Carbene-Catalyzed α-Carbon Amination of Chloroaldehydes for Enantioselective Access to Dihydroquinoxaline Derivatives

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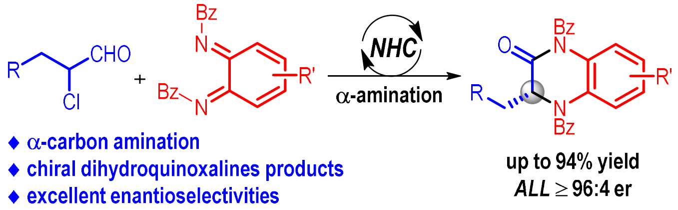
Supporting Information Placeholder



ABSTRACT: An NHC-catalyzed α-carbon amination of chloroaldehydes was developed. Cyclohexadiene-1,2-diimines are used as amination reagents and four-atom synthons. Our reaction affords optically enriched dihydroquinoxalines that are core structures in natural products and synthetic bioactive molecules.

Dihydroquinoxalines and their derivatives are frequently found as core structures in natural and non-natural molecules with proven biological activities.[1] They have been intensively studied as potential drugs for the treatments of multiple diseases such as HIV infections,[1a] atherosclerosis,[1b] and allergies[1c] (Figure 1a). Considerable attentions have therefore been paid on the synthesis of dihydroquinoxalines especially in enantiomerically enriched forms.[2-5] Main approaches include chiral amine catalyzed hetero-Diels–Alder reactions of *o*-benzoquinone diimides with various carbonyl compounds,[3] copper-catalyzed cross-couplings of α-amino acids with substituted anilines,[4] and asymmetric hydrogenation of substituted quinoxaline derivatives enabled by either transition-metals or chiral Brønsted acids.[5] Despite of these elegant progresses, metal-free and operationally simple methods are still needed for the asymmetric synthesis of these molecules.

N-heterocyclic carbene (NHC) organic catalysis[6] can in principle offer effective solutions in this direction. Studies have shown that asymmetric carbon-nitrogen bonds can be constructed via NHC catalysis by using diazenes as the electronic amination reagents (Figure 1b), as reported by Scheidt,[7] Ye,[8] Smith[9] and Zhong.[10] These methods provide pyrazolidinones,[7] 1,3,4-oxadiazin-6-ones,[8a,10] α-hydrazino esters,[9] and dihydropyridazinones[8b] as the products. We recently reported nucleophilic β-carbon-atom amination of enals, in which a protected hydrazine behaved as a nucleophilic nitrogen reaction center.[11] In these studies from us and others,[12] the amination reagents behave as two-atom synthons and end up with a "C-N-N-C" fragment in the final products (Figure 1b). Here we disclose that cyclohexadiene-1,2-diimine can behave as an effective amination reagent that functionalize the α-carobn of chloroaldehydes under NHC catalysis (Figure 1c). The cyclohexadiene-1,2-diimine reacts as a four-atom synthon and leads to a cyclic "C-N-C-C-N-C" fragment fused with a benzene that is exactly the core component in dihydroquinoxaline derivatives (Figure 1a). The dihydroquinoxaline products were all obtained with excellent yields and er values. It is worth noting that Lactka and co-workers have pioneered the asymmetric construction of the cyclic "C-N-C-C-N-C" fragment with ketene enolates and the cyclohexadiene-1,2-diimines through a co-operative catalytic strategy with chiral cinchona alkaloid catalysts and achiral Lewis acid co-catalysts.[3a] The key enolate intermediates in Lectka's and our studies are different. Our approach involves acylazolium enolate generated from aldehyde substrates under NHC catalysis, which possesses different reactivities from Lectka's enolate intermediates generated from acyl chlorides (via ketenes) and cinchona alkaloids.[3a] The Lewis acid co-catalysts used in Lectka's approach is not required in our approach.

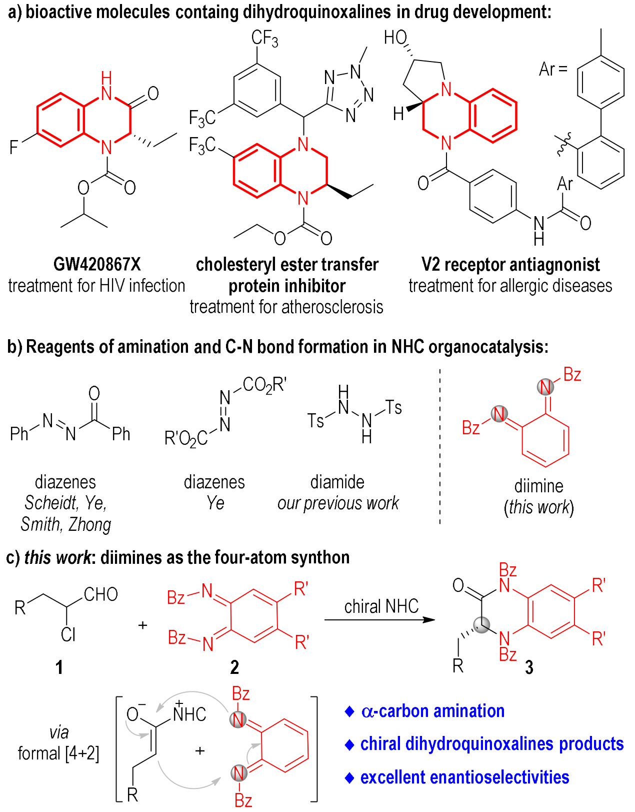
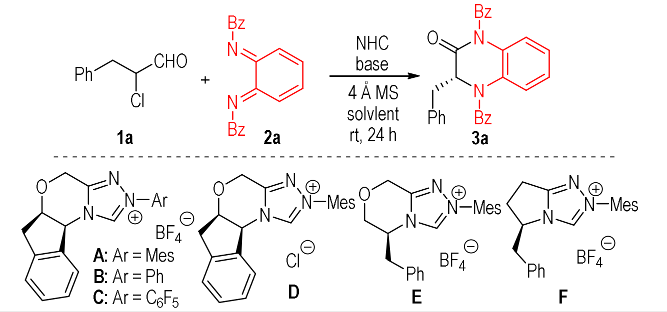


Figure 1. Bioactive Dihydroquinoxalines and Construction of Two C-N Bonds with NHC Organocatalysis.

Different NHC pre-catalysts were first examined for this aza-[2 + 4] cycloaddition reaction between α-chloroaldehyde **1a** and cyclohexadiene-1,2-diimine **2a** (Table 1, entries 1-6). The N-mesityl substituted triazolium NHC pre-catalyst **A**[13] derived from amino-indanol skeleton could give the product **3a** in better yield and er value than those bearing an N-Ph[14] or N-pentafluorobenzene[15] group (entry 1 vs entries 2-3). The product yield could be further increased by switching the NHC pre-catalyst **A** into the corresponding chloride salt **D**[16] (entry 4). Other NHC pre-catalysts we tested did not provide any better results in this transformation (e.g., entries 5-6). Organic bases generally gave the enantio-enriched dihydroquinoxaline products in lower yields, while the inorganic bases we tested could provide us with the products in better yields without erosion of the enantioselectivities (e.g., entry 7-9). To our delight, NaOAc could give the product **3a** in up to 88% isolated yield with an excellent 98:2 er value (entry 9). Additional screening of the reaction solvents could not further increase either of the product yield or er value (entries 10-12).

With the optimized reaction conditions in hand, we next examined the reaction scope using α-chloroaldehydes with different substituents or substitution types (Scheme 1). Both electron-donating and electron-withdrawing groups could be installed on the β-phenyl ring of the α-chloroaldehyde **1**, with the corresponding dihydroquinoxaline products **3** afforded in good to excellent yields with excellent enantioselectivities (**3b** to **3k**). The β-phenyl ring of the α-chloroaldehyde **1a** could also be switched to aliphatic groups, with both of the product yields and er values remained high (**3l** to **3m**). The benzyl group on the α-chloroaldehyde **1a** could be replaced with a phenyl group (**3n**), and α-chloroacetaldehyde could react fine as well (**3o**), albeit with low yields under the standard condition without additional optimizations. As a technical note, the formation of chiral products **3n** and **3o** was not reported in Lectka's study.[3]

Table 1. Optimization of Reaction Conditions.[a]



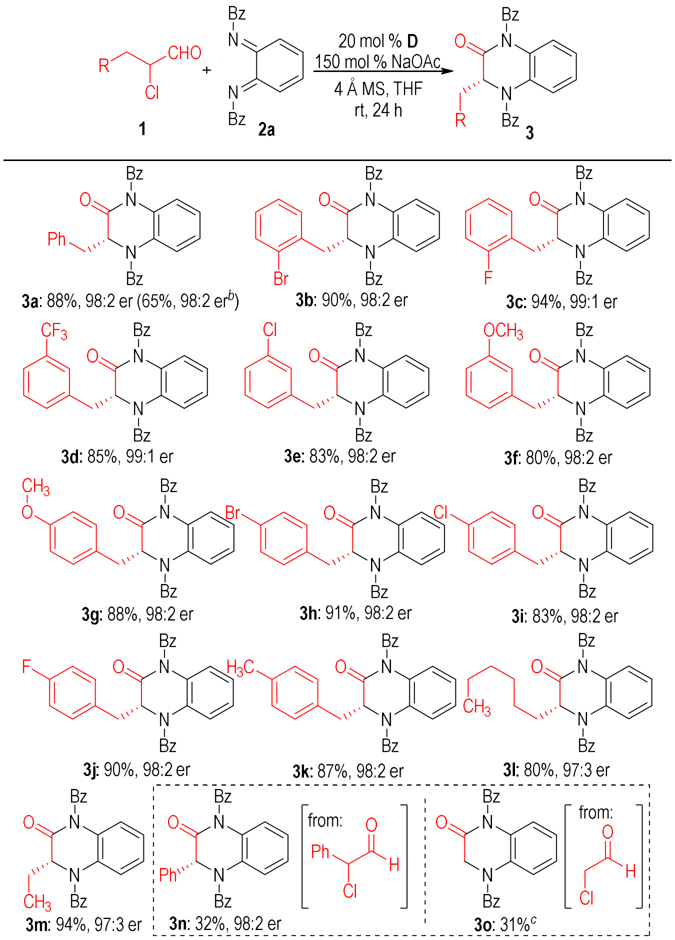
entry	NHC	base	solvent	yield (%)[b]	er[c]
1	**A**	Et_3N	THF	52	98:2
2	**B**	Et_3N	THF	31	96:4
3	**C**	Et_3N	THF	43	72:28
4	**D**	**Et_3N**	**THF**	**62**	**98:2**
5	**E**	Et_3N	THF	27	99:1
6	**F**	Et_3N	THF	29	97:3
7	**D**	DBU	THF	20	89:11
8	**D**	Cs_2CO_3	THF	67	98:2
9	**D**	**NaOAc**	**THF**	**88**	**98:2**
10	**D**	NaOAc	CH_3CN	29	92:8
11	**D**	NaOAc	Toluene	47	96:4
12	**D**	NaOAc	EA	65	97:3

[a] General conditions (unless otherwise specified): **1a** (0.15 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), base (0.15 mmol), 4 A MS (50 mg), solvent (1.0 mL), rt, 24 h. [b] Isolated yield of **3a**. [c] Er was determined via HPLC on chiral stationary phase.

Various substituted cyclohexadiene-1,2-diimine **2** also worked well in this asymmetric cycloaddition reaction (Scheme 2). Cyclohexadiene-1,2-diimines bearing electron-withdrawing groups gave the corresponding products in lower yields, which were probably due to the decomposition of the unstable starting materials under the current reaction conditions (e.g., **3p**). However, electron-rich cyclohexadiene-1,2-diimines **2** could give the desired products in good to excellent yields with excellent enantioselectivities, regardless of the substitution patterns existed on the α-chloroaldehyde **1** used in these transformations (**3q** to **3t**, **3u** / **3u′**). It is worth noting that electron-donating group existed on the cyclohexadiene-1,2-diimine **2** could decrease the electrophilicity of the imine group on its para-position due to the conjugate effect, which might result in the good regioselectivities observed in the formation of the products **3u** / **3u′**. The absolute configurations of the products **3** were assigned based on the X-ray analysis on the single crystal of the product **3b**.

In addition to α-chloroaldehydes, saturated aldehydes (such as 3-phenylpropionic aldehyde) could also be used as substrates to generate the azolium enolate intermediates under oxidative NHC catalysis (Scheme 3). For example, with **DQ** used as an oxidant, dihydroquinoxaline product **3a** could be formed from 3-phenylpropionic aldehyde (**4a**) with 47% yield and excellent enantioselectivity by using the same NHC catalyst (**D**). Phenyl acetaldehyde could also be used in this oxidative [2 + 4] cycloaddition reaction to form product **3n** with excellent enantioselectivity, albeit with a low yield under current condition.

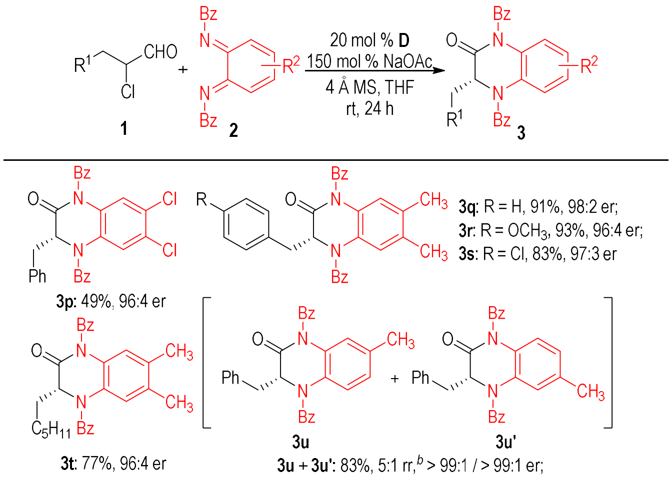
Scheme 1. Scope of α-Chloroaldehydes 1.[a]



[a]Reaction conditions as stated in Table 1, entry 9. Yields are isolated yields after purification via SiO_2 column chromatography. Er values were determined via HPLC on chiral stationary phase. [b]The reaction was carried out at 1.0 mmol scale. [c]α-Chloroacetaldehyde (40% aq.) was used as the reaction starting material.

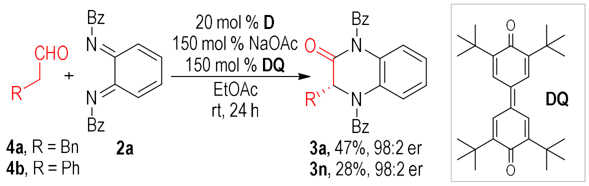
To demonstrate the operational simplicity of our NHC-catalyzed enolate reaction for the synthesis of chiral dihydroquinoxaline derivatives, we next combined the substrate preparation step and the NHC catalytic reaction step in a one-pot operation. The cyclohexadiene-1,2-diimine substrates (**2**) used in our reactions (Schemes 1 & 2) were prepared via oxidation of the corresponding diamide substrates (e.g., **5a** and **5b**, Scheme 4). This substrate preparation step can be combined with the NHC catalytic step in a one-pot operation to furnish the cycloaddition products (**3a** and **3q**, Scheme 4).

Scheme 2. Scope of Cyclohexadiene-1,2-diimine 2.[a]

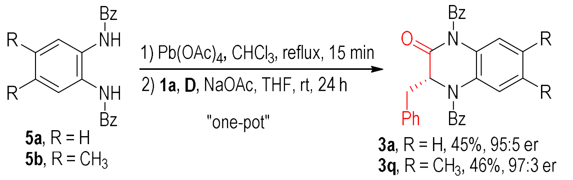


[a]Reaction conditions as stated in Table 1, entry 9. Yields are isolated yields after purification via SiO_2 column chromatography. Er values were determined via HPLC on chiral stationary phase. [b]Regio-selective ratios of the products **3s** / **3s′** were determined by ^1H NMR of the isolated mixture of both products and confirmed by X-ray analysis.

Scheme 3. Saturated Aldehyde as Enolate Precursor under Oxidative NHC Catalysis.

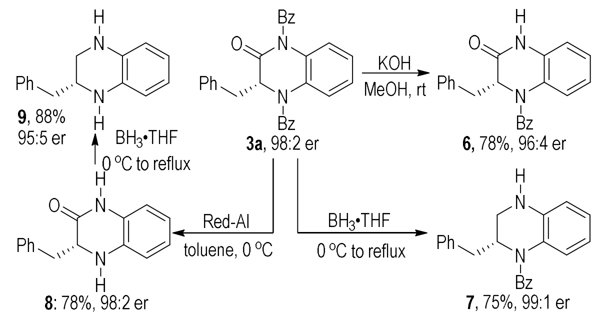


Scheme 4. One-Pot Operation by Combining Substrate Preparation with NHC-Catalyzed Cycloaddition



The Bz group on the lactam moiety of the chiral dihydroquinoxaline **3a** could be selectively removed under basic conditions to give product **6** in good yield with little erosion of the product er value.[17] The lactam moiety of **3a** could also be stereoselectively reduced by $BH_3{\cdot}THF$ to afford the secondary amine product **7** in good yield with a slight increase of the optical purity.[18] Both of the Bz protecting group could be removed with the assistance of Red-Al and the corresponding amide **8** could be formed in 78% yield with retention of the enantioselectivity.[19] Lactam **8** could be further reduced by $BH_3{\cdot}THF$ and give the diamine product **9** in good yield with excellent er value (Scheme 5).

Scheme 5. Synthetic Transformations of 3a.



9, 88%
95:5 er

3a, 98:2 er

6, 78%, 96:4 er

8: 78%, 98:2 er

7, 75%, 99:1 er

In summary, we have developed an NHC-catalyzed amination and cycloaddition reactions of α-chloroaldehydes. In our reaction, 1,2-diimine compounds were used as amination reagents and four-atom synthons, with two C-N bonds formed. The reactions afford substituted dihydroquinoxaline derivatives with excellent enantioselectivities. The chiral dihydroquinoxaline products afforded in this reaction could be efficiently transformed to various functional molecules via simple protocols. Further synthetic transformation and bioactivity evaluation of the dihydroquinoxalines are in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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