ACS Catalysis

pubs.acs.org/acscatalysis Letter

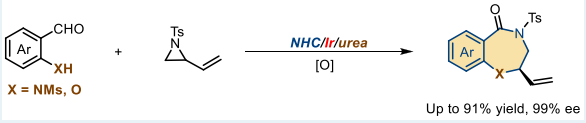
Enantioselective Formal [4 + 3] Annulations to Access Benzodiazepinones and Benzoxazepinones via NHC/Ir/Urea Catalysis

Yang-Yang Li, Shuai Li, Tao Fan, Zi-Jing Zhang, Jin Song,* and Liu-Zhu Gong*

Cite This: *ACS Catal.* 2021, 11, 14388–14394 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

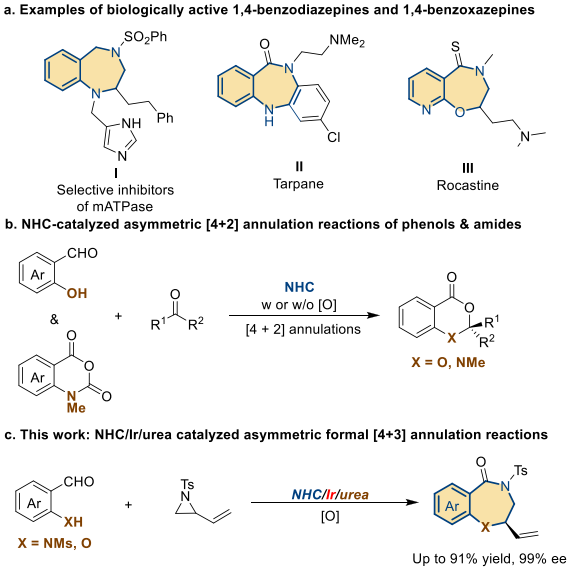
ABSTRACT: A robust and scalable formal [4 + 3] annulation reaction for the synthesis of optically pure 1,4-benzodiazepinones and 1,4-benzoxazepinones has been established by a combined catalytic system consisting of a chiral NHC, a chiral Ir/phosphine-olefin complex, and an achiral urea, enabling the asymmetric synthesis of a selective inhibitor of mitochondrial F_1F_0 ATP hydrolase.



KEYWORDS: *N-heterocyclic carbene, iridium, multicatalysis, formal [4 + 3] annulations, 7-membered heterocycles*

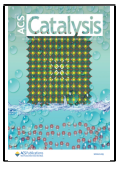
Both 1,4-benzodiazepine and 1,4-benzoxazepine scaffolds containing fused heterocycles are ubiquitous in natural products, bioactive molecules, and pharmaceuticals (Scheme 1a).[1] Indeed, several of these seven-membered heterocycles have been identified as selective inhibitors of mitochondrial F_1F_0 ATP hydrolase (**I**),[2] as well as antihistaminic and antianaphylactic agents (tarpane, **II**).[3] Rocastine (**III**) shows potent antihistaminic activity, and more importantly, its optical isomers with a stereodefined chiral Csp[3] at C-2 show marked differences in the antihistaminic potency.[4] Consequently, the interest associated with the pharmacological activities of 1,4-benzodiazepine and 1,4-benzoxazepine scaffolds justifies a continuation of the work on efficient synthetic methods,[5] and the catalytic enantioselective synthesis of these seven-membered heterocycles remains yet to be discovered.[6]

Scheme 1. Asymmetric Formal [4 + 3] Annulations via NHC/Ir/Urea Catalysis



Chiral N-heterocyclic carbene (NHC) chemistry has emerged as a unique and versatile synthetic toolbox to access a range of enantioenriched heterocyclic systems in a convergent manner.[7] However, NHC-mediated synthetic routes to access 1,4-benzodiazepine or 1,4-benzoxazepine scaffolds in a highly enantioselective fashion remain underexplored.[8] Over the recent years, NHC/metal asymmetric dual catalysis[9] has been recognized as a promising strategy for accessing fundamentally new reactivity and can open up new reaction pathways otherwise inaccessible for conventional reactions.[10] Recently, the Chi group[11] and Scheidt group[12] demonstrated elegant examples of asymmetric [4 + 2] annulation reactions of NHC-activated salicylaldehydes and isatoic anhydrides with reactive ketone substrates (Scheme 1b). The Ye group successfully applied salicylaldehydes as 1,4-dipole synthons in the synthesis of racemic 1,4-benzoxazepinones via NHC/copper-cocatalyzed [4 + 3] annulation reactions.[13] We envisaged that the successful coupling of anthranilaldehydes with chiral metal complex mediated 1,3-dipole electrophiles would provide direct access to the highly valuable seven-membered heterocycles via an asymmetric [4 + 3] annulation reaction. In the past decades, vinyl aziridines[14] have been commonly used as the three-atom component in the

Received: October 2, 2021
Revised: October 30, 2021
Published: November 15, 2021

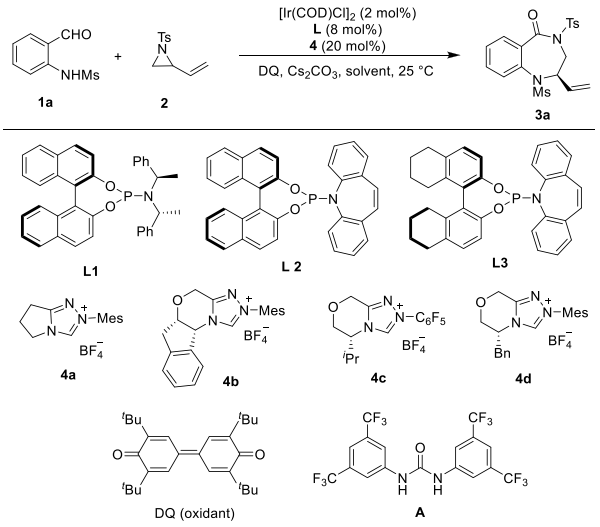


construction of a plentiful family of enantioenriched heterocycles.[15] However, the development of efficient methodologies for the construction of seven-membered chiral skeletons is still rather limited.[16] Herein, we further advance the NHC/TM dual catalysis by demonstrating, for the first time, the NHC/Ir/urea cocatalyzed highly enantioselective formal [4 + 3] annulation reaction of anthranilaldehydes and salicylaldehydes with vinyl aziridines, rapidly assembling enantioenriched seven-membered heterocycles (Scheme 1c).

The reaction of anthranilaldehyde **1a** with vinyl aziridine **2** was initially treated with $[Ir(COD)Cl]_2$ (2 mol %),[15g,16b,17] an achiral triazolium catalyst **4a**, oxidant quinone (DQ),[18] and a range of chiral ligands (**L1**-**L3**) in THF at 25 °C (entries 1−3, Table 1). The use of the phosphine-olefin ligand[19] **L3** resulted in a slightly diminished yield (entry 6 vs 4). A survey of triazolium precatalysts **4** showed no improvement in either yield or selectivity (entries 7 and 8). Subsequently, a brief examination of the organic solvents was carried out (entries 9−11), and dichloromethane (DCM) was found to afford the desired product **3a** with improved yield (80%) and enantioselectivity (97% ee) (entry 11). The control reactions carried out without urea A under the optimized reaction conditions further demonstrate its cocatalytic effect (entry 12).

Under the optimized reaction conditions, the generality of the asymmetric formal [4 + 3] annulation for various substituted anthranilaldehydes was explored (Scheme 2).

Table 1. Optimization of Reaction Conditions[a]

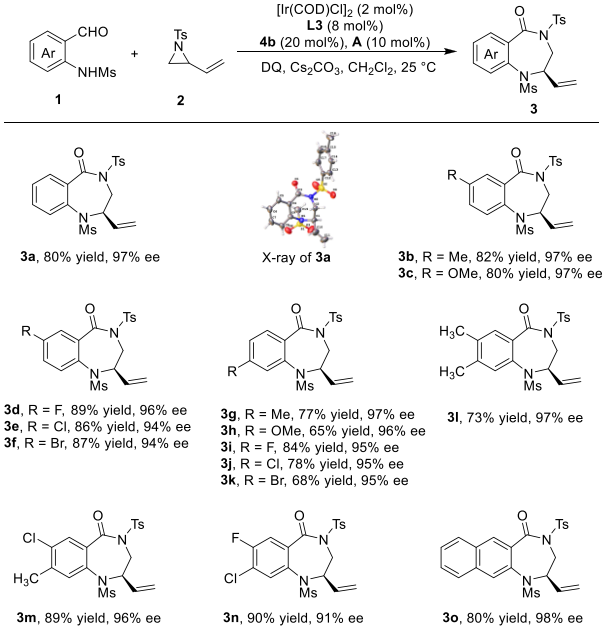


entry	L	4	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	**4a**	THF	<5	
2	**L2**	**4a**	THF	56	55
3	**L3**	**4a**	THF	71	71
4	**L3**	**4b**	THF	57	91
5	**L3**	*ent*-**4b**	THF	40	80
6[d]	**L3**	**4b**	THF	50	94
7[d]	**L3**	**4c**	THF	66	93
8[d]	**L3**	**4d**	THF	66	83
9[d]	**L3**	**4b**	CH_3CN	58	68
10[d]	**L3**	**4b**	toluene	57	87
11[d]	**L3**	**4b**	DCM	80	97
12	**L3**	**4b**	DCM	67	91

[a]Reactions were performed by using $[Ir(COD)Cl]_2$ (2 mol %), **L** (8 mol %), **4** (20 mol %), **1a** (0.1 mmol), **2** (0.2 mmol), DQ (0.11 mmol), and Cs_2CO_3 (0.02 mmol) in solvent (2.0 mL) at 25 °C. [b]Isolated yields after chromatography are shown. [c]The ee values were determined by chiral high-performance liquid chromatography (HPLC) analysis. [d]In the presence of **A** (10 mol %). THF = tetrahydrofuran. DCM = dichloromethane.

enabled the formation of **3a** in 71% yield and with 71% ee (entry 3). The introduction of a chiral triazolium catalyst **4b** further enhanced the enantioselectivity to 91% ee (entry 4), while its enantiomer *ent*-**4b** exerted a mismatched effect along with the chiral ligand **L3** (entry 5). The addition of urea **A**, which has shown cooperative catalytic reactivity with NHC,[11,20−22] provided improved enantioselectivity but

Scheme 2. Substrate Scope[a]



[a]Reactions were performed by using $[Ir(COD)Cl]_2$ (2 mol %), **L3** (8 mol %), **4b** (20 mol %), **A** (10 mol %), **1** (0.1 mmol), **2** (0.2 mmol), DQ (0.11 mmol), and Cs_2CO_3 (0.02 mmol) in CH_2Cl_2 (2.0 mL) at 25 °C. Isolated yields. The ee values were determined by HPLC.

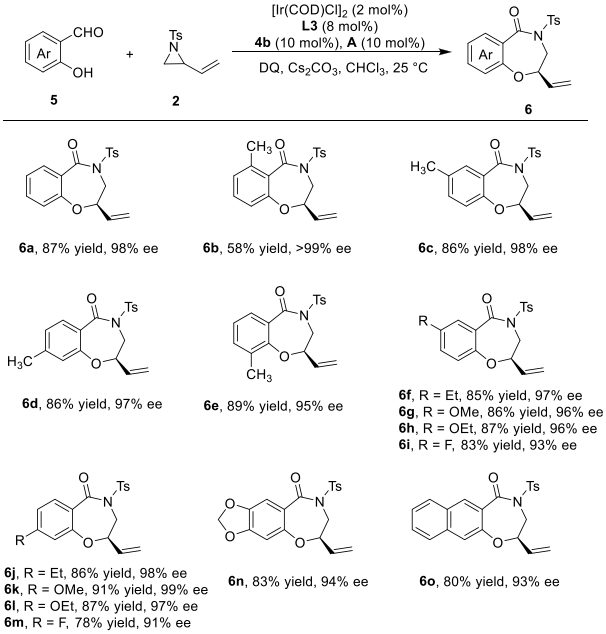
Anthranilaldehydes **1** with substituents at the *meta* position to the carbonyl groups were well tolerated, and the desired products were obtained in great yields and enantioselectivities (**3b** and **3c**). Substrates possessing a halogen substituent at 4-position of the benzene ring underwent the reaction smoothly to provide decent yields and excellent enantioselectivities (**3d**−**3f**). Moreover, the presence of 5-substituent on **1** was also allowed and the desired benzodiazepine derivatives (**3g**−**3k**) were obtained in satisfactory yields of 65−84% and with excellent enantioselectivities (95−97% ee). The reactions of disubstituted anthranilaldehyde substrates also provided products **3l**−**3n** in high yields (73−90%) and excellent levels of stereoselectivity (91%−97% ee). In addition, 3-amino-2-naphthaldehyde participated in a clean reaction to generate **3o** in 80% yield and with 98% ee. The absolute configuration was determined by single-crystal X-ray diffraction analysis of **3a**.[23]

Such NHC/Ir/urea catalytic system is also amenable to the enantioselective synthesis of 1,4-benzoxazepinones via the formal [4 + 3] annulation reaction between salicylaldehydes **5** and vinyl aziridine **2** (see Table S1 in the SI for the detailed condition optimizations). The salicylaldehyde **5a** reacted

https://doi.org/10.1021/acscatal.1c04541
ACS Catal. 2021, 11, 14388−14394

smoothly with vinyl aziridine **2** to afford the desired product **6a** in 87% yield and with 98% ee (Scheme 3). The generality of

Scheme 3. Scope of Salicylaldehydes 5[a]

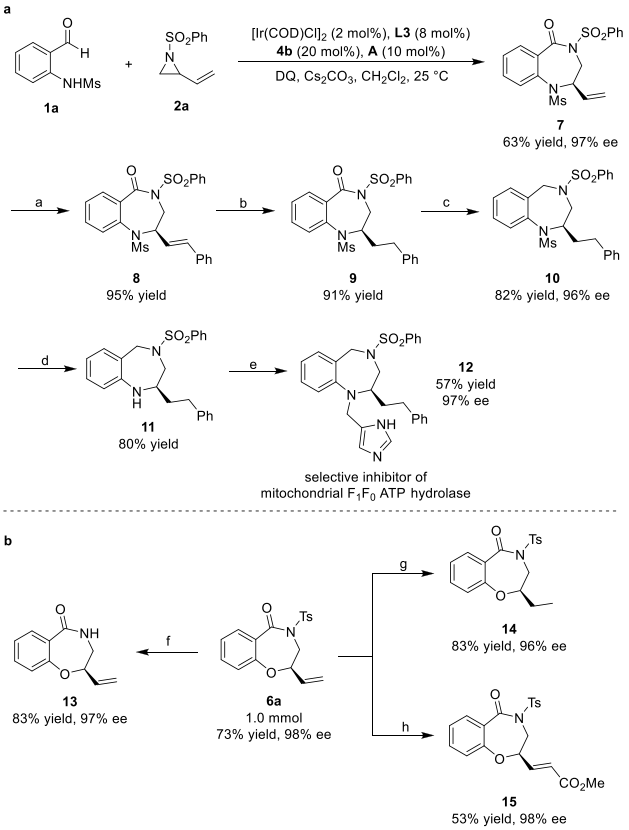


[a]Reactions were performed by using $[Ir(COD)Cl]_2$ (2 mol %), **L3** (8 mol %), **4b** (10 mol %), **A** (10 mol %), **5** (0.1 mmol), **2** (0.15 mmol), DQ (0.11 mmol), and Cs_2CO_3 (0.02 mmol) in $CHCl_3$ (2.0 mL) at 25 °C. Yields of isolated products. The ee values were determined by HPLC.

this procedure for various salicylaldehydes was then explored. The introduction of a methyl group and the variation of substitution pattern were tolerated, and the products **6b**−**6e** were obtained in good yields and enantiomeric excesses. The alternation of electron density of benzene ring by introducing an electronically rich or deficient substituent exerted a considerable effect on the reaction efficiency and stereoselectivity, as indicated by the cases generating **6f**−**6m** (78−91% yields, 91−99% ee). Besides, both 4,5-(methylenebisoxy)-salicylaldehyde and 3-hydroxy-2-naphthaldehyde also delivered good results (**6n** and **6o**).

Further transformations successfully exemplified the synthetic utility of the benzodiazepinones and benzoxazepinones obtained from this reaction (Scheme 4). The asymmetric formal [4 + 3] annulation reaction established was ultimately applied to the asymmetric synthesis of a selective inhibitor of mitochondrial F_1F_0 ATP hydrolase[24] (Scheme 4a). Under the optimized reaction conditions, the annulation of anthranilaldehyde **1a** and vinyl aziridine **2a** gave **7** in 63% yield and with 97% ee. A Heck coupling reaction of **7** and iodobenzene provided the desired product **8** in 95% yield. Subsequent hydrogenation of **8** over Pd/C, and followed by a reduction process with borane-dimethyl sulfide, furnished **10** in decent results (82% yield, 96% ee). A subsequent deprotection of the N-Ms group of **10** was accomplished with Red-Al in toluene, leading to a free amine **11** in 80% yield. Finally, a reductive amination with the imidazolyl aldehyde[24] afforded the selective inhibitor of mitochondrial F_1F_0 ATP hydrolase **12** in 57% yield and with 97% ee.

Scheme 4. Synthetic Utility[a]



[a]Reagents and Conditions: (a) $Pd(OAc)_2$, PhI, NEt_3, CH_3CN, 80 °C, 24 h. (b) Pd/C, H_2 (1 atm), MeOH/DCM, 25 °C, 24 h. (c) $BH_3{\bullet}Me_2S$, THF, 80 °C, 36 h. (d) Red-Al, toluene, 25 °C, 12 h. (e) 1*H*-imidazole-5-carboxaldehyde, $Na(OAc)_3BH$, HOAc, DCE, 25 °C, 48 h. (f) SmI_2, THF, 25 °C, 4 h. (g) Pd/C, H_2 (1 atm), MeOH/DCM, 25 °C, 24 h. (h) Grubbs II, methyl acrylate, DCM, 50 °C, 24 h.

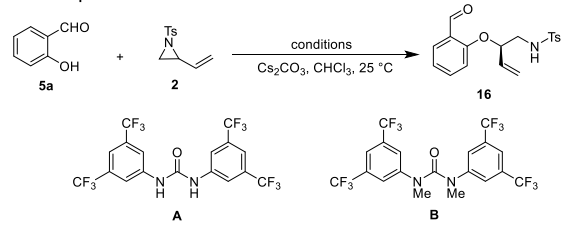
The NHC/Ir/urea-catalyzed formal [4 + 3] annulation is readily scaled up. The reaction of salicylaldehyde **5a** and vinyl aziridine **2** performed on one millimole-scale under standard conditions gave the benzoxazepinone **6a** in 73% yield and with 98% ee (Scheme 4b). The benzoxazepinone **6a** can be converted into various chiral molecules by easily operational reaction conditions as shown in Scheme 4b. For example, the exposure of **6a** to SmI_2 removed the N-Ts protecting group to afford **13** in 83% yield and with 97% ee. Hydrogenation of the C−C double bond in **6a** catalyzed by Pd/C led to an alkyl-substituted product **14**. In addition, the vinyl moiety of **6a** underwent cross-metathesis with methyl acrylate in the presence of the Grubbs II catalyst to generate **15** in 53% yield and with maintained ee values.

A preliminary mechanistic study was carried out to shed light on the reaction pathway and active catalytic species (Table 2). In monitoring the reaction of salicylaldehyde **5a** with vinyl aziridine **2** under the standard reaction conditions shown in Scheme 3, the rapid formation of *O*-allylation product **16** accompanied by the disappearance of the starting materials was observed in a few minutes, and the aldehyde **16** was then smoothly transformed to product **6a** in the following 3 h. Accordingly, we speculated that the formal [4 + 3] annulation reaction might proceed through a relay catalytic pathway. Thus, we carried out some control experiments to investigate the stereocontrol elements in the iridium catalyzed

https://doi.org/10.1021/acscatal.1c04541
ACS Catal. 2021, 11, 14388−14394

Table 2. Mechanistic Studies[a]

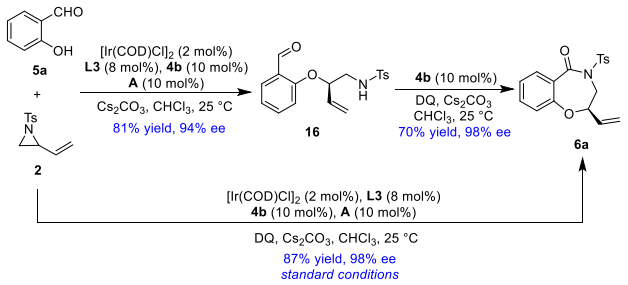
a. Control experiments[a]



entry	conditions	yield (%)	ee (%)
1	$[Ir(COD)Cl]_2$ (2 mol%), **L3** (8 mol%)	70	47
2	$[Ir(COD)Cl]_2$ (2 mol%), **L3** (8 mol%), **4b** (10 mol%)	80	64
3	$[Ir(COD)Cl]_2$ (2 mol%), **L3** (8 mol%), **4b** (10 mol%), **A** (10 mol%)	81	94
4	$[Ir(COD)Cl]_2$ (2 mol%), **L3** (8 mol%), **4b** (10 mol%), **B** (10 mol%)	82	66

[a]Yields of isolated products **16**. The ee values were determined by HPLC.

b. Stepwise experiments:



[a]Yields of isolated products **16**. The ee values were determined by HPLC.

intermolecular allylic etherification reaction[25,26] of salicylaldehyde **5a** with aziridine **2**, which is the initial step in the relay catalytic pathway (Table 2a). In the presence of $[Ir(COD)Cl]_2$ (2 mol %) and **L3** (8 mol %), the aldehyde **16** was afforded with moderate enantioselectivity of 47% ee (entry 1, Table 2a). The stereoselectivity was improved to 64% ee upon the addition of 10 mol % of NHC **4b** (entry 2), suggesting that the NHC could enhance the catalytic performance of the iridium species by serving as an activating ligand.[27,28] As such, a hybrid [Ir(**L3**)(**4b**)] species[10h,29] was prompted to form (detected by ESI-MS spectroscopy, see SI, Figure S1) and responsible for the stereocontrol. Interestingly, the stereocontrol could be further improved by adding catalytic amounts of urea **A** (entry 3), whereas the use of methylated urea **B** to supersede **A** under the otherwise identical conditions gave results similar to those without urea additive (entry 4 vs 2), suggesting that the free NH group of the urea **A** might get involved in noncovalent interactions to benefit stereochemical control.[11,20−22] Next, we performed the oxidation annulation of the chiral aldehyde intermediate **16** with 94% ee under the catalysis of NHC **4b** (Table 2b), and the 1,4-benzoxazepinone **6a** was obtained in 70% yield and 98% ee. The enhancement in enantioselectivity (from 94% ee to 98% ee) can be explained by the kinetic resolution process[30] that exists in the chiral NHC-mediated oxidative lactamization event (see Table S3 in SI). The similar results obtained from the one-pot reaction and the stepwise addition (**6a** in Scheme 3 vs Table 2b) lead to a conclusion that the reaction proceeds through a relay catalytic pathway.

On the basis of the experimental results, a plausible catalytic cycle for the formal [4 + 3] annulation reaction is described in Figure 1. Initially, vinyl aziridine **2** coordinates with [Ir(I)]* complex and undergoes oxidative addition to furnish the (η^3-allyl)iridium(III) species **I**. The asymmetric allylic etherification of intermediate **I** with salicylaldehyde **5a** gives adduct **16** as a key intermediate. Subsequently, the addition of NHC to aldehyde **16** delivers the Breslow intermediate **II**, which is oxidized by bisquinone (DQ) to afford the acyl azolium intermediate **III**. The intermolecular lactamization of the intermediate **III** finally leads to the formal [4 + 3] annulation product **6a** and regenerates the NHC catalyst.

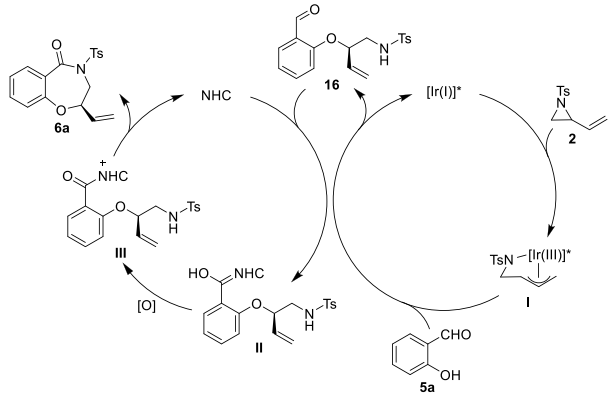


Figure 1. Proposed catalytic cycle.

In summary, we have established an efficient synthesis of highly enantioenriched 1,4-benzodiazepinones and 1,4-benzoxazepinones by NHC/Ir/urea cocatalyzed formal [4 + 3] annulation reaction. The integrated action of the chiral NHC, the chiral Ir/phosphine-olefin complex, and the achiral urea enables excellent stereochemical control. The NHC catalyst serves not only as a chiral ligand of the iridium to tune the catalytic performance but also as an organocatalyst of the asymmetric oxidative lactamization event. The achiral urea cocatalyst also works cooperatively with an iridium catalyst to facilitate the control of stereoselectivity. The utility of this methodology has been demonstrated in the context of catalytic asymmetric synthesis of a selective inhibitor of mitochondrial F_1F_0 ATP hydrolase and flexible modulation of the benzodiazepinone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c04541.

General information, experimental section, compound characterization, and NMR spectra (PDF)

X-ray data for **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

Liu-Zhu Gong − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China; Center for Excellence in Molecular Synthesis of Chinese Academy of Sciences, Hefei 230026, China;* orcid.org/0000-0001-6099-827X; Email: gonglz@ustc.edu.cn

Jin Song − *Institutes of Physical Science and Information Technology, Anhui University, Hefei 230601, China;* orcid.org/0000-0003-0449-1727; Email: jill@ahu.edu.cn

https://doi.org/10.1021/acscatal.1c04541
ACS Catal. 2021, 11, 14388−14394

Authors

Yang-Yang Li − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China*

Shuai Li − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China*

Tao Fan − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China*

Zi-Jing Zhang − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.1c04541

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (grant nos. 21831007 and 22071229), and the Fundamental Research Funds for the Central Universities (WK2060190083).

■ REFERENCES

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures. *Chem. Rev.* **2003**, *103*, 893. (b) Gill, R. K.; Kaushik, S. O.; Chugh, J.; Bansal, S.; Shah, A.; Bariwal, J. Recent Development in [1,4]Benzodiazepines as Potent Anticancer Agents:A Review. *Mini-Rev. Med. Chem.* **2014**, *14*, 229. (c) Kaur, M.; Garg, S.; Malhi, D. S.; Sohal, H. S. A Review on Synthesis, Reactions and Biological Properties of Seven Membered Heterocyclic Compounds: Azepine, Azepane, Azepinone. *Curr. Org. Chem.* **2021**, *25*, 449.

(2) Hamann, L. G.; Ding, C. Z.; Miller, A. V.; Madsen, C. S.; Wang, P.; Stein, P. D.; Pudzianowski, A. T.; Green, D. W.; Monshizadegan, H.; Atwal, K. S. Benzodiazepine-based Selective Inhibitors of Mitochondrial F_1F_0 ATP Hydrolase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1031.

(3) Hunziker, F.; Lauener, H.; Smutz, J. Zur Chemie und Pharmakologie von in 10-Stellung basisch substituierten 5-Dibenzo-[b, e][1,4J-diazepin-Derivaten. *Arzneim.-Forsch.* **1963**, *13*, 324.

(4) Sleevi, M. C.; Cale, A. D.; Gero, T. W.; Jaques, L. W.; Welstead, W. J.; Johnson, A. F.; Kilpatrick, B. F.; Demian, I.; Nolan, J. C.; Jenkins, H. Optical Isomers of Rocastine and Close Analogues: Synthesis and H1 Antihistaminic Activity of Its Enantiomers and Their Structural Relationship to the Classical Antihistamines. *J. Med. Chem.* **1991**, *34*, 1314.

(5) (a) Kaur, N.; Kishore, D. Synthetic Strategies Applicable in the Synthesis of Privileged Scaffold: 1,4-Benzodiazepine. *Synth. Commun.* **2014**, *44*, 1375. (b) Lévai, A. Synthesis and Chemical Transformations of 1,4-, 4,1-, and 1,5-Benzoxazepines. *J. Heterocycl. Chem.* **2001**, *38*, 1011.

(6) (a) Pan, B.; Ouyang, J.-S.; Zhang, Y.; Liang, H.; Ni, Q.; Chen, B.; Pu, X.; Jiang, L.; Cao, R.; Qiu, L. Iridium-catalyzed Intramolecular Asymmetric Allylic Etherification of Salicylic Acid Derivatives with Chiral-bridged Biphenyl Phosphoramidite Ligands. *Org. Chem. Front.* **2021**, *8*, 4514. (b) Velasco-Rubio, Á.; Bernárdez, R.; Varela, J. A.; Saá, C. Enantioenriched α-Vinyl 1,4-Benzodiazepines and 1,4-Benzoxazepines via Enantioselective Rhodium-Catalyzed Hydrofunctionalizations of Alkynes and Allenes. *J. Org. Chem.* **2021**, *86*, 10889. (c) Jiang, X.; Pan, B.; Qian, X.; Liang, H.; Zhang, Y.; Chen, B.; He, X.; Chan, H. S.; Chan, A. S. C.; Qiu, L. Enantioselective Construction of Pyrimidine-Fused Diazepinone Derivatives Bearing a Tertiary Stereogenic Center Enabled by Iridium-Catalysed Intramolecular Allylic Substitution. *Adv. Synth. Catal.* **2021**, *363*, 3227.

(7) For selected reviews, 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 Organocatalysts. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. A Continuum of Progress: Applications of N-Hetereocyclic Carbene Catalysis in Total Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. (d) Vora, H. U.; Wheeler, P.; Rovis, T. Exploiting Acyl and Enol Azolium Intermediates via N-Heterocyclic Carbene-Catalyzed Reactions of α-Reducible Aldehydes. *Adv. Synth. Catal.* **2012**, *354*, 1617. (e) Bugaut, X.; Glorius, F. Organocatalytic Umpolung: N-heterocyclic Carbenes and Beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511. (f) Ryan, S. J.; Candish, L.; Lupton, D. W. Acyl Anion Free N-heterocyclic Carbene Organocatalysis. *Chem. Soc. Rev.* **2013**, *42*, 4906. (g) Bode, J. W. An internal affair. *Nat. Chem.* **2013**, *5*, 813. (h) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-heterocyclic Carbenes. *Nature* **2014**, *510*, 485. (i) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307. (j) Yetra, S. R.; Patra, A.; Biju, A. T. Recent Advances in the N-Heterocyclic Carbene (NHC)-Organocatalyzed Stetter Reaction and Related Chemistry. *Synthesis* **2015**, *47*, 1357. (k) Mondal, S.; Yetra, S. R.; Mukherjee, S.; Biju, A. T. NHC-Catalyzed Generation of α,β-Unsaturated Acylazoliums for the Enantioselective Synthesis of Heterocycles and Carbocycles. *Acc. Chem. Res.* **2019**, *52*, 425. (l) Chen, X.; Wang, H.; Jin, Z.; Chi, Y. R. N-Heterocyclic Carbene Organocatalysis: Activation Modes and Typical Reactive Intermediates. *Chin. J. Chem.* **2020**, *38*, 1167.

(8) (a) Izquierdo, J.; Orue, A.; Scheidt, K. A. A Dual Lewis Base Activation Strategy for Enantioselective Carbene-Catalyzed Annulations. *J. Am. Chem. Soc.* **2013**, *135*, 10634. (b) Lv, H.; Jia, W. Q.; Sun, L. H.; Ye, S. N-Heterocyclic Carbene Catalyzed [4 + 3] Annulation of Enals and o-Quinone Methides: Highly Enantioselective Synthesis of Benzo-ε-Lactones. *Angew. Chem., Int. Ed.* **2013**, *52*, 8607. (c) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. N-Heterocyclic Carbene-Catalyzed [3 + 4] Cycloaddition and Kinetic Resolution of Azomethine Imines. *J. Am. Chem. Soc.* **2014**, *136*, 1214. (d) Guo, C.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. N-Heterocyclic Carbene Catalyzed Switchable Reactions of Enals with Azoalkenes: Formal [4 + 3] and [4 + 1] Annulations for the Synthesis of 1,2-Diazepines and Pyrazoles. *J. Am. Chem. Soc.* **2014**, *136*, 17402. (e) Wang, M.; Rong, Z.-Q.; Zhao, Y. Stereoselective Synthesis of ε-lactones or Spiro-Heterocycles through NHC-catalyzed Annulation: Divergent Reactivity by Catalyst Control. *Chem. Commun.* **2014**, *50*, 15309. (f) Liang, Z. Q.; Yi, L.; Chen, K. Q.; Ye, S. N-Heterocyclic Carbene-Catalyzed [3 + 4] Annulation of Enals and Alkenyl Thiazolones: Enantioselective Synthesis of Thiazole-Fused ε-Lactones. *J. Org. Chem.* **2016**, *81*, 4841. (g) Wu, Z.; Wang, J. Enantioselective Medium-Ring Lactone Synthesis through an NHC-Catalyzed Intramolecular Desymmetrization of Prochiral 1,3-Diols. *ACS Catal.* **2017**, *7*, 7647. (h) Fang, C.; Lu, T.; Zhu, J.; Sun, K.; Du, D. Formal [3 + 4] Annulation of α,β-Unsaturated Acyl Azoliums: Access to Enantioenriched N-H-Free 1,5-Benzothiazepines. *Org. Lett.* **2017**, *19*, 3470. (i) Lang, M.; Wang, J. N-Heterocyclic Carbene-Catalyzed Enantioselective β-Amination of α-Bromoenals Enabled by a Proton-Shuttling Strategy. *Eur. J. Org. Chem.* **2018**, *2018*, 2958. (j) Lu, S.; Ong, J.-Y.; Yang, H.; Poh, S. B.; Liew, X.; Seow, C. S. D.; Wong, M. W.; Zhao, Y. Diastereo- and Atroposelective Synthesis of Bridged Biaryls Bearing an Eight-Membered Lactone through an Organocatalytic Cascade. *J. Am. Chem. Soc.* **2019**, *141*, 17062. (k) Chen, K. Q.; Gao, Z. H.; Ye, S. Bifunctional N-heterocyclic Carbene Catalyzed [3 + 4] Annulation of Enals with Azadienes: Enantioselective Synthesis of Benzofuroazepinones. *Org. Chem. Front.* **2019**, *6*, 405. (l) Wu, X.; Zhou, L.; Maiti, R.; Mou, C.; Pan, L.; Chi, Y. R. Sulfinate and Carbene Co-catalyzed Rauhut-Currier Reaction for Enantioselective Access to Azepino[1,2-a]indoles. *Angew. Chem., Int. Ed.* **2019**, *58*, 477.

(9) (a) Wang, M. H.; Scheidt, K. A. Cooperative Catalysis and Activation with N-Heterocyclic Carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912. (b) Lu, H.; Liu, J.-Y.; Li, H.-Y.; Xu, P.-F. Recent Developments in N-Heterocyclic Carbene and Transition-Metal Cooperative Catalysis. *Huaxue Xuebao* **2018**, *76*, 831. (c) Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene (NHC)/Metal Cooperative Catalysis. *Top. Curr. Chem.* **2019**, *377*, 35.

(10) (a) DiRocco, D. A.; Rovis, T. Catalytic Asymmetric α-Acylation of Tertiary Amines Mediated by a Dual Catalysis Mode: N-Heterocyclic Carbene and Photoredox Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 8094. (b) Namitharan, K.; Zhu, T.; Cheng, J.; Zheng, P.; Li, X.; Yang, S.; Song, B.-A.; Chi, Y. R. Metal and Carbene Organocatalytic Relay Activation of Alkynes for Stereoselective Reactions. *Nat. Commun.* **2014**, *5*, 3982. (c) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. Cooperative N-Heterocyclic Carbene/Palladium-Catalyzed Enantioselective Umpolung Annulations. *J. Am. Chem. Soc.* **2016**, *138*, 7840. (d) Guo, C.; Janssen-Müller, D.; Fleige, M.; Lerchen, A.; Daniliuc, C. G.; Glorius, F. Mechanistic Studies on a Cooperative NHC Organocatalysis/Palladium Catalysis System: Uncovering Significant Lessons for Mixed Chiral Pd(NHC)(PR_3) Catalyst Design. *J. Am. Chem. Soc.* **2017**, *139*, 4443. (e) Chen, J.; Yuan, P.; Wang, L.; Huang, Y. Enantioselective β-Protonation of Enals via a Shuttling Strategy. *J. Am. Chem. Soc.* **2017**, *139*, 7045. (f) 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. (g) Zhang, Z.-J.; Zhang, L.; Geng, R.-L.; Song, J.; Chen, X.-H.; Gong, L.-Z. N-Heterocyclic Carbene/Copper Cooperative Catalysis for the Asymmetric Synthesis of Spirooxindoles. *Angew. Chem., Int. Ed.* **2019**, *58*, 12190. (h) Singha, S.; Serrano, E.; Mondal, S.; Daniliuc, C. G.; Glorius, F. Diastereodivergent Synthesis of Enantioenriched α,β-Disubstituted γ-Butyrolactones via Cooperative N-Heterocyclic Carbene and Ir Catalysis. *Nat. Catal.* **2020**, *3*, 48. (i) Zhou, L.; Wu, X.; Yang, X.; Mou, C.; Song, R.; Yu, S.; Chai, H.; Pan, L.; Jin, Z.; Chi, Y. R. Gold and Carbene Relay Catalytic Enantioselective Cycloisomerization/Cyclization Reactions of Ynamides and Enals. *Angew. Chem., Int. Ed.* **2020**, *59*, 1557. (j) Zhang, Z.-J.; Wen, Y.-H.; Song, J.; Gong, L.-Z. Kinetic Resolution of Aziridines Enabled by N-Heterocyclic Carbene/Copper Cooperative Catalysis: Carbene Dose-Controlled Chemo-Switchability. *Angew. Chem., Int. Ed.* **2021**, *60*, 3268. (k) Zhang, J.; Gao, Y.-S.; Gu, B.-M.; Yang, W.-L.; Tian, B.-X.; Deng, W.-P. Cooperative N-Heterocyclic Carbene and Iridium Catalysis Enables Stereoselective and Regiodivergent [3 + 2] and [3 + 3] Annulation Reactions. *ACS Catal.* **2021**, *11*, 3810.

(11) Chen, X.; 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.

(12) Lee, A.; Zhu, J. L.; Feoktistova, T.; Brueckner, A. C.; Cheong, P.; Scheidt, K. A. Carbene-Catalyzed Enantioselective Decarboxylative Annulations to Access Dihydrobenzoxazinones and Quinolones. *Angew. Chem., Int. Ed.* **2019**, *58*, 5941.

(13) Han, Y.-F.; Gao, Z.-H.; Zhang, C.-L.; Ye, S. NHC/Copper-Cocatalyzed [4 + 3] Annulations of Salicylaldehydes with Aziridines for the Synthesis of 1,4-Benzoxazepinones. *Org. Lett.* **2020**, *22*, 8396.

(14) (a) For a book and reviews, see: Ohno, H. In *Aziridines and Epoxides in Asymmetric Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 2, p 37. (b) Ohno, H. Synthesis and Applications of Vinylaziridines and Ethynylaziridines. *Chem. Rev.* **2014**, *114*, 7784. (c) Wu, Y.; Zhou, X.; Xiao, W.; Chen, J. Recent Progress in Applications of Vinylaziridines in Organic Synthesis. *Youji Huaxue* **2020**, *40*, 3760.

(15) For selected examples, see: (a) Trost, B. M.; Fandrick, D. R. Dynamic Kinetic Asymmetric Cycloadditions of Isocyanates to Vinylaziridines. *J. Am. Chem. Soc.* **2003**, *125*, 11836. (b) Trost, B. M.; Osipov, M.; Dong, G. Palladium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Vinyl Aziridines with Nitrogen Heterocycles: Rapid Access to Biologically Active Pyrroles and Indoles. *J. Am. Chem. Soc.* **2010**, *132*, 15800. (c) Xu, C.-F.; Zheng, B.-H.; Suo, J.-J.; Ding, C.-H.; Hou, X.-L. Highly Diastereo- and Enantioselective Palladium-Catalyzed [3 + 2] Cycloaddition of Vinyl Aziridines and α,β-Unsaturated Ketones. *Angew. Chem., Int. Ed.* **2015**, *54*, 1604. (d) Li, T.-R.; Cheng, B.-Y.; Fan, S.-Q.; Wang, Y.-N.; Lu, L.-Q.; Xiao, W.-J. Highly Stereoselective [3 + 2] Cycloadditions of Chiral Palladium-Containing N^1-1,3-Dipoles: A Divergent Approach to Enantioenriched Spirooxindoles. *Chem. - Eur. J.* **2016**, *22*, 6243. (e) Næsborg, L.; Tur, F.; Meazza, M.; Blom, J.; Halskov, K. S.; Jørgensen, K. A. Synergistic Catalysis for the Asymmetric [3 + 2] Cycloaddition of Vinyl Aziridines with α,β-Unsaturated Aldehydes. *Chem. - Eur. J.* **2017**, *23*, 268. (f) Suo, J.-J.; Liu, W.; Du, J.; Ding, C.-H.; Hou, X.-L. Diastereo- and Enantioselective Palladium-Catalyzed Dearomative [3 + 2] Cycloaddition of 3-Nitroindoles. *Chem. - Asian J.* **2018**, *13*, 959. (g) Chen, Z.-C.; Chen, Z.; Yang, Z.-H.; Guo, L.; Du, W.; Chen, Y.-C. Cooperative Tertiary Amine/Chiral Iridium Complex Catalyzed Asymmetric 4 + 3 and 3 + 3 Annulation Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 15021.

(16) (a) Zhu, C.-Z.; Feng, J.-J.; Zhang, J. Rhodium(I)-Catalyzed Intermolecular Aza-[4 + 3] Cycloaddition of Vinyl Aziridines and Dienes: Atom-Economical Synthesis of Enantiomerically Enriched Functionalized Azepines. *Angew. Chem., Int. Ed.* **2017**, *56*, 1351. (b) Jiang, F.; Yuan, F.-R.; Jin, L.-W.; Mei, G.-J.; Shi, F. Metal-Catalyzed (4 + 3) Cyclization of Vinyl Aziridines with para-Quinone Methide Derivatives. *ACS Catal.* **2018**, *8*, 10234.

(17) (a) Wang, G.; Franke, J.; Ngo, C. Q.; Krische, M. J. Diastereo- and Enantioselective Iridium Catalyzed Coupling of Vinyl Aziridines with Alcohols: Site-Selective Modification of Unprotected Diols and Synthesis of Substituted Piperidines. *J. Am. Chem. Soc.* **2015**, *137*, 7915. (b) Lin, T.-Y.; Wu, H.-H.; Feng, J.-J.; Zhang, J. Divergent Access to Functionalized Pyrrolidines and Pyrrolines via Iridium-Catalyzed Domino-Ring-Opening Cyclization of Vinyl Aziridines with β-Ketocarbonyls. *Org. Lett.* **2017**, *19*, 6526.

(18) De Sarkar, S.; Studer, A. NHC-Catalyzed Michael Addition to α,β-Unsaturated Aldehydes by Redox Activation. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266.

(19) (a) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. Iridium-Catalyzed Synthesis of Primary Allylic Amines from Allylic Alcohols: Sulfamic Acid as Ammonia Equivalent. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (b) Rössler, S. L.; Petrone, D. A.; Carreira, E. M. Iridium-Catalyzed Asymmetric Synthesis of Functionally Rich Molecules Enabled by (Phosphoramidite, Olefin) Ligands. *Acc. Chem. Res.* **2019**, *52*, 2657.

(20) (a) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107*, 5713. (b) Hong, L.; Sun, W.; Yang, D.; Li, G.; Wang, R. Additive Effects on Asymmetric Catalysis. *Chem. Rev.* **2016**, *116*, 4006.

(21) (a) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. Direct Nucleophilic Acylation of Nitroalkenes Promoted by a Fluoride Anion/Thiourea Combination. *J. Am. Chem. Soc.* **2006**, *128*, 4932. (b) Jin, Z.; Xu, J.; Yang, S.; Song, B.-A.; Chi, Y. R. Enantioselective Sulfonation of Enones with Sulfonyl Imines by Cooperative N-Heterocyclic-Carbene/Thiourea/Tertiary-Amine Multicatalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 12354. (c) Youn, S. W.; Song, H. S.; Park, J. H. Asymmetric Domino Multicatalysis for the Synthesis of 3-Substituted Phthalides: Cinchonine/NHC Cooperative System. *Org. Lett.* **2014**, *16*, 1028. (d) Wang, M. H.; Cohen, D. T.; Schwamb, C. B.; Mishra, R. K.; Scheidt, K. A. Enantioselective β-Protonation by a Cooperative Catalysis Strategy. *J. Am. Chem. Soc.* **2015**, *137*, 5891. (e) Murauski, K. J. R.; Walden, D. M.; Cheong, P. H.-Y.; Scheidt, K. A. A Cooperative Ternary Catalysis System for Asymmetric Lactonizations of α-Ketoesters. *Adv. Synth. Catal.* **2017**, *359*, 3713. (f) Liu, Y.; Luo, G.; Yang, X.; Jiang, S.; Xue, W.; Chi, Y. R.; Jin, Z. Carbene-Catalyzed Enantioselective Aromatic N-Nucleophilic Addition of Heteroarenes to Ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 442.

(22) Gao, J.; Zhang, J.; Fang, S.; Feng, J.; Lu, T.; Du, D. Synergistic N-Heterocyclic Carbene/Palladium-Catalyzed [3 + 2] Annulation of

https://doi.org/10.1021/acscatal.1c04541
ACS Catal. 2021, 11, 14388−14394

Vinyl Enolates with 1-Tosyl-2-vinylaziridine. *Org. Lett.* **2020**, *22*, 7725.
(23) **3a**: CCDC 2109677. See the Supporting Information for details.
(24) Hamann, L. G.; Ding, C. Z.; Miller, A. V.; Madsen, C. S.; Wang, P.; Stein, P. D.; Pudzianowski, A. T.; Green, D. W.; Monshizadegan, H.; Atwal, K. S. Benzodiazepine-Based Selective Inhibitors of Mitochondrial F_1F_0 ATP Hydrolase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1031.
(25) For reviews, see: (a) Hartwig, J. F.; Stanley, L. M. Mechanistically Driven Development of Iridium Catalysts for Asymmetric Allylic Substitution. *Acc. Chem. Res.* **2010**, *43*, 1461. (b) Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Iridium-Catalyzed Diastereo-, Enantio-, and Regioselective Allylic Alkylation with Prochiral Enolates. *ACS Catal.* **2016**, *6*, 6207. (c) Qu, J.; Helmchen, G. Applications of Iridium-Catalyzed Asymmetric Allylic Substitution Reactions in Target-Oriented Synthesis. *Acc. Chem. Res.* **2017**, *50*, 2539. (d) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855.
(26) For selected examples, see: (a) López, F.; Ohmura, T.; Hartwig, J. F. Regio- and Enantioselective Iridium-Catalyzed Intermolecular Allylic Etherification of Achiral Allylic Carbonates with Phenoxides. *J. Am. Chem. Soc.* **2003**, *125*, 3426. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. Readily Available [2.2.2]-Bicyclooctadienes as New Chiral Ligands for Ir(I): Catalytic, Kinetic Resolution of Allyl Carbonates. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (c) Stanley, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. Iridium-Catalyzed Kinetic Asymmetric Transformations of Racemic Allylic Benzoates. *J. Am. Chem. Soc.* **2010**, *132*, 8918.
(27) (a) For a book, see: *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer, Heidelberg, 2007. (b) For reviews, see: César, V.; Bellemin-Laponnaz, S.; Gade, L. H. Chiral N-Heterocyclic Carbenes as Stereodirecting Ligands in Asymmetric Catalysis. *Chem. Soc. Rev.* **2004**, *33*, 619. (c) Díez-González, S.; Marion, N.; Nolan, S. P. N-Heterocyclic Carbenes in Late Transition Metal Catalysis. *Chem. Rev.* **2009**, *109*, 3612. (d) Fortman, G. C.; Nolan, S. P. N-Heterocyclic Carbene (NHC) Ligands and Palladium in Homogeneous Cross-Coupling Catalysis: A Perfect Union. *Chem. Soc. Rev.* **2011**, *40*, 5151. (e) Iglesias, M.; Oro, L. A. A Leap Forward in Iridium-NHC Catalysis: New Horizons and Mechanistic Insights. *Chem. Soc. Rev.* **2018**, *47*, 2772. (f) Sipos, G.; Dorta, R. Iridium Complexes with Monodentate N-Heterocyclic Carbene Ligands. *Coord. Chem. Rev.* **2018**, *375*, 13.
(28) (a) Ye, K.-Y.; Cheng, Q.; Zhuo, C.-X.; Dai, L.-X.; You, S.-L. An Iridium(I) N-Heterocyclic Carbene Complex Catalyzes Asymmetric Intramolecular Allylic Amination Reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 8113. (b) Yang, Z.-P.; Jiang, R.; Zheng, C.; You, S.-L. Iridium-Catalyzed Intramolecular Asymmetric Allylic Alkylation of Hydroxyquinolines: Simultaneous Weakening of the Aromaticity of Two Consecutive Aromatic Rings. *J. Am. Chem. Soc.* **2018**, *140*, 3114. (c) Bao, C.-C.; Zheng, D.-S.; Zhang, X.; You, S.-L. Iridium/N-Heterocyclic Carbene Complex-Catalyzed Intermolecular Allylic Alkylation Reaction. *Organometallics* **2018**, *37*, 4763.
(29) (a) Reetz, M. T. Combinatorial Transition-Metal Catalysis: Mixing Monodentate Ligands to Control Enantio-, Diastereo-, and Regioselectivity. *Angew. Chem., Int. Ed.* **2008**, *47*, 2556. (b) Ding, K. Synergistic Effect of Binary Component Ligands in Chiral Catalyst Library Engineering for Enantioselective Reactions. *Chem. Commun.* **2008**, 909.
(30) For a review, see: (a) De Risi, C.; Bortolini, O.; Di Carmine, G.; Ragno, D.; Massi, A. Kinetic Resolution, Dynamic Kinetic Resolution and Asymmetric Desymmetrization by N-Heterocyclic Carbene Catalysis. *Synthesis* **2019**, *51*, 1871. (b) For selected examples, see: Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. Enantioselective Synthesis of cis-4-Formyl-β-lactams via Chiral N-Heterocyclic Carbene-Catalyzed Kinetic Resolution. *Adv. Synth. Catal.* **2008**, *350*, 1258. (c) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. Catalytic Kinetic Resolution of Cyclic Secondary Amines. *J. Am. Chem. Soc.* **2011**, *133*, 19698.

https://doi.org/10.1021/acscatal.1c04541
ACS Catal. 2021, 11, 14388−14394