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Communication

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# Nickel-Catalyzed C-F/N-H Annulation of Aromatic Amides with Alkynes: Activation of C-F Bonds under Mild Reaction Conditions

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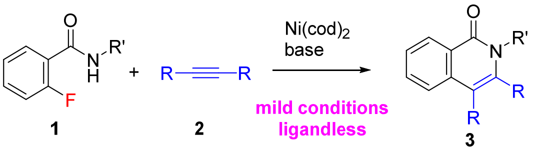
**ABSTRACT:** The Ni-catalyzed reaction of *ortho*-fluoro-substituted aromatic amides with alkynes results in C-F/N-H annulation to give 1(2H)-isoquinolinones. A key to the success of the reaction is the use of $KOBu^t$ or even weak base, such as $Cs_2CO_3$. The reaction proceeds in the absence of a ligand and under mild reaction conditions (40-60 °C). Competition experiments and DFT calculations suggest that the pathway for this Ni-catalyzed C-F/N-H annulation involves NH deprotonation, oxidative addition of C-F bond, migratory insertion of an alkyne, and reductive elimination pathway to form 1(2H)-isoquinolinone derivatives.

The use of reactive chemical bonds has long been the primary focus of organic synthesis. However, various unreactive chemical bonds, such as C-H,[1] C-C,[2] and C-O[3] bonds are now beginning to be used in organic transformations, thus providing new possibilities for developing new synthetic methodologies. C-F bonds are an example of such unreactive chemical bonds that have great potential.[4] In fact, a variety of Ni-catalyzed cross-coupling reactions of aryl fluorides with nucleophiles have been reported thus far,[5] however the reaction patterns including C-F bond activation as a key step are still limited mainly to cross-coupling reactions. In this context, C-F bond activation still remains a relatively undeveloped area of research and there is considerable room for the subject to continue to evolve.

**Scheme 1.** Ni-Catalyzed C-F/N-H Annulation of Aromatic Amides with Alkynes



In various pharmaceuticals, natural products and biologically active molecules, isoquinolin-1(2H)-one serves as a key structural unit that is crucial to their bioactivities and their derivatives are also widely used as key intermediates in various organic transformations.[6] A number of synthetic methods for the construction of an isoquinolin-1(2H)-one core have been developed over the past few decades.[7] One straightforward method includes Ni-catalyzed C-I/N-H annulation with alkynes.[8] More atom-economical methods involving C-H/N-H annulation with alkynes including C-H bond activation have also been extensively studied.[9,10]

Herein, we report the Ni-catalyzed C-F/N-H annulation of *ortho*-fluoro-substituted aromatic amides with alkynes, leading to the production of isoquinolin-1(2H)-ones, the formation of which involves the activation of a C-F bond (Scheme 1).[11]

**Table 1.** Ni-Catalyzed C-F/N-H Annulation of Aromatic Amide **1a** with Diphenylacetylene (**2a**)

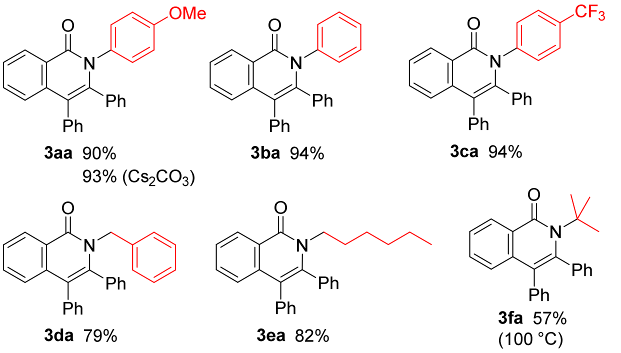
| entry | base | solvent | deviations from the reaction conditions[a] | NMR yields **3aa** / **1a** (%) |
|---|---|---|---|---|
| 1 | $NaO^tBu$ | dioxane | dtbbpy 0.05 mmol | 97 / trace |
| 2 | $NaO^tBu$ | dioxane | $PPh_3$ 0.05 mmol | 97 / 3 |
| 3 | $NaO^tBu$ | dioxane | | 88 / trace |
| 4 | $NaO^tBu$ | toulene | | 41 / 63 |
| 5 | $NaO^tBu$ | xylene | | 70 / 22 |
| 6 | $NaO^tBu$ | DMF | | 99 / trace |
| 7 | KOMe | dioxane | | 87 / trace |
| 8 | $KO^tBu$ | dioxane | | 99/ trace |
| 9 | $K_2CO_3$ | dioxane | | no reaction |
| 10 | no base | dioxane | | no reaction |
| 11 | $NaO^tBu$ | dioxane | $Ni(OAc)_2$ | 68 / 22 |
| 12 | $KO^tBu$ | dioxane | 60 °C | 89 / 7 |
| 13 | $KO^tBu$ | DMF | | 99 / trace |
| **14** | **$KO^tBu$** | **DMF** | **40 °C, 6 h** | **99 / trace** |
| 15 | $KO^tBu$ | DMF | no catalyst | no reaction |
| **16** | **$Cs_2CO_3$** | **DMF** | **60 °C, 14 h** | **97 / 3%** |

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), Ni(cod)$_2$ (0.025 mmol), base (0.25 mmol), solvent (0.25 mL), 100 °C for 14 h.

The reaction of 2-fluoro-*N*-(4-methoxyphenyl)benzamide (**1a**) with diphenylacetylene (**2a**) in the presence of

$Ni(cod)_2$ and 4,4'-di-tert-butyl-2,2'-dipyridyl (dtbbpy) in 1,4-dioxane at 100 °C gave 2-(4-methoxyphenyl)-3,4-diphenylisoquinolin-1(2H)-one (**3aa**) in 97% NMR yield (entry 1 in Table 1). Curiously, **3aa** was obtained in high yield, even when the reaction was carried out in the absence of a ligand (entry 3). Among the solvents examined, 1,4-dioxane and DMF gave **3aa** in high yield (entires 3 and 6). No reaction took place when the reaction was carried out in the presence of $K_2CO_3$ or in the absence of a base (entries 9 and 10). It was found that $Ni(OAc)_2$ also shows a catalytic activity (entry 11). Interestingly, the reaction in 1,4-dioxane, even at 60 °C gave **3aa** in 89% yield, along with 7% of **1a** being recovered (entry 12). Because the amide was only sparingly soluble in dioxane, DMF was used as a solvent (entry 13). Gratifyingly, it was found that the reaction proceeds smoothly, even at 40 °C in DMF for 6 h (entry 14). Interestingly, the use of 1 equiv of a weak base, such as $Cs_2CO_3$, also gave **3aa** in 97% NMR yield (entry 16).[12] Finally, we determined the reaction conditions shown in entries 14 and 16 as standard reaction conditions. We previously reported the Ni-catalyzed oxidative C-H/N-H annulation of aromatic amides with alkynes.[10] However, such a reaction was not observed in all cases. If the *ortho* C-H bond in **1a** could be activated, the product would be **3ia** (see Scheme 3). However, only **3aa** was produced in all cases.

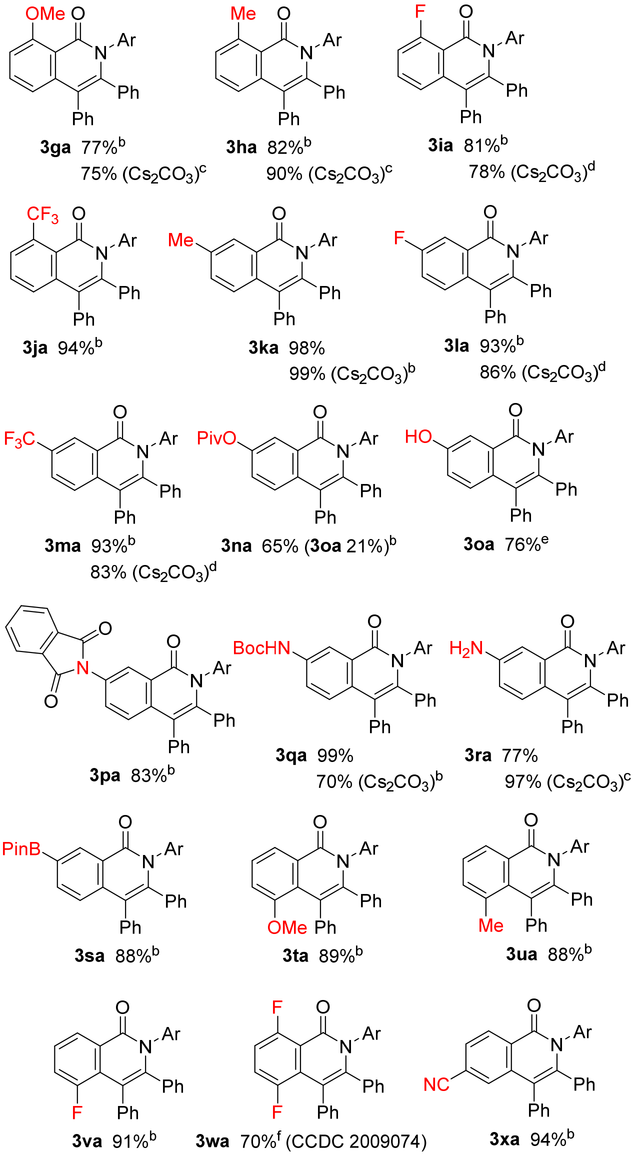
**Scheme 2.** Effect of *N*-substituents



The effect of substituents on the amide nitrogen was examined under the optimized conditions (entry 14 in Table 1). The scope of N-substituents was wide and aryl groups containing both electron-donating (OMe) and electron-withdrawing ($CF_3$) groups gave the corresponding isoquinolinones, **3aa** and **3ca** in high yields. The presence of an alkyl group, such as benzyl, hexyl, and tert-butyl groups also gave the corresponding products, **3da**, **3ea**, and **3fa**.

The scope of this annulation reaction was investigated with respect to the 2-fluoro-*N*-(4-methoxyphenyl)benzamide derivatives (Scheme 3). It was found that the reaction of *ortho*-substituted substrates required a slightly higher reaction temperature, i.e. 60 °C. While nickel complexes are known to activate C-O,[3] C-F,[4,5] and CN bonds,[2b] these bonds did not react, as in **3ga**, **3ia**, **3la**, **3na**, **3ta**, **3va**, **3wa**, and **3xa** because the present reaction proceeds smoothly, even at a low temperature. The reaction shows a high functional group compatibility. Even free $NH_2$ and OH groups were tolerated in the reaction. Remarkably, a boryl group was also tolerated in the reaction, which allowed further elaboration to produce useful and complex molecules by cross-coupling reactions. Even sterically hindered substrates, such as **1t** and **1u** reacted with **2a** to give **3ta** and **3ua** in high yields. These types of products cannot be obtained through C-H/N-H oxidative annulation because the less hindered C-H bonds are selectively activated in most cases.

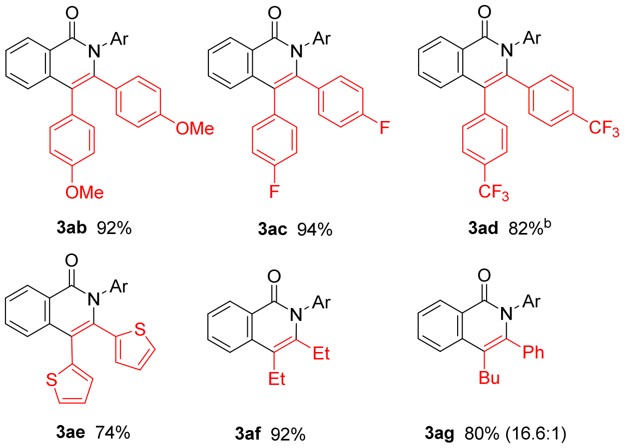
**Scheme 3.** Scope of Amides in the Ni-Catalyzed C-F/N-H Annulation of Aromatic Amides **1** (Ar = 4-MeO$C_6H_5$) with Diphenylacetylene (**2a**)[a]



[a]Reaction conditions: amide **1** (0.25 mmol), diphenylacetylene (**2a**) (0.3 mmol), $Ni(cod)_2$ (0.025 mmol), KO$^t$Bu (0.25 mmol), and DMF (0.25 mL) at 40 °C for 6 h. [b]The reaction was carried out at 60 °C for 14 h. [c]$Cs_2CO_3$ (2 equiv), DMF (0.5 mL) at 100 °C for 24 h. [d]At 100 °C for 14 h. [e]KO$^t$Bu (2 equiv). [f]At 80 °C for 24 h.

The scope of alkynes was also investigated (Scheme 4). Various diarylacetylenes, including diarylacetylenes and 1,2-di(thiophen-2-yl)ethyne reacted readily to give the corresponding isoquinolinones, **3ab**-**3ae**. Alkyl-substituted alkynes, such as 3-hexyne also participated in the reaction to give **3af** in high yield. The reaction with unsymmetrical alkynes, such as 1-phenylpropyne gives the corresponding 1(2H)-isoquinolinones in a regioselective manner.

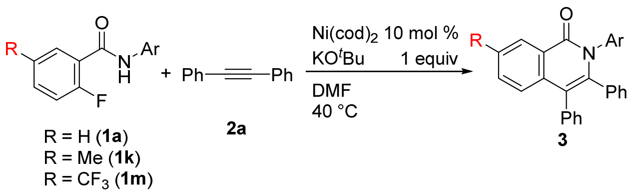
**Scheme 4.** Scope of Alkynes in Ni-Catalyzed C-F/N-H Annulation of Aromatic Amide 1a with Alkynes[a]

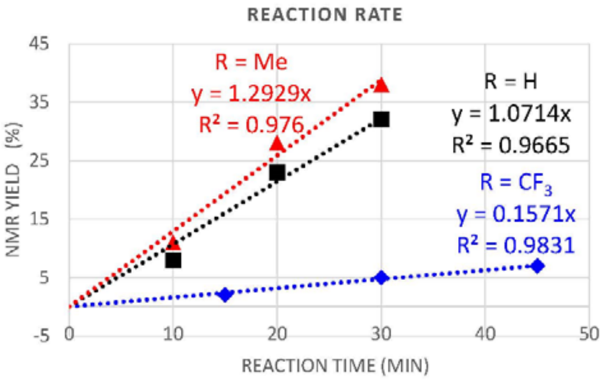


[a]Reaction conditions: amide **1a** (0.25 mmol), alkyne (0.3 mmol), Ni(cod)$_2$ (0.025 mmol), KO$^t$Bu (0.25 mmol), and DMF (0.25 mL) at 40 °C for 6 h. Isolated yield. [b]The reaction was carried out at 60 °C for 14 h.

To gain mechanistic insights into the reaction, competition experiments using **1a**, **1k** and **1m** were examined (Scheme 5). An electron-withdrawing group dramatically decelerates the reaction, suggesting that C-F bond activation appears not to be a rate-determining step.

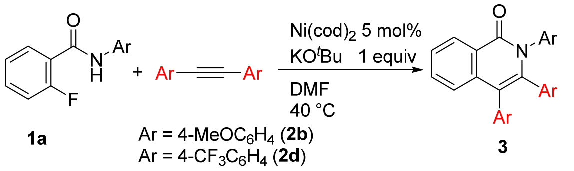
**Scheme 5.** Electronic Effects: Aromatic Amides

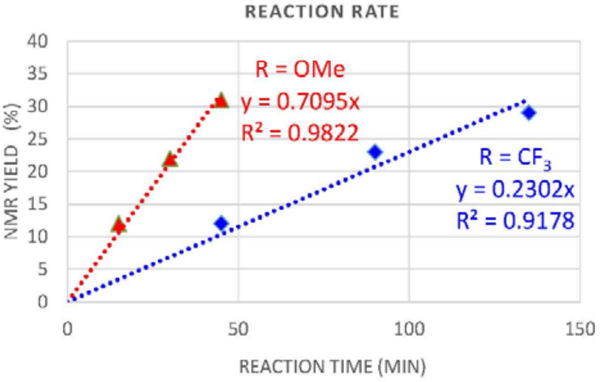




We next examined the electronic effects of a substituent on alkynes in the reaction of **1a**. In the case of the methoxy-substituted alkyne **2b**, the reaction was very fast and reached completion within 20 min under the standard conditions. the reaction was then carried out using a lower catalyst loading (5 mol % Ni(cod)$_2$). It was found that the presence of an electron-rich methoxy group resulted in a significant acceleration in the reaction (Scheme 6).

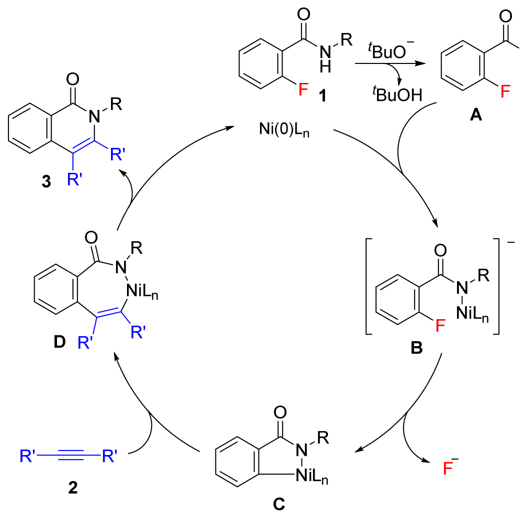
**Scheme 6.** Electronic Effects: Alkynes





A proposed mechanism for the above reaction is shown in Scheme 7, based on the results of competition experiments. The base abstracts the NH proton of the amide **1** to generate the amidate anion **A**, which reacts with Ni(0) followed by C-F activation to give the nickelacycle **C** through the nickel ate complex **B**.[10c,13] The insertion of an alkyne into the C-Ni bond in **C** gives the seven-membered nickalacycle **D**. Reductive elimination gives the isoquinolinone **3** with the regeneration of Ni(0). As shown in Scheme 5, the presence of an electron-donating group on an aromatic ring accelerates the reaction, suggesting that C-F bond cleavage is not involved in the rate-determining step, instead the insertion of the alkyne appear to be the rate-determining step.

**Scheme 7.** Proposed Reaction Mechanism



A detailed computational study was performed to investigate the mechanism for this Ni-catalyzed C-F/N-H annulation of aromatic amides with alkynes. The calculated Gibbs energy profiles for oxidation addition, migratory insertion and reductive elimination pathway are shown in Figure 1, where the Ni(0) species **CP1** was set as the relative zero point.[14] Ligand exchange of the deprotonated substrate **1a'** with the cyclooctadiene moiety in **CP1** gives the amido-Ni(0) complex **CP2** with an endothermal energy of 5.9 kcal/mol. The C-F bond in **1a** is then activated by coordination with the Ni(0) center in **CP3**. The subsequent oxidative addition of the C-F bond onto Ni(0) occurs via the transition state **TS1** with an energy barrier of 18.7 kcal/mol, in which the five-membered nickelacycle **CP4** is generated. In **TS1**, the lengths of the breaking C-F bond and the forming C-Ni bond are 1.59 and 2.02 A, respectively. KF is then released from the Ni(II) center in **CP4** to yield **CP5** with an endothermal energy of 6.5 kcal/mol. The subsequent migratory insertion of the C-C triple bond into Ni-C(aryl) bond with the coordination of the diphenylacetylene **2a** to the Ni(II) center gives the alkenyl-Ni(II) intermediate **CP6** via the transition state **TS2** with an energy barrier of 19.9 kcal/mol. Structural information regarding **TS2** shows that the lengths of the forming C-C bond and the breaking the C-Ni bond are 2.05 and 1.95A, respectively. The calculations indicate that the migratory insertion step is the rate-determining step in the catalytic cycle, which is consistent with the results of competition experiments shown in Scheme 5, and the overall activation free energy for this reaction is 30.4 kcal/mol. It should also be noted that the free energy difference between **TS1** and **TS2** is small, which would result in the rate-determining step of this reaction being changed depending on the effect of the substituent on **1a** and the alkyne being used. The calculations indicate that the migratory insertion step without the coordination of an extra diphenylacetylene to the Ni(II) center occurs via the transition state **TS4** with an overall free energy of activation of 37.6 kcal/mol, which is 7.2 kcal/mol higher than that of **TS2**. The vinyl-Ni(II) intermediate **CP6** would isomerize into the seven-membered vinyl-Ni(II) intermediate **CP7**. The C(vinyl)-N reductive elimination takes place via the transition state **TS3** with an energy barrier of only 10.9 kcal/mol to give the $\eta^3$-coordinated Ni(0) species **CP8**. In **TS3**, the length of the forming C-N bond is 1.95 A. The ligand exchange of **1a'** with the isoquinoline product **3aa** gives the active catalytic intermediate **CP2**, thus completing the catalytic cycle.

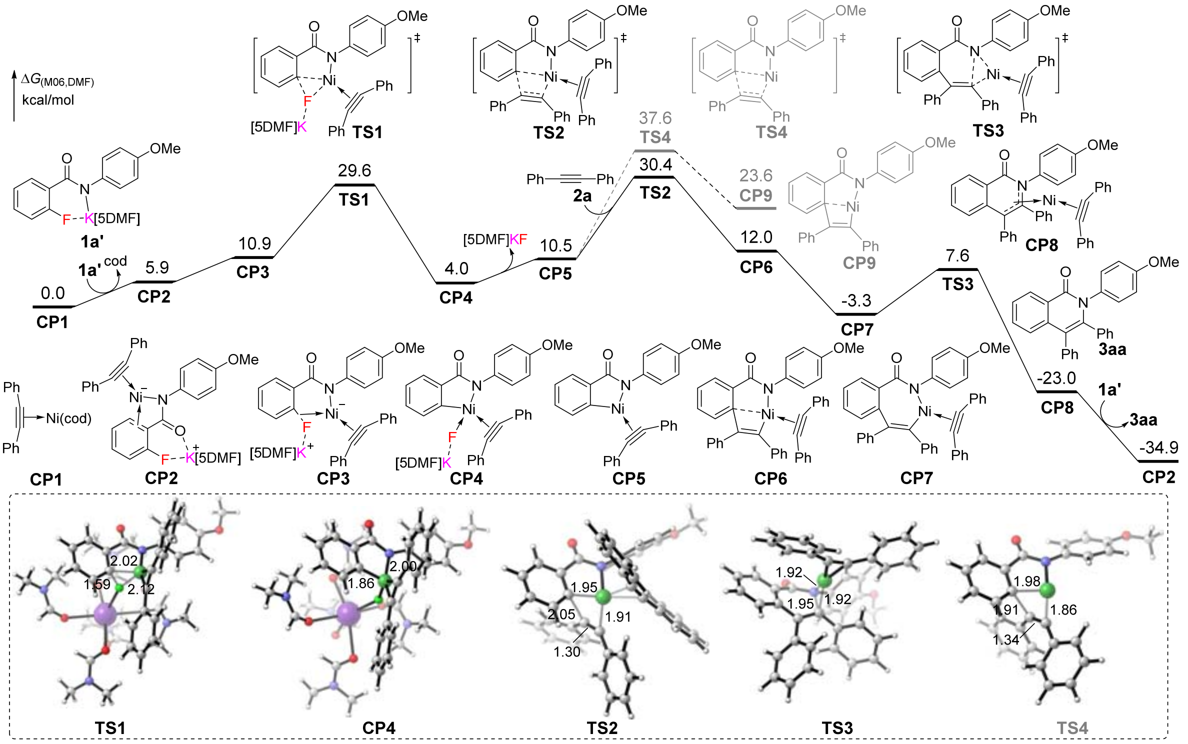


**Figure 1.** Free energy profiles for oxidation addition, migratory insertion and reductive elimination pathway of the Ni-catalyzed C-F/N-H annulation of aromatic amides with alkynes.

In summary, we report herein on the Ni-catalyzed C-F/N-H annulation of *ortho*-fluoro-substituted aromatic amides with alkynes, leading to the production of 1(2H)-isoquinolinones, in which activation of C-F bond is a key step.[15] The reaction proceeds in the absence of a ligand and under mild reaction conditions (40-60 °C). The new methodology reported herein, such as the amidate-promoted activation of C-F bonds is applicable to the activation of other unreactive bonds. Studies of the use of this methodology are currently underway and will be reported in due course.

## ASSOCIATED CONTENT

**Supporting Information**. The Supporting Information is available free charge at http://pubs.acs.org.
Experimental procedure, synthesis of starting materials, and characterization of compounds. Computational Studies.
X-ray structural information of **3wa** (CCDC-2009074).

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### Notes

There are no conflicts to declare.

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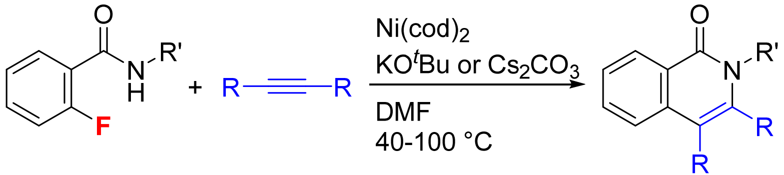
## REFERENCES

1. For recent selected reviews on C-H activation, see: (a) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A Comprehensive Overview of Directing Groups Applied in Metal-Catalysed C⍰H Functionalisation Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603–6743. (b) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C⍰H Activation. *Chem. Rev.* **2019**, *119*, 2192–2452. (c) Rej, S.; Chatani, N. Rhodium-Catalyzed $C(sp^2)$–H or $C(sp^3)$–H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 8304-8329. (d) Khake, S. M.; Chatani, N. Chelation-Assisted Nickel-Catalyzed C-H Functionalizations. *Trends in Chem.* **2019**, *1*, 524-539. (e) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C-H Bond Functionalization Chemistry for the Expedient Construction of C-C Bonds. *Chem. Rev.* **2020**, *120*, 1788-1887.
2. For a recent review on C-C activation, see: (a) Li, H.; Shi, Z.-J. Catalysis in C-C Activation, Edited by Shi, Z.-J. Homogeneous Catalysis for Unreactive Bond Activation (2015), 575-619, John Wiley & Sons, Inc. (b) Nakao, Y. Catalytic C-CN Bond Activation. *Topics in Current Chem*. **2014**, *346*, 33-58. (c) Deng, L.; Dong, G. Carbon-Carbon Bond Activation of Ketones. *Trends in Chem.* **2019**, *2*, 183-198.
3. For recent selected reviews on C-O activation, see: (a) Tobisu, M.; Chatani, N. Cross-Couplings Using Aryl Ethers via C-O Bond Activation Enabled by Nickel Catalysts. *Acc. Chem. Res.* **2015**, *48*, 1717-1726. (b) Bisz, E.; Szostak, M. Iron-Catalyzed C-O Bond Activation: Opportunity for Sustainable Catalysis. *ChemSusChem* **2017**, *10*, 3964-3981.
4. For recent reviews on C-F activation, see: Yang, S.-D. Homogeneous transition-metal-catalyzed C-F activation, Edited by Shi, Z.-J. Homogeneous Catalysis for Unreactive Bond Activation (2015), 203-268, John Wiley & Sons, Inc.
5. For selected papers on cross-coupling reactions involving C-F activation, see: (a) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. Nickel-Catalyzed Suzuki-Miyaura Reaction of Aryl Fluorides. *J. Am. Chem. Soc.* **2011**, *133*, 19505-19511. (b) Liu, X.-W.; Echavarren, J.; Zarate, C.; Martin, R. Ni-Catalyzed Borylation of Aryl Fluorides via C-F Cleavage. *J. Am. Chem. Soc.* **2015**, *137*, 12470-12473. (c) Niwa, T.; Ochiai, H.; Watanabe, Y.; Hosoya, T. Ni/Cu-Catalyzed Defluoroborylation of Fluoroarenes for Diverse C-F Bond Functionalizations. *J. Am. Chem. Soc.* **2015**, *137*, 14313-14318. (d) Ogawa, H.; Yang, Z.-K.; Minami, H.; Kojima, K.; Saito, T.; Wang, C.; Uchiyama, M. Revisitation of Organoaluminum Reagents Affords a Versatile Protocol for C-X (X = N, O, F) Bond-Cleavage Cross-Coupling: A Systematic Study. *ACS Catal.* **2017**, *7*, 3988-3994. (e) Harada, T.; Ueda, Y.; Iwai, T.; Sawamura, M. Nickel-Catalyzed Amination of Aryl Fluorides with Primary Amines. *Chem. Commun.* **2018**, *54*, 1718-1721. (f) Li, J.; Wu, C.; Zhou, B.; Walsh, P. J. Nickel-Catalyzed $C(sp^3)$-H Arylation of Diarylmethane Derivatives with Aryl Fluorides. *J. Org. Chem.* **2018**, *83*, 2993-2999. (g) Ho, Y. A.; Leiendecker, M.; Liu, X.; Wang, C.; Alandini, N.; Rueping, M. Nickel-Catalyzed $Csp^2$-$Csp^3$ Bond Formation via C-F Bond Activation. *Org. Lett.* **2018**, *20*, 5644-5647. (h) Zhao, X.; Wu, M.; Liu, Y.; Cao, S. LiHMDS-Promoted Palladium or Iron-Catalyzed ipso-Defluoroborylation of Aryl Fluorides. *Org. Lett.* **2018**, *20*, 5564-5568. (i) Lim, S.; Song, D.; Jeon, S.; Kim, Y.; Kim, H.; Lee, S.; Cho, H.; Lee, B. C.; Kim, S. E.; Kim, K. Cobalt-Catalyzed C-F Bond Borylation of Aryl Fluorides. *Org. Lett.* **2018**, *20*, 7249-7252. (j) Tian, Y.-M.; Guo, X.-N.; Kuntze-FechnerIvo, M. W.; Krummenacher, I.; Braunschweig, H.; Radius, U.; Steffen, A.; Marder, T. B. Selective Photocatalytic C-F Borylation of Polyfluoroarenes by Rh/Ni Dual Catalysis Providing Valuable Fluorinated Arylboronate Esters. *J. Am. Chem. Soc.* **2018**, *140*, 17612-17623.
6. (a) Pettit, G. R.; Meng, Y. H.; Herald, D. L.; Graham, K. A. N.; Pettit, R. K.; Doubek, D. L. Isolation and Structure of Ruprechstyril from Ruprechtia tangarana. *J. Nat. Prod.* **2003**, *66*, 1065–1069. (b) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. Studies on the Narciclasine Alkaloids: Total Synthesis of (+)-Narciclasine and (+)-Pancratistatin. *J. Am. Chem. Soc.* **2000**, *122*, 6624–6628. (c) Guo, S.; Sun, L.; Liu, Y.; Ma, N.; Zhang, X.; Fan, X. Rh(III)-Catalyzed Oxidative Spirocyclization of Isoquinolones with α-Diazo-1,3-indandiones. *Org. Lett.* **2019**, *21*, 4082–4086.
7. For selected examples, see: (a) Kajita, Y.; Matsubara, S.; Kurahashi, T. Nickel-Catalyzed Decarbonylative Addition of Phthalimides to Alkynes. *J. Am. Chem. Soc.* **2008**, *130*, 6058-6059. (b) Miura, T.; Yamauchi, M.; Murakami, M.

Synthesis of 1(2H)-Isoquinolones by the Nickel-Catalyzed Denitrogenative Alkyne Insertion of 1,2,3-Benzotriazin-4(3H)-ones. *Org. Lett.* **2008**, *10*, 3085-3088. (c) Norager, N. G.; Juhl, K. Conjugate Addition-SNAr Domino Reaction for the Synthesis of Benzo- or Pyridyl-Fused Lactams and Sultams. *Synthesis* **2010**, *24*, 4273-4281. (d) Poater, A.; Vummaleti, S. V. C.; Cavallo, L. Catalytic Role of Nickel in the Decarbonylative Addition of Phthalimides to Alkynes, *Organometallics* **2013**, *32*, 6330-6336. (e) Wang, H.; Yu, S. Synthesis of Isoquinolones Using Visible-Light-Promoted Denitrogenative Alkyne Insertion of 1,2,3-Benzotriazinones. *Org. Lett.* **2015**, *17*, 4272-4275. (f) Fang, Z.-J.; Zheng, S.-C.; Guo, Z.; Guo, J.-Y.; Tan, B.; Liu, X.-Y. Asymmetric Synthesis of Axially Chiral Isoquinolones: Nickel-Catalyzed Denitrogenative Transannulation *Angew. Chem., Int. Ed.* **2015**, *54*, 9528–9532. (g) Min, X.-T.; Ji, D.-W.; Zheng, H.; Chen, B.-Z.; Hu, Y.-C.; Wan, B.; Chen, Q.-A. Cobalt-Catalyzed Regioselective Carboamidation of Alkynes with Imides Enabled by Cleavage of C–N and C–C Bonds. *Org. Lett.* **2020**, *22*, 3386-3391.

8. Liu, C.-C.; Parthasarathy, K.; Cheng, C.-C. Synthesis of Highly Substituted Isoquinolone Derivatives by Nickel-Catalyzed Annulation of 2-Halobenzamides with Alkynes. *Org. Lett.* **2010**, *12*, 3518-3521. Weng, W.-Z.; Xie, J.; Zhang, B. Mild and Efficient Synthesis of Indoles and Isoquinolones via a Nickel-Catalyzed Larock-Type Heteroannulation Reaction. *Org. Biomol. Chem.* **2018**, *16*, 3983-3988.
9. For recent selected papers on the synthesis of isoquinolin-1(2H)-one derivatives including C-H/N-H coupling with alkynes, see: (a) Tang, S.; Wang, D.; Liu, Y.; Zeng, L.; Lei, A. Cobalt-catalyzed electrooxidative C-H/N-H [4+2] annulation with ethylene or ethyne. *Nat. Commun.* **2018**, *9*, 798. (b) Kalsi, D.; Dutta, S.; Barsu, N.; Rueping, M.; Sundararaju, B. Room-Temperature C–H Bond Functionalization by Merging Cobalt and Photoredox Catalysis. *ACS Catal.* **2018**, *8*, 8115-8120. (c) Mei, R.; Sauermann, N.; Oliveira, J. C. A.; Ackermann, L. Electroremovable Traceless Hydrazides for Cobalt-Catalyzed Electro-Oxidative C–H/N–H Activation with Internal Alkynes *J. Am. Chem. Soc.*, **2018**, *140*, 7913-7921.
10. For papers from this laboratory on the Ni-catalyzed C-H/N-H coupling with alkynes, see: (a) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. Nickel-Catalyzed Chelation-Assisted Transformations Involving Ortho C-H Bond Activation: Regioselective Oxidative Cycloaddition of Aromatic Amides to Alkynes. *J. Am. Chem. Soc.* **2011**, *133*, 14952-14955. (b) Obata, A.; Ano, Y.; Chatani, N. Nickel-Catalyzed C-H/N-H Annulation of Aromatic Amides with Alkynes in the Absence of a Specific Chelation System. *Chem. Sci.* **2017**, *8*, 6650-6655. (c) Yamazaki, K.; Obata, A.; Sasagawa, A.; Ano, Y.; Chatani, N. Computational Mechanistic Study on the Nickel-Catalyzed C-H/N-H Oxidative Annulation of Aromatic Amides with Alkynes: The Role of the Nickel(0) Ate Complex. *Organometallics* **2019**, *38*, 248-255. (d) Obata, A.; Sasagawa, A.; Yamazaki, K.; Ano, Y.; Chatani, N. Nickel-Catalyzed Oxidative C-H/N-H Annulation of N-Heteroaromatic Compounds with Alkynes. *Chem. Sci.* **2019**, *10*, 3242-3248.
11. Xie, H.; Xing, Q.; Shan, Z.; Xiao, F.; Denga, G.-J. Nickel-Catalyzed Annulation of o-Haloarylamidines with Aryl Acetylenes: Synthesis of Isoquinolone and 1-Aminoisoquinoline Derivatives. *Adv. Synth. Catal.* **2019**, *361*, 1896.
12. Walden, D. M.; Jaworski, A. A.; Johnston, R. C.; Hovey, M. T.; Baker, H. V.; Meyer, M. P.; Scheidt, K. A.; Cheong, P. H.-Y. Formation of Aza-*ortho*-quinone Methides Under Room Temperature Conditions: $Cs_2CO_3$ Effect. *J. Org. Chem.* **2017**, *82*, 7183-7189.
13. Iwasaki, T.; Min, X.; Fukuoka, A.; Kuniyasu, H.; Kambe, N. Nickel-Catalyzed Dimerization and Alkylarylation of 1,3-Dienes with Alkyl Fluorides and Aryl Grignard Reagents. *Angew. Chem., Int. Ed.* **2016**, *55*, 5550.
14. See the supporting information in detail.
15. During the preparation of the manuscript, Ackermann, Ribas, and coworkers reported the Ni-catalyzed reaction of *ortho*-fluoro-aromatic amides with alkynes using an 8-aminoquinoline directing group. Capdevila, L.; Meyer, T. H.; Roldan-Gomez, S.; Lius, J. M.; Ackermann, L.; Ribas, X. *ACS Catal.* **2019**, *9*, 11074-11081. In this study, the reaction required high reaction temperature (140 °C) and a mixture of double-alkyne-insertion homologation or alkyne monoannulation (1(2H)-isoquinolinones) products were formed. Only when an electron-deficient alkynes are used, 1(2H)-isoquinolinones were selective obtained.

# Nickel-Catalyzed C-F/N-H Annulation of Aromatic Amides with Alkynes: Activation of C-F Bonds



- **C-F activation**
- **mild reaction conditions**
- **ligandless**
- **high functional group tolerance**