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Authors: Liuzhu Gong, Zi-Jing Zhang, Yu-Hua Wen, and Jin Song

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Kinetic Resolution of Aziridines Enabled by N-Heterocyclic Carbene/Copper Cooperative Catalysis: Carbene Dose-Controlled Chemo-Switchability

Zi-Jing Zhang, Yu-Hua Wen, Jin Song,* and Liu-Zhu Gong*

Abstract: Asymmetric methods that convert racemic starting materials to enantioenriched products are inherently significant in chemical synthesis. Catalytic kinetic resolution (KR) and dynamic kinetic asymmetric transformation (DyKAT) are alternative and complementary avenues to access chiral stereoisomers of both starting materials and reaction products. The development of highly efficient chiral catalytic systems for kinetically controlled processes has therefore been one of the linchpins in asymmetric synthesis. N-Heterocyclic carbene (NHC)/copper cooperative catalysis has enabled highly efficient KR and DyKAT of racemic *N*-tosylaziridines via [3 + 3] annulation with isatin-derived enals, leading to highly enantioenriched *N*-tosylaziridine derivatives (up to >99% e.e.) and a large library of spirooxindole derivatives with high structural diversity and stereoselectivity (up to >95:5 d.r., >99% e.e.). Mechanistic studies suggest that NHC can bind reversibly to the copper catalyst without compromising its catalytic activity and regulate the catalytic activity of the copper complex to switch the chemoselection between KR and DyKAT.

Introduction

Catalytic asymmetric synthesis of optically pure compounds is increasingly in demand in the pharmaceutical, fine chemicals, and agricultural industries.[1] Catalytic kinetic resolution (KR)[2] and dynamic kinetic asymmetric transformation (DyKAT)[3] of racemic mixtures are two alternative strategies to access enantioenriched chiral molecules (Figure 1a). In the KR process, the chiral catalyst preferentially accelerates the reaction of one enantiomeric reagent (S_R) over the other (S_S), with a theoretical maximum 50% yield of the desired product (P_R) and the reserved enantiomer (S_S).[2] DyKAT involves a chiral catalyst-mediated racemization of substrate enantiomers (S_R and S_S) and the catalytic transformation of a racemic starting material into a single enantioenriched product (P_R), with 100% theoretical yield.[3] Thus, the discovery of robust chiral catalyst systems for KR and DyKAT to access enantiopure chiral adducts is of great importance in terms of skeletal and stereochemical diversity.

N-Heterocyclic carbene (NHC) catalysis has been met with great success in the past few decades.[4] The integration of metal catalysis with NHC catalysis can achieve extra activation modes, allowing unprecedented chemical reactions to ensue.[5] One of the core issues of concern lies in the research on coordination events between NHCs and metals (Figure 1b).[4d,6] Successful cooperative catalysis of NHCs and hard Lewis acids,[7] such as early transition metals, alkali and alkaline-earth metals, can be achieved as a result of their weak interactions. On the other hand, in the case of combining NHCs with late transition metals,[8] the generation of NHC-ligated metal complexes ([M]·NHC) is unavoidable due to their strong interactions[4d] and would quench the catalytic activity of the individual catalyst. As such, a switchable interaction between NHCs and transition metals has proven difficult to achieve, and active catalyst switching between 'on' and 'off' states through a 'releasing/binding' event between NHCs and metals has rarely been realized.

Aziridines are featured in many biologically active molecules, natural products, and pharmaceuticals[9] and have therefore stimulated great interest in catalytic asymmetric synthesis.[10] Due to their unique and strained core structure, aziridines can also serve as versatile chiral building blocks for the construction of synthetically and biologically significant nitrogenous compounds.[11] In this context, the development of straightforward methods that permit the conversion of racemic aziridines to enantioenriched amine products is highly desirable.[12] Regiodivergent KR,[13] reductive cross-coupling,[14] and DyKAT[15] of racemic styrenyl aziridines via enantioselective ring-opening or annulation with various nucleophiles have been extensively investigated (Figure 1c). However, to date, NHC-bound nucleophiles[16] have not been applied to stereoselectively open the aziridine ring[17] for manufacturing enantiomerically enriched N-heterocyclic compounds. We envisioned that an NHC-based homoenolate[18] could associate with copper complex-activated styrenyl aziridines[13g,15] to accomplish NHC/copper cooperatively catalyzed[8b,8e,8g] asymmetric [3 + 3] annulation, leading to KR-produced enantioenriched spirooxindolyl lactams[19] and aziridines,[9] which have been both recognized as functional core units in numerous natural products and biologically active molecules (Figure 1d and 1e). Herein, we report highly enantioselective KR of racemic aziridines via asymmetric [3 + 3] annulation with enals enabled by copper/NHC cooperative catalysis. In this case, the NHC not only is involved in the organocatalytic cycle but also modulates the catalytic activity of the copper complex as an additional ligand. More interestingly, chemoselection between KR and DyKAT can be switched by tuning the dose of NHC.

Results and Discussion

On the basis of the synergistic catalysis design plan, we investigated the KR of racemic 2-phenyl-*N*-tosyl aziridine **2a** with isatin-derived enal **1a**, entailing both enantiomerically enriched annulation products and aziridines at the same time (Table 1).

[*] Z.-J. Zhang, Y.-H. Wen, Dr. J. Song, Prof. L.-Z. Gong
Hefei National Laboratory for Physical Sciences at the Microscale, Department of Chemistry, and Center for Excellence in Molecular Synthesis of CAS, University of Science and Technology of China, Hefei, 230026, China
E-mail: jill@ustc.edu.cn; gonglz@ustc.edu.cn

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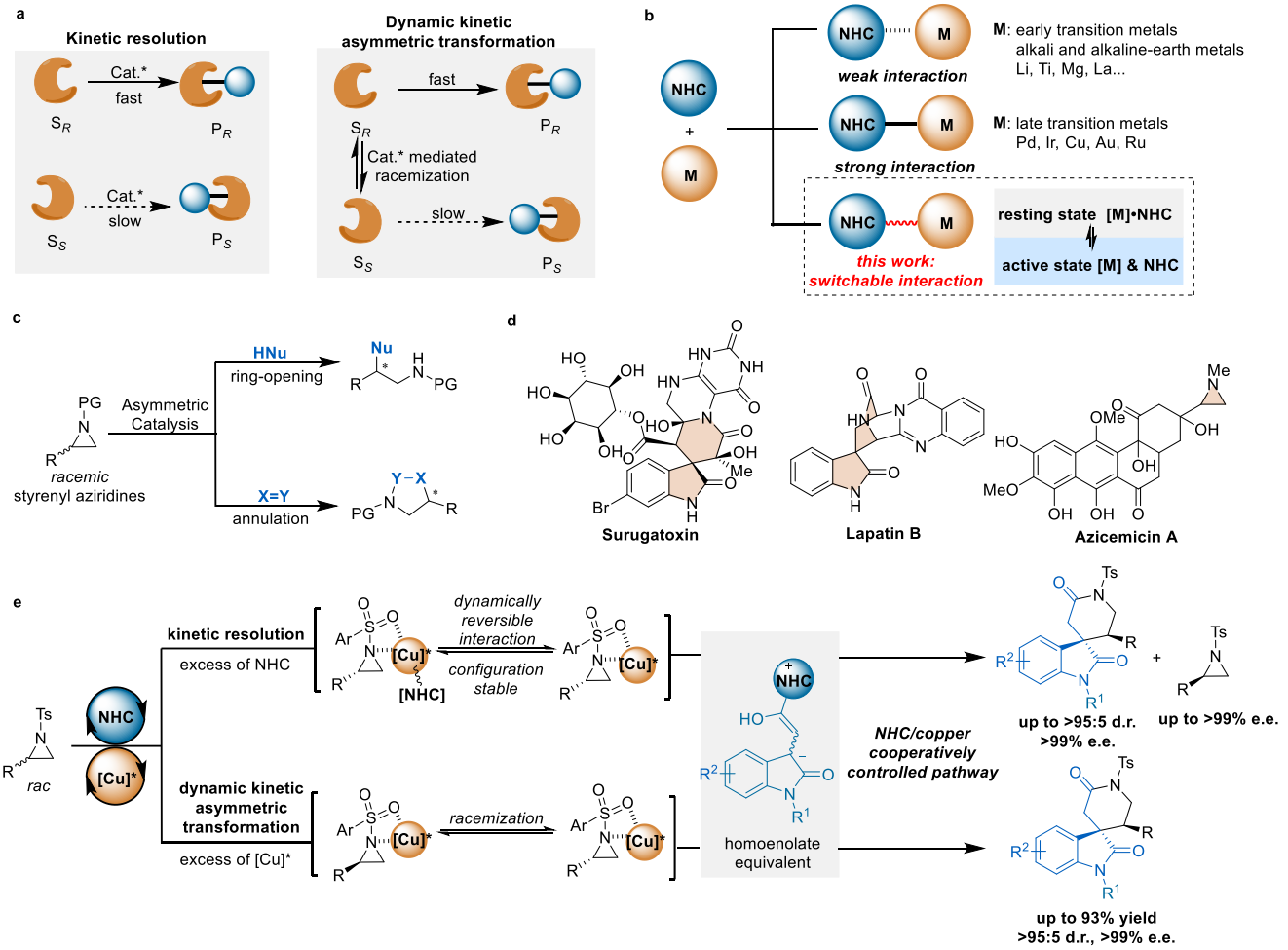

Figure 1. Design plan for the kinetic resolution (KR) and dynamic kinetic asymmetric transformation (DyKAT) of aziridines via NHC/Cu cooperative catalysis. **a**, Schematic of the KR and DyKAT. Substrate enantiomers (S_R, S_S); product enantiomers (P_R, P_S); chiral catalyst (Cat*). **b**, Coordination events between NHCs and metals in cooperative catalysis. **c**, Asymmetric ring-opening and annulation transformation of racemic styrenyl aziridines. **d**, Representative examples of naturally occurring spirocyclic oxindole lactams and aziridines. **e**, This work: cooperative NHC/copper-catalyzed switchable KR and DyKAT.

Under the cooperative catalysis of chiral NHC generated in situ from **4a** and a copper complex with BINAP (**L1**), the desired [3 + 3] annulation product **3aa** was obtained in 22% yield with 94:6 diastereoselectivity (d.r.) and 94% enantiomeric excess (e.e.) at room temperature (entry 1). Evaluation of chiral NHC precatalysts (**4a**-**4e**, entries 1–5) revealed that improved results were obtained with the use of **4c** (entry 3). Then, a series of chiral diphosphine ligands (**L**) were tested in combination with NHC precatalyst **4c** (see the Supporting Information for details), and the chiral diphosphine ligand **L2** was shown to be optimal (entry 6). The use of an inorganic base such as Na_2CO_3 further improved the reaction results, and the e.e. value of recovered **2a** increased to >99% (entry 7). Gratifyingly, the best results were obtained by using half of the combined catalyst (entry 8), and a superefficient KR process was identified. In the absence of either copper, chiral diphosphine ligand, or NHC precatalyst, less than 5% yield of the desired product was obtained, indicating that both the chiral copper complex and NHC were required (entries 9–11). The chirality of NHC **4c** and chiral phosphine **L2** was identified to be matched for stereochemical control (entry 8 vs entries 12-15). The combination of an achiral NHC precatalyst **4f** and chiral copper complex Cu^{I}(**L2**) enabled the reaction to give **3aa** with moderate enantioselectivity, indicating that NHC played a key role in the stereochemical control (entry 12). The use of an achiral ligand **L3** or *rac*-**L1** dramatically eroded the reaction efficiency, further verifying the superiority of synergistic catalysis in the KR process (entries 13 and 14). Significantly, the diastereomer of **3aa** was obtained by simply taking the enantiomer of the diphosphine ligand **L2** in concert with the NHC precatalyst **4c**; however, the KR results were not satisfactory (entry 15). Additionally, a large-scale experiment and the condition–based sensitivity screening[20] were conducted under optimized conditions to further highlight the robustness of this method (see the Supporting Information for details).

With the optimized procedure, we proceeded to evaluate the substrate scope of the KR reaction of racemic *N*-tosyl aziridines **2** with isatin-derived enals **1** (Figure 2). As expected, a broad range of N-substituents (R^1), including Me, Et, Bn, and Ph, were

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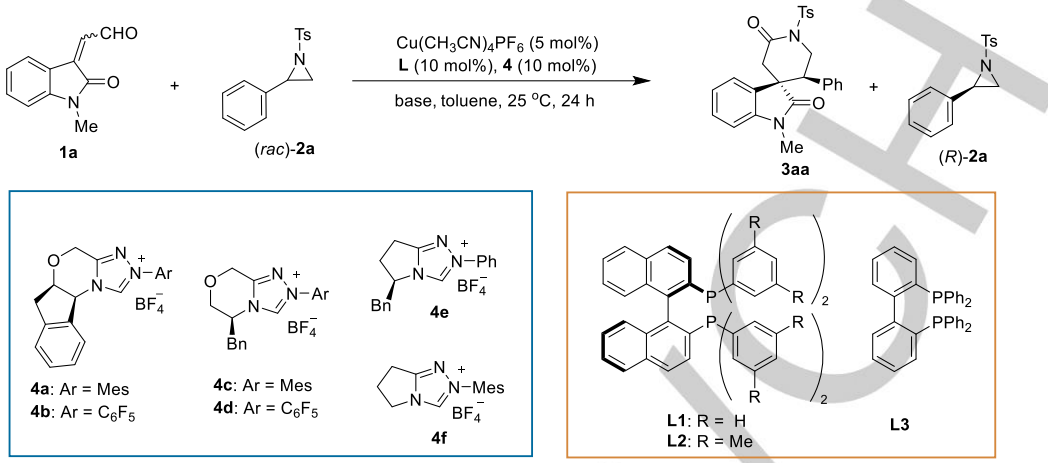
Table 1. Reaction optimization[a]



entry	4	L	base	3aa			2a	
				yield [%]	d.r.	e.e. [%]	yield [%]	e.e. [%]
1	**4a**	**L1**	NEt_3	22	94:6	94	75	26
2	**4b**	**L1**	NEt_3	<5	-	-	-	-
3	**4c**	**L1**	NEt_3	29	95:5	94	68	39
4	**4d**	**L1**	NEt_3	22	68:32	88	75	29
5	**4e**	**L1**	NEt_3	8	88:12	76	91	7
6	**4c**	**L2**	NEt_3	44	>95:5	97	56	75
7	**4c**	**L2**	Na_2CO_3	50	>95:5	97	49	>99
8[b]	**4c**	**L2**	Na_2CO_3	50(50)	>95:5	99	49(48)	>99
9[b,c]	**4c**	**-**	Na_2CO_3	-	-	-	-	-
10[b]	**4c**	**-**	Na_2CO_3	<5	-	-	-	-
11[b]	**-**	**L2**	Na_2CO_3	-	-	-	-	-
12[b]	**4f**	**L2**	Na_2CO_3	33	93:7	87	64	48
13[b]	**4c**	**L3**	Na_2CO_3	<5	-	-	-	-
14[b]	**4c**	*rac*-**L1**	Na_2CO_3	15	89:11	70	82	10
15[b]	**4c**	*ent*-**L2**	Na_2CO_3	25	40:60	92[d]	73	31[e]

[a] Reaction conditions: **1a** (0.075 mmol), **2a** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (5 mol%), diphosphine ligand **L** (10 mol%), NHC precatalyst **4** (10 mol%), and base (0.1 mmol) in toluene (1.0 mL) at 25 °C for 24 h under N_2. The yield and diastereomeric ratio (d.r.) were determined by ^1H NMR spectroscopy (isolated yield in parentheses). The enantiomeric excess (e.e.) was determined by HPLC. [b] $Cu(CH_3CN)_4PF_6$ (2.5 mol%), **L2** (5 mol%), NHC precatalyst **4c** (5 mol%), 30 h. [c] In the absence of $Cu(CH_3CN)_4PF_6$. [d] e.e. value of the major diastereomer. [e] (*S*)-**2a** was obtained.

tolerated to give annulation products (**3aa**–**3da**) in good yields and with excellent levels of stereoselectivity (>95:5 d.r. for all and up to >99% e.e.) (Figure 2a). A wide variety of isatin-derived enals containing either electron-withdrawing or electron-donating substituents on the phenyl ring (R^2) performed well and provided the corresponding products **3ea**–**3la** with excellent diastereo- and enantioselectivities, accompanied by the recovered (*R*)-**2a** with up to >99% e.e. (Figure 2a). The absolute configuration of product **3aa** was determined by X-ray crystallography (see the Supporting Information). We next investigated the scope of this cooperatively catalyzed KR reaction with respect to racemic aziridines **2** (Figure 2b). The KR of aziridines **2b**-**2h** with various substituents on the benzene ring proceeded smoothly with almost 50% conversion and delivered excellent KR results in all cases, irrespective of the electronic nature and substitution pattern of the substituents. The corresponding chiral spirooxindoles **3ab**-**3ah** were all obtained in good yields and with excellent stereoselectivities (up to >95:5 d.r., 99% e.e.). 2-Naphthyl substituted aziridine **2i** provided good selectivity. Vinyl aziridines **2j** and **2k** also worked well to deliver annulation products **3aj** and **3ak** with high levels of stereoselectivity, while both unreacted enantiomeric aziridines were recovered with >99% e.e. However, due to the unique effect of the 2-(*p*-methoxy)phenyl (PMP) substituent of aziridine **2l**, the KR process gave unsatisfactory results for this substrate.

In contrast to the elegant chiral diphosphine-copper(I)-catalyzed DyKATs of electron-rich aryl-substituted aziridines reported by Chai and coworkers,[15] the KR resolution of these substrates has remained unexplored. The great challenge in obtaining access to the KR mainly resulted from the rapid copper-catalyzed substrate racemization. NHCs can form a relatively stable complex with copper salts,[8b,8g] which would impact the catalytic performance of the copper-diphosphine complex. Thus, we hypothesized that fine-tuning the proportions of copper, diphosphine ligand, and NHC would be able to leverage the racemization rate of electron-rich aryl-substituted aziridines so that either the KR or DyKAT of electron-rich aryl-substituted

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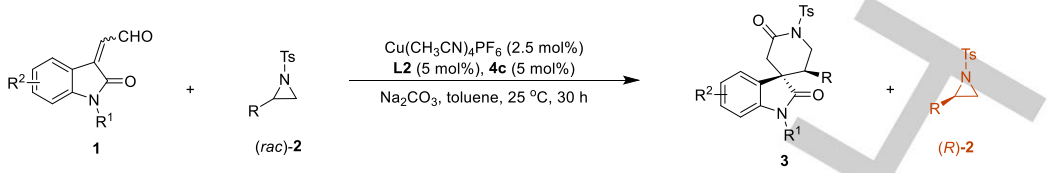
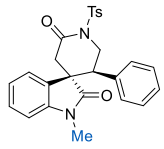
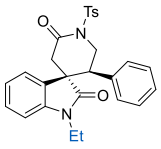
aziridines could be accessed (Figure 3). Indeed, the ratio of ternary catalysts had a considerable effect on the success of the KR, and premixing $Cu(CH_3CN)_4PF_6$, diphosphine **L2**, and NHC **4a** in a ratio of 1:2:2 enabled the generation of a hybrid



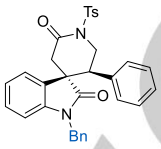
(a) Substrate scope for the kinetic resolution of racemic 2-phenyl-*N*-tosyl aziridine 2a



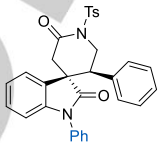
3aa, 50% yield, >95:5 d.r., 99% e.e.
2a, 48% yield, >99% e.e.



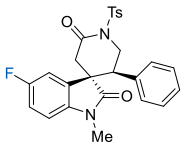
3ba, 47% yield, >95:5 d.r., 99% e.e.
2a, 50% yield, 98% e.e.



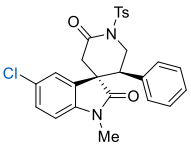
3ca, 41% yield, >95:5 d.r., >99% e.e.
2a, 58% yield, 71% e.e.



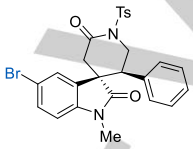
3da, 48% yield, >95:5 d.r., >99% e.e.
2a, 51% yield, 95% e.e.



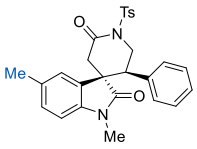
3ea, 49% yield, >95:5 d.r., 98% e.e.
2a, 49% yield, >99% e.e.



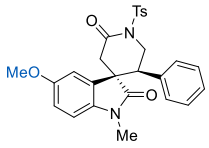
3fa, 49% yield, >95:5 d.r., 99% e.e.
2a, 50% yield, >99% e.e.



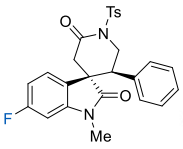
3ga, 49% yield, >95:5 d.r., >99% e.e.
2a, 49% yield, 97% e.e.



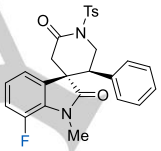
3ha, 48% yield, >95:5 d.r., 99% e.e.
2a, 48% yield, 99% e.e.



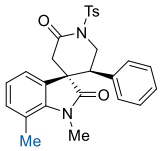
3ia, 50% yield, >95:5 d.r., 98% e.e.
2a, 49% yield, >99% e.e.



3ja, 49% yield, >95:5 d.r., 98% e.e.
2a, 50% yield, >99% e.e.

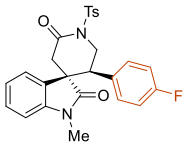


3ka, 49% yield, >95:5 d.r., 99% e.e.
2a, 49% yield, >99% e.e.

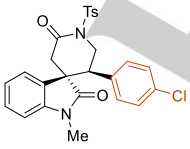


3la, 48% yield, >95:5 d.r., 98% e.e.
2a, 50% yield, 99% e.e.

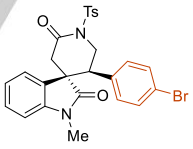
(b) Substrate scope for the kinetic resolution of racemic aziridines 2



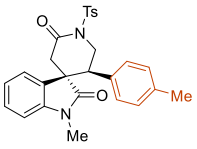
3ab, 50% yield, 94:6 d.r., 96% e.e.
2b, 47% yield, >99% e.e.



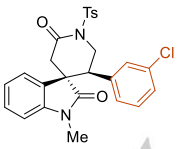
3ac, 47% yield, 95:5 d.r., 97% e.e.
2c, 46% yield, >99% e.e.



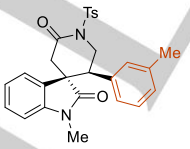
3ad, 50% yield, >95:5 d.r., 97% e.e.
2d, 49% yield, >99% e.e.



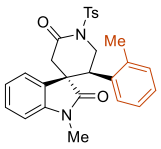
3ae, 49% yield, >95:5 d.r., 97% e.e.
2e, 48% yield, >99% e.e.



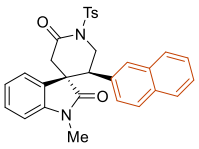
3af, 44% yield, >95:5 d.r., 99% e.e.
2f, 53% yield, 84% e.e.



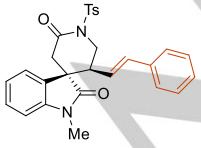
3ag, 49% yield, >95:5 d.r., 97% e.e.
2g, 49% yield, >99% e.e.



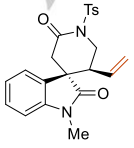
3ah, 47% yield, >95:5 d.r., 97% e.e.
2h, 47% yield, 95% e.e.



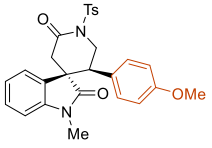
3ai, 56% yield, 91:9 d.r., 96% e.e.
2i, 41% yield, >99% e.e.



3aj, 55% yield, 85:15 d.r., 88% e.e.
2j, 42% yield, >99% e.e.



3ak, 49% yield, 91:9 d.r., 97% e.e.
2k, 46% yield, >99% e.e.



3al, 68% yield, 83:17 d.r., 81% e.e.
2l, 30% yield, 96% e.e.

Figure 2. Substrate scope for the kinetic resolution of racemic *N*-tosyl aziridines via NHC/Cu cooperative catalysis. Reaction conditions: **1** (0.075 mmol), **2** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (2.5 mol%), diphosphine ligand **L2** (5 mol%), NHC precatalyst **4c** (5 mol%), and Na_2CO_3 (0.1 mmol) in toluene (1.0 mL) at 25 °C for 30 h under N_2. The diastereomeric ratio (d.r.) was determined by ^1H NMR spectroscopy. Isolated yields. The enantiomeric excess (e.e.) was determined by HPLC.

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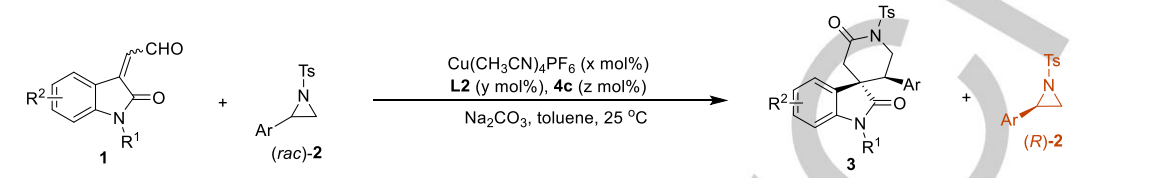
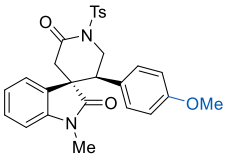
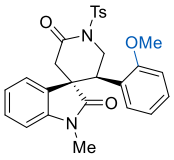
NHC/diphosphine Cu(I) complex[21] and consumed the active Cu(I) diphosphine species responsible for the racemization of aziridines,[15] thereby enabling KR (Figure 3a). As anticipated, in the presence of such an in situ-generated hybrid copper complex, the KR of 2-PMP-substituted aziridine **2l** with enal **1a** successfully afforded desired product **3al** in 48% yield, >95:5 d.r., 94% e.e., accompanied by the recovery of **2l** in 47% yield with 96% e.e. Consequently, this KR of electron-rich aryl-substituted aziridines was highly efficient, as excellent enantioselectivities were obtained for both desired products **3am**-**3ao** (93–95% e.e.) and the recovered aziridines **2m**–**2o** (92–>99% e.e.). Since tuning the ratio of NHC to the copper complex can alter the racemization rate of electron-rich aryl-substituted aziridines **2**, we next turned our attention to establishing the DyKATs of these substrates (Figure 3b). The presence of 2.5 mol% NHC **4c**, 5 mol% $Cu(CH_3CN)_4PF_6$ and 10 mol% diphosphine **L2** was identified as the best combined



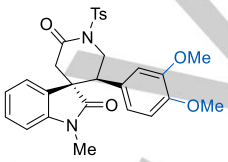
a **Kinetic resolution: $Cu(CH_3CN)_4PF_6$: L2: 4c = 1: 2: 2[a]**



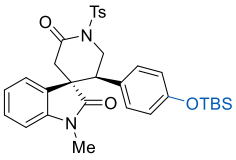
3al, 48% yield, >95:5 d.r., 94% e.e.
2l, 47% yield, 96% e.e.
3al[c], 51% yield, 94:6 d.r., 91% e.e.
2l, 45% yield, 94% e.e.



3am[d], 49% yield, 95:5 d.r., 95% e.e.
2m, 46% yield, 98% e.e.

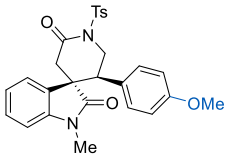


3an, 54% yield, 94:6 d.r., 93% e.e.
2n, 42% yield, 92% e.e.

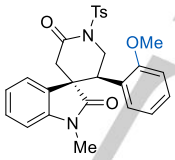


3ao, 48% yield, >95:5 d.r., 93% e.e.
2o, 47% yield, >99% e.e.

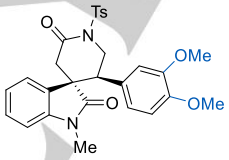
b **Dynamic kinetic asymmetric transformation: $Cu(CH_3CN)_4PF_6$: L2: 4c = 1: 2: 0.5[b]**



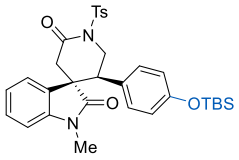
3al, 36 h, 91% yield
>95:5 d.r., >99% e.e.
3al[e], 36 h, 86% yield
>95:5 d.r., 98% e.e.



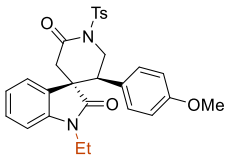
3am, 48 h, 70% yield
92:8 d.r., 92% e.e.



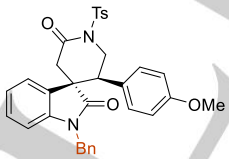
3an: 36 h, 88% yield
>95:5 d.r., 98% e.e.



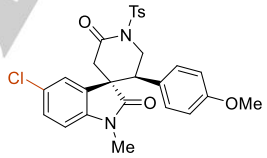
3ao: 48 h, 84% yield
>95:5 d.r., 93% e.e.



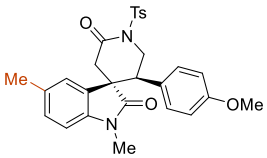
3bl: 36 h, 92% yield
>95:5 d.r., 98% e.e.



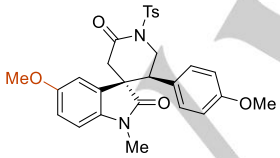
3cl, 36 h, 93% yield
>95:5 d.r., >99% e.e.



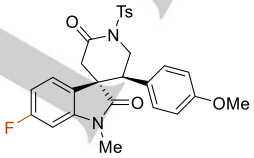
3fl, 36 h, 90% yield
93:7 d.r., 96% e.e.



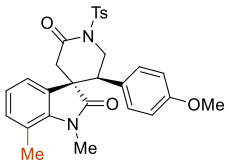
3hl, 36 h, 89% yield
95:5 d.r., 96% e.e.



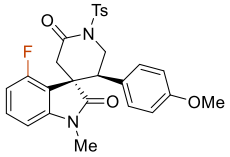
3il, 36 h, 90% yield
95:5 d.r., 96% e.e.



3jl, 36 h, 93% yield
>95:5 d.r., >99% e.e.



3ll, 60 h, 72% yield
95:5 d.r., 94% e.e.



3ml, 48 h, 83% yield
>95:5 d.r., 98% e.e.

Figure 3. Substrate scope for the kinetic resolution and dynamic kinetic asymmetric transformation of electron-rich aryl-substituted aziridines via NHC/Cu cooperative catalysis. [a] Kinetic resolution. Reaction conditions: $Cu(CH_3CN)_4PF_6$ (2.5 mol%), diphosphine ligand **L2** (5 mol%), NHC precatalyst **4c** (5 mol%), and Na_2CO_3 (0.1 mmol) were stirred in toluene (1.0 mL) at 25 °C for 1 h; then, **1a** (0.06 mmol), **2** (0.1 mmol), and toluene (1.0 mL) were added to the reaction mixture and stirred for 12 h under N_2. After completion of the reaction, 50 μL of NEt_3 was added. The diastereomeric ratio (d.r.) was determined by ^1H NMR spectroscopy. Isolated yields. The enantiomeric excess (e.e.) was determined by HPLC. [b] Dynamic kinetic asymmetric transformation. Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (5 mol%), diphosphine ligand **L2** (10 mol%), NHC precatalyst **4c** (2.5 mol%), and Na_2CO_3 (0.1 mmol) in toluene (1.0 mL) at 25 °C under N_2. [c] $Cu(CH_3CN)_4PF_6$ (2.5 mol%), diphosphine ligand **L2** (2.5 mol%), NHC precatalyst **4c** (5 mol%). [d] With **1a** (0.075 mmol), 60 h. [e] $Cu(CH_3CN)_4PF_6$ (5 mol%), diphosphine ligand **L2** (5 mol%), NHC precatalyst **4c** (2.5 mol%).

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catalyst system for the DyKAT. The dynamic kinetic annulation reaction of enal **1a** with aziridine (*rac*)-**2l** proceeded cleanly and generated desired spirooxindole product **3al** in 91% yield, >95:5 d.r. and >99% e.e. Variations in the substituent and substitution pattern of enals **1** were tolerated with 2-PMP-substituted aziridine **2l** and its analogs (**2m**-**2o**), and the corresponding products (**3al**-**3ml**) were obtained in good yield (70-93%) and with excellent diastereoselectivity and enantioselectivity (up to >95:5 d.r., >99% e.e.).

Both spirooxindole and aziridine can be transformed into synthetically significant compounds by subjecting them to facile reaction conditions, as shown in Figure 4. Under the action of SmI_2 at room temperature, the tosyl group (Ts) of **3aa** could be easily removed to give compound **5** without loss of enantiopurity. The reduction of **3aa** with $LiAlH_4$ successfully generated spiroindolinepiperidine **6**. In addition, hydrogenation of **3ak** over Pd/C led to spirooxindole **7** in 97% yield with maintained enantiopurity. The enantioenriched aziridine (*R*)-**2a** obtained from the KR is synthetically useful because of its propensity to undergo ring opening reactions to give a series of functionalized molecules. Chiral diamine **8** was obtained in 93% yield and >99% e.e. from the treatment of anilines with (*R*)-**2a**. In the presence of catalytic $Pd(PhCN)_2Cl_2$, the addition of excess 1,3,5-trimethoxybenzene to (*R*)-**2a** afforded amide **9** with almost complete retention of the stereochemical integrity.[22]

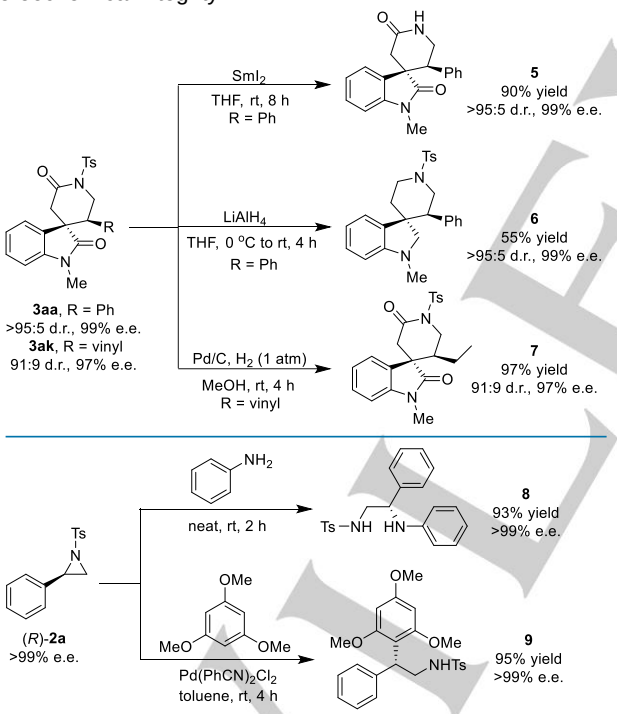

Figure 4. Synthetic transformations.

To understand the NHC-controlled switchable reaction pathway between the KR and DyKAT of aziridines, a series of kinetic studies were conducted (Figure 5). The racemization profile of (*R*)-**2l** (99% e.e.) was first investigated with different catalyst systems (Figure 5a). The combination of 5 mol% $Cu(CH_3CN)_4PF_6$ with either 5 mol% or 10 mol% chiral phosphine **L2** showed a superior ability to promote rapid racemization; thus, optically pure (*R*)-**2l** became racemic within 4 h (Figure 5a, conditions 1 and 2). In particular, the 1:1 complexation of copper and **L2** enabled a faster racemization process (Figure 5a, condition 1 vs 2). In contrast, the racemization of (*R*)-**2l** promoted by the 1:1 copper-**L2** complex slowed with increasing amounts of NHC **4c** (Figure 5a, conditions 3 and 4) and was completely inhibited by the addition of 10 mol% **4c** (Figure 5a, conditions 5 and 6). To identify the copper complex species existing under these conditions and to determine which one altered the reaction pathway, ^{31}P NMR studies were carried out (Figure 5b). The standard ^{31}P NMR spectra of **L2**, Cu^{I}(**L2**) and Cu^{I}(**L2**)(**4c**) complexes were collected and are shown in b1-b3 (Figure 5b). The ^{31}P NMR spectrum of the catalyst system of $Cu(CH_3CN)_4PF_6$, **L2**, and **4c** in a ratio of 1:1:2 found that a considerable amount of the Cu^{I}(**L2**)(**4c**) complex formed, as indicated by a signal (δ -1.17 ppm) similar to that observed in the standard spectrum of the Cu^{I}(**L2**)(**4c**) complex, but the Cu^{I}(**L2**) complex existed in trace amounts (Figure 5b, b4). Considering that racemization is difficult in the presence of such a catalyst system (Figure 5a, conditions 5 and 6), we can conclude that the Cu^{I}(**L2**)(**4c**) complex shows no catalytic activity for racemization. In contrast, in the ^{31}P NMR spectrum of the catalyst mixture of $Cu(CH_3CN)_4PF_6$, **L2**, and **4c** in a ratio of 1:1:0.5, two signals assigned to the Cu^{I}(**L2**)(**4c**) complex (δ -1.17 ppm) and the Cu^{I}(**L2**) complex (δ -1.42 ppm), respectively, were found by comparison with the standard spectra in b2 and b3, showing that **L2** was almost completely consumed in the reaction (Figure 5b, b5). The existence of the Cu^{I}(**L2**) complex may account for the racemization in the presence of this 1:1:0.5 catalyst system (Figure 5a, condition 3). Even more interestingly, the signal for the Cu^{I}(**L2**) complex appeared again with the addition of enal **1a** to the catalyst mixture (1:1:2) (Figure 5b, b6), presumably arising from the formation of the homoenolate that consumes some NHC **4c**. The addition of aziridine **2l** caused the signal for the Cu^{I}(**L2**) complex to disappear again, together with the release of **L2** (Figure 5b, b7). These observations suggest that NHC can be released from the Cu^{I}(**L2**)(**4c**) complex[8g] along with the addition of enal **1a** and can continue acting as an organocatalyst to activate the enal. In addition, the absence or presence of the Cu^{I}(**L2**) complex governs the reaction pathway toward the enantioselective KR or DyKAT of **2l**.

On the basis of these experimental results, a plausible catalytic cycle is proposed for the KR of aziridines (Figure 6). Initially, the NHC/diphosphine Cu(I) complex catalyst, [Cu^{I}(**L2**)(**4c**)], is formed from the coordination reaction of $Cu(CH_3CN)_4PF_6$, **L2**, and NHC precatalyst **4c** under basic conditions and has been identified in the standard reaction by ESI-MS (see the Supporting Information). The addition of isatin-based enal **1a** to NHC **4c** generates Breslow intermediate **I**, which represents azolium homoenolate species **II** in mesomeric form, and concurrently releases some catalytically active Cu^{I}(**L2**) species via the dissociation of NHC **4c** from the Cu^{I}(**L2**)(**4c**) complex. Principally, a catalyst resting state [Cu^{I}(**L2**)(**4c**)][21,23] might exist, which, after the loss of NHC **4c**, can participate in the catalytic cycle (left cycle, copper catalysis) as an active species.[13g,15] The N atom of the aziridine and one of the O atoms of the Ts group coordinate to the copper center to deliver electrophilic intermediates **III** and **IV**. Thereafter, complexes **III**

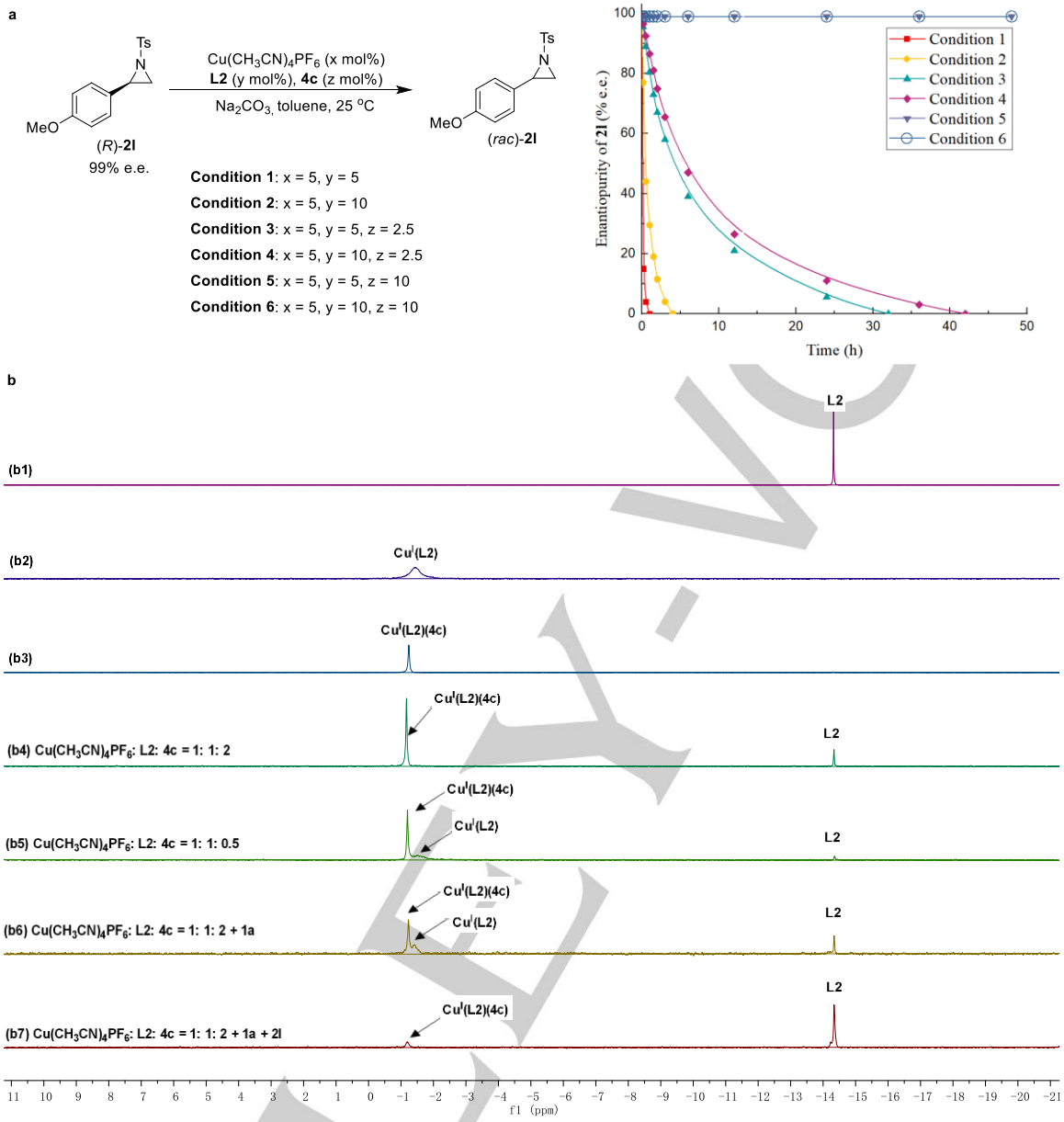

Figure 5. Mechanistic studies. **a**, Racemization profile of (*R*)-**2l** with different catalyst systems. (*R*)-**2l** was added after prestirring the combined catalyst and base for 1 h. **b**, ^{31}P NMR studies on the coordination effect between a copper complex of diphosphine ligand **L2** and NHC catalyst **4c**.

and **IV** can undergo S_N2-type substitution with NHC-bound nucleophile **II** at the 2-position of the aziridines at different rates. Since the diastereomeric complex [(*S*)-**2**[Cu]*] (**IV**) is more reactive and undergoes a much faster reaction than [(*R*)-**2**[Cu]*] (**III**) does, intermediate **V** is primarily generated, and (*R*)-**2** remains with high enantiopurity. Finally, the N-acylation cyclization of intermediate **V** furnishes final product **3** and regenerates the organocatalyst NHC-**4c** and the copper complex Cu^{I}(**L2**) or Cu^{I}(**L2**)(**4c**).

Conclusion

In summary, highly efficient KR and DyKAT of racemic *N*-tosylaziridines with isatin-derived enals have been achieved by the cooperative catalysis of chiral NHCs and copper complexes, leading to highly enantioenriched *N*-tosylaziridines and spirooxindole derivatives with high structural diversity. The NHC catalyst not only serves as a Lewis base organocatalyst but also acts as a ligand coordinating to the copper complex of diphosphine to regulate the catalytic activity. The chemoselection between the KR and DyKAT is switchable by tuning the dose of the chiral NHC, and the absence or presence of the Cu complex of diphosphine governs the reaction pathway. This interplay of NHC between ligand and organocatalyst is highly beneficial for

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tuning the activity of metal catalysts and very likely a general concept for the development of new asymmetric transformations by cooperative NHC/metal catalysis.

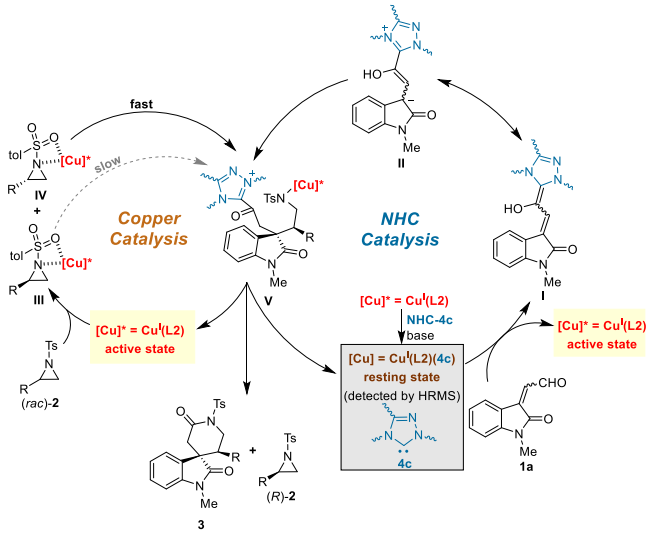

Figure 6. Plausible reaction mechanism.

Acknowledgements

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Keywords: N-heterocyclic carbene • copper • cooperative catalysis • kinetic resolution • dynamic kinetic asymmetric transformation

[1] a) Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions, ed. H. U. Blaser, E. Schmidt, VCH, Weinheim, **2004**; b) R. Noyori, *Adv. Synth. Catal.* **2003**, *345*, 15–32.

[2] a) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5–26; b) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001; *Angew. Chem.* **2005**, *117*, 4040–4069; c) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 1613–1666.

[3] a) J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, *14*, 8060–8072; b) V. Bhat, E. R. Welin, X. Guo, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 4528−4561.

[4] a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000; *Angew. Chem.* **2007**, *119*, 3046–3058; c) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511–3522; d) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485–496; e) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307–9387; f) H. Ohmiya, *ACS Catal.* **2020**, *10*, 6862–6869.

[5] a) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53–57; b) M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2016**, *55*, 14912–14922; *Angew. Chem.* **2016**, *128*, 15134–15145; c) H.-Y. Li, H. Lu, J.-Y. Liu, P.-F. Xu, *Acta Chim. Sinica* **2018**, *76*, 831–837; d) K. Nagao, H. Ohmiya, *Top. Curr. Chem.* **2019**, *377*, 35.

[6] S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676.

[7] a) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345–5347; b) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766–771.

[8] a) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094−8097; b) K. Namitharan, T. Zhu, J. Cheng, P. Zheng, X. Li, S. Yang, B.-A. Song, Y. R. Chi, *Nat. Commun.* **2014**, *5*, 3982−3988; c) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2016**, *138*, 7840–7843; d) C. Guo, D. Janssen-Müller, M. Fleige, A. Lerchen, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2017**, *139*, 4443−4451; e) J. Chen, P. Yuan, L. Wang, Y. Huang, *J. Am. Chem. Soc.* **2017**, *139*, 7045−7051. f) S. Singha, T. Patra, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2018**, *140*, 3551−3554; g) Z.-J. Zhang, L. Zhang, R.-L. Geng, J. Song, X.-H. Chen, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2019**, *58*, 12190–12194; *Angew. Chem.* **2019**, *131*,12318–12322; h) S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc, F. Glorius, *Nat. Catal.* **2020**, *3*, 48−54; i) L. Zhou, X. Wu, X. Yang, C. Mou, R. Song, S. Yu, H. Chai, L. Pan, Z. Jin, Y. R. Chi, *Angew. Chem. Int. Ed.* **2020**, *59*, 1557–1561; *Angew. Chem.* **2020**, *132*,1573–1577.

[9] a) C. Botuha, F. Chemla, F. Ferreira, A. Perez-Luna, Aziridines in natural product synthesis. In Heterocycles in Natural Product Synthesis; p 3, **2011**; b) F. M. D. Ismail, D. O. Levitsky, V. M. Dembitsky, *Eur. J. Med. Chem.* **2009**, *44*, 3373−3387.

[10] a) L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881−7929; b) G. S. Singh, *Adv. Heterocycl. Chem.* **2019**, *129*, 245–335.

[11] S. Sabir, G. Kumar, V. P. Verma, J. L. Jat, *ChemistrySelect* **2018**, *3*, 3702–3711.

[12] Z. Chai, *Synthesis* **2020**, *52*, 1738−1750.

[13] a) B. Wu, J. R. Parquette, T. V. RajanBabu, *Science* **2009**, *326*, 1662; b) J. Cockrell, C. Wilhelmsen, H. Rubin, A. Martin, J. B. Morgan, *Angew. Chem. Int. Ed.* **2012**, *51*, 9842–9845; *Angew. Chem.* **2012**, *124*, 9980–9983; c) K. Ohmatsu, Y. Hamajima, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 8794−8797; d) K. Ohmatsu, Y. Ando, T. Ooi, *J. Am. Chem. Soc.* **2013**, *135*, 18706−18709; e) Y. Xu, K. Kaneko, M. Kanai, M. Shibasaki, S. Matsunaga, *J. Am. Chem. Soc.* **2014**, *136*, 9190−9194; f) M. R. Monaco, B. Poladura, M. Diaz de Los Bernardos, M. leutzsch, R. Goddard, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 7063 –7067; *Angew. Chem.* **2014**, *126*, 7183–7187; g) Z. Chai, Y.-M. Zhu, P.-J. Yang, S. Wang, S. Wang, Z. Liu, G. Yang, *J. Am. Chem. Soc.* **2015**, *137*, 10088−10091; h) C. Ge, R.-R. Liu, J.-R. Gao, Y.-X. Jia, *Org. Lett.* **2016**, *18*, 3122−3125; i) Z. Chai, P.-J. Yang, H. Zhang, S. Wang, G. Yang, *Angew. Chem. Int. Ed.* **2017**, *56*, 650−654; *Angew. Chem.* **2017**, *129*, 665–669.

[14] B. P. Woods, M. Orlandi, C.-Y. Huang, M. S. Sigman, A. G. Doyle, *J. Am. Chem. Soc.* **2017**, *139*, 5688−5691.

[15] P.-J. Yang, L. Qi, Z. Liu, G. Yang, Z. Chai, *J. Am. Chem. Soc.* **2018**, *140*, 17211−17217.

[16] a) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295–2309; b) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040–5052.

[17] L. D. S. Yadav, V. K. Rai, S. Singh, P. Singh, *Tetrahedron Lett.* **2010**, *51*, 1657–1662.

[18] a) C. Burstein, F.Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205–6208; *Angew. Chem.* **2004**, *116*, 6331–6334; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*,14370–14371; c) C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418–2439; d) L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2016**, *55*, 11110–11114; *Angew. Chem.* **2016**, *128*,11276–11280; e) L. Wang, S. Li, M. Blümel, R. Puttreddy, A. Peuronen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2017**, *56*, 8516–8521; *Angew. Chem.* **2017**, *129*, 8636–8641.

[19] a) B. Yu, D.-Q. Yu, H.-M. Liu, *Eur. J. Med. Chem.* **2015**, *97*, 673–698; b) N. Ye, H. Chen, E. A. Wold, P.-Y. Shi, J. Zhou, *ACS Infect. Dis.* **2016**, *2*, 382–392.

10.1002/anie.202013679

[20] L. Pitzer, F. Schäfers, F. Glorius, *Angew. Chem. Int. Ed.* **2019**, *58*, 8572 –8576; *Angew. Chem.* **2019**, *131*, 8860–8864.

[21] S. Guo, M. H. Lim, H. V. Huynh, *Organometallics* **2013**, *32*, 7225−7233.

[22] Y.-M. Huang, C.-W. Zheng, L. Pan, Q.-W. Jin, G. Zhao, *J. Org. Chem.* **2015**, *80*, 10710–10718.

[23] Reactions of aziridine **2l** with 1,3-dimethylindole, aldehydes, electron-rich (hetero)arenes, and amines, which prove to be successful reactants under the catalysis of Cu^{I}**L*** (see ref. 13g, 13i, and 15), all failed to deliver desired products under the catalysis of $Cu(CH_3CN)_4PF_6$, **L2**, and **4c** in a ratio of 1: 2: 2.

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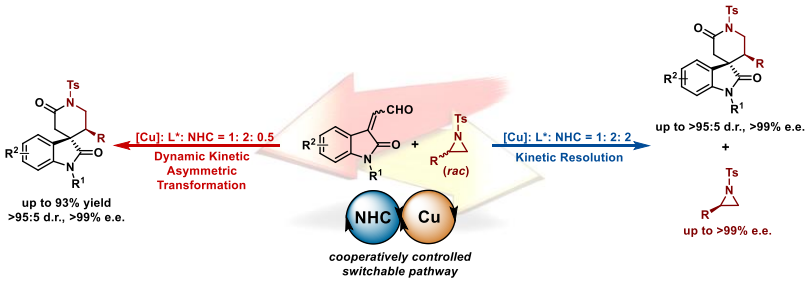

Highly efficient KR and DyKAT of racemic *N*-tosylaziridines with isatin-derived enals have been achieved by the cooperative catalysis of chiral NHCs and copper complexes, leading to highly enantioenriched *N*-tosylaziridines and spirooxindole derivatives with high structural diversity.

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Kinetic Resolution of Aziridines Enabled by N-Heterocyclic Carbene/Copper Cooperative Catalysis: Carbene Dose-Controlled Chemo-Switchability