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

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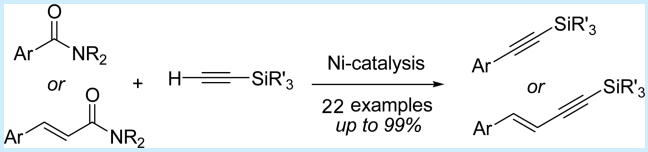
Supporting Information

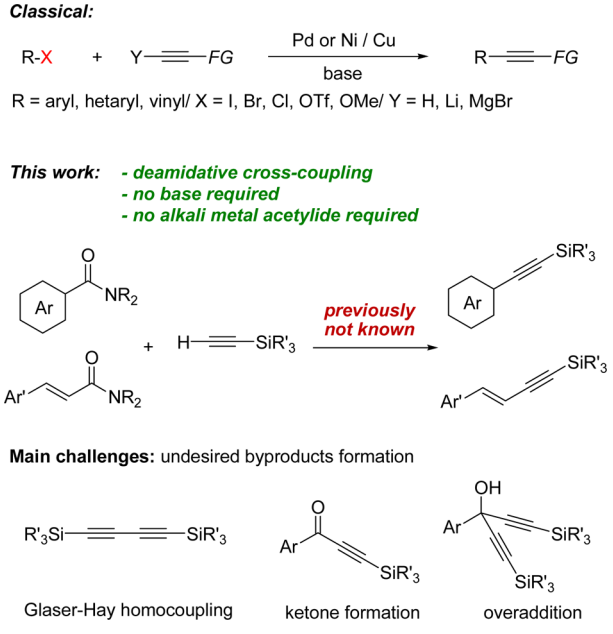
ABSTRACT: A nickel-catalyzed deamidative cross-coupling reaction of amides with terminal alkynes as coupling partners was disclosed. This newly developed methodology allows the direct interconversion of amides to alkynes and enables a facile route for C(sp2)−C(sp) bond formation in a straightforward 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.[1] Although this well-known reaction shows a superior ability to incorporate alkynyl units into organic molecules and has 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 environmentally friendly synthetic protocols has stimulated research aimed at finding alternative cross-coupling partners that avoid corrosive halide-containing waste production in transition-metal-catalyzed reactions. The establishment of decarbonylative transformations[2] 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.[3] Besides their capacity to undergo subsequent transformations,[3] silylated alkynes can undergo protodesilylation to afford terminal alkynes that hold great potential for further functional group interconversion.[4] In addition, sila-Sonogashira reaction[5] provides an ideal protocol to convert silylated alkynes into internal alkynes.[6]

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) as well as enyne formation 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 ketones and tertiary alcohols through addition of copper acetylide to the amide substrate has to be prevented (Scheme 1).

Scheme 1. Cross-Coupling Alkynylation Reactions



Given the above considerations, 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[7−12] were found to activate the amide in the alkynylation reaction.[13] Subsequently, different ligands were evaluated (Table 1, entries 1−10). Monodentate phosphine

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Table 1. Optimization of the Nickel-Catalyzed Deamidative C(sp^2)−C(sp) Coupling[a]

entry	ligand	base	solvent	yield (%)
1	PCy_3	K_3PO_4	toluene	60
2	$PnBu_3$	K_3PO_4	toluene	55
3	dcype	K_3PO_4	toluene	67
4	dcypf	K_3PO_4	toluene	<5
5	dcypp	K_3PO_4	toluene	58
6	dcypm	K_3PO_4	toluene	60
7	dcypb	K_3PO_4	toluene	51
8	dtbbpy	K_3PO_4	toluene	46
9	SIPr · HCl	K_3PO_4	toluene	34
10	IMes · HCl	K_3PO_4	toluene	42
11	dcype	CsF	toluene	16
12	dcype	Cs_2CO_3	toluene	0
13	dcype	K_3PO_4	dioxane	70
14[b]	dcype	K_3PO_4	dioxane	73
15[b,c]	dcype	K_3PO_4	dioxane	44
16[b,d]	dcype	K_3PO_4	dioxane	0
17[b]		K_3PO_4	dioxane	0
18[e]	dcype	K_3PO_4	dioxane	30
19[b]	dcype		dioxane	99
20[b,f]	dcype		dioxane	99
21[b]	PCy_3		dioxane	86
22[b,f]	PCy_3		dioxane	80

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Ni(cod)2 (20 mol %), ligand (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 $Ni(cod)_2$. [e]Without CuI. [f]Using $Ni(cod)_2$ (5 mol %) and dcype (20 mol %).

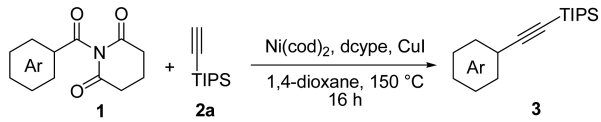
ligands PCy_3 and $PnBu_3$ afforded the expected alkynylation product **3a** in moderate yield (Table 1, entries 1 and 2). A slightly higher yield was obtained using the bidentate phosphine ligand dcype [1,2-bis(dicyclohexylphosphino)-ethane] (Table 1, entry 3). Evaluation of further ligands did not improve the yield of the reaction (Table 1, entries 4−10).[14] The use of different bases such as Cs_2CO_3 or CsF provided unsatisfactory results (Table 1, entries 11 and 12). Changing the solvent to 1,4-dioxane resulted in an increased yield of 70% (Table 1, entry 13). Changing the catalyst to ligand ratio resulted in a considerably lower yield (Table 1, entry 15). A control experiment showed that no desired product was formed in the absence of the nickel catalyst and dcype ligand (Table 1, entries 16 and 17).

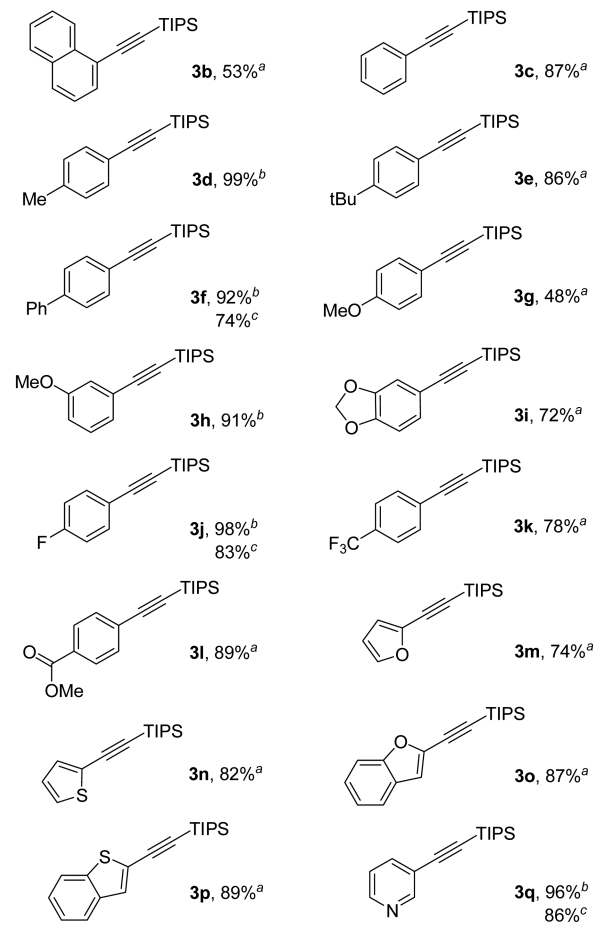
Furthermore, the copper iodide is essential for achieving good yields of the desired product (Table 1, entry 18 vs 13). Notably, when the reaction was performed in the absence of base, the desired product was obtained in an excellent yield of 99% (entry 19). In addition, performing the reaction with a lower catalyst loading also resulted in an excellent yield of 99% for the desired product (entry 20). We have also tested $CuCl_2$ and $Cu(OAc)_2$; however, the yields obtained are lower (59%, 56%) when compared with the yield obtained with CuI (99%).

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 Scheme 2.[16] Regarding the

Scheme 2. Scope of Nickel-Catalyzed Sonogashira Cross-Coupling with Aryl Amides[a,b]





[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.0 mmol), $Ni(cod)_2$ (20 mol %), dcype (40 mol %), CuI (10 mol %) in dioxane (0.2 M) at 150 °C, 16 h. [b]Using $Ni(cod)_2$ (5 mol %) and dcype (20 mol %). Yields for isolated products. [c]Reactions performed with $Ni(acac)_2$ (5 mol %) and dcype (20 mol %).[15]

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, thiophene, benzofuran, benzothiophene, 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 (Scheme 3).[17] Trimethylsilyl and triethylsilyl alkynes **2b,c** performed smoothly in the cross-

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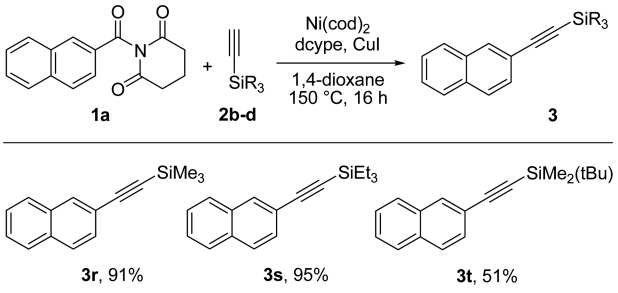
Scheme 3. Scope of Nickel-Catalyzed Cross-Coupling of Amides with Terminal Silyl Alkynes[a]

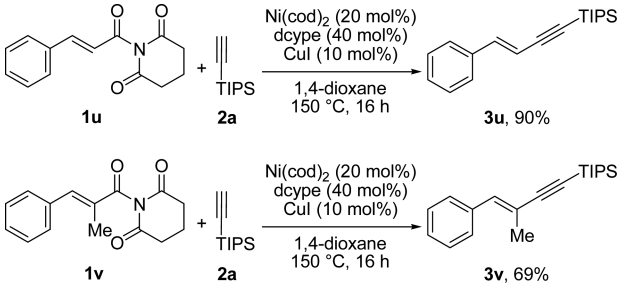


[a]Reaction conditions: **1a** (0.2 mmol), **2b–d** (1.0 mmol), $Ni(cod)_2$ (20 mol %), dcype (40 mol %), CuI (10 mol %) in dioxane (0.2 M) at 150 °C, 16 h, yields for isolated products **3r–t**.

coupling with 2-naphthylamide **1a** to provide the corresponding products **3r,s** in 91% and 95% yield, respectively. The steric effect of the *tert*-butyldimethylsilyl group had a detrimental impact on the rate of the reaction, and the product **3t** was obtained in moderate yield.

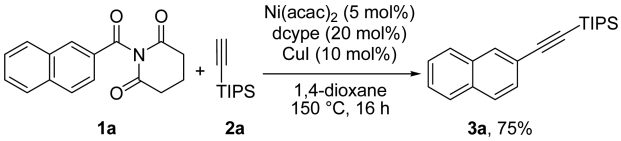
To show the applicability of the method, the synthesis of conjugated enynes **3u** and **3v** starting from unsaturated amides **1u** and **1v** and alkyne **2a** was attempted. Pleasingly, by applying our developed protocol, enynes **3u** and **3v** were obtained in 90% and 69% yield, respectively (Scheme 4).[18]

Scheme 4. Preparation of Enynes via Nickel-Catalyzed Sonogashira Cross-Coupling



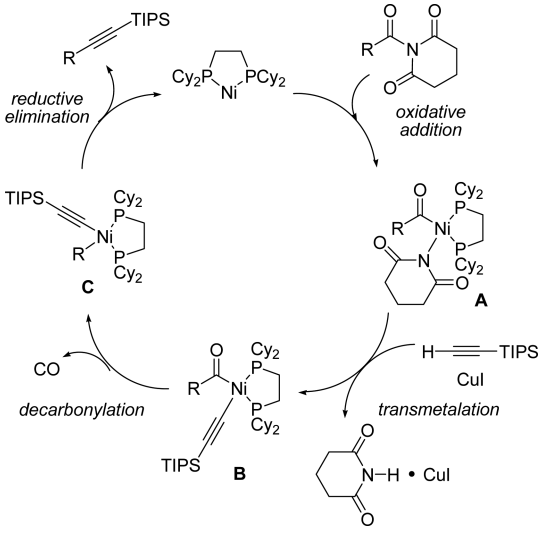
Furthermore, a gram-scale reaction was carried out in order to demonstrate the scalability of our method. Importantly, the inexpensive and air-stable $Ni(acac)_2$ was found to provide the alkynyl arene **3a** in 75% yield,[15] which offers a great opportunity for further applications in the industry (Scheme 5).

Scheme 5. Gram-scale Nickel-Catalyzed Sonogashira Cross-Coupling



A proposed mechanism for this new nickel-catalyzed alkynylation of amides is depicted in Scheme 6. 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

Scheme 6. Proposed Mechanism for the Nickel-Catalyzed Deamidative Alkynylation Reaction



complete the catalytic cycle. The role of copper cocatalyst is to activate the terminal alkyne, and the glutarimide moiety stemming from the substrate acts as a base and removes a proton.

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 $C(sp^2)–C(sp)$ 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01194.

Detailed experimental procedures, spectral data for all compounds, and ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Formation of the enyne dimerization product was sometimes observed during the optimization studies.

(15) For details on the optimization screening table of nickel(II) catalyzed cross-coupling reactions of amides, see Table S1 in the Supporting Information.

(16) *N*-Ph,Me and *N*-Bn,Boc amides were also tested in the reaction; however, only the starting materials were recovered.

(17) Acetylenes, such as phenylacetylene and *n*-butylacetylene, were also tested; unfortunately, we did not isolate any trace of the desired product.

(18) Attempts to synthesize a diyne compound were not successful under the present reaction conditions.

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