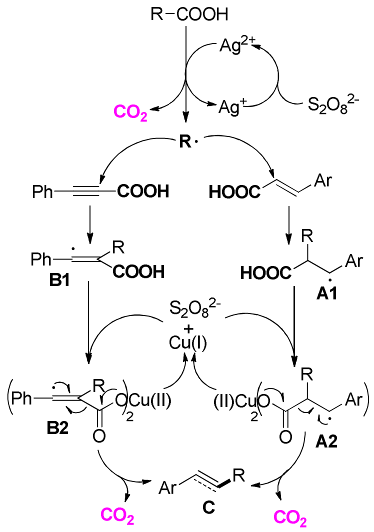
next extended the method to the coupling of alkynyl and alkyl carboxylic acids. To our delight, effective reaction was carried out with the otherwise conditions identical to the optimized conditions but just by elevating the reaction temperature to 110℃, both secondary and tertiary aliphatic acids underwent high efficient decarboxylative processes with phenylpropiolic acid to afford the corresponding products **4a'a-4a'c, 4a'f** and **4a'k** in excellent yields (Scheme 2). This reaction provides a new and efficient method for C(sp)−C(sp^3) bond formation.[17]



Scheme 2 Cu/Ag-catalyzed double decarboxylative coupling between phenylpropiolic acid and aliphatic acids.

Based on the results of our investigation (See ESI) and previous studies[12-14], a plausible mechanism is proposed in Scheme 3. At first, Ag(I) is oxidized to Ag(II) by persulfate and the latter induces the aliphatic acid to generate alkyl radical. Afterwards, alkyl radical attacks α-position of cinnamic acid or phenylpropiolic acid to produce intermediate **A1** or **B1** respectively. Then, **A2** and **B2** which are produced by **A1** and **B1** undergo SET process to release CO_2 and form product **C** by the assistance of Cu(II) (Scheme 3). Aromatic ring in cinnamic acid or phenylpropiolic acid is very important because it could stabilize the benzyl radical and help the intermediate to finish the decarboxylative step fast and the final products are relatively stable under the oxydic conditions.



Scheme 3 Proposed preliminary mechanism.

In summary, we have developed a Cu/Ag bimetallic tandem catalysis for selective alkenylation or alkynylation of alkanes[18] via double decarboxylative cross-couplings of cinnamic acids or phenylpropiolic acid and aliphatic acids which have never been reported before. The reaction could proceed in aqueous solution using catalytic amount of metals and both substrates are cheap and readily available without prefunctionalization. Further studies on this transformation are ongoing in our laboratory.

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