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

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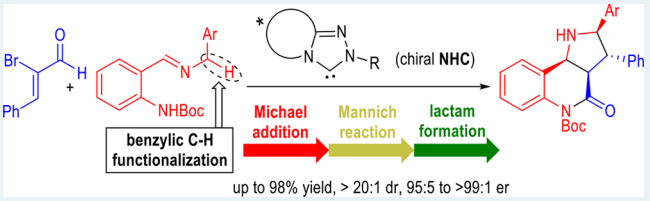
Supporting Information

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 carbon[3] and nitrogen[4] 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 precursors[9] 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

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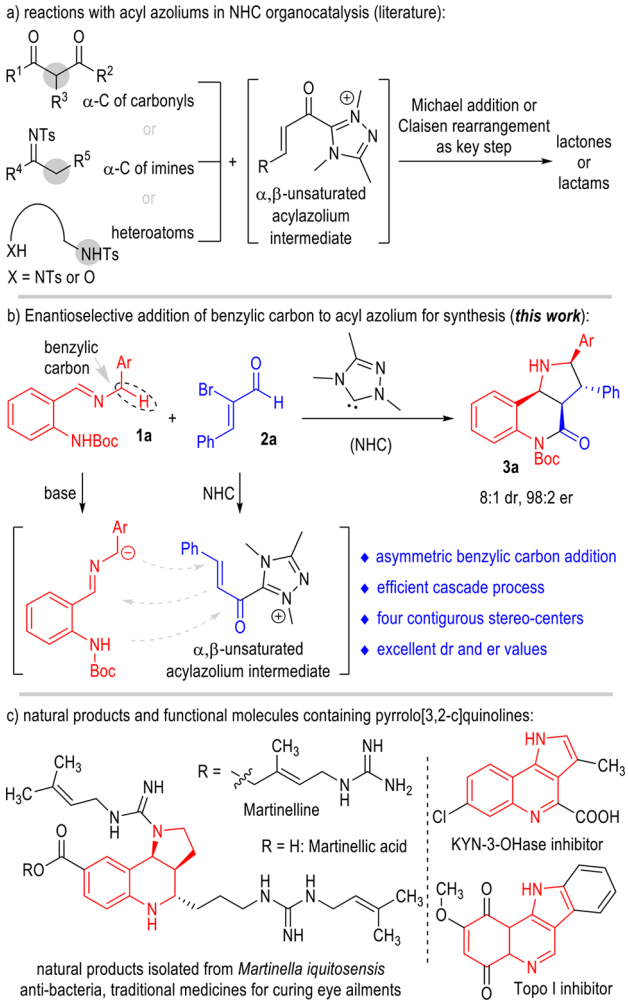
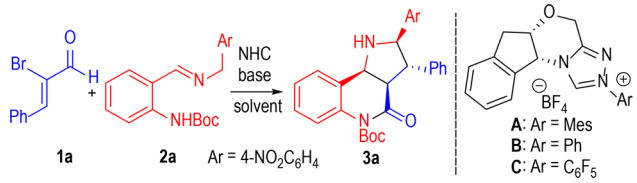


Figure 1. Reactions with acyl azoliums and benzylic carbon functionalizations in *N*-heterocyclic carbene (NHC) organocatalysis.

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_3N	THF	56	99:1	6:1
2	**B**	Et_3N	THF	<5		
3	**C**	Et_3N	THF	<5		
4	**A**	DIEA	THF	33	99:1	5:1
5	**A**	DBU	THF	<5		
6	**A**	Cs_2CO_3	THF	<5		
7	**A**	KOAc	THF	0		
8	**A**	Et_3N	EtOAc	53	98:2	3:1
9	**A**	Et_3N	toluene	31	99:1	4:1
10[e]	**A**	Et_3N	THF	70	98:2	8:1
11[f]	**A**	Et_3N	THF	58	98:2	6:1

[a]General 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. [b]Isolated yield of **3a**. [c]The er value was determined via HPLC on chiral stationary phase. [d]The diastereomeric ratio (dr) was determined by ^{1}H NMR on the crude reaction mixture. [e]**1a** (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. [f]Same 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 gorups 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-$NO_2C_6H_4$ group in substrate **2a** with a 2-$NO_2C_6H_4$ 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 $NHCOCH_3$ 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

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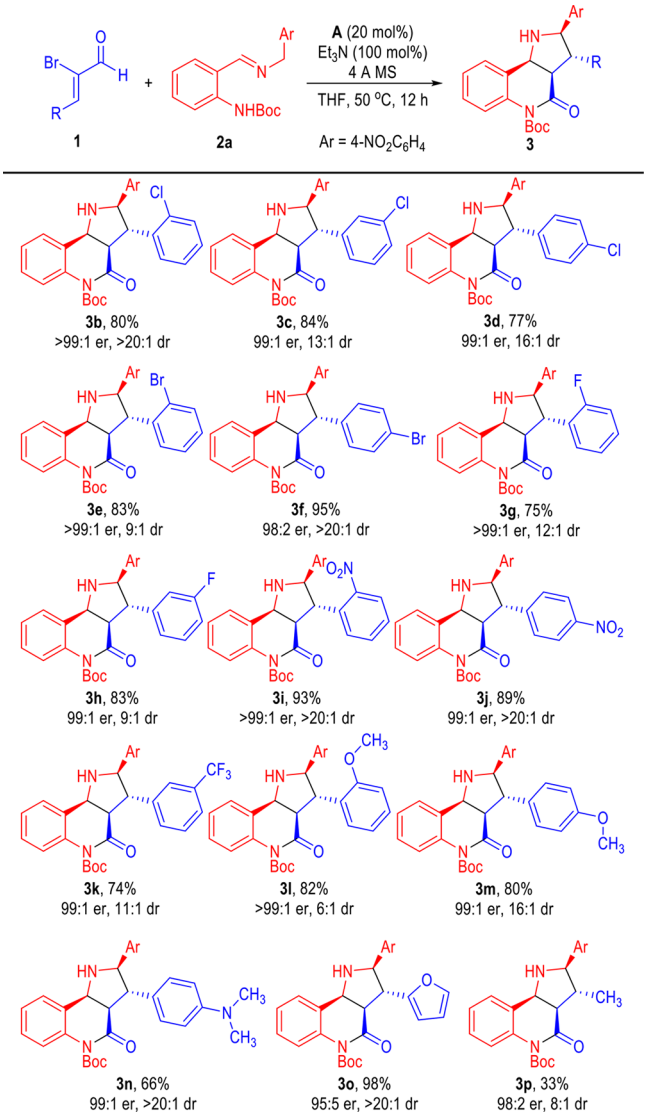
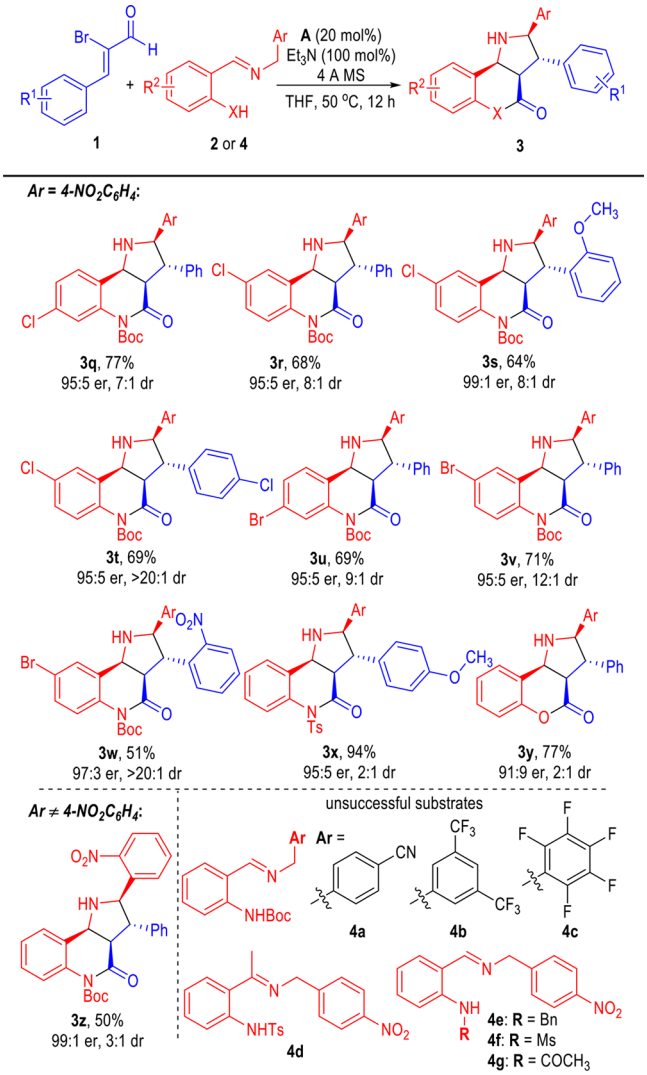
Scheme 1. Scope of α-Bromo Enals 1[a]



[a]Reaction conditions as stated in Table 1, entry 10. Yields are isolated yields after purification via SiO_2 column chromatography. Enantiomeric ratio (er) values were determined via HPLC on chiral stationary phase. Diastereomeric ratio (dr) values were determined by ^{1}H NMR on the crude reaction mixture.

Scheme 2. Scope of Substrate 2[a]



[a]Reaction conditions as stated in Table 1, entry 10. Yields are isolated yields after purification via SiO_2 column chromatography. Enantiomeric ratio (er) values were determined via HPLC on chiral stationary phase. Diastereomeric ratio (dr) values were determined by ^{1}H NMR on the crude reaction mixture.

effects provided by the chiral NHC moiety, the Si face of the β-sp^2 carbon of the acyl azolium intermediate **II** is favored to be attacked by the Re face of the nucleophilic sp^2 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 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 protocals 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 Evodiae 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

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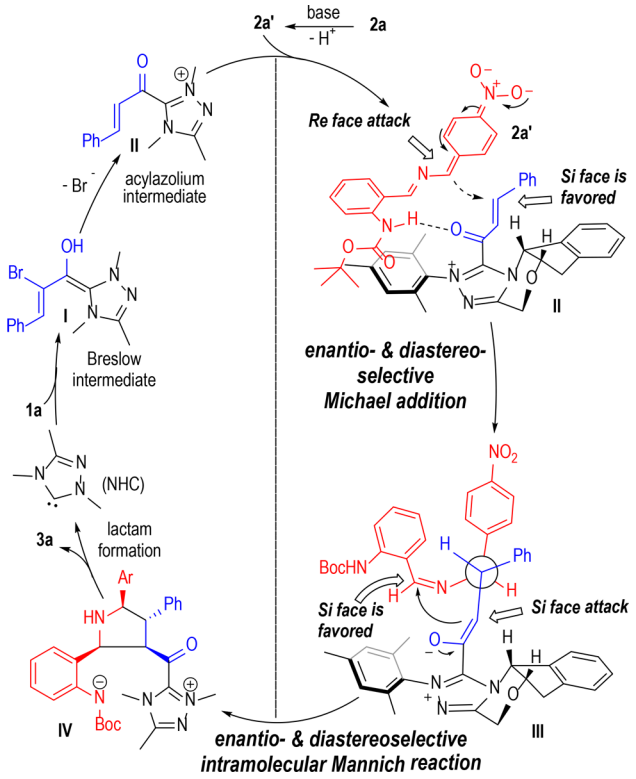

Figure 2. Postulated reaction mechanism.

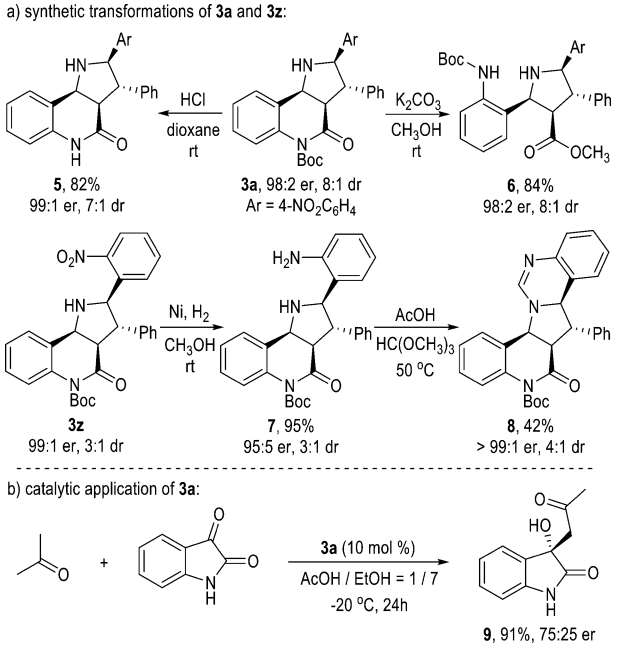

Figure 3. Synthetic transformations and catalytic applications of chiral products **3**.

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(sp^3)–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 enantiomerical 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02651.

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

CIF data for $C_{28}H_{26}N_4O_7$ (CIF)

checkCIF/PLATON report (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107*, 5606. (b) Marion, N.; Díez-González, S.; Nolan, S. P. N-Heterocyclic Carbenes as Organocatalysis. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Nair, V.; Vellalath, S.; Babu, B. P. Recent Advances in Carbon–Carbon Bond-Forming Reactions involving Homoenolates Generated by NHC Catalysis. *Chem. Soc. Rev.* **2008**, *37*, 2691. (d) Biju, A. T.; Kuhl, N.; Glorius, F. Extending NHC-Catalysis Aldehydes with Unconventional Reaction Partners. *Acc. Chem. Res.* **2011**, *44*, 1182. (e) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. Employing Homoenolates Generated by NHC Catalysis in Carbon-Carbon Bond-Forming Reactions: State of the Art. *Chem. Soc. Rev.* **2011**, *40*, 5336. (f) Douglas, J.; Churchill, G.; Smith, A. D. NHCs Asymmetric Organocatalysis: Recent Advances in Azolium Enolate Generation

DOI: 10.1021/acscatal.8b02651
ACS Catal. 2018, 8, 9859–9864

and Reactivity. *Synthesis* **2012**, *44*, 2295. (g) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. A Continuum of Progress: Applications of N-Heterocyclic Carbene Catalysis in Total Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. (h) Ryan, S. J.; Candish, L.; Lupton, D. W. Acyl Anion Free N-Heterocyclic Carbene Organocatalysis. *Chem. Soc. Rev.* **2013**, *42*, 4906. (i) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485. (j) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307.

(2) For pioneering works on the generation of α,β-unsaturated acylazoliums from aldehydes, see: (a) Zeitler, K. Stereoselective Synthesis of (E)-α,β-Unsaturated Esters via Carbene-Catalyzed Redox Esterification. *Org. Lett.* **2006**, *8*, 637. (b) De Sarkar, S.; Studer, A. NHC-Catalyzed Michael Addition to α,β-Unsaturated Aldehydes by Redox Activation. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266. (c) Sun, F.-G.; Sun, L.-H.; Ye, S. N-Heterocyclic Carbene-Catalyzed Enantioselective Annulation of Bromoenal and 1,3-Dicarbonyl Compounds. *Adv. Synth. Catal.* **2011**, *353*, 3134. (d) Mo, J.; Shen, L.; Chi, Y. R. Direct β-Activation of Saturated Aldehydes to Formal Michael Acceptors through Oxidative NHC Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 8588. For pioneering works on the generation of α,β-unsaturated acylazoliums from carboxylic acid derivatives, see: (e) Ryan, S. J.; Candish, L.; Lupton, D. W. N-Heterocyclic Carbene-Catalyzed Generation of α,β-Unsaturated Acyl Imidazoliums: Synthesis of Dihydropyranones by Their Reaction with Enolates. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (f) Cheng, J.; Huang, Z.; Chi, Y. R. NHC Organocatalytic Formal LUMO Activation of α,β-Unsaturated Esters for Reaction with Enamides. *Angew. Chem., Int. Ed.* **2013**, *52*, 8592. (g) Chen, X.-Y.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S. N-Heterocyclic Carbene Catalyzed Cyclocondensationo of α,β-Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 11611. (h) Liu, B.; Wang, W.; Huang, R.; Yan, J.; Wu, J.; Xue, W.; Yang, S.; Jin, Z.; Chi, Y. R. Direct Activation of b-sp3-Carbon of Saturated Carboxylic Esters as Electrophilic Carbons via Oxidative Carbene Catalysis. *Org. Lett.* **2018**, *20*, 260.

(3) For selected examples, see: (a) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. Enantioselective N-Heterocyclic Carbene-Catalyzed Michael Addition to α,β-Unsaturated Aldehydes by Redox Oxidation. *Org. Lett.* **2011**, *13*, 4080. (b) Biswas, A.; De Sarkar, S.; Frohlich, R.; Studer, A. Highly Stereoselective Synthesis of 1,2,3-Trisubstituted Indanes via Oxidative N-Heterocyclic Carbene-Catalyzed Cascades. *Org. Lett.* **2011**, *13*, 4966. (c) Li, J.-L.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. Conjugate Umpolung of β,β-Disubstituted Enals by Dual Catalysis with an N-Heterocyclic Carbene and a BrØnsted Acid: Facile Construction of Contiguous Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2014**, *53*, 10515. (d) Axelsson, A.; Hammarvid, E.; Ta, L.; Sunden, H. Asymmetric Aerobic Oxidative NHC-Catalyzed Synthesis of Dihydropyranones utilising a System of Electron Transfer Mediators. *Chem. Commun.* **2016**, *52*, 11571. (e) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. Enantioselective Synthesis of Spirocyclohexadienones by NHC-Catalyzed Formal [3 + 3] Annulation Reaction of Enals. *Angew. Chem., Int. Ed.* **2016**, *55*, 268.

(4) (a) Wu, X.; Liu, B.; Zhang, Y.; Jeret, M.; Wang, H.; Zheng, P.; Yang, S.; Song, B.-A.; Chi, Y. R. Enantioselective Nucleophilic β-Carbon-Atom Amination of Enals: Carbene-Catalyzed Formal [3 + 2] Reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 12280. (b) Wu, X.; Hao, L.; Zhang, Y.; Rakesh, M.; Reddi, R. N.; Yang, S.; Song, B.-A.; Chi, Y. R. Construction of Fused Pyrrolidines and β-Lactones by Carbene-Catalyzed C-N, C-C, and C-O Bond Formations. *Angew. Chem., Int. Ed.* **2017**, *56*, 4201.

(5) For a discussion of the mechanism of the Claisen-type pathway, see: (a) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. Chiral N-Heterocyclic Carbene-Catalyzed Annulations of Enals and Ynals with Stable Enols: A Highly Enantioselective Coates−Claisen Rearrangement. *ACS Catal.* **2012**, *2*, 494. (b) Lyngvi, E.; Bode, J. W.; Schoenebeck, F. A Computational Study of the Origin of Stereoinduction in NHC-Catalyzed Annulation Reactions of α,β-Unsaturated Acyl Azoliums. *Chem. Sci.* **2012**, *3*, 2346. (c) Samanta, R. C.; Maji, B.; De Sarkar, S.; Bergander, K.; Frohlich, R.; Muck-Lichtenfeld, C.; Mayr, H.; Studer, A. Nucleophilic Addition of Enols and Enamines to α,β-Unsaturated Acyl Azoliums: Mechanistic Studies. *Angew. Chem., Int. Ed.* **2012**, *51*, 5234.

(6) (a) Li, B.-S.; Wang, Y.; Proctor, R. S.; Zhang, Y.; Webster, R. D.; Yang, S.; Song, B.; Chi, Y. R. Carbene-Catalysed Reductive Coupling of Nitrobenzyl Bromides and Activated Ketones or Imines via Single-Electron-Transfer Process. *Nat. Commun.* **2016**, *7*, 12933. (b) Wang, Y.; Du, Y.; Huang, X.; Wu, X.; Zhang, Y.; Yang, S.; Chi, Y. R. Carbene-Catalyzed Reductive Coupling of Nitrobenzyl Bromide and Nitroalkene via the Single-Electron-Transfer (SET) Process and Formal 1,4-Addition. *Org. Lett.* **2017**, *19*, 632. (c) Wang, Y.; Wu, X.; Chi, Y. R. Synthesis of Indanes via Carbene-Catalyzed Single-Electron-Transfer Processes and Cascade Reactions. *Chem. Commun.* **2017**, *53*, 11952.

(7) (a) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. Martinelline and Martinellic Acid, Novel G-Protein Linked Receptor Antagonists from the Tropical Plant Martinella Iquitosensis (Bignoniaceae). *J. Am. Chem. Soc.* **1995**, *117*, 6682. (b) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. First Total Synthesis of Martinellic Acid, a Naturally Occurring Bradykinin Receptor Antagonist. *Org. Lett.* **2001**, *3*, 2189. (c) Ikeda, S.; Shibuya, M.; Iwabuchi, Y. Asymmetric Total Synthesis of Martinelline and Martinellic acid. *Chem. Commun.* **2007**, No. 5, 504. (d) Zhang, Z.; Zhang, Q.; Yan, Z.; Liu, Q. One-Step Synthesis of the Tricyclic Core of Martinellic Acid from 2-(Cyanomethyl)-3-oxo-N-arylbutanamides. *J. Org. Chem.* **2007**, *72*, 9808. (e) Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata, O. Efficient Entry into 2-Substituted Tetrahydroquinoline Systems through Alkylative Ring Expansion: Stereoselective Formal Synthesis of (±)-Martinellic Acid. *J. Org. Chem.* **2010**, *75*, 914. (f) Hu, J.; Hirao, H.; Li, Y.; Zhou, J. Palladium-Catalyzed Asymmetric Intermolecular Cyclization. *Angew. Chem., Int. Ed.* **2013**, *52*, 8676.

(8) (a) Nieman, J. A.; Ennis, M. D. Enantioselective Synthesis of the Pyrroloquinoline Core of the Martinellines. *Org. Lett.* **2000**, *2*, 1395. (b) Snider, B. B.; Ahn, Y.; O'Hare, S. M. Total Synthesis of (±)-Martinellic Acid. *Org. Lett.* **2001**, *3*, 4217. (c) Comesse, S.; Sanselme, M.; Daich, A. New and Expeditious Tandem Sequence Aza-Michael/Intramolecular Nucleophilic Substitution Route to Substituted γ-Lactams: Synthesis of the Tricyclic Core of (±)-Martinellines. *J. Org. Chem.* **2008**, *73*, 5566. (d) Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D.-J.; Sucunza, D.; Naito, T. Total Synthesis of (−)-Martinellic Acid via Radical Addition-Cyclization-Elimination Reaction. *J. Org. Chem.* **2008**, *73*, 4464. (e) Sridharan, V.; Suryavanshi, P. A.; Menendez, C. Advance in the Chemistry of Tetrahydroquinolines. *Chem. Rev.* **2011**, *111*, 7157.

(9) (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. A Highly Enantioselective Catalytic Intramolecular Stetter Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (b) Kerr, M. S.; Rovis, T. Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (c) He, M.; Struble, J. R.; Bode, J. W. Highly Enantioselective Azadiene Diels-Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

(10) (a) Johnson, T. W.; Corey, E. J. Enantiospecific Synthesis of the Proposed Structure of the Antitubercular Marine Diterpenoid Pseudopteroxazole: Revision of Stereochemistry. *J. Am. Chem. Soc.* **2001**, *123*, 4475.

(11) (a) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. First Total Synthesis of Hinckdentine A. *Org. Lett.* **2009**, *11*, 197. (b) Torres-Ochoa, R. O.; Buyck, T.; Wang, Q.; Zhu, J. Heteroannulation of Arynes with a-Amino Imides: Synthesis of 2,2-Disubstituted Indolin-3-ones and Application to the Enantioselective Total Synthesis of (+)-Hinckdentine A. *Angew. Chem., Int. Ed.* **2018**, *57*, 5679.

DOI: 10.1021/acscatal.8b02651
ACS Catal. 2018, 8, 9859−9864

(12) (a) Decker, M. Novel Inhibitors of Acetyl- and Butyrylcholinesterase Derived from the Alkaloids Dehydroevodiamine and Rutaecarpine. *Eur. J. Med. Chem.* **2005**, *40*, 305. (b) Chen, Z.; Hu, G.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y. Synthesis and Vasodilator Effects of Rutaecarpine Analogues which Might Be Involved Transient Receptor Potential Vanilloid Subfamily, Member 1 (TRPV1). *Bioorg. Med. Chem.* **2009**, *17*, 2351.

(13) Yadav, G. D.; Singh, S. N-Arylprolinamide as an Organocatalyst for the Direct Asymmetric Aldol Reaction of Acetone with Isatin. *Tetrahedron: Asymmetry* **2016**, *27*, 123.

DOI: 10.1021/acscatal.8b02651
ACS Catal. 2018, 8, 9859−9864