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COMMUNICATION

Zinc(II)-catalyzed Intramolecular Hydroarylation-Redox Cross-Dehydrogenative Coupling of *N*-Propargylanilines with Diverse Carbon Pronucleophiles: Facile Access to Functionalized Tetrahydroquinolines

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Zinc(II)-catalyzed intramolecular hydroarylation-redox cross-dehydrogenative coupling of *N*-propargylanilines with two types of carbon pronucleophiles (nitromethane as a sp^3 carbon pronucleophile and phenylacetylenes as sp carbon pronucleophiles) proceeded to give the 2-substituted tetrahydroquinolines in good yields with 100% atomic utilization without any additional external oxidants.

Tetrahydroquinoline is one of the most important heterocyclic compounds which are widely applied in the pharmaceutical and agrochemical industries.[1] Particularly, 1,2,3,4-tetrahydro-quinolines bearing a substitution at the C2-position possess key role in a class of compounds widely present in natural products and biologically active molecules with a broad bioactivity spectrum, including antimalarial, antivirus, antifungal, antitumor activities and acting on pharmacological targets such as ion channels and membrane receptors (Figure 1).[2]

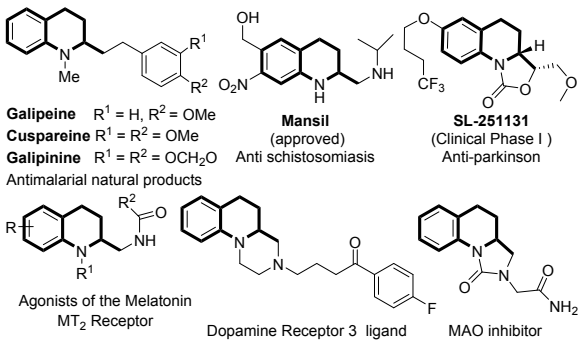
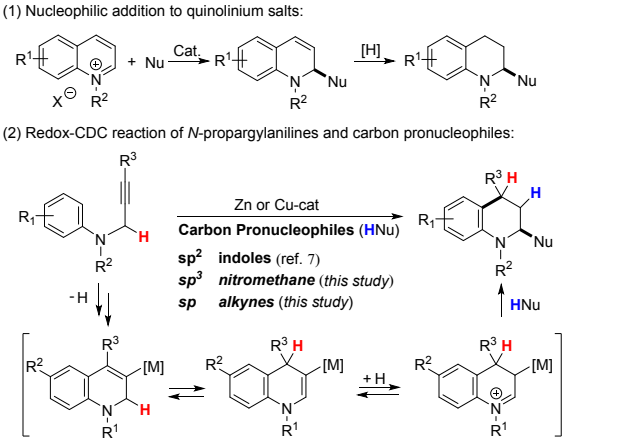


Figure 1. The chemical structures of representative natural and bioactive 2-substituted tetrahydroquinolines.

So far, a variety of convenient and versatile synthetic methods have been developed to access these 2-substituted tetrahydroquinoline motifs. The most broadly applicable methods of the ring construction include intramolecular cyclizations,[3] Povarov reaction,[4] and partial hydrogenations of quinolines.[5] Besides, the attack of nucleophiles to the quinoline salts provides an efficient strategy for a direct access to the 2-substituted 1,2-dihydroquinolines, which can be readily converted to 2-substituted 1,2,3,4-tetrahydroquinolines through hydrogenation (Scheme 1, eq 1).[6] Zinc(II)-catalyzed intramolecular hydrogenation-redox cross-dehydrogenative coupling (redox CDC) reaction of *N*-propargylaniline with indole was firstly reported by our group for preparing 2-indoltetrahydroquinoline compounds (Scheme 1, eq 2).[7] Briefly, dihydroquinoline was generated from intramolecular cyclization firstly, followed by isomerization to give an imine cation, which would undergo nucleophilic addition with indole (sp^2 carbon nucleophile) to afford the final product. In this reaction, three C-H bonds (two sp^2 and one sp^3) were activated in one shot. With the propargylic triple bond in the molecule acting as an internal oxidant to trap these hydrogens, there was no additional external oxidant needed, and notably the atomic



Scheme 1. The synthetic strategy of constructing 2-substituted tetrahydroquinolines.

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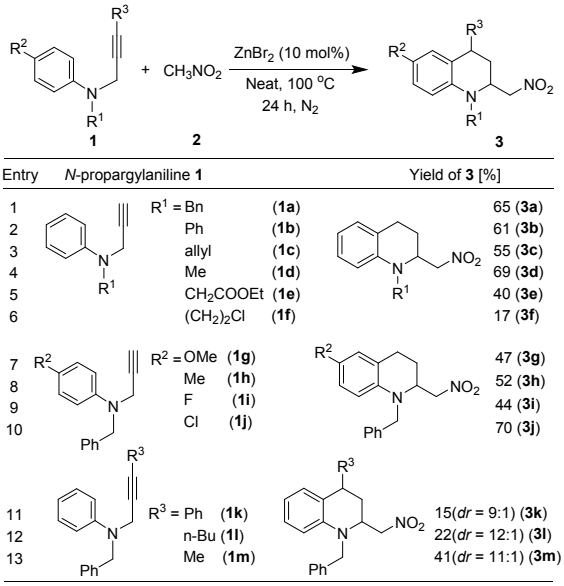
utilization was 100%. Inspired by these findings, we speculated that the activation of these C-H bonds might take place among two sp^3 and one sp^2 carbons and/or among sp^3, sp^2, and sp carbons. Herein, we employed nitromethane (sp^3 carbon nucleophile) and phenylacetylenes (sp carbon nucleophiles) as pronucleophiles in the redox CDC reaction with *N*-propargylanilines, and constructed structurally diverse 2-substituted tetrahydroquinolines.

Firstly, we chose *N*-benzyl-*N*-(2-propynyl)aniline) (**1a**) and nitromethane (**2**) as the model substrates to examine the hydroarylation-redox CDC reaction. The reaction was performed in the presence of $Zn(OAc)_2$ (20 mol%) at 100 °C for 24 h under nitrogen atmosphere in neat conditions. Disappointingly, the yield of final product **3a** was only 10% (Table S1, entry 14 in the Supporting Information). However, from the screening of Lewis acid catalysts, it was surprisingly found that the reaction was greatly accelerated by only 10 mol% of $ZnBr_2$. Then the other parameters (*e.g.* catalyst concentration, reaction temperature and solvents etc.) were further optimized. As shown in Table S1, the highest yield of target product **3a** (65% isolated yield, Table S1, entry 15) was achieved in the presence of $ZnBr_2$ (10 mol%) at 100 °C for 24 h under nitrogen atmosphere in neat condition.

Under this optimized reaction condition, the intramolecular hydroarylation-redox CDC reaction with various *N*-propargyl-anilines were evaluated. The results are summarized in Table 1. *N*-(2-propynyl)anilines ($R^2 = R^3 = H$) bearing various substituents at R^1, such as phenyl (**1b**), allyl (**1c**), methyl (**1d**) and methyl acetate (**1e**) which underwent the intramolecular hydroarylation-redox CDC reaction with nitromethane (**2**) smoothly gave the corresponding *N*-substituted-1,2,3,4-tetrahydroquinolines **3b**-**e** (Table 1, entries 2-5) in good yields. *N*-Ethylchloride-*N*-(2-propynyl)aniline **1f** was converted to **3f** in 17% yield (Table 1, entry 6). The low conversion might be ascribed to the competitive intramolecular Friedel-Crafts alkylation reaction of an alkyl halide with benzene ring in the presence of metallic Lewis acid. Then, the effect of substituents at the para position (R^2 group) of aniline moiety was examined. *N*-Benzyl-*N*-(2-propynyl)anilines (R^1 = Bn, R^3 = H) with various functional groups at R^2, such as electron-donating groups: methoxy (**1g**) and methyl (**1h**), electron-withdrawing groups: chloro (**1i**) and fluoro (**1j**), also compatible with the reaction, provided corresponding 2-substituted *N*-benzyl-1,2,3,4-tetrahydroquino-lines **3g**-**j** (Table 1, entries 7-10) in moderate to good yields. Apart from that, the intramolecular hydroarylation-redox CDC reaction of *N*-propargylanilines having a substituent at R^3 such as phenyl (**1k**), *n*-butyl (**1l**) and methyl (**1m**) with nitromethane were examined to interestingly give respective product **3k**-**m** in low to moderate yields with *trans* diastereoselectivity (Table 1, entries 11-13).

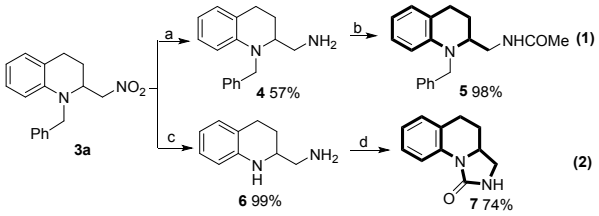
Thus, 2-nitromethyltetrahydroquinolines can be readily obtained from various *N*-(2-propynyl)anilines with nitromethane through the intramolecular hydroarylation-redox CDC reaction. Nitroalkanes are known to be broadly versatile building groups in organic synthesis. Not only because of their widely use in C-C bond formation, including nitro-aldol (Henry reaction), Michael addition, and Diels-Alder reaction, but also can the nitro group be converted into other different functional groups, such as the carbonyl groups by the Nef reaction and the amines by reduction.[8] As shown in Scheme 2, compound **3a** was reduced by *Raney Ni* to afford amine **4** as a crucial intermediate for the preparation of MT_2 receptor agonist **5**.[2c] Similarly, the hydrogenation of **3a** by Pd/C afforded amine **6** which was treated with 1,1-carbonyldiimidazole (CDI) to give the corresponding tricyclic product **7**, as a synthetic precursor of MAO inhibitor, in 74% yield.[2d]

Table 1. Intramolecular hydroarylation-redox CDC reaction of various *N*-propargylanilines with nitromethane.



Entry	*N*-propargylaniline **1**		Yield of **3** [%]
1	R^1 = Bn	(**1a**)	65 (**3a**)
2	Ph	(**1b**)	61 (**3b**)
3	allyl	(**1c**)	55 (**3c**)
4	Me	(**1d**)	69 (**3d**)
5	CH_2COOEt	(**1e**)	40 (**3e**)
6	$(CH_2)_2Cl$	(**1f**)	17 (**3f**)
7	R^2 = OMe	(**1g**)	47 (**3g**)
8	Me	(**1h**)	52 (**3h**)
9	F	(**1i**)	44 (**3i**)
10	Cl	(**1j**)	70 (**3j**)
11	R^3 = Ph	(**1k**)	15(*dr* = 9:1) (**3k**)
12	n-Bu	(**1l**)	22(*dr* = 12:1) (**3l**)
13	Me	(**1m**)	41(*dr* = 11:1) (**3m**)

[a]Rection conditios: **1** (0.25 mmol), **2** (0.5 ml) and $ZnBr_2$ (10 mol%) were heated in a closed vial tube under N_2 atmosphere at 100 °C for 24 h.



Reagents and conditions: (a) Raney *Ni* (30%),THF, H_2, 6 atm, 30 °C,12 h;(b) THF, acetic anhydride (1.5 eqv.), 30 °C, 2 h; (c) Pd/C (30%),CH_3OH, H_2, 30 °C, 6 h; (d) CDI (2.4 eqv.), THF/DMF, N_2

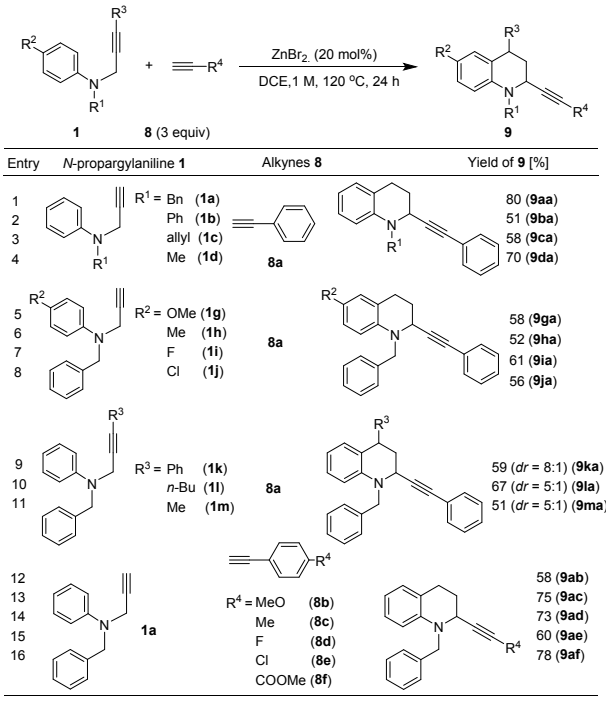
Scheme 2. Synthesis of important intermediates.

Next, the intramolecular hydroarylation-redox CDC reaction of *N*-benzyl-*N*-(2-propynyl)aniline (**1a**) with phenylacetylene was examined in the presence of catalytic amount of $ZnBr_2$ (20 mol%). It was particularly gratifying that this reaction proceeded smoothly in 1,2-dichloroethane (DCM) for 24 h to afford *N*-benzyl-2-ethylbenzene-1,2,3,4-tetrahydroquinoline (**9aa**) in 80% yield (Table 2, entry 1). The screening of metal Lewis acid catalysts showed that CuBr exhibited similar catalytic effects with $ZnBr_2$ (75% yield in Table S2, entry 1). Subsequent assessment of the concentration of catalyst, the equivalent ratio of phenylacetylene and the reaction temperature, indicated that the optimal yield of target product **9aa** was

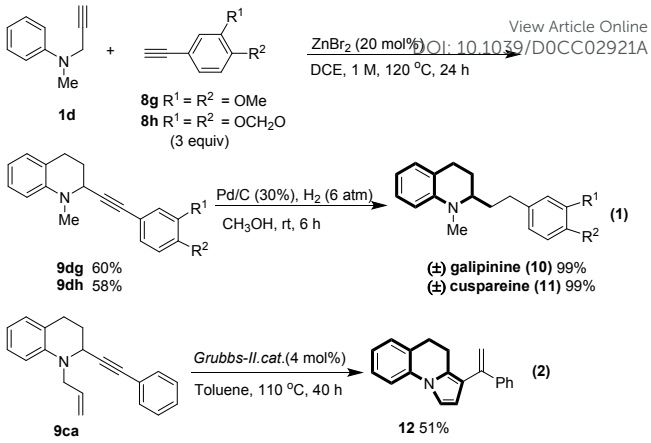
gained in the presence of $ZnBr_2$ (20 mol%) at 120 °C for 24 h under nitrogen atmosphere.

After establishing optimized reaction conditions, we explored the scopes of the *N*-(2-propynyl)anilines. *N*-(2-propynyl)anilines (R^2 = R^3 = H) having diverse substituents at R^1, such as phenyl (**1b**), allyl (**1c**) and methyl (**1d**) proceeded smoothly with phenylacetylene to afford the corresponding 2-alkynyltetrahydoquinolines **9ba-9da** in moderate to high yields (Table 2, entries 2-4). *N*-Benzyl-*N*-(2-propynyl)anilines having different functional groups at R^2, such as the electron-donating groups, methoxy (**1g**) and methyl (**1h**), and the electron-withdrawing groups, chloro (**1i**) and fluoro (**1j**) groups, gave the corresponding 2-alkynyltetrahydoquinolines **9ga–9ja** in good yields (Table 2, entries 5-8). The intramolecular hydroarylation-redox CDC reaction was able to be employed to *N*-benzyl-*N*-(2-propynyl)-anilines having substituents at R^3, such as phenyl (**1k**), *n*-butyl (**1l**) and methyl (**1m**) with **8a**, and the corresponding 2-alkynyltetrahydoquinolines **9ka-9ma** were obtained in good yields (Table 2, entries 9-11). The diastereomeric ratios of products **9la** and **9ma** were approximately 5:1 as calculated from ^{1}H NMR data. We explored the scopes of intramolecular hydroarylation-redox CDC reaction with respect to the various substituted aryl alkynes. It turned out that this reaction had an excellent tolerance with various aromatic groups from electron-rich to electron-deficient ones, and giving 2-alkynyltetrahydoquinolines **9ab-9af** in 58-78% yields (Table 2, entries 12-16).

Table 2. Intramolecular hydroarylation-redox CDC reaction of various *N*-propargylanilines with alkynes.

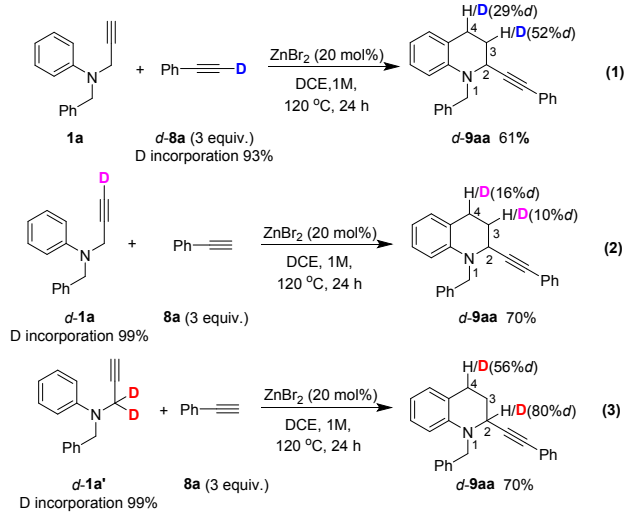


[a]Rection conditios: **1** (0.25 mmol), **8** (0.75 mmol, 3 equiv) and $ZnBr_2$ (20 mol%) were heated in dichloroethane in a closed vial tube under N_2 atmosphere at 120 °C for 24 h.



Scheme 3. Synthesis of natural alkaloids and important intermediate.

The current zinc(II)-catalyzed intramolecular hydroarylation-redox CDC reaction is useful for synthesis of tetrahydroquinoline framework-containing natural products. Galipinine and cuspareine, as natural alkaloids isolated from the trunk bark of *Galipea Officinalis* Hancock (Rutaceae),[2a,2b] were able to be synthesized from *N*-methyl-*N*-(2-propynyl)aniline (**1d**) as shown in Scheme 3. The reaction of **1d** with alkynes **8g** and **8h** proceeded smoothly to give the desired 2-alkynyltetrahydroquinolines **9dg** and **9dh** in 60% and 58% yields,
respectively. Hydrogenation of **9dg** and **9dh** proceeded quantitatively to afford (±)-galipinine (**10**) and (±)-cuspareine (**11**) respectively (Scheme 3, eq 1). It should be noted that the synthesis of these natural alkaloids only requires two steps from readily available aniline such as **1d**. Furthermore, 2-phenylethynyl-*N*-allyl-1,2,3,4-tetrahydroquinoline **9ca** obtained from **1c** and **8a** underwent intramolecular olefin metathesis in the presence of the Grubbs-II catalyst to afford the unique aza tricyclic compound **12** (Scheme 3, eq 2).



Scheme 4. Deuterium labeling study for the intramolecular hydroarylation-redox CDC reaction of *N*-propargylanilines and phenylacetylenes.

The deuterium labeling experiments were further carried

out. As shown in Scheme 4, deuterium was incorporated at C3 and C4 positions of *d*-**9aa** from both reactions of **1a** with *d*-**8a** (Scheme 4, eq 1) and *d*-**1a** with **8a** (Scheme 4, eq 2), suggesting that both terminal alkyne hydrogens (**1a** and **8a**) were readily exchanged into each other under the conditions. Because deuterium was not incorporated at C2 position of *d*-**9aa**, the allene intermediate suggested by Zhang *et al.* would not be involved in the reaction mechanism (Scheme S3).[9] Furthermore, the results that 80% and 56% of deuterium was incorporated at C2 and C4 positions of *d*-**9aa**, respectively, from the reaction of *d*-**1a′** with **8a** (Scheme 4, eq 3) are consistent with our proposed mechanism shown in Scheme 1, eq. 2.

In conclusion, we have developed a zinc-catalyzed intramolecular hydroarylation-redox CDC reaction of *N*-propargyl anilines with two types of carbon pronucleophiles (nitromethane as a sp^3 carbon pronucleophile and phenylacetylenes as sp carbon pronucleophiles) without using any external oxidants for preparation of the 2-substituted and 2,4-disubstituted tetrahydroquinolines at 100% atomic utilization rate. The reaction tolerates a wide range of substrates. Not only the conversion between a plurality of functional groups or a complex ring system construction, but also the synthesis of 2-substituted tetrahydroquinoline bioactive substance or natural products could be realized easily and efficiently. The reaction mechanism that we previously proposed was also verified by multiple deuterium labeling experiments. Because the direct functionalization to tetrahydroquinolines has not been fully established yet, we believe that the current intramolecular hydroarylation-redox CDC is one of the most efficient strategies for the construction of functionalized tetrahydroquinolines.

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Conflicts of interest

There are no conflicts to declare.

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Redox cross-dehydrogenative coupling of *N*-propargylanilines with diverse carbon pronucleophiles offers a general and efficient synthetic method to construct functionalized tetrahydroquinolines.

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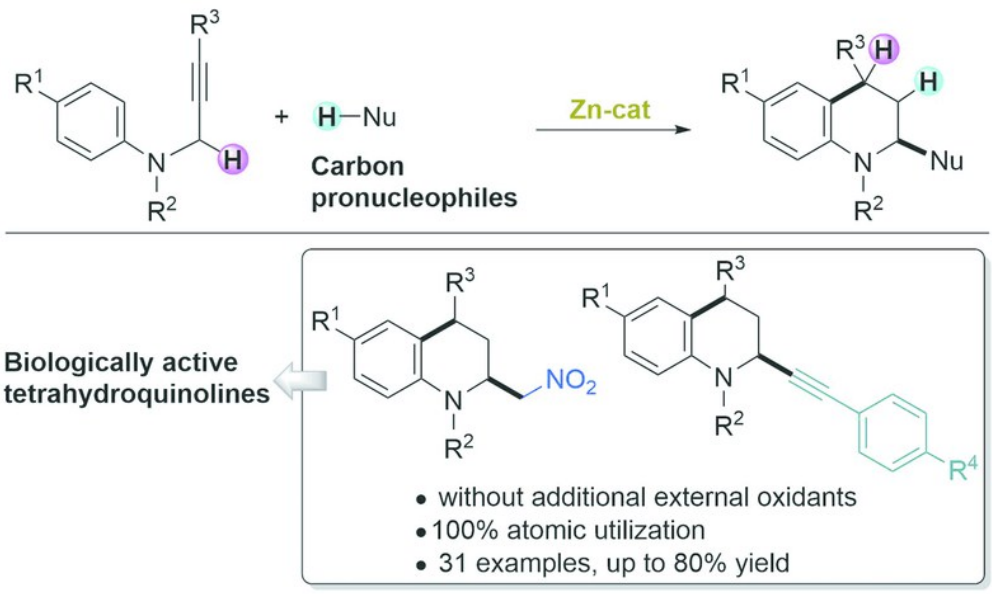

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