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Palladium-Catalyzed Oxidative Carbonylative Coupling of Arylallenes, Arylboronic Acids, and Nitroarenes

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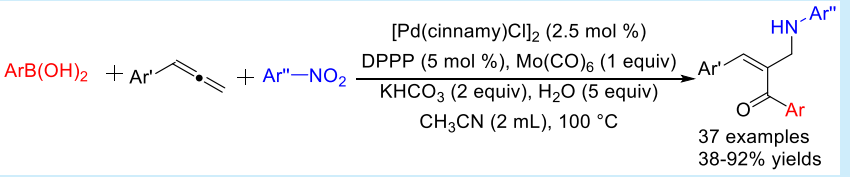
Supporting Information



ABSTRACT: In this Letter, a palladium-catalyzed multicomponent procedure for the selective synthesis of α-substituted α,β-unsaturated ketones has been developed. With readily available allenes, arylboronic acids, and nitroarenes as the substrates, the reaction proceeds selectively to the desired α-substituted enones. Notably, no manipulation of carbon monoxide gas is needed here, and $Mo(CO)_6$ has been applied as a stable solid CO source instead. Additionally, as an oxidative coupling reaction, nitroarenes are used as both the amine source and the oxidant to regenerate the active palladium species.

In modern organic synthesis, in particular, under the background of sustainable development and green chemistry, the request for high reaction efficiency has reached a new level.[1] One aspect of reaction efficiency is the number of newly formed chemical bonds in one reaction: the new chemical bond formation efficiency. Among the various options, the multicomponent reaction offers an ideal choice.[2] However, when combining multiple reactive reagents, it is a great challenge to find a balance between the reactivity and the selectivity.[3] This task has been taken on by chemists in the past decades, and many novel multicomponent procedures have been established.[1,2,4]

On the contrary, palladium-catalyzed carbonylative transformations have experienced great progress since their first report in the 1970s.[5] Numerous carbonyl-containing compounds can be easily prepared by carbonylation procedures. In these procedures, the acylpalladium complex is the common key intermediate, which is highly reactive and nonstable. Hence it is even more labyrinthine with the presence of an acylpalladium complex in the multicomponent reactions.[6] Concerning the substrates applicable, the reaction complexity will increase even more when using allene as one of the starting materials. Allenes are useful materials in synthetic chemistry due to the exceptional reactivity of the 1,2-diene moiety. They allow the rapid construction of complexed molecules.[7] As expected, various novel carbonylative transformations of allenes have been explored as well, which are mainly three-component reactions (including carbon monoxide).[8,9] Additionally, anilines are commonly applied nucleophiles in carbonylation chemistry and are produced from the corresponding nitroarenes. Here nitroarenes have three traits: (1) stable and abundant, (2) can be reduced by CO, and (3) can be used as an oxidant for catalyst regeneration. Hence we have become interested in developing a carbonylation procedure for allene transformation with nitroarenes as the amine source and oxidant.

Initially, we chose commercially available phenylallene, phenylboronic acid, and 1-methyl-4-nitrobenzene as the model substrates to establish the catalyst system. Notably, from a theory point of view, at least 18 different kinds of products are possible. (For a full list, see the Supporting Information.) Indeed, when the reaction was tested with $Pd(TFA)_2$ as the catalyst and Na_2CO_3 as the base in MeCN at 100 °C, a real mixture of many nonidentifiable compounds was obtained. To our delight, we were finally able to confirm that 8% of (*Z*)-1,3-diphenyl-2-((*p*-tolylamino)methyl)prop-2-en-1-one (**P1**) was formed in our first testing (Table 1, entry 1). With these encouraging results in hand, various inorganic bases were subsequently tested (Table 1, entries 2−8). The obtained yields varied with bases, and a 52% yield of the target product was formed with $KHCO_3$ as the base (Table 1, entry 8). Only a 16% yield was obtained when NEt_3 or DiPEA (*N*,*N*-diisopropylethylamine) was used as the base (Table 1, entries 9 and 10). The yield decreased when using a lower loading base (Table 1, entry 11). Subsequently, several palladium precursors were tested (Table 1, entries 12−16). The target product was isolated in 55% yield with $[Pd(cinnamyl)Cl]_2$ as the catalyst (Table 1, entry 16). Additional efforts were made to vary the other reaction parameters as well, such as the reaction temperature, the ratio of reagents, the catalyst loading, the water amount, and so on; however, no further improvement of the yield could be realized.

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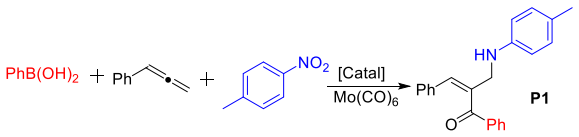
Table 1. Optimization of Reaction Conditions[a]



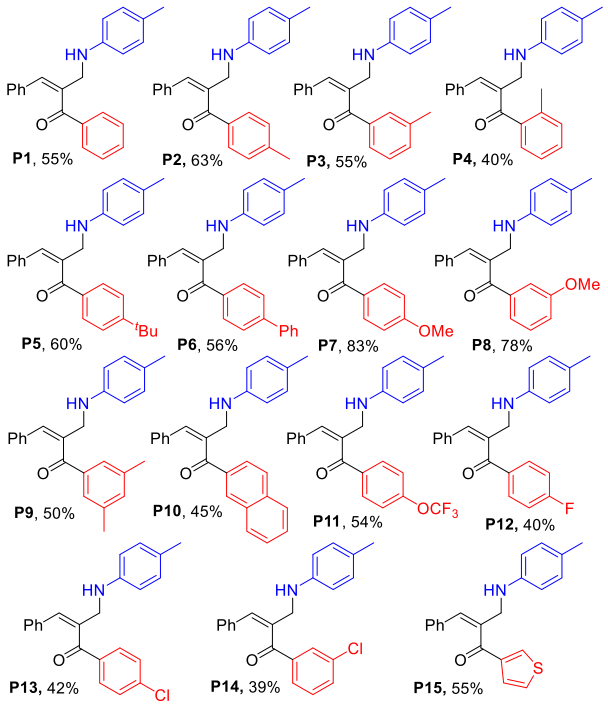
entry	palladium	base	yield
1	$Pd(TFA)_2$	Na_2CO_3	8
2	$Pd(TFA)_2$	Cs_2CO_3	9
3	$Pd(TFA)_2$	K_2CO_3	28
4	$Pd(TFA)_2$	$NaHCO_3$	20
5	$Pd(TFA)_2$	K_3PO_4	34
6	$Pd(TFA)_2$	K_2HPO_4	40
7	$Pd(TFA)_2$	KH_2PO_4	0
8	$Pd(TFA)_2$	$KHCO_3$	52
9	$Pd(TFA)_2$	NEt_3	16
10	$Pd(TFA)_2$	DiPEA	16
11	$Pd(TFA)_2$	$KHCO_3$	29[b]
12	$Pd(OAc)_2$	$KHCO_3$	22
13	$PdCl_2$	$KHCO_3$	43
14	$Pd(MeCN)_2Cl_2$	$KHCO_3$	44
15	Pd_2dba_3	$KHCO_3$	37[c]
16	$[Pd(cinnamyl)Cl]_2$	$KHCO_3$	55[c]
17	$[Pd(cinnamyl)Cl]_2$	$KHCO_3$	24[d]
18	$[Pd(cinnamyl)Cl]_2$	$KHCO_3$	22[e]

[a]Reaction conditions: phenylboronic acid (0.5 mmol), phenylallene (1.2 equiv), 1-methyl-4-nitrobenzene (3 equiv), $Pd(TFA)_2$ (5 mol %), DPPP (5 mol %), $Mo(CO)_6$ (1 equiv), base (2 equiv), H_2O (5 equiv), CH_3CN (2 mL), 100 °C, 14 h, yields determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]$KHCO_3$ (1 equiv). [c]2.5 mol %, isolated yield. [d]$[Pd(cinnamyl)Cl]_2$(2.5 mol %), 1-methyl-4-nitrobenzene (2 equiv). [e]$[Pd(cinnamyl)Cl]_2$(2.5 mol %), 1-methyl-4-nitrobenzene (10 equiv).

With the best reaction conditions in hand, we tested the effects of arylboronic acids (Scheme 1). As we expected, the yields were increased when arylboronic acid was substituted with electron-donating groups (Scheme 1, P2−P9). In the case of using 4-methoxyphenylboronic acid as one of the starting materials, 83% of the target molecular can be isolated (Scheme 1, P7). Because of the steric effect, the yield of the target product decreased when arylboronic acid contained an ortho substitution (Scheme 1, P4). This type of steric effect can be decreased if the substitution is substituted at the meta or the better para position (Scheme 1, P3, P8). Besides fluoro- and chloro-substituted arylboronic acids, thiophen-3-ylboronic acid can be applied as the substrate as well, and moderate yields of the corresponding products can be isolated in all cases (Scheme 1, P11−P15).

Then, we keep 4-methoxyphenylboronic acid and phenylallene as the standard substrates, and various nitroarenes were tested under our typical reaction conditions (Scheme 2). Moderate to excellent yields can be obtained, in general. From the obtained results, the position of the substitution in nitroarene has shown a low effect on the reaction outcome. Both electron-donating and electron-withdrawing functional groups can be well tolerated. Notably, thioether and terminal alkene can also be tolerated and gave the corresponding products in 72 and 54% isolated yield, respectively (Scheme 2, P20 and P22). These two functional groups are easily oxidized in the presence of the standard oxidant, which also proves the advantage of using nitroarene as the oxidant. It is important to mention that we have proven nitroarene to act in the oxidation

Scheme 1. Synthesis of α-Substituted Enones from Arylboronic Acids[a]



[a]Reaction conditions: arylboronic acid (0.5 mmol), phenylallene (1.2 equiv), 1-methyl-4-nitrobenzene (3 equiv), $[Pd(cinnamy)Cl]_2$ (2.5 mol %), DPPP (5 mol %), $Mo(CO)_6$ (1 equiv), $KHCO_3$ (2 equiv), H_2O (5 equiv), CH_3CN (2 mL), 100 °C, 14 h, isolated yields.

in our control experiments as well. (See the Supporting Information.) In more detail, no desired product could be detected by using *p*-toluidine instead of 1-methyl-4-nitrobenzene, and a mixture of two products was obtained when a combination of *p*-toluidine (1 equiv) and nitrobenzene (2 equiv) was used under standard conditions. However, no desired product could be detected when nitroalkanes were tested, such as nitromethane and nitroethane.

Finally, the generality of the applicable allenes was checked as well (Scheme 3). Various arylallenes were prepared and reacted under our conditions; good yields of the corresponding enones were produced. In particular, the chloride-decorated products were ready for further transformations via cross-coupling reactions.[10] It is also worth mentioning that aliphatic allenes were prepared and tested as well, but no desired product could be detected.

On the basis of our results and literature,[8,9] a possible reaction mechanism is proposed as well (Scheme 4). The reaction started with a base-promoted transmetalation of arylboronic acid with the active palladium(II) complex to give the corresponding aryl−Pd(II) intermediate. Then, carbon monoxide inserted into the C−Pd bond via coordination with free CO or ligand exchange with $Mo(CO)_6$ to give the acyl−palladium complex as the key intermediate. Subsequently, the active acyl−palladium complex reacted with the internal carbon (which is more reactive) of allene, followed by the nucleophilic attack of aniline to give the final enone products. Meanwhile, the active palladium complex was regenerated for the next catalytic cycle.

In summary, a palladium-catalyzed multicomponent procedure for the selective synthesis of α-substituted α,β-

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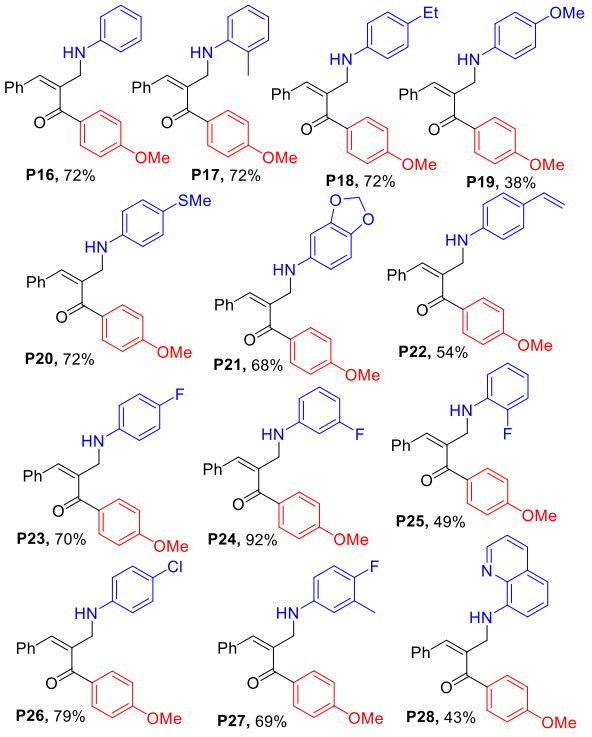
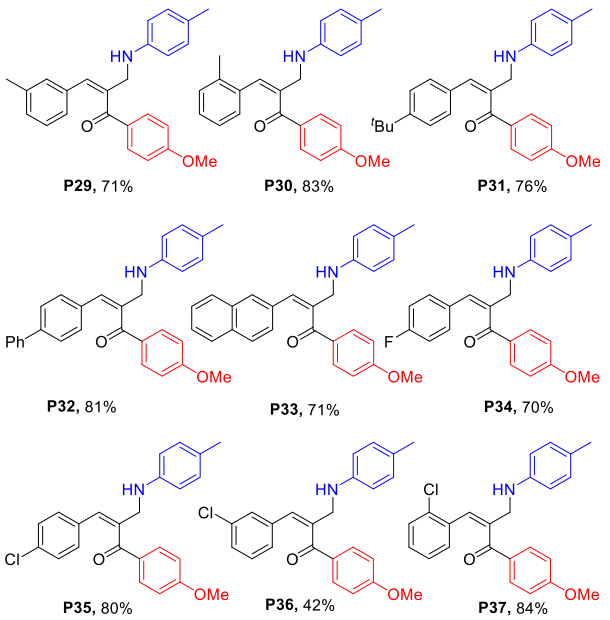
Scheme 2. Synthesis of α-Substituted Enones from Nitroarenes[a]



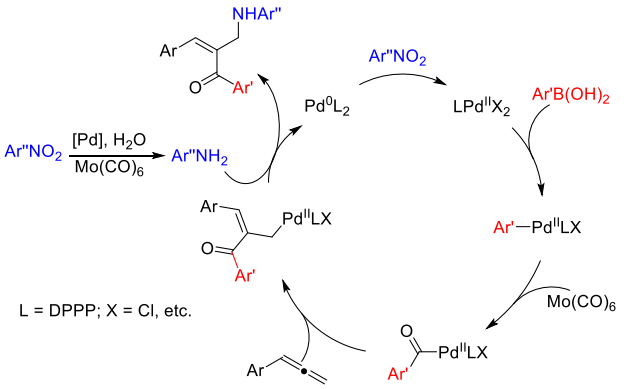
[a]Reaction conditions: 4-Methoxyphenylboronic acid (0.5 mmol), phenylallene (1.2 equiv), nitroarene (3 equiv), $[Pd(cinnamy)Cl]_2$ (2.5 mol %), DPPP (5 mol %), $Mo(CO)_6$ (1 equiv), $KHCO_3$ (2 equiv), H_2O (5 equiv), CH_3CN (2 mL), 100 °C, 14 h, isolated yields.

Scheme 3. Synthesis of α-Substituted Enones from Allenes[a]



[a]Reaction conditions: 4-Methoxyphenylboronic acid (0.5 mmol), allenes (1.2 equiv), 1-methyl-4-nitrobenzene (3 equiv), $[Pd(cinnamy)Cl]_2$ (2.5 mol %), DPPP (5 mol %), $Mo(CO)_6$ (1 equiv), $KHCO_3$ (2 equiv), H_2O (5 equiv), CH_3CN (2 mL), 100 °C, 14 h, isolated yields.

Scheme 4. Proposed Reaction Mechanism



unsaturated ketones has been developed. With readily available allenes, arylboronic acids, and nitroarenes as the substrates, the reaction proceeds selectively to the desired α-substituted enones in moderate to excellent yield. Notably, no manipulation of carbon monoxide gas is needed here, and $Mo(CO)_6$ has been applied as a stable solid CO source instead. Additionally, as an oxidative coupling reaction, nitroarenes are used as both the amine source and the oxidant to regenerate the active palladium species

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02925.

General comments, general procedure, optimization details, analytic data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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