

# Amide to Alkyne Interconversion via a Nickel/Copper Catalyzed Deamidative Cross-Coupling of Aryl and Akenyl Amides

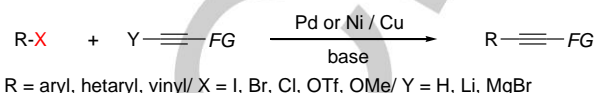
Watchara Srimontree, Adisak Chatupheeraphat, Hsuan-Hung Liao, and Magnus Rueping\*

**Abstract:** A nickel catalyzed deamidative cross-coupling reaction of amides with terminal alkynes as coupling partners was developed. This newly developed methodology allows the direct interconversion of amides to alkynes and enables a facile route for C(sp<sup>2</sup>)-C(sp) bond formations in a straightforward and mild fashion.

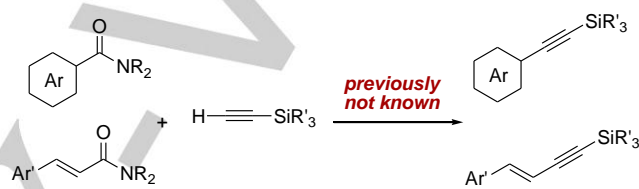
Transition metal catalyzed cross-coupling reactions represent one of the most successful domains in modern organic chemistry. Among the developed transformations, the Sonogashira reaction has emerged as one of the most straightforward and powerful methods to facilitate linkages between carbon atoms.<sup>[1]</sup> Although this well-known reaction shows superior ability to incorporate alkynyl units into organic molecules and found applications in industrial and laboratory settings, the electrophilic coupling partners for the Sonogashira reactions are often limited to aryl and vinyl halides. Recently, increasing emphasis on the development of environmental friendly synthetic protocols has stimulated research aimed at finding alternative cross-coupling partners, which avoid the corrosive halide-containing waste production in transition metal catalyzed reactions. The establishment of decarbonylative transformations<sup>[2]</sup> making use of carboxylic acids, anhydrides, acid chlorides, esters and amides is significant in realizing this concept. With these considerations in mind, our attention was drawn to the cross coupling reaction of amide derivatives with silylated acetylenes as nucleophilic coupling partners. If successful, this protocol would allow the synthesis of alkynes which are versatile intermediates in organic synthesis and important structural motifs of various biologically active molecules.<sup>[3]</sup> Beside their capacity to undergo subsequent transformations,<sup>[3]</sup> silylated alkynes can undergo protodesilylation to afford terminal alkynes which hold great potential for further functional group interconversion.<sup>[4]</sup> In addition, sila-Sonogashira reaction<sup>[5]</sup> provides an ideal protocol to convert silylated alkynes into internal alkynes.<sup>[6]</sup>

However, in order to develop a successful catalytic amide to alkyne interconversion procedure, there are several challenges that need be to addressed: 1) the formation of alkyne homocoupling products (Glaser-Hey coupling) has to be suppressed; 2) the use of strong bases which limits functional group tolerance needs to be avoided; and 3) the undesired formation of ketons and tertiary alcohols through addition of copper acetylide to the amide substrate has to be prevented (Scheme 1).

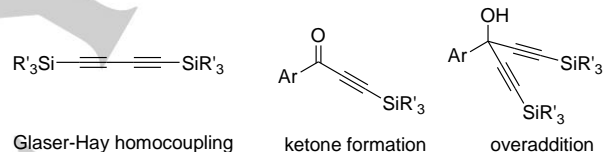
## Classical:



**This work:** - deamidative cross-coupling  
- no base required  
- no alkali metal acetylide required



**Main challenges:** undesired byproducts formation

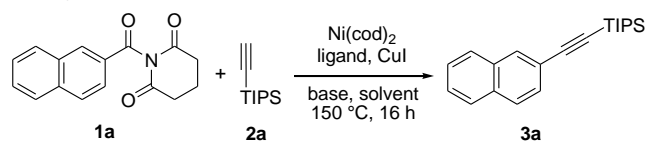


**Scheme 1.** Cross-coupling alkynylation reactions.

Given the considerations above, we started to investigate a deamidative cross-coupling reaction with amide **1a** and (triisopropylsilyl)acetylene (**2a**) as reaction partners (Table 1). Among the different metal catalysts tested nickel complexes<sup>[7-11]</sup> were found to activate the amide in the alkynylation reaction.<sup>[12]</sup> Subsequently different ligands were evaluated. Monodentate phosphine ligand P(Cy)<sub>3</sub> afforded the expected alkynylation product **3a** in moderate yield (Table 1, entry 1). A slightly higher yield was obtained using the bidentate phosphine ligand dcype [1,2-bis(dicyclohexyl phosphino)ethane] (Table 1, entry 2). The use of different bases such as Cs<sub>2</sub>CO<sub>3</sub> or CsF provided unsatisfactory results (Table 1, entries 4, 5). Changing the solvent to 1,4-dioxane resulted in an increased yield of 70% (Table 1, entry 6). Changing the catalyst to ligand ratio resulted in a considerably lower yield (Table 1, entry 8). A control experiment showed that no desired product was formed in the absence of the nickel catalyst and dcype ligand (Table 1, entries 9 and 10). Furthermore, the copper iodide is essential for achieving good yields of the desired product (Table 1, entry 11 vs 6). Notably, when the reaction was performed in the absence of base, the desired product was obtained in an excellent yield of 99% (entry 12). In addition, performing the reaction with a lower catalyst loading resulted also in an excellent yield of 99% for the desired product (entry 13).

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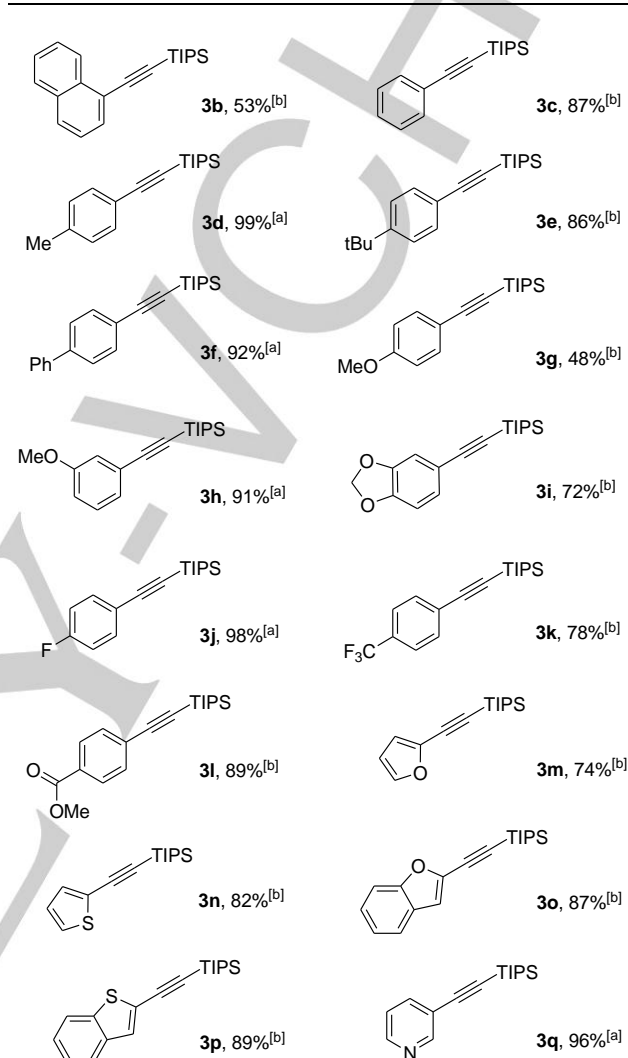
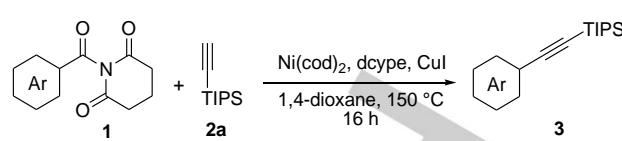
**Table 1:** Optimization of the nickel catalyzed deamidative Csp<sup>2</sup>-Csp coupling.<sup>[a]</sup>

Entry	Ligand	Base	Solvent	Yield (%)
1	PCy <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	toluene	60
2	dcype	K <sub>3</sub> PO <sub>4</sub>	toluene	67
3	dcypf	K <sub>3</sub> PO <sub>4</sub>	toluene	<5
4	dcype	CsF	toluene	16
5	dcype	Cs <sub>2</sub> CO <sub>3</sub>	toluene	0
6	dcype	K <sub>3</sub> PO <sub>4</sub>	dioxane	70
7 <sup>[b]</sup>	dcype	K <sub>3</sub> PO <sub>4</sub>	dioxane	73
8 <sup>[b,c]</sup>	dcype	K <sub>3</sub> PO <sub>4</sub>	dioxane	44
9 <sup>[b,d]</sup>	dcype	K <sub>3</sub> PO <sub>4</sub>	dioxane	-
10 <sup>[b]</sup>	-	K <sub>3</sub> PO <sub>4</sub>	dioxane	-
11 <sup>[e]</sup>	dcype	K <sub>3</sub> PO <sub>4</sub>	dioxane	30
12 <sup>[b]</sup>	dcype	-	dioxane	99
13 <sup>[b,f]</sup>	dcype	-	dioxane	99

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Ni(cod)<sub>2</sub> (10 mol%), dcype (40 mol%), CuI (10 mol%), base (2.0 equiv.), solvent (1 mL), 150 °C, 16 h, yield after isolation; [b] Using **2a** (1.0 mmol); [c] Using dcype (20 mol%); [d] Without Ni(cod)<sub>2</sub>; [e] Without CuI; [f] Using Ni(cod)<sub>2</sub> (5 mol%) and dcype (20 mol%).

With the optimized reaction conditions in hand, we further investigated the scope of this newly developed nickel catalyzed Sonogashira cross-coupling reaction with a variety of amides and terminal alkynes. Initially, a number of different amide substrates **1b-q** bearing a broad range of substituents were studied and the results are summarized in Table 2. Regarding the application of phenyl derivatives, electron-neutral as well as electron rich and poor phenyl derived amides **1c-l** were alkynylated, providing products **3c-l** with excellent yields. In addition, substrates bearing methoxy, fluorine and methyl ester groups underwent reaction without affecting the substituents. The latter observation is interesting as methoxy as well as fluorine substituents have been reported as coupling partners in nickel catalyzed reactions. Furthermore, heterocyclic amides including furan, thiophen, benzofuran, benzothiophen and pyridine derivatives **1m-q** are also tolerated under our reaction conditions and provided the products **3m-q** in high yields.

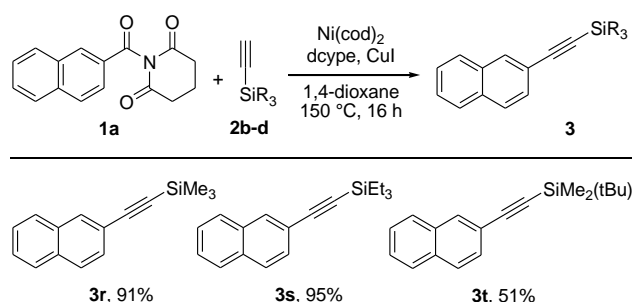
We next examined the scope of the reaction with respect to alkynes bearing different silyl groups (Table 3).

**Table 2:** The scope of nickel catalyzed Sonogashira cross-coupling with aryl amides.<sup>[a,b]</sup>

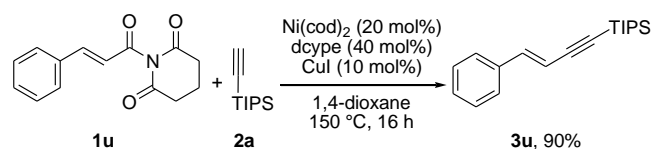
[a] Reaction conditions: **1** (0.2 mmol), **2a** (1.0 mmol), Ni(cod)<sub>2</sub> (5 mol%), dcype (20 mol%), CuI (10 mol%) in dioxane (0.2 M) at 150 °C 16 h. [b] Using Ni(cod)<sub>2</sub> (20 mol%), dcype (40 mol%). Yields for isolated products.

Trimethylsilyl and triethylsilyl alkynes **2b, c** performed smoothly in the cross-coupling with 2-naphthylamide **1a** to provide the corresponding products **3r, s** in 91% and 95% yield, respectively. The steric effect of the tertbutyldimethylsilyl group had a detrimental impact on the rate of the reaction and the product **3t** was obtained in moderate yield.

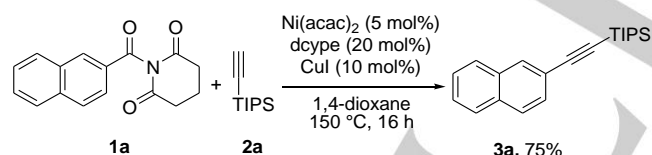
To show the applicability of the method, the synthesis of conjugated enyne **3u** starting from unsaturated amide **1u** and alkyne **2a** was attempted. Pleasingly, by applying our developed protocol, enyne **3u** was obtained in 90% yield (Scheme 2).

**Table 3:** The scope of nickel catalyzed cross-coupling of amides with terminal silyl alkynes.<sup>[a]</sup>

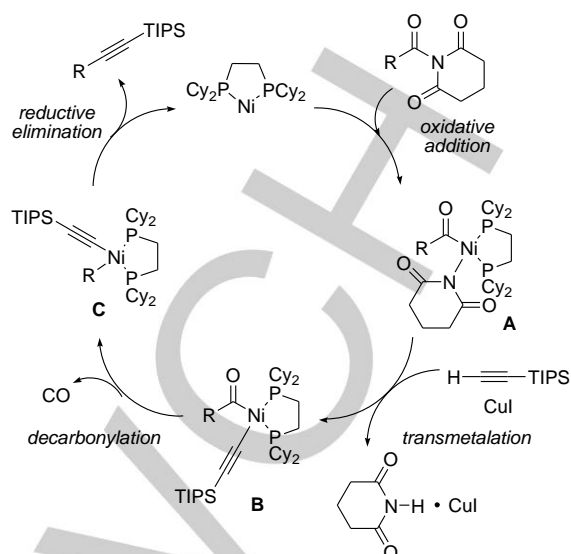
[a] Reaction conditions: **1a** (0.2 mmol), **2b-d** (1.0 mmol),  $\text{Ni}(\text{cod})_2$  (20 mol%), dcype (40 mol%), Cul (10 mol%) in dioxane (0.2 M) at 150 °C, 16 h, yields for isolated products **3r-t**.

**Scheme 2.** Preparation of enynes via nickel catalyzed Sonogashira cross-coupling.

Furthermore, a gram scale reaction was carried out in order to demonstrate the scalability of our method. Importantly, the cheap and air stable  $\text{Ni}(\text{acac})_2$  was found to be able to provide the alkynyl arene **3a** in 75% yield,<sup>[13]</sup> which offers a great opportunity for further applications in the industry (Scheme 3).

**Scheme 3.** A gram scale nickel catalyzed Sonogashira cross-coupling.

A proposed mechanism for this new nickel catalyzed alkynylation of amides is depicted in Scheme 4. Oxidative addition of nickel into the C(acyl)-N amide bond generates Ni complex **A**. Transmetalation provides the corresponding nickel complex **B** which undergoes CO-extrusion to form Ni intermediate **C**. Lastly, selective cross-coupling via reductive elimination delivers alkynylation product **3** and nickel(0) to complete the catalytic cycle. The role of copper co-catalyst is to activate the terminal alkyne and the glutarimide moiety stemming from the substrate acts as a base and removes a proton.

**Scheme 4.** Proposed mechanism for the nickel catalyzed deamidative alkynylation reaction.

In summary, we have developed a new and selective cross-coupling reaction of amides with terminal alkynes as coupling partners. The direct one step transformation of an aryl or alkenyl amide to the corresponding alkyne was previously not known and is, with conventional methods, difficult to achieve. Thus, the newly developed methodology enables a facile route for C(sp<sup>2</sup>)-C(sp) bond formation in a straightforward fashion by successful suppression of the undesired homocoupling process. Various terminal silyl alkynes and a wide range of aromatic amides bearing various substituents are tolerated in this process which afforded products in good to excellent yields. The utility of this newly developed protocol has been demonstrated in the synthesis of enynes as well as large scale synthesis of silylated alkynes. Given the simplicity and generality of the protocol it is anticipated that it should find application in synthesis, retrosynthesis and late stage modification.

## Acknowledgements

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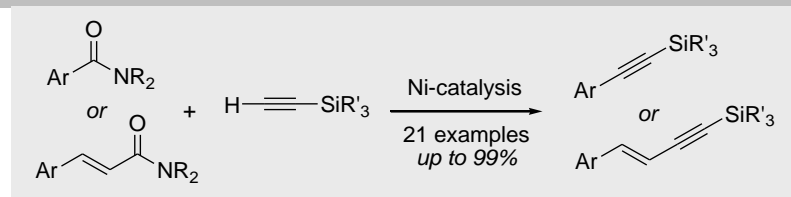
**Keywords:** Sonogashira • Decarbonylation • Aryl Amide • Nickel Catalysis

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- [13] For details on the optimization screening table of nickel(II) catalyzed cross-coupling reactions of amides, see Table S2 in the Supporting Information.

Layout 2:

## COMMUNICATION



Watchara Srimontree, Adisak Chatupheeraphat, Hsuan-Hung Liao, and Magnus Rueping\*

Page No. – Page No.

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