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Base-Catalyzed Cascade Reaction of *ortho*-(Propargylamino)aryl Ketones with N-, O-, or S-Based Nucleophiles for the Synthesis of 3-Functionalized Quinoline Scaffolds

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Abstract: A metal-free and base-catalyzed cascade reaction of *ortho*-(propargylamino)aryl ketones with primary alcohols, secondary amines, including various N-heterocycles, and thiols through 1,4-benzoxazepine intermediates was developed, providing a series of synthetically and medically valuable 3-functionalized quinoline derivatives. The reaction process was easily manipulable and environmentally benign, producing 1.0 equiv of water as the sole byproduct. Furthermore, bimolecular reactions for the synthesis of products containing two quinoline units were also succesful by utilizing this newly developed protocol.

Keywords: metal-free; *ortho*-(propargylamino)aryl ketones; 1,4-benzoxazepine; 3-functionalized quinolines; bimolecular reactions.

Quinoline scaffolds are probably the most ubiquitous heterocycles that widely exist in natural products,[1] medicinal agents,[2] as well as important intermediates for asymmetric synthesis.[3] Especially, 3-functionalized quinolines display a range of biological activities and are exploited as synthetic intermediates in the preparation of drugs and functional materials (Figure 1).[4] Classical methods for quinoline synthesis mainly include some name reactions, such as Skraup, Doebner−Von Miller, Friedländer, and Povarov reactions.[5,6] However, these approaches mostly suffer from the requirement of prefunctionalized substrates and expensive transition metals. Therefore, the development of metal-free and environmentally friendly methods for quinoline synthesis is of great significance and highly pursued in synthetic chemistry and pharmaceutical chemistry.

The development of cascade reactions for the synthesis of synthetically valuable frameworks from easily available substrates is strongly demanded in organic chemistry. Fully unsaturated monocyclic 1,4-oxazepine, which is not very stable but difficult to be obtained owing to antiaromatic character, is often emerged as a reactive species for the construction of molecular complexity.[7]

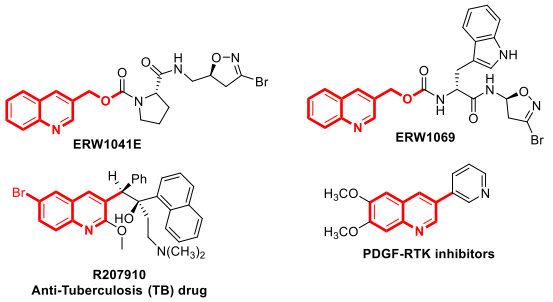

Figure 1. Representative examples of bioactive 3-substituted quinolines.

Recently, N-propargylic β-enaminones, readily accessible synthetic intermediates, have attracted much attention[8] and could be employed as precursors of 1,4-oxazepines.[9] For example, in 2015, Cui's group has described a base-promoted N-pyridylation of heteroarenes *via* 1,4-oxazepine intermediates from N-propargyl enaminones with N-based nucleophiles to deliver 2,3-disubstituted pyridines.[9a] They also found that N-based nucleophiles could be *in situ* generated from N-propargyl enaminones and trapped by 1,4-oxazepines.[9b] In 2017, they also reported alcohols and thiols were also adopted as nucleophiles, thereby providing similar products via consecutive 6π-electrocyclization and walk rearrangement processes (Scheme 1a).[9c] Moreover, Cui and Zhang's groups simultaneously reported terminal carbon of N-propargyl enaminones could also be used as nucleophiles to trap extern aryl aldehydes or N-sulfonyl imines, providing pyridine-fused heterocycles.[9c,d] Encouraged by above achievements, we wondered whether 1,4-benzoxazepine[10] could also be used as reactive intermediate to induce new

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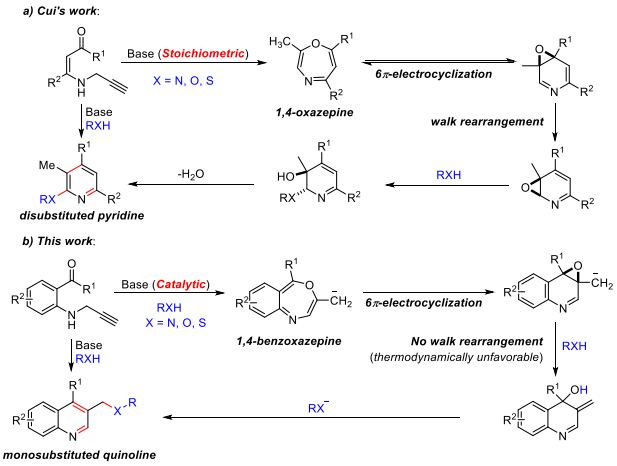
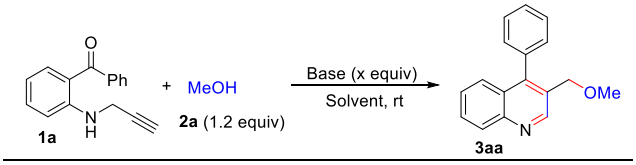
cascade reactions. Herein, we report a metal-free and base-catalyzed cascade reaction of *ortho*-(propargylamino)aryl ketones with N-, O-, or S-based nucleophiles to construct various monosubstituted quinoline scaffolds without walk rearrangement process (Scheme 1b).



Scheme 1. 1,4-oxazepine *vs* 1,4-benzoxazepine intermediates for synthesis of N-heterocycles.

Table 1. Optimization of the reaction conditions for the synthesis of **3aa**[a,b]

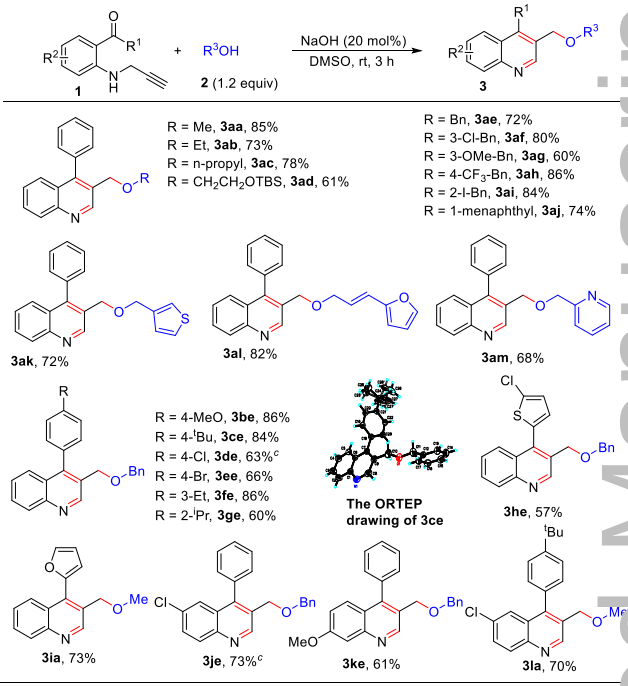


Entry	Base	x (equiv)	Solvent	Yield (%)
1	NaOH	2.0	DMSO	80
2	NaOH	1.0	DMSO	79
3	***NaOH***	***0.2***	***DMSO***	***85***
4	KOH	0.2	DMSO	83
5	Cs_2CO_3	0.2	DMSO	65[c]
6	K_2CO_3	0.2	DMSO	46[c]
7	Na_2CO_3	0.2	DMSO	41[c]
8	Et_3N	0.2	DMSO	N R[d]
9	NaOH	0.2	DMF	76
10	NaOH	0.2	MeCN	N R
11	NaOH	0.2	DCE	N R
12	-	-	DMSO	N R

[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), MeOH (0.24 mmol, 1.2 equiv), base (x equiv), solvent (2.0 mL), rt (25 °C) for 3 h. [b] Isolated yield. [c] for 6 h. [d] No Reaction.

With this working hypothesis in mind, we commenced our studies by employing phenyl(2-(prop-2-yn-1-ylamino)phenyl)methanone **1a** with methanol **2a** to simply optimize the reaction conditions. In the presence of the equivalent amount of NaOH (2.0 or 1.0 eq.), we were able to obtain 3-(methoxymethyl)quinoline **3aa** in 80% and 79% yields, respectively (Table 1, entries 1-2). Surprisingly, the reaction still performed well to give the corresponding product **3aa** in 85% yield when the catalytic amount of NaOH was applied (Table 1, entry 3). Then, the influence of base was investigated, and we found that only inorganic bases including KOH, Cs_2CO_3, K_2CO_3, and Na_2CO_3 could catalyze the reaction and NaOH gave the best reaction outcome (Table 1, entries 4-7). However, organic base Et_3N led to a deleterious effect on the reaction efficiency and the reaction became sluggish (Table 1, entry 8). Solvent effect was also examined, and we found that the solvent strongly influenced the reaction outcomes. It was identified that only strongly polar solvents such as dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF) could catalyze the reaction smoothly, whereas MeCN and 1,2-dichloroethane (DCE) had no reaction efficiency probably due to the lower solubility of inorganic base (Table 1, entries 9-11). Moreover, no desired product was obtained when no base was added (Table 1, entry 12).

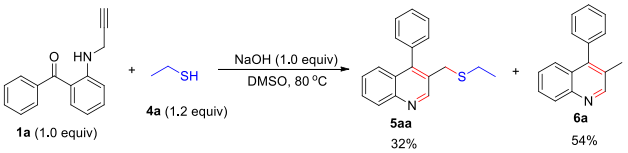
Table 2. Reaction Scope: synthesis of 3-functionalized quinolines from *ortho*-(propargylamino)aryl ketones and alcohols[a,b]



[a] Reaction conditions: **1** (0.20 mmol), R^3OH **2** (0.24 mmol, 1.2 equiv), NaOH (0.04 mmol, 0.20 equiv) DMSO, rt (25 °C), 3 h. [b] Isolated yield. [c] KOH was used as catalyst instead of NaOH.

With the optimized reaction conditions in hands, we began to survey the reaction scope of this reaction and the results are shown in Table 2. Various primary alkyl alcohols were tolerable, providing the corresponding products **3aa-3ad** in good yields ranging from 61% to 85%. As for benzyl alcohols, both electron-deficient and electron-rich ones were compatible, furnishing alkoxymethyl-substituted quinolines **3ae-3aj** in good yields ranging from 60% to 86%, and the former seemed to show better reaction activity. Moreover, heterocyclic benzyl alcohols were also suitable substrates, and the desired products **3ak-3am** were obtained without the erosion of the heterocyclic subunits under the standard reaction conditions. Then the scope of R^1 was examined as follows: when R^1 was aryl group, the reactions proceeded smoothly to give the desired products **3be-3ge** in good yields ranging from 60% to 86%. However, electron-rich substituents gave higher yield than electron-poor ones, which is opposite to the electronic effect of alcohols. Heterocyclic groups including thienyl and furyl were also examined, affording the corresponding products **3he** and **3ia** in 57% and 73% yields, respectively. Disappointingly, the reaction

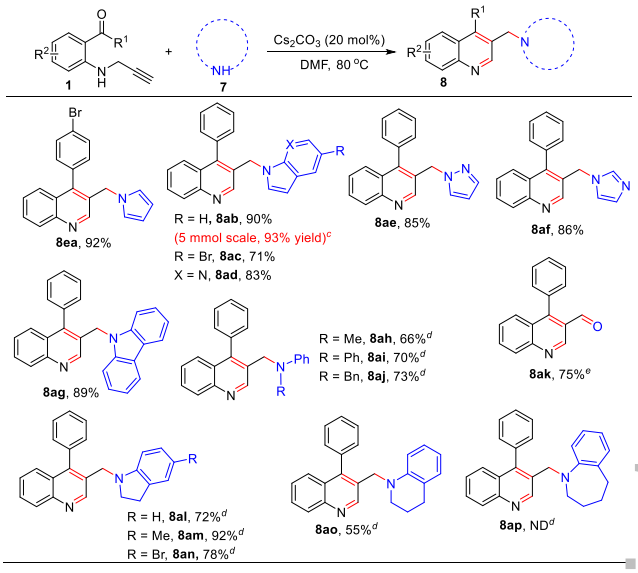
became sluggish when R^1 was substituted by alkyl groups or hydrogen atom. This cascade reaction also proceeded smoothly when the phenyl ring of aniline moiety was substituted by OMe or Cl group, affording products **3je** and **3ke** in 73% and 61% yields, respectively, indicating the electrocyclization process was not affected by substituents. Finally, both phenyl rings substituted substrate **1l** was also amenable, delivering product **3la** in 70% yield. It should be noted that secondary and tertiary alcohols presented poor reaction activity. The structure of **3ce** has been also confirmed by single crystal X-ray analysis, and its ORTEP drawing is shown in Table 2.[11] When the nucleophile was turned to thiol **4a**, a mixture of desired product of **5aa** and byproduct **6a** was formed in 32% and 54% yields, respectively in the presence of the equivalent amount of base (Scheme 2).



Scheme 2. Further investigation of thiol.

Furthermore, we explored the reaction scope of *N*-based nucleophiles in Table 3. We firstly screened the optimized reaction conditions as follows: **1** and **7** in a molar ratio of 1:1.2 in the presence of 20 mol% Cs_2CO_3 in DMF at 80 °C under argon atmosphere. Various N-heterocycles including pyrrole, indol, 1*H*-pyrrolo[2,3-*b*]pyridine, pyrazole, imidazole, and carbazole were tolerable for the synthesis of **8ea-8ag** in good yields ranging from 71% to 92%. Scalable synthesis was also achieved, providing 1.55 grams of **8ab** in 93% yield from 5.0 mmol scale of **1a** and **7b**. Notably, substituted anilines were also suitable substrates in this reaction if using KOH as the catalyst at room temperature, delivering products **8ah-8aj** in moderate yields ranging from 66% to 73%. However, aniline failed to provide the corresponding product, probably because of its lower nucleophilicity. Interestingly, when the sulfamide **7k** was employed, quinoline-3-carbaldehyde **8ak**, which is a valuable synthetic intermediate for further transformation,[12] was obtained in 75% yield (For the details, see Scheme S1 in the Supporting Information). Furthermore, hydrogenated heterocycles including indoline and tetrahydroquinoline were also compatible, thereby delivering products **8al-8an** in good yields ranging from 55% to 92%. However, 1-benzazepine **1o** failed to give the corresponding product **8ao**. The structures of **8ab** and **8ak** have been also confirmed by single crystal X-ray analysis and their ORTEP drawings are shown in Figure 2.[13]

Table 3. Reaction Scope: synthesis of 3-functionalized quinolines from amines[a,b]



[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv), **7** (0.24 mmol, 1.2 equiv), Cs_2CO_3 (0.04 mmol, 0.20 equiv), DMF, 80 °C, 3 h. [b] Isolated yield. [c] **1a** was used to react with **7b** in the presence of 40 mol% Cs_2CO_3 on 5 mmol scale, providing 1.55 grams of **8ab** in 93% yield. [d] KOH as base and T = rt. [e] Reaction conditions: **1** (0.20 mmol, 1.0 equiv), NHMeMs (0.40 mmol, 2.0 equiv), KOH (0.04 mmol, 0.20 equiv), DMF, 80 °C, 2 h.

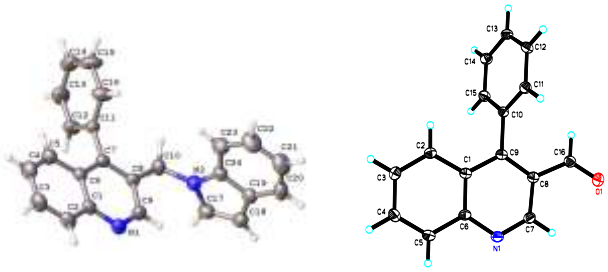
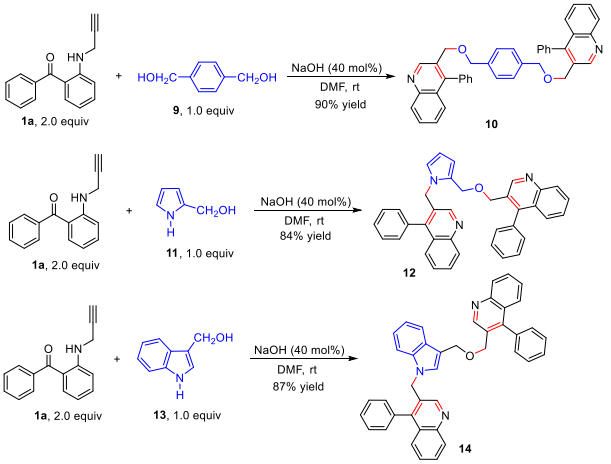


Figure 2. X-ray crystal structure of products **8ab** and **8ak**.

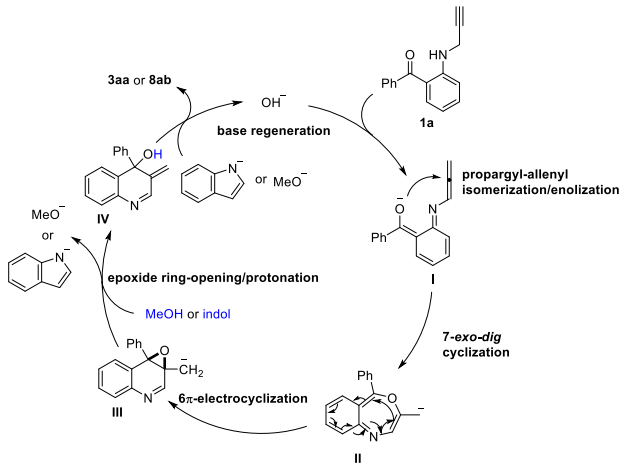
To further extend the reaction scope of this newly developed protocol, a series of bimolecular reactions were conducted. As shown in Scheme 3, 1,4-phenylenedimethanol **9**, (1*H*-pyrrol-2-yl)methanol **11** and (1H-indol-3-yl)methanol **13**, which contain two reaction sites, were used to react with **1a**; the corresponding bimolecular products **10**, **12** and **14** containing two quinoline units were obtained in high yields up to 90% (for the details, see Scheme S2 in the Supporting Information).



Scheme 3. Bimolecular reactions.

Based on the above results and previously reported

literature,[9] a proposed reaction mechanism is depicted in Scheme 4. In the presence of a base catalyst, propargyl-allenyl isomerization followed by enolization of **1a** provides an iminoenolate intermediate **I**, which may undergo a 7-*exo-dig* cyclization to afford a 1,4-benzoxazepine anion **II**. Then epoxide anion **III** was formed via 6π-electrocyclization process, which was not very stable to undergo expoxide ring-opening with the assistance of methanol or indol, delivering an allyl alcohol intermediate **IV**. Walk rearrangement process reported by Cui's group[9a,b,c] dose not take place from the intermediate **III**, because dearomatization of phenyl ring is thermodynamically unfavorable in this case. Meanwhile, methoxyl or indol anion is generated, which probably assists the construction of the 3-substituted quinoline scaffold along with the regeneration of a base catalyst.



Scheme 4. Proposed reaction mechanism.

In summary, we have developed a simple and convenient access to 3-functionalized quinoline scaffolds through base-catalyzed cascade reaction of *ortho*-(propargylamino)aryl ketones with primary alcohols, secondary amines including various N-heterocycles and thiols via 1,4-benzoxazepine intermediates. The reactions exhibit broad substrate scope, good yield and functional group tolerance. Moreover, bimolecular reactions providing compounds containing two quinoline units were also available under the standard reaction conditions. Further extension of the scope and the potential utilization are currently under investigation.

Experimental Section

General Procedure for Synthesis of 3 and 8

General Procedure for the Preparation of 3: **1** (0.2 mmol, 1.0 equiv) and NaOH (0.04 mmol, 0.02 equiv) were dissolved in dry DMSO (2.0 mL), then primary alcohols **2** (0.24 mmol, 1.2 equiv) was added dropwise and the resulting reaction mixture was stirred at room temperature (25 °C). The reaction was stopped after 3 h and the mixture was extracted with EtOAc for 3 times. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether / ethyl acetate = 10 / 1) to afford the product **3** in good to excellent yield.

General Procedure for 8: A solution of **1** (0.2 mmol, 1.0 equiv) and Cs_2CO_3 (0.04 mmol, 0.02 equiv) and amine **7** (0.24 mmol, 1.2 equiv) in DMF was stirred at 80 °C. The reaction was stopped after 3 h and the mixture was extracted with EtOAc for 3 times. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether / ethyl acetate = 4 / 1) to afford the product **8** in good to excellent yield.

Supporting Information Available

Detailed descriptions of experimental procedures and their spectroscopic data as well as the crystal structures are presented in the Supporting Information. CCDC 1588718 (**3ce**), CCDC 1587921 (**8ab**), 1811105 (**8ak**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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[13] CCDC-1587921 and CCDC-1811105 contain the supplementary crystallographic data of **8ab** and **8ak** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Full Paper

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