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Carbene-Catalyzed Enantioselective Addition of Benzylic Carbon to Unsaturated Acyl Azolium for Rapid Synthesis of Pyrrolo[3,2-*c*]quinolines

Jilan Wang,^{†,§} Yongjia Li,^{†,§} Jun Sun,[†] Hongling Wang,[†] Zhichao Jin,^{*,†} and Yonggui Robin Chi^{*,†}

[†]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China

[‡]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371

^{*}Supporting Information

ABSTRACT: A carbene-catalyzed enantioselective addition of benzylic carbon to α,β -unsaturated acyl azolium intermediate generated via *N*-heterocyclic carbene catalysis is disclosed. This addition is followed by a stereoselective Mannich reaction and a chemo-selective lactam formation cascade to afford pyrrolo[3,2-*c*]quinolones as the products with excellent yields and optical purities. This work constitutes an effective asymmetric benzyl sp^3 -carbon functionalization and single-step rapid access to multicyclic heterocycles bearing four contiguous chiral centers.

KEYWORDS: carbene organocatalysis, asymmetric synthesis, α,β -unsaturated acylazolium, pyrrolo[3,2-*c*]quinoline, four contiguous chiral centers, benzylic carbon reaction

N-heterocyclic carbenes (abbreviated as NHCs or carbenes) have been proven to be a class of powerful organic catalysts.¹ Among the various reactive species generated under NHC catalysis, α,β -unsaturated acyl azolium intermediate bears several reactive carbons and may be used for quick assembly of sophisticated molecules via cascade processes.² Both carbon³ and nitrogen⁴ atoms have been used as nucleophiles to react with α,β -unsaturated acyl azoliums. The carbon nucleophiles are typically the α -carbons of carbonyl compounds or imines; and the reaction is believed to proceed through a Michael-type addition or a Claisen rearrangement pathway as the key step (see Figure 1a).⁵ Recently, we reported that the 4-nitrobenzylic carbon can participate in new bond-forming events under NHC catalysis.⁶ In these earlier studies from our laboratories, the reaction enantioselectivity could not be controlled by the NHC catalysts. We envisioned that the benzylic C-H bonds of 4-nitrobenzyls were acidic enough to participate in conjugate additions with α,β -unsaturated carbonyl compounds.

Here, we disclose that the benzylic carbon can undergo a direct 1,4-addition to α,β -unsaturated acyl azolium in a highly enantioselective manner (Figure 1b). This addition step is then followed by a stereoselective Mannich reaction and a lactam formation cascade to afford pyrrolo[3,2-*c*]quinolines. Four contiguous chiral centers were generated during the catalytic reaction, and the quinoline derivatives were obtained with excellent enantioselectivities. Notably, pyrrolo[3,2-*c*]quinolines are frequently found as key structural units in natural products and synthetic functional molecules with proven biological

activities (Figure 1c).⁷ It is particularly challenging to synthesize this class of multicyclic heterocycles in enantioselective manners.⁸ Our catalytic approach, initiated by the addition of a benzylic carbon to unsaturated acyl azolium intermediate as a key step, offers a single-step quick access to this class of heterocycles with high optical purities.

Chiral aminoindanol-derived NHC precursors⁹ were evaluated for the asymmetric cascade reaction between α -bromo enal 1a and the multifunctional substrate 2a (see Table 1, entries 1–3). NHC catalyst A bearing an *N*-mesityl group could give the desired pyrrolo[3,2-*c*]quinoline product 3a in moderate yield and excellent er value (Table 1, entry 1). The NHC catalysts with less electron-donating *N*-aryl substituents provided only trace amount of the target product (Table 1, entries 2 and 3). Weak organic bases such as DIEA was effective (e.g., Table 1, entry 4), while other organic bases with strong basicities (e.g., Table 1, entry 5) or inorganic bases (e.g., Table 1, entries 6 and 7) could not mediate the formation of 3a. The reaction could be performed in various organic solvents without erosion of the product optical purities, although the yields and dr values were slightly decreased (e.g., Table 1, entries 8 and 9). Finally, the product yield and dr value could be significantly improved with retention of the er value when a slightly excess amount of 2a was used in this catalytic reaction (Table 1, entry 10). Note that, when the

a) reactions with acyl azoliums in NHC organocatalysis (literature):

b) Enantioselective addition of benzylic carbon to acyl azolium for synthesis (**this work**):

c) natural products and functional molecules containing pyrrolo[3,2-c]quinolines:

Figure 1. Reactions with acyl azoliums and benzylic carbon functionalizations in *N*-heterocyclic carbene (NHC) organocatalysis.

NHC catalyst loading was reduced from 20 mol % (Table 1, entry 10) to 10 mol % (Table 1, entry 11), a drop in reaction yield was observed (Table 1, entry 11). As a technical note, using cinnamaldehyde as the α,β -unsaturated acyl azolium precursor under oxidative conditions resulted in only trace product formation (<5% yield) at this moment (for details, see the Supporting Information).

With the optimized reaction conditions at hand (Table 1, entry 10), we first evaluated the scope of various substituted α -bromo enals 1 (see Scheme 1). Electron-withdrawing groups were well-tolerated on the β -benzene rings of substrate 1 in this catalytic cascade process. Multicyclic products 3 with excellent optical purities could be afforded in good to excellent yields and diastereoselectivities (3b–3k). α -Bromo enals 1 bearing electron-donating substituents on the β -benzene rings also worked well in this reaction, although the product yields and diastereoselectivities were slightly decreased in some cases (3l–3n). Moreover, the β -benzene ring on the substrate 1a could also be switched to a 2-furanyl group, with the corresponding product afforded in excellent yield and enantioselectivity as a single diastereomer (3o). Interestingly, aliphatic α -bromo enals could also be used in this transformation, although the product yields were not satisfactory under the current catalytic conditions (e.g., 3p).

Table 1. Optimization of Reaction Conditions^a

entry	NHC	base	solvent	yield ^b (%)	enantiomeric ratio, er ^c	dr ^d
1	A	Et ₃ N	THF	56	99:1	6:1
2	B	Et ₃ N	THF	<5		
3	C	Et ₃ N	THF	<5		
4	A	DIEA	THF	33	99:1	5:1
5	A	DBU	THF	<5		
6	A	Cs ₂ CO ₃	THF	<5		
7	A	KOAc	THF	0		
8	A	Et ₃ N	EtOAc	53	98:2	3:1
9	A	Et ₃ N	toluene	31	99:1	4:1
10 ^e	A	Et ₃ N	THF	70	98:2	8:1
11 ^f	A	Et ₃ N	THF	58	98:2	6:1

^aGeneral conditions (unless otherwise specified): 1a (0.10 mmol), 2a (0.05 mmol), NHC (0.01 mmol), base (0.05 mmol), 4 A MS (100 mg), THF (1.0 mL), 50 °C, 24 h. ^bIsolated yield of 3a. ^cThe er value was determined via HPLC on chiral stationary phase. ^dThe diastereomeric ratio (dr) was determined by ¹H NMR on the crude reaction mixture. ^e1a (0.10 mmol), 2a (0.15 mmol), A (0.02 mmol), base (0.10 mmol), 4 A MS (150 mg), THF (2.0 mL), 50 °C, 12 h. ^fSame condition as entry 10, except A (0.01 mmol) was used.

Substituents could also be installed on the benzene rings of substrate 2 without erosion of the product yields or stereoselectivities (Scheme 2, 3q–3w). However, displacement of the NHBoc unit with other nucleophilic heteroatom-centered groups such as NHTs and OH groups resulted in drops in both of the product enantioselectivities and diastereoselectivities (e.g., 3x and 3y). This indicates that the steric hindrance and a more-defined hydrogen bonding by the NHBoc unit have played critical roles in the steric control in this transformation. Displacing the 4-NO₂C₆H₄ group in substrate 2a with a 2-NO₂C₆H₄ group led to drops of the reaction yield and diastereoselectivity, although the product 3z could be obtained in an exceptional optical purity. Other electron-deficient aromatic groups, such as the 4-cyanobenzene group (4a), 3,5-bis(trifluoromethyl)benzene group (4b), or the pentafluorobenzene group (4c), resulted in no formation of the desired products. Ketimine substrate 4d did not work in this catalytic transformation under the current reaction condition. Substrates bearing an NHBn (4e), NHMs (4f), or NHCCH₃ group (4g), instead of the NHBoc group, also failed in facilitating the target products through this cascade cyclization process.

The absolute configurations of the products 3 were assigned by the X-ray analysis on the single crystals of 3i. Based on this result, together with the previous works reported by us and other groups, a plausible reaction mechanism was postulated as summarized in Figure 2. The α -bromo enal substrate 1a is first attacked by the NHC catalyst and affords the Breslow intermediate I. Bromide elimination of intermediate I gives the α,β -unsaturated acyl azolium intermediate II, which could then react with the nucleophilic intermediate 2a' generated from the substrate 2a under basic conditions. Because of the intermolecular hydrogen-bond interactions and the steric

Scheme 1. Scope of α -Bromo Enals 1^a

^aReaction conditions as stated in Table 1, entry 10. Yields are isolated yields after purification via SiO₂ column chromatography. Enantiomeric ratio (er) values were determined via HPLC on chiral stationary phase. Diastereomeric ratio (dr) values were determined by ¹H NMR on the crude reaction mixture.

effects provided by the chiral NHC moiety, the Si face of the β -sp² carbon of the acyl azolium intermediate II is favored to be attacked by the Re face of the nucleophilic sp² carbon of the intermediate 2a'. The enantioselective and diastereoselective Michael addition between 2a' and the intermediate II gives the chiral adduct III, which then goes through an asymmetric intramolecular Mannich reaction to afford the chiral pyrrole intermediate IV. A lactam formation process within intermediate IV finally leads to the desired pyrrolo[3,2-c]quinoline product 3a and releases the NHC catalyst for further catalytic cycles.

The chiral pyrrolo[3,2-c]quinoline products obtained from this NHC-catalyzed cascade cyclization reaction bear multiple functional groups and can be subjected to further transformations (see Figure 3a). For example, the Boc protecting group on the amide motif in product 3a could be removed under acidic conditions to produce 5 in good yield without

Scheme 2. Scope of Substrate 2^a

^aReaction conditions as stated in Table 1, entry 10. Yields are isolated yields after purification via SiO₂ column chromatography. Enantiomeric ratio (er) values were determined via HPLC on chiral stationary phase. Diastereomeric ratio (dr) values were determined by ¹H NMR on the crude reaction mixture.

erosion of both enantioselectivities and diastereoselectivities. The C–N bond of the lactam motif in the quinoline ring could be broken under mild basic conditions to give the heavy substituted chiral pyrrole product 6 in good yields and stereoselectivities.¹⁰ The nitro group on the benzene ring in product 3z could be efficiently transformed to a primary amino group through simple protocols with retention of the optical purity. The afforded triamino product 7 could be converted to sophisticated chiral molecule 8 bearing up to five fused ring structures with excellent enantioselectivity.¹¹ Note that the quinazoline motif in product 8 are found in alkaloid natural products such as evodiamine and rutaecarpine, which are two major quinazolinocarbolin alkaloidal components in Evodia Fructus used as traditional Chinese medicines in the treatment of hypertension.¹²

The optically pure products 3 obtained from our developed methodology could also be used as efficient chiral organic catalysts for asymmetric transformations (see Figure 3b). For example, the aldol reaction between acetone and isatin could

Figure 2. Postulated reaction mechanism.

a) synthetic transformations of 3a and 3z:

b) catalytic application of 3a:

Figure 3. Synthetic transformations and catalytic applications of chiral products 3.

be promoted by the chiral compound 3a, with the corresponding product 9 afforded in excellent yield and encouraging enantioselectivity without much optimization.¹³

In summary, we have developed an NHC-catalyzed cascade reaction for the synthesis of pyrrolo[3,2-c]quinoline derivatives. Multicyclic product with four contiguous chiral centers could be afforded in excellent optical purities. An asymmetric benzyl C(sp³)-H functionalization was involved in this

process. The chiral products obtained through this method could be transformed to functional molecules such as free amide and primary amine compounds with retention of the enantiomeric purities. Further investigations into other C-H functionalizations via NHC organocatalysis, and the employment of NHC-catalyzed reactions for the synthesis of sophisticated molecules are underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (PDF)

CIF data for C₂₈H₂₆N₄O₇ (CIF)

checkCIF/PLATON report (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: zcjin@gzu.edu.cn (Z. Jin).

*E-mail: robinchi@ntu.edu.sg (Y. R. Chi).

ORCID

Zhichao Jin: 0000-0003-3003-6437

Yonggui Robin Chi: 0000-0003-0573-257X

Author Contributions

[§]These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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