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Research Article

NiH-Catalyzed Hydroamination/Cyclization Cascade: Rapid Access to Quinolines

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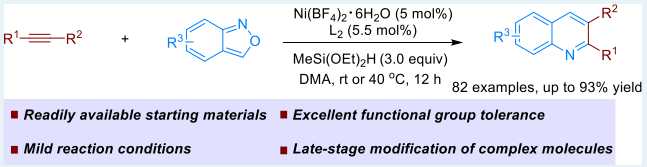
ABSTRACT: Despite the significant success of metal-H-catalyzed hydroamination methodologies, considerable limitations still exist in the selective hydroamination of alkynes, especially for terminal alkynes. Herein, we develop a highly efficient NiH catalytic system that activates readily available alkynes for a cascade hydroamination/cyclization reaction with anthranils. This mild, operationally simple protocol is amenable to a wide array of alkynes including terminal and internal, aryl and alkyl, electron-deficient and electron-rich ones, delivering structurally diverse quinolines in useful to excellent yields (>80 examples, up to 93% yield). The utility of this procedure is exhibited in the late-stage functionalization of several natural products and in the concise synthesis of an antitumor molecule graveolinine and a triplex DNA intercalator. Preliminary mechanistic experiments suggest an alkenylnickel-mediated alkyne hydroamination and an intramolecular cyclization/aromatization of putative enamine intermediates.



KEYWORDS: *NiH catalysis, hydroamination, alkynes, anthranils, quinolines*

Within the field of synthetic organic chemistry, the efficient and selective construction of C−N bonds is of critical importance because of the presence of nitrogen-containing compounds in many natural products,[1] medicinally relevant molecules,[2] and functional materials.[3] Apart from the state-of-the-art C−N cross-coupling,[4] traditional hydroamination of alkenes and alkynes enabled by rare-earth and noble metals has been extensively investigated for decades (Scheme 1a, method A).[5] In recent years, a polarity-reversed strategy that utilizes metal hydrides in combination with an electrophilic aminating reagent has emerged as a powerful means to prepare complex amines because of attractive advantages such as low cost, mild conditions, as well as high regio- and stereoselectivity (Scheme 1a, method B).[6] Pioneered by Buchwald,[7] Miura,[8] Hirano, and others,[9] CuH-catalyzed hydroamination of alkenes has been developed for the formation of sp^3 C−N bonds. However, to the best of our knowledge, metal-H-mediated alkyne hydroamination for sp^2 C−N bond formation has been largely unsuccessful and remains as a challenging task in this field. This is probably attributed to the fast protodemetalation of the in-situ-generated alkenylcopper intermediate, which may result in the semireduction of alkynes to alkenes.[10] Moreover, the instability of enamine products is also a crucial issue that hinders the advancement on alkyne hydroamination. The group of Buchwald has achieved an interesting CuH-catalyzed hydroamination of internal aryl alkynes (Scheme 1b, path A).[11] However, in this catalytic system, alkylamines are competitively formed via a sequential semireduction/hydroamination of alkynes (Scheme 1b, path B). A similar chemoselectivity has also been recently observed in a cobalt-catalyzed system reported by Lu et al.[12a] Miura and Hirano et al. developed Zr/Cu sequential catalysis for the formal hydroamination of terminal aryl alkynes in two steps.[12b]

Compared with the widespread success of CuH catalytic systems in alkene functionalization, NiH catalysis is more commonly used in the hydrofunctionalization of alkynes probably due to the slow protodemetalation of alkenylnickel intermediates.[13] Recently, Chang and Seo achieved the first NiH-catalyzed hydroamidation of alkynes with dioxazolones for the selective synthesis of enamides.[14] Given the intrinsic reactivity of NiH complexes,[15] we recently questioned whether a NiH catalytic system could be applied to further expand the research on hydroamination of simple alkynes which is a long-standing challenge in Cu or Co catalytic systems. The rational choice of an appropriate electrophilic amine reagent is critical for the success of this type of reaction. On the one hand, the aminating reagent should be stable under reductive conditions. On the other hand, the reaction of the aminating reagent with alkenylnickel intermediates should completely outcompete the protodemetalation process. In addition, the in-situ-generated enamine product should also be stable, or it can be rapidly trapped by electrophiles for the assembly of other high-value N-containing molecules.

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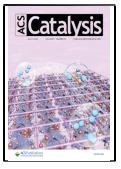

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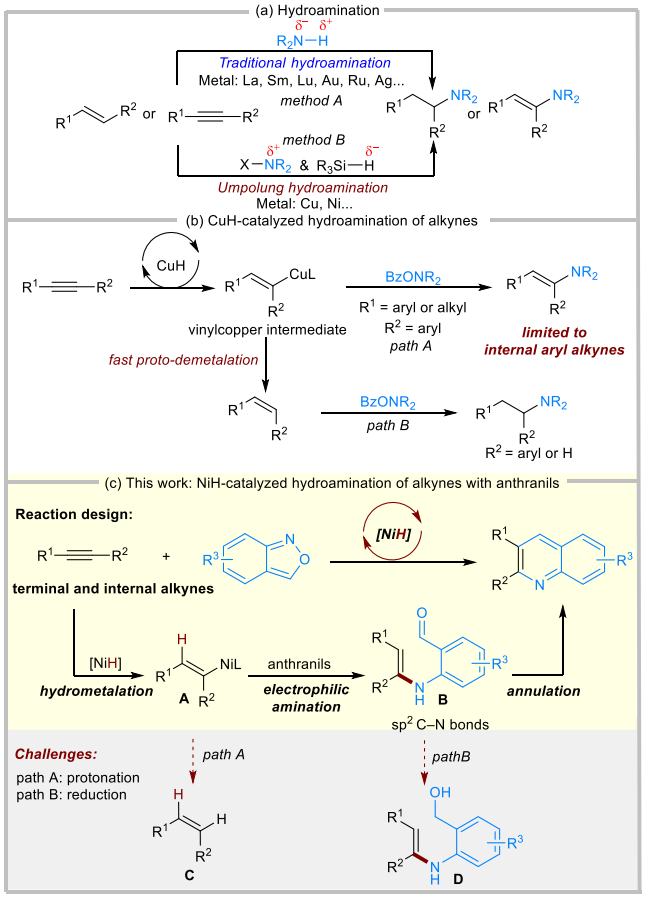
Scheme 1. Hydroamination Reaction for C−N Bond Formation and Reaction Design



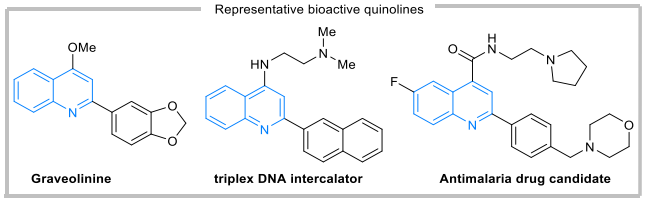
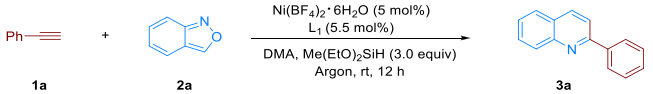


Figure 1. Representative biologically important quinolines.

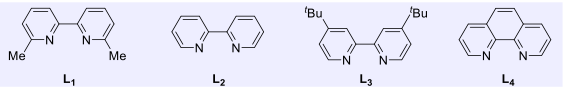
Anthranils are stable and readily available, which have been used as versatile aminating reagents in many C−N formation reactions.[16] Moreover, they are usually regarded as polarity-reversed 2-carbonyl anilines, which may provide a possibility for the trapping of enamine intermediates by the carbonyl group.[17] For instance, Knochel et al. have recently disclosed a convenient Co-catalyzed cross-coupling of alkenylzinc pivalates and anthranils for the synthesis of quinolines.[17b] In addition, anthranils were successfully applied in a copper-catalyzed hydroamination of vinylarenes.[18] Inspired by these precedents and our ongoing interests in anthranil chemistry[16,17a] and *N*-heterocycle synthesis,[19] herein, we envisaged to develop a new alkyne hydroamination strategy based on an efficient NiH-catalyzed polarity-reversed reaction mode with the use of anthranils as electrophilic aminating sources. The specific mechanistic details of our proposed NiH-catalyzed hydroamination/cyclization cascade are outlined in Scheme 1c. In the presence of hydrosilane, the reactive NiH-catalyst is in-situ-generated, which would readily react with alkynes to form the

Table 1. Summary of the Effects of Reaction Parameters



1a 2a 3a

entry	deviation from standard conditions[a]	yield (%)[b]
1	none	90 (86)[c]
2	DMPU, NMP or DMF instead of DMA	72, 83, 45
3	no $Ni(BF_4)_2·6H_2O$	0
4	$NiBr_2$, $Ni(acac)_2·2H_2O$ or $Ni(OAc)_2$ instead of $Ni(BF_4)_2·6H_2O$	43, 14, 9
5	no ligand	27
6	L_2, L_3 or L_4 instead of L_1	16, 12, 31
7	no $Me(OEt)_2SiH$	0
8	$(EtO)_3SiH$ or PMHS instead of $Me(OEt)_2SiH$	73, 87
9	KF or Cs_2CO_3 as additional additives	0, 42
10[d]	H_2O, EtOH or ^{i}PrOH as additional additives	87, 89, 86
11	10.0 equiv. H_2O was added	90



[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), $Ni(BF_4)_2·6H_2O$ (5 mol %), L_1 (5.5 mol %), $Me(OEt)_2SiH$ (3.0 equiv), DMA (1.0 mL) under an argon atmosphere at room temperature for 12 h. DMA refers to *N*,*N*-dimethylacetamide. [b]Yields determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [c]The yield in parentheses is the isolated yield. [d]0.2 mmol proton source was added.

key alkenylnickel species **A**. The resulting intermediate **A** is expected to couple with anthranils to produce enamine intermediates **B** with an adjacent carbonyl group. Subsequent intramolecular cyclization/aromatization of enamine **B** would afford the desired quinoline products. The key challenges for this cascade reaction can be attributed to the following points: (1) the compatibility of anthranils in the NiH catalytic system; (2) semihydrogenation of alkynes (Scheme 1c, path A);[10−12] (3) the reduction of the carbonyl group by the NiH species before intramolecular cyclization (Scheme 1c, path B).[18] We believe that the rational combination of the Ni catalyst and reductant may provide a solution to these challenges.

Quinolines are one of the most prevalent N-heterocycles in pharmaceuticals, natural products, and materials (Figure 1).[20] Traditional methods often rely on harsh reaction conditions and specialized substrates,[21] which largely limits their applications in practical synthesis. We developed a novel NiH catalytic system that activates readily available alkynes for a cascade hydroamination/cyclization reaction with anthranils, furnishing a wide range of quinolines in good yields. The remarkable features of this protocol include mild conditions, simple operation, excellent regioselectivity, and broad substrate scope, providing a general and convenient platform for the construction of quinolines.

To test the feasibility of this hydroamination/cyclization reaction, phenylacetylene (**1a**) and benzo[*c*]isoxazole (**2a**) were chosen as the model substrates, and various catalysts, ligands, hydrosilanes, and solvents were systematically

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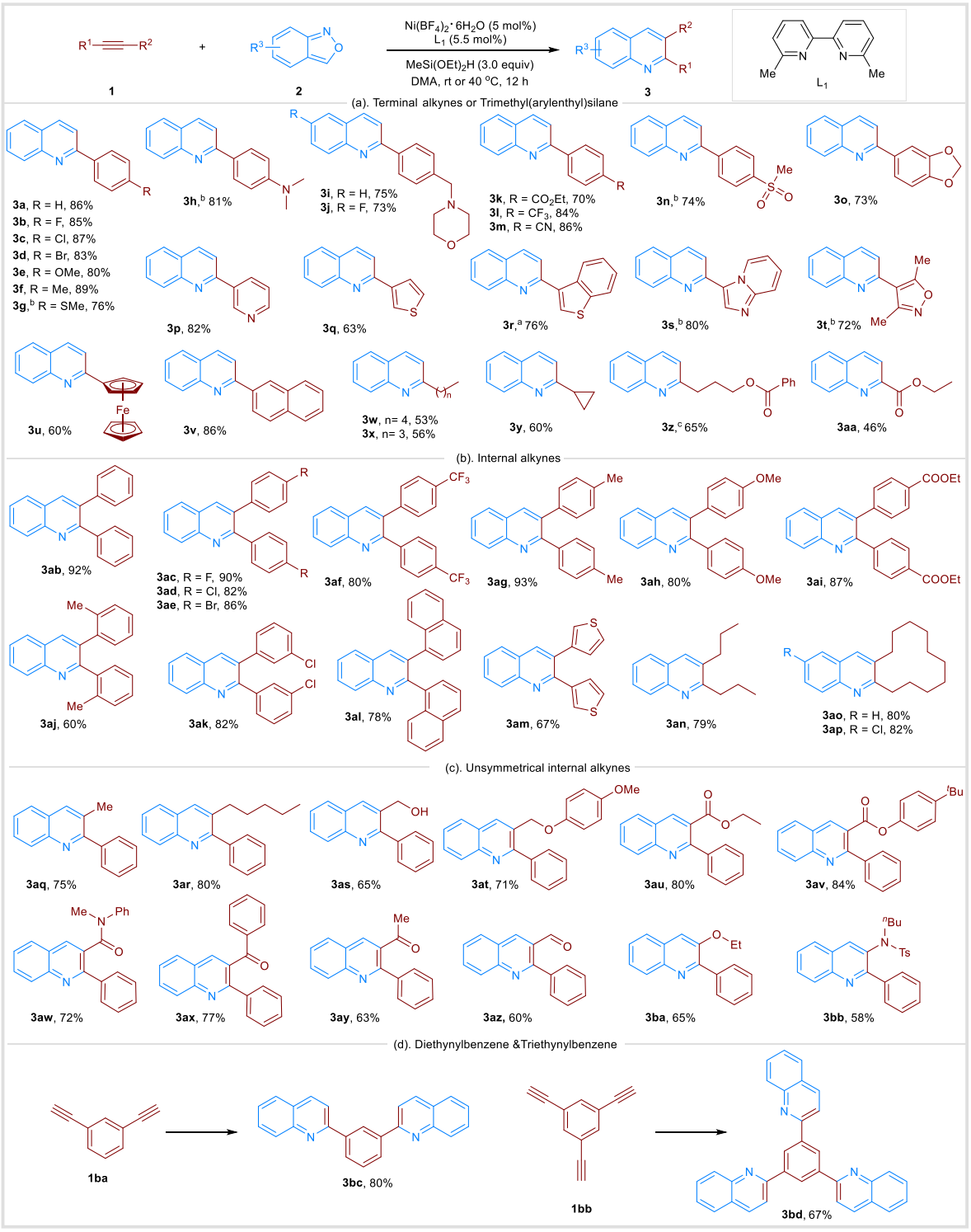
Scheme 2. Scope of Alkynes[a]



[a]Reactions were run with **1** (0.3 mmol) and **2** (0.33 mmol) under standard reaction conditions at room temperature (for terminal alkynes) or 40 °C (for internal alkynes) for 12 h. Reported yields are the isolated ones. [b]Trimethyl(arylethynyl)silane was used as the substrate. [c]3-Alkyl substituted isomer was detected by crude ^{1}H NMR, and the ratio of 2-alkyl quinoline **3z**:3-alkyl quinoline **3z′** is 20:1.

investigated (Table 1). We first tested the commonly used copper catalysts to promote the proposed reaction. However, these copper catalysts were found to be ineffective for this reaction (see Table S1 for the screening of copper catalysts). In CuH catalytic systems, byproducts 2-aminobenzaldehyde and styrene were observed via the competitive reduction of anthranil **2a** and phenylacetylene, respectively. To our delight, nickel catalysts exhibit remarkable activity for the formation of quinoline product **3a**. The yield of **3a** can be achieved in 90% using $Ni(BF_4)_2{\cdot}6H_2O$ (5 mol %) as the catalyst, 6,6′-dimethyl-2,2′-bipyridine (L_1) as the ligand, and $Me(OEt)_2SiH$ as the hydride source in dimethylacetamide (DMA) at room

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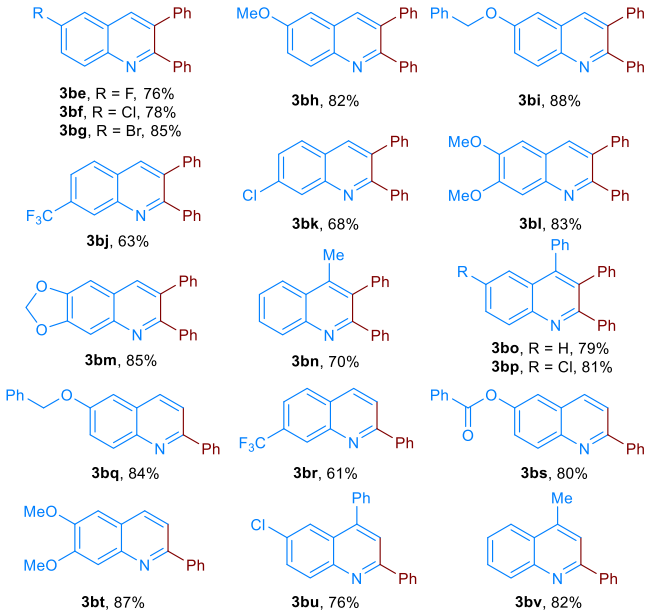
Scheme 3. Scope of Anthranils[a]



[a]Reactions were run with **1** (0.3 mmol) and **2** (0.33 mmol) under standard reaction conditions. Reported yields are the isolated ones.

temperature (entry 1). Notably, 2-phenylquinoline was formed with exclusive regioselectivity presumably because of the stabilization of the alkenylnickel species by an adjacent phenyl group.[11a] The screening of reaction solvents indicated that other solvents such as *N, N′*-dimethylpropyleneurea (DMPU), *N*-methyl-2-pyrrolidone (NMP), or dimethylformamide (DMF) led to diminished yields (entry 2). The counter anion of nickel salt has a significant influence on the reaction outcome. $Ni(BF_4)_2{\cdot}6H_2O$ proved to be the optimal catalyst, while $NiBr_2$, $Ni(acac)_2{\cdot}2H_2O$, or $Ni(OAc)_2$ resulted in decreased yields (entry 4). The strong cationic nickel center in $Ni(BF_4)_2{\cdot}6H_2O$ may promote the initial NiH formation step because of the weak coordination of BF_4^- anions. Although the ligand is not indispensable for this reaction to proceed, the use of 6,6′-dimethyl-2,2′-bipyridine (L_1) as a supporting ligand can improve the yield (entries 5 and 6). $Me(OEt)_2SiH$ (3.0 equiv) proved to be the most efficient hydride source, and other tested silanes resulted in decreased yields (entry 8). Base additives were found to have detrimental influence on the reaction (entry 9). As expected, control experiments demonstrated that the nickel catalyst and silane were essential for this reaction (entries 3 and 7). In addition, the influence of proton sources has been investigated. This cascade reaction proceeded smoothly when 1.0 equivalent of H_2O, EtOH, or ^{i}PrOH was added to the reaction mixture (entry 10). Moreover, product **3a** can be obtained in good yields even with the addition of 10 equiv H_2O in the system (entry 11). These results strongly support that the expected hydroamination completely outcompetes the semireduction process in this NiH catalytic system. Compared with the easy protonation of well-established alkenylcopper intermediates, the protodemetalation of the alkenylnickel species is unfavorable because of the relatively high energy barrier.[14]

As shown in Scheme 2, a large variety of alkynes including terminal and internal, electron-deficient and electron-rich, aryl and alkyl ones were compatible in this reaction. Under the optimized conditions, alkynes bearing different functional groups such as fluoro (**3b**), chloro (**3c**), bromo (**3d**), methoxy (**3e**), methylthio (**3g**), amino (**3h**), ester (**3k**), trifluoromethyl (**3l**), cyano (**3m**), sulfone (**3n**), and even free hydroxyl group (**3as**) were tolerated well. A series of valuable bis(hetero)aryls (**3p**−**3v**) can be obtained in good yields, which are privileged π-conjugated structural cores in biologically active molecules and organic functional materials.[22] Remarkably, terminal aliphatic alkynes reacted smoothly with anthranils to give the desired 2-alkyl quinolines in moderate yields (**3w**−**3z**). The high regioselectivity of aliphatic alkynes is probably attributed to the stability of the α-alkenyl nickel species.[13e] Ethyl propiolate afforded the desired ethyl quinoline-2-carboxylate (**3aa**) in 46% yield with excellent regioselectivity. Diarylacetylenes are successfully converted into expected products in generally good to excellent yields (**3ab**−**3am**). Oct-4-yne (**3an**) and cyclododecyne (**3ao** and **3ap**) participated in this transformation with a high reaction efficiency. For unsymmetrical internal alkynes bearing an aryl substituent (**3aq**−**3at**), these reactions proceed in high regioselectivity with C−N bond formation occurring adjacent to the aryl group.[11a] The electron-deficient alkynes including alkynyl esters (**3au** and **3av**), alkynamide (**3aw**), alkynone (**3ax**−**3az**), and electron-rich ones such as alkynyl ether (**3ba**) and ynamide (**3bb**) are compatible with this catalytic system, producing the corresponding quinolines in good yields (58−84%). Significantly, 1,3-diethynylbenzene and 1,3,5-triethynylbenzene also proved to be suitable, furnishing the expected products **3bc** and **3bd** in 80% and 67% yields, respectively.

We next turned our attention to the scope of anthranils in this new NiH catalytic system. As shown in Scheme 3, various substituents including F (**3be**), Cl (**3bf**), Br (**3bg**), OMe (**3bh**), benzyl (**3bi**), CF_3 (**3bj**), and acetal (**3bm**) were well tolerated, giving rise to the desired polysubstituted quinolines in good yields (61−88%). Notably, 3-aryl- and alkyl-substituted anthranils were found to participate readily in this transformation (**3bn**−**3bp**, **3bu**, and **3bv**).

To further exemplify the utility of this protocol, we applied this NiH-catalyzed hydroamination/cyclization cascade reaction in the late-stage modification of several readily available natural products and pharmaceutical derivatives. As outlined in Scheme 4a, the alkynes derived from some bioactive molecules such as estrone (**3bw**), vitamin E (**3bx**), nerol (**3by**), menthol (**3bz**), cholesterol (**3ca**), ibuprofen (**3cb**), and galactose (**3cc**) reacted smoothly with anthranils, delivering high-functionalized quinolines in synthetically useful yields. The success of these reactions demonstrated the synthetic potential of this methodology in organic chemistry and industrial applications.

Alkynes can be easily accessed from aryl bromide via Sonogashira coupling.[23] The gram-scale experiment involving 2-bromo-9H-fluoren-9-one as the starting material proceeded efficiently, furnishing the corresponding quinoline **3cd** in 72% (0.92 g) yield (Scheme 4b). In addition, transition-metal-catalyzed C−H alkynylation has been well established to prepare alkynes.[24] We can start from the commercially available acetophenone to synthesize the bioactive quinoline **3ce** via a sequential iridium-catalyzed *ortho*-C−H alkynylation and NiH-mediated hydroamination/cyclization cascade (Scheme 4c). Moreover, this mild NiH catalytic system can be successfully applied to the concise synthesis of biologically active compounds. For instance, graveolinine, which exhibits antibacterial, spasmolytic, and antitumor activities, can be concisely synthesized from **3o** (Scheme 4d).[25] 2-(2-Naphthyl)-quinoline derivative **3ci**, that has been designed to target

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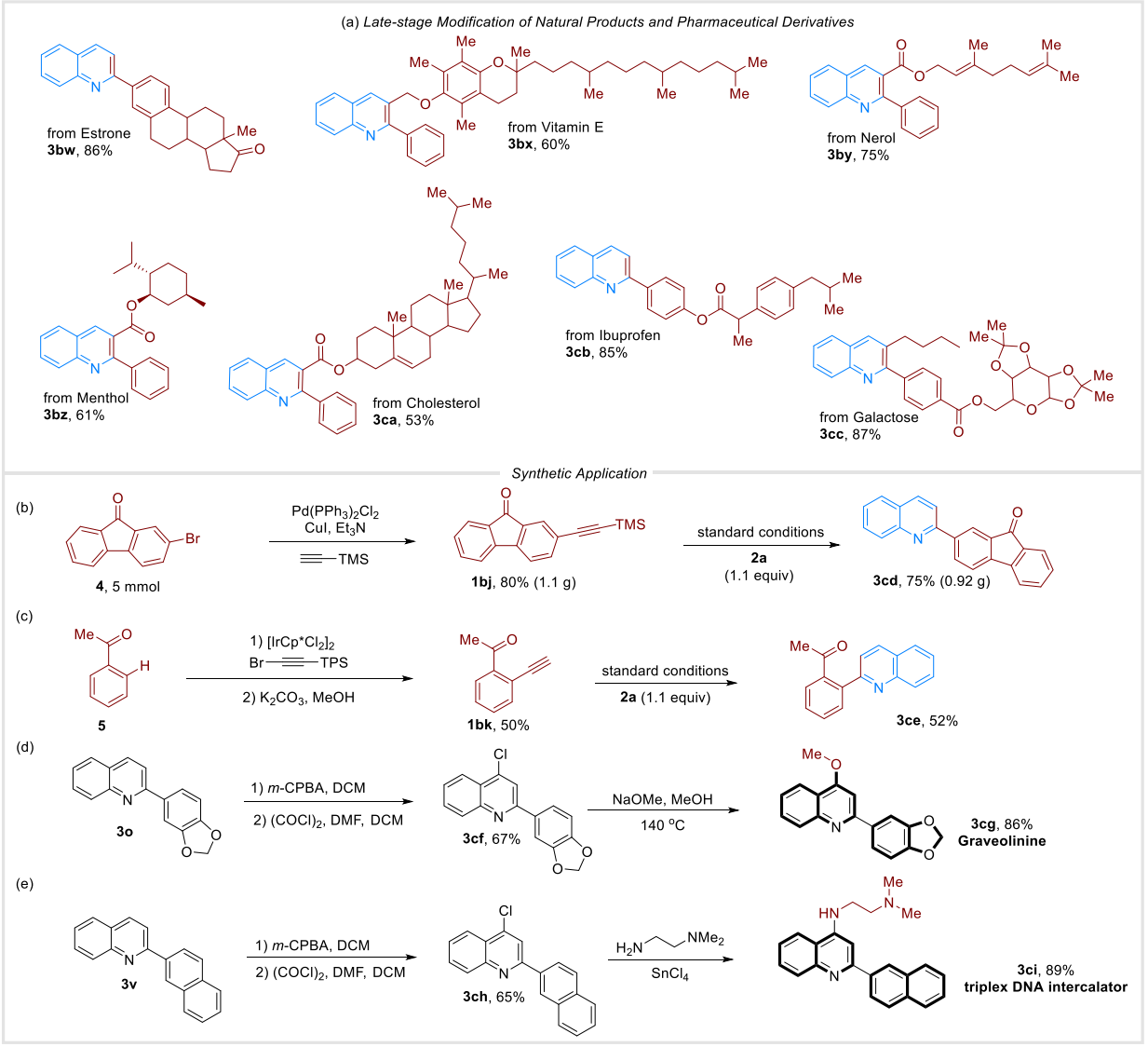
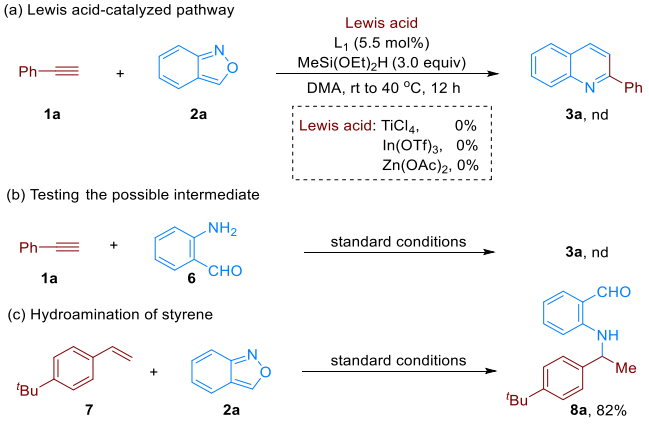
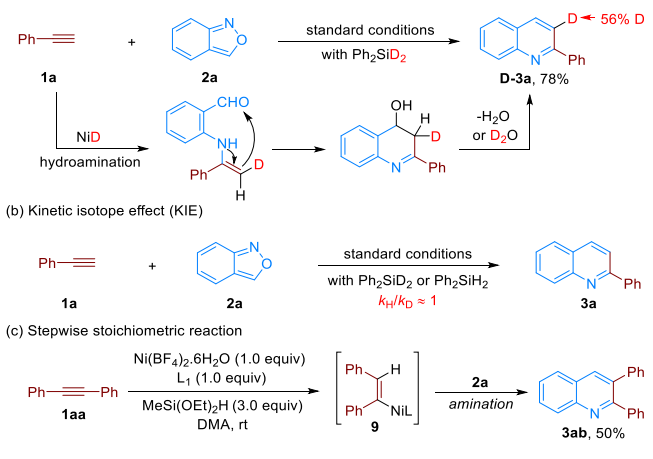
Scheme 4. Late-Stage Modification of Natural Products and Pharmaceutical Derivatives and Synthetic Applications



Scheme 5. Lewis Acid-Catalyzed Pathway (a), Testing the Possible Intermediate (b), and Hydroamination of Styrene (c)



Scheme 6. Deuteration with Ph_2SiD_2 (a), Kinetic Isotope Effect (b), and Stepwise Stoichiometric Reaction (c)



triplex DNA, was efficiently constructed from product **3v** via two simple operations (Scheme 4e).[26]

To understand the mechanism, a series of control experiments were conducted (Scheme 5). Anthranils have been

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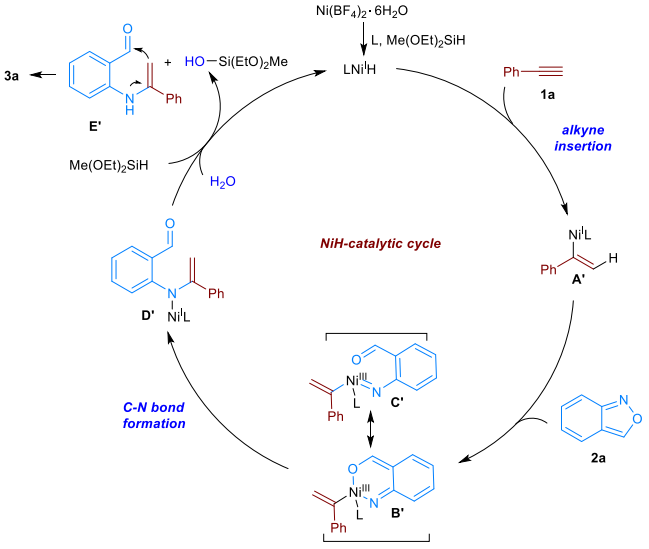
Scheme 7. Proposed Mechanism



reported to undergo Diels−Alder (DA) reaction with enamines in the presence of $TiCl_4$ as a catalyst.[27] To probe this possibility, Lewis acids including $TiCl_4$, $Zn(OAc)_2$, and $In(OTf)_3$ were tested; however, all of these catalysts turned out to be ineffective for this reaction in the presence or absence of a ligand (Scheme 5a). Therefore, a tandem process, involving a Lewis-acid-catalyzed DA reaction of anthranils and alkynes, and subsequent reduction by silane, could be excluded. Although a small amount of 2-aminobenzaldehyde (**6**) can be detected in the reaction, it is not likely an intermediate for this reaction because no desired product was detected when 2-aminobenzaldehyde was subjected to the reaction system (Scheme 5b). Notably, under the current conditions, the reaction of styrene **7** and anthranil **2a** proceeded smoothly to give the hydroamination product **8a** in good yields (Scheme 5c). This important result confirms that anthranils can serve as efficient electrophilic aminating reagents in NiH-catalyzed hydroamination reactions. In addition, the aldehyde group is left intact in the reductive system, opening an opportunity for the NiH-catalyzed hydroamination/cycloisomerization cascade reaction of alkynes with anthranils.

Moreover, an isotope labeling experiment was conducted with the use of Ph_2SiD_2 as the reductant (Scheme 6a). As a result, 56% deuterium incorporation at the 3-position of compound **3a** was observed, which indicated that deuterium is provided by silyldeuteride from the generated NiD species. The partly loss of deuterium may occur in the intramolecular condensation step in which a hydrogen or deuterium is eliminated. In addition, there are no significant kinetic isotope effects in parallel experiments, which indicates that the Si-H bond cleavage is not likely to be involved in the rate-determining step (Scheme 6b). The intermediary of the alkenylnickel species was demonstrated by the success of a stepwise reaction of **1aa** and **2a** (Scheme 6c) (see the Supporting Information for details).

According to the above mentioned results and previous studies, a plausible NiH-catalytic cycle is proposed in Scheme 7. First, a LNiH species is generated from the reaction of $Ni(BF_4)_2{\cdot}6H_2O$, $Me(OEt)_2SiH$, and ligand.[14,15] Then, alkyne insertion occurs with high regioselectivity to give reactive alkenylnickel intermediate **A′**[13,14] that further undergoes oxidative insertion into the N−O bond of anthranils, giving rise to species **B′** and its resonance structure **C′**.[28] The subsequent reductive elimination of **B′** affords the key enamine intermediate **D′**. The resulting intermediate **D′** then reacts with $Me(OEt)_2SiH$ to deliver intermediate **E′** with the regeneration of an active NiH catalyst for the next catalytic cycle. It should be noted that the presence of H_2O may help release the Ni catalyst from intermediate **D′** and enhance the generation of the active NiH species.[14] Finally, the intermediate **E′** undergoes intramolecular cyclization to deliver the desired quinoline product.

In summary, an efficient NiH-catalyzed hydroamination/cyclization cascade of alkynes and anthranils has been developed, which opens up a convenient route for the synthesis of various highly substituted quinolines. This new protocol features good regioselectivity, mild reaction conditions, simple operation, and broad substrate scope. Beyond the synthetic application displayed herein, we anticipate that this protocol can be widely used in a concise synthesis of other valuable targets. Moreover, the success of NiH catalysis in alkyne hydroamination may stimulate the rapid development of new catalytic systems for the transformation of simple alkynes into various high-value compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02055.

Detailed experimental procedures and ^1H and ^{13}C NMR spectra for all the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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