

A Multicomponent *aza*-Prins Strategy for the Diastereoselective Synthesis of Piperidine-Fused Dihydroquinazolinones

Lovisa Dybeck, Morgane Baudoin, and Luke R. Odell*

Dihydroquinazolinones (DHQs) and piperidines are widely acknowledged as privileged structures and are of significant interest for the development of new drug candidates. Herein, a novel *aza*-Prins strategy is presented for the synthesis of piperidine-fused DHQs through a domino multicomponent reaction. Homoallylic ammonium halide salts are found to react with

bifunctional aldehydes under acidic conditions to give halide-substituted fused piperidines in a diastereoselective fashion. The reaction can be extended to the incorporation of alcohol nucleophiles *via* fine tuning of the reaction conditions. Finally, the utility of the substituted compounds is demonstrated by performing a variety of functionalization reactions on the scaffold.

1. Introduction

Quinazolinones are well-known *N*-heterocyclic motifs and display a wide array of biological activities.^[1,2] Its closely related saturated counterpart, dihydroquinazolinone (DHQ), is a privileged scaffold and can be found in several approved drugs,^[3] for example, olcegepant, a calcitonin gene-related peptide receptor (CGRPR) antagonist used as a migraine medication and pemigatinib, a novel fibroblast growth factor receptor (FGFR) inhibitor^[4] as well as numerous compounds in pre-clinical development^[3,5] (Figure 1).

Piperidine is another privileged structure, recognized as one of the most important nitrogen-containing heterocycles and a common building block in drug synthesis.^[6] Despite the ubiquity of DHQ and piperidine scaffolds in drug discovery, there are surprisingly few reports on compounds containing the potentially synergistic fused piperidine/DHQ skeleton.^[7–10] Furthermore, the majority of studies describe large polycyclic structures that lack a synthetic handle amenable to rapid analog preparation.^[11–13] Therefore, the development of a simple method to access fused piperidine–DHQ scaffolds suitable for library generation is of considerable interest. Halogens are appealing options in this context, as they are excellent synthetic handles in numerous general reaction manifolds. In addition, they are also prevalent functionalities within current drugs on the market due to their unique properties and binding abilities.^[6]

The *aza*-Prins reaction is an elegant and powerful method for the synthesis of a wide range of substituted

piperidines.^[14,15] The reaction proceeds *via* cyclization of an alkene onto an iminium ion and subsequent nucleophilic trapping.^[16] Halogens are commonly incorporated in this process to afford halogen-substituted piperidines, although this typically requires the addition of strong Lewis acids.^[9,17–19] In our previous work, we disclosed a domino DHQ formation/*aza*-Prins reaction to afford ester-substituted DHQ–piperidines through a multicomponent strategy based on homoallylic amines, benzaldehyde derivatives, and acetic acid.^[20] While this method afforded high yields and stereoselectivities, the utility of the ester substituent for further library development was limited. Inspired by a recent study by Hernandez et al.^[10] a single example from Frank and Aubé,^[21] and a similar approach by Katamura et al.^[22] we targeted the synthesis of halogen-substituted fused piperidine–DHQs. To eliminate the need for strong Lewis acids, we first aimed to use homoallyl amine hydrochloride to provide both the required π -nucleophile for cyclization and a chloride source. We reasoned that treatment of a bifunctional aldehyde with homoallyl amine hydrochloride under the influence of an acidic promotor would initiate a domino reaction to yield chlorinated piperidines with high diastereoselectivity. Herein, we present the optimization of this process and exploration of additional nucleophiles and their synthetic utility.

2. Results and Discussion

We began our investigation with a model reaction using aldehyde **1a**, homoallyl amine hydrochloride **2a**, and acetic acid in toluene or chloroform (Table 1, entries 1 and 2). In both cases, the desired chlorinated piperidine **4a** was formed; however, this was accompanied by acetate derivative **3a** resulting from competing nucleophilic trapping by acetic acid. Therefore, we continued our optimization by investigating several acidic promotors. Trifluoroacetic acid (entry 3) and dichloroacetic acid (entry 4) led to formation of the corresponding esters **3b** and **3c**, respectively, as the main reaction

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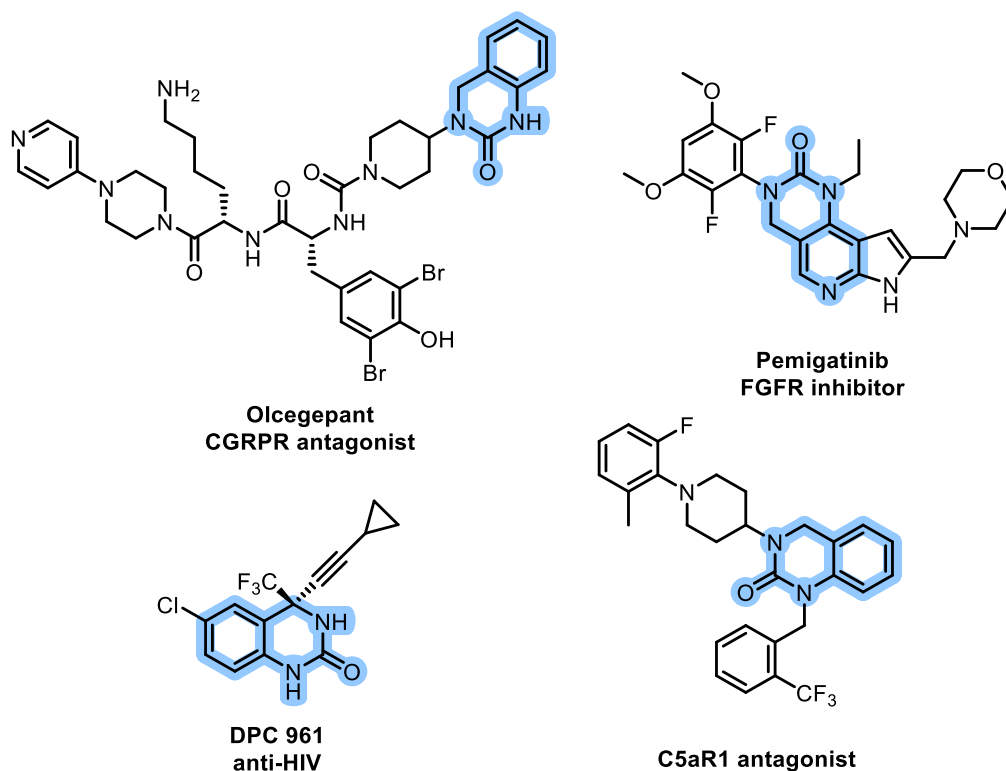


Figure 1. Examples of the DHQ scaffold in approved drugs and pre-clinical candidates.

Table 1. Optimization of reaction conditions.

1a + 2a $\xrightarrow[\text{MW } 140^\circ\text{C, 20 min}]{\text{Acid, Solvent}}$ 3a-d + 4a

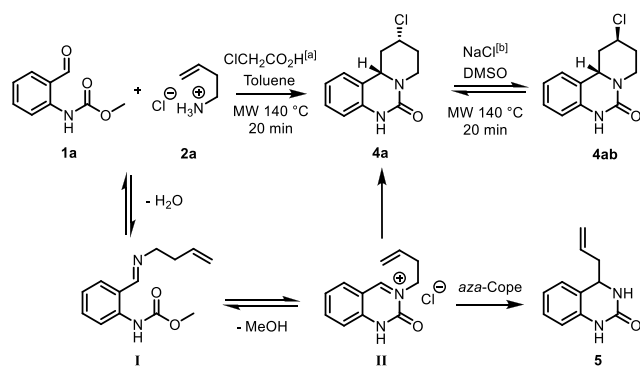
3a: R=O₂CCH₃
3b: R=O₂CCF₃
3c: R=O₂CCHCl₂
3d: R=O₂CCH₂Cl

Entry	Solvent	Acid ^{a)}	Equivalent acid	Yield [%] ^{b)}	3a-d:4a ^{c)}
1	Toluene	AcOH	8	65	16:84
2	CHCl ₃	AcOH	8	68	34:66
3	CHCl ₃	TFA	8	n.d.	93:7 ^{d)}
4	CHCl ₃	Cl ₂ CHCO ₂ H	8	n.d. ^{e)}	93:7 ^{d)}
5	CHCl ₃	ClCH ₂ CO ₂ H	8	76	>1:99
6	CHCl ₃	ClCH ₂ CO ₂ H	10	91	>1:99
7	CHCl ₃	ClCH ₂ CO ₂ H	2.5	99	>1:99
8	CHCl ₃	ClCH ₂ CO ₂ H	1.5	86	>1:99
9	Toluene	ClCH ₂ CO ₂ H	1.5	98 ^{f)}	>1:99

^{a)}Reaction conditions: 0.223 mmol of 1a, 2.0 equiv. of 2a, and 1 mL of solvent, subjected to microwave irradiation. ^{b)}Yields determined by ¹H NMR using dimethylacetamide as the internal standard. ^{c)}Estimated from crude ¹H NMR. ^{d)}Estimated from LC chromatogram. ^{e)}1a was not consumed. ^{f)}When performed on a 0.450 mmol scale, 1a was not completely consumed.

products. However, chloroacetic acid (entry 5) was found to exhibit the right balance between pK_a and nucleophilicity, yielding only 4a with no traces of the undesired esterified product 3d. The amount of acid could be reduced to 2.5 equivalents (entries 6 and 7)

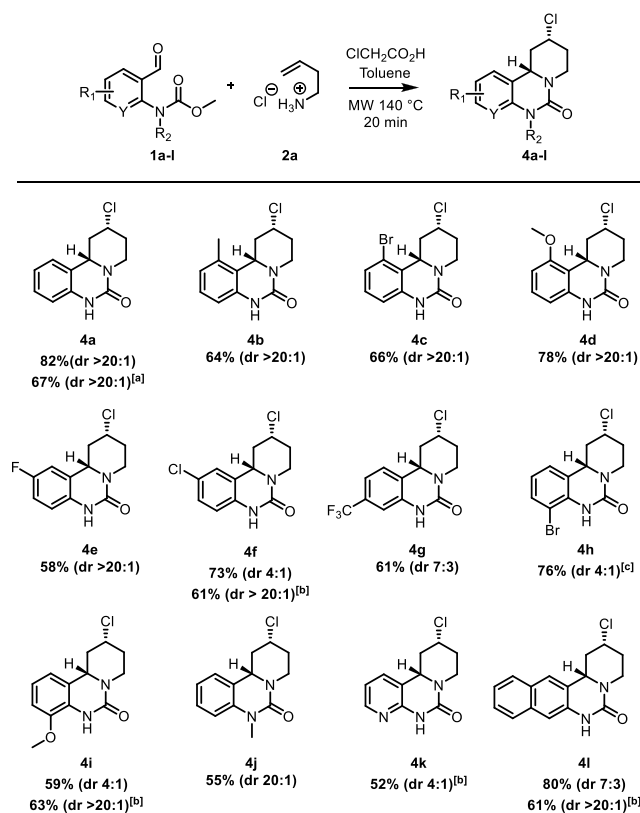
without any decrease in yield, and a further reduction to 1.5 equivalents resulted in 86% yield (entry 8). To avoid the use of chlorinated solvents, we tested toluene again, given that the yields did not differ largely between entries 1 and 2.



Scheme 1. Proposed reaction pathway. a) Reaction conditions: 0.223 mmol of **1a**, 1.2 equiv. of **2a**, and 2.5 equiv. of chloroacetic acid in 1 mL of toluene. b) Reaction conditions: 0.085 mmol of **4a**, 5 equiv. of NaCl, and 1 mL of DMSO subjected to microwave irradiation.

Entry 9 indeed shows that toluene and chloroform are interchangeable, but when the reaction was performed on a larger scale, full conversion of the starting material **1a** was not achieved. Hence, we continued with the optimized conditions of entry 9, but again increased the amount of chloroacetic acid to 2.5 equivalents. While optimizing the reaction conditions, we identified side product **5**, which forms *via* the competing *aza*-Cope pathway (**Scheme 1**). As the *aza*-Cope reaction mechanism is kinetically favored, we lowered the temperature to 120 °C. Although this prevented the formation of the side product, 10 equivalents of chloroacetic acid were needed to drive the reaction to completion along with a reaction time of 40 min. While noteworthy, we did not deem this to be advantageous compared to the optimized method and we therefore continued with the conditions from Table 1. During this process, we also noted the formation of a second diastereomer, **4ab**. The reaction pathway (**Scheme 1**) consists of multiple steps: imine formation (intermediate I), cyclization and *N*-acyliminium ion formation (intermediate II), intramolecular *aza*-Prins cyclization, and nucleophilic trapping. The last two steps are well studied^[23,24] and proceed through a concerted mechanism, leading to high levels of diastereoselectivity. In our case, the *N*-acyliminium ion is fixed in *Z*-configuration, which ultimately directs the nucleophilic attack and leads to a *cis* relationship between the hydrogens. However, diastereomer formation can also occur postcyclization due to chloride substitution on **4a**. To probe this, we added sodium chloride to a solution of **4a** and subjected it to microwave irradiation, resulting in the formation of an \approx 1:1 ratio between **4a** and **4ab** in the solution. To mitigate this risk, the amount of **2a** was therefore successfully reduced to 1.2 equivalents without any impact on the reaction yield.

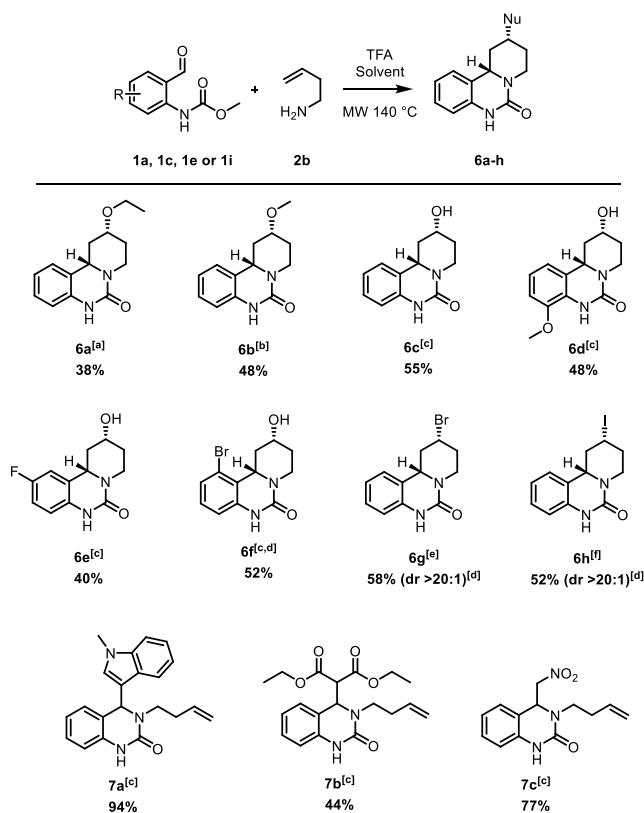
We moved on to investigate the scope of the reaction with a range of substrates. Overall, both electron-poor and electron-rich substrates were tolerated, as well as sterically hindered ones, allowing substitution at all positions (**Scheme 2**). The original substrate **4a** was isolated with a yield of 82% based on the conditions from Table 1. Substrates **1b**, **1d**, and **1i** with electron-donating substituents gave methylated product **4b** and methoxy substituted products **4d** and **4i** in 64, 78, and 59% yields, respectively. Electron-poor substrates **1g** and **1k** gave the corresponding products **4g** and **4k** in 61% and 52% yields,



Scheme 2. Substrate scope for chlorinated piperidines. Reaction conditions: 0.223 mmol of **1a–1l**, 1.2 equiv. of **2a**, and 1 mL of toluene subjected to microwave irradiation. Isolated yields. The diastereomeric ratio was determined from ¹H NMR. a) Performed on a 1 mmol scale. b) Conventional heating at 80 °C. c) Performed with 0.098 mmol of **1h**.

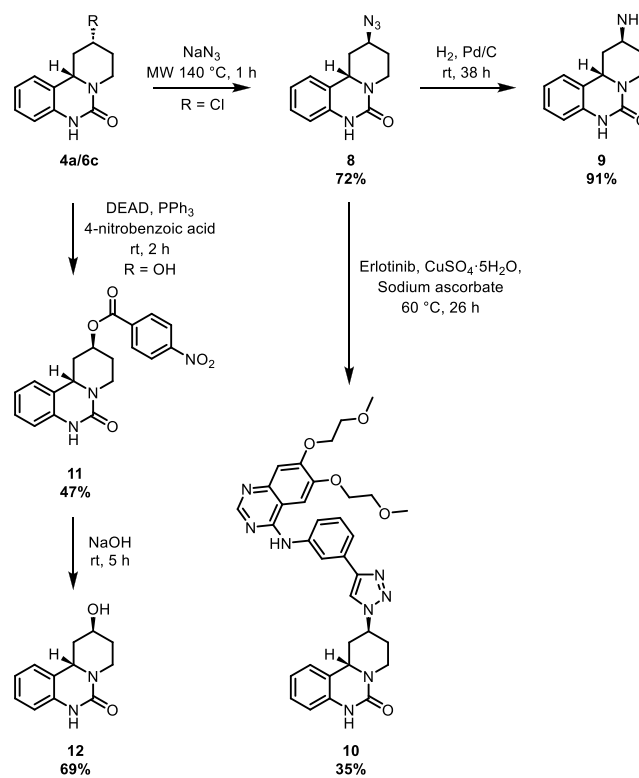
respectively. In the case of **4k**, lowering the temperature led to a cleaner reaction and facilitated purification. Several halogenated substrates were tolerated and gave rise to **4c**, **4e**, **4f** and **4h** with yields ranging from 58% to 76%. The reaction with the *N*-methylated substrate proceeded smoothly, yielding 55% of product **4j**. Tetracyclic naphthalene derivative **4l** was also synthesized in 80% yield. Scalability was probed with compound **4a** by performing the reaction on a 1 mmol scale, which resulted in a slightly lower yield (67%) of the purified product.

The crude diastereomeric ratio was measured by integrating GC-MS data (see Supporting Information). The stereoselectivity was in general high and products **4a–4e** were isolated as single diastereomers, but in cases where lower stereoselectivity was observed, this could be improved by reducing the reaction temperature. This was investigated for substrates **1f**, **1i** and **1l**, for which the reaction was conducted at 80 °C to reduce post-cyclization substitution, yielding 61–63% of the desired products as single diastereomers. For these substrates, the diastereoselectivity was clearly improved, supporting our hypothesis. After the successful application of various substrates to our optimized method, we moved on to investigate nucleophiles beyond chlorine. We reasoned that this would be possible by using the homoallylamine (**2b**) together with an appropriate acidic promotor. To this end, several nucleophiles were investigated. Pleasingly, ethanol, methanol, and H₂O were



Scheme 3. Substrate scope for additional nucleophiles. Reaction conditions: 0.500 mmol of **1a**, **1c**, **1e**, or **1i**, 1.2 equiv. of **2b**, 2.5 equiv. of TFA, and 2 mL of solvent subjected to microwave irradiation. Isolated yields. The diastereomeric ratio was determined from ^1H NMR. a) EtOH as the solvent. b) MeOH as the solvent. c) 5 equiv. of the nucleophile and toluene as the solvent. d) Conventional heating at 80°C . e) Performed with homoallyl amine hydrobromide **2c**. f) Performed with homoallyl amine hydroiodide **2d**.

all competent nucleophiles (Scheme 3) and the products **6a–6f** were isolated in 38–55% yield with excellent diastereoselectivity. Interestingly, in these reactions, TFA was the acid of choice and no competing ester forming side-reactions were observed. When synthesizing **6f**, we discovered that the *aza*-Cope side product was favored at a higher temperature for this particular substrate. This was, however, mitigated by performing the reaction at 80°C . Notably, there are only a few recent reports on the synthesis of 4-hydroxypiperidines *via* the *aza*-Prins pathway,^[25–27] and this is the first example of a water-based protocol. At this point, we also wanted to study the corresponding homoallyl amine hydrobromide and hydroiodide salts. Both **6g** and **6h** were synthesized at 80°C , yielding the target compounds in 58% and 52%, respectively. The diastereomeric ratio was excellent for both compounds, despite the expected greater propensity for post-cyclization halide exchange. Importantly, the synthesis of a 4-iodo-piperidine derivative through the *aza*-Prins pathway has only been reported twice using GaI_3/I_2 ^[28] and TMSI ^[29], highlighting the importance of this work. In contrast to the other nucleophiles, C–H acidic nucleophiles and electron-rich arenes afforded only the substituted DHQ products **7a–7c** due to the direct reaction with intermediate II (Scheme 1) prior to *aza*-Prins cyclization.



Scheme 4. Functionalization reactions on DHQ scaffolds **4a** and **6c**. Reaction conditions: 0.200 mmol of **4a** and 0.380 mmol of **6c**.

As we now had access to a unique scaffold with several reactive handles, we decided to explore a number of possible functionalizations (Scheme 4). An obvious choice was to use the secondary alkyl chloride for $\text{S}_{\text{N}}2$ reactions. We first investigated the addition of NaN_3 to a solution of **4a** in DMF. The reaction worked smoothly, yielding azide **8** in 72%, with excellent inversion of the stereocenter. Subsequent reduction with H_2 , Pd/C yielded amine **9** in 91% that is perfectly poised for diversification via amine functionalization. Furthermore, due to the rising interest in drug conjugates as well as bioconjugation chemistry, we wanted to explore a copper-catalyzed azide alkyne cycloaddition by reacting **8** with the marketed cancer drug erlotinib. This afforded novel conjugated product **10** in an isolated yield of 35%. We were also interested in the use of **6c** for a Mitsunobu reaction. With the addition of 4-nitrobenzoic acid, **11** was furnished in 47% yield using a standard Mitsunobu protocol. Upon ester hydrolysis, we could regenerate the secondary alcohol motif with an overall inversion of the C–OH bond (**12**, 69% yield), demonstrating high stereochemical control.

3. Conclusion

A new synthetic tool to provide easy access to novel DHQ–piperidine scaffolds has been successfully developed. We have demonstrated the trapping of halides and alcohols through an intramolecular *aza*-Prins cyclization, utilizing a multi-component strategy, and their subsequent functionalization.

The diastereoselectivity can be controlled by the choice of reaction temperature, with an overall good functional group tolerance. With this discovery, we hope to enable the ongoing search for new pharmaceuticals and accelerate the discovery of novel drug candidates.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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