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Palladium-catalyzed hydroaminocarbonylation of alkenes with amines promoted by weak acid

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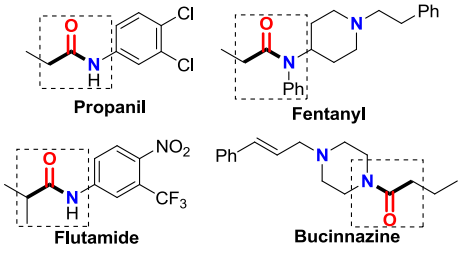
ABSTRACT

The weak acid has been identified as an efficient basicity-mask to overcome the basicity barrier imparted by aliphatic amines in the Pd-catalyzed hydroaminocarbonylation, which enables both aromatic and aliphatic amines to be applicable in the palladium-catalyzed hydroaminocarbonylation reaction. Notably, by using this protocol, the marketed herbicide of Propanil and drug of Fentanyl could be easily obtained in a one-pot manner.

Introduction

As one of the most important fundamental structural motifs, amide has been considered as a privileged structure in natural products, pharmaceuticals, pesticides, and functional materials.[1] For instance, the core structure of Propanil (herbicide),[2] Fentanyl (potent anesthesia and analgesic drug),[3] Flutamide (antiandrogen drug),[4] and Bucinnazine (potent analgesic drug)[5] is amide (Scheme 1). Therefore, the development of sustainable and atom-economic method for the synthesis of amides continues attracting much interest in academic research and industrial chemistry.

Driven by this prevalence, various methods have been developed for the synthesis of amides in recent decades.[6,7] One of the most promising methods is hydroaminocarbonylation of simple alkenes with amines in the presence of CO, which represents an ideal and atom economic approach to amides without formation of any by-products. Various catalysts, such as Ru, Rh, Pd, Co, and Ni complexes, have been reported for this method.[8] However, to the best of our knowledge, these reported methods suffer from forcing reaction conditions and only being applicable for aromatic amines. As for the palladium-catalyzed system, the conceivable reasons for the dependence of reactivity on nature of amines might be attributed to the fact that the key Pd-hydride catalytic species only can survive under relatively acidic conditions.[8] To circumvent



Scheme 1. Amide-containing pesticide and pharmaceuticals.

this substrate inhibition, we developed a ternary catalyst system composed of Pd/acid/paraformaldehyde effective for the conversion with both aromatic amines and aliphatic amines, in which the paraformaldehyde was utilized to mask the basicity of aliphatic amines to facilitate producing the key active Pd–H species.[9] Inspired by this result and in connection with our interests in the carbonylation reactions,[10] we present herein a practical and efficient palladium-catalytic system for the hydroaminocarbonylation of simple alkenes with both aromatic and aliphatic amines under CO atmosphere, thus allowing the synthesis of the linear amides with high selectivity (Scheme 2). The stoichiometric amount of weak acid used in this catalytic system has been identified as an effective basicity-mask to overcome the basicity barrier imparted by the aliphatic amines and thus facilitating the hydroaminocarbonylation. Notably, in a one-pot manipulation, the Propanil and

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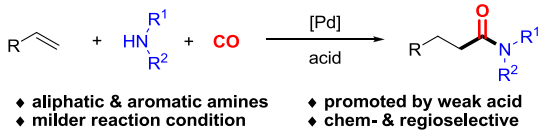


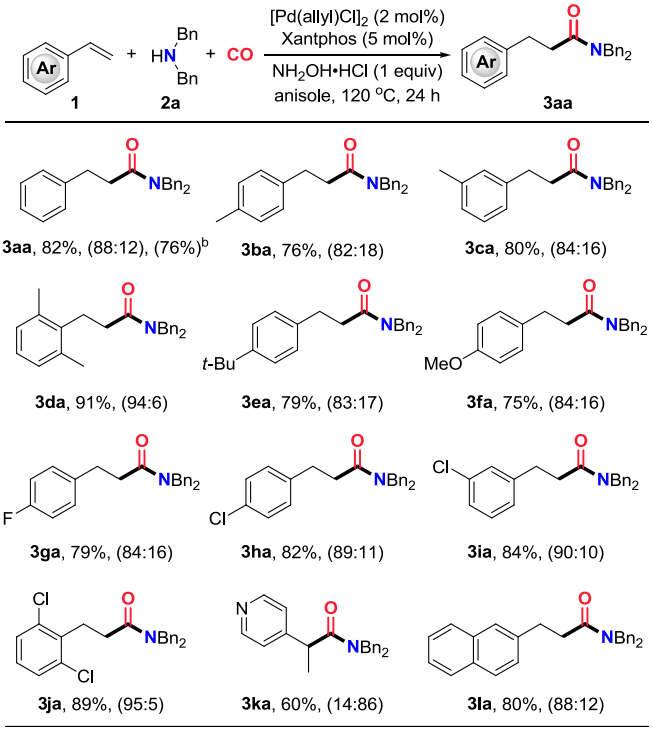
Scheme 2. Catalytic hydroaminocarbonylation of alkenes.

Fentanyl can be obtained in gram scale with high yields from simple ethene and corresponding amines.

Results and discussion

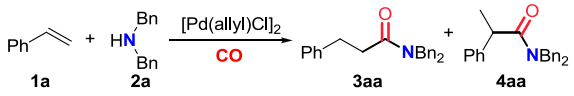
On the basis of our experience with palladium catalyzed hydroaminocarbonylation reactions, styrene (**1a**) and dibenzylamine (**2a**) were chosen as model substrates, and the reaction was performed under 10 atm of CO at 120 °C for 24 h. With DPPPen as the ligand and $[Pd(allyl)Cl]_2$ as the catalyst precursor, the reaction proceeded well in the presence of one equivalent of $NH_2OH{\cdot}HCl$ to give the desired amide in 89% yield with relatively lower regioselectivity (Table 1, entry 1). Encouraged by this result, various phosphine ligands were examined (Table 1, entries 2–9) and it was found that Xantphos was the most effective, affording 99% yield of the desired products with good regioselectivity. Next, various acids were evaluated. Only a trace amount of the product was detected when organic acids, such as HCO_2H, CH_3CO_2H, and $NH_2CH_2CO_2H$ served as additives (Table 1, entries 10–12). In addition, other acids such as TsOH, $NH_2CH_2CO_2Me{\cdot}HCl$, $NH(Me)(OMe){\cdot}HCl$, and $NEt_3{\cdot}HCl$ did not improve the reactivity and regioselectivity for this carbonylation reaction (Table 1, entries 13–17). Finally, control experiments revealed that both the palladium catalyst and acid are essential to this reaction (Table 1, entry 18).

With the optimized reaction conditions established, substrate scope of the styrenes was first investigated and the results are summarized in Scheme 3. Styrenes with various substituents on the *para*-, *meta*-, and *ortho*-positions, such as alkyl-, alkoxy-, and halogen groups, were suitable to give the corresponding products **3aa**–**3ja** in good to excellent yields with high regioselectivity. The *ortho*-substituted alkenes exert positive effect on the reactivity



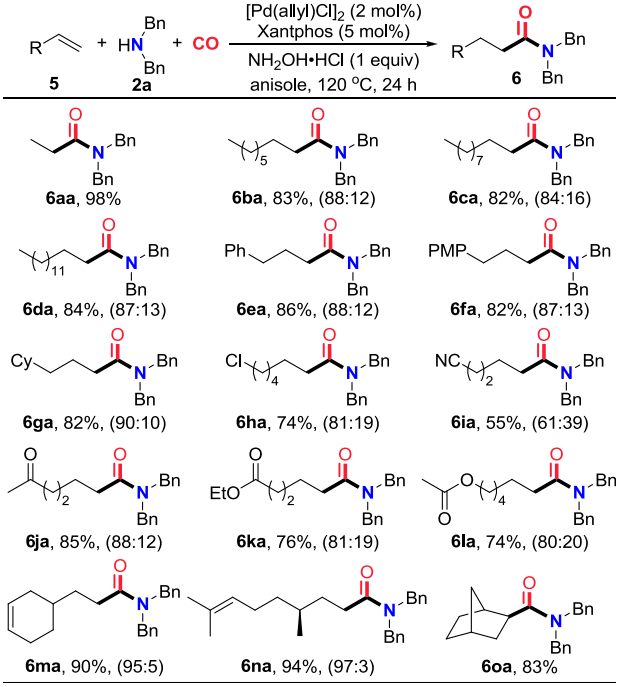
Scheme 3. Scope of aromatic alkenes[a]. [a]Reaction conditions: **1** (1.0 mmol), **2a** (0.5 mmol), $[Pd(allyl)Cl]_2$ (0.01 mmol), Xantphos (0.025 mmol), $NH_2OH{\cdot}HCl$ (0.5 mmol), anisole (2.0 mL), CO (10 atm), 120 °C, 24 h. Isolated of **3**; the **L/B** within parentheses were determined by GC and GC–MS analyses. [b]Gram scale.

Table 1
Optimization of reaction conditions[a]



Entry	Ligand	Acid	**3 + 4** (%)[b]	**3/4**[c]
1	DPPPen	$NH_2OH{\cdot}HCl$	89	70:30
2	DPPB	$NH_2OH{\cdot}HCl$	<5	—
3	DPPH	$NH_2OH{\cdot}HCl$	76	33:65
4	BINAP	$NH_2OH{\cdot}HCl$	<5	—
5	DPEphos	$NH_2OH{\cdot}HCl$	49	84:16
6	Xantphos	$NH_2OH{\cdot}HCl$	99	88:12
7	NiXantphos	$NH_2OH{\cdot}HCl$	99	84:16
8	*t*-BuXantphos	$NH_2OH{\cdot}HCl$	<5	—
9	PPh_3[d]	$NH_2OH{\cdot}HCl$	<5	—
10	Xantphos	HCO_2H	8	77:23
11	Xantphos	CH_3CO_2H	7	72:28
12	Xantphos	$NH_2CH_2CO_2H$	5	88:12
13	Xantphos	TsOH	43	88:12
14	Xantphos	NH_2SO_3H	82	77:23
15	Xantphos	$NH_2CH_2CO_2Me{\cdot}HCl$	65	88:12
16	Xantphos	$NH(Me)(OMe){\cdot}HCl$	82	82:18
17	Xantphos	$NEt_3{\cdot}HCl$	23	75:25
18	Xantphos	—	<5	—

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), $[Pd(allyl)Cl]_2$ (0.01 mmol), ligand (0.025 mmol), acid (0.5 mmol), anisole (2.0 mL), CO (10 atm), 120 °C, 24 h.
[b] Yields were determined by GC analysis using *n*-cetane as the internal standard.
[c] The ratios of **3aa**:**4aa** (**L/B**) were determined by GC and GC–MS analyses.
[d] PPh_3 (0.05 mmol).



Scheme 4. Scope of aliphatic alkenes. Reaction conditions: **5** (1.0 mmol), **2a** (0.5 mmol), $[Pd(allyl)Cl]_2$ (0.01 mmol), Xantphos (0.025 mmol), $NH_2OH{\cdot}HCl$ (0.5 mmol), anisole (2.0 mL), CO (10 atm), 120 °C, 24 h. Isolated of **6**; the **L/B** within parentheses were determined by GC and GC–MS analyses.