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Palladium-Catalyzed Decarbonylative Alkynylation of Amides

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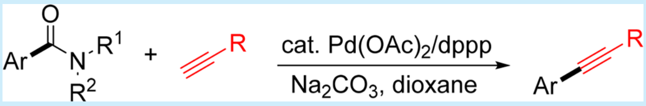
Supporting Information

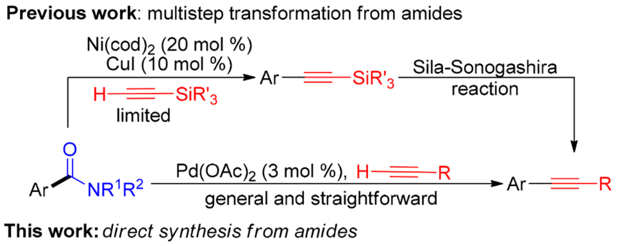
ABSTRACT: A palladium-catalyzed decarbonylative alkynylation of amides via C−N bond activation is developed. Compared with the reported Ni/Cu catalyzed reaction, which only proceeded well with silylacetylenes, this transformation was also applicable to both aromatic and aliphatic terminal alkynes, including those bearing functional groups, and thus provided a general and straightforward access to diverse internal alkynes.



Internal alkynes are fundamental structural motifs found in numerous bioactive compounds and functional materials.[1] Because of the flexible reactivity of the unsaturated C≡C triple bond, internal alkynes are also widely applied in organic synthesis.[1,2] In this context, the development of efficient methods for preparing those compounds is very important. Among the existing synthetic methods,[3−6] transition-metal catalyzed Sonogashira coupling of terminal alkynes with aryl halides represents a powerful and convenient access to internal alkynes.[4] During the past decades, this reaction has been extensively studied and many novel electrophilic reagents such as arenediazonium salts, sodium sulfonates, arylhydrazines, arylsulfonyl hydrazides, etc. have been successfully developed as the coupling partners instead of halides.[5] Despite the high efficiency of those coupling reagents, from economic and environmental points of view, the ideal ones would be naturally abundant and less pollutant.[6]

Amides are widespread raw materials.[7] In the past three years, transition-metal catalyzed C−N activation has emerged as a powerful strategy for amide conversions. By using this strategy, a series of excellent coupling reactions for constructing carbon−carbon and carbon−heteroatom bonds were reported by Garg,[8] Szostak,[9] Shi,[10] Zeng[11] et al.,[12,13] making amides a promising electrophilic reagent in coupling chemistry. Very recently, an efficient Ni/Cu-catalyzed decarbonylative cross-coupling of amides with terminal alkynes was developed by Rueping (Scheme 1).[14] However, probably due to the quick polymerization of other aromatic and aliphatic terminal acetylenes under the Ni-catalyzed reaction conditions, this reaction was only applicable to silylacetylenes.[15] Despite the fact that other internal alkynes could be prepared from the silylated alkynes through further sequential protodesilylation and Sonogashira reaction or sila-Sonogashira reaction, a more general and straightforward method was highly desirable.

Scheme 1. Internal Alkyne Construction via C−N Bond Activation of Amide



Herein, we report a palladium-catalyzed decarbonylative alkynylation of amides with terminal alkynes via C−N bond activation. This reaction overcame the substrate limitation of Rueping's catalytic system; all three kinds of terminal alkynes, i.e. aryl, alkyl, and silyl acetylenes, were applicable, and thus provided a general and straightforward method for the synthesis of internal alkynes.

Initially, *N*-acyl-glutarimides[16] **1a** reacted with phenylacetylene **2a** (3.0 equiv) in the presence of $Pd(OAc)_2$ (5 mol %), 1,1-bis(diphenylphosphino)methane (dppm, 10 mol %), and Na_2CO_3 (1.0 equiv) in dioxane at 150 °C under N_2 for 16 h. To our delight, the decarbonylative alkynylation product 2-(phenylethynyl)naphthalene **3a** was generated in 26% yield (Table 1, entry 1). It should be noted that no trace amount of this internal alkyne was produced in the previous Ni/Cu catalytic system.[14] This result encouraged us to further screen the reaction conditions. Among the ligands investigated, 1,3-bis(diphenylphosphanyl)propane (dppp) provided the best result, and **3a** was given in 79% yield (Table 1, entries 1−5). A phosphine ligand was essential in this reaction; no desired product was detected in its absence. Only a 28% yield of **3a** was obtained when 5 mol % dppp was loaded, whereas further increasing the loading of dppp to 15 mol % also did not improve the reaction efficiency (Table 1, entries 6−8). Other bases such as NaOAc, $NaHCO_3$, Li_2CO_3, K_2CO_3, and K_3PO_4

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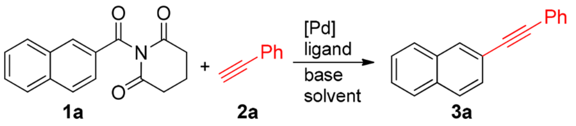
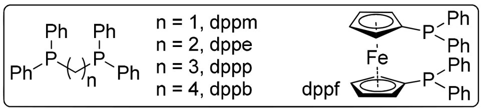
Table 1. Optimization of the Reaction Conditions[a,b]



entry	cat. Pd	ligand	base	solvent	yield (%)
1	$Pd(OAc)_2$	dppm	Na_2CO_3	dioxane	26
2	$Pd(OAc)_2$	dppe	Na_2CO_3	dioxane	73
3	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	79
4	$Pd(OAc)_2$	dppb	Na_2CO_3	dioxane	16
5	$Pd(OAc)_2$	dppf	Na_2CO_3	dioxane	45
6	$Pd(OAc)_2$	none	Na_2CO_3	dioxane	0
7[c]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	28
8[d]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	78
9[e]	$Pd(OAc)_2$	dppp	NaOAc	dioxane	37
10[e]	$Pd(OAc)_2$	dppp	$NaHCO_3$	dioxane	74
11	$Pd(OAc)_2$	dppp	Li_2CO_3	dioxane	73
12	$Pd(OAc)_2$	dppp	K_2CO_3	dioxane	26
13	$Pd(OAc)_2$	dppp	K_3PO_4	dioxane	22
14[f]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	61
15[g]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	75
16	$Pd(OAc)_2$	dppp	Na_2CO_3	t-AmlyOH	51
17	$Pd(OAc)_2$	dppp	Na_2CO_3	PhOMe	22
18	$Pd(OAc)_2$	dppp	Na_2CO_3	toluene	trace
19	$PdCl_2$	dppp	Na_2CO_3	dioxane	16
20	$Pd(dppf)Cl_2$	dppp	Na_2CO_3	dioxane	78
21[h]	$Pd_2(dba)_3$	dppp	Na_2CO_3	dioxane	78
22[i]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	82
23[j]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	61
24[k]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	79
25[l]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	54
26[m]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	62
27[n]	$Pd(OAc)_2$	dppp	Na_2CO_3	dioxane	69

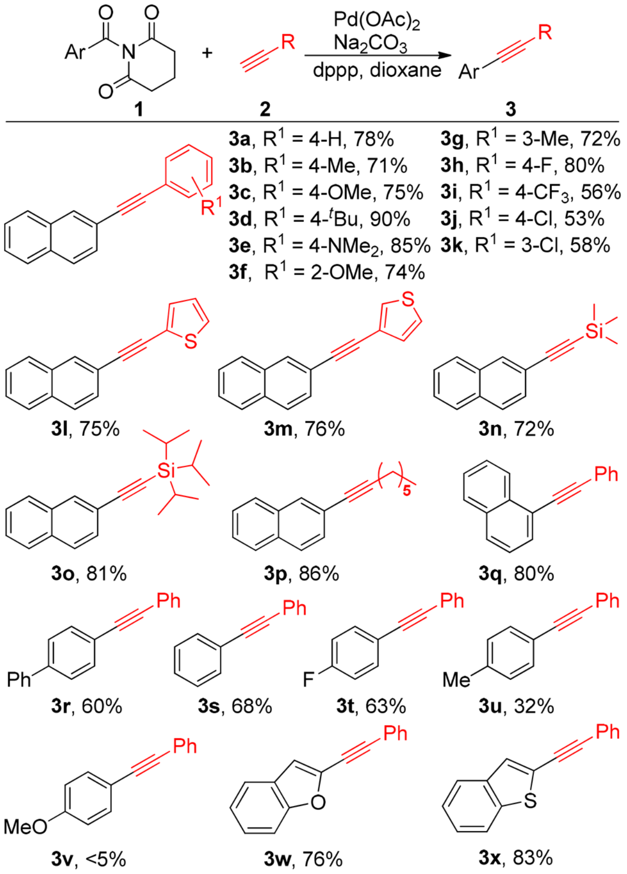


[a] Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv), [Pd] (5 mol %), ligand (10 mol %), and base (1.0 equiv) in the solvent (2 mL) at 150 °C under N_2 for 16 h. [b] GC yield using tridecane as an internal standard. [c] dppp (5 mol %). [d] dppp (15 mol %). [e] base (2.0 equiv). [f] Na_2CO_3 (0.5 equiv). [g] Na_2CO_3 (1.5 equiv). [h] $Pd_2(dba)_3$ (2.5 mol %). [i] $Pd(OAc)_2$ (3 mol %), dppp (6 mol %). [j] $Pd(OAc)_2$ (1 mol %), dppp (2 mol %). [k] 160 °C. [l] 130 °C. [m] **2a** (1.0 equiv), 24 h. [n] **2a** (2.0 equiv).

could also promote the reaction, despite the fact that relatively low yields of **3a** were afforded (Table 1, entries 9−13). The loading of base was also screened. A low yield was given with 0.5 equiv of Na_2CO_3, while increasing the amount of base did not enhance the reaction efficiency (Table 1, entries 14 and 15). As for the solvents, dioxane was the best choice (Table 1, entries 16−18). $PdCl_2$, $Pd(dppf)Cl_2$, and $Pd_2(dba)_3$ were also effective under similar reaction conditions (Table 1, entries 19−21). When 3 mol % $Pd(OAc)_2$ was used, a slightly higher yield of **3a** (82%) was obtained; however, further reduction of the catalyst to 1 mol % led to the decrease in yield (Table 1, entries 22 and 23). Reaction temperature was also investigated. Elevating the reaction temperature did enhance the yield, whereas a low yield was afforded at 130 °C (Table 1, entries 24 and 25). It seems that excessive **2a** was necessary, since decreasing the loading of **2a** led to a decrease in the yield (Table 1, entries 26 and 27). It should be mentioned that no alkynone product was detected under those reaction conditions, indicating that this catalyst system bears high capability in facilitating decarbonylation.

With the optimized reaction conditions in hand, the substrate scope and generality of this decarbonylative alkynylation reaction were investigated, and the results are summarized in Scheme 2. Diverse terminal alkynes including aryl, alkyl, and silyl acetylenes were good substrates, giving the corresponding internal alkynes in good to excellent yields. Under the optimized conditions, **3a** was obtained in 78% isolated yield. Other aromatic terminal alkynes, bearing electronic-donating groups such as 4-Me (**3b**), 3-Me (**3g**), OMe (**3c, 3f**), ^{t}Bu (**3d**), and NMe_2 (**3e**); halo groups such as F (**3h**), 4-Cl (**3j**), and 3-Cl (**3k**); and the electron-withdrawing group CF_3 (**3i**) on the benzene ring all served well under the reaction conditions, furnishing the desired products in 53−90% yields. Worth noting is that a sterically hindered terminal alkyne was transformed into the expected internal alkyne in a comparable yield (**3c** vs **3f**). The heteroaromatic alkynes were workable under the reaction conditions. When 2-ethynylthiophene or 3-ethynylthiophene reacted with **1a**, the corresponding heterocycle-containing internal alkynes were produced in 75% and 76% yields, respectively (**3l** and **3m**). In addition, silylated alkynes were also successfully constructed in this catalytic system (**3n** and **3o**). Aliphatic alkynes such as oct-1-yne also worked well, generating the expected product in 86% yield (**3p**).

Scheme 2. Substrate Scope[a,b]



[a] Reaction conditions: amides **1** (0.2 mmol), terminal alkynes **2** (3.0 equiv), Pd(OAc) (3 mol %), dppp (6 mol %), Na_2CO_3 (1.0 equiv) in dioxane (2 mL) at 150 °C under N_2 for 16 h. [b] Isolated yields.

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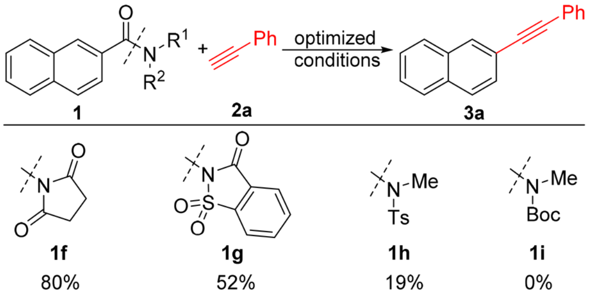
As for the amides' applicability, 1-(1-naphthoyl)piperidine-2,6-dione was a good substrate for this reaction; the corresponding product **3q** was isolated in 80% yield. Phenyl derivatives including those with 4-Ph and 4-F substituents were suitable to this transformation, giving the corresponding internal alkynes in 60−68% yields (**3r−t**). However, substrates bearing an electron-donating group such as 4-Me and 4-OMe on the benzene ring gave a low yield under the reaction conditions (**3u** and **3v**). Delightfully, heteroaromatic amides such as benzofuran-2-carboxamide and benzo[*b*]thiophene-2-carboxamide worked well, furnishing the valuable heteroaryl-containing internal alkynes in 76% and 83% yields, respectively (**3w** and **3x**). The effect of different N-substituents on amides was investigated next. As shown in Scheme 3, the less distorted amide **1f** was feasible,[17] producing **3a** in 80% yield. A promising yield of **3a** was also obtained by the reaction of *N*-acylsaccharin **1g**[18] with terminal alkyne **2a**. Consistent with metal insertion into the neutral amide C−N bond,[9d,19] amides **1h** and **1i** resulted in low yields of **3a**.

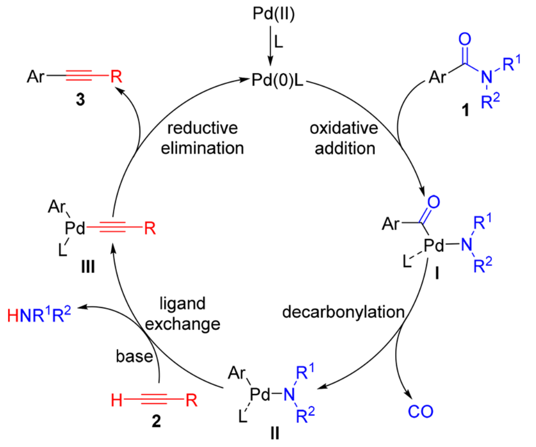
Scheme 3. Effect of Different N-Substituents[a]



[a] GC yield using tridecane as an internal standard.

Although the specific mechanism remains unclear, a tentative pathway was proposed based on the previous literature.[8−14] As shown in Scheme 4, the in situ formed Pd(0) species undergoes oxidative addition with the C−N bond in amide **1** affording intermediate **I**, followed by decarbonylation to give intermediate **II**. Assisted by base, ligand exchange of **II** with terminal alkyne **2** then occurs to form intermediate **III** with release of HNR^1R^2. Intermediate **III** proceeds with reductive elimination to produce the desired internal alkyne **3** and regenerate a Pd(0) catalyst to close the catalytic cycle.[20]

Scheme 4. Possible Reaction Mechanism



In conclusion, we have developed a Sonogashira-type cross-coupling reaction of amides with terminal alkynes via palladium-catalyzed C−N bond activation. In addition to the high capability of decarbonylation, this reaction overcame the substrate limitation of the Ni/Cu catalytic system and provided a straightforward access to diverse internal alkynes, including aryl, alkyl, and silyl substituents in good to excellent yields, which, to some extent, broadened the utility of the abundant and readily available amides for chemical synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00949.

Experimental procedures, full spectroscopic data, and copies of ^1H and ^{13}C spectroscopies (PDF)

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Notes

The authors declare no competing financial interest.

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(20) At the present stage, it is not very clear for palladium catalysis whether the decarbonylation took place ahead of ligand exchange or not. Prof. Shi studied the mechanism on the counterpart nickel-catalyzed decarbonylation coupling in detail (ref 10b). Shi isolated the key intermediates involved in the catalytic cycle and found that decarbonylative process was extremely fast. Considering the similarity between palladium and nickel, we preferred the decarbonylation-first path. However, the ligand-exchange-first path could not be excluded, particularly for palladium catalysis. On the other hand, Prof. Szostak described a palladium-catalyzed decarbonylation cross-coupling of amide with P(O)−H compounds, in which the ligand exchange was proposed to occur first; see: Reference 9b.