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Ligand- and Additive-Controlled Pd-Catalyzed Aminocarbonylation of Alkynes with Aminophenols: Highly Chemo- and Regioselective Synthesis of *α,β*-Unsaturated Amides

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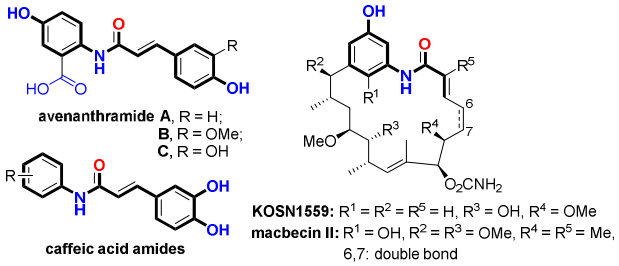
ABSTRACT: This work describes the chemo- and regioselective direct aminocarbonylation of alkynes and aminophenols to form hydroxy-substituted *α,β*-unsaturated amides in good-to-excellent yields. The latter are valuable compounds in pharmaceuticals and natural products. By simply choosing different ligands and additives, branched or linear isomers could be selectively formed in excellent regioselectivity. Using a combination of boronic acid and 5-chlorosalicylic acid ('BCSA') as the additives, linear amides were obtained in high yields and selectivities using 1,2-*bis*(di*tert*butylphosphinomethyl)benzene (DTBPMB) as the ligand. On the other hand, branched amides could be approached by introducing 1,3-*bis*(diphenylphosphino)propane as the ligand and *p*-TsOH·H_2O as the additive. In addition to the hydroxyl group, other functional substituents, such as carboxyl and vinyl groups could also be tolerated using this method. As the application of this strategy, the natural product avenanthramide **A** could be synthesized directly in 84% yield and in 99% regioselectivity *via* the carbonylation of 2-amino-5-hydroxybenzoic acid and 4-ethynylphenol. Further studies show that the ligands and the additives are key to good yields and selectivity.

INTRODUCTION

α,β-Unsaturated amides are important intermediates in organic synthesis, functional subunits in materials, natural products and biological systems, and are of pharmaceutical interest as active structures.[1-4] For instance (Fig. 1), avenanthramides, a group of oat phenolics demonstrating antiinflammatory and antioxidant capability, have been widely used as nutrition additives and in clinical trials.[2] The caffeic acid amides, which are abundant in nature, are extremely versatile and have a number of biologically active properties such as antitumor, antiviral, and MMP-2/9 inhibitory activity.[3] Moreover, the derivatives of geldanamycin KOSN1559 and macbecin II are highly efficient Hsp90 inhibitors in the area of antitumor agents.[4] However, only limited methods are known to directly synthesize *α,β*-unsaturated amides compared with their ester counterparts. Conventional strategies to generate *α,β*-unsaturated esters, such as aldol condensation,[5a-c] Wittig,[5d-f] and Horner-Wadsworth-Emmons reactions,[5f-i] are not transplantable, since the acidic hydrogen (N-H) is not compatible under the basic conditions. *α,β*-Unsaturated amides can be prepared *via* nucleophilic substitution of activated carboxylic acid derivatives.[1a,6] However, some starting materials are not easy to access, and certain functional groups, such as the OH and CO_2H groups of substrates, are not tolerated here. Furthermore, these methods usually use at least a stoichiometric amount of the coupling reagent, and produce waste. Recently, new methods have been developed to prepare amides, but many of them suffer from multiple steps, complicated substrates, or the need for activating reagents.[6c,d,7] An important objective is to construct *α,β*-unsaturated amides directly and selectively with readily available reactants in an atom-economic and environmentally benign mannar.[8]

Figure 1. Examples of the Applications of Hydroxyl-*α,β*-unsaturated Amides.

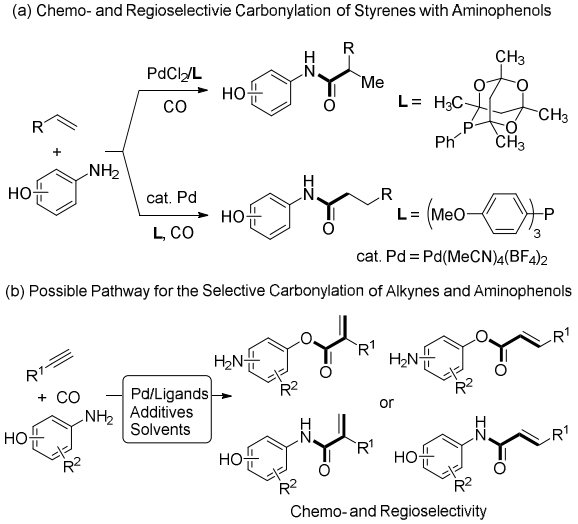


Carbonylation reactions can provide a facile approach to amides through the assembly of unsaturated compounds,[9a-e] halides,[9a,b,f-h] amines and CO in one step. By choosing appropriate transition-metal catalysts and ligands, high chemo-, regio- and stereoselectivity can be realized.[9-10] Since the pioneering work of Reppe,[11] the transition-metal catalytic carbonylation of alkenes, alkynes,

1,3-dienes or allenes has been developed and provides a promising strategy for the selective preparation of diverse carbonyl compounds.[9a-e,12-14] *α,β*-Unsaturated amides could be obtained directly by using alkynes by this methodology. However, in contrast to alkenes,[13] there have only been a few examples showing the selective synthesis of amides *via* the aminocarbonylation of alkynes, and most of these publications focused on the preparation of branched *α,β*-unsaturated amides (2-substituted acrylamides).[9a,14a-m] For example, 2-substituted acrylamides could be selectively obtained by the Pd-catalyzed aminocarbonylation of alkynes in a strong acidic medium, in an ionic liquid [bmin][Tf_2N] or in the presence of organic iodides, H_2 or sulfonic acids (MsOH, *p*-TsOH).[14a-l] Through the tin-radical-catalyzed carbonylation pathway, acrylamides were formed by the coupling of alkynes, alkyl amines and CO.[14m] Thus far, few examples demonstrate the preference for the linear *α,β*-unsaturated amides.[14g,h,n] In 2002, EI Ali and co-workers attempted to prepare branched or linear amides selectively, but the linear selectivity was not high, and only aliphatic alkynes were used.[14g,h] Recently, Beller and co-workers investigated the synthesis of *N*-alkyl linear amides with $Fe_3(CO)_{12}$ catalysis, yet the application scope was quite limited using alkyl amines.[14n] To our knowledge, there is no example of successful research leading to the synthesis of both the linear and branched *α,β*-unsaturated amides with broad substrate scope and high regioselectivity.

Recently, we successfully introduced aminophenols as nucleophiles for the Pd-catalyzed aminocarbonylation of alkenes, and the OH group was retained in the final products. With the employment of different ligands, branched or linear amides were isolated in good yields and in high selectivity (Scheme 1, a).[13u] Considering that OH substituted *α,β*-unsaturated amides are useful compounds for pharmaceuticals, natural products as well as biological systems, etc. (see Fig. 1),[2-4] we assumed that the alkynes can be applied instead of alkenes to construct OH substituted *α,β*-unsaturated amides. Compared with alkenes, however, alkynes exhibit different reactivity and electronic properties, and this can result in complications when aminophenols react to form esters and amides. On the basis of our previous studies on carbonylations[12c,f,13g-i,u,14j,k,15] and given the interest to explore the selectivity, we herein report the Pd-based ligand- and additive-controlled aminocarbonylation reactions of alkynes and aminophenols, which exhibit excellent chemo- and regioselectivities to form both branched and linear OH substituted *α,β*-unsaturated amides in good-to-excellent yields.

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

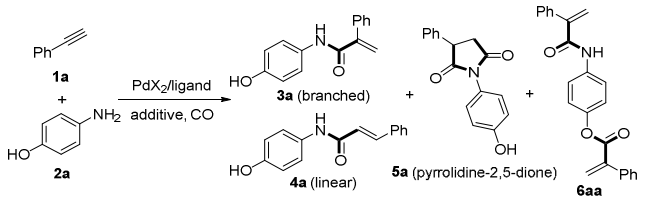


RESULTS AND DISCUSSION

Initially, phenylacetylene (**1a**) and 4-aminophenol (**2a**) were chosen as model substrates to optimize the reaction conditions (Table 1). In the presence of 5 mol% of $PdCl_2$ and 20 mol% of PPh_3 in THF at 120 °C under a CO atmosphere (450 psi), the carbonylation of **1a** and **2a** afforded the branched amide **3a**, linear amide **4a** and dicarbonylation imide **5a** in 90% total yield in a 52/41/7 ratio, and no esters were detected (entry 1). Encouraged by this result, we tried other conditions to further optimize the regioselectivity of the reaction. When MeCN was employed as the solvent, the total yield of amides **3-5a** decreased slightly to 85%, but a better b/l ratio was observed (entry 2, b/l = 71/26). Other solvents, such as DMF, DCE, toluene, etc., and reactions at different temperatures were studied. The yields and the branched selectivities were lower than that in the case of MeCN at 120 °C (for details, see Table S1, SI). Different palladium precursors were investigated. As shown in Table 1, although the total yield of amides **3-4a** was lower than that in the case of $PdCl_2$, the branched selectivity was significantly increased to 94% by the use of $Pd(OAc)_2$, and no imide **5a** was formed (compare entry 3 with entries 1-2). Several other selected Pd precursors were employed, but none was superior to $Pd(OAc)_2$ (entries 4-6). The effect of ligand was then investigated in the presence of $Pd(OAc)_2$ in MeCN. Only a small amount of amides **3-5a** was isolated in the absence of PPh_3 (entry 7, 14% total yield). Considering that bidentate ligands were often used for carbonylation processes, a variety of bidentate ligands were screened for the reaction. These ligands demonstrated good branched selectivity but the yields of amides ranged widely (entries 8-12). With DPPE as the ligand, the yield of amides increased to 88% (entry 8). Utilization of ligand DPPP increased the yield to 91%, though accompanied by 7% of **6aa** (entry 9). **6aa** is an ester which arose by the further carbonylation of amide **3a**. Further investigation showed that the yields of amides decreased with the increase of the length of the carbon chain of the ligands (entries 9-11). Another bidentate ligand, BIPHEP, also worked well but the yield was a little lower than DPPP (compare entry 12 with entry 9). When the reaction was carried out using the tridentate ligand

Triphos, the yield and the branched selectivity both decreased (entry 13). In addition, the effect of additives was investigated using the catalytic system with DPPP as the ligand. The yield of amides, and the branched selectivity, both increased when 1.0 mol% of *p*-TsOH·H_2O was added, affording the amides **3a** and **4a** in 92% total yield, and the branched selectivity increased to 98% (entry 14). However, product **6aa** was also isolated in 4% yield under these conditions. Thereafter, use of a different amount of *p*-TsOH·H_2O was evaluated. Although the ratio of l/b was as high as 58/10 with 100 mol% of acid used, the yield of amides **3-5a** decreased to 51%, accompanied by 16% of imide **5a** (entries 15-16). Given that no **6aa** was detected using THF as the solvent, we chose THF instead of MeCN in the presence of $Pd(OAc)_2$/DPPP and *p*-TsOH·H_2O for the reaction, affording amides **3a** and **4a** in 97% yield (entry 17). By using the mixed solvent MeCN/THF, amides **3a** and **4a** were isolated in 96% yield and in 98% branched selectivity (entry 18).

Table 1. Optimization of the Reaction Conditions for the Branched Amide 3a[a]

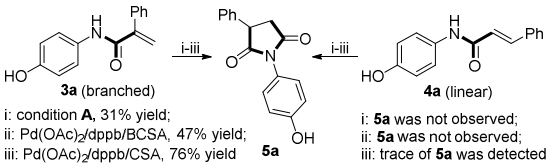


entry	PdX_2/L	additive (mol%)	yield (%)[b]	**3a**/**4a**/**5a**[c], **6aa**[d]
1[e,f]	$PdCl_2/PPh_3$		90	52/41/7, 0
2	$PdCl_2/PPh_3$		85	71/26/3, 0
3	$Pd(OAc)_2/PPh_3$		71	94/6/0, 0
4	$Pd(TFA)_2/PPh_3$		82	78/20/2, 0
5[e]	$Pd(MeCN)_4(BF_4)_2$/ PPh_3		80	64/35/1, 0
6[e]	$Pd_2(dba)_3/PPh_3$		29	61/33/6, 0
7	$Pd(OAc)_2$/-		14	37/56/7, 0
8	$Pd(OAc)_2$/DPPE		88	95/5/0, 2
9	$Pd(OAc)_2$/DPPP		91	95/5/0, 7
10[g]	$Pd(OAc)_2$/DPPB		77	94/6/0, 0
11[g]	$Pd(OAc)_2$/DPPPen		58	94/6/0, 0
12[h]	$Pd(OAc)_2$/BIPHEP		84	95/5/0, 2
13[h]	$Pd(OAc)_2$/Triphos		64	70/29/1, 0
14[h]	$Pd(OAc)_2$/DPPP	TsOH/1	92	98/2/0, 4
15[e]	$Pd(OAc)_2$/DPPP	TsOH/10	83	71/25/4, 0
16[e]	$Pd(OAc)_2$/DPPP	TsOH/100	51	10/58/31, 0
17[g,f]	$Pd(OAc)_2$/DPPP	TsOH/1	97	97/3/0, 0
18[g,i]	**$Pd(OAc)_2$/DPPP**	**TsOH/1**	**96**	**98/2/0, <2**

[a]Conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % of Pd, Pd/P = 1/4, 5 mL of MeCN, CO (450 psi), 120 °C, 24 h. [b]total isolated yield of **3a**, **4a** and **5a**. [c]determined by ^{1}H NMR. [d]isolated yield. [e]48 h. [f]5 mL of THF was used as the solvent. [g]72 h. [h]30 h. [i]5 mL of mixed solvent MeCN/THF (v/v = 1:4) was used. TsOH: *p*-TsOH·H_2O. DPPE = 1,2-*bis*(diphenylphosphino)ethane. DPPP = 1,3-*bis*(diphenylphosphino)propane. DPPB = 1,4-*bis*(diphenylphosphino)butane. DPPPen = 1,5-*bis*(diphenylphosphino)pentane. BIPHEP = 2,2'-*bis*(diphenylphosphanyl)-1,1'-biphenyl. Triphos = (2-((diphenylphosphanyl)methyl)-2-methylpropane-1,3-diyl)*bis*(diphenylphosphane).

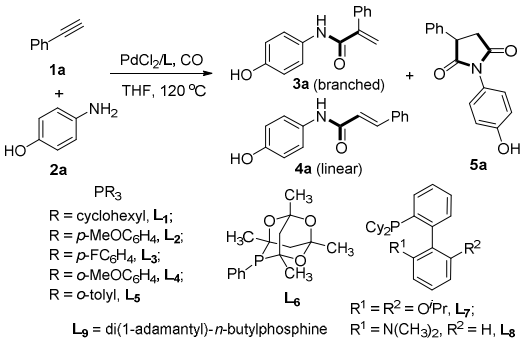
The question arose whether the dicarbonylated imide **5a** was generated from **3a** or **4a** or both. To determine whether or not this is the case, **3a** and **4a** were isolated and reacted with CO under conditions i-iii, respectively. The results demonstrated that **3a** could be transformed to **5a** in 31-76% yields. However, there was none or only a trace amount of **5a** furnished from **4a** (Scheme 2).

Scheme 2. The Possible Production Path for Imide 5a



Since the $PdCl_2$/Ligand catalytic system in THF showed high activity (Table 1, entries 1 and 17), we then introduced a series of ligands under these conditions. As expected, when bidentate phosphine ligands were used, the branched amide **3a** was formed as the predominant product (Table 2, entries 1-4). Up to 95% branched selectivity was observed by using BIPHEP (entry 4). Monodentate phosphine ligands also showed good activity. As demonstrated in Table 2, employment of electron-donating ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ afforded higher yields, while the less electron-donating ligand $\mathbf{L_3}$ resulted in relatively lower product yield (entries 5-7). For ligands $\mathbf{L_2}$ and $\mathbf{L_4}$ with similar electron-donating property, $\mathbf{L_4}$ has a substantial steric effect, resulting in lower product yield (entry 8). Similarly, the utilization of $\mathbf{L_5}$ inhibited the reaction (entry 9). Surprisingly, when ligand $\mathbf{L_6}$ was employed, the regioselectivity was reversed with the linear isomer **4a** obtained as the major product (entry 10). In addition, ligands $\mathbf{L_{7\text{-}9}}$ with strong electron-donating capabilities and bulky structures, were introduced, to selectively afford the linear amide **4a** as the major isomer in excellent yields (entries 11-13).

Table 2. Effect of Ligands on the Aminocarbonylation Reaction[a]

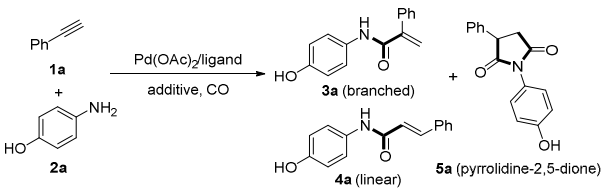


entry	ligand	yield (%) [b]	**3a/4a/5a**[c]
1	DPPE	72	92/8/0
2	DPPP	96	93/7/0
3	DPPB	44	81/17/2
4	**BIPHEP**	**90**	**95/5/0**
5	$\mathbf{L_1}$	99	65/34/1
6	$\mathbf{L_2}$	92	68/29/3
7	$\mathbf{L_3}$	82	66/30/4
8	$\mathbf{L_4}$	27	41/52/7
9	$\mathbf{L_5}$	trace	-
10	$\mathbf{L_6}$	96	33/66/2
11	$\mathbf{L_7}$	91	21/72/7
12	$\mathbf{L_8}$	94	36/63/1
13	$\mathbf{L_9}$	96	44/56/0

[a]Conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol % of $PdCl_2$, Pd/P = 1/4, 5 mL of THF, CO (450 psi), 120 °C, 48 h. [b]total isolated yield of **3a**, **4a** and **5a**. [c]determined by ^{1}H NMR. Condition **C**: BIPHEP was used as the ligand. Condition **D**: $\mathbf{L_6}$ was used as the ligand.

Considering that linear amides (e.g., cinnamamides) are more desirable due to their utilization in many research fields, we focused our effort to optimize the reaction conditions to achieve better linear selectivity. However, as alluded to earlier, the linear isomer is significantly more difficult to generate relative to the branched isomer. As illustrated in Table 3, by using $Pd(OAc)_2$/DPPB as the catalyst in MeCN at 120 °C, the reaction still gave branched **3a** as the major product (entry 1). However, we were pleased to observe that the regioselectivity was reversed by the addition of 'BCSA'[16] (compare entry 1 with 2). Employment of $B(OH)_3$ or 5-chlorosalicylic acid alone gave increased branched selectivity (**5a** was formed from **3a**, see Scheme 2), demonstrating that the intermediate BCSA, generated from $B(OH)_3$ and 5-chlorosalicylic acid *in situ*, was the key to promote linear isomer formation and reverse the overall selectivity. The above results indicate that 5-chlorosalicylic acid and *p*-$TsOH{\cdot}H_2O$ could promote the second carbonylation process (Table 3, entry 4 and Table 1, entry 16). Unexpectedly, the addition of another additive, MeOH,[17] led to a further increase in linear selectivity to 89%, albeit with a small amount of ester (entry 5). MeOH may act as another proton-donor, to improve the generation of the key intermediate Pd-H species (see Scheme 3). Other palladium precursors and ligands were investigated, demonstrating that $Pd(OAc)_2$/DPPB was a better choice (for details, see Table S2, SI). Furthermore, when DPPB was replaced by DTBPMB[12a,j,13m,s,18], there was almost 100% linear selectivity in the presence of BCSA and MeOH (entry 7). To avoid the generation of ester, trials were conducted without MeOH. Fortunately, the regioselectivity was still as high as 97%, and the amides were isolated in 90% yield (entry 8). In addition, increasing the amount of alkyne **1a** to 1.2 equiv and decreasing the proportion of $Pd(OAc)_2$/DTBPMB and BCSA to 2.5 mol%/5 mol% and 0.075 equiv, the linear selectivity was 97%, and the yield increased to 94% (entry 9). Further reduction of the amount of catalyst led to the decrease of the yield of amides (entry 10).

Table 3. Optimization of the Reaction Conditions for the Linear Amide 4a[a]



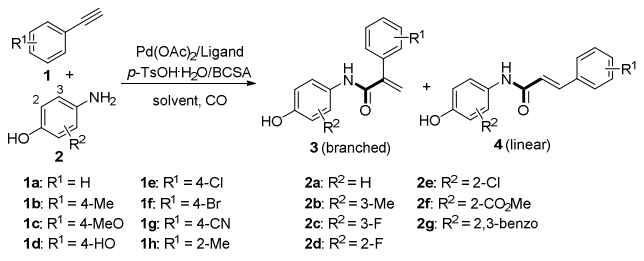
entry	ligand	additive	yield (%)[b]	**4a/3a/5a**[c]
1[d]	DPPB		77	6/94/0
2	DPPB	BCSA/-	85	69/2/29
3	DPPB	$B(OH)_3$/-	81	24/76/0
4	DPPB	Cl-SA/-	78	17/12/71
5	DPPB	BCSA/MeOH	83	89/6/5
6	DPPB	BSA/MeOH	85	84/3/13
7	DTBPMB	BCSA/MeOH	87	99.7/0.3/0
8	DTBPMB	BCSA/-	90	97/3/0
9[e,f]	**DTBPMB**	**BCSA/-**	**94**	**97/3/0**
10[e,g]	DTBPMB	BCSA/-	67	96/4/0

[a]Conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, 5 mol% of $Pd(OAc)_2$, 10 mol% of ligand, 5 mL of MeCN, CO (350 psi), 110 °C, 48 h. [b]total isolated yield of **3a**, **4a** and **5a**. [c]determined by ^{1}H NMR. [d]120 °C. [e]1.2 equiv of **1a** was used based on **2a**. [f]2.5 mol% of $Pd(OAc)_2$, 5 mol% of DTBPMB and 7.5 mol% of BCSA were used. [g]1.5 mol% of $Pd(OAc)_2$, 3 mol% of DTBPMB and 4.5 mol% of BCSA were used. BCSA: mixture of 1.0 equiv of $B(OH)_3$ and 2.0 equiv of 5-chlorosalicylic acid. BSA: mixture of 1 equiv of $B(OH)_3$ and 2 equiv of salicylic acid. DTBPMB = 1,2-*bis*(di*tert*butylphosphinomethyl)benzene.

With the above optimized conditions (defined as condition **A** (Table 1, entry 18) and **B** (Table 3, entry 9)) in hand, a series of phenylacetylenes **1** and 4-aminophenols **2** were employed to determine the scope and regioselectivities of these aminocarbonylation reactions (Table 4). Both electron-withdrawing and electron-donating substituted phenylacetylenes **1** reacted with 4-aminophenol (**2a**) smoothly, controllably affording branched or linear amides in high regioselectivity (entries 1-8). When 4-Me, 4-MeO, 4-HO and 4-Cl group substituted phenylacetylenes (**1b-e**) were employed under condition **A**, the branched selectivity was over 99%, and the corresponding products **3ba-ea** were isolated in excellent yield (91-95% yields, entries 2-5). Under condition **B**, the corresponding linear products **4ba-ea** could be generated in 86-91% yields, and with up to 96-98% regioselectivities (entries 2-5). The

above results demonstrated the OH substituted phenylacetylene could also be tolerated in these reactions (entry 4). Notably, the Br substituent of 4-bromophenylethyne **1f** remained intact under both conditions (entry 6). However, when **1f** and 4-cyanophenylethyne (**1g**) were reacted under condition **A**, the yields of branched amides **3fa** and **3ga** decreased to 46% and 41%, respectively. Gratifyingly, **3fa** and **3ga** were isolated in 74% and 80% yields with good selectivity using condition **C** (entries 6-7). In contrast, the reactions of **1f** and **1g** under condition **B** afforded linear amides **4fa** and **4ga** in good yields and in 98% and 92% regioselectivity, respectively (entries 6-7). It was not yet clear why the selectivity of the linear isomer **4ga** was a little lower, but it is possible that the cyano group acted as a co-ligand. Interestingly, with the utilization of MeOH in the reaction of **1g**, the linear selectivity could be increased to 99% with the yield of **4ga** not affected (entry 7, condition **B**). Substrate 2-methylphenylethyne **1h** having a methyl group near the ethynyl substituent, was experiencing steric hindrance, but could still react with **2a** smoothly, affording amides **3ha** and **4ha** in good yields and in 97% and 99% regioselectivity (entry 8). On the other hand, differently substituted 4-aminophenols were also successfully applied to the reaction. As shown in Table 4, the methyl group or electron-withdrawing group such as F, Cl or CO2Me (**2b-f**) could all be tolerated, affording the corresponding branched or linear amides in good-to-excellent yields and in high regioselectivity (entries 9-13). Substrate **2b** with a methyl substituted *ortho* to the amino group, gave amide **3ab** in 94% yield, and 98% regioselectivity. The linear product **4ab** was isolated in 75% yield and 98% selectivity under condition **B** (entry 9). 4-Aminophenols with a fluorine substituent at a different position led to similar excellent selectivity under both conditions **A** and **B**. Amides **3ac**/**3ad** and **4ac**/**4ad** were generated smoothly and in good yields (entries 10 and 11). The yield of linear amide **4ae** decreased slightly in the case of chlorine substituted 4-aminophenol **2e** under condition **B** (entry 12). In contrast, the substrate with a CO2Me group (**2f**) afforded **4af** in excellent yield (96%, condition **B**, entry 13). When 4-aminonaphthalenol **2g** reacted with **1a**, high selectivity for the branched or linear amide was achieved, although the yield was lower (entry 14).

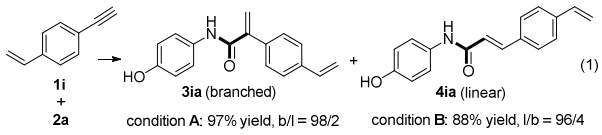
Table 4. Selective Carbonylation of Phenylacetylene with 4-Aminophenols



entry	1	2	condition **A**		condition **B**	
			3/yield (%)[a]	**3**/**4**[b]	**4**/yield (%)[a]	**4**/**3**[b]
1	**1a**	**2a**	**3a**/92	98/2	**4a**/90 (88)[d]	97/3 (>99/1)[d]
2	**1b**	**2a**	**3ba**/91	>99/1	**4ba**/86 (89)[d]	97/3 (>99/1)[d]
3	**1c**	**2a**	**3ca**/94	>99/1	**4ca**/91	97/3
4	**1d**	**2a**	**3da**/91	>99/1	**4da**/89	98/2
5	**1e**	**2a**	**3ea**/95	>99/1	**4ea**/90	96/4
6	**1f**	**2a**	**3fa**/46 (74)[c]	>99/1 (98/2)[c]	**4fa**/82	98/2
7	**1g**	**2a**	**3ga**/41 (80)[c]	95/5 (94/6)[c]	**4ga**/87 (85)[d]	92/8 (99/1)[d]
8	**1h**	**2a**	**3ha**/86	97/3	**4ha**/77	>99/1
9	**1a**	**2b**	**3ab**/94	98/2	**4ab**/75	98/2
10	**1a**	**2c**	**3ac**/88	>99/1	**4ac**/83	99/1
11	**1a**	**2d**	**3ad**/90	>99/1	**4ad**/80	97/3
12	**1a**	**2e**	**3ae**/87	>99/1	**4ae**/72	99/1
13	**1a**	**2f**	**3af**/83	>99/1	**4af**/96	98/2
14	**1a**	**2g**	**3ag**/78	98/2	**4ag**/53	97/3

Condition **A**: 0.5 mmol of **1**, 0.5 mmol of **2**, 5 mol % of $Pd(OAc)_2$, 10 mol% of DPPP, 1.0 mol% of *p*-TsOH·H_2O. 1 mL of MeCN and 4 mL of THF, CO (450 psi), 120 °C, 72 h. Condition **B**: 0.6 mmol of **1**, 0.5 mmol of **2**, 2.5 mol % of $Pd(OAc)_2$, 5 mmol of DTBPMB, 7.5 mol% of $B(OH)_3$, 15 mol% of 5-chlorosalicylic acid and 5 mL of MeCN, CO (350 psi), 110 °C, 48 h. [a]isolated yield of **3** or **4**. [b]determined by ^{1}H NMR. [c]Condition **C**: 0.5 mmol of **1**, 0.5 mmol of **2**, 5 mol% of $PdCl_2$, 10 mol% of BIPHEP, 5 mL of THF, CO (450 psi), 120 °C, 48 h. [d]160 μL (8.0 equiv) of MeOH was added.

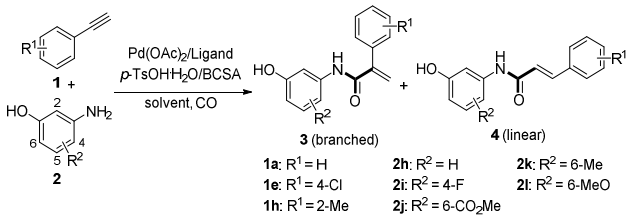
We next examined a reactant with both terminal carbon-carbon double and triple bonds in one substrate (**1i**), to assess the degree of selectivity between the vinyl and the ethynyl groups. The vinyl group still remained intact under both conditions, and the corresponding branched and linear amides **3ia** and **4ia** were obtained in good yields and in high selectivities (eq 1). This result might be due to the different reactivity between these two kinds of unsaturated bonds under the reaction conditions.



3-Aminophenols with a variety of substituents (**2h-l**) were explored under reaction conditions **A** and **B** (Table 5). High selectivity for both branched and linear amides was observed (entries 1-5). The yield of **3ah** could be further improved by using 1.1 equiv of **2h**, and the corresponding dicarbonylation product **6** could be suppressed successfully (entry 1). The electronic property of substituents on 3-aminophenols also affected the yield and regioselectivity. As indicated by the result, under both conditions **A** and **B**, the electron-donating group on 3-aminophenols could increase the yields of amides as compared with an electron-withdrawing group (compare entries 4-5 with 2-3). By employing methoxyl substituted

3-aminophenol **2l**, the corresponding branched and linear amides **3al** and **4al** were generated in 98% and 96% yield, respectively (entry 5). When **2j** with a CO_2Me group at the *ortho* position of the hydroxyl substituent was used, the branched amide **3aj**, and linear amide **4aj**, were isolated in 67% and 92% yields (entry 3). Alternatively, the yield of **3aj** could be improved to 83% under condition **C** (entry 3). By choosing an electron-withdrawing group (Cl) and an electron-donating group (Me) substituted phenylacetylenes **1e** and **1h**, the carbonylation afforded the corresponding amides in good yields and in high regioselectivity (entries 6-7). It is noteworthy that the selectivity was not affected greatly by steric hindrance when using **1h** as the substrate.

Table 5. Selective Carbonylation of Phenylacetylene with 3-Aminophenols

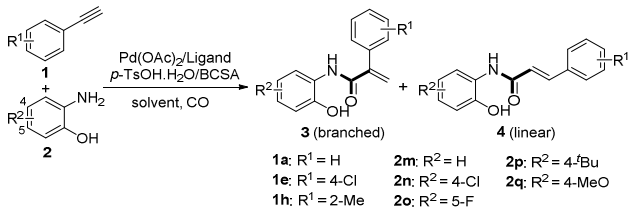


entry	1	2	Condition **A**		Condition **B**	
			3/yield (%)[a]	b/l[b]	**4**/yield (%)[a]	l/b[b]
1	**1a**	**2h**	**3ah**/87 (81)[c]	96/4	**4ah**/95	98/2
2	**1a**	**2i**	**3ai**/85	95/5	**4ai**/93	98/2
3	**1a**	**2j**	**3aj**/67 (83)[d]	>99/1 (96/4)[d]	**4aj**/92	97/3
4	**1a**	**2k**	**3ak**/92	98/2	**4ak**/95	99/1
5	**1a**	**2l**	**3al**/98	>99/1	**4al**/96	97/3
6	**1e**	**2h**	**3eh**/88	>99/1	**4eh**/94	97/3
7	**1h**	**2h**	**3hh**/79	96/4	**4hh**/96	98/2

Condition **A**: 0.5 mmol of **1**, 0.55 mmol of **2**, 5 mol % of $Pd(OAc)_2$, 10 mol% of DPPP, 1 mol% of *p*-$TsOH{\cdot}H_2O$. 1 mL of MeCN and 4 mL of THF, CO (450 psi), 120 °C, 72 h. Condition **B**: 0.6 mmol of **1**, 0.5 mmol of **2**, 2.5 mol % of $Pd(OAc)_2$, 5 mmol of DTBPMB, 7.5 mol% of $B(OH)_3$, 15 mol% of 5-chlorosalicylic acid and 5 mL of MeCN, CO (350 psi), 110 °C, 48 h. [a]isolated yield of **3** or **4**. [b]determined by ^1H NMR. [c]0.5 mmol of **2** was used. [d]Condition **C**: 0.5 mmol of **1**, 0.5 mmol of **2**, 5 mol% of $PdCl_2$, 10 mol% of BIPHEP, 5 mL of THF, CO (450 psi), 120 °C, 48 h.

The selective carbonylation was also applied to 2-aminophenols, affording amides in good-to-excellent yields and in high regioselectivity (Table 6). With the introduction of electron-withdrawing (such as F and Cl) and electron-donating (such as ^{t}Bu and MeO) groups on 2-aminophenols, the reactions showed a similar trend with 3-aminophenols (entries 2-5). By utilizing 4-chloro-2-aminophenol (**2n**) under condition **A**, the regioselectivity decreased slightly to 94% (entry 2). When 8.0 equiv of MeOH was added to the reaction under condition **B**, **4am** was formed in 98% regioselectivity (entry 1). In addition, the carbonylation of substituted phenylacetylenes **1e** and **1h** with 2-aminophenol (**2m**) afforded the corresponding amides in good yields and high regioselectivity, similar to using 3-aminophenol (**2h**) (compare table 6, entries 6-7 with table 5, entries 6-7). As indicated by these results, the hydroxyl group close to the reaction center does not interfere in the reaction.

Table 6. Selective Carbonylation of Phenylacetylene with 2-Aminophenols



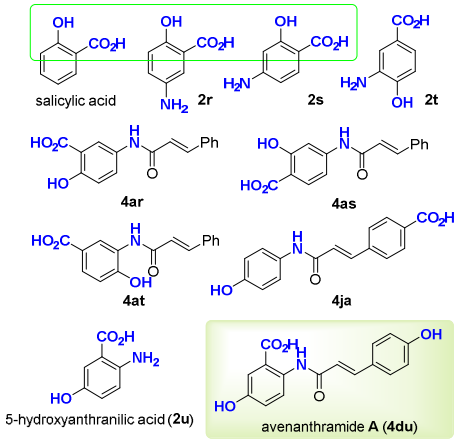
entry	1	2	Condition **A**		Condition **B**	
			3/yield (%)[a]	b/l[b]	**4**/yield (%)[a]	l/b[b]
1	**1a**	**2m**	**3am**/91 (83)[c]	>99/1	**4am**/94 (90)[d]	96/4 (98/2)[d]
2	**1a**	**2n**	**3an**/87	94/6	**4an**/92	97/3
3	**1a**	**2o**	**3ao**/84	98/1	**4ao**/91	95/5
4	**1a**	**2p**	**3ap**/96	>99/1	**4ap**/97	98/2
5	**1a**	**2q**	**3aq**/82	97/3	**4aq**/96	98/2
6	**1e**	**2m**	**3em**/81	99/1	**4em**/90	97/3
7	**1h**	**2m**	**3hm**/85	95/5	**4hm**/93	99/1

Condition **A**: 0.5 mmol of **1**, 0.55 mmol of **2**, 5 mol % of $Pd(OAc)_2$, 10 mol% of DPPP, 1 mol% of *p*-$TsOH{\cdot}H_2O$. 1 mL of MeCN and 4 mL of THF, CO (450 psi), 110 °C, 72 h. Condition **B**: 0.6 mmol of **1**, 0.5 mmol of **2**, 2.5 mol % of $Pd(OAc)_2$, 5 mmol of DTBPMB, 7.5 mol% of $B(OH)_3$, 15 mol% of 5-chlorosalicylic acid and 5 mL of MeCN, CO (350 psi), 80 °C, 48 h. [a]isolated yield of **3** or **4**. [b]determined by ^1H NMR. [c]0.5 mmol of **2** was used. [d]160 μL (8.0 equiv) of MeOH was added.

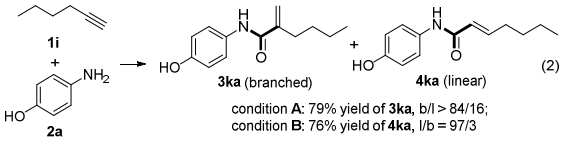
Considering that the CO_2H group could be tolerated under condition **B** (additive: 5-chlorosalicylic acid), we were then interested to introduce 5-amino-2-hydroxybenzoic acid (**2r**), bearing a CO_2H moiety at the *ortho* position of the OH substituent, to react with phenylacetylene (**1a**) in the presence of $B(OH)_3$ without additional 5-chlorosalicylic acid (Fig. 2). To our surprise, the carbonylation of **2r** could give the corresponding amide **4ar** in 89% yield and in over 99% regioselectivity, demonstrating that substrate **2r** and $B(OH)_3$ also served as the additive simultaneously. Similarly, the substrate 4-amino-2-hydroxybenzoic acid (**2s**), could also be employed in the reaction smoothly, affording **4as** in 78% yield and 98% selectivity. Furthermore, 3-amino-4-hydroxybenzoic acid (**2t**), with the CO_2H group not at the *ortho* position of OH, was also examined and the chelation compound could not

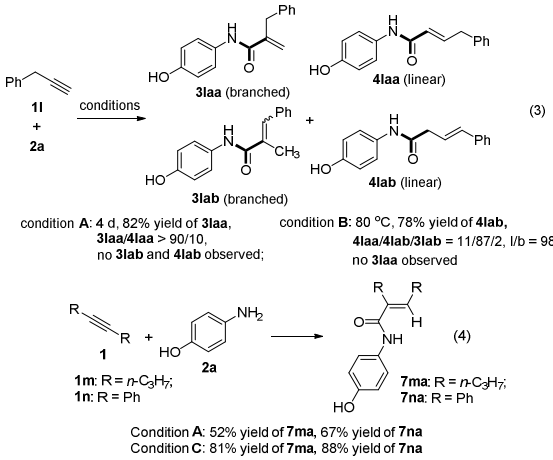
be formed with $B(OH)_3$ like salicylic acid. With the aid of additive BCSA (7.5 mol%), the carbonylation of **2t** with **1a** could react smoothly, the corresponding amide **4at** was isolated in 93% yield with over 99% selectivity. When using the CO_2H substituted phenylacetylene **1j** as the substrate under condition **B**, the corresponding amide **4ja** was successfully isolated in 88% yield with 99% regioselectivity. Interestingly, the natural product avenanthramide **A** (**4du**) could be constructed directly through this method by using 4-ethynylphenol (**1d**) and 5-hydroxyanthranilic acid (**2u**), affording **4du** in 84% yield and over 99% selectivity.

Figure 2. Synthesis of OH and CO_2H Substituted Cinnamamides

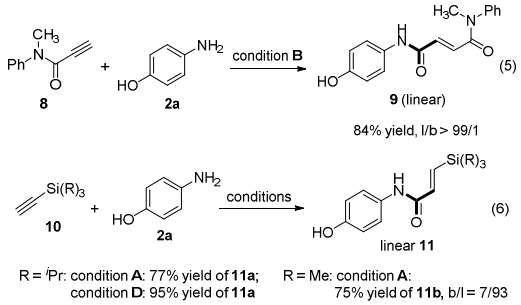


In addition, alkyl acetylenes were then utilized to further determine the scope of this carbonylation reaction. As demonstrated in eq. 2, *n*-1-hexyne (**1k**) could be applied smoothly, giving the corresponding amide **3ka** and **4ka** in 79% and 76% yields, and in good selectivity under conditions **A** and **B**, demonstrating that aliphatic alkynes could be well tolerated using this method. Another kind of alkyl acetylene, 3-phenyl-1-propyne (**1l**), was then examined (eq 3), and the branched amide **3laa** was generated in 84% yield and good selectivity under condition **A**. However, under condition **B**, three amide products **3lab**, **4laa** and **4lab** were detected, with the rearrangement amide **4lab** isolated as the major product (78% yield). The linear selectivity was up to 98%, although the ratio of **4lab** and **4laa** was 87:11. Furthermore, internal alkynes **1m** and **1n** were also applied and found compatible in these reactions, to afford the corresponding amides **7ma** and **7na** in good yields (eq 4). The configuration of **7ma** was established by the NOESY study (see SI).

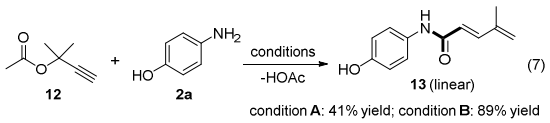




Other than aryl and alkyl alkynes, we were further interested in exploring other types of alkynes for this carbonylation reaction. For example, substrate *N*-methyl-*N*-phenylpropiolamide (**8**), bearing a strong electron-deficient carbon-carbon triple bond, could also react with **2a** smoothly under condition **B**. The reaction afforded the linear amide **9** in 84% isolated yield and in over 99% selectivity (eq 5). However, no desired amide was detected under condition **A**. On the contrary, ethynyltriisopropylsilane (**10a**), substituted with a strong electron donor moiety ($Si(^iPr)_3$), could also react with 4-aminophenol (**2a**), and only the linear isomer **11a** was isolated under conditions **A** and **D** (eq 6). The branched isomer was not formed, which may largely be due to the steric effect of the $Si(^iPr)_3$ group. When ethynyltrimethylsilane (**10b**) was employed as the reactant, the branched amide was observed, while the linear isomer **11b** resulted as the major product under condition **A**.

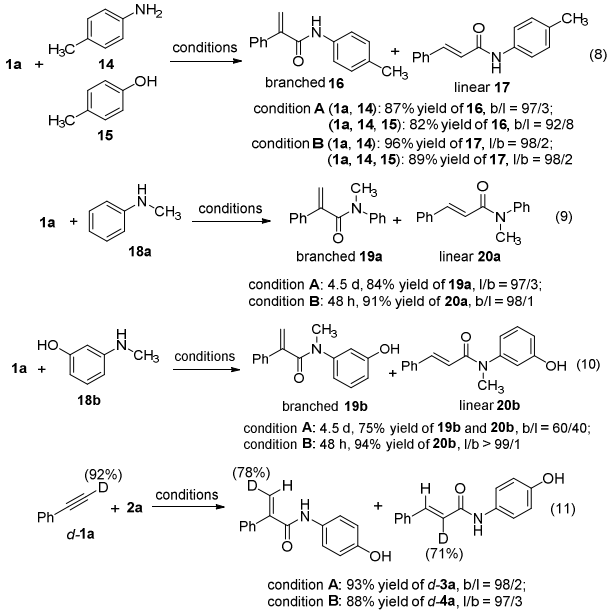


In addition, substrate **12**, having a sterically encumbered group, was tested (compare with **10**) and afforded the linear amide **13** as the sole product in 41% and 89% yields under conditions **A** and **B** (eq 7). It was interesting that the OAc group was eliminated to form 1,3-diene **13**, which provided a readily accessible strategy to 1,3-diene amides.



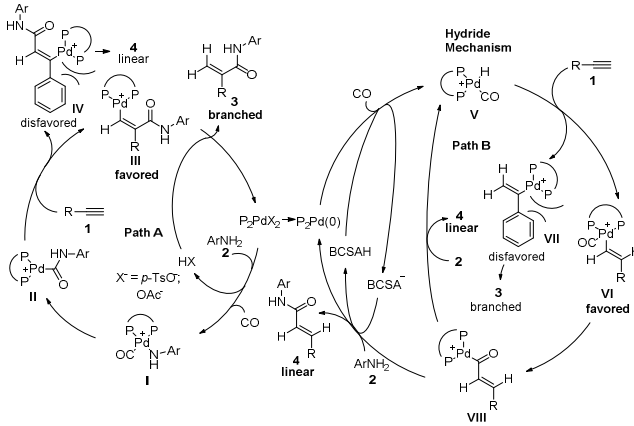
To verify the chemo- and regioselectivity of the reaction, controlled reactions were conducted by employing phenylacetylene (**1a**) with a mixture of 4-methylaniline (**14**) and 4-methylphenol (**15**) (eq 8). In the presence of phenol **15**, the reaction selectively afforded the branched amide

16 in 82% yield (condition **A**) and the linear amide **17** in 89% (condition **B**) yield, with no ester observed. Furthermore, *N*-methylaniline (**18a**) and *N*-methyl 3-aminophenol (**18b**), with a methyl group on the nitrogen atom which may cause steric hindrance, were also investigated (eqs 9-10). Under condition **B**, the linear amides **20a** and **20b** were isolated in 91% and 94% yields with 98% and over 99% regioselectivity, respectively. Interestingly, the branched amide **19a** could also be readily obtained when using **18a** as the substrate under condition **A** (eq 9). However, when **18b** was used under condition **A**, **19b** and **20b** were isolated in 75% yield, and in a 60/40 ratio (eq 10). These results demonstrated that the *N*-methyl group did not affect the chemoselectivity under both conditions **A** and **B**, but reduced the activity of the reactions to form branched amides **19a** and **19b** under condition **A**. When 4-methylphenol (**15**, eq 8) or the phenolic hydroxyl moiety (**18b**, eq 10) were present, the linear selectivity increased more or less under condition **A**, which indicates that the branched or the linear amide may be formed *via* different Pd intermediates. The phenolic hydroxyl group may act as the proton-donor to promote the generation of Pd-H species, which was the key intermediate leading to the formation of linear amides (see Scheme 3). Moreover, the reactions of phenyl acetylene-*d* (*d*-**1a**, 92% D) with 4-aminophenol (**2a**) under conditions **A** and **B** were carried out to determine the position of deuterium in the final product (eq 11). Under condition **A**, the corresponding branched amide *d*-**3a** was isolated in 93% yield with 98% branched selectivity, and content of deuterium in *d*-**3a** (78%) was confirmed through ^{1}H NMR analysis. On the other hand, the linear isomer *d*-**4a** was generated in 88% yield with 97% linear selectivity, and the content of deuterium in *d*-**4a** was 71%.



The above experimental results showed that the branched amides could be generated without adding any additives (Tables 1 and 2). On the contrary, the linear selectivity was increased in the presence of additives (*p*-TsOH·H_2O, Table 1, entries 15 and 16; BCSA, Table 3; phenol, eq 8). On the basis of these results, two mechanistic pathways are proposed for the aminocarbonylation reactions.[19] As indicted in Scheme 3, the arylcarbamoyl group (Path **A**) and the hydride (Path **B**) can serve as the carriers. In the arylcarbamoyl mechanism (Path **A**), the substrate reacts with the arylcarbamoylpalladium species **II** (formed *via* the reaction of the arylaminopalladium species **I**) to generate the intermediates **III** and **IV**. The latter intermediates subsequently react to produce the final branched and linear products by protonation with *p*-TsOH·H_2O, hydroxyl and/or amino groups. On the other hand, in the hydride mechanism (Path **B**), the Pd(II) is reduced to Pd(0) first, which could generate palladium hydride **V** in the presence of acid (BCSA).[20] The next step involves migration of **V** to the substrate forming species **VI** and **VII**, which produce the final products **4** and **3** *via* CO insertion and amination of aminophenol. The C-C bond forming reaction is significantly different between these two pathways. As a result of steric effects, the migration reactions would be expected to favor products in which the palladium atom and the phenyl group (R) end up attached to different carbon atoms (intermediates **III** and **VI**). This promotes the carbamoyl mechanism to give the branched product **3** *via* intermediate **III**, whilst the hydride mechanism should favor the linear product **4** through intermediate **VI**. In both cases *cis* addition (of Pd and CONHAr or of Pd and H) during the migratory insertion step should lead to the corresponding isomer. When the reactions were conducted in the absence of alkyne **1**, the hydroformation product of aminophenol were observed. *N*-(4-Hydroxyphenyl)formamide (**21**) was isolated in 13% yield in the presence of BCSA. However, only a trace amount of **21** was yield without acid (BCSA).[21]

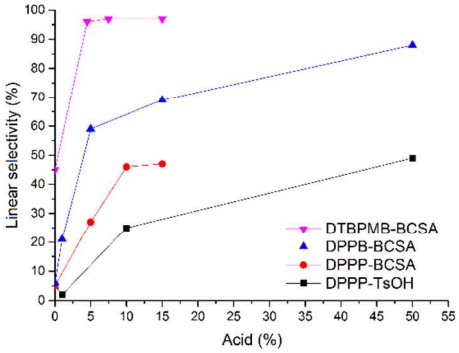
Scheme 3. Proposed mechanism



As shown in Scheme 3, the pivotal catalyst species may be $L_nPd(CO)NHAr$ **I** and $L_nPd(CO)$-H **V** in the two possible mechanistic pathways. The generation amount and speed by which the intermediate $L_nPd(CO)$-H reacts, may determine the reaction pathways and the regioselectivity of the reaction, as well as the yield. Besides the effect of the structure and electronic properties of the ligands, the proton-donor (e.g., *p*-TsOH·H_2O or BCSA) is another key factor to control the generation of $L_nPd(CO)$-H. As demonstrated in Figure 3, when DPPP was employed as

the ligand, BCSA afforded better linear selectivity than *p*-TsOH·H_2O (compare *p*-TsOH·H_2O line with BCSA line). Furthermore, when the reactions were carried out using DPPB instead of DPPP, increased linear selectivity were observed. Superb linear selectivity resulted using DTBPMB as the ligand. However, only 7% of desired amides were isolated with 45% linear selectivity in the absence of BCSA (for details, see Table S3, SI). These results indicate that BCSA serves as a proton-donor to promote the generation of the L_nPd-H species, which is key to improving the hydride based catalytic cycle (Scheme 3, Path **B**), and afford the linear amides.

Figure 3. Effect of the Ligands as well as Amount and the Nature of the Acid (for the original data of this Figure, see Table S3, SI)



CONCLUSION

In summary, the ligand- and additive-controlled palladium catalyzed aminocarbonylation reaction of alkynes and aminophenols provide direct OH substituted *α,β*-unsaturated amides. By simply changing the ligand and the additives, branched or linear amides were formed in excellent chemo- and regioselectivities, and in good-to-excellent yields. Mechanistic studies were conducted to gain some insight into these two catalytic reactions which may proceed *via* different reaction pathways. Other than the property and the structure of ligand, the additive (proton-donor) can also act in a constructive manner to promote the generation of L_nPd-H intermediates, which are critical to the regioselectivity and to form the linear products in high selectivity. With the high chemo- and regioselectivity, wide substrate scope, high atom-economy property and excellent product yield, this strategy provides an economical and facile synthetic approach to *α,β*-unsaturated amides.

ASSOCIATED CONTENT

Supporting Information.
Additional experimental results, experimental procedures and spectral data. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) 'BCSA', a combination (or a mixture) of 1 equiv of $B(OH)_3$ and 2 equiv of 5-chlorosalicylic acid, was used as the additive in the alkoxycarbonylation of alkynes, or in the carbonylation of alkenes. For details, see ref. 12i and ref. 13u.

(17) As reported by EI Ali and co-workers, the regioselectivity of the carbonylation of alkynes could be affected by the nucleophiles. While using MeOH as the nucleophile, the selectivity were changed with preference to afford the linear esters. For details, see ref. 14l.

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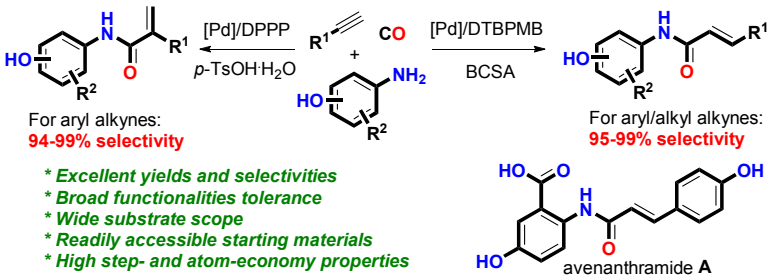
(20) Usually, the Pd(II) hydride complex is formed by oxidative ligation of hydrogen to Pd(0). To verify this point, the reaction of **1a** and **2a** was conducted using the Pd(0) precursor (Pd(DPPB)2), instead of Pd(OAc)2, under condition **B**, and the corresponding product **4a** was isolated in 95% yield and in 95% linear selectivity. The reaction result indicated that Pd(0) could smoothly catalyze the reaction. (a) Hu, Y.; Shen, Z.; Huang, H. *ACS Catal.* **2016**, *6*, 6785. (b) Broggi, J.; Jurčík, V.; Songis, O.; Poater, A.; Cavallo, L.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2013**, *135*, 4588. (c) Vyas, D. J.; Larionov, E.; Besnard, C.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2013**, *135*, 6177. (d) Sergeev, A. G.; Spannenberg, A.; Beller. M. *J. Am. Chem. Soc.* **2008**, *130*, 15549. (e) Dobbs, K. D.; Marshall, W. J.; Grushin, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 30. (f) Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466.

(21) The reactions of 4-aminophenol (**2a**) and CO with or without BCSA under Pd(OAc)2/DTBPMB or DPPP were carried out. In the presence of BCSA, and the product *N*-(4-hydroxyphenyl)formamide (**21**) was observed and isolated in 13% yield. However, only a trace amount of **21** was observed without BCSA. These results demonstrated that the acid may act as the key component to form the Pd-H intermediate which could generate **21** *via* CO insertion and amination of 4-aminophenol, or protonation of the arylcarbamoylpalladium intermediate **II** through Path **A**.

TOC graphic specifications.



* *Excellent yields and selectivities*
* *Broad functionalities tolerance*
* *Wide substrate scope*
* *Readily accessible starting materials*
* *High step- and atom-economy properties*

avenanthramide **A**