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Enantioselective Indole N−H Functionalization Enabled by Addition of Carbene Catalyst to Indole Aldehyde at Remote Site

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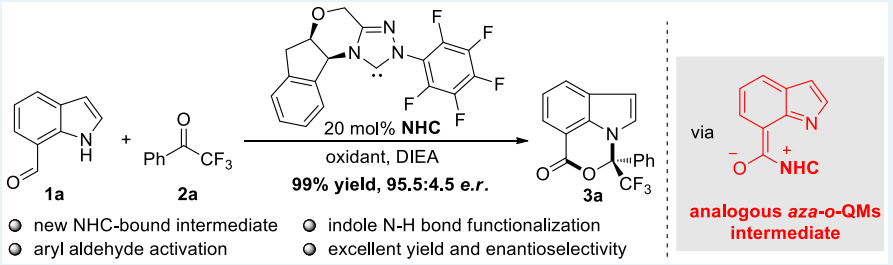
Supporting Information



ABSTRACT: An enantioselective functionalization of the indole NH group is developed. The reaction stereoselectivity is controlled by an N-heterocyclic carbene catalyst that adds to an aldehyde moiety at the C7-carbon of indole. The NH group participating in the carbene-catalyzed reaction is part of the heteroaromatic rings of the indole substrate. Our reactions afford multicyclic products bearing pyrroloquinazoline or oxazinoindole scaffolds widely present in bioactive molecules. Our study will encourage further exploration of carbene-catalyzed reactions of aromatic molecules and asymmetric transformation of heteroatoms in various functional molecules.

KEYWORDS: *N-heterocyclic carbene, N−H functionalization, indoles, asymmetric catalysis, heterocyclic compounds*

The selective functionalization of (hetero)aromatic molecules continues to be a research focus in synthetic chemistry. Most of the progress in this field comes from transition-metal-catalyzed processes.[1] It remains much less developed to use organic catalysts to activate and functionalize aromatic molecules. One important progress in this direction involves combined photoredox and organocatalysis for radical reactions, as pioneered by MacMillan,[2a] Melchiorre,[2b] and Phipps.[2c] Another type of elegant aromatic molecule functionalization reactions involve amino catalysis, as reported by Jørgensen,[2d] Chen,[2e] and Xu.[2f] N-Heterocyclic carbene (NHC) organic catalysis has found impressive success for asymmetric reactions of aldehydes,[3] esters,[4] and related carbonyl compounds.[5] We are interested in exploring NHCs for asymmetric transformation of aromatic molecules.[6] Indeed, the benzylic carbons of indoles[7] and benzenes[8] could be activated and further converted enabled via addition of NHC catalysts to the adjacent aryl aldehyde moieties, as reported by Glorius,[8a] Rovis,[8b] and us.[7,8c] We have also found that through addition of an NHC catalyst to an aldehyde at the ortho-carbon, the phenolic OH group could be functionalized enantioselectively.[9] Recently, Scheidt and co-workers reported that carbene catalyst could enable an asymmetric decarboxylative annulations via *aza-o*-quinone methides (*aza-o*-QMs) intermediate (Figure 1a).[10]

Here we disclose that the indole NH groups can undergo enantioselective addition to ketones under the influence of chiral NHC catalysts (Figure 1b). The enantioselectivity is controlled by the NHC catalyst that adds to a remote aryl aldehyde moiety on the C7-carbon of the indole. Key steps in this process include the formation of acyl azolium ester intermediate[4f] (**I**) that upon proton transfer forms *aza-o*-QMs-containing intermediate **II**.[11] Formal [4 + 2] reaction of **II** with a reactive ketone substrate forms the acetal product (**3a**) with 99% yield and 95:5 er. The products (e.g., **3a**) obtained from our method bear pyrroloquinazoline or oxazinoindole scaffolds that are widely presented in bioactive molecules (Figure 1c).[12]

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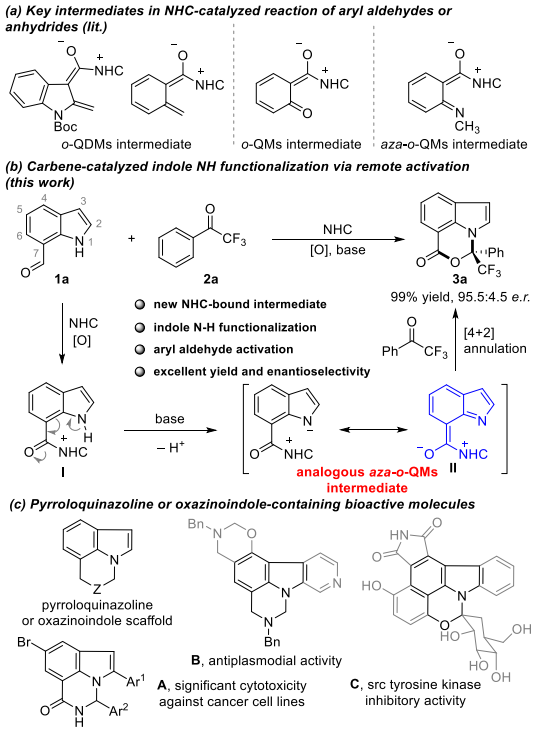


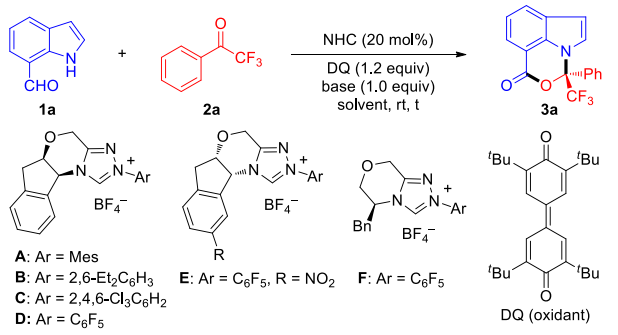
Figure 1. Research background and related bioactive molecule scaffolds.

Notably, the reactive nitrogen atom in our reaction is part of the aromatic ring of the substrate, which is different from previous studies involving oxygen[9] or nitrogen[10] atoms attached to benzenes as the reactive sites. It is also worthwhile to note that asymmetric construction of aminal and *N,O*-acetal units as those in our product is of significant synthetic values.[13] Our present study will encourage further development of asymmetric heteroatom functionalization methods for heteroaromatic compounds.

Notably, asymmetric functionalization of indole involving NHC organocatalysis has attracted considerable attentions, with impressive studies reported by Enders,[3h] Studer[3i] and Biju.[3j] In these previous studies,[3h−j] the indole moiety behaves as a partner to react with another substrate that is activated by the NHC catalysts; the indole moiety itself is not activated by the catalyst. In our present study, activation of the indole substrate by the NHC catalyst is the critical step for the reaction to proceed.

Key results of condition optimization using indole-7-carbaldehyde **1a** and trifluoroacetophone **2a** as model substrates are summarized in Table 1. The aminoindanol-derived triazolium precatalyst (**A**) with an *N*-mesityl substituent,[14] an excellent catalyst in a large set of reactions, was ineffective here (entry 1). Replacing the *N*-mesityl unit with an *N*-(2,6-diethyl)phenyl group (precatalyst **B**)[15] gave similar results (entry 2). We then found that when the electron-deficient trichlorophenyl was used as the *N*-substituent of the precatalyst (**C**),[16] the reaction could proceed to form **3a** with an encouraging 90:10 er, albeit in a low yield (8%) (entry 3). The product yield was dramatically improved when NHC precatalyst **D** with an *N*-pentafluorophenyl group was used as the reaction catalyst.[17] The product was obtained in 90% yield and 95.5:4.5 er, with Cs_2CO_3 as the base, CH_2Cl_2 as the solvent, and DQ as the oxidant (entry 4).[18] Installing a NO_2 group on the indane moiety of catalyst **D** (to get catalyst **E**) led to a small improvement on the product er value but with drop on the reaction yield (entry 5). Phenylalanine-derived catalyst **F**[19] was also efficient for this transformation, with the product **3a** afforded in 70% yield and 91:9 er (entry 6). Various organic and inorganic bases could be used in this transformation (entries 7−9), and DIEA was found as the most efficient one that could give **3a** in quantitative yield without erosion of the er value (entry 9). Screening of different reaction solvents did not show further improvements in either the product yields or enantioselectivities (entries 10−11).

Table 1. Optimization of the Reaction Conditions[a]



entry	NHC	base	solvent	*t* (h)	yield (%)[b]	e.r.[c]
1	**A**	Cs_2CO_3	CH_2Cl_2	24	trace	-
2	**B**	Cs_2CO_3	CH_2Cl_2	24	trace	-
3	**C**	Cs_2CO_3	CH_2Cl_2	24	8	90:10
4	**D**	Cs_2CO_3	CH_2Cl_2	3	90	95.5:4.5
5	**E**	Cs_2CO_3	CH_2Cl_2	3	74	3.5:96.5
6	**F**	Cs_2CO_3	CH_2Cl_2	3	70	91:9
7	**D**	K_2CO_3	CH_2Cl_2	12	24	95.5:4.5
8	**D**	DBU	CH_2Cl_2	12	51	95:5
9	**D**	DIEA	CH_2Cl_2	3	99	95.5:4.5
10	**D**	DIEA	THF	3	56	95.5:4.5
11	**D**	DIEA	toluene	3	57	92:8

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), base (1.0 equiv), NHC (20 mol %), and DQ (1.2 equiv) in solvent (1.0 mL) at rt. [b]Isolated yield; [c]Enantiomeric ratio of **3a** was determined via HPLC on a chiral stationary phase.

Having established the optimal reaction conditions, we set out to explore the generality of this protocol. First, the scope of electron-deficient ketone substrates was examined (Table 2). Aromatic trifluoromethyl ketones with halogen atoms (**3b−d**), electron-donating (**3e** and **3f**), and electron-withdrawing (**3g**) groups on the *para*-position of the phenyl rings were well tolerated, with all of the target products obtained in excellent yields and er values. Substitutions on the *meta*-position of the phenyl rings resulted in slight drops on the enantioselectivities (**3h** and **3i**). The benzene ring of the trifluoromethyl ketone **2a** could be switched into fused aromatic groups such as 2-naphthalene group and 3-indolene group, with corresponding products afforded in excellent yields and enantioselectivities (**3j** and **3k**). To our great delight, aliphatic trifluoromethyl ketones also worked well in this process under the current reaction condition, and the desired products were generated in good to excellent yields and optical purities (**3l** and **3m**). Furthermore, difluoromethyl ketone and α-ketoester were also found as suitable reactants in this catalytic transformation, and both of the target products could be obtained in good yields with excellent er values (**3n** and **3o**).

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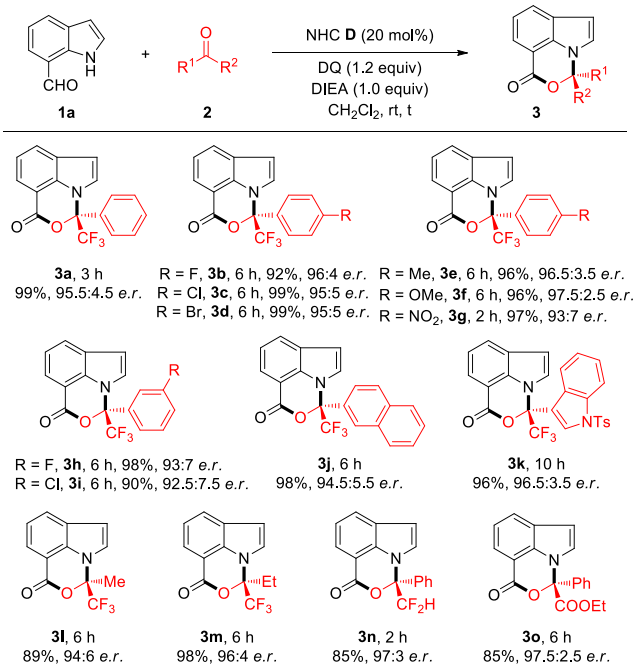
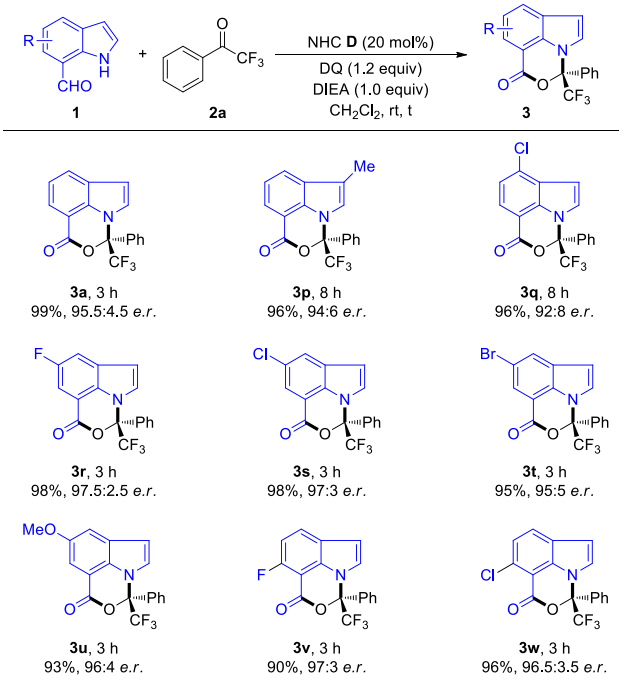
Table 2. Scope of Acyclic Ketones[a]



[a]Reaction conditions: **1a** (0.15 mmol), **2** (0.1 mmol), DIEA (1.0 equiv), NHC **D** (20 mol %), and DQ (1.2 equiv) in CH_2Cl_2 (1.0 mL) at rt.

Next, we turned our attention to investigate the scope of indole-7-carbaldehydes **1** with trifluoroacetophone **2a** as the model substrate. The results are summarized in Table 3. Installing a methyl group at the indole 3-position (**3p**) or chloroatom at 4-position (**3q**), the products were obtained in excellent yields with good enantioselectivities. Substitutions on the indole 5- and 6-positons could give the desired products in excellent yields and optical purities, regardless of the electronic properties (**3r** to **3w**).

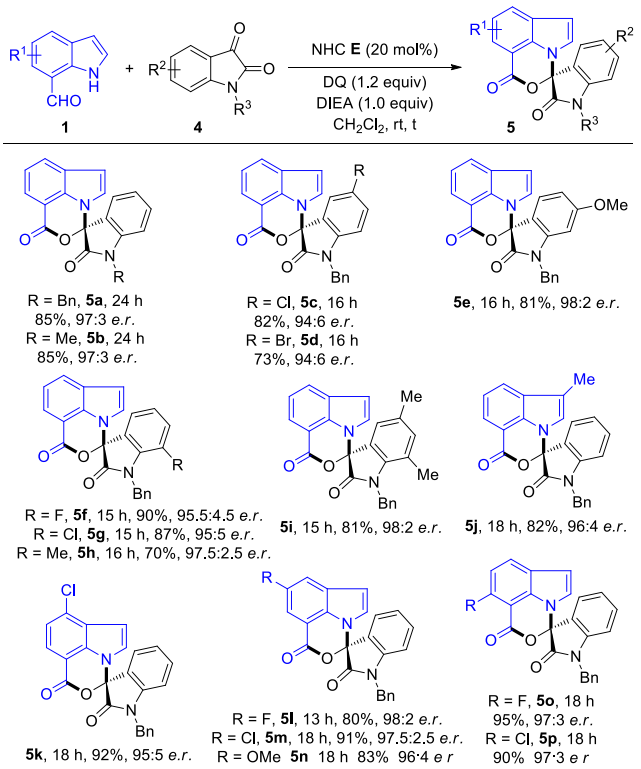
Table 3. Scope of Indole-7-carbaldehydes[a]



[a]Reaction conditions: **1** (0.15 mmol), **2a** (0.1 mmol), DIEA (1.0 equiv), NHC **D** (20 mol %), and DQ (1.2 equiv) in CH_2Cl_2 (1.0 mL) at rt.

To further demonstrate the generality and utility of our synthetic protocol, we next explored the reaction using isatin derivatives as the substrates to construct spiro-cyclic compounds **5** (Table 4). It has been well documented that

Table 4. Asymmetric N−H Functionalization of Indole-7-carbaldehydes with Isatins[a]



[a]Reaction conditions: **1** (0.15 mmol), **4** (0.1 mmol), DIEA (1.0 equiv), NHC **E** (20 mol %), and DQ (1.2 equiv) in CH_2Cl_2 (1.0 mL) at rt.

many indole- and isatin-containing molecules exhibited interesting and important bioactivities, such as antitumor, anti-HIV, and antimicrobial activities.[20] After identification of the optimal reaction conditions (see SI), we found that NHC precatalyst **E** could give the product **5a** in excellent yield and enantioselectivity. A wide range of isatin substrates were then smoothly converted into the spiro-cyclic compounds **5** in good yields with excellent enantioselectivities (**5a−i**). In addition, indole-7-carbaldehydes bearing various substituents were employed in this process, which provided the products in good to excellent yields with excellent er values (**5j−p**).

Imine substrates were also tested for this catalytic transformation. After screening of different imine electrophiles (see SI), the electron-deficient imine **6** could react smoothly with indole-7-carbaldehyde **1a** and give product **7** in 95% yield and 83:17 er. The er value of the afforded product could be improved to 97:3 after a simple recrystallization from ethyl acetate (Scheme 1a). To evaluate the practicality of our method, a scale-up reaction was carried out. By treating of **1i** (3.0 mmol, 0.3 M) and **2a** (2.0 mmol, 0.2 M) using 5 mol %

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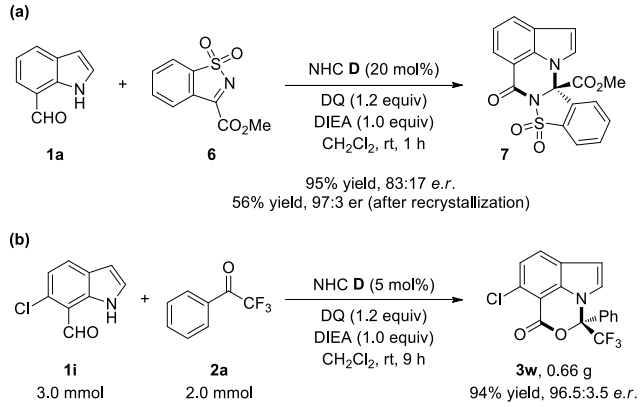
Scheme 1. (a) Asymmetric N−H Functionalization of Indole-7-carbaldehyde 1a with Imine 6 and (b) Scale-up Synthesis with a Lower Catalyst Loading



NHC precatalyst **D**, product **3w** (0.66 g) was obtained with 94% yield and 96.5:3.5 er value that are comparable to the small-scale reaction (96% yield, 96.5:3.5 er) (Scheme 1b).

The plausible [4 + 2] annulation pathway is shown in Figure 2. The addition of NHC to aldehyde **1a** forms Breslow

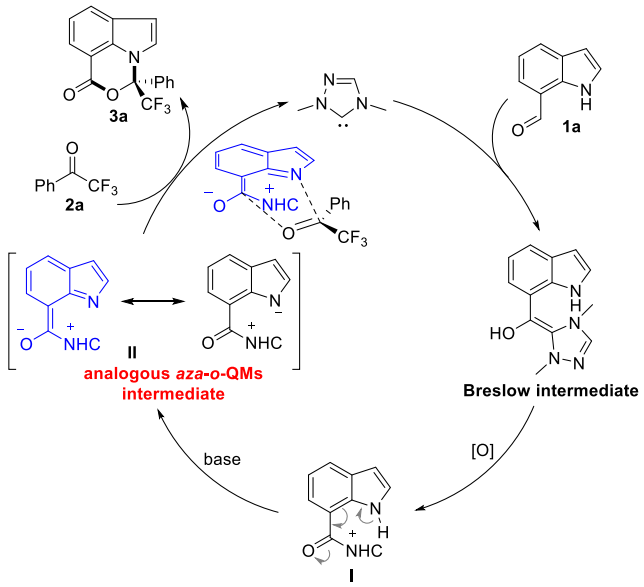


Figure 2. Proposed catalytic cycle for formal [4 + 2] cycloaddition.

intermediate, which undergoes oxidation reaction to generate acylazolium intermediate **I**. After deprotonation of intermediate **I**, the analogous *aza-o*-QMs intermediate (**II**) is formed. Finally, a formal [4 + 2] annulation reaction between intermediate **II** and trifluoroacetophone **2a** provides the desired product **3a** and regenerates the NHC catalyst. We calculated Mulliken atomic charges for intermediate **II** and found that the O and N atoms have partial negative charges of −0.481 and −0.631, respectively. These fractional charges indicate that **II** cannot be described as either of the two extreme resonance structures depicted in Figure 2. The real state of analogous *aza-o*-QMs intermediate should lie somewhere in between.

In summary, we have realized the first enantioselective functionalization of indole N−H group through NHC catalysis. The addition of the NHC catalyst to the aldehyde moiety at a remote site of indole (indole-7-carbaldehydes) initiates the reaction and controls the stereoselectivity. Our study demonstrates that the nitrogen atom in heteroaromatic molecules can undergo asymmetric formal cycloaddition reactions with the catalysis of NHCs. The multicyclic *N,O*-acetal and aminal products could be obtained in up to quantitative yields with excellent er values. Further development of asymmetric heteroatom functionalization and their synthetic applications are in progress 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.9b03163.

Experimental procedures, analytical and spectroscopic data for new compounds, and copies of NMR and HPLC spectra (PDF)

Crystallographic data for **3k** (CIF)

Crystallographic data for **5a** (CIF)

Crystallographic data for **7** (CIF)

(PDF)

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¶X.Y. and G.L. contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition metal-catalyzed C-H activation reactions: diastereoselectivity and enantioselectivity. *Chem. Soc. Rev.* **2009**, *38*, 3242−3272. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. C-H activation for the construction

DOI: 10.1021/acscatal.9b03163
ACS Catal. 2019, 9, 10971−10976

of C-B bonds. *Chem. Rev.* **2010**, *110*, 890−931. (c) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a substrate-activating strategy in homogeneous transition-metal catalysis. *Chem. Rev.* **2010**, *110*, 681−703. (d) Bellina, F.; Rossi, R. Transition metal-catalyzeddirect arylation of substrates with activated sp(3)-hybridized C-H bonds and some of their synthetic equivalents with aryl halides and pseudohalides. *Chem. Rev.* **2010**, *110*, 1082−1146. (e) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. Direct sp(3) alpha-C-H activation and functionalization of alcohol and ether. *Chem. Soc. Rev.* **2011**, *40*, 1937−1949. (f) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C-H transformation via iron catalysis. *Chem. Rev.* **2011**, *111*, 1293−1314. (g) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild metal-catalyzed C-H activation: examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936. (h) Yang, Y.-F.; Hong, X.; Yu, J.-Q.; Houk, K. N. Experimental computational synergy for selective Pd(II)-catalyzed C-H activation of aryl and alkyl groups. *Acc. Chem. Res.* **2017**, *50*, 2853−2860. (i) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic enantioselective transformations involving C-H bond cleavage by transition-metal complexes. *Chem. Rev.* **2017**, *117*, 8908−8976.

(2) (a) Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. A general strategy for organocatalytic activation of C-H bonds via photoredoxcatalysis: direct arylation of benzylic ethers. *J. Am. Chem. Soc.* **2014**, *136*, 626−629. (b) Dell'Amico, L.; Vega-Penaloza, A.; Cuadros, S.; Melchiorre, P. Enantioselective organocatalytic Diels-Alder trapping of photochemically generated hydroxy-*o*-quinodimethanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 3313−3317. (c) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. Catalytic enantioselective Minisci-type addition to heteroarenes. *Science* **2018**, *360*, 419−422. (d) Jiang, H.; Rodríguez-Escrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. Organocatalytic activation of polycyclic aromatic compounds for asymmetric Diels-Alder reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 10271−10274. (e) Li, J. L.; Yue, C. Z.; Chen, P. Q.; Xiao, Y. C.; Chen, Y. C. Remote enantioselective Friedel-Crafts alkylations of furans through HOMO activation. *Angew. Chem., Int. Ed.* **2014**, *53*, 5449−5452. (f) Xu, D.-Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xu, Z.-Y. A novel enantioselective catalytic tandem oxa-Michael-Henry reaction: one-pot organocatalytic asymmetric synthesis of 3-nitro-2H-chromenes. *Adv. Synth. Catal.* **2008**, *350*, 2610−2616.

(3) Selected examples on asymmetric reaction of aldehydes: (a) Zhao, X.; Ruhl, K. E.; Rovis, T. *N*-heterocyclic-carbene-catalyzedasymmetric oxidative hetero-Diels-Alder reactions with simple aliphatic aldehydes. *Angew. Chem., Int. Ed.* **2012**, *51*, 12330−12333. (b) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. Enantioselective, NHC-catalyzed annulations of trisubstituted enals and cyclic N-sulfonylimines via *α,β*-unsaturated acyl azoliums. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433−9436. (c) Dong, X.; Yang, W.; Hu, W.; Sun, J. *N*-heterocyclic carbene catalyzedenantioselective alpha-fluorination of aliphatic aldehydes and alpha-chloroaldehydes: synthesis of alpha-fluoroesters, amides, and thioesters. *Angew. Chem., Int. Ed.* **2014**, *54*, 660−663. (d) Li, F.; Wu, Z.; Wang, J. Oxidative enantioselective alpha-fluorination of aliphatic aldehydes enabled by *N*-heterocyclic carbene catalysis. *Angew. Chem., Int. Ed.* **2014**, *54*, 656−659. (e) Bera, S.; Daniliuc, C. G.; Studer, A. Enantioselective synthesis of substituted delta-lactones by cooperative oxidative *N*-heterocyclic carbene and Lewis acid catalysis. *Org. Lett.* **2015**, *17*, 4940−4943. (f) Chen, X.-Y.; Liu, Q.; Chauhan, P.; Li, S.; Peuronen, A.; Rissanen, K.; Jafari, E.; Enders, D. *N*-heterocyclic carbene catalyzed [4 + 2] annulation of enals via a double vinylogous Michael addition: asymmetric synthesis of 3,5-diaryl cyclohexenones. *Angew. Chem., Int. Ed.* **2017**, *56*, 6241−6245. (g) Singha, S.; Patra, T.; Daniliuc, C. G.; Glorius, F. Highly enantioselective [5 + 2] annulations through cooperative *N*-heterocyclic carbene (NHC) organocatalysis and palladium catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 3551−3554. (h) Ni, Q. J.; Zhang, H.; Grossmann, A.; Loh, C. C. J.; Merkens, C.; Enders, D. Asymmetric synthesis of pyrroloindolones by *N*-heterocyclic carbene catalyzed [2 + 3] annulation of alpha-chloroaldehydes with nitrovinylindoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 13562−13566. (i) Bera, S.; Daniliuc, C. G.; Studer, A. Oxidative *N*-heterocyclic carbene catalyzeddearomatization of indoles to spirocyclic indolenines with a quaternary carbon stereocenter. *Angew. Chem., Int. Ed.* **2017**, *56*, 7402−7406. (j) Mukherjee, S.; Shee, S.; Poisson, T.; Besset, T.; Biju, A. T. Enantioselective *N*-heterocyclic carbene-catalyzedcascade reaction for the synthesis of pyrroloquinolines via N-H functionalization of indoles. *Org. Lett.* **2018**, *20*, 6998−7002.

(4) Selected examples on asymmetric reaction of esters: (a) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W.; Chi, Y. R. beta-Carbon activation of saturated carboxylic esters through *N*-heterocyclic carbene organocatalysis. *Nat. Chem.* **2013**, *5*, 835−839. (b) Liu, B.; Wang, W.-H.; Huang, R.-Y.; Yan, J.-K.; Wu, J.-C.; Xue, W.; Yang, S.; Jin, Z.-C.; Chi, Y. R. Direct activation of beta-sp(3)-carbons of saturated carboxylic esters as electrophilic carbons via oxidative carbene catalysis. *Org. Lett.* **2018**, *20*, 260−263. (c) Fu, Z.-Q.; Jiang, K.; Zhu, T.-S.; Torres, J.; Chi, Y. R. Access to oxoquinoline heterocycles by *N*-heterocyclic carbene catalyzedester activation for selective reaction with an enone. *Angew. Chem., Int. Ed.* **2014**, *53*, 6506−6510. (d) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. First example of chiral *N*-heterocyclic carbenes as catalysts for kinetic resolution. *Chem. Commun.* **2004**, 2770−2771. (e) Kano, T.; Sasaki, K.; Maruoka, K. Enantioselective acylation of secondary alcohols catalyzed by chiral *N*-heterocyclic carbenes. *Org. Lett.* **2005**, *7*, 1347−1349. (f) For reaction and mechanistic studies of acyl azolium intermediates, see: Samanta, R. C.; Maji, B.; De Sarkar, S.; Bergander, K.; Fröhlich, R.; Mück-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*, 5234−5238.

(5) Selected examples on asymmetric reaction of other carbonyl compounds: (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *N*-heterocyclic carbene-catalyzed (4 + 2) cycloaddition/decarboxylation of silyl dienolethers with alpha, beta-unsaturated acid fluorides. *J. Am. Chem. Soc.* **2011**, *133*, 4694−4697. (b) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. Chiral *N*-heterocyclic carbene-catalyzedformal [4 + 2] cycloaddition of ketenes with enones: highly enantioselective synthesis of *trans*- and *cis*-delta-lactones. *Chem. - Eur. J.* **2008**, *14*, 8473−8476. (c) Shen, L.-T.; Shao, P.-L.; Ye, S. *N*-heterocyclic carbene-catalyzedcyclization of unsaturated acyl chlorides and ketones. *Adv. Synth. Catal.* **2011**, *353*, 1943−1948. (d) Lee, A.; Scheidt, K. A. *N*-heterocyclic carbene-catalyzed enantioselective annulations: a dual activation strategy for a formal [4 + 2] addition for dihydrocoumarins. *Chem. Commun.* **2015**, *51*, 3407−3410. (e) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. Enantioselective annulations for dihydroquinolones by in situ generation of azoliumenolates. *J. Am. Chem. Soc.* **2014**, *136*, 10589−10592. (f) For reviews, see: Bugaut, X.; Glorius, F. Organocatalytic umpolung: *N*-heterocyclic carbenes and beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511−3522. (g) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. A continuum of progress: applications of *N*-hetereocycliccarbene catalysis in total synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686−11698. (h) Cohen, D. T.; Scheidt, K. A. Cooperative Lewis acid/*N*-heterocyclic carbene catalysis. *Chem. Sci.* **2012**, *3*, 53−57. (i) Ryan, S. J.; Candish, L.; Lupton, D. W. Acyl anion free *N*-heterocyclic carbene organocatalysis. *Chem. Soc. Rev.* **2013**, *42*, 4906−4917. (j) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of *N*-heterocyclic carbenes. *Nature* **2014**, *510*, 485−496. (k) Mahatthananchai, J.; Bode, J. W. On the mechanism of *N*-heterocyclic carbene-catalyzedreactions involving acyl azoliums. *Acc. Chem. Res.* **2014**, *47*, 696−707. (l) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic reactions enabled by *N*-heterocyclic carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387. (m) Wang, M. H.; Scheidt, K. A. Cooperative catalysis and activation with *N*-heterocyclic carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912−14922. (n) Chen, X.-Y.; Liu, Q.; Chauhan, P.; Enders, D. *N*-heterocyclic carbene catalysis via azoliumdienolates: an efficient strategy for remote enantioselective functionalizations. *Angew. Chem., Int. Ed.* **2018**, *57*, 3862−3873. (o) Murauski, K. J. R.; Jaworski, A. A.; Scheidt, K. A. A continuing challenge: *N*-heterocyclic carbene-

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ACS Catal. 2019, 9, 10971−10976

catalyzed syntheses of gamma-butyrolactones. *Chem. Soc. Rev.* **2018**, *47*, 1773−1782. (p) Mondal, S.; Yetra, S. R.; Mukherjee, S.; Biju, A. T. NHC-catalyzedgeneration of alpha, beta-unsaturated acylazoliums for the enantioselective synthesis of heterocycles and carbocycles. *Acc. Chem. Res.* **2019**, *52*, 425−436.

(6) (a) Zhuo, S.; Zhu, T.; Zhou, L.; Mou, C.; Chai, H.; Lu, Y.; Pan, L.; Jin, Z.; Chi, Y. R. Access to all-carbon spirocycles through a carbene and thiourea cocatalyticdesymmetrizationcascade reaction. *Angew. Chem., Int. Ed.* **2019**, *58*, 1784−1788. (b) Huang, Z.; Huang, X.; Li, B.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. Access to *P*-stereogenicphosphinatesvia *N*-heterocyclic carbene-catalyzeddesymmetrization of bisphenols. *J. Am. Chem. Soc.* **2016**, *138*, 7524−7527. (c) Li, B.; Wang, Y.; Proctor, R. S. J.; Jin, Z.; Chi, Y. R. Carbene-catalyzeddesymmetrization of 1,3-diols: access to optically enriched tertiary alkyl chlorides. *Chem. Commun.* **2016**, *52*, 8313−8316.

(7) Chen, X.-K.; Yang, S.; Song, B.-A.; Chi, Y. R. Functionalization of benzylic C(sp(3))-H bonds of heteroaryl aldehydes through *N*-heterocyclic carbene organocatalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 11134−11137.

(8) (a) Janssen- Müller, D.; Singha, S.; Olyschläger, T.; Daniliuc, C. G.; Glorius, F. Annulation of *o*-quinodimethanes through *N*-heterocyclic carbene catalysis for the synthesis of 1-isochromanones. *Org. Lett.* **2016**, *18*, 4444−4447. (b) Chen, D.-F.; Rovis, T. *N*-heterocyclic carbene and chiral Brønstedacid cooperative catalysis for a highly enantioselective [4 + 2] annulation. *Synthesis* **2016**, *49*, 293−298. (c) Wang, H.; Chen, X.; Li, Y.; Wang, J.; Wu, S.; Xue, W.; Yang, S.; Chi, Y. R. Addition of *N*-heterocyclic carbene catalyst to aryl esters induces remote C-Si bond activation and benzylic carbon functionalization. *Org. Lett.* **2018**, *20*, 333−336. (d) Hu, Y.; Pan, D.; Cong, L.; Yao, Y.-B.; Yu, C.-X.; Li, T.-J.; Yao, C.-S. NHC-catalyzed efficient syntheses of isoquinolinones or isochromanones through formal [4 + 2] cycloaddition of *o*-quinodimethanes with acylhydrazones or ketones. *Chemistry Select* **2018**, *3*, 1708−1712.

(9) Chen, X.-K.; Wang, H.; Doitomi, K.; Ooi, C. Y.; Zheng, P.; Liu, W.; Guo, H.; Yang, S.; Song, B.-A.; Hirao, H.; Chi, Y. R. A reaction mode of carbene-catalysed aryl aldehyde activation and induced phenol OH functionalization. *Nat. Commun.* **2017**, *8*, 15598.

(10) Lee, A.; Zhu, J. L.; Feoktistova, T.; Brueckner, A. C.; Cheong, P.; Scheidt, K. A. Carbene-catalyzedenantioselective decarboxylative annulations to access dihydrobenzoxazinones and quinolones. *Angew. Chem., Int. Ed.* **2019**, *58*, 5941−5945.

(11) For detailed mechanism studies, see Supporting Information. An alternative pathway may involve a dynamic kinetic resolution (DKR) process to form the same product. Although the two pathways (formal [4 + 2] reaction pathway and DKR process) are difficult to be distinguished, preliminary results from DFT calculation suggest that the formal cycloaddition pathway likely operates in our reactions.

(12) (a) Mphahlele, M. J.; Khoza, T. A.; Mabeta, P. Novel 2,3-dihydro-1H-pyrrolo[3,2,1-ij]quinazolin-1-ones: synthesis and biological evaluation. *Molecules* **2017**, *22*, 55. (b) Bouaziz, Z.; Issa, S.; Gentili, J.; Gratz, A.; Bollacke, A.; Kassack, M.; Jose, J.; Herfindal, L.; Gausdal, G.; Doskeland, S.; Mullie, C.; Sonnet, P.; Desgrouas, C.; Taudon, N.; Valdameri, G.; Di Pietro, A.; Baitiche, M.; Le Borgne, M. Biologically active carbazole derivatives: focus on oxazinocarbazoles and related compounds. *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 180−188. (c) Conchon, E.; Anizon, F.; Aboab, B.; Golsteyn, R. M.; Léonce, S.; Pfeiffer, B.; Prudhomme, M. Synthesis, checkpoint kinase 1 inhibitory properties and in vitro antiproliferative activities of new pyrrolocarbazoles. *Bioorg. Med. Chem.* **2008**, *16*, 4419−4430.

(13) Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. Catalytic asymmetric reactions with *N, O*-aminals. *ACS Catal.* **2016**, *6*, 5747−5763.

(14) 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*, 8418−8420.

(15) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. Cooperative *N*-heterocyclic carbene/Lewis acid catalysis for highly stereoselective annulation reactions with homoenolates. *J. Am. Chem. Soc.* **2010**, *132*, 5345−5346.

(16) Lathrop, S. P.; Rovis, T. A photoisomerization-coupled asymmetric Stetter reaction: application to the total synthesis of three diastereomers of (−)-cephalimysin A. *Chem. Sci.* **2013**, *4*, 1668−1673.

(17) Kerr, M. S.; Rovis, T. Enantioselective synthesis of quaternary stereocenters via a catalytic asymmetric Stetter reaction. *J. Am. Chem. Soc.* **2004**, *126*, 8876−8877.

(18) De Sarkar, S.; Studer, A. NHC-catalyzed Michael addition to alpha, beta-unsaturated aldehydes by redox activation. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266−9269.

(19) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. Enantioselective synthesis of alpha, alpha-disubstituted cyclopentenes by an *N*-heterocyclic carbene-catalyzeddesymmetrization of 1,3-diketones. *J. Am. Chem. Soc.* **2007**, *129*, 10098−10099.

(20) (a) Singh, G. S.; Desta, Z. Y. Isatinsas privileged molecules in design and synthesis of spiro-fused cyclic frameworks. *Chem. Rev.* **2012**, *112*, 6104−6155. (b) Cao, Z.-Y.; Zhou, F.; Zhou, J. Development of synthetic methodologies via catalytic enantioselective synthesis of 3,3-disubstituted oxindoles. *Acc. Chem. Res.* **2018**, *51*, 1443−1454.

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