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Carbene-Catalyzed Chemo-selective Reactions of Enals and Aminobenzaldehydes for Access to Chiral Dihydroquinolines

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Abstract: A carbene-catalyzed reaction between α -bromo enals and 2-aminoaldehydes is developed. Key steps include chemo-selective reaction of the carbene catalyst with one of the aldehyde substrates (the bromoenal) to eventually generate 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 lead to chiral dihydroquinolines with high optical purities. The dihydroquinoline products, quickly prepared via our methods, can be readily transformed to 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 1a).^[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 attentions.^[5,6] The development of efficient and stereoselective methods for quick access to chiral quinoline derivatives is of significant values.

N-heterocyclic carbene (abbreviated as NHC or carbene) 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, chemo-selectivity becomes a problem.^[8] For example, it still remains difficult to achieve cross benzoin reactions using two different aldehydes.^[8a–i] When enals are activated (via homo enolate intermediate) to react with another aldehyde (such as benzaldehyde) to form β -lactone

Figure 1. Quinolines and Their Synthesis via Carbene-catalyzed Reactions.

adducts (Figure 1b), complete suppression of the homo coupling reactions of two enals is also challenging.^[8j–m] Here we disclose that through proper substrate designs, two aldehydes (an α -bromo α,β -unsaturated aldehyde and an aminobenzaldehyde) can undergo chemo-selective reaction to eventually form quinolines with excellent optical purities (Figure 1c). Homo coupling reaction of either aldehyde substrate is not observed. Our desired reaction process starts with addition of carbene catalyst to α -bromo enal (**1a**) to generate α,β -unsaturated acylazolium intermediate **I** that bears a reactive electrophilic β -

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carbon. Under the basic reaction condition, 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 chemo-selective reaction of carbene 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** (via intramolecular aldol reaction and β -lactone formation) gives intermediate **IV** that undergoes decarboxylation to afford quinolone **3a** in 74% yield and 94 er. The quinolone products from our reactions can be readily transformed to 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** bearing an N-Mes^[10] group could promote the reaction smoothly in both chemo- and enantio-selective fashion and gave the dihydroquinoline product **3a** in moderate yield and excellent enantioselectivity (entry 1). NHC catalysts bearing N-Ph^[11] or N-C₆F₅^[12] groups were not efficient for this transformation (entries 2 to 3). Switching DBU to weak organic bases or various inorganic bases led to drops on the product yields (e.g., entries 4 to 5). The reactions could be carried out in solvents with high polarities, although the product yields were decreased (e.g., entry 6). No or trace amount of the desired products could be observed when carrying out the reactions in solvents with lower polarities (e.g., entries 7 to 8). Finally, with 1.8 equiv. of enal **1a** used, the enantiomerically enriched dihydroquinoline product **3a** could be afforded in 74% yield without erosion on the reaction enantioselectivity (entry 9).

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 ₃ N	THF	35	94:6
5	A	Cs ₂ CO ₃	THF	38	97:3
6	A	DBU	DMF	32	92:8
7	A	DBU	CH ₂ Cl 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] Isolated yield of **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.

Having identified an optimal reaction condition 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 (Scheme 1). 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 enantioselectivities (Scheme 1, **3b** to **3n**). The β -phenyl group of the α -bromoenal **1a** could be switched into heteroaromatic groups without erosion of the product enantioselectivities (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 (Scheme 1, **3q** to **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.

Scheme 1. The Scope of α -Bromoentials **1** and 2-Aminobenzaldehydes **2**.^[a]

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

The chiral 3,4-dihydroquinoline products (**3**) obtained from this methodology could be transformed into various functional molecules through simple protocols (Figure 2). For instance, the 3,4-double bond in **3a** could be reduced to give the tetrahydroquinoline **4** in quantitative yield with a slightly increased er value. The afforded tetrahydroquinoline **4** could be both enantioselectively oxidized to give dihydroquinolinone **5**^[13] and reduced to give the free amine **6**^[14] through reported procedures. Moreover, **3a** could also be epoxidized to give epoxide **7** as a single diastereomer with an even increased er

value.^[15] Treating the solution of **3a** in dichloromethane with Br₂ 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 in an aqueous atmosphere gave the chiral amino alcohol **9** in good yield with retention of the product er value. The aromatized 2-phenylquinoline **10** could also be easily obtained in almost quantitative yield from **3a** under basic conditions.

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

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

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Layout 2:

COMMUNICATION

A carbene-catalyzed chemo-selective reactions of bromoenals and aminobenzaldehydes is developed for quick access to dihydroquinolines with excellent enantioselectivities.

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