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Nickel-Catalyzed [4 + 2] Annulation of Nitriles and Benzylamines by C−H/N−H Activation

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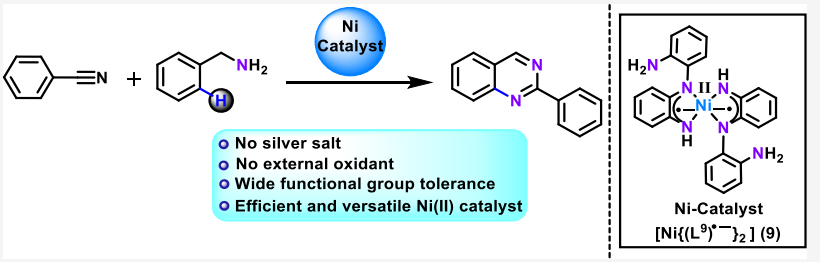

ABSTRACT: Nickel-catalyzed [4 + 2] annulation of benzylamines and nitriles via C−H/N−H bond activation, providing straightforward atom-economic access to a wide variety of multisubstituted quinazolines, is reported. Mechanistic investigation revealed that the in situ formed amidines from the coupling of benzylamines and nitriles direct the nickel catalyst to activate the *ortho*-C−H bond of the phenyl ring of the benzylamine.

INTRODUCTION

Transition-metal-catalyzed C−H functionalization has evolved as one of the most promising and powerful tools for the straightforward and step-economical synthesis of various functional molecules starting from readily available and inexpensive starting precursors.[1] A variety of transition-metal complexes involving Ru,[2] Rh,[3] Pd,[4] and Ir[5] have been used extensively as catalysts for C−H functionalization reactions. In recent years, for sustainable development, a continuous effort is devoted to finding earth-abundant and low-cost alternatives to these expensive and relatively scarce noble metals to achieve various chemical transformations, including C−H functionalization reactions.[1b,6]

The application of abundantly available and inexpensive first-row transition-metal complexes, especially nickel complexes as catalysts in the functionalization of C−H bonds, has attracted recent attention (Scheme 1).[1b,6,7] Significant advances have also been made; however, most of the nickel-catalyzed C−H functionalization reactions are mostly confined to some specific substrates containing activated acidic C−H bonds.[7] For example, using substrates like azoles,[7c,d] pyridines,[7e,f] indoles,[7g] or perfluorinated benzene,[7h] a few groups reported C−H functionalization reactions using nickel as the catalyst. Nickel-catalyzed functionalization of C(sp^2-H) bonds in the phenyl ring are still rare, although the C(sp^2)-H activation in benzene ring has long been reported via coordination-enabled cylcometalation of azobenzene by the Cp_2Ni complex.[8]

In the past decade, the directing group-assisted C−H bond activation has emerged as an excellent approach to functionalize the otherwise unactivated C−H bonds.[9] The precoordination of the functional directing group with the metal guides the regioselectivity. After the initial report by Satoh and Miura[10] on the chelation-assisted sequential functionalization of *ortho*- and *meta*-C−H bonds using a pyrazole directing group, this strategy has been successfully extended by several other groups using 2-phenol,[11] pyridine,[12] and amide[13] moieties as the directing groups. Recently, this area has further been enriched by Ackermann,[14] Glorius,[15] Chatani,[16] Maiti,[17] and others[18] using various chelating/coordinating groups. Despite significant advantages, the removal of the directing functional groups at the end of the reaction is a laborious task as well as it generates copious amounts of undesired waste. In this regard, in situ removal of directing groups can be an alternative, and if the coupling partner(s) itself acts as a directing group in a traceless manner,[9b,19c] it makes the synthetic route much simpler.

Herein, we report a nickel-catalyzed [4 + 2] annulation of benzylamines and nitriles via C−H/N−H bond activation. A wide variety of multisubstituted quinazolines were synthesized in moderate to good yields starting from various readily available benzylamines and nitriles. It is worth mentioning here that alkenes,[3c,16a] alkynes,[16a] and allenes[3c,5c] in combination

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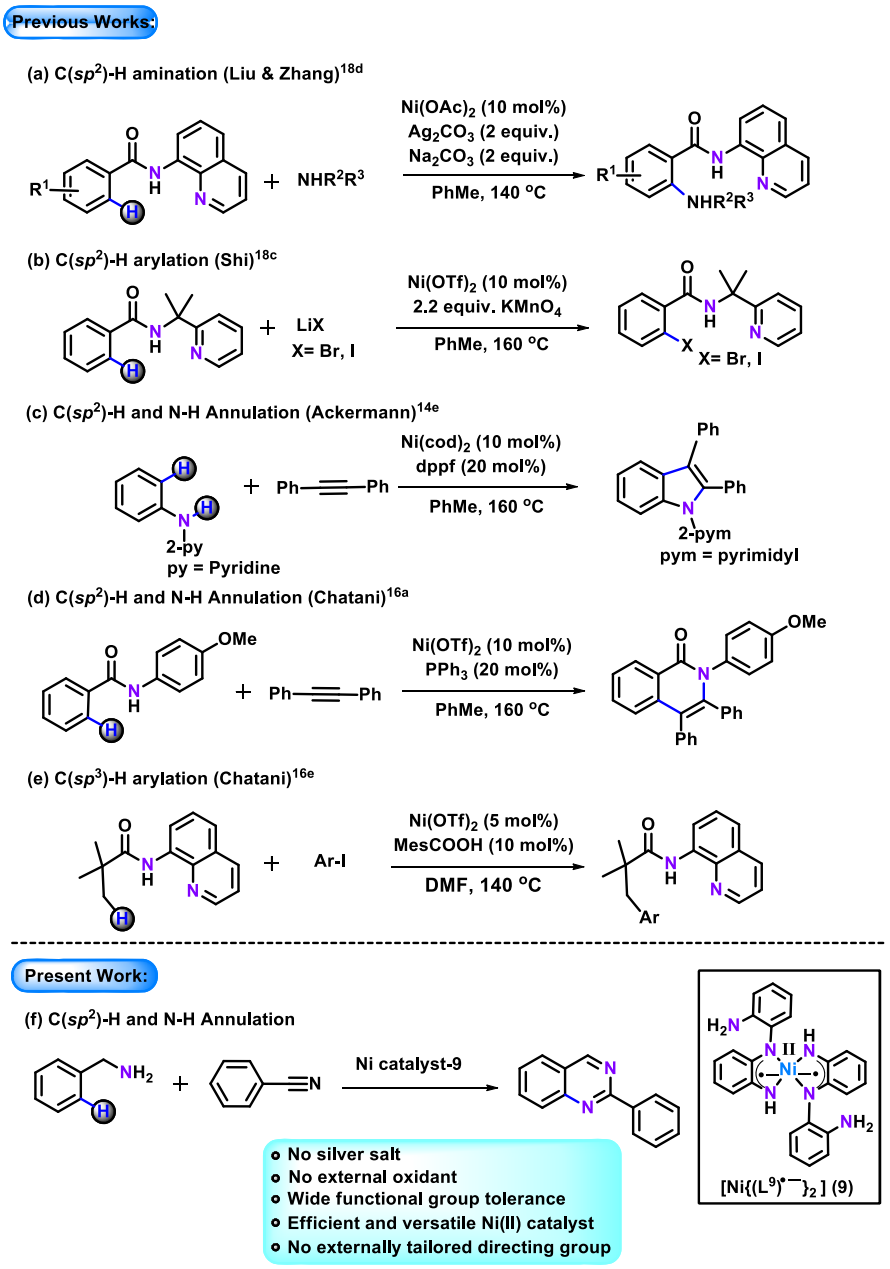
Scheme 1. Ni-Catalyzed C−H Activation Reactions



with N-unsubstituted imines,[6f] N-substituted amides,[16a] and monofunctionalized arenes[16a] were extensively studied as coupling partners in the transition-metal-catalyzed synthesis of various nitrogen heterocycles via C−H activation. However, to the best of our knowledge, simple benzylamines and nitriles have not been used as coupling partners for the construction of N−Heterocycles.

RESULT AND DISCUSSION

The present work begins with the reaction of benzonitrile (**10**) and benzylamine (**11**) in the presence of some chosen nickel catalysts (Figure 1). We envisioned that the coupling of benzylamine and nitrile would form an amidine intermediate, which would then assist the nickel catalyst to activate the *ortho*-C−H bond of the phenyl ring of the benzylamine moiety, leading to the formation of quinazoline. To find out the best catalyst and the optimal reaction conditions, we screened various nickel catalysts (Figure 1). First, we examined a few commercially available simple nickel salts such as $NiCl_2{\cdot}6H_2O$, $Ni(ClO_4)_2{\cdot}6H_2O$, $Ni(OAc)_2{\cdot}6H_2O$, and $Ni(COD)_2$. The reaction did not proceed well with these nickel salts; only 5% of quinazoline was isolated using $NiCl_2{\cdot}6H_2O$ as the catalyst at 140 °C in the presence of anhydrous NaOAc in *m*-xylene under inert conditions. Next, we screened a combination of a variety of nickel salts with some chosen organic ligands (Figure 1). Being unsatisfied with these results, finally, we focused on screening some chosen well-defined nickel catalysts,[20] **1**−**9** (Figure 1). The reaction did not proceed at all with catalysts **1**, **3**, **5**, and **7**, while **12** was obtained in either trace amount or in very low yields in the presence of catalysts **2**, **4**, and **6** (Table 1, entries 1−7). The yield of **12** increases to 35% using catalyst **8** (Table 1, entry 8). Catalyst **9** containing two antiferromagnetically coupled one-electron oxidized N^1-(2-aminophenyl)benzene-1,2-diamine

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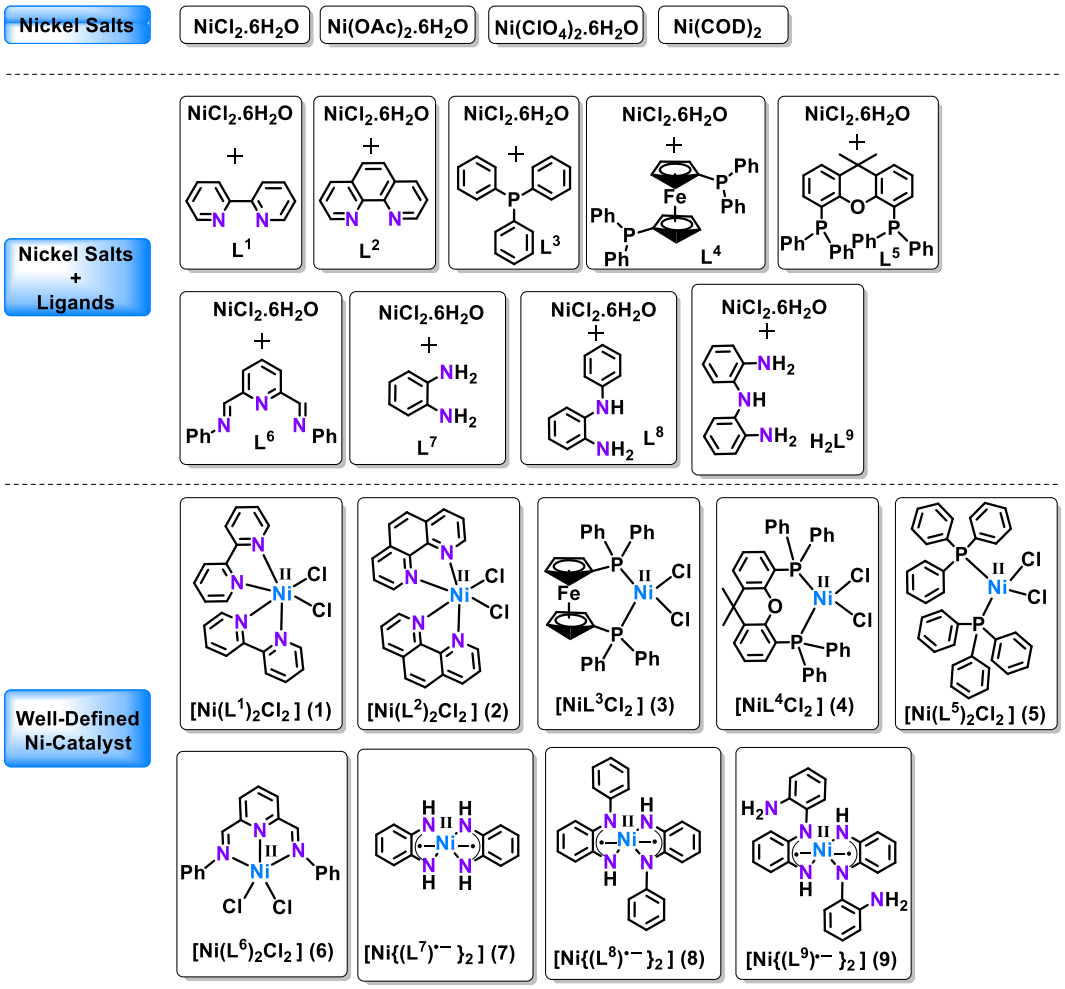

Figure 1. Catalysts studied in this work.

(H_2L^9) ligands was found to be most efficient (Table 1, entry 9).[20i] Among the series of bases examined, the reaction proceeds well in the presence of NaOAc, while with other bases, the desired 2-phenylquinazoline (**12**) was obtained in low or trace amounts (Table 1, entries 9−16). The highest yield of **12** was obtained when the reaction of **10** and **11** was carried out in the presence of 8.0 mol % catalyst **9** and 1.0 equiv of NaOAc in *m*-xylene at 140 °C under an inert atmosphere for 36 h (Table 1, entry 9). Increasing the catalyst loading or temperature beyond the optimized conditions did not lead to any notable improvement of the yield of **12**, while decreasing the temperature below 140 °C or catalyst loading below 8.0 mol % led to a significant lowering of the yield of **12**. Control experiments confirmed that **12** was not formed in the absence of catalyst **9** (Table 1, entry 22).

Once we established the optimized reaction conditions, the scope of nitriles was first examined (Table 2). Substituted nitriles were explored as a coupling partner with benzylamine. Benzonitriles bearing both electron-donating and -withdrawing groups provided the desired quinazolines in moderate to good yields. Quinazolines were obtained in slightly lower yields in the presence of substitution at the ortho-position of benzonitrile (Table 2, entries 2 and 5). In the presence of electron-donating methyl, methoxy, and tert-butyl groups at meta- or para-positions, the respective quinazolines were isolated in 62−75% yields (Table 2, entries 4−9). With 2,4-dimethoxybenzonitrile, the desired quinazoline **12g** was isolated in 60% yield (Table 2, entry 8). Catalyst **9** was found to be well tolerant of a wide variety of electron-withdrawing groups. Compared to electron-donating substituents, the respective quinazolines were obtained in higher yields in the presence of electron-withdrawing functionalities, irrespective of their positions in the phenyl ring. In the presence of electron-withdrawing halogens, the respective quinazolines were obtained in 66−85% yields (Table 2, entries 10−15). Reactions proceed well even with strongly electron-withdrawing substituents such as −CN, $-NO_2$, and $-CF_3$ groups yielding the desired quinazolines in moderate to good yields (Table 2, entries 17−21). Heteroaryl nitriles were also found to be compatible, affording the respective quinazolines **12u**, **12v**, and **12w** in 46−59% isolated yields (Table 2, entries 22−24). Reactions also proceed with aliphatic nitriles. Reactions of cyclopropanecarbonitrile or pentanenitrile with **11** yielded the desired quinazolines **12x** and **12y** in 30 and 18% yields, respectively (Table 2, entries 25 and 26).

Next, the scope of benzylamines was explored using benzonitrile (**10**) as the coupling partner (Table 3). Various substituted benzylamines (**11a**−**d**) reacted with **10** readily to produce the corresponding quinazolines in moderate to good yields (Table 3, entries 1−6). Benzylamines bearing both electron-donating and -withdrawing functionalities proved to be suitable. The reaction proceeds well even in the presence of both electron-donating and -withdrawing groups in the

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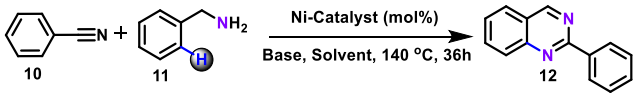
Table 1. Optimization of the Reaction Conditions[a−c]



entry	Ni-catalyst (mol %)	solvent	base	yield (%)
1	**1** (8.0 mol %)	*m*-xylene	NaOAc	N.R
2	**2** (8.0 mol %)	*m*-xylene	NaOAc	trace
3	**3** (8.0 mol %)	*m*-xylene	NaOAc	N.R
4	**4** (8.0 mol %)	*m*-xylene	NaOAc	12
5	**5** (8.0 mol %)	*m*-xylene	NaOAc	N.R
6	**6** (8.0 mol %)	*m*-xylene	NaOAc	8
7	**7** (8.0 mol %)	*m*-xylene	NaOAc	N.R
8	**8** (8.0 mol %)	*m*-xylene	NaOAc	35
9	**9** (8.0 mol %)	*m*-xylene	NaOAc	77
10	**9** (8.0 mol %)	*m*-xylene	KO^{t}Bu	15
11	**9** (8.0 mol %)	*m*-xylene	Cs_2CO_3	37
12	**9** (8.0 mol %)	*m*-xylene	K_2CO_3	trace
13	**9** (8.0 mol %)	*m*-xylene	K_3PO_4	24
14	**9** (8.0 mol %)	*m*-xylene	NEt_3	trace
15	**9** (8.0 mol %)	*m*-xylene	KOH	N.R
16	**9** (8.0 mol %)	*m*-xylene	NaO^{t}Bu	trace
17	**9** (8.0 mol %)	1,2-dichlorobenzene	NaOAc	20
18	**9** (8.0 mol %)	DMF	NaOAc	N.R
19	**9** (8.0 mol %)	toluene	NaOAc	trace
20	**9** (8.0 mol %)	DMSO	NaOAc	N.R
21	**9** (5.0 mol %)	*m*-xylene	NaOAc	62
22		*m*-xylene	NaOAc	N.R
23	**9** (8 mol %)	*m*-xylene		12

[a]Stoichiometry: benzonitrile (**10**) (1.0 mmol; 1.0 equiv) and benzylamine (**11**) (1.5 mmol; 1.5 equiv). [b]1.0 equiv of base (NaOAc). [c]Isolated yields after column chromatography.

benzylamine moiety, yielding the desired product in good yield (Table 3, entry 6).

To probe the reaction mechanism, a set of experiments were performed (Scheme 2). We anticipated that in the presence of a base, nitriles and benzylamines undergo coupling to form an amidine[21] intermediate, which would then direct the nickel catalyst to activate the *ortho*-C−H bond of benzylamines, leading to the formation of quinazolines. In line with our expectation, when **10** and **11** were reacted in the presence of only NaOAc, we isolated amidine intermediate **14** in 42% yield (Scheme 2a). Starting from preformed **14**, desired quinazoline **12** was obtained in 77% under the optimized conditions in the presence of nickel catalyst **9** (Scheme 2c). It is worth mentioning here that when the mixture of **14** and **9** was investigated using HRMS, we observed a molecular-ion peak at 685.230 amu, indicating the formation of [**9**−**14**]$^+$-type intermediate (see the SI).

To identify any other plausible intermediates, we stopped the reaction of **10** and **11** after 24 h under the optimal conditions (before completion) and purified the reaction mixture in a preparative TLC plate using a 10:1 mixture of hexane/ethyl acetate as the eluent. We obtained **12** in 62% isolated yield along with a new band isolated in 8% yield. Characterization of this new band using NMR and HRMS confirms the formation of 2-phenyl-3,4-dihydroquinazoline (**15**) as one of the intermediates (see the SI). Notably, when preformed **15** was subjected to dehydrogenation in the presence of nickel catalyst **9** under the optimized conditions, the desired product **12** was obtained in 83% yield (Scheme 2e). It is worth mentioning that in our previous studies we observed that catalyst **9** undergoes deprotonation in the presence of a base to form the active catalyst [**9**]$^-$.[22] To check the involvement of [**9**]$^-$ in the present reactions, we performed the catalytic as well as the control reactions mentioned above using the preformed [**9**]$^-$ as the catalyst. In agreement with our previous results,[22] species [**9**]$^-$ showed similar catalytic activity as observed with **9** (see the SI).

Next, to check the possibility of the alternative mechanism involving benzyl-imine-type intermediate, known for [4 + 2] annulation of alkynes and imines,[6e] we investigated the possibility of formation of imines from the corresponding benzylamines under the optimal conditions. However, no benzyl-imines (**16**, **18**) were obtained when benzylamine (**11**) and *N*-benzylaniline (**17**) were subjected to dehydrogenation in the presence of **9** under the optimized conditions (Scheme 2f,g). Starting from the preformed secondary amine **17** and imine **20**, no desired quinazolines were obtained (Scheme 2h,i). The reaction did not proceed in the presence of a radical inhibitor like TEMPO or DPPH (Scheme 2j).

In addition, we performed a set of kinetic isotope effect (KIE) experiments. The reaction of **10** with a 1:1 mixture of **11a** and **11a-D$_2$** under the optimized conditions showed a KIE value of 0.29 (Scheme 3a). On the other hand, dehydrogenation of **15-D** under the optimized conditions exhibited an unusually high k_H/k_D value of 14.28. In the literature, such high k_H/k_D values are reported to be associated with radical-type hydrogen atom transfer (HAT) mechanisms.[23] Usually, a significant contribution from quantum mechanical tunneling (QMT) under ambient conditions makes the k_H/k_D value abnormally high during HAT processes.[23] In agreement with our previous results with **9**, the dehydrogenation of **15** seems to proceed via the HAT pathway, where we believe that one of the nickel-bound ligand-centered radicals present in catalyst **9** abstracts the benzylic hydrogen atom, as observed before during **9**-catalyzed dehydrogenation of alcohols.[22a]

Based on the above experimental results, a plausible mechanistic cycle is proposed in Scheme 4. The reaction begins with the formation of amidine intermediate **14** via coupling of benzylamine and benzonitrile.[21] The in situ formed amidine undergoes deprotonation and binds with active catalyst [**9**]$^-$ to form intermediate **9A**. As observed in our previous work, the deprotonated ligand present in [**9**]$^-$ may abstract the −NH proton from the amidine.[22b,c] Subsequently, a seven-membered nickelacycle **9B** is formed, which releases the intermediate 2-phenyl-3,4-dihydroquinazoline (**15**). Intermediate **15** upon **9**-catalyzed dehydrogenation via HAT yielded the desired quinazoline.[22a,23] The formation of **9B** from **9A** is believed to involve an oxidative addition step. During oxidative addition and reductive elimination processes, it is believed that both nickel and one of the coordinated ligands participate synergistically, as observed previously.[22]

CONCLUSIONS

In conclusion, our present work provides expedient access to a wide array of multisubstituted quinazolines via nickel-catalyzed [4 + 2] annulation of simple and readily available benzylamines and nitriles. This transformation represents the first example of nickel-catalyzed annulation of benzylamines and nitriles via C−H/N−H activation. The present protocol has a broad substrate scope, is highly atom-economical, and does not require any externally tailored directing groups and oxidants. Mechanistic investigation revealed that base-promoted coupling of benzylamines and nitriles in situ form the amidine intermediates,

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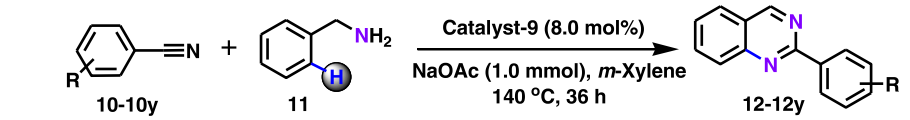
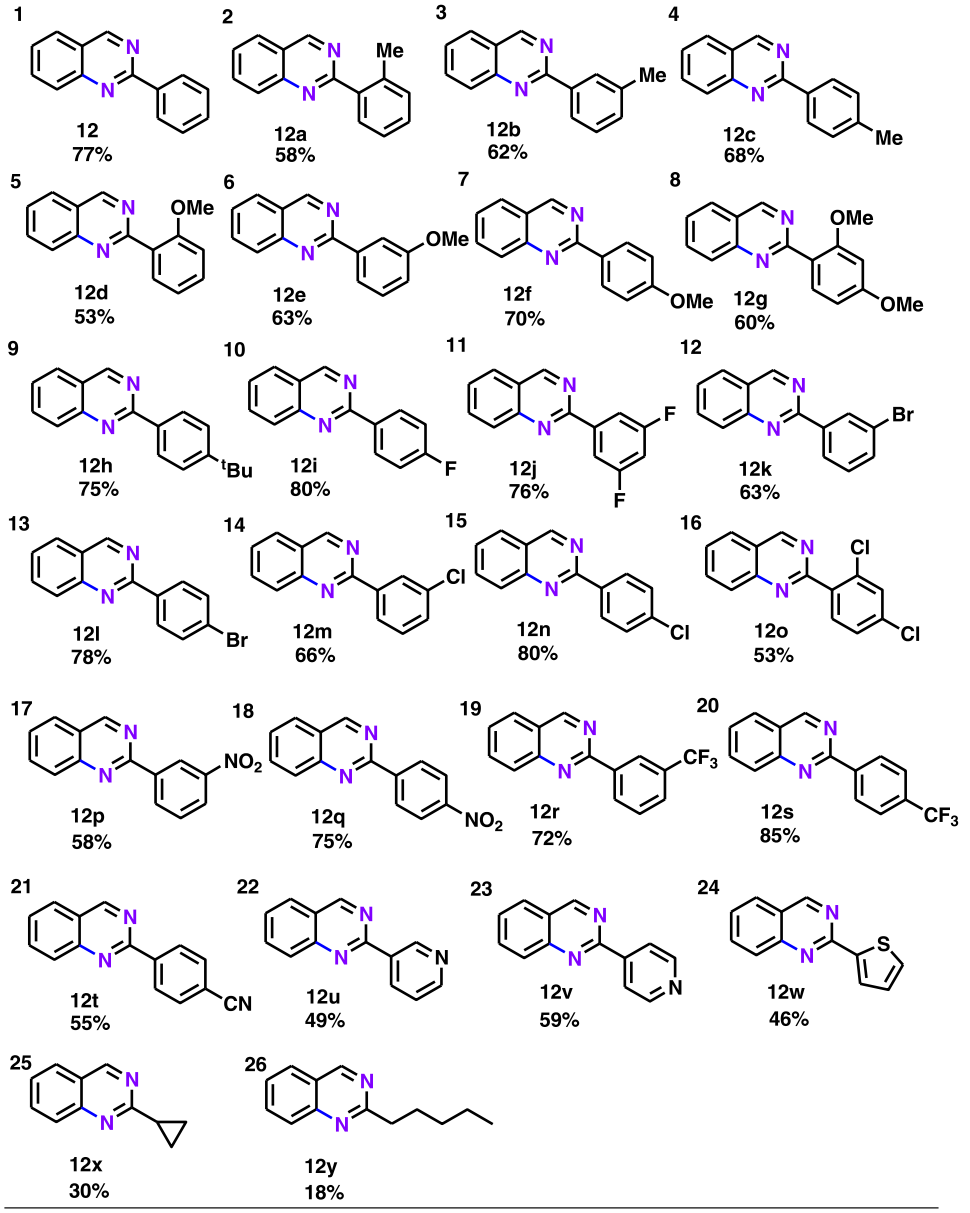
Table 2. Substrate Scope of Various Substituted Benzonitriles[a−c]





[a]Stoichiometry: benzonitrile (**10**−**10y**) (1.0 mmol, 1.0 equiv) and benzylamine (**11**) (1.5 mmol, 1.5 equiv). [b]1.00 equiv of base. [c]Temperature 140 °C.

which then direct the nickel catalyst to activate the *ortho*-C−H bond of the phenyl ring of benzylamine. Our present results would open up new other interesting chemical transformations via transition-metal-catalyzed C−H activation using nitriles as the coupling partner.

EXPERIMENTAL SECTION

General Information. All reactions were carried out using the standard Schlenk technique under an argon atmosphere. Toluene and *m*-xylene were refluxed over sodium/benzophenone, distilled under the argon atmosphere, and stored over 4 Å molecular sieves. Benzonitrile(s) was purchased from Sigma-Aldrich, and all other chemicals were purchased from commercial suppliers and used as received without further purification. Analytical TLC was performed on a Merck 60 F254 silica gel plate (0.25 mm thickness), and column chromatography was performed on Merck 60 silica gel (60−120 mesh). NMR spectra were recorded on Bruker DPX-300(300 MHz), Bruker DPX-400(400 MHz), and Bruker DPX-500(500 MHz) spectrometers. TMS (tetramethylsilane) was used as the internal standard. ESI mass spectra were recorded on a Micromass Q-TOF mass spectrometer (serial no. YA 263).

Catalyst Synthesis. Catalysts **1**−**9** were synthesized following the available literature procedures.[20]

General Procedure for Synthesis of 2-Phenylquinazoline. Under an argon atmosphere, benzylamine (1.5 mmol), benzonitrile

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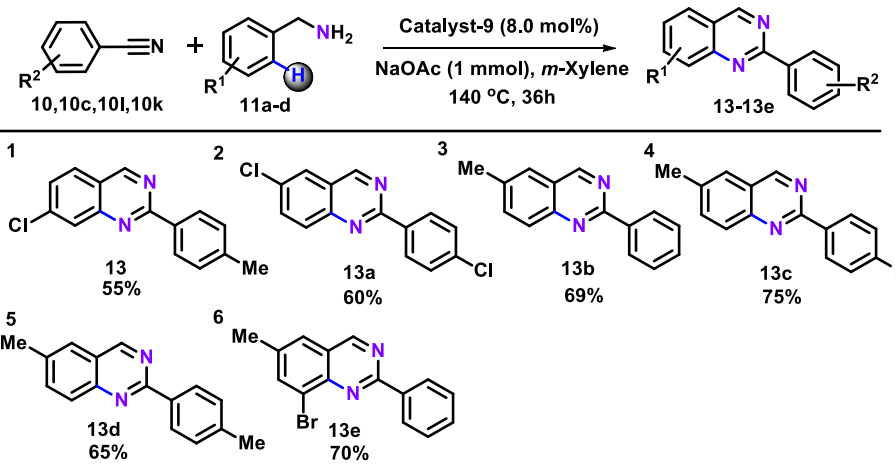
Table 3. Substrate Scope of Various Substituted Benzylamines[a−c]



[a]Stoichiometry: benzonitrile (**10, 10c, 10l, 10k**) (1.0 mmol, 1.0 equiv) and benzylamine (**11a−d**) (1.5 mmol, 1.5 equiv). [b]1.00 equiv of base. [c]Temperature 140 °C.

(1.0 mmol), catalyst **9** (8.0 mol %), and anhydrous NaOAc (1.0 mmol) were added to an oven-dried Schlenk tube containing a Teflon-coated magnetic stir bar. Dry and degassed *m*-xylene (5.0 mL) was added to the Schlenk tube through a syringe. Then, the Schlenk tube was capped with a rubber septum and wrapped tightly with Teflon. The Schlenk tube was placed in a preheated oil bath at 140 °C and stirred for 36 h. Once the reaction was complete, the solvent was removed in *vacuo* and the product was purified by column chromatography on a silica gel using hexane/ethyl acetate (10:1) as an eluent.

General Procedure for Synthesis of 15-D.[24a] Under an argon atmosphere, 2-phenylquinazoline (1.0 mmol) was taken in an oven-dried Schlenk tube containing a Teflon-coated magnetic stir bar. Dry and degassed methanol (10 mL) was added to the Schlenk tube through a syringe. Then, the Schlenk tube was capped with a rubber septum and wrapped tightly with Teflon. To an ice-cold solution of this reaction mixture, $NaBD_4$ (1.0 mmol) was added with constant stirring. After the addition of $NaBD_4$, the reaction mixture was stirred for 1 h at 0 °C and an additional 1 h at room temperature. After completion of the reaction, the mixture was diluted with water and extracted with diethyl ether. The solvent was then removed in vacuo, and the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (9:1) as an eluent. A white solid (yield: 63 mg, 30%) product was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.00 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.30-7.23 (m, 2H), 7.16 (t, J = 8.0 Hz, 3H), 7.07 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H).

Characterization Data of the Isolated Compounds. *2-Phenylquinazoline (**12**).*[22a] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 159 mg, 77%). Mp 97−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.47 (s, 1H), 8.62 (d, J = 8.0 Hz, 2H,), 8.10 (d, J = 8.0 Hz, 1H), 7.94−7.89 (m, 2H), 7.62 (t, J = 4.0 Hz, 1H), 7.55−7.51 (m, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 161.2, 160.6, 150.9, 138.2, 134.2, 130.7, 128.7 (m), 127.3, 123.8.

*2-o-Tolylquinazoline (**12a**).*[25a] Eluent: petroleum ether/ethyl acetate (10:1). Yellow solid (yield: 128 mg, 58%). Mp 100−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.47 (s, 1H), 8.62 (d, J = 8.0 Hz, 2H), 8.10 (d, J = 8.0 Hz, 1H), 7.94−7.89 (m, 2H), 7.62 (t, J = 4.0 Hz, 1H), 7.55−7.51 (m, 3H), 2.16 (s, 3H).

*2-m-Tolylquinazoline (**12b**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 136 mg, 62%). Mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.45 (s, 1H), 8.42 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.91−7.87 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.45−7.42 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 161.3, 160.5, 151.0, 138.4, 138.1, 134.2, 131.5, 129.2, 128.7, 128.6, 127.3, 127.2, 125.9, 123.7, 21.6.

*2-p-Tolylquinazoline (**12c**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 150 mg, 68%). Mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.39 (s, 1H), 8.52 (d, J = 4.0 Hz, 2H), 8.05 (d, J = 4.0 Hz, 1H), 7.83 (t, J = 4.0 Hz, 2H), 7.51 (t, J = 4.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 161.0, 160.4, 150.7, 140.8, 135.3, 134.0, 129.4, 128.6, 128.5, 127.0, 127.0, 123.5, 21.5.

*2-(2-Methoxyphenyl)quinazoline (**12d**).*[25a] Eluent: petroleum ether/ethyl acetate (24:1). White solid (yield: 125 mg, 53%). Mp 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.52 (s, 1 H), 8.12 (d, J = 8.0 Hz, 1H), 7.97−7.91 (m, 2H), 7.78 (d, J = 4.0 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.12−7.06 (m, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 162.5, 160.1, 157.8, 150.7, 134.3, 131.9, 131.0, 128.9, 128.7, 127.7, 127.2, 123.2, 120.9, 112.1, 56.2.

*2-(3-Methoxyphenyl)quinazoline (**12e**).*[22c] Eluent: petroleum ether/ethyl acetate (24:1). White solid (yield: 149 mg, 63%). Mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.46 (s, 1 H), 8.22 (t, J = 8.0 Hz, 2H), 8.11 (d, J = 4.0 Hz, 1H), 7.92−7.89 (m, 2H), 7.60 (t, J = 4.0 Hz, 1H), 7.45 (t, J = 4.0 Hz, 1H), 7.07 (d, J = 4.0 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.9, 160.5, 160.2, 150.8, 139.5, 134.2, 129.7, 128.7, 127.4, 127.2, 123.7, 121.3, 117.4, 113.2, 55.5.

*2-(4-Methoxyphenyl)quinazoline (**12f**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 165 mg, 70%). Mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.39 (s, 1H), 8.58 (d, J = 4.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.86−7.83 (m, 2H), 7.53 (t, J = 4.0 Hz, 1H), 7.04 (d, J = 4.0 Hz, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 162.0, 160.8, 160.5, 150.7, 134.2, 130.6, 130.4, 128.3, 127.2, 126.9, 123.3, 114.0, 55.4.

*2-(2,4-Dimethoxyphenyl)quinazoline (**12g**).*[22a] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 160 mg, 60%). Mp 90−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.74 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.03−7.99 (m, 3H), 7.71−7.69 (m, 1H), 6.68−662 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 163.7, 160.0, 159.8, 150.3, 135.9,135.0, 133.7, 133.3, 128.5, 128.2, 127.9, 127.5, 122.4, 106.0, 99.3, 56.5, 55.7.

*2-(4-tert-Butylphenyl)quinazoline (**12h**).*[22a] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 196 mg, 75%). Mp 82−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.45 (s, 1H), 8.54 (d, J = 8.0 Hz, 2H), 8.10 (d, J = 4.0 Hz, 1H), 7.92−7.88 (m, 2H), 7.59−7.55(m, 3H).

*2-(4-Fluorophenyl)quinazoline (**12i**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 180 mg, 80%). Mp 122−123

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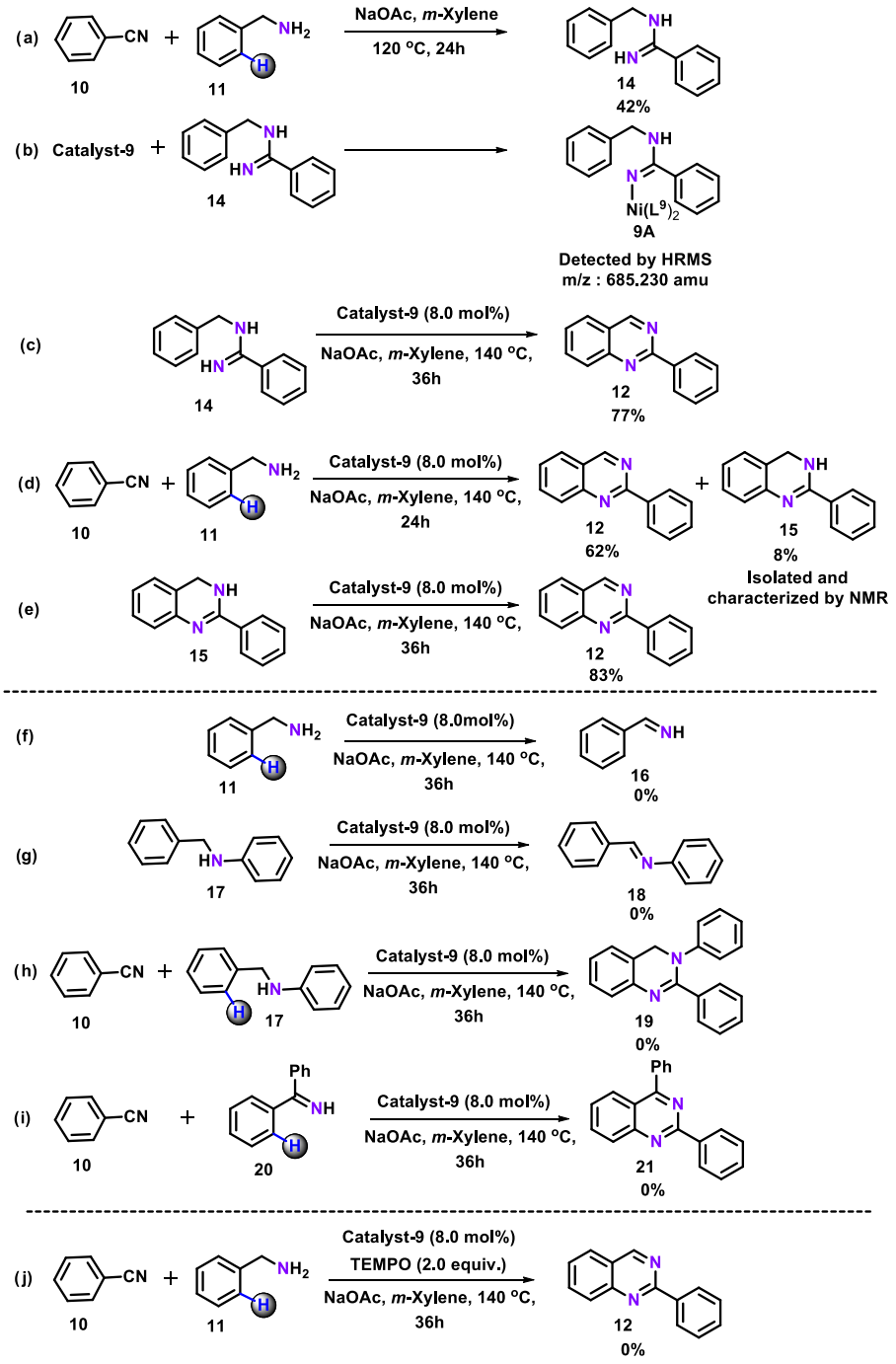
Scheme 2. Control Experiments for Mechanistic Investigation



°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.42(s, 1H), 8.64−8.60 (m, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 8.0 Hz, 2H), 7.59(t, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 166.0 (d, $^1J_{C-F}$ = 240.0 Hz), 160.4, 160.2, 150.8, 134.3, 130.8 (d, $^3J_{C-F}$ = 8.0 Hz), 128.6, 127.3, 127.1, 123.6, 115.6 (d, $^2J_{C-F}$ = 21.0 Hz).

*2-(3,5-Difluorophenyl)quinazoline (**12j**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 184 mg, 76%). Mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.45 (s, 1H), 8.16 (d, J = 4.0 Hz, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.96−7.92 (m, 2H), 7.66 (t, J = 8.0 Hz, 1H), 6.93 (t, J = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm)= 164.7 (d, $^1J_{C-F}$ = 246.0 Hz), 162.2 (d, $^1J_{C-F}$ = 245.0 Hz), 160.7, 158.7 (t, $^4J_{C-F}$ = 4.0 Hz), 150.6, 141.5 (t, $^3J_{C-F}$ = 10.0 Hz), 134.7, 128.8, 128.2, 127.3, 124.0, 111.4 (q, $^3J_{C-F}$ = 8.0 Hz), 106.0 (t, $^2J_{C-F}$ = 25.0 Hz).

*2-(3-Bromophenyl)quinazoline (**12k**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 180 mg, 63%). mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.46 (s, 1H), 8.79 (s,1H), 8.56 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.42−7.41 (m,1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.8, 159.5, 150.7, 140.0, 134.7, 133.7, 131.8, 130.3, 128.8, 127.9, 127.4, 127.3, 123.8, 123.1.

*2-(4-Bromophenyl)quinazoline (**12l**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 222 mg, 78%). Mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.45 (s, 1H), 8.50 (d, J = 4.0 Hz, 2H), 8.07(d, J = 8.0 Hz, 1H), 7.91 (t, J = 8.0 Hz, 2H), 7.66−7.61 (m, 1H), 7.59 (d, J = 4.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.7, 159.7, 150.8, 140.2, 134.4, 133.6, 131.7, 130.2, 128.8, 127.7, 127.3, 127.2, 123.9, 123.0.

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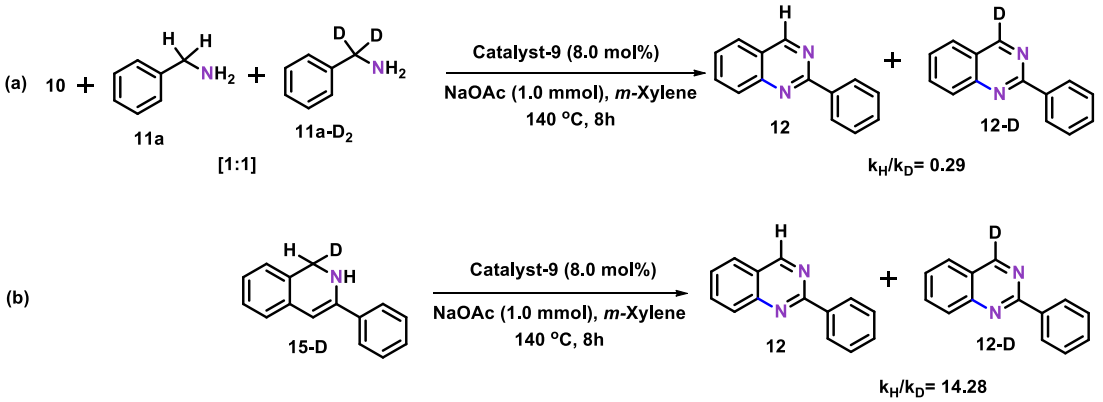
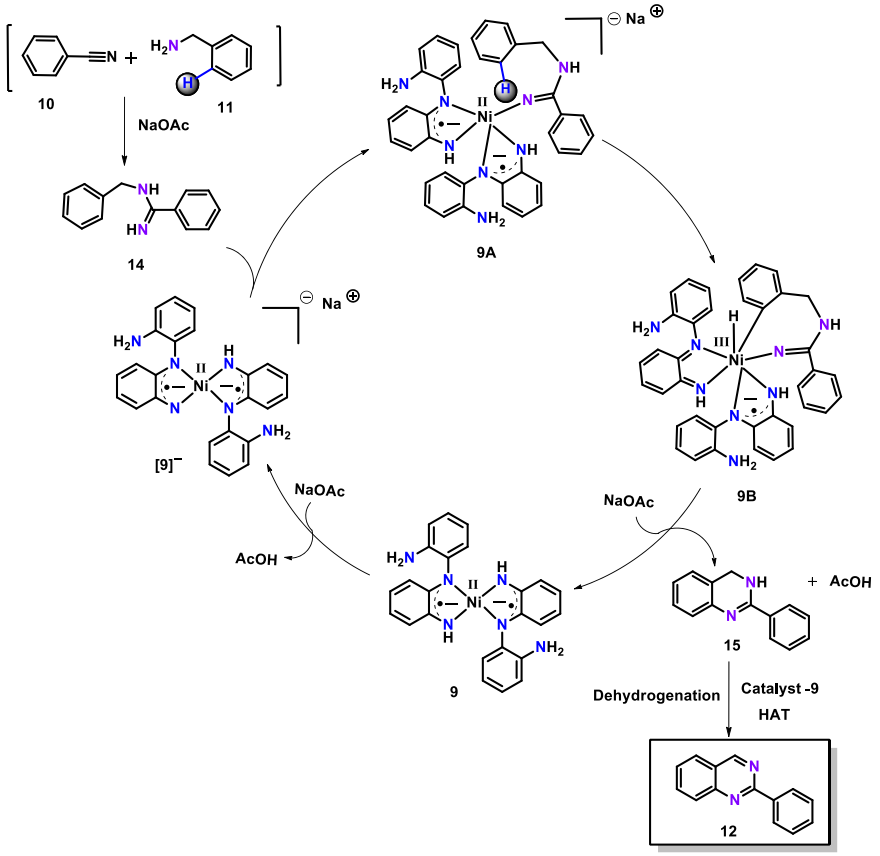
Scheme 3. Kinetic Isotopic Effect (KIE) Experiments



Scheme 4. Proposed Mechanism



*2-(3-Chlorophenyl)quinazoline (**12m**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 159 mg, 66%). Mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.47 (s, 1H), 8.63 (s, 1H), 8.53 (d, J = 4.0 Hz, 1H), 8.11(d, J = 8.0 Hz, 1H), 7.93 (t, J = 8.0 Hz, 2H), 7.65 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.7, 159.7, 150.7, 139.8, 134.9, 134.6, 130.7, 130.0, 128.8, 128.7, 127.8, 127.3, 126.8, 123.8.

*2-(4-Chlorophenyl)quinazoline (**12n**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 192 mg, 80%). Mp133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.43 (s, 1H), 8.56 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 8.0 Hz, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.6, 160.2, 150.8, 137.0, 136.7, 134.5, 130.0, 128.9, 128.7, 127.6, 127.3, 123.8.

*2-(2,4-Dichlorophenyl)quinazoline (**12o**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 146 mg, 53%). Mp 109−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.52 (s, 1H), 8.11(d, J = 4.0 Hz, 1H), 8.00−7.95 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 4.0 Hz, 1H), 7.56 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.9, 160.3, 150.3, 136.6, 135.7, 134.5, 133.8, 132.8,130.4, 128.6, 128.3, 127.2, 123.3. HRMS (ESI, positive ions): m/z calcd for $C_{14}H_9Cl_2N_2^+$ [M + H$^+$] 275.0137, found 275.0155.

*2-(3-Nitrophenyl)quinazoline (**12p**).*[22c] Eluent: petroleum ether/ethyl acetate (10:2). White solid (yield: 146 mg, 58%). Mp 161−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.65 (s, 1H), 8.58 (d, J = 4.0 Hz, 2H), 8.32(d, J = 4.0 Hz, 1H), 7.90 (d, J = 4.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 3H),7.63(t, J = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 158.1, 151.0, 148.9, 139.6, 135.9, 134.5, 131.1, 129.0, 128.2, 125.9, 124.3, 122.4.

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*2-(4-Nitrophenyl)quinazoline (**12q**).*[25b] Eluent: petroleum ether/ethyl acetate (10:2). White solid (yield: 188 mg, 75%). Mp 218−219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.65 (s, 1H), 8.58 (d, J = 4.0 Hz, 2H), 8.32(d, J = 4.0 Hz, 1H), 7.90 (d, J = 4.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 3H), 7.63(t, J = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 158.1, 151.0, 148.9, 139.6, 135.9, 134.5, 131.1, 129.0, 128.2, 125.9, 124.3, 122.4.

*2-(3-(Trifluoromethyl)phenyl)quinazoline (**12r**).*[25c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 197 mg, 72%). Mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.45 (s, 1H), 8.92 (s, 1H), 8.81 (d, J = 4.0 Hz, 1H), 8.08 (d, J = 12.0 Hz, 1H), 7.93−7.91 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.65−7.61(m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.6, 159.5, 150.6, 138.8, 134.3, 131.7, 131.1 (q, $^2J_{C-F}$ = 33.0 Hz), 129.0, 128.7, 127.4 (q, $^3J_{C-F}$ = 4.0 Hz), 126.9, 125.4 (q, $^3J_{C-F}$ = 4.0 Hz), 124.3 (q, $^1J_{C-F}$ = 270.0 Hz), 123.8.

*2-(4-(Trifluoromethyl)phenylquinazoline (**12s**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). White solid (yield: 233 mg, 85%). Mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.45 (s, 1H), 8.92 (s, 1H), 8.81 (d, J = 4.0 Hz, 1H), 8.08 (d, J = 12.0 Hz, 1H), 7.93−7.91 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.65−7.61(m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.7, 159.6, 150.7, 141.3, 134.4, 132.3 (q, $^2J_{C-F}$ = 32.0 Hz), 129.0, 128.8, 128.06, 127.3, 125.6 (q, $^3J_{C-F}$ = 4.0 Hz), 124.5 (q, $^1J_{C-F}$ = 271.0 Hz), 123.9.

*4-(Quinazolin-2-yl)benzonitrile (**12t**).*[22a] Eluent: petroleum ether/ethyl acetate (10:1). Light yellow solid (yield: 233 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.49 (s, 1H), 8.74 (d, J = 8.0 Hz, 2H), 8.10 (d, J = 4.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.69−7.60 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.7, 159.1, 150.6, 142.1, 134.5, 132.4, 129.0, 128.8, 128.2, 127.2, 123.9, 118.9, 113.8.

*2-(Pyridine-3-yl)quinazoline (**12u**).*[22c] Eluent: petroleum ether/ethyl acetate (10:3). White solid (yield: 101 mg, 49%). Mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.87 (s, 1H), 9.50 (s, 1H), 9.07 (d, J = 8.0 Hz, 1H,), 8.77 (s, 1H), 8.11 (d, J = 4.0 Hz, 1H,), 7.97 (t, J = 8.0 Hz, 2H), 7.66 (t, 1H, J = 8.0 Hz), 7.48−7.45 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.8, 158.8, 150.7, 150.7, 149.3, 137.0, 136.9, 134.6, 128.8, 128.1, 127.3, 124.0, 123.9.

*2-(Pyridine-4-yl)quinazoline (**12v**).*[22c] Eluent: petroleum ether/ethyl acetate (10:3). Gray solid (yield: 122 mg, 59%). Mp 134−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.50 (s, 1H), 8.80 (s, 2H), 8.45 (d, J = 4.0 Hz, 2H), 8.12 (d, J = 12.0 Hz, 1H), 7.96 (t, J = 8.0 Hz, 2H), 7.69 (t, J = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.8, 159.0, 150.6, 150.5, 145.5, 134.6, 129.0, 128.4, 127.3, 124.3, 122.5.

*2-(Thiophen-2-yl)quinazoline (**12w**).*[22a] Eluent: petroleum ether/ethyl acetate (10:3). White solid (yield: 98 mg, 46%). Mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.36 (s, 1H), 8.21 (s, 1H), 8.05 (s, 1H), 7.88 (d, J = 4.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.53(d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H).

*2-(Cyclopropyl)quinazoline (**12x**).*[22c] Eluent: petroleum ether/ethyl acetate (10:1). Yellowish oil (yield: 51 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.23 (s, 1H), 7.19−7.82 (m, 3H), 7.54−7.50 (m, 1H), 2.42−2.36 (m, 1H), 1.29−1.17 (m, 2H), 1.16−1.11 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 168.4, 160.3, 150.3, 134.0, 127.5, 127.1, 126.3, 123.2, 18.6, 10.6.

*2-Pentylquinazoline (**12y**).*[25d] Eluent: petroleum ether/ethyl acetate (10:1). Yellowish oil (yield: 51 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.39 (s, 1H), 8.05 (s, 1H), 7.92 (t, J = 4.0 Hz, 2H), 7.63 (t, J = 8.0 Hz, 1H), 3.16−3.14 (m, 2H), 1.94−1.91(m, 2H), 1.40 (s, 2H), 1.24 (s, 2H), 0.91−0.88 (m, 3H).

*7-Chloro-2-(p-tolylphenyl)quinazoline (**13**).*[22a] Eluent: petroleum ether/ethyl acetate (24:1). White solid (yield: 140 mg, 55%). Mp 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.39 (s, 1H), 8.48 (d, J = 8.0 Hz, 2H), 8.05 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 162.0, 160.1, 151.4, 141.5, 140.4, 135.0, 129.6, 128.8, 128.5, 128.3, 127.8, 127.3, 122.0, 21.7.

*6-Chloro-2-(p-chlorophenyl)quinazoline (**13a**).*[25e] Eluent: petroleum ether/ethyl acetate (20:1). Yellow solid (yield: 165 mg, 60%). Mp 206−207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.45 (s, 1H), 8.52 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 4.0 Hz, 2H), 7.90−7.87 (m, 2H), 7.60−7.55 (m, 2H).

*6-Methyl-2-phenylquinazoline (**13b**).*[25e] Eluent: petroleum ether/ethyl acetate (24:1). White solid (yield: 151 mg, 69%). Mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.40 (s, 1H), 8.61 (d, J = 8.0 Hz, 2H), 8.03(d, J = 4.0 Hz, 1H), 7.75 (d, J = 4.0 Hz, 1H), 7.68 (s, 1H), 7.55−7.50 (m, 3H), 2.56 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.2, 159.9, 149.3, 137.8, 137.0, 130.7, 128.8, 128.7, 128.3, 126.0, 123.7, 21.8.

*6-Methyl-2-(p-Bromophenyl)quinazoline (**13c**).*[25f] Eluent: petroleum ether/ethyl acetate (24:1). Yellow solid (Yield: 224 mg, 75%). Mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.37 (s, 1H), 8.48 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 2.57 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 159.9, 159.3, 149.2, 137.8, 136.9, 136.7, 131.7, 130.0, 128.2, 125.9, 125.2, 123.6, 21.7.

*6-Methyl-2-(p-tolyl)quinazoline (**13d**).*[25f] Eluent: petroleum ether/ethyl acetate (24:1). Yellow solid (Yield: 152 mg, 65%). Mp 157−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.23 (s, 1H), 8.39 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz,1H), 7.59 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.51, 159.70, 149.39, 140.59, 137.15, 136.32, 135.48, 129.39, 128.40, 128.20, 125.80, 123.51, 21.61, 21.50.

*8-Bromo-6-methyl-2-phenylquinazoline (**13e**).*[22a] Eluent: petroleum ether/ethyl acetate (24:1). Yellow solid (yield: 209 mg, 70%). Mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.40 (s, 1H), 8.68 (d, J = 8.0 Hz, 2H), 7.73−7.74 (m, 2H), 7.56−7.51 (m, 3H), 7.47 (t, J = 8.0 Hz, 1H), 2.85 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.5, 159.9, 149.8, 138.4, 137.2, 134.0, 130.6, 128.6 (d, J = 2.0 Hz), 127.0, 125.0, 123.6, 17.0.

*N-Benzylbenzimidamide (**14**).*[21c] Eluent: petroleum ether/ethyl acetate (10:2). White solid (yield: 100mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.06 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 4.0 Hz, 2H), 7.49−7.25 (m, 5H), 4.50 (d, J = 4.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) = 166.1, 139.6, 134.3, 131.1, 128.23, 128.2, 127.2, 127.1, 126.6, 42.5.

*2-Phenyl-3,4-dihydroquinazoline(**15**).*[24b] Eluent: petroleum ether/ethyl acetate (9:1). White solid (yield: 16mg, 8%). Mp 91−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.94 (d, J = 8.0 Hz, 2H), 7.71 (br, s, 1H), 7.31−7.27 (m, 2H), 7.23−7.17 (m, 3H), 7.08 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.54 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 152.0, 138.2, 134.2, 132.7, 129.9, 128.8, 127.5, 127.4, 125.6, 123.7, 122.8, 120.4, 45.7.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02069.

Experimental procedures and NMR data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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