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Nickel-Catalyzed Direct Alkynylation of C(sp^2)-H Bonds of Amides: An "Inverse Sonogashira Strategy" to *ortho*-alkynylbenzoic acids†

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Nickel-catalyzed direct alkynylation of C(sp^2)-H bonds of amides using commercially available, inexpensive 8-aminoquinoline as a removable bidentate directing group is described. The present *ortho*-alkynylation has a broad substrate scope, functional group tolerance, high regiocontrol and can be scaled up. The efficiency and selectivity of this strategy provide sustainable routes to a diverse array of *ortho*-alkynylbenzoic acids under Ni(II)-catalyzed conditions.

Functionalized alkynes occupy a privileged position in contemporary organic synthesis as they can be found in drugs, biomolecules, and material science.[1] In addition, alkyne moiety is of significant importance for various organic transformations including cycloaddition, metathesis, click reaction *etc*. Thus, the development of an efficient strategy for the construction of alkynyl scaffolds is a key motivation in organic synthesis and is usually achieved by the Sonogashira cross-coupling reaction between an aryl halide and a terminal alkyne.[2] However, there has been increasing interest in the development of a complementary approach, an "inverse Sonogashira coupling" involving the direct conversion of inert C-H bonds into C-alkynyl bonds with easily accessible alkynyl halides.[3-4]

The activation of a C-H bond is a highly challenging yet fundamentally important process in organic chemistry, since C-H bonds are known to be strong, lack polarity, and are generally un-reactive. These features render C-H bond activation a demanding task. Considering that essentially all chemicals ultimately derive from fossil resources (contain mostly C-H and C-C bonds) the success of C-H activation can potentially revolutionize the industrial manufacture of fine chemicals and thus more efficiently use these non-renewable resources. Hence, successful C-H bond activation can dramatically impact organic synthesis and natural product chemistry.[5] Despite substantial growth in this active research area, unreactive C-H bond functionalization requires the assistance of a directing group embedded in the substrate that is able to coordinate to a metal center and deliver the active catalyst to a proximal C-H bond, typically *via* the formation of a five- or a six-membered metallacyclic intermediate.[6] After Daugulis's promising work[7] on the palladium-catalyzed chelation-assisted functionalization of C-H bonds using an 8-aminoquinoline as *N,N'*-bidentate directing group, many researchers started to use this chelating strategy for inert C-H bond activation.[8] The utilization of 8-aminoquinoline as a bidentate directing group has recently gained much attention in transition-metal catalyzed C-H bond functionalization reactions because of its commercial availability, economical, chelating ability, relatively acidic nature of N-H bond, and rigid backbone.[8b,8d-e]

Chatani and co-workers have reported Pd(II)-catalyzed alkynylation of non-acidic β C-H bonds with (triisopropylsilyl)ethynyl bromide with the assistance of 8-aminoquinoline as a directing group.[9a] Ruthenium- and palladium- catalyzed alkynylation of inert C-H bonds with the assistance of different directing groups were also independently reported by Chatani[4e,4o,9b] and Yu *et al*.[10] Alkynylation of *N*-aryl-2-aminopyridine with (triisopropylsilyl)acetylene was achieved by Chang and co-workers under Pd-catalyzed condition.[11] Recently, Glorius,[12] Loh[13] and others[14] have independently reported Rh-catalyzed alkynylation of C(sp^2)-H bonds with hypervalent alkynyl iodine reagents. Copper-mediated alkynylation of arenes with terminal alkynes have been developed by research groups of Yu,[15] and Shi.[16] Several catalytic alkynylation of heteroarenes have also been developed using various metals based on Gevorgyan's pioneering work on the palladium-catalyzed alkynylation of *N*-fused heteroarenes.[3a,4c-d,4f] Among the various metals employed in this emerging area, nickel has gained significant attention owing to its abundance, economical and versatile reactivity.[17] Recently, nickel-catalyzed chelation-assisted C-H bond activation to construct

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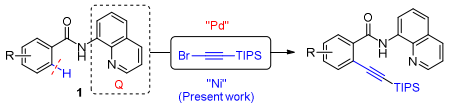
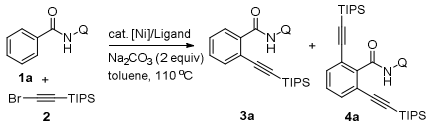
† Electronic Supplementary Information (ESI) available: [details of experimental procedure, reaction optimization, characterization of compounds and copy of NMR data]. See DOI: 10.1039/x0xx00000x

carbon-carbon bond and carbon-heteroatom bond with the aid of bidentate directing groups has been developed by fewer groups.[8a,8c,17-18] Inspired by these studies, we were motivated to test the possibility of alkynylation of **1** using (triisopropylsilyl)ethynyl bromide **2** as a coupling partner (Scheme 1). Herein we disclose nickel(II)-catalyzed C(sp^2)-H alkynylation of benzamides using 8-aminoquinoline as a removable bidentate directing group to synthesise various *ortho*-alkynylbenzoic acids.[19-20] The present nickel-catalyzed C(sp^2)-alkynylation has a broad substrate scope and functional group tolerance. Notably, many synthetically valuable groups such as halide (Cl, Br) could be reserved under our reaction reactions, which give chances for further modification of the products, wherein synthesis of such products using the traditional approach, "Sonogashira coupling" is very difficult and rather scare.



Scheme 1. The bidentate directing group assisted transition-metal catalyzed C-H alkynylation of unactivated arenes.

Table 1. Optimization of the nickel-catalyzed "inverse Sonogashira coupling" of benzamides (**1**)[a]



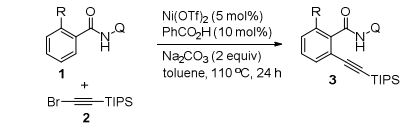
Entry	Catalyst	Ligand	Yield[b] 3a	Yield[b] 4a (%)	Conversion of 1 (%)[b]
1	$Ni(OTf)_2$	$PhCO_2H$	45%	25%	81%
2	$Ni(OTf)_2$	---	30%	24%	62%
3[c]	$Ni(OTf)_2$	$PhCO_2H$	19%	54%	77%
4[d]	$Ni(OTf)_2$	$PhCO_2H$	trace	---	6%
5	$Ni(OTf)_2$	$MesCO_2H$	16%	41%	63%
6	$Ni(OAc)_2$	$PhCO_2H$	15%	21%	47%
7	$NiCl_2$	$PhCO_2H$	17%	27%	55%
8	$NiBr_2$	$PhCO_2H$	15%	22%	46%
9	$Ni(acac)_2$	$PhCO_2H$	26%	29%	63%
10	$Ni(COD)_2$	$PhCO_2H$	22%	10%	41%

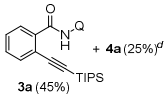
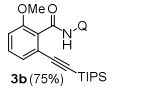
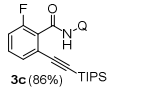
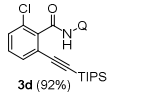
[a] Reaction conditions: **1a** (0.1 mmol), Ni catalyst (5 mol%), ligand (10 mol%), **2** (0.2 mmol), Na_2CO_3 (2 equiv), and toluene (1 mL) 110 °C for 24 hrs. [b] Conversion based on recovered yield of **1a**. [c] 3 equiv of **2**. [d] In the absence of Na_2CO_3.

Preliminary studies revealed that *N*-(quinolin-8-yl)benzamide (**1a**) and (triisopropylsilyl)ethynyl bromide **2** (2 equiv), Na_2CO_3 (2 equiv) as a base and in the presence of $Ni(OTf)_2$ (5 mol %) as a catalyst and 10 mol% of benzoic acid as an additive (see ESI for other ligands/additives) at 110 °C (reflux temperature of toluene) after 24 hrs, afforded both mono- (**3a**) and bis-alkynylated products (**4a**) with the conversion of **1a** in 81%. Both mono- (**3a**) and bis-alkynylated products (**4a**) were isolated separately and the yields of **3a** and **4a** are 45% and 25% respectively (Table 1, entry 1). In the absence of benzoic acid the yield of alkynylated products was decreased from 70% to 54% (Table 1, entry 2). However, the efficiency of the reaction was significantly affected in the absence of Na_2CO_3 (Table 1, entry 4) and clearly revealed the coordination of the amide **1a** to the Ni(II) followed by a ligand exchange with HX (X = -OTf, -Br, $PhCO_2$-) generation has been accelerated by the base.[22] This is because 8-aminoquinoline has a more acidic NH bond, which facilitates ligand exchange (promoted by a base). A series of nickel salts ($NiCl_2$, $NiBr_2$, and $Ni(acac)_2$) was evaluated under the optimal reaction condition (Table 1, entries 6-9) and it was observed that $Ni(OTf)_2$ showed improved reactivity (entry 1). Importantly, a Ni(0) complex also showed a catalytic activity, resulting in moderate yields of the *ortho*-alkynylated product (Table 1, entry 10). In all cases, unreacted starting material **1a** was recovered.

The scope of amides and selectivity of products under our reaction conditions is shown in Tables 2a-c. The reaction is general and a variety of amides (aromatic, heteroaromatic and α,β-unsaturated) were compatible with this transformation. With the optimized reaction conditions in hand (Table 1), various *ortho*-substituted benzamides were effectively alkynylated with excellent yields (up to 92%) under standard conditions (Table 2a).

Table 2a. The scope of 8-aminoquinolinyl (*ortho*-substituted) amides.[a]



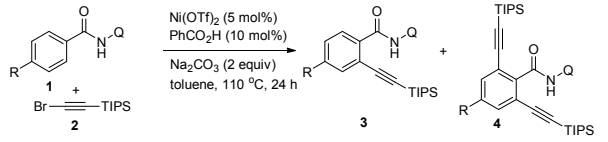
Entry	Amides	Conversion of 1 (%)[b]	Yield (%)[c]
1	 1a	81%	 + 4a (25%)[d] 3a (45%)
2	 1b	84%	 3b (75%)
3	 1c	93%	 3c (86%)
4	 1d	~98%	 3d (92%)

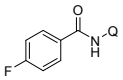
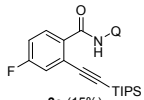
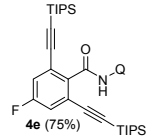
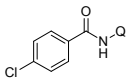
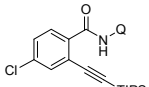
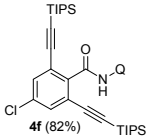
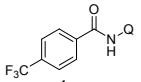
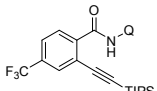
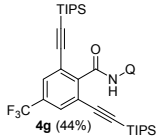
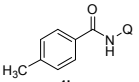
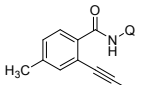
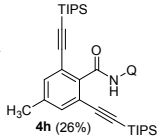
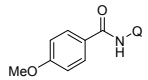
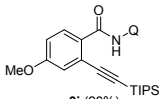
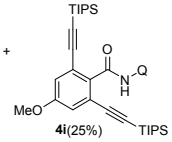
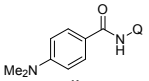
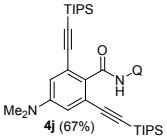
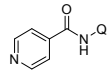
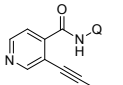
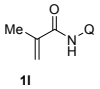
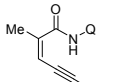
[a] Reaction conditions: **1** (0.1 mmol), catalyst (5 mol%), $PhCO_2H$ (10 mol%), **2** (0.2 mmol), Na_2CO_3 (2 equiv), and toluene (1 mL) at 110 °C for 24 hrs under argon. [b] Conversion based yield of recovered amide **1**. [c] Isolated yields. [d] Yield of bis-alkynylated product.

As shown in Table 2b, both electron-withdrawing (**1g**) and electron-donating groups (**1i-1j**) in the phenyl ring were well tolerated and to give alkynylated product in good yields. It is noteworthy that halide substituents were tolerated, as this is advantageous for further synthetic elaborations with transition-metal catalysis thereby broadening the diversity of the products. Thus, benzamides bearing halides such as chloro, bromo groups (**1c** in Table 2a, **1f** in Table 2b, and **1n-1o** in Table 2c) proceeded efficiently and leading to the corresponding alkynylated products in good yields under our catalytic conditions, wherein synthesis of such compounds using the traditional approach, "Sonogashira coupling" is very

difficult and rather scare. In addition, alkynylation of heteroaromatic amide (**1k**) smoothly occurred under standard conditions and affording **3k** in 42% yield. To our delight, challenging α,β-unsaturated amide (**1l**) also gave the corresponding alkynylated product in moderate yield (**3l** in 56% yield).

Table 2b. The scope of 8-aminoquinolinyl (*para*-substituted) amides.[a]

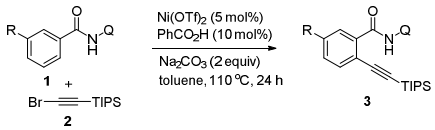


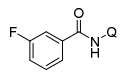
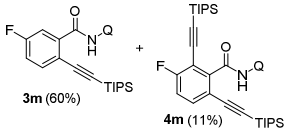
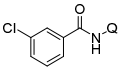
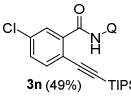
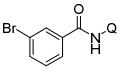
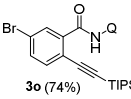
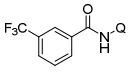
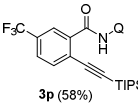
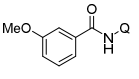
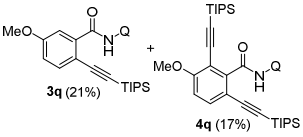
Entry	Amides	Conversion of **1** (%)[b]	Isolated yields (%) mono (**3**)	Isolated yields (%) di (**4**)
1	 **1e**	94%	 **3e** (15%)	 **4e** (75%)
2	 **1f**	91%	 **3f** (6%)	 **4f** (82%)
3	 **1g**	89%	 **3g** (40%)	 **4g** (44%)
4	 **1h**	65%	 **3h** (32%)	 **4h** (26%)
5	 **1i**	60%	 **3i** (28%)	 **4i**(25%)
6	 **1j**	78%	---	 **4j** (67%)
7	 **1k**	58%	 **3k** (42%)	---
8	 **1l**	65%	 **3l** (56%)	---

[a] Reaction conditions: **1** (0.1 mmol), catalyst (5 mol%), $PhCO_2H$ (10 mol%), **2** (0.3 mmol), Na_2CO_3 (2 equiv), and toluene (1 mL) at 110 °C for 24 hrs under argon. [b] Conversion based yield of recovered amide **1**.

When *meta*-substituted benzamides were used, the C-H alkynylation proceeded selectively at the less hindered position, providing the 1,2,5-trisubstituted amides with high regiocontrol (Table 2c).

Table 2c. Regioselective C(sp^2)-alkynylation of 8-aminoquinolinyl (*meta*-substituted) amides.[a]

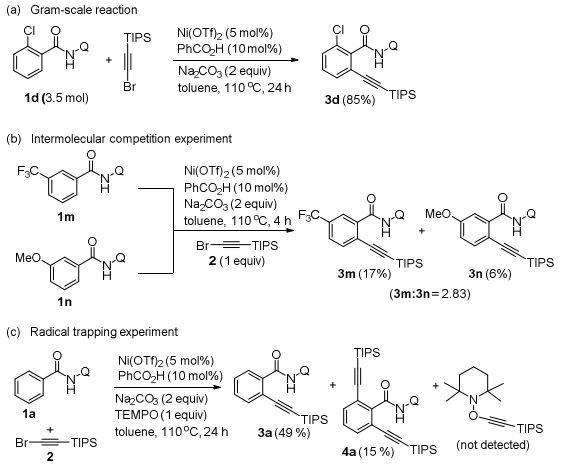


Entry	Amides	Conversion of **1** (%)[b]	Yield (%)[c]
1	 **1m**	78%	 **3m** (60%) **4m** (11%)
2	 **1n**	57%	 **3n** (49%) ---
3	 **1o**	83%	 **3o** (74%) ---
4	 **1p**	67%	 **3p** (58%) ---
5	 **1q**	41%	 **3q** (21%) **4q** (17%)

[a] Reaction conditions: **1** (0.1 mmol), catalyst (5 mol%), $PhCO_2H$ (10 mol%), **2** (0.2 mmol), Na_2CO_3 (2 equiv), and toluene (1 mL) at 110 °C for 24 hrs under argon. [b] Conversion based yield of recovered amide. [c] Isolated yields.

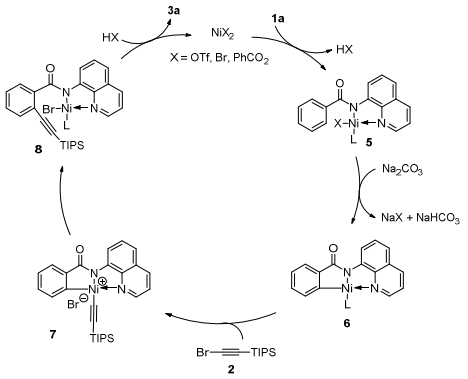
We have also successfully shown the scalability of this catalytic protocol under standard conditions to prepare 1.38 g of **3d** (Scheme 2a). A competition experiment with a different electronic substituent (*m*-CF_3 (**1p**) *vs* *m*-OCH_3 (**1q**); Scheme 2b) revealed that the reaction favours the electron-withdrawing group. This finding showed that the acidity of the *ortho* C-H bond is important and the cleavage of the *ortho* C-H bond may experience a concerted metalation-deprotonation (CMD) mechanism. Similar trend also was observed in previously reported palladium-catalyzed alkynylation reaction.[4o] To further gain some insights into the active catalytic species (Ni(II) *vs* Ni(0); Table 1) involved in this C(sp^2)-alkynylation reaction, a series of product distribution studies were performed under standard conditions.[21] These studies clearly indicate that nickel(II) is the actual key catalytic species and not the nickel(0). In case of, Ni(0) salt (Table 1, entry 10), the nickel(0) is oxidized to Ni(II) by the (triisopropylsilyl)ethynyl bromide under the reaction conditions and leading to the formation of (triisopropylsilyl)acetylene (**11**) *via* protonation and a self-coupled product 1,4-bis(triisopropylsilyl)buta-1,3-

diyne (**12**) demonstrating that the actual catalytically active species is Ni(II) (Scheme 4). Furthermore, performing the reaction in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under standard conditions, the reaction was not inhibited and no *O*-alkynylated-TEMPO product also was detected, indicating that the single-electron transfer (SET) in this reaction could be ruled out (Scheme 2c). Notably, alkynylation reaction progressed smoothly without the use of an oxidant.



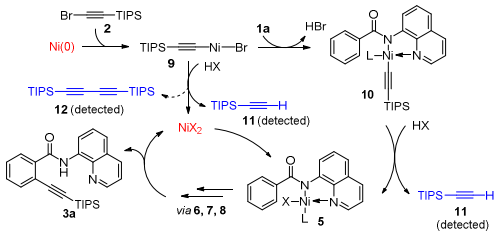
Scheme 2. Mechanistic experiments.

As shown in Scheme 3, the coordination of the amide **1a** to the Ni(II) followed by a ligand exchange with HX generation gives the complex **5**. This is because 8-aminoquinoline has a more acidic NH bond, which facilitates ligand exchange (promoted by a base). The complex **5** then undergoes cyclometalation to generate **6**, probably *via* a concerted metalation-deprotonation mechanism. The oxidative addition of TIPS-alkynyl bromide **2** leads to the formation of intermediate **7**. This is followed by a reductive elimination to give intermediate **8**, which is then protonated to afford the final alkynylated product with the regeneration of the active Ni(II) species. Surprisingly, other less hindered alkynyl halides (1-iodo-2-(trimethylsilyl)acetylene and (bromoethynyl)benzene) were not reactive, presumably a strong coordination of the alkyne moiety with the nickel center and thus may prevent the oxidative addition step, the amide-linked 8-aminoquinoline directing group can be easily removed using previously reported strategy (Scheme 5).[4o]



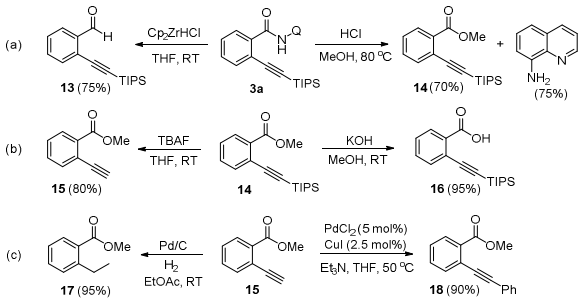
Scheme 3. A plausible mechanism for the Ni(II)-catalyzed *ortho*-alkynylation of benzamides (**1a**) with **2.**

In the case of the Ni(0) catalyst, the reaction of the Ni(0) complex with **2** to form the oxidative addition product TIPS–Ni–Br (**9**) which can react with the benzamide **1a** and generates the Ni(II) complex **10**. This is followed by ligand exchange with HX gives the complex **5** with the formation of (triisopropylsilyl)acetylene (**11**) or the intermediate **9** can react with HX to generate catalytically active Ni(II) species with the generation of **11**. Alternatively, **9** can also give a self-coupled product 1,4-bis(triisopropylsilyl)buta-1,3-diyne (**12**) with the generation of a Ni(II) complex. Both the products (**11** and **12**) were experimentally observed under standard conditions (Scheme 4).



Scheme 4. Formation of Ni(II) from Ni(0) and identification of intermediates.

To further broaden the synthetic utility of this alkynylated product, several interesting organic transformations of **1a** were carried out (Scheme 5).



Scheme 5. Removal of directing group and synthetic utility of alkynylated amide.

In conclusion, we have reported a mild and regioselective nickel-catalyzed direct alkynylation of C(sp^2)-H bonds of amides using commercially available, inexpensive 8-aminoquinoline as a removable bidentate directing group. Diverse halide substituted benzamides were selectively alkynylated under our conditions where as synthesis of such compounds using the traditional approach, "Sonogashira coupling" is very difficult and rather scare. The present *ortho*-alkynylation has a broad substrate scope as well as functional group tolerance, and can be scaled up.

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21 See supporting information.

22 Other bases such as LiOAc, NaOAc, CsOAc, Li_2CO_3, K_2CO_3, and Cs_2CO_3 did not improve the yield of the alkynylated products under optimal conditions.