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# Basicity-Controlled [3 + 2] Cyclization of 3-Hydroxyquinolin-ones and $\beta$ -Chlorinated Nitrostyrenes

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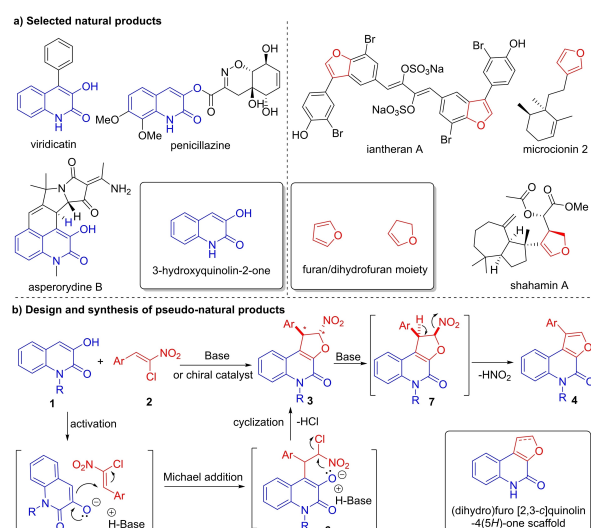
The construction of novel skeletons through the recombination of natural products ring systems is attractive. Herein, a basicity-controlled synthesis of (dihydro)furo[2,3-*c*]quinolin-4(5*H*)-one derivatives through (3 + 2) cyclization between 3-hydroxyquino-

lin-2-ones and  $\beta$ -chlorinated nitrostyrenes was developed. In addition, preliminary study gave the chiral dihydrofuro[2,3-*c*]quinolin-4(5*H*)-one derivatives with up to 83 % ee.

## Introduction

Quinolin-2-one is a privileged nitrogen-containing heterocycle, as the corresponding derivatives are widely found in natural products,<sup>[1,2]</sup> biological active molecules,<sup>[3–6]</sup> and functional materials.<sup>[7,8]</sup> In this context, the development of novel synthetic methodology for the facile construction of diverse quinolin-2-one derivatives is essential, which may have potential applications in leading compound discovery and material science. Among various quinolin-2-one scaffolds, the 3-hydroxyquinolin-2-one, which is widely embedded in natural products (Scheme 1a) and biological active molecules,<sup>[9–11]</sup> is a promising building block in synthetic chemistry (Scheme 1a). Surprisingly, the reactivity of this easily accessible synthon is far from well-developed.<sup>[12–18]</sup>

Recently, the concept of “Pseudo-natural products” revealed that the recombination of natural products ring systems will generate novel NP-like biologically relevant skeletons not covered by nature, which may bear the potential for unexpected bioactivity.<sup>[19–25]</sup> Inspired by this concept and our ongoing interest in the chemistry of  $\beta$ -chlorinated nitrostyrenes,<sup>[26–31]</sup> the recombination of quinolin-2-one and (dihydro)furan rings<sup>[32–35]</sup> from natural products afforded the (dihydro)furo[2,3-*c*]quinolin-4(5*H*)-one skeleton, which is not



Scheme 1. Design of (dihydro)furo[2,3-*c*]quinolin-4(5*H*)-one scaffold.

covered by nature (Scheme 1b). In detail, we hypothesized that the 3-hydroxyquinolin-2-one derivatives **1** could undergo Michael addition/cyclization process<sup>[36–38]</sup> through intermediates **5** and **6** to give dihydrofuro[2,3-*c*]quinolin-4(5*H*)-one derivatives **3** in the presence of simple base or chiral catalyst (Scheme 1b). Moreover, the further elimination of HNO<sub>2</sub> with suitable base could furnish the aromatized furo[2,3-*c*]quinolin-4(5*H*)-one derivatives **4**. Herein, we report the preliminary investigation of the reactivity of 3-hydroxyquinolin-2-one for the construction of (dihydro)furo[2,3-*c*]quinolin-4(5*H*)-one scaffold.

## Results and Discussion

Initially, 3-hydroxyquinolin-2-one **1a** and chlorinated nitrostyrene **2a** were selected to test our hypothesis (Table 1). As shown in entry 1, in the presence of the stoichiometric amount of *N,N*-diisopropylethylamine (DIPEA), the Michael addition/ cyclization reaction proceeded smoothly to afford the desired (3 + 2)

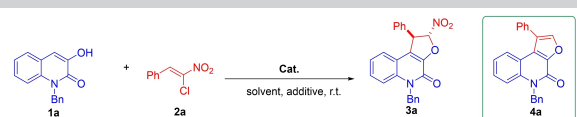
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**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>


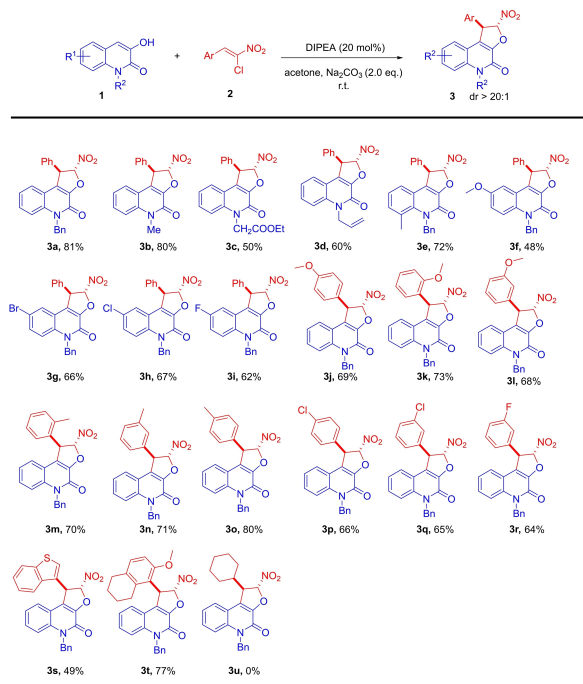
Entry	Cat	Solvent	Additive	T [h]	Yield [%] <sup>b</sup>
1	–	DCE	DIPEA	24	41
2	–	DCE	DABCO	24	27
3	–	DCE	Et <sub>3</sub> N	24	38
4	–	DCE	DMAP	24	11
5	–	DCE	DBU	24	71 <sup>c</sup>
6	–	DCE	Na <sub>2</sub> CO <sub>3</sub>	24	56
7	–	DCE	K <sub>2</sub> CO <sub>3</sub>	24	trace
8	–	DCE	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	24	35
9	–	DCE	Na <sub>2</sub> CO <sub>3</sub>	43	75
10	Et <sub>3</sub> N	DCE	Na <sub>2</sub> CO <sub>3</sub>	24	58
11	DIPEA	DCE	Na <sub>2</sub> CO <sub>3</sub>	24	77
12	DIPEA	EtOH	Na <sub>2</sub> CO <sub>3</sub>	43	75
13	DIPEA	THF	Na <sub>2</sub> CO <sub>3</sub>	24	77
14	DIPEA	EA	Na <sub>2</sub> CO <sub>3</sub>	24	78
15	DIPEA	DCM	Na <sub>2</sub> CO <sub>3</sub>	24	76
16	DIPEA	Acetone	Na <sub>2</sub> CO <sub>3</sub>	3	81
17	DIPEA	MeCN	Na <sub>2</sub> CO <sub>3</sub>	24	72
18	DIPEA	Acetone	–	24	26
19	–	Acetone	Na <sub>2</sub> CO <sub>3</sub>	24	57

[a] Reaction conditions: the mixture of **1a** (0.10 mmol), **2a** (0.12 mmol), catalyst (20 mol%), and additive (0.2 mmol) were stirred in solvent (1 mL) at r.t. [b] Isolated yield of the product **3a** (dr > 20:1 for all the cases). [c] **4a** was isolated as the product.

cyclization product dihydrofuro[2,3-*c*]quinolin-4(5*H*)-one derivative **3a** in 41% yield with excellent diastereoselectivity (> 20:1 dr). Other commonly used organic bases such as triethylamine, triethylene diamine (DABCO), and 4-dimethylaminopyridine did not improve the yield (entries 2–4). Interestingly, the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with stronger basicity promoted the further 1,2-elimination step of **3a** to give the aromatized product **4a** in 71% yield (entry 5).<sup>[28]</sup> To further improved the yield of **3a**, the test of inorganic base revealed that the sodium carbonate gave the best yield of **3a** in 56% within 24 h (entries 6–8). Extended the reaction time further improved the yield to 75% (entry 9). Considering the low solubility of sodium carbonate, the addition of an organic base as a co-catalyst could accelerate the reaction. To our delight, with 20 mol% of DIPEA, the reaction could finish within 24 h to give product **3a** in 77% yield (entry 11). Next, the effect of the solvent was investigated (entries 12–17). Finally, with acetone as the solvent, the reaction went to end in 3 h to obtain the product **3a** in 81% yield, mainly because of the better solubility of Na<sub>2</sub>CO<sub>3</sub> in acetone (entry 16). For comparison, the absence of catalyst

DIPEA or the absence of inorganic base Na<sub>2</sub>CO<sub>3</sub> both slowed down the reaction and decreased the yields (entries 18–19).

With the optimized conditions in hand, the scope of 3-hydroxyquinolin-ones **1** and chlorinated nitrostyrenes **2** were investigated (Scheme 2). Firstly, the substitutions on the nitrogen atom of 3-hydroxyquinolin-ones **1** were well tolerated, affording the products **3a–3d** in 50–81% yields. The protection of the nitrogen atom was essential as no product was observed when R<sup>2</sup> was H. In addition, both electron-withdrawing and



**Scheme 2.** Evaluation of the substrate scope. General reaction condition: the mixture of **1a** (0.20 mmol), **2a** (0.24 mmol), catalyst (20 mol%), and additive (0.4 mmol) were stirred in acetone (2 mL) at r.t.

electron-donating substituents on the phenyl ring of 3-hydroxyquinolin-ones **1** were compatible in this reaction. As the 8-Me and 6-OMe substituents gave the products **3e** and **3f** in 72% and 48% yields, respectively. The observation of the further elimination caused the relatively low yield of **3f**. Furthermore, the halogenated 3-hydroxyquinolin-ones **1** with electro-withdrawing properties gave the corresponding **3g–3i** in good yields. Next, the tolerance of the nitrostyrenes **2** were tested. The substituents with electron-donating properties on *ortho*-, *meta*-, and *para*-positions were installed. The corresponding products were obtained in 68–73% yields (**3j–3l**, **3m–3o**). For electron-withdrawing groups, the chlorinated or fluorinated products **3p–3r** were furnished in the same level of yield. Considering the importance of heterocycles in medicinal chemistry,<sup>[39–41]</sup> the benzothiophene was fixed into the nitrostyrene, and the desired product **3s** was furnished in 49% yield. Interestingly, the 2,6-disubstituted nitrostyrene with strong steric hindrance was also capable to afford the product **3t** in 77% yield. At last, the aliphatic nitroalkene failed to give the product **3u** under the optimal conditions, because of the relatively higher electron density of the C–C double bond of nitroalkane.

With the successful synthesis of various dihydrofuro[2,3-*c*]quinolin-4(5*H*)-one derivatives, as well as the preliminary observation of the formation of **4a** (entry 5, Table 1), the conditions for the construction of aromatized furo[2,3-*c*]quinolin-4(5*H*)-one derivatives were quickly screened (Table 2). The presence of 3 equiv. DBU in acetone promoted the

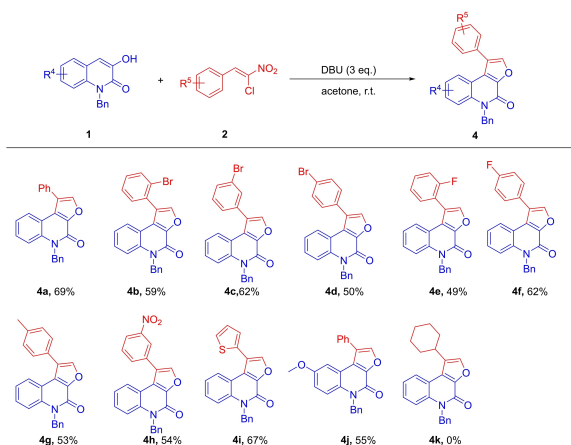
**Table 2.** Optimization of the reaction conditions.<sup>[a]</sup>

Entry	Solvent	Eq. [DBU]	T [h]	Yield [%] <sup>b</sup>
1	DCE	2.0	24	71
2	DCE	3.0	48	73
3	Acetone	3.0	7	69
4	EA	3.0	7	68

[a] Reaction conditions: the mixture of **1a** (0.10 mmol), **2a** (0.12 mmol), and DBU were stirred in solvent (1 mL). [b] Isolated yield of product **4a**.

reaction to the end within 7 h, affording the desired product **4a** in 69% yield (entry 3, Table 2). With these conditions, the scope of the DBU promoted Michael addition/cyclization/ elimination process was studied (Scheme 3). Generally, *s* substituents both on 3-hydroxyquinolin-ones **1** and chlorinated nitrostyrenes **2** were tested. The bromination at different position of the phenyl ring of nitrostyrenes gave the products **4b–4d** in 50–62% yield. Other substituents, such as 2-F, 4-F, 4-Me, and 3-NO<sub>2</sub> all furnished the corresponding products in moderate yields (**4e–4h**). In addition, the 2-thiophenyl nitrostyrene could afford the products **4i** in 67% yield. The 6-OMe substituted 3-hydroxyquinolin-one finally furnished the product **4j** in 55% yield. Similarly with the situation of **3u**, the cyclohexyl substituted nitroalkene was not tolerated.

Recently, the enantioselective construction of optical active molecules was one of the most important tasks in organic chemistry, as the significance of chirality in medicinal chemistry and other related areas.<sup>[42–44]</sup> In this context, the preliminary attempt to develop the enantioselective version of this (3+2) cyclization process was essential. Firstly, the well-defined cinchona alkaloid derived bifunctional catalysts **C1** and **C2** were used to catalyze the reaction in the presence of stoichiometric K<sub>2</sub>HPO<sub>4</sub>·3H<sub>2</sub>O in CHCl<sub>3</sub> (entries 1 and 2, Table 3). The results



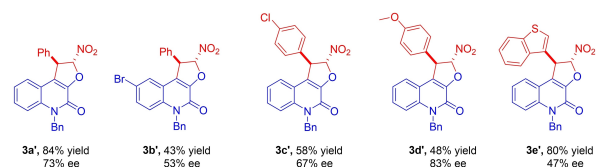
**Scheme 3.** Evaluation of substrate scope. General reaction condition: **2** (0.2 mmol) and **3** (0.24 mmol) in acetone (2 mL) for 7 h at room temperature.

revealed that the squaramide moiety in the catalyst was more efficient than thiourea moiety in controlling the enantioselectivity of the reaction. The replacement of the cinchona alkaloid skeleton by a chiral hexanediamine did not improve the enantioselectivity, albeit the yield was increased (entries 3 and 4). In addition, the installation of extra stereogenic elements into the squaramide moiety also failed to improve the enantioselectivity (entries 5 and 6). Fortunately, the product **3a'** was obtained in 69% yield with increased 57% ee with Rawal's catalyst **C7** (entry 7).<sup>[45]</sup> The catalyst **C8** afforded the product in 19% ee, which indicated the importance of the trifluoromethyl group (entry 8). Next, with **C7** as the catalyst, the solvent and additive were investigated (entries 9–13) (see more details in Supporting Information). The dichloroethane and anhydrous K<sub>2</sub>HPO<sub>4</sub> gave **3a'** in 83% yield with 63% ee (entry 13). Moreover, decreasing the temperature to –20 °C improved the ee of **3a'** to 73% (entry 14). Further lowering the temperature to –30 °C decreased the ee to 66% (entry 15).

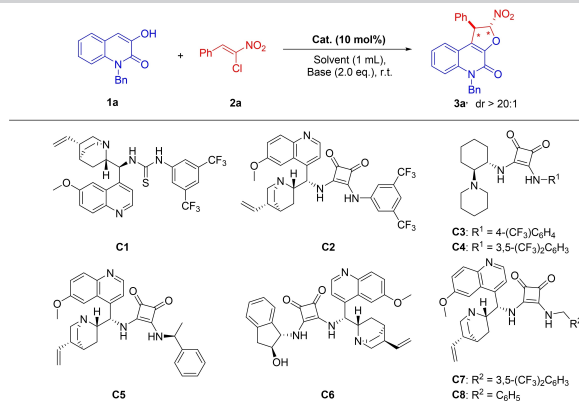
With these preliminary conditions in hand, several different substrates were tested to show the capability (Figure 1). The 6-bromo-substituted substrate **1b** afforded the product **3b'** in 43% yield with 53% ee. Moreover, both 4-Cl and 4-OMe substituted nitrostyrenes were also tolerated to furnish the products **3c'** and **3d'** in 58% yield with 67% ee, and in 48% yield with 83% ee, respectively. The benzothiophene moiety was also successfully installed, affording the product **3e'** in 80% yield with 47% ee.<sup>[46]</sup>

## Conclusions

In summary, a facile basicity-controlled synthesis of novel natural products inspired (dihydro)furo[2,3-*c*]quinolin-4(5*H*)-one derivatives was developed. These Michael addition initiated cascade reactions between 3-hydroxyquinolin-ones and chlorinated nitrostyrenes feature the advantages of mild conditions, wide substrate scope, and high yields. Preliminary studies revealed that the chiral dihydrofuro [2,3-*c*]quinolin-4(5*H*)-one derivatives could be obtained through the Rawal's catalyst catalyzed enantioselective version of this cascade reaction. Further investigation on the improvement of the enantioselectivity and the biological activity test of this intriguing structure are still in progress in our lab.



**Figure 1.** Preliminary substrate scope of the enantioselective version. **1a** (0.2 mmol), **2a** (0.24 mmol), **C7** (10 mol %) and K<sub>2</sub>HPO<sub>4</sub> (0.4 mmol) were stirred in DCE (2.0 mL) at –20 °C for 60 h; Isolated yield of **3** was reported (>20:1 dr).

**Table 3.** Optimization of the reaction conditions.<sup>[a]</sup>

Entry	Cat.	Solvent	Additive	Yield [%] <sup>b</sup>	ee [%]
1	C1	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	60	10
2	C2	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	34	29
3	C3	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	75	17
4	C4	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	68	10
5	C5	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	70	17
6	C6	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	79	13
7	C7	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	69	57
8	C8	CHCl <sub>3</sub>	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	68	19
9	C7	DCM	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	56	60
10	C7	DCE	K <sub>2</sub> HPO <sub>4</sub> ·3H <sub>2</sub> O	65	63
11	C7	DCE	Et <sub>3</sub> N	18	38
12	C7	DCE	Na <sub>2</sub> CO <sub>3</sub>	75	62
13	C7	DCE	K <sub>2</sub> HPO <sub>4</sub>	83	63
14 <sup>c</sup>	C7	DCE	K <sub>2</sub> HPO <sub>4</sub>	84	73
15 <sup>d</sup>	C7	DCE	K <sub>2</sub> HPO <sub>4</sub>	70	66

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (10 mol%) and base (2.0 mmol) were stirred in solvents (1.0 mL) at room temperature for 24 h. [b] Isolated yield. [c] At  $-20\text{ }^\circ\text{C}$  for 60 h. [d] At  $-30\text{ }^\circ\text{C}$  for 90 h.

## Experimental Section

**General Information:** Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (100–200 mesh). Enantiomeric excesses (*ee*) were determined by HPLC using corresponding commercial chiral columns as stated at  $30\text{ }^\circ\text{C}$  with UV detector at 254 nm. All  $^1\text{H}$  NMR and  $^{19}\text{F}$  NMR spectra were recorded on a Bruker Avancell400 MHz or 500 MHz and Bruker Avance III 376 MHz respectively,  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avancell 101 MHz or Bruker Avance III 126 MHz with chemical shifts reported as ppm (in CDCl<sub>3</sub>, TMS as internal standard). Data for  $^1\text{H}$  NMR are recorded as follows: chemical shift ( $\delta$ , ppm), multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br=broad singlet, dd=doublet doublet, coupling constants in Hz, integration). HRMS (ESI) was obtained with a HRMS/MS instrument (LTQ Orbitrap XL TM).

**General Procedure for the synthesis of 3:** 3-hydroxyquinolin-2(1*H*)-one **1** (0.2 mmol) was dissolved in 2 mL of acetone, then DIPEA (20 mol%), Na<sub>2</sub>CO<sub>3</sub> (0.4 mmol) and nitroolefin **2** (0.24 mmol) were added in sequence. The resulting mixture was stirred at room temperature and monitored by TLC. The desired product **3** was purified by column purification with silica gel (petroleum ether/ethyl acetate = 5:1 to 2:1).

**General Procedure for the synthesis of 3':** 3-hydroxyquinolin-2(1*H*)-one **1** (0.2 mmol), **C7** (10 mol%), and K<sub>2</sub>HPO<sub>4</sub> (0.4 mmol) were added in 2 mL of DCE, and stirred at  $-20\text{ }^\circ\text{C}$  for 10 min. Then, nitroolefin **2** (0.24 mmol) was added. The resulting mixture was

stirred at  $-20\text{ }^\circ\text{C}$  and monitored by TLC. The desired product **3'** was purified by column purification with silica gel (petroleum ether/ethyl acetate = 5:1 to 2:1).

**General Procedure for the synthesis of 4:** 3-hydroxyquinolin-2(1*H*)-one **1** (0.2 mmol) was dissolved in 2 mL of acetone, then DBU (3 equiv.) and nitroolefin **2** (0.24 mmol) were added. The resulting mixture was stirred at room temperature and monitored by TLC. The desired product **4** was purified by column purification with silica gel (petroleum ether/ethyl acetate = 5:1 to 2:1).

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

Research data are not shared.

**Keywords:** synthetic methods · enantioselectivity · heterocycles · Michael addition · (3 + 2) cyclization

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