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Highly Ligand-Controlled Regioselective Pd-Catalyzed Aminocarbonylation of Styrenes with Aminophenols

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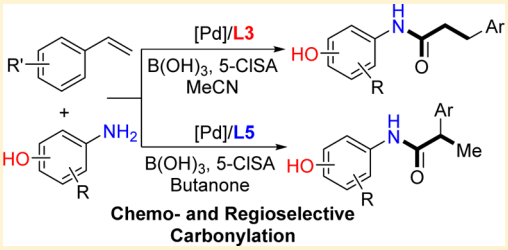
Supporting Information

ABSTRACT: Achieving chemo- and regioselectivity simultaneously is challenging in organic synthesis. Transition metal-catalyzed reactions are effective in addressing this problem by the diverse ligand effect on the catalyst center. Ligand-controlled regioselective Pd-catalyzed carbonylation of styrenes with aminophenols was realized, chemoselectively affording amides. Using a combination of boronic acid and 5-chlorosalicylic acid as the additives, linear amides were obtained in high yields and selectivity using tris(4-methoxyphenyl)phosphine (**L3**) in acetonitrile, while branched amides were obtained in high yields and selectivity in butanone by changing the ligand to 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (**L5**). Further studies show that the nature of the ligand is key to the regioselectivity. Cone angle and Tolman electronic parameter (TEP) have been correlated to the reactivity and regioselectivity. Studies on the acid additives show that different acids act as the proton source and the corresponding counterion can help enhance the reactivity and selectivity.



INTRODUCTION

Achieving selective transformations is a key goal in organic synthesis including chemoselectivity for reactive functional groups, regioselectivity for unsaturated chemical bonds, enantioselectivity for chiral centers, etc. There are challenges for traditional chemical synthesis for selective functionalization. Fortunately, catalysis provides genuine opportunities to attain these objectives.[1,2] For example, transition-metal catalysts have been developed with palladium complexes being widely used for different applications.[3] Furthermore, ligand design affords more opportunities for palladium catalysts by subtly tuning the electronic property of the catalytic center.[4]

Amides are important motifs in natural products, materials, bioactive compounds and synthetic intermediates.[5] Traditionally, activation of carboxylic acids and coupling reagents are used to synthesize amides, which could produce stoichiometric amounts of waste and increase the cost for industrial production.[6] Transition metal-catalyzed aminocarbonylation of aryl (pseudo)halides or unsaturated compounds (alkenes, alkynes, allenes, dienes, etc.) is a promising alternative for the synthesis of diverse functionalized amides.[7,8] Compared with alkoxycarbonylation of alkenes,[9] there are only a few of reports using Pd-catalyzed aminocarbonylation of alkenes and amines which represent an efficient and high atom economical route to produce amides.[10−12] Recently, Beller[11a] and Cole-Hamilton[11b] and co-workers independently reported the Pd-catalyzed aminocarbonylation of alkenes to form linear amides as major products, while Liu[11c] and co-workers developed a method to obtain branched amides as the principal products using $PdCl_2$/tris(2-methoxyphenyl)phosphine. Only aromatic amines were used in these cases.[10h,12] Later, Huang and co-workers developed a strategy to provide *N*-alkyl linear amides as the major products by using aminals or a combination of amine and paraformaldehyde as the amine sources.[11d] Despite these achievements, the methods could not reverse the selectivity to afford the other corresponding amides. Aminophenols which have more complex reactivity and electronic properties were not studied, and may not react under these conditions.[13] Relevant to the investigation of the effect of ligands and additives for Pd-catalyzed carbonylation,[14] we previously reported the carbonylation of aminophenols with iodoarenes to selectively form amides or esters directed by ligand/base pairs (Scheme 1, a).[14a] According to the conventional mechanism of alkoxy- and aminocarbonylation of alkenes, L_nPd-H intermediates are usually proposed as the key species to start the reaction and critical to the selectivity of the branched or linear products. We were wondering if the selectivity of the carbonylation reaction between alkenes and aminophenols could be altered by simply changing the ligands and/or additives (Scheme 1, b). The latter could be very useful synthetically and also provide some mechanistic insight. Herein we describe the first palladium based ligand-controlled regioselective aminocarbonylation of styrenes with aminophenols.

RESULTS AND DISCUSSION

Initially, the carbonylation of styrene (**1a**) and 4-aminophenol (**2a**) was used to optimize the reaction conditions (Table 1). In the presence of $PdCl_2/PPh_3$ and using THF as the solvent, the

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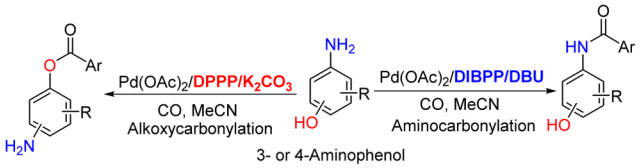
Scheme 1. Proposed Pathways for Pd-Catalyzed Selective Carbonylation of Aminophenols

(a) Pd-Catalyzed Chemoselective Carbonylation of Aminophenols with Iodoarenes



(b) Hypothesis for the Selective Carbonylation of Styrenes with Aminophenols

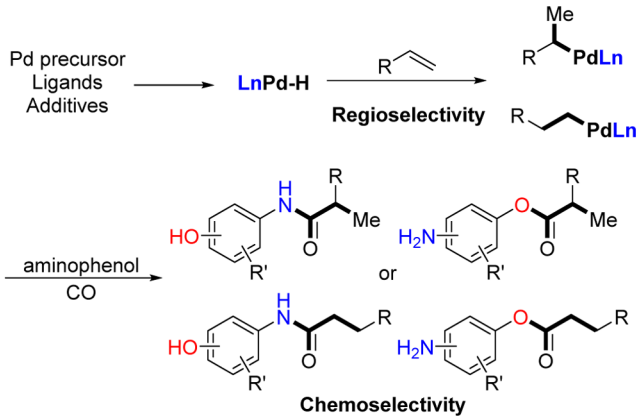
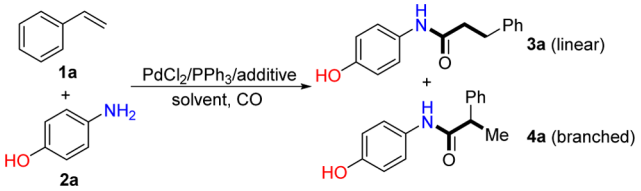


Table 1. Screening of the Reaction Conditions for the Carbonylation of Styrene with 4-Aminophenol[a]



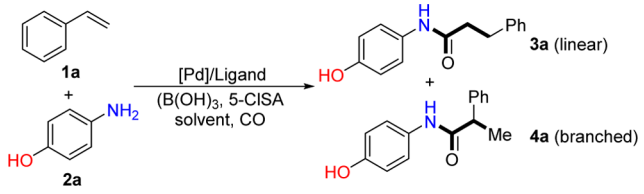
entry	additive (mol %)	solvent	yield (%)[b]	l/b[c]
1		THF	9	1/67
2		MeCN	43	2.6/1
3		DCE	15	1/17
4[d]		MeCN	0	
5	*p*-TsOH·H_2O/10	MeCN	83	2.1/1
6	*p*-TsOH·H_2O/10	DCE	32	1/8.7
7	*p*-TsOH·H_2O/10	THF	21	1/27
8	H_2 (20 bar)	MeCN	63	1.6/1
9	K_2CO_3/10	MeCN	0	
10	$B(OH)_3$/10	MeCN	44	1.9/1
11	$B(OH)_3$/10 SA/20	MeCN	73	3.4/1
12	$B(OH)_3$/10 5-ClSA/20	MeCN	85	3.7/1

[a]Conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % of Pd, Pd:P = 1:2, 5 mL of solvent, 20 bar of CO, 120 °C, 20–24 h. [b]Total isolated yield of **3a** and **4a**. [c]Determined by ^{1}H NMR. [d]Without PPh_3.

carbonylation of **1a** and **2a** afforded amides in 9% yield, and esters were not detected (Table 1, entry 1). When MeCN was used as the solvent, the yield of amides increased to 43%, with a 2.6/1 l/b ratio (entry 2). Branched amide **4a** was obtained as the major product in 15% total yield of amides when 1,2-dichloroethane (DCE) was used as the solvent (entry 3). Other solvents, such as toluene, DMF, DMSO, etc. were also studied, but gave poor results (see Table S1). No desired product was obtained in the absence of PPh_3 using MeCN as the solvent (entry 4). Different additives were investigated to improve the yield and selectivity of the reaction (see Table S2). The yield of amides increased when 10 mol % of *p*-TsOH·H_2O was added, affording the amides in 83%, 32% and 21% yields, respectivelyusin MeCN, DCE and THF as the solvent (entries 5–7). Hydrogen also promoted the carbonylation, affording amides in 63% yield but with poor selectivity (entry 8). When the inorganic base K_2CO_3 was used, none of the desired product was formed (entry 9). Boronic acid was also used as the additive, affording amides in 44% yield (entry 10, 1/b = 1.9/1). Then the effect of the combination of boronic acid and salicylic acid or 5-chlorosalicylic acid was studied,[9l,m,15] affording the amides in 73% and 85% yields, respectively, with higher selectivity for the linear amide (entries 11 and 12).

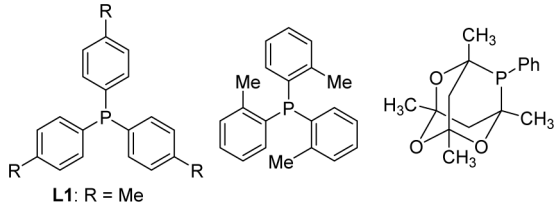
The effect of ligands and palladium precursors were further investigated using boronic acid and 5-chlorosalicylic acid as the additive in MeCN (Table 2). First, different substituted triphenylphosphines were studied (entries 1–4). The *para*-methyl substituted ligand **L1** can improve the selectivity for the linear amide, giving the former in a l/b ratio of 4.3/1, while the *ortho*-methyl substituted ligand **L2** provided no carbonylation (entries 1 and 2). The ligand tris(4-methoxyphenyl)phosphine (**L3**) afforded higher linear selectivity (entry 3, l/b = 4.5/1). A

Table 2. Effects of Ligands and Palladium Precursors[a]



entry	cat.	ligand	yield (%)[b]	l/b[c]
1	$PdCl_2$	L1	85	4.3/1
2	$PdCl_2$	L2	trace	
3	$PdCl_2$	L3	87	4.5/1
4	$PdCl_2$	L4	65	1.8/1
5	$PdCl_2$	L5	36	1/5
6	$Pd(OAc)_2$	L3	63	5.5/1
7	$Pd(PPh_3)_2Cl_2$	L3	84	4.8/1
8	$Pd(acac)_2$	L3	64	7/1
9	$Pd_2(dba)_3$	L3	75	5.5/1
10[d]	**$Pd(CH_3CN)_4(BF_4)_2$**	**L3**	**83**	**7.9/1**
11[d,f]	$Pd(CH_3CN)_4(BF_4)_2$	L3	66	5.9/1
12[e,f]	**$PdCl_2$**	**L5**	**96**	**1/40**

[a]Conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % of Pd, Pd:*P* = 1:2, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of MeCN, 20 bar of CO, 120 °C, 20–24 h. [b]Total isolated yield of **3a** and **4a**. [c]Determined by ^{1}H NMR. [d]60 h. [e]48 h. [f]Butanone instead of MeCN.



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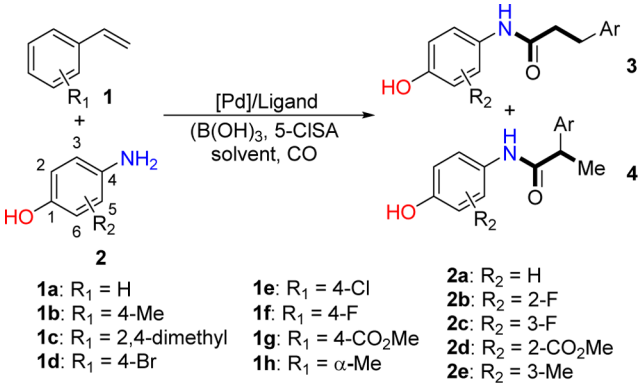
ligand with electron-withdrawing substituents such as fluorine (**L4**) decreased the yield and selectivity (entry 4). However, electron-rich ligands tris(4-dimethylaminophenyl)phosphine or tributylphosphine gave only traces of amides, while poor results were obtained using the bidentate ligands dppp or 1,10-Phen (see Table S3). Interestingly, when a phospha-adamantane ligand **L5** (1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6- phosphaadamantane) was used, the regioselectivity was reversed, affording the branched amide as the major product (entry 5). The results demonstrate that the ligands can significantly influence the selectivity and the yield. Furthermore, different palladium precursors were investigated using **L3** as the ligand, including $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(acac)_2$, $Pd_2(dba)_3$, etc. (see Table S4). Among the precursors, the cationic catalyst $Pd(CH_3CN)_4(BF_4)_2$ gave the best selectivity for the linear amide **3a** (entry 10, 83% yield, l/b = 7.9/1). Efforts were then attempted to selectively form the branched amide in high yield, but the product yields were modest (<40% yield). We tried to reverse the chemoselectivity to obtain the ester by using acetone as a masked reagent, but these conditions still afforded the amides. When butanone was used as the solvent instead of MeCN, the amides were obtained in 66% yield in a 5.9/1 l/b ratio using boronic acid and 5-chlorosalicylic acid as the additive in the presence of $Pd(CH_3CN)_4(BF_4)_2$/**L3** (entry 11). Considering the ligand **L5** could reverse the regioselectivity, butanone was used as the solvent in the $PdCl_2$/**L5** system, affording the branched amide in high yield and regioselectivity (entries 5 and 12). The results indicate that the synergistic effect of ligand, additive and solvent can effectively reverse the regioselectivity and yield.

The regioselective carbonylation of styrenes and 4-aminophenols was then applied under conditions **A** and **B** (Table 3). Both electron-donating and electron-withdrawing substituted styrenes reacted with 4-aminopheol smoothly, affording branched or linear amides in high regioselectivity (Table 2, entries 1−7). Styrenes with electron-donating substituents gave lower yields and regioselectivity under condition **B** (**4a**−**e**), while electron-withdrawing substituents on styrenes have little effect on the yields of amides (**1e**−**g**, entries 5−7). The steric effect seems to be more influential than the electronic effect for styrene **1c** with an *ortho*-methyl substituent, strongly favoring the formation of the linear amide **3c** under **A** conditions, but disfavored the formation of the branched amide **3c** under **B** conditions (entries 2 and 3). Substituents with greater electron-withdrawing ability (Br, Cl and F) could lead to higher selectivity for the branched amides under condition **B** (entries 4−6). Notably, the C−Br bond in 4-bromostyrene remained intact under both conditions (entry 4). Different substituted 4-aminophenols were applied to the selective carbonylation with styrene. The yields and selectivity for linear amides decreased for 4-aminophenols with electron-donating or electron-withdrawing substituents under condition **A** (entries 8−11). Substrates with electron-withdrawing substituents (F, CO_2Me) reacted with styrene under condition **B**, affording amides in slightly lower yields (entries 8−10). The position of the fluorine substituent on the 4-aminophenol led to selectivity differences (entries 8 and 9), which might be due to the different electron-withdrawing effects at the *ortho*- or *meta*-position of NH_2. Electron-withdrawing substituents on 4-aminophenols can increase the selectivity for the branched amide (entries 9 and 10). Substrate **2e** with a methyl substituent *ortho* to the amino group, formed amides with little change in yield and only a slight decrease in regioselectivity (**4k**, entry 11). When *α*-methylstyrene (**1h**) reacted with 4-aminophenol, high selectivity for the linear amide **3l** was achieved under condition **A** and only trace product was observed under condition **B** (entry 12), indicating that the regioselectivity could be dramatically affected by the steric effect of the double bond of the styrene.

Table 3. Selective Carbonylation of Styrenes with 4-Aminophenols[a]



1a: R_1 = H
1b: R_1 = 4-Me
1c: R_1 = 2,4-dimethyl
1d: R_1 = 4-Br
1e: R_1 = 4-Cl
1f: R_1 = 4-F
1g: R_1 = 4-CO_2Me
1h: R_1 = α-Me
2a: R_2 = H
2b: R_2 = 2-F
2c: R_2 = 3-F
2d: R_2 = 2-CO_2Me
2e: R_2 = 3-Me

			condition **A**		condition **B**	
entry	1	2	major/yield (%)[b]	3/4[c]	major/yield (%)[b]	4/3[c]
1	**1a**	**2a**	**3a**/83	7.9	**4a**/96	40
2	**1b**	**2a**	**3b**/71	6.5	**4b**/64	33
3	**1c**	**2a**	**3c**/74	13	**4c**/67	4
4	**1d**	**2a**	**3d**/83	6.4	**4d**/65	10
5	**1e**	**2a**	**3e**/80	9.1	**4e**/92	25
6	**1f**	**2a**	**3f**/83	8.8	**4f**/91	33
7	**1g**	**2a**	**3g**/81	9.7	**4g**/92	25
8	**1a**	**2b**	**3h**/68	7.1	**4h**/82	5.1
9	**1a**	**2c**	**3i**/70	4.3	**4i**/77	33
10	**1a**	**2d**	**3j**/61	6.5	**4j**/79	67
11	**1a**	**2e**	**3k**/65	7.1	**4k**/93	33
12	**1h**	**2a**	**3l**/50	27	trace	

[a]Condition **A**: 0.5 mmol of **1**, 0.5 mmol of **2**, 5 mol % $Pd(CH_3CN)_4(BF_4)_2$, 10 mol % **L3**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of MeCN, 20 bar of CO, 120 °C, 60 h; Condition **B**: 0.5 mmol of **1**, 0.5 mmol of **2**, 5 mol % $PdCl_2$, 10 mol % **L5**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of butanone, 20 bar of CO, 120 °C, 48 h. [b]Total isolated yield of **3** and **4**. [c]Determined by ^{1}H NMR.

Next, the reaction conditions were applied to the carbonylation of styrenes with 3-aminophenols (Table 4). When 3-aminophenol (**2f**) reacted with styrene (entry 1), there was high selectivity for the linear amide **3m** under condition **A** (l/b = 9.1), but much lower selectivity for the branched amide **4m** under condition **B** (b/l = 5.3). The yield and selectivity of **4m** could be improved by using two equivalents of **2f** (b/l = 20). The possible formation of imine may be the reason that the carbonylation of 3-aminophenols was more complicated than 4-aminophenols under condition **B**. The position of substituents on 3-aminophenols (**2g** and **2h**) also influenced the yields and regioselectivity (entries 2 and 3). When **2i** with a fluorine group at the ortho position of the amino substituent, was applied to the reaction, affording the linear amide **3p** (condition **A**) and branched amide **4p** (condition **B**) in 24% and 93% yields, respectively (entry 4). The carbonylation of styrenes **1c** and **1f** with 3-aminophenol afforded the corresponding amides in moderate to good yields, respectively, showing the substantial steric effect in the formation of **4q** (entries 5 and 6).

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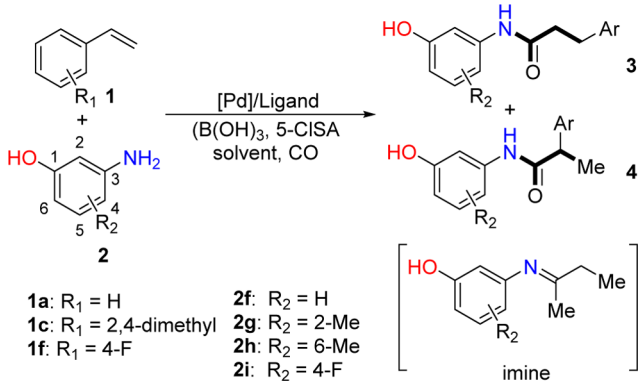
Table 4. Selective Carbonylation of Styrenes with 3-Aminophenols[a]



1a: R_1 = H
1c: R_1 = 2,4-dimethyl
1f: R_1 = 4-F

2f: R_2 = H
2g: R_2 = 2-Me
2h: R_2 = 6-Me
2i: R_2 = 4-F

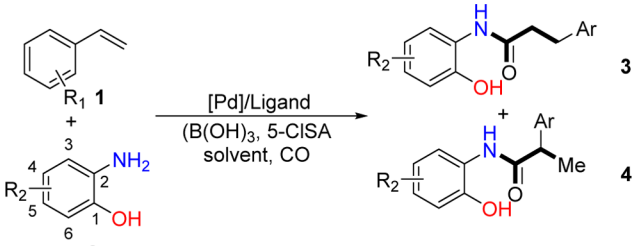
			condition A		condition B	
entry	1	2	major/yield (%)[b]	3/4[c]	major/yield (%)[b]	4/3[c]
1	**1a**	**2f**	**3m**/65	9.1	**4m**/71 (65)[d]	20 (5.3)[d]
2	**1a**	**2g**	**3n**/64	12	**4n**/86	40
3	**1a**	**2h**	**3o**/65	8.3	**4o**/46	10
4	**1a**	**2i**	**3p**/24	7.7	**4p**/93	50
5	**1c**	**2f**	**3q**/65	9.1	**4q**/45	4.3
6	**1f**	**2f**	**3r**/75	11	**4r**/62	18

[a]Condition **A**: 0.5 mmol of **1**, 0.5 mmol of **2**, 5 mol % $Pd(CH_3CN)_4(BF_4)_2$, 10 mol % **L3**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of MeCN, 20 bar of CO, 120 °C, 60 h; Condition **B**: 0.5 mmol of **1**, 1.0 mmol of **2**, 5 mol % $PdCl_2$, 10 mol % **L5**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of butanone, 20 bar of CO, 120 °C, 24 h. [b]Total isolated yield of **3** and **4**. [c]Determined by ^{1}H NMR. [d]Using 0.5 mmol of **2f**.

The regioselective carbonylation was also successfully applied to the reactions of styrenes with 2-aminophenols, affording amides in moderate to good yields and in fine regioselectivity (Table 5). When 2-aminophenol (**2j**) reacted with 2,4-dimethylstyrene (**1c**) and 4-fluorostyrene (**1f**), respectively, the results showed a similar trend to 3- and 4-aminophenols (entries 1−3). 2-Amino-4-cholorophenol (**2k**) reacted with styrene in a similar manner to that of **2j** (entry 4). However, 2-amino-4-*tert*-butyl-phenol (**2l**) reacted with styrene affording higher regioselectivity for both linear and branched amides under conditions **A** and **B**, respectively, which indicated different substituent effects from that of 3- or 4-aminophenols (entry 5). The adjacent hydroxyl group may be a contributing factor here.

Control reactions of styrene with a mixture of 4-methylaniline and 4-methylphenol were carried out to verify the chemo- and regioselectivity of the reaction (eq 1). We were pleased to find that our method worked well in the presence of 4-methylphenol, affording the linear amide **7a** in 60% (condition **A**) and the branched amide **7b** in 91% (condition **B**) isolated yields, respectively. The possible formation of imine did not affect the conversion and selectivity. In addition, no ester was formed. Styrene **1i** with a hydroxyl substituent was also applied to the carbonylation reaction with 4-aminophenol, affording the branched amide **8a** as the major product under both conditions **A** and **B** (eq 2). The coordination of the hydroxyl group to palladium may reverse the selectivity under **A** conditions, which promoted the formation of the branched amide under **B** conditions (b/l > 100).

Table 5. Selective Carbonylation of Styrenes with 2-Aminophenols[a]

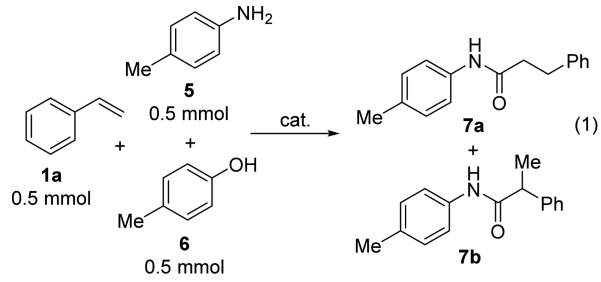


1a: R_1 = H
1c: R_1 = 2,4-dimethyl
1f: R_1 = 4-F

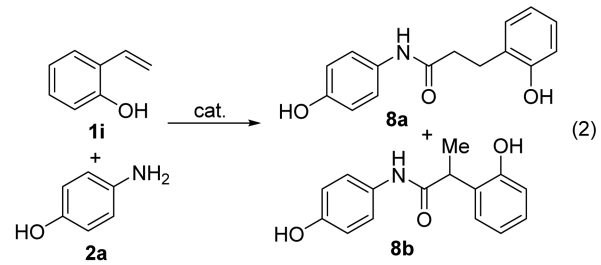
2j: R_2 = H
2k: R_2 = 4-Cl
2l: R_2 = 4-^{t}Bu

			condition A		condition B	
entry	1	2	major/yield (%)[b]	3/4[c]	major/yield (%)[b]	4/3[c]
1	**1a**	**2j**	**3s**/45	5.6	**4s**/90 (47)[d]	40 (29)[d]
2	**1c**	**2j**	**3t**/58	7.5	**4t**/62	11
3	**1f**	**2j**	**3u**/64	9.4	**4u**/78	50
4	**1a**	**2k**	**3v**/63	5	**4v**/78	42
5	**1a**	**2l**	**3w**/59	7.7	**4w**/55	67

[a]Condition **A**: 0.5 mmol of **1**, 0.5 mmol of **2**, 5 mol % $Pd(CH_3CN)_4(BF_4)_2$, 10 mo % **L3**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of MeCN, 20 bar of CO, 120 °C, 60 h; Condition **B**: 0.5 mmol of **1**, 1.0 mmol of **2**, 5 mol % $PdCl_2$, 10 mol % **L5**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of butanone, 20 bar of CO, 120 °C, 48 h. [b]Total isolated yield of **3** and **4**. [c]Determined by ^{1}H NMR. [d]Using 0.5 mmol of **2k**.



	condition A	condition B
1a + mixture of **5** and **6**	67%, **7a**/**7b** = 9	93%, **7b**/**7a** = 57
1a + **5**	85%, **7a**/**7b** = 8.8	96%, **7b**/**7a** = 60



condition **A**: 44% total yield, **8b**:**8a** = 3.2:1
condition **B**: 43% total yield, **8b**:**8a** > 100:1

The aminocarbonylation of *β*-methylstyrene, allylbenzene and 1-dodecene with 4-aminophenol was then investigated (Scheme 2). The carbonylation of *β*-methylstyrene with **2a** afforded the same products as that of allylbenzene, forming *γ*-amidation product **9a** as the principal product under condition **A** but no product was obtained using condition **B** (eq 3). The amide **9a** may be formed by the addition and elimination of

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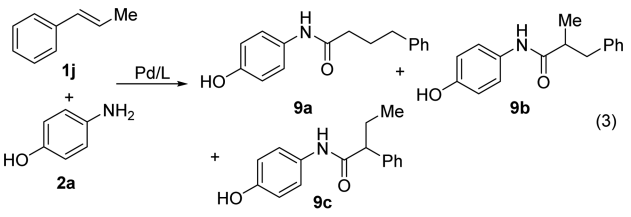
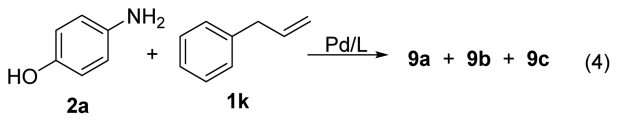
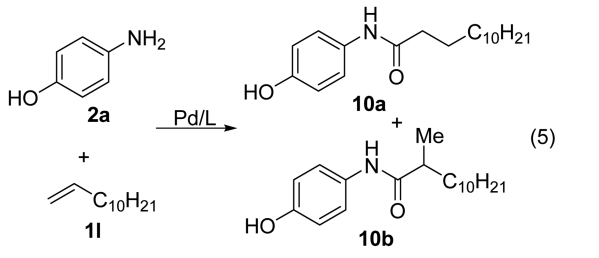
Scheme 2. Aminocarbonylation of β-Methylstyrene, Allylbenzene and 1-Dodecene with 4-Aminophenol







L_nPd-H to the double bond. The reaction cannot occur under condition **B** due to steric hindrance. When both conditions were applied to allylbenzene, three products were detected, but with a high linear selectivity under condition **A**. The linear amide **10a** was the major product for the carbonylation of 1-dodecene, but condition **A** afforded higher yield and linear selectivity. These results indicate that the L_nPd-H species might be the key intermediate to start the reaction, and has strict steric requirements.

Different acids were used as additive instead of the combination of boronic acid and 5-chlorosalicylic acid (Table 6). *p*-TsOH·H_2O afforded a similar yield and linear amide selectivity to that of boronic acid and 5-chlorosalicylic acid, while CH_3COOH and CF_3SO_3H gave a lower linear selectivity under condition **A**. However, poor yield of amides was obtained when CH_3COOH was used under condition **B**, the other additives CF_3SO_3H, *p*-TsOH·H_2O and $B(OH)_3$/5-ClSA afforded high yield and selectivity for branched amide. These results show that additives work as the proton source for the carbonylation, but the corresponding counterion can affect the yield and selectivity.

Table 6. Effect of Acid Additives in the Carbonylation of 1a and 2a under Condition A and B[a]

		condition A		condition B	
entry	acid	yield (%)[b]	3a/4a[c]	yield (%)[b]	4a/3a[c]
1	CH_3COOH	79	5.9	35	27
2	CF_3SO_3H	87	6.5	94	66
3	*p*-TsOH·H_2O	74	8.3	97	54
4	$B(OH)_3$/5-ClSA	83	7.9	96	40

[a]Condition **A**: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % $Pd(CH_3CN)_4(BF_4)_2$, 10 mo % **L3**, 10 mol % acid, 5 mL of MeCN, 20 bar of CO, 120 °C, 60 h; Condition **B**: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % $PdCl_2$, 10 mol % **L5**, 10 mol % acid, 5 mL of butanone, 20 bar of CO, 120 °C, 48 h. [b]Total isolated yield of **3a** and **4a**. [c]Determined by ^1H NMR.

The properties of ligands such as cone angle and Tolman electronic parameter (TEP),[16] were used to study the effects of the ligand on the reactivity and selectivity (Table 7 and Table S3). First, the ligand effect for the selective formation of the linear amide was studied. Compared with PPh_3, more electron-donating ligands without changing of cone angle, such as P(*p*-$MeC_6H_4)_3$ and P(*p*-$MeOC_6H_4)_3$, afforded higher selectivity for the linear amide **3a** (entries 1, 2 and 4), while less electron-donating ligand P(*p*-$FC_6H_4)_3$ resulted in lower selectivity and yield (entry 5). On the other hand, ligands P(*p*-$MeC_6H_4)_3$ and P(*o*-$MeC_6H_4)_3$ have similar electron-donating ability; however, P(*o*-$MeC_6H_4)_3$ shows a dramatic steric effect and gave no product (entries 2 and 3). The ligand with strong electron-donating ability or much less electron-donating ability shows no reactivity for the reaction (entries 6 and 7).

Table 7. Effect of Ligands on the Selective Formation of the Linear Amide 3a[a]

entry	ligand	cone angle (deg)	TEP	yield (%)[b]	3a/4a[c]
1	PPh_3	145	2068.9	85	3.7
2	P(*p*-$MeC_6H_4)_3$	145	2066.7	85	4.3
3	P(*o*-$MeC_6H_4)_3$	194	2066.6	trace	
4	P(*p*-$MeOC_6H_4)_3$	145	2066.1	87	4.5
5	P(*p*-$FC_6H_4)_3$	145	2071.3	65	1.8
6	PBu_3	132	2060.3	trace	
7	$P(C_6F_5)_3$	184	2090.9	trace	

[a]Conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % $PdCl_2$, 10 mo % **L3**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of MeCN, 20 bar of CO, 120 °C, 20–24 h. [b]Total isolated yield of **3a** and **4a**. [c]Determined by ^1H NMR.

Then the effect of ligands on the selectivity of the branched amide **4a** was studied (Table 8). Ligands with strong electron-donating ability and bulky structure, such as $P(Cy)_3$, P(*t*-$Bu)_3$ and di(1-adamantyl)-*n*-butylphosphine (cataCXiumA), were used instead of **L5**, selectively affording the branched amide in high yield and selectivity. And the ligand with larger cone angle gave better regioselectivity (entries 1 and 2).

Table 8. Effect of Ligands on the Selective Formation of the Branched Amide 4a[a]

entry	ligand	cone angle (deg)	TEP	yield (%)[b]	4a/3a[c]
1	$P(Cy)_3$	170	2056.4	89	21
2	P(*t*-$Bu)_3$	182	2056.1	81	51
3	L5			96	40
4	cataCXiumA			98	53

[a]Conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % $PdCl_2$, 10 mol % **L5**, 10 mol % of $B(OH)_3$, 20 mol % of 5-ClSA, 5 mL of butanone, 20 bar of CO, 120 °C, 48 h. [b]Total isolated yield of **3a** and **4a**. [c]Determined by ^1H NMR.

On the basis of our experimental results, a possible reaction mechanism is proposed in Scheme 3. Initially, the L_nPd-H intermediate (**I**) could be formed from the palladium catalyst precursor, ligand and additives. The starting materials styrenes

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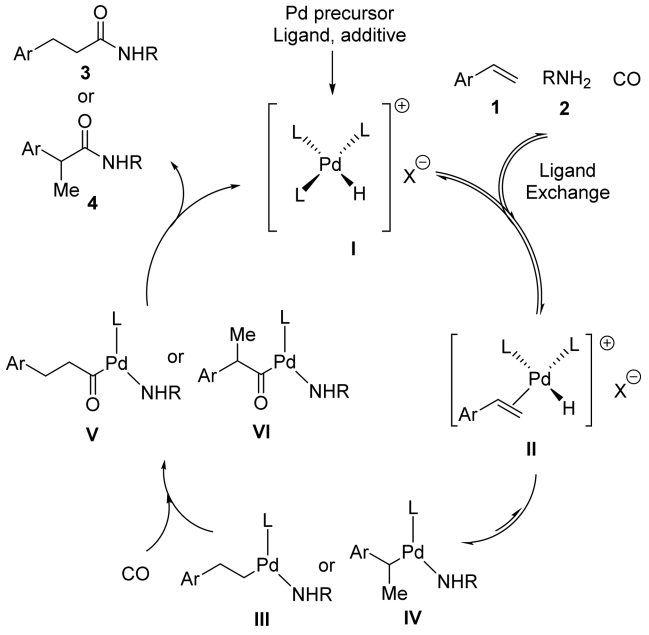
Scheme 3. Proposed Mechanism for the Selective Carbonylation



(**1**), aminophenol (**2**), CO and even solvent molecule can coordinate to palladium by exchanging with the ligands in (**I**) to form intermediate (**II**). This process may be reversible but critical for the catalytic cycle. The ligand should allow the coordination of styrene to palladium and protect the catalyst from poisoning by the aminophenol which has strong coordination ability. For example, 1,10-Phen or $P(C_6F_5)_3$ has no reactivity. Then insertion of styrene to Pd−H could form intermediate (**III**) or (**IV**). In this step, the regioselectivity was determined by the nature of the ligand. The corresponding counterion can assist to improve the selectivity. In our previous work, we found the combination of ligands and bases can tune the chemoselectivity of aminophenols to selectively form amides or esters. In the case of the carbonylation of alkenes, the reaction environment is acidic, which seems to assist the chemoselectivity to form amides.

The electronic property of the catalytic metal center is critical to the catalytic activity and selectivity. To selectively get the branched amides means formation of the Pd−C bond at the internal carbon of the double bond of styrene, which is electronically favored by using the bulky and electron-rich ligand. And the conjugation with the aromatic ring can increase the regioselectivity. So styrenes with an electron-withdrawing group afford higher branched selectivity (Table 3, entries 1, 2, and 4−6, Me, Br, Cl, F). When the electronic preference between internal and terminal carbon was reduced, the selectivity for branched product dropped. For example, when reactions utilizing allylbenzene or 1-dodecene were subjected to conditions **A** and **B**, linear amides were obtained as the major product because there is much less difference electronically of the two carbons of double bond. The steric effect has more influence for the selectivity which favors the linear product. On the contrary, ligand **L3** (tris(4-methoxyphenyl)phosphine) could dramatically reduce the electronic preference of styrene by acting on the Pd center, and make the steric effect as the determining factor to selectively form the linear amides.

After formation of intermediates (**III**) and (**IV**) from (**II**) by insertion of the double bond to Pd−H, acyl Pd intermediate (**V**) and (**VI**) could be formed by CO insertion. The RHN(C═O)Pd species cannot be ruled out as an intermediate, because urea formation was detected.[17] Finally, reductive elimination generates the product and releases the catalyst.

CONCLUSION

In summary, we have developed the ligand-controlled selective aminocarbonylation of styrenes with aminophenols using the same additives, affording branched or linear amide by simply changing the ligand. These results demonstrate that the ligand properties are critical to the selectivity of the carbonylation process. Preliminary mechanistic analysis shows the regioselectivity is dependent on the ligands.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03161.

Additional experimental results, experimental procedures and spectral data. (PDF)

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Notes

The authors declare no competing financial interest.

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