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Palladium-catalyzed oxidative carbonylation of *N*-aryl enamino esters with CO and alcohols: synthesis of *N*-aryl aminomethylenemalonates

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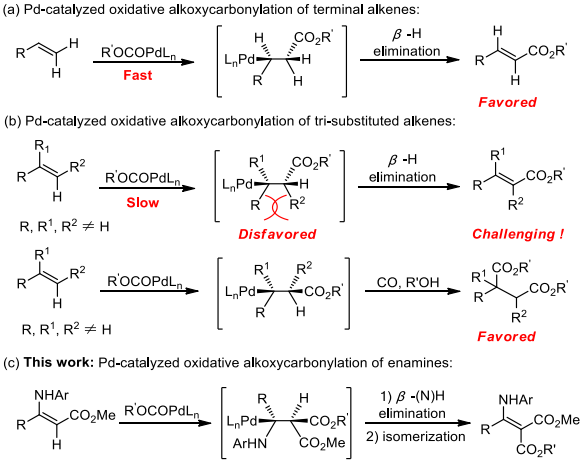
A novel palladium-catalyzed regioselective oxidative carbonylation of tri-substituted alkenes with CO and alcohols for the synthesis of α,β-unsaturated esters has been developed. Experimental studies and DFT calculations suggested that the reaction processed through alkoxylation of palladium(II) catalyst, CO and C=C double bond migratory insertion, β-(N)H elimination and tautomerization cascade steps. The reaction tolerates a wide range of groups and produces valuable aminomethylenemalonates in high yields.

Carbonylation reaction is one of the most dominant themes in modern synthetic chemistry.[1] Transition-metal catalyzed carbonylation of organic halides or pseudohalides,[2] alkenes,[3] alkynes,[4] organometallic reagents,[5] and C-H bonds of hydrocarbons[6] have been extensively studied and widely applied in organic synthesis. Especially, transition-metal catalyzed reductive carbonylation of alkenes, such as hydroformylation,[7] hydroesterification,[8] and hydroamidation[9] has been well-established for the synthesis of various alkyl carbonyl compounds. For example, hydroformylation of alkenes for the synthesis of aldehydes has been one of the largest processes in chemical industry.[9,10] However, since the reductive property of carbon monoxide and steric sensitive of the carbonylations,[6c] transition-metal catalyzed oxidative carbonylation of alkenes for the synthesis of valuable α,β-unsaturated carbonyl compounds has remained largely undeveloped.[11] Recently, a few elegant palladium-catalyzed oxidative carbonylation of alkenes for atom-economic synthesis of α,β-unsaturated esters have emerged.[12] However, due to the steric sensitive cis-β-H elimination was involved, this class of reaction was generally restricted to using terminal alkenes, and less steric-hindered primary alcohols as the substrates (Scheme 1a). In comparison with the terminal alkenes, the low binding affinity of tri-substituted alkenes to the palladium center and slow migratory insertion make this process challenging.[13] Furthermore, the intrinsic steric hindrance of tri-substituted alkenes prohibits the key β-H elimination of the palladium complex, thus making the dicarbonylation products favored (Scheme 1b).[14] Therefore, palladium-catalyzed oxidative carbonylation of tri-substituted alkenes for the regioselective synthesis of α,β-unsaturated carbonyl compounds remains a great challenge.



Scheme 1 Palladium-catalyzed oxidative alkoxycarbonylation of alkenes.

Methylenemalonates are a class of versatile building blocks in organic synthesis. Especially, *N*-aryl aminomethylenemalonates are the key synthetic precursors for the preparation of quinolones, 1,3,4-oxadiazoles, 3H-indole alkaloids, 4-phenylthioquinolines, and chiral amino acid derivatives. The laters are prevalent structural motifs in drugs, such as norfloxacin, flumequine, ciprofloxacin, fleroxacin, moxifloxacin, gemifloxacin, grepafloxacin and antibacterial reagents.[15] However, *N*-aryl aminomethylenemalonates were not easily accessible by traditional protocols.[16] In connection with our interest in carbonylations,[17] we hypothesized that palladium-catalyzed oxidative carbonylation of readily available *N*-aryl enamino esters with CO and alcohols would be an ideal and straightforward method for the synthesis of *N*-aryl aminomethylenemalonates. However, additional challenges should be overcome: (a) palladium-catalyzed intramolecular oxidative cyclization of *N*-aryl enamino esters towards indoles must be suppressed,[18] (b) palladium-catalyzed

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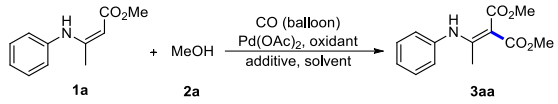
carbonylation of N-H bond of enamino esters to form ureas or carbamates should also be inhibited.[17d] In this paper, we describe the development of a novel palladium-catalyzed oxidative carbonylation of *N*-aryl enamino esters with CO and alcohols for the synthesis of *N*-aryl aminomethylenemalonates under mild conditions (Scheme 1c).

Table 1 Optimization of the reaction conditions[a]



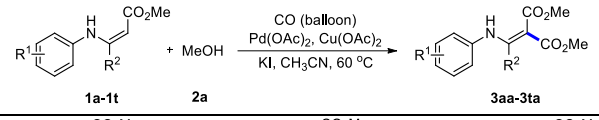
1a 2a 3aa

Entry	Oxidant	Additive	Solvent	Yield of **3aa** (%)
1[b]	$Cu(OAc)_2$		DMF	5
2	Oxone		DMF	0
3	$Cu(OAc)_2$		DMF	18
4	$Cu(OAc)_2$		1,4-dioxane	9
5	$Cu(OAc)_2$		Toluene	11
6	$Cu(OAc)_2$		DMSO	28
7	$Cu(OAc)_2$		CH_3CN	51
8	$Cu(OAc)_2$	KI	CH_3CN	72
9	$Cu(OAc)_2$	NaI	CH_3CN	71
10	$Cu(OAc)_2$	TBAI	CH_3CN	69
11	$Cu(OAc)_2$	I_2	CH_3CN	56
12	$Cu(OAc)_2$	KBr	CH_3CN	42
13[c]	$Cu(OAc)_2$	KI	CH_3CN	36
14[d]	$Cu(OAc)_2$	KI	CH_3CN	80
15[e]	$Cu(OAc)_2$	KI	CH_3CN	n.r.

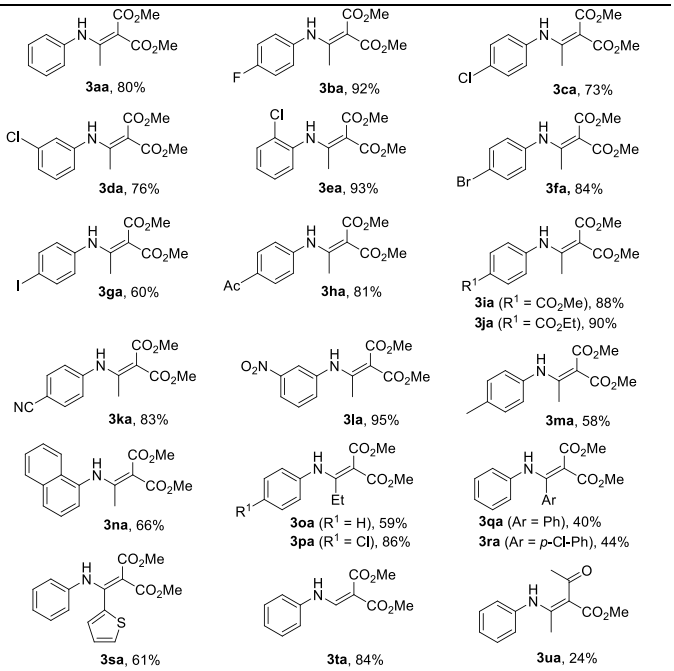
[a] Reaction conditions: **1a** (0.2 mol), MeOH (5.0 equiv), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.2 equiv), KI (0.2 equiv), solvent (2 mL), CO (balloon pressure), 80 °C; isolated yield. [b] $Cu(OAc)_2$ (3.0 equiv). [c] 100 °C. [d] 60 °C. [e] 40 °C, n.r.= no reaction.

We began our study with the palladium-catalyzed oxidative carbonylation of the readily available *N*-phenyl enamino ester **1a** with CO and methanol. The carbonylation product *N*-phenyl aminomethylenemalonate **3aa** was formed in only 5% yield along with indole and acetanilide as the byproducts in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ at 80 °C in DMF (Table 1, entry 1). Importantly, the carbonylation of enamino ester was observed. Encouraged by this preliminary result, we have tried to optimize the reaction conditions for this palladium-catalyzed oxidative carbonylation (Table 1). Firstly, different oxidants, such as $CuCl_2$, Oxone and $K_2S_2O_8$ were screened (Table 1, entry 2). No **3aa** was observed under these conditions, but *N*,*N*'-diphenylurea, which generated from palladium-catalyzed N-H bond carbonylation of aniline (hydrolyzed from *N*-phenyl enamine ester **1a**), was obtained as the main product in the presence of $CuCl_2$.[17d] Therefore, $Cu(OAc)_2$ was retried as the oxidant. Fortunately, the acetanilide and indole byproduct were significant suppressed by verification of the loading of $Cu(OAc)_2$ oxidant (Table 1, entry 3). Then, different solvent were optimized for further improving the reaction efficiency (Table 1, entries 4-7). To our delight, the desired *N*-phenyl aminomethylenemalonate **3aa** was obtained in 51% yield in CH_3CN (Table 1, entry 7). Next, KI which has been shown to improve the efficiency of palladium-catalyzed carbonylations in our previous reports,[17] was added as an additive to the current reaction. The yield of **3aa** was further improved to 72% (Table 1, entry 8). Other iodide compounds such as NaI, TBAI, and I_2 are inferior to KI in this reaction (Table 1, entries 9-11). And KBr was less effect (entry 8 vs 12). Finally, the reaction temperature was also varied, and 60 °C gave the best yield (80%) of **3aa** (Table 1, entries 13-15).

Table 2 Palladium-catalyzed carbonylation of various *N*-aryl enamino esters **1** with CO and methanol[a]



1a-1t 2a 3aa-3ta



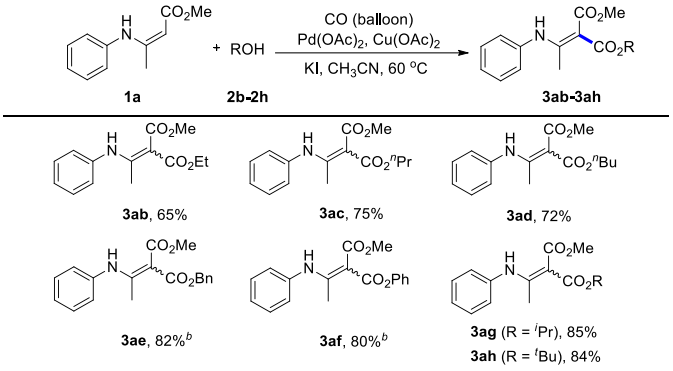
[a] Reaction conditions: **1** (0.2 mmol), MeOH (5.0 equiv), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.2 equiv), KI (0.2 equiv), CH_3CN (2 mL) at 60 °C under CO (balloon pressure); isolated yield.

With the optimized reaction conditions established, the scope of the reaction was investigated (Table 2). This new carbonylation reaction displayed high functional group tolerance and proved to be a quite general methodology. *N*-Aryl enamino ester with *p*-fluoro on aryl ring **1b** gave the desired product **3ba** in 92% yield. All of the *o*-, *m*- and *p*-chloro substituted *N*-Aryl enamino esters **1c**-**1e** were tolerated in the reaction, and *o*-chloro substituted *N*-Aryl enamino ester **1e** gave the highest yield (93%). Notably, sensitive functional groups in the palladium-catalyzed cross-coupling reactions, such as bromo and iodo, were tolerated as well, thus resulting the corresponding bromo or iodo substituted products **3fa**-**3ga** in 84% and 60% yields, respectively. *N*-Aryl enamino esters with various electron-withdrawing groups on aryl ring **1h**-**1l**, such as acetyl, ester, cyano and nitro, proceeded smoothly to produce the desired carbonylation products **3ha**-**3la** in 81-95% yields. However, the substrates bearing electron-donating group, such as methyl, afforded the desired carbonylation product **3ma** in slightly lower yield.

N-Naphthyl enamino ester **1n** was also allowed to produce the *N*-naphthyl aminomethylenemalonate **3na** in 66% yield under the reaction conditions. Furthermore, different groups on α-position of *N*-phenyl enamino esters were

investigated under the standard conditions. The *α*-ethyl substituted *N*-phenyl enamino esters **1o-1p** produce the corresponding carbonylation product **3oa-3pa** in good to high yields. *α*-Aryl (or *α*-hetero-aryl) substituted *N*-phenyl amino-methylenemalonates **3qa-3sa** were achieved by the carbonylation reaction albeit in slightly low yields. Notably, (*Z*)-Methyl-3-(phenylamino)-acrylate was found compatible with the reaction and afforded the corresponding aminomethylenemalonate **3ta** in 84% yield. In addition, the expected carbonylation product **3ua** was only obtained in 24% yield when (*Z*)-4-(phenylamino)pent-3-en-2-one **1u** was used as the substrate.

Table 3 Palladium-catalyzed carbonylation of *N*-phenyl enamino ester **1a** with CO and various alcohols **2**[a]

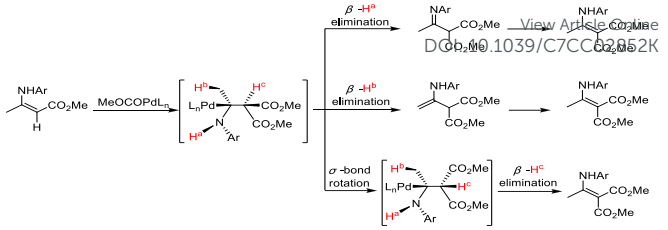


[a] Reaction conditions: **1a** (0.2 mmol), alcohol (5.0 equiv), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.2 equiv), KI (0.2 equiv), CH_3CN (2.0 mL) at 60 °C under CO (balloon pressure), isolated yield (for all of products E/Z ≈ 1). [b] alcohol (2.0 equiv).

Different alcohols were also studied to determine their reactivity in the carbonylation reaction (Table 3). It was noteworthy that all of the primary alcohols, phenol, secondary alcohol and even tertiary alcohol were tolerated in the reaction. Primary alcohols, such as ethanol, *n*-propanol, *n*-butanol, and benzyl alcohol, produced the corresponding carbonylation products **3ab-3ae** in 65-82% yields. In particular, phenol converted to the desired product **3af** in 80% yield under oxidative reaction conditions. Due to the transition-metal catalyzed carbonylation was generally sensitive in steric effects, secondary and tertiary alcohol are generally inactive in carbonylation reactions.[19] However, 2-propanol and *tert*-butyl alcohol reacted smoothly to produce the corresponding *N*-phenyl aminomethylenemalonates **3ag** and **3ah** in 85% and 84% yields, respectively, under the reaction conditions.

Palladium-catalyzed oxidative carbonylation of alkenes always proceeds via migratory insertion of C=C double bond into acylpalladium complex sequential with β-H elimination steps.[12] Thus, β-H^a, β-H^b, and β-H^c elimination were possible for this carbonylation in principle (Scheme 2). However, the smooth reaction of **1q**-**1t** indicates that the β-H^b elimination is prohibited in current reaction situation. In order to clarify which route in β-H^a or β-H^c elimination was the real reaction pathway, DFT calculations has been performed.

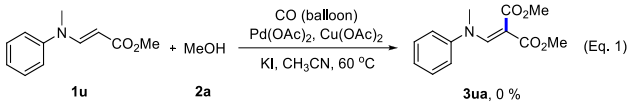
The free energy profile for the carbonylation reaction pathway is show in supplementary information, Fig. S1 (obtained at M06/6-311++G** level with B3LYP/6-31G*



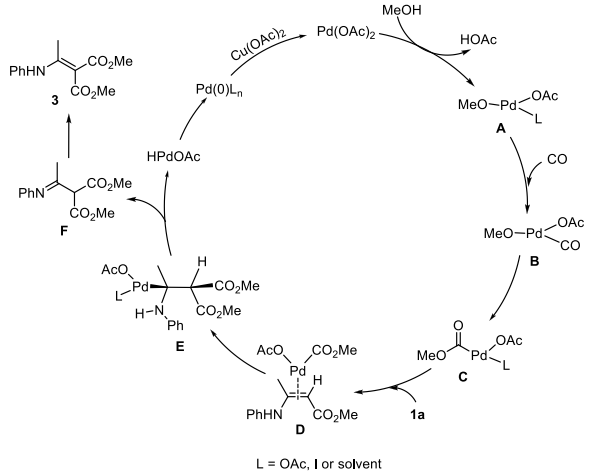
Scheme 2 Possible pathways for the carbonylation reaction.

optimized geometries (SDD basis was used for Pd)). The reaction process starts with a stepwise addition of methanol to the $Pd(OAc)_2$ via hydrogen bond mediated **TS-1** and 8-membered ring **TS-2** transition structures. Then an intramolecular proton transfer occurs, the H from 1st added methanol migrates to the acetate group via transmission of the 2nd methanol. The second step is carbonyl insertion, the carbon monoxide addition and methanol-acetic acid dimer dissociation to the Pd center occurs simultaneously. The intermediate **B** isomerizes to **C** via a three-membered ring transition structure **TS-5** (ΔG = 9.0 Kcal/mol) and then coordinates to the C=C double bond in enamino ester **1a** to give rise to intermediate **D**. In **1a**, the lone pair electrons in N atom and double bond would form a delocalized π bonds with four electrons distributed in three atoms. The N atom and C_{Ester} atom in double bond are electronically negative and C_{Amino} atom in double bond is electronically positive. Therefore, the Pd would insert to the C_{Ester} atom first, while in the four-membered ring form transition state for the ester migration, the coordination center for Pd transfer to C_{Amino} atom, and this process has been verified by the intrinsic reaction coordinate (IRC) path calculation. Upon intermediate **E**, there are three possible elimination pathways β-H^a, β-H^b, and β-H^c, as discussed above and illustrated in Scheme 2. As β-H^b elimination path is experimentally excluded, we will focus on the competition between the remained two pathways. As shown in Fig. S2 (see supplementary information), the Pd atom and β-H^a are in cis position, while the β-H^c is in trans-position. Thus, only in case the -$CH(CO_2Me)_2$ group rotates for 180º, the β-H^c elimination pathway is conformationally accessible. Moreover, the oxygen atom of esters group coordinate with the Pd central, the rotation of the -$CH(CO_2Me)_2$ group is prohibited. Hence, only the β-H^a elimination pathway is conformational and energetically available. The β-(N)H is extracted by Pd-acetate group via **TS-7** and departed with them to form intermediate **F**. The last step in this route is the isomerization from imines **F** to the carbonylation product *N*-phenyl aminomethylenemalonate **3**. In addition, we also explored the palladium-catalyzed C-H activation and carbonylation pathway,[17b] and which has been energetically ruled out as the high barrier for the formation of octahedron Pd(IV) intermediates (see supplementary information, Fig. S3).

To further confirm the reaction mechanism, the carbonylation of *N*-methyl enamino ester **1u**, which has no hydrogen on nitrogen atom, was conducted under the standard conditions. Conformable, no reaction was observed (Eq. 1). This result also suggested that the β-(N)H elimination pathway is more likely.



On the basis of aforementioned results, a proposed catalytic cycle was depicted in Scheme 3. Initially, an alkoxylpalladium species **A** was generated from ligand exchange by loss of HOAc. Then, alkoxylpalladium **A** underwent coordination of CO to form intermediate **B**. Migratory insertion of CO into the MeO-Pd bond of the intermediate **B** produces intermediate **C**. Next, the coordination and 1,2-migratory insertion of C=C double bond into intermediate **C** generates intermediate **E**. β-(N)H Elimination of **E** delivers the imine intermediate **F** and palladium hydride species. Finally, isomerization of imine intermediate **F** gives the carbonylation product **3**. The palladium hydride species was oxidized by $Cu(OAc)_2$ to regenerate $Pd(OAc)_2$ and complete the catalytic cycle.



Scheme 3 Proposed mechanism for palladium-catalyzed oxidative carbonylation of *N*-aryl enamino esters with CO and alcohols.

In conclusion, we have developed a novel palladium-catalyzed oxidative carbonylation of tri-substituted alkenes with CO and alcohols for the synthesis of α,β-unsaturated esters. The use of N-H enamino esters as the substrates was significant for the oxidative carbonylation reaction, which was making the challenging β-H elimination step proceeded smoothly. The resulted *N*-aryl aminomethylenemalonates products are valuable for pharmaceutical chemistry. The experiment results and DFT calculations suggested that the oxidative carbonylation proceeded through alkoxylation of palladium catalyst, CO and alkenyl C=C double bond migratory insertion, β-(N)H elimination and tautomerization cascade steps. The readily available *N*-aryl enamino esters, valuable *N*-aryl aminomethylenemalonates, good functional groups tolerance, mild conditions and high yields make this unprecedented oxidative carbonylation reaction attractive for organic synthesis. Further scope and mechanistic studies of the reaction are underway in our laboratory.

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