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Nickel-catalyzed C–O/N–H, C–S/N–H, and C–CN/N–H annulation of aromatic amides with alkynes: C–O, C–S, and C–CN activation†

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The Ni-catalyzed reaction of *ortho*-phenoxy-substituted aromatic amides with alkynes in the presence of LiO^tBu as a base results in C–O/N–H annulation with the formation of 1(2*H*)-isoquinolinones. The use of a base is essential for the reaction to proceed. The reaction proceeds, even in the absence of a ligand, and under mild reaction conditions (40 °C). An electron-donating group on the aromatic ring facilitates the reaction. The reaction was also applicable to carbamate (C–O bond activation), methylthio (C–S bond activation), and cyano (C–CN bond activation) groups as leaving groups.

Introduction

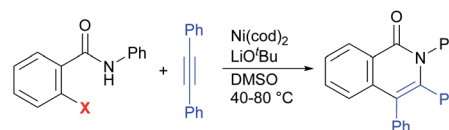
The cleavage of C(aryl)–O bonds mediated by transition metal complexes is of significant interest for the development of cross-coupling reactions and biomass utilization.¹ A variety of cross-coupling reactions that utilize phenol-derived electrophiles, such as pivalates, carbamates, sulfonates, and anisoles as an alternative to aryl halide coupling partners has been developed, because these are readily available and no halogen-containing waste products are generated during the reaction. The most broadly used catalysts in cross-coupling reactions of oxygen-based electrophiles are Ni complexes. The cleavage of inert C(aryl)–O bonds by a Ni complex generally requires a high reaction temperature along with the addition of a strong donor ligand, such as trialkylphosphines or an *N*-heterocyclic carbene (NHC) ligand, which leads to a decrease in functional group tolerance. While transformations that involve C(aryl)–O bond activation as a key step have been extensively studied, most of the reactions reported thus far are largely limited to cross-coupling reactions.² In this context, C(aryl)–O bond activation continues to be a relatively undeveloped area of research. We recently reported that the Ni-catalyzed C–F/N–H annulation of aromatic secondary amides with alkynes proceeds even in the absence of a ligand and at low reaction temperatures (40–100 °C).³ A key to the success of this reaction is the use of a base, which functions to abstract a proton from an aromatic amide resulting in the formation of an amidate species. Because one equivalent of a base is used, the amidate is a bona fide substrate, which reacts with a Ni(0) complex to give a highly active nickel ate complex. We were interested in whether this

methodology would be applicable to the activation of other unreactive bonds.

We herein report that the C–O/N–H annulation of aromatic amides with alkynes results in the production of isoquinolinones (Scheme 1).^{4,5} Remarkably, the reaction was also applicable to C–S/N–H and C–CN/N–H annulation, which proceed *via* C–S and C–CN bond activation.

Results and discussion

We began our studies by examining 2-phenoxy-*N*-phenylbenzamide (**1a**) as a model substrate and diphenylacetylene (**2a**) as a coupling partner with Ni(cod)₂ as a catalyst to evaluate the optimal reaction conditions for such a reaction (Table 1). The reaction of **1a** with **2a** (1.5 equiv.) in the presence of 10 mol% of Ni(cod)₂ and KO^tBu (1 equiv.) in DMF (0.5 mL) at 40 °C for 2 h gave the expected product **3aa** in 69% yield, along with 30% of **1a** being recovered and a trace amount of amide **4a**, which appears to be formed *via* the transfer of a phenyl group from an oxygen atom in **1a** to a nitrogen atom (Table 1, entry 1). After screening a series of solvents, it was found that the product yield could be improved to 85% when DMSO was used as a solvent (entries 2–4). Curiously, the presence of ligands, such as PPh₃, dppe, and dtbbpy in the reaction mixture resulted in



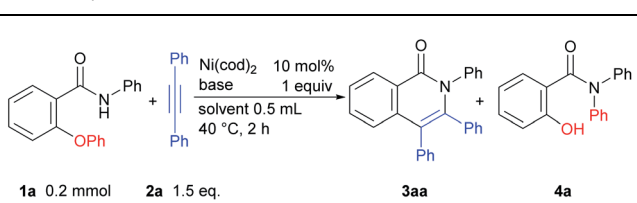
X = OPh, OCONPr₂, SMe, CN
■ C–O, C–S, C–CN bond activation

Scheme 1 Nickel-catalyzed C–O/N–H, C–S/N–H, C–CN/N–H annulation of aromatic amides with alkynes.

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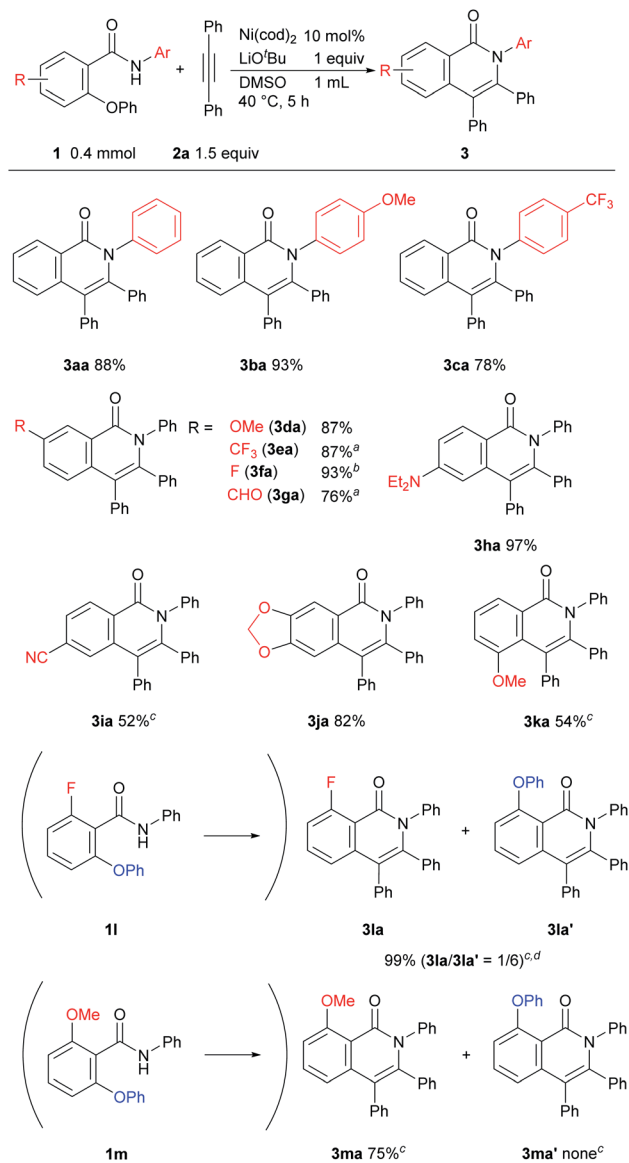
Table 1 Optimization of reaction conditions^a


Entry	Solvent	Ligand	Base	NMR yields ^b 3aa/4a/1a
1	DMF	None	KO ^t Bu	69%/trace/30%
2	Toluene	None	KO ^t Bu	10%/none/>99%
3	1,4-Dioxane	None	KO ^t Bu	48%/none/56%
4	DMSO	None	KO ^t Bu	85%/2%/7%
5	DMSO	PPh ₃	KO ^t Bu	57%/3%/47%
6	DMSO	dppf	KO ^t Bu	33%/3%/70%
7	DMSO	dtbbpy	KO ^t Bu	12%/5%/89%
8	DMSO	None	NaO ^t Bu	93%/none/trace
9	DMSO	None	LiO ^t Bu	93%/none/4%
10 ^c	DMSO	None	LiO ^t Bu	>99% (88%/)none/none ^e
11 ^d	DMSO	None	LiO ^t Bu	None/3%/>99%

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Ni(cod)₂ (0.02 mmol), and base (0.2 mmol) in solvent (0.5 mL) at 40 °C for 2 h. ^b NMR yields were determined from ¹H NMR with 1,1,1,2-tetrachloroethane as the internal standard. ^c 0.4 mmol scale, for 5 h. ^d Without Ni(cod)₂. ^e Isolated yield.

a decreased product yield (entries 5–7). When the reaction was carried out using NaO^tBu or LiO^tBu, the yield of the product was improved and the formation of byproduct **4a** was suppressed (entries 8 and 9). When the reaction was carried out using LiO^tBu for 5 h, the starting amide was completely consumed and the desired product was obtained in 88% isolated yield (entry 10). The reaction did not proceed in the absence of the Ni catalyst (entry 11). Finally, we determined the conditions for the reaction as shown in entry 10 as the standard conditions.

The results of a survey of substrate scope are shown in Scheme 2. First, the effect of the substituent group on the amide nitrogen atom was examined (**3ba** and **3ca**). An electron-withdrawing group on the nitrogen atom caused a slight decrease in the product yield. Various functional groups on the aromatic ring, such as methoxy, trifluoromethyl, fluoro, cyano, diethylamino, and even aldehyde groups were tolerated in the reaction. It was also found that when a substrate bearing an electron-withdrawing group was used, a longer reaction time or a higher reaction temperature was needed, as in **3ea**, **3fa**, **3ga**, and **3ia** suggesting that the cleavage of the C–O bond is not the rate-determining step.^{6,7} While it is well known that Ni complexes can be used to activate C–OMe,¹ C–F,⁸ and CN bonds,⁹ these bonds remained intact, as in **3ba**, **3da**, **3fa**, **3ka**, and **3ma**. Substrates bearing a substituent at the *ortho* position of the phenoxy group were also applicable to this reaction to give **3ka** in spite of the steric hinderance imposed by the phenoxy group. An amide bearing both C–OPh and C–F bonds at the *ortho* position **1l** reacted with **2** to give a mixture of two products, **3la** and **3la'** in favor of **3la'**, indicating that C–F bond activation predominated over C–O bond activation under the reaction conditions used. In the reaction of amide **1m**, which

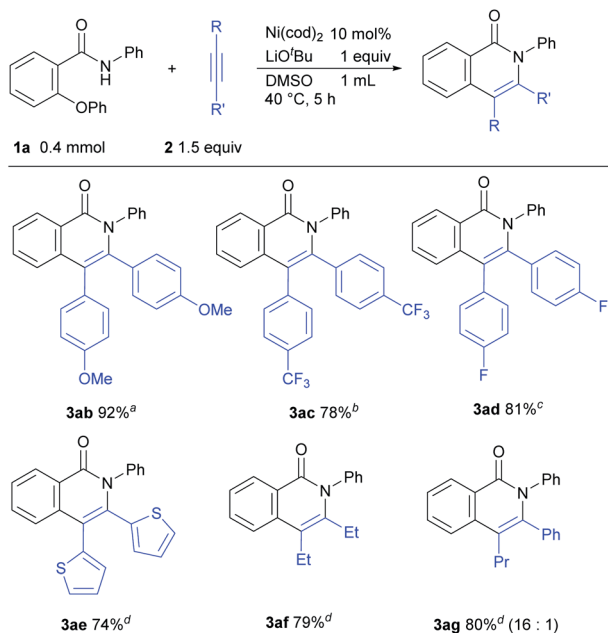


Scheme 2 Scope of amides for the reaction. Reaction conditions: amide (0.4 mmol), **2a** (0.6 mmol), Ni(cod)₂ (0.04 mmol), LiO^tBu (0.4 mmol) in DMSO (1 mL) at 40 °C for 5 h. Yields shown are isolated yields. ^a60 °C. ^b24 h. ^c80 °C. ^dThe product yield and the ratio of products were determined by ¹H NMR.

contains both OMe and OPh groups at the *ortho*-position, only the C–OPh bond was selectively cleaved to give **3ma** in 75% yield.

The scope of the reaction with respect to alkynes was also examined (Scheme 3). An alkyne bearing an electron-donating group **2b** reacted efficiently to give **3ab** in 92% isolated yield. This reaction was carried out in DMF as a solvent due to the insolubility of **2b** to DMSO. The reaction of electron-deficient alkynes required higher temperatures or longer reaction times (**3ac** and **3ad**). Alkynes with a thiophene ring and an aliphatic alkyne were also applicable for this reaction (**3ae** and **3af**). When an unsymmetrical alkyne **2g** was used, the product **3ag** was obtained in a regioselective manner.





Scheme 3 Scope of alkynes. Reaction conditions: **1a** (0.4 mmol), alkyne (0.6 mmol), $\text{Ni}(\text{cod})_2$ (0.04 mmol), LiOtBu (0.4 mmol) in DMSO (1 mL) at 40 °C for 5 h. Yields shown are the isolated yields. ^aDMF was used instead of DMSO as a solvent. ^b80 °C. ^c24 h. ^d60 °C.

In the course of our examination of other oxygen-based leaving groups, carbamates **5** were also found to participate in the reaction. Under the same reaction conditions as those used in the reaction of the phenoxy substrate **1a**, the expected products **3aa** were formed, but the undesired by-product **6aa** was also produced. After the brief optimization of the reaction conditions using **5c** as a substrate, toluene was determined to be the solvent of choice at 100 °C.¹⁰ The effect of substituents on the nitrogen-atom was next examined (Table 2). A carbamate

having two methyl groups on the nitrogen atom **5a** gave the desired product **3aa** in 52% yield, but the chromone derivative **6aa** was also obtained in 2% yield as a by-product (entry 1). The chromone **6aa** appears to be produced by acyl transfer from the oxygen atom to the nitrogen atom (see ESI[†]). When a carbamate with two isopropyl groups **5d** was used in the reaction, the desired product **3aa** was obtained in high yield and the formation of **6aa** was not observed (entry 4). The use of **5e** gave **3aa** in only 3% yield, although the starting material was completely consumed (entry 5).

The results of reactions in which a carbamate is used as the leaving group are shown in Scheme 4. The reaction of substrates bearing an electron-donating group proceeded efficiently to give good yields of the desired products **3da** and **3na**. The reaction of carbamates with an electron-withdrawing fluoro group required a higher reaction temperature (120 °C) for good yields of **3oa** to be obtained. The electronic effects of substituents on the alkyne had no effect on product yields (**3ab** and **3ac**). In the reaction of heteroaromatic acetylene and aliphatic acetylene derivatives, a longer reaction time was necessary (**3ae** and **3af**). When pivalate was used as a leaving group instead of a carbamate, in **5i**, the desired product **3aa** was obtained in lower yield and *N*-phenyl salicylamide was also produced in 38% NMR yield, which shows that the pivalate is unstable under basic conditions and C(O)–O bond is cleaved.

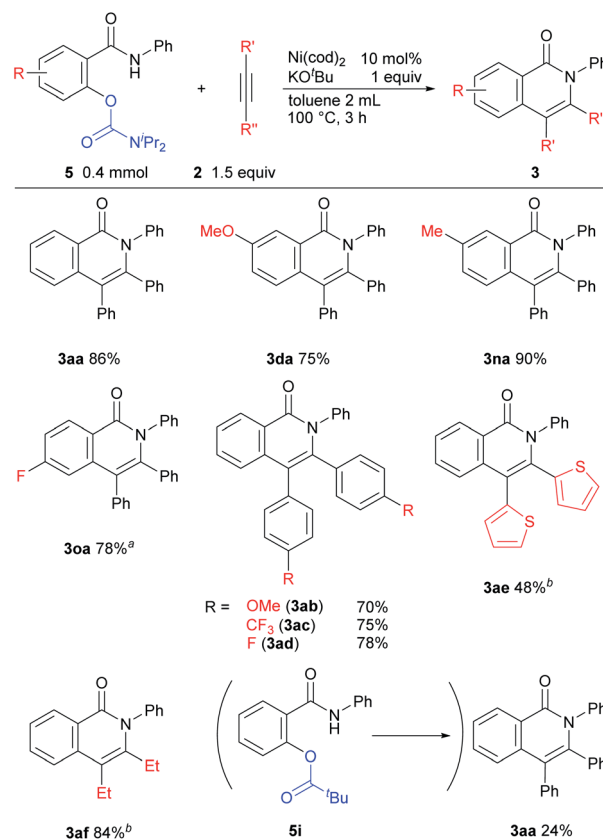


Table 2 Scope of substituents on the nitrogen atom^a

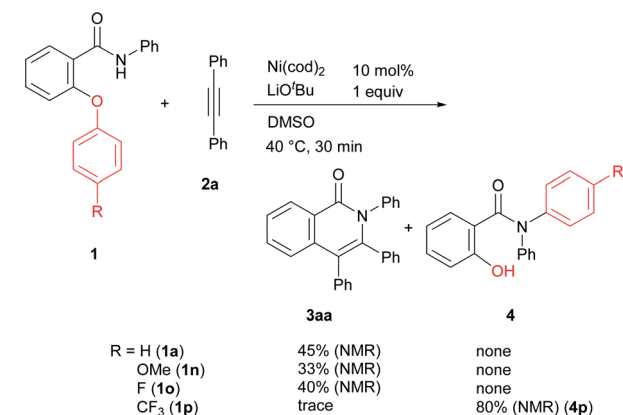
Entry ^a	R, R'	NMR yields ^b 3aa/6aa
1	Me, Me (5a)	52%/2%
2	Me, Et (5b)	74%/6%
3	Et, Et (5c)	90%/4%
4	iPr, iPr (5d)	98%/none
5	Ph, Ph (5e)	3%/none

^a Reaction conditions: **5** (0.2 mmol), **2a** (0.3 mmol), $\text{Ni}(\text{cod})_2$ (0.02 mmol), and KOtBu (0.2 mmol) in toluene (1 mL) at 100 °C for 3 h. ^b Yields were determined from ¹H NMR with 1,1,2,2-tetrachloroethane as the internal standard.

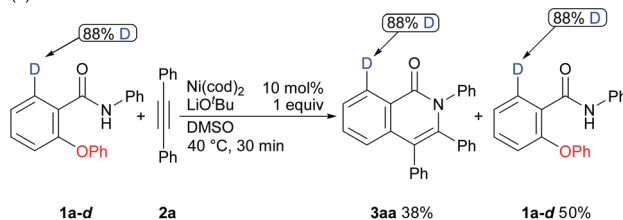
Scheme 4 Substrate scope for the reaction of carbamates. Reaction conditions: amide (0.4 mmol), alkyne (0.6 mmol), $\text{Ni}(\text{cod})_2$ (0.04 mmol), KOtBu (0.4 mmol) in toluene (2 mL) for 3 h at 100 °C. Yields shown are isolated yields. ^a120 °C. ^b22 h.



(a) electronic effect on leaving groups



(b) C-H vs C-O

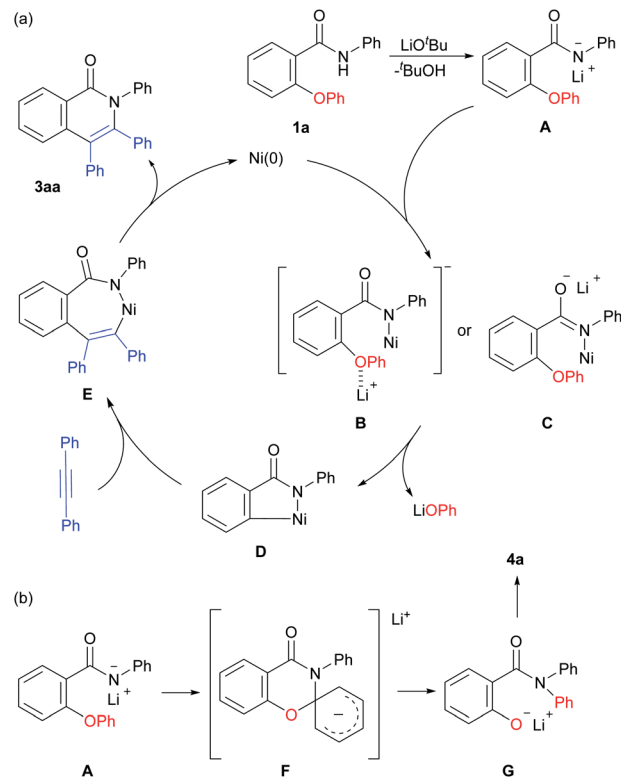


Scheme 5 Mechanistic studies.

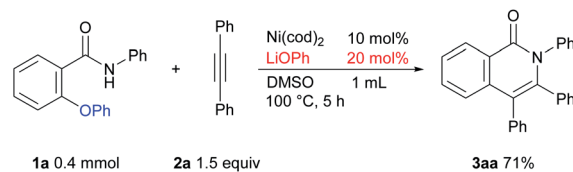
Some mechanistic studies were conducted to gain insights into the reaction mechanism (Scheme 5). Only a negligible effect was observed in the case of **1a**, **1n**, and **1o** (Scheme 1a). In sharp contrast, the product **3aa** was not formed, but, rather, an aryl group transfer product **4p** was produced as a sole product in the reaction of aromatic amide **1p** containing a substituted trifluoromethyl group, suggesting that a trifluoromethyl group promotes an aryl group transfer from an oxygen atom to a nitrogen atom. The reaction of the deuterium labeled substrate **1a-d** was also examined (Scheme 1b). In this case, no H/D exchange was observed in both the starting material and the product. This result indicates that C–H bond activation did not occur under the reaction conditions employed¹¹ and that only C–O bond activation took place in the reaction.

A plausible reaction mechanism is shown in Scheme 6. The amide **1a** reacts with a base to produce the lithium amidate **A**. The amidate **A** reacts with a Ni catalyst to give the anionic Ni amidate complex **B** or **C**. The oxidative addition of a C–O bond produces a five-membered nickelacycle **D** with the generation of LiOPh. The insertion of an alkyne followed by reductive elimination gives the product **3aa** with the regeneration of the Ni(0) species. A possible pathway for the formation of **4a** involves an intramolecular S_NAr type reaction *via* **F**, which is consistent with the experimental results showing that a trifluoromethyl group facilitates the formation of **4a**, as shown in Scheme 5a.

In the above mechanism, LiOPh is generated in the reaction. We hypothesized that a catalytic amount of LiOPh could be used instead of a stoichiometric amount of LiOtBu. As expected, the reaction proceeded even in the presence of a catalytic amount of LiOPh (Scheme 7). However, a higher reaction temperature was



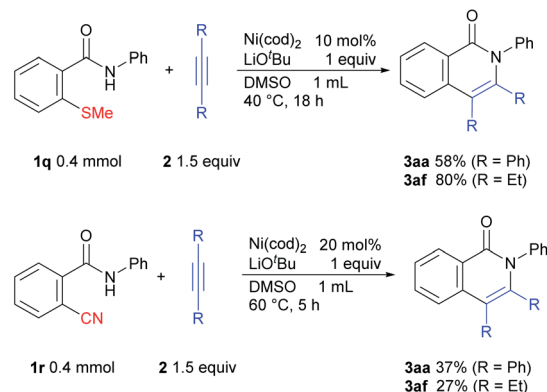
Scheme 6 A plausible mechanism.



Scheme 7 The reaction using a catalytic amount of LiOPh.

necessary for the reaction to proceed efficiently, so we concluded that LiOtBu was the optimal base.

We also examined the issue of whether this methodology might also be applicable to other strong bonds (Scheme 8).



Scheme 8 C–S and C–CN bond activation reactions.



Gratifyingly, it was found that C–S bond activation also occurs to give the desired products.¹² We also examined the possibility of C–CN bond activation, which afforded the desired products.¹³

Conclusions

In summary, we report herein on the Ni-catalyzed C–O/N–H, C–S/N–H and C–CN/N–H annulation of amides with alkynes, leading to the production of 1(2*H*)-isoquinolinones. The reaction proceeded in the absence of ligands under low temperature and a wide variety of important functional groups was tolerated. The new methodology reported herein, such as the amidate-promoted activation of C–O bonds is applicable to the activation of other unreactive bonds, such as C–S and C–CN. Studies of the use of this methodology are currently underway and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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