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NHC-Catalyzed Chemoselective Reactions of Enals and Aminobenzaldehydes for Access to Chiral Dihydroquinolines

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Abstract: *An N-heterocyclic carbene (NHC)-catalyzed reaction between α-bromoenals and 2-aminoaldehydes has been developed. Key steps include chemoselective reaction of the NHC catalyst with one of the aldehyde substrates (the bromoenal) to eventually generate an α,β-unsaturated acylazolium intermediate. Addition of the nitrogen atom of aminoaldehyde to the unsaturated azolium ester intermediate followed by intramolecular aldol reaction, β-lactone formation, and decarboxylation leads to chiral dihydroquinolines with high optical purity. The dihydroquinoline products, which are quickly prepared by using this method, can be readily transformed into a diverse set of functional molecules such as pyridines and chiral piperidines.*

Quinoline scaffolds are frequently found in natural and non-natural compounds with proven biological activities (Figure 1 a).[1] For example, (−)-*angustureine* and related molecules isolated from the plant *angostura* possess a variety of medicinal properties.[2] *Martinellic acid*, an alkaloid isolated from the roots of the tropical plant *Martinella iquitosensis*, have been used as novel nonpeptide antagonists of the bradykinin B1 and B2 receptors.[3] Various synthetic molecules containing quinoline cores have been extensively studied in the development of antiviral, antibacterial, antifungal, and anticancer reagents.[4] Therefore, the construction of quinoline compounds has received considerable attention.[5,6] The development of efficient and stereoselective methods for quick access to chiral quinoline derivatives is of significant value.

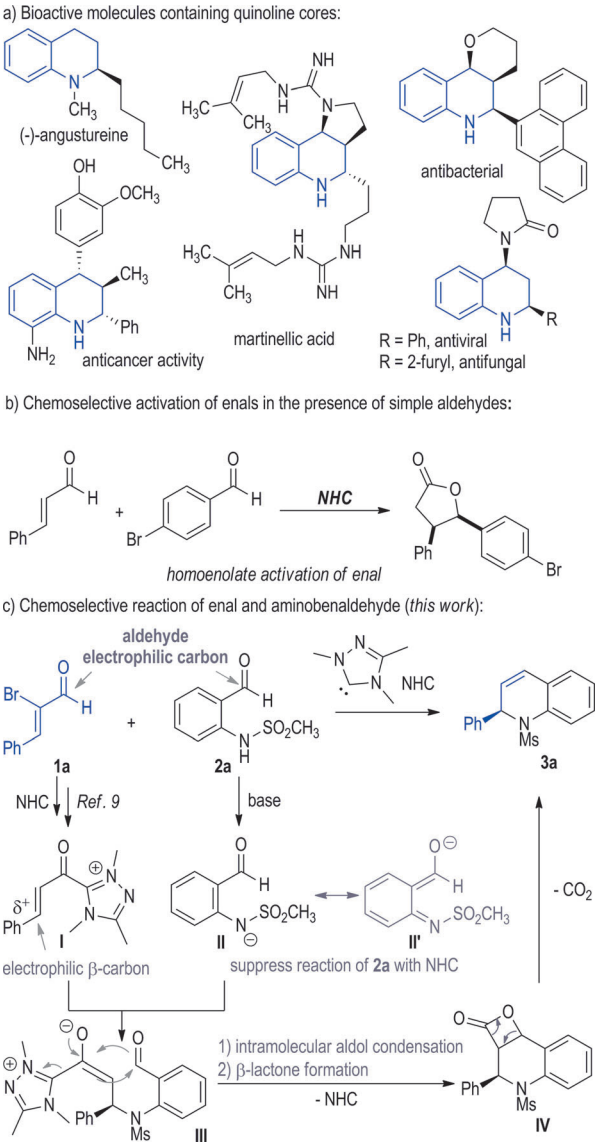

Figure 1. Quinolines and their synthesis through NHC-catalyzed reactions.

N-heterocyclic carbene (NHC) organic catalysis offers versatile reaction modes in asymmetric synthesis.[7] Simple and readily accessible carbonyl compounds such as aldehydes, enals, and carboxylic derivatives can be activated by NHCs to react with a broad set of electrophilic or nucleophilic substrates. However, when both reaction partners contain aldehyde moieties, chemoselectivity becomes a problem.[8] For example, it remains difficult to achieve cross-benzoin

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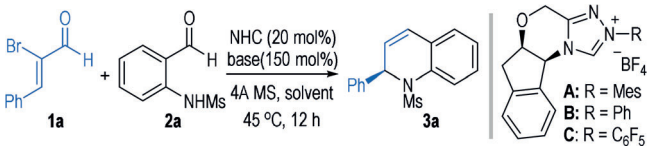
reactions using two different aldehydes.[8a–i] When enals are activated (via a homoenolate intermediate) to react with another aldehyde (such as benzaldehyde) to form γ-lactone adducts (Figure 1b), complete suppression of the homo-coupling reactions of two enals is also challenging.[8j–m] Herein, we report that through proper substrate design, two aldehydes (an α-bromo α,β-unsaturated aldehyde and an aminobenzaldehyde) can react chemoselectively to eventually form quinolines with excellent optical purity (Figure 1c). Homo-coupling reactions of either aldehyde substrate are not observed. Our desired reaction process starts with addition of the NHC catalyst to α-bromo enal (**1a**) to generate α,β-unsaturated acyl azolium intermediate **I**, which bears a reactive electrophilic β-carbon. Under the basic reaction conditions, deprotonation on the sulfonamide prepares the nitrogen atom as a nucleophilic reaction centre (**II**). This deprotonation process also decreases the electrophilicity of aldehyde moiety of substrate **2a**, and thus promotes chemoselective reaction of the NHC catalyst with **1a** over **2a**. Addition of the nitrogen atom of intermediate **II** to the β-carbon of intermediate **I** gives intermediate **III**, with a new carbon–nitrogen bond formed in a highly enantioselective manner. Further reaction of **III** (through intramolecular aldol reaction and β-lactone formation) gives intermediate **IV**, which undergoes decarboxylation to afford quinoline **3a** in 74% yield and 94 *ee*. The quinoline products from our reactions can be readily transformed into various molecules such as pyridines and chiral piperidine derivatives.

α-Bromoenal **1a** was selected as the α,β-unsaturated acylazolium precursor to react with 2-aminoaldehyde **2a** under the catalysis of various NHC catalysts (Table 1, entries 1 to 3). NHC catalyst **A**, which bears an N-Mes[10] group, was able to promote the reaction smoothly in a chemo- and enantioselective fashion and gave the dihydroquinoline product **3a** in moderate yield and excellent enantioselectivity (entry 1). NHC catalysts bearing N-Ph[11] or N-C_6F_5[12] groups were not efficient for this transformation (entries 2 to 3). Switching DBU for weak organic bases or various inorganic bases led to a decrease in the product yields (entries 4 to 5). The reactions could be carried out in solvents with high polarity, although the product yields were reduced (entry 6). No or trace amounts of the desired products were observed when carrying out the reactions in solvents with lower polarity (entries 7 to 8). Finally, when 1.8 equiv of enal **1a** was used, the enantiomerically enriched dihydroquinoline product **3a** was afforded in 74% yield without erosion of enantioselectivity (entry 9).

Having identified optimal reaction conditions for the formal aza- [2+4] cycloaddition/decarboxylation cascade process, we next examined the reaction scope using both substrates **1** and **2** with different substitution patterns (Table 2). Both electron-withdrawing and electron-donating substituents could be installed on each position of the benzene ring of the α-bromoenal substrate **1a**, with the corresponding products afforded in moderate to good yields with excellent enantioselectivity (Table 2, **3b** to **3n**). The β-phenyl group of the α-bromoenal **1a** could be exchanged for

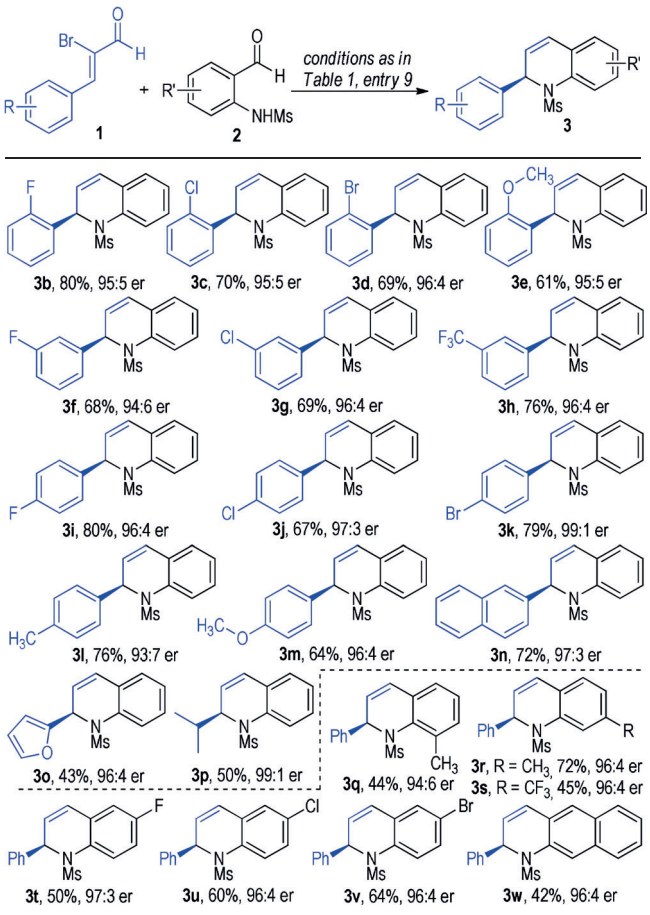
Table 1: Initial studies and reaction optimization.[a]



Entry	NHC	Base	Solvent	Yield [%][b]	er[c]
1	**A**	DBU	THF	58	95:5
2	**B**	DBU	THF	–	–
3	**C**	DBU	THF	–	–
4	**A**	Et_3N	THF	35	94:6
5	**A**	Cs_2CO_3	THF	38	97:3
6	**A**	DBU	DMF	32	92:8
7	**A**	DBU	CH_2Cl_2	10	95:5
8	**A**	DBU	EtOAc	–	–
9[d]	**A**	DBU	THF	74	97:3

[a] Unless otherwise specified, the reactions were conducted with **1a** (0.12 mmol), **2a** (0.1 mmol), NHCs (0.02 mmol), bases (0.12 mmol) and solvents (2.0 mL) at 45 °C for 12 h. [b] Yield of isolated **3a**. [c] The er values were determined via HPLC on chiral stationary phase. [d] Reaction conditions: **1a** (0.18 mmol), **2a** (0.1 mmol), **A** (0.02 mmol), DBU (0.15 mmol), THF (2.0 mL), 45 °C, 12 h. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

Table 2: Scope with respect to α-bromoenals **1** and 2-aminobenzaldehydes **2**.[a]



[a] Reaction conditions as stated in Table 1, entry 9. Yields are yields of isolated product after purification by column chromatography. er values were determined by HPLC with a chiral stationary phase.

heteroaromatic groups without erosion of enantioselectivity (e.g., **3o**). Aliphatic α-bromoenal could also be used as a suitable reaction substrate in this transformation, with the desired product **3p** afforded in moderate yield and excellent enantioselectivity.

Substituents were also well tolerated on the benzene ring of the 2-aminobenzaldehyde **2a**, with all the products afforded in moderate yields and excellent er values regardless of their electronic properties and substitution patterns (Table 2, **3q**–**3w**). It is worth noting that salicylaldehyde cannot be used instead of the 2-aminobenzaldehyde **2a** to react with enal substrates (**1**) through this process.

The chiral 3,4-dihydroquinoline products (**3**) can be transformed into various functional molecules through simple methods (Figure 2). For instance, the 3,4 double

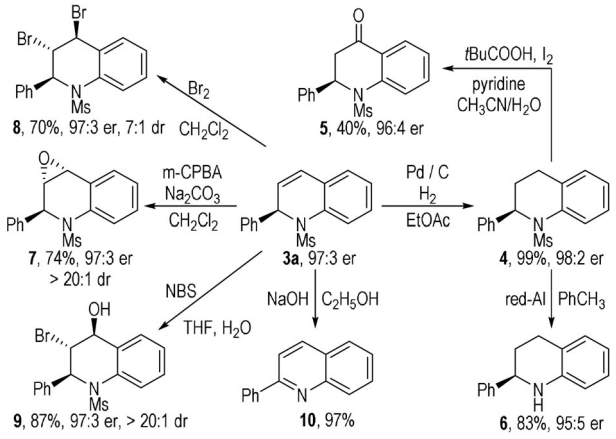


Figure 2. Synthetic transformations of **3a**.

bond in **3a** was reduced to give the tetrahydroquinoline **4** in quantitative yield with a slightly increased er value. The afforded tetrahydroquinoline **4** can be both enantioselectively oxidized to give dihydroquinolone **5**[13] and reduced to give the free amine **6**[14] through reported procedures. Moreover, **3a** was epoxidized to give epoxide **7** as a single diastereomer with an increased er value.[15] Treating the solution of **3a** in dichloromethane with Br_2 led to the dibrominated product **8** in good yield and dr value without obvious erosion on the product optical purity. Hydrobromination of **3a** with NBS under aqueous conditions gave the chiral amino alchohol **9** in good yield with retention of the product er value. The aromatized 2-phenylquinoline **10** was also easily obtained in almost quantitative yield from **3a** under basic conditions.

In summary, we have developed a chemo- and enantioselective strategy for accessing dihydroquinoline molecules. α-Bromoenals are selectively activated by NHC catalysts through a LUMO activation pathway in the presence of 2-aminobenzaldehydes. A broad scope of functional groups are well tolerated on both of the α-bromoenal and 2-aminobenzaldehyde substrates, with all the corresponding products afforded in good to excellent yields and enantioselectivity. The chiral products obtained through this method are amenable to further transformations. A variety of functional molecules can be obtained from the chiral dihydroquinoline products in up to quantitative yields without erosion of optical purity. Further investigation into chemoselective activations of different carbonyl compounds with NHC organic catalysts are currently in progress.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chemoselectivity · dihydroquinolines · N-heterocyclic carbenes · organocatalysis

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Communications

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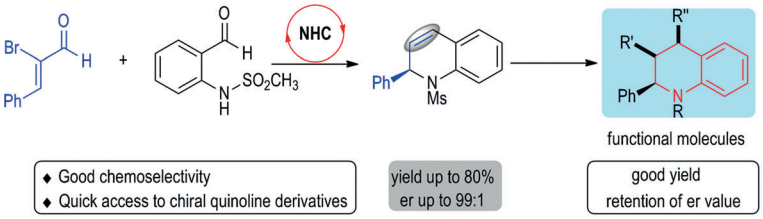

Quick access: An N-heterocyclic carbene (NHC)-catalyzed chemoselective reaction of bromoenals and aminobenzaldehydes was developed for quick access to dihydroquinolines with excellent enantioselectivity. The dihydroquinoline products can be readily transformed into a diverse set of functional molecules such as pyridines and chiral piperidines.