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Convergent synthesis of triarylamines *via* Ni-catalyzed dual C(sp^2)–H amination from benzamides with benzohydroxamic acids†

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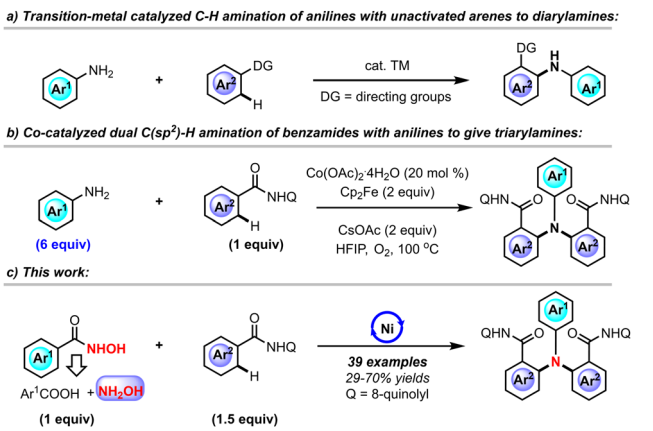
An unprecedented method of nickel-catalyzed dual C(sp^2)–H amination of *N*-quinolylbenzamides with benzohydroxamic acids is developed to access triarylamines in one pot. For the first time, broad-spectrum hydroxylamine is employed as an amino source for C–H amination, featuring good chemo-selectivity and functional group tolerance. Furthermore, the catalytic system could be further extended to *N*-(pivaloyloxy)benzamide, dioxazolone, isocyanate and aniline for C–H amination.

Arylamine, particularly triarylamine, is a significant structural unit that widely occurs in pharmaceuticals, bioactive molecules, and optoelectric materials.[1] Among them, the antitumor medicine Gleevec and the drug for treating schizophrenia Aripiprazole both possess a triarylamine skeleton.[2] Furthermore, triarylamine derivatives have broad practical utility in the material field because of their specific photophysical properties, such as applying for organic light-emitting diodes and organic field-effect transistors.[3] Consequently, developing robust and expeditious pathways to accommodate triarylamine frameworks has been a long-standing research hotspot in organic synthesis and aroused extensive attention from industry and academia.

Over the past few decades, transition-metal-catalyzed C–N bond formation reactions, no doubt, have emerged as sought-after protocols to produce arylamine motifs.[4] Among these methods, transition-metal-catalyzed directed C–H/N–H dehydrogenative coupling of anilines with unactivated arenes has attracted wide attention on account of its good step-economy and efficiency (Scheme 1(a)).[5–9] In this respect, Chatani,[5] Chang,[6] Yu,[7] and others[8,9] have developed elegant works, but most reports are limited to affording diarylamines. To our knowledge, there is merely one example regarding triarylamine synthesis,[10] which is demonstrated by Song and Niu's co-workers through the cobalt-catalyzed dual C(sp^2)–H amination of benzamide derivatives with anilines (Scheme 1(b)). Though progress, much excess of aniline is required, and the strong coordinating characteristics of anilines might render transition metal poisoning. Moreover, the conventional route to prepare anilines is based on nitration and reduction processes under harsh reaction conditions. Hence, it is of great significance to open up new, readily accessible, and stable aminating reagents to fabricate the desired triarylamines *via* the C(sp^2)–H amination course.

Benzamide and its derivatives within favorable stability and diversity have been widely exploited in the C–H functionalization domain. Not only can they serve as auxiliaries to facilitate the C–H activation,[11] but they can also be utilized as amidating coupling partners.[12–15] Up to now, a range of benzamide analogs, covering bare benzamides,[12] carbamate variants,[13] dioxazolones,[14] and *N*-methoxyamides,[15] have been used as reactants to construct amido bonds. Hydroxamic acid as a versatile benzamide counterpart could be effortlessly synthesized from broad-spectrum



Scheme 1 Transition-metal catalyzed dehydrogenative amination.

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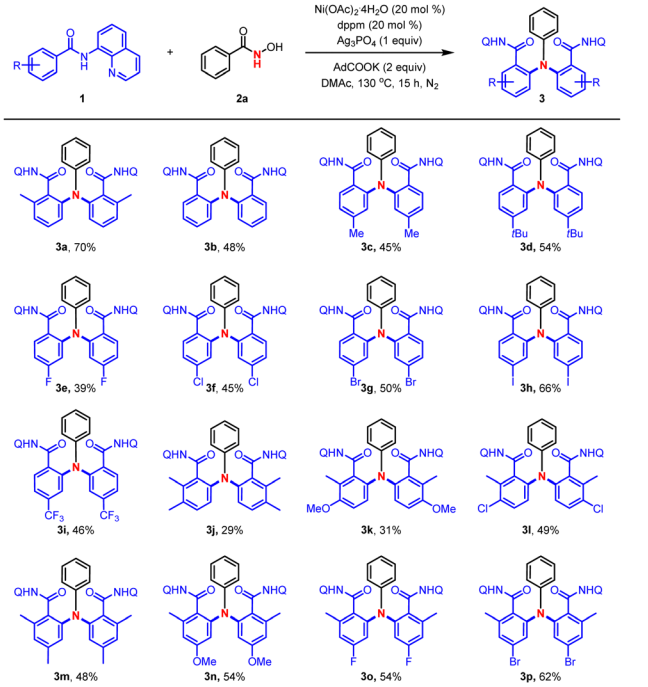
carboxylic acids and hydroxylamine hydrochloride. Inspired by Dai's work of Rh-catalyzed C–H activation/Lossen rearrangement to produce spirooxindole,[16] we envisaged that hydroxamic acid could be turned into an amino source *via* the Lossen rearrangement followed by straightforward C–H amination. Prompted by our ongoing interest in earth-abundant, nickel-catalyzed dehydrogenative couplings,[17] we herein report a new method to furnish triarylamines from *N*-quinolyl benzamides with benzohydroxamic acids by nickel-catalyzed dual C–H amination using hydroxylamine as the amino source (Scheme 1(c)). It should be noted that this reaction could run smoothly without excess hydroxamic acids. The reaction features simple operation, good step economy and excellent chemo-selectivity, and tolerates a number of functional groups. Mechanistic investigations unveiled that this transformation might be based on the nickel-catalyzed Lossen rearrangement, dual C–H activation, and C–N bond formation sequences in a single-step manner.

To verify our hypothesis, we chose simple *N*-hydroxybenzamide (**2a**) and 2-methyl-*N*-(quinolin-8-yl)benzamide (**1a**) as benchmarks to commence our study. We first adopted the reaction conditions of Song's work,[10] but only the benzamide dimer was observed.[18] Delightfully, the targeted triarylamine product (**3a**) could be indeed obtained in the presence of $Ni(acac)_2$, PPh_3, AdCOOK, and Ag_3PO_4 using DMAc as a solvent at 130 °C under an N_2 atmosphere. We further investigated the reaction parameters for this dual C–H amination (Table S1, ESI†). It was found that $Ni(OAc)_2{\cdot}4H_2O$ was the optimal catalyst to improve the aminating product (**3a**) to 57% yield (entries 1–3). The screening of the solvent indicated that other polar nonprotic solvents, including DMSO, DMF, and NMP, gave inferior yields (entries 4–6). Among diverse Ag-salts, Ag_3PO_4 was the best candidate (entries 7–9). Upon exploration of diverse bases and ligands, it was found that AdCOOK showed preferable efficiency (entries 10–13), and the dppm ligand could facilitate the C–H amination helpfully (entries 14–19). Control experiments proved that both $Ni(OAc)_2{\cdot}4H_2O$, AdCOOK, and Ag_3PO_4 were crucial to this amination reaction (entries 20–22). Other common transition metal catalysts, including $Pd(TFA)_2$, $Cu(OAc)_2$, and $Co(OAc)_2$, were invalid in this reaction (entries 23–25), underlying the superior catalytic performance of nickel catalysts. The optimization of directing groups revealed that the 8-aminoquinoline auxiliary group is a prerequisite for this C–H amination (see ESI,† Table S2).

Having established the optimal reaction conditions, we first explored the substrate scope and compatibility of *N*-quinolylbenzamides, as shown in Table 1. In general, both electron-rich and electron-deficient benzamides could participate in this reaction to produce the aimed triarylamines smoothly (**3a–3p**). Bare *N*-quinolylbenzamides, *para*-methyl, and *tert*butyl substituted *N*-quinolylbenzamides could couple with hydroxamic acid (**2a**), giving the triarylamine products in 48%, 45%, and 54% yields, respectively (**3b–3d**). It should be noted that substrates with fluoro, chloro, bromo, and iodo, were tolerated well (**3e–3h**), which could be transformed into more complicated motifs *via* cross-couplings. Importantly, *N*-quinolylbenzamide with a strong electron-withdrawing $-CF_3$ substituent afforded the targeted product favorably (**3i**). Furthermore, this reaction was suitable for 2, 3- and 2,4-disubstituted *N*-quinolylbenzamides, containing –Me, –OMe, –Cl, –F, and –Br, leading to the desired products in 29%–62% yields (**3j–3p**).

Table 1 Scope of *N*-quinolylbenzamides[ab]

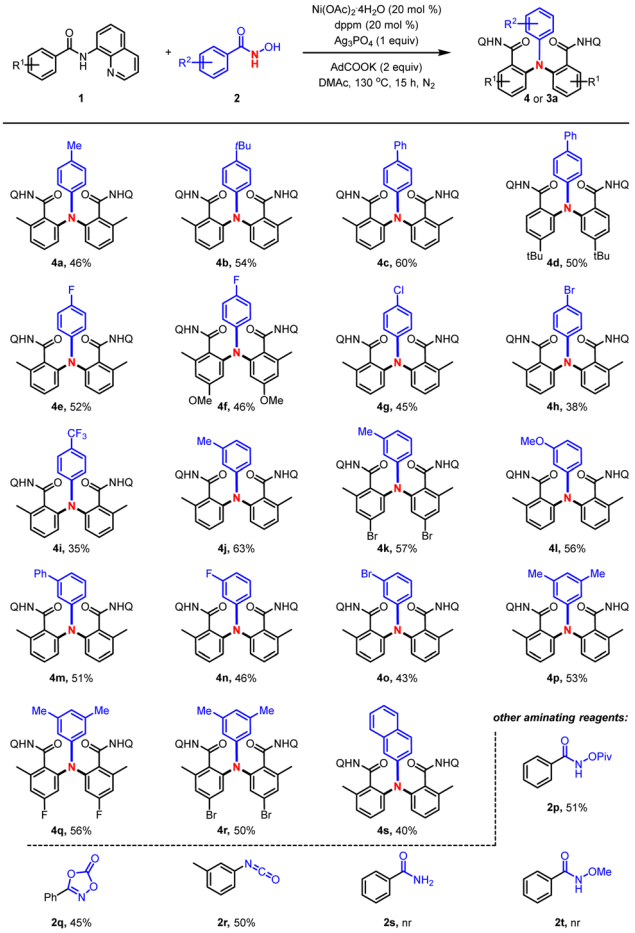


[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.1 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (20 mol%), dppm (20 mol%), Ag_3PO_4 (1 equiv.), AdCOOK (2 equiv.), DMAc (1 mL), 130 °C, 15 h, N_2. [b] Isolated yields.

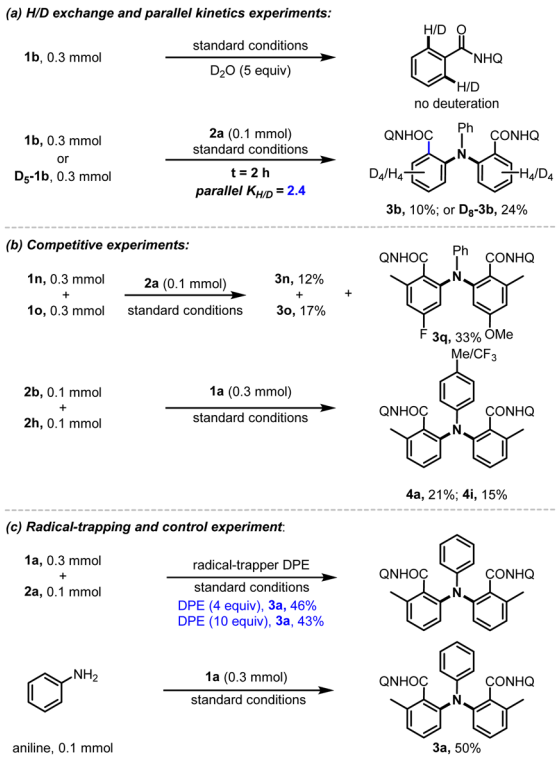
We next attempted to investigate the generality and tolerance of benzohydroxamic acids and other aminating reagents (Table 2). In principle, benzohydroxamic acids bearing electron-donating substituents exhibited better efficiency than the electron-withdrawing ones (**4a–4i**). Similar yields were obtained between *para*-substituted and *meta*-substituted benzohydroxamic acids, indicating that steric hindrance has a negligible influence on this reaction (**4c**, **4e**, **4h**, **4m–4o**). Numerous functional groups, including methyl, *tert*butyl, phenyl, halogens, trifluoromethyl, and methoxyl could be compatible well (**4a–4c**, **4e–4i**, **4l**). Moreover, *N*-hydroxy-3,5-dimethylbenzamide and *N*-hydroxy-2-naphthamide were feasible to generate the targeted products in moderate yields (**4p–4s**). Satisfyingly, when alternatives, such as *N*-(pivaloyloxy)benzamide (**2p**), 3-phenyl-1,4,2-dioxazol-5-one (**2q**), and 1-isocyanato-3-methylbenzene (**2r**), were subjected to the reaction, these substrates could selectively serve as amination trials for synthesizing the desired triarylamines with moderate yields. Subsequently, we tested the reactivity of bare benzamide (**2s**) and *N*-methoxybenzamide (**2t**), which were common model amidation feedstocks,[12,15] but unfortunately, no amidated or aminating products were observed during the reaction course.

To illuminate the intrinsic mechanism of this amination transformation, a set of experiments was carried out, as described in Scheme 2. With the treatment of benzamide (**1b**) by 5 equiv. D_2O under standard conditions, no deuterium

Table 2 Scope of benzohydroxamic acids and other aminating reagents[ab]



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.1 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (20 mol%), dppm (20 mol%), Ag_3PO_4 (1 equiv.), AdCOOK (2 equiv.), DMAc (1 mL), 130 °C, 15 h, N_2. [b] Isolated yields.

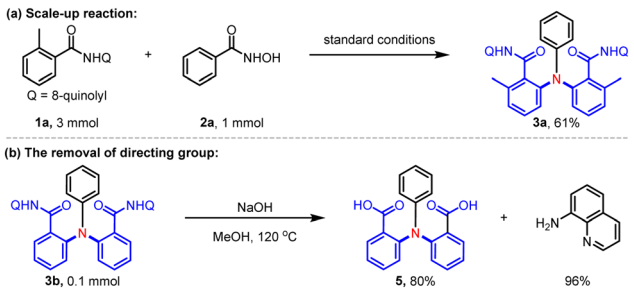


Scheme 2 Mechanistic studies.

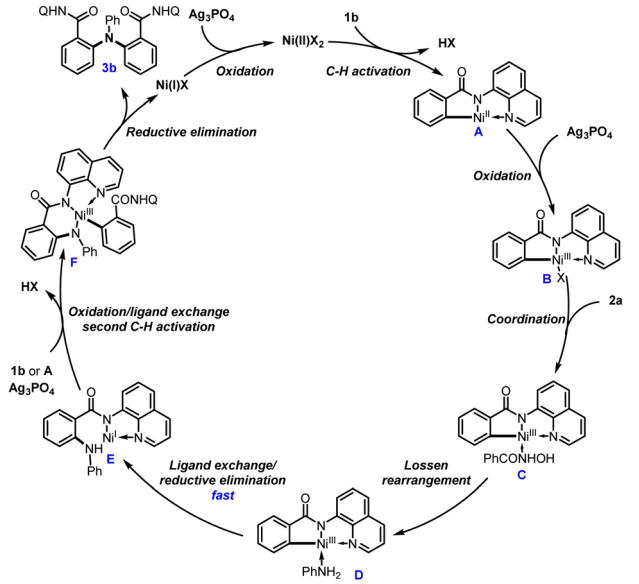
incorporation was detected on the *ortho* C–H bonds, which indicated that the Ni-catalyzed dual C–H activation process was an irreversible step (Scheme 2(a), up). The KIE value measured by the parallel kinetics experiments of benzamide (**1b**) or deuterated benzamide (**D_5-1b**) reacting with *N*-hydroxybenzamide (**2a**) for 2 h was 2.4, revealing that the C–H activation course might be the rate-determining step (Scheme 2(a), bottom). The competitive experiments of benzamides **1n** and **1o** showed that electron-deficient *N*-quinolylbenzamide gave a slightly higher efficiency. It was noteworthy that the cross-over unsymmetric triarylamine product (**3q**) could be obtained in 33% yield in the meantime (Scheme 2(b), up). The electron-rich *N*-hydroxybenzamide (**2b**) displayed a slightly higher reactivity than the electron-deficient one (**2h**) (Scheme 2(b), bottom). We carried out the radical-trapping experiment by adding an additional 10 equivalent DPE (1, 1-diphenylethylene) and still obtained the aminating product **3a** in 43% yield. Accordingly, the radical pathway might not be involved in this transformation (Scheme 2(c), up). Notably, when benzohydroxamic acid was replaced with aniline, the desired triarylamine could be afforded in 50% yield (Scheme 2(c), bottom), and it was found that only a trace amount of aniline was detected under the standard reaction. These results implied that aniline might be the key intermediate for this C–H amination and formed by the Lossen rearrangement of benzohydroxamic acid with the assistance of cyclometalated species,[16] and then it was consumed rapidly through the subsequent C–N bond formation process.

Afterward, we focused on exploring the synthetic potential of this protocol, as displayed in Scheme 3. The reaction could be easily carried out on a 1 mmol scale, affording the targeted triarylamine product (**3a**) in 61% yield. Furthermore, the 8-aminoquinolyl auxiliary could be removed in the presence of NaOH and MeOH to give the triarylamine skeleton containing carboxyl groups (**5**).

Based on the experimental results and previous literature,[17,19] a tentative mechanism for this C–H amination is proposed (Scheme 4). At first, the nickel catalyst reacts with the benzamide substrate *via* an irreversible C–H activation



Scheme 3 Synthetic applications.



Scheme 4 Proposed reaction mechanism.

process to afford the key cyclometalated complexes **A**, which is further oxidated by Ag_3PO_4 to give the Ni(III) species **B**. The coordination of benzohydroxamic acid (**2a**) with intermediate **B** generates species **C**, then followed by Lossen rearrangement to produce the pivotal nickel(III)-aniline complexes **D**.[19] The subsequent ligand exchange and reductive elimination sequence of species **D** furnishes the aminating intermediate Ni(I) **E**, which experiences oxidation, ligand exchange, and a second C–H activation cascade to form intermediate **F**.[10] The reductive elimination of complexes **F** delivers the targeted triarylamine product (**3b**) and Ni(I) species. Finally, the further oxidation of Ni(I) completes the catalytic cycle.

In summary, we have developed a new expeditious pathway for the synthesis of triarylamines from readily accessible benzamide derivatives and benzohydroxamic acids in a one pot pattern. It should be noted that benzohydroxamic acid is utilized as an aminating agent for inert C–H amination rather than amidation, for the first time, featuring good functional group tolerance and chemo-selectivity. This conversion could be further extended to *N*-(pivaloyloxy)benzamide, dioxazolone, isocyanate, and aniline for C–H amination. Mechanistic investigations shed light on the fact that this amination might involve nickel-catalyzed Lossen rearrangement, dual C(sp^2)–H activation, and two C–N bond formation sequences. Further investigations toward Ni-catalyzed dual C–H activation for fabricating other high-value-added frameworks are underway in our laboratory.

N. L. conceived the project. W. L., R. W. and Z. L performed the experiments, J. C., Y. Z. and N. L. analyzed and interpreted the experimental data. N. L. and Y. Z. drafted the paper. All of the authors discussed the results and contributed to the preparation of the final manuscript.

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Conflicts of interest

There are no conflicts to declare.

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