OL Organic Letters

pubs.acs.org/OrgLett Letter

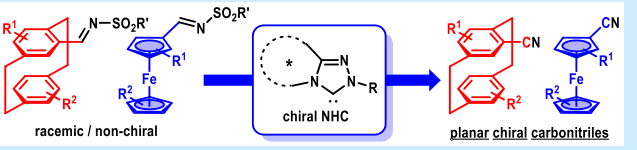
Asymmetric Synthesis of Planar Chiral Carbonitriles and Amines via Carbene-Catalyzed Kinetic Resolution

Ya Lv,[‖] Chengli Mou,[‖] Qian Liu, Liangzhen Shu, Yuanlin Cai, Xiaokang Lv, Zhichao Jin,* and Yonggui Robin Chi*

Cite This: https://doi.org/10.1021/acs.orglett.3c04342 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We have developed a catalytic method using chiral N-heterocyclic carbene (NHC) as the sole organic catalyst to synthesize planar chiral carbonitriles asymmetrically, resulting in optically pure, multifunctional compounds. The method demonstrates remarkable tolerance toward diverse substituents and substitution patterns through kinetic resolution (KR) or desymmetrization processes. The resulting optically pure planar chiral products hold significant potential for applications in asymmetric synthesis and antibacterial pesticide development.



Planar chirality, as an important component of chirality, has shown distinct characteristics in the fields of organic synthesis and functional materials. Both [2.2]paracyclophane (pCp)[1] and ferrocene[2] are representative examples of planar chiral structures, boasting distinctive structural attributes that imbue them with exceptional properties. Particularly, substituted pCps and ferrocenes display captivating planar chirality, which has extensive applications in asymmetric catalysis,[3] functional material development,[4] and medicinal chemistry[5] (Figure 1a). Substituted pCps have been employed as chiral *P,N*- or *N,O*-ligands in asymmetric dialkylzinc additions to aldehydes, asymmetric cyclopropanation reactions, and asymmetric epoxidation reactions. Planar chiral iodoarenes based on pCp have been used to catalyze the enantioselective fluorination of β-keto esters. In addition, a series of functional materials with chiral pCps have been widely applied in the field of materials science for the development of polymers and optoelectronic devices. Ferrocenes with planar chirality are extensively utilized as ligands or catalysts in asymmetric catalysis, particularly notable for their industrial applications in pharmaceuticals and agrochemicals production, such as (R,S_p)-PPFA and (R,S_p)-Josiphos. Ferroquine, a compound designed to combat the malaria parasite, demonstrates promising efficacy in malaria treatment.

Over the years, a variety of synthetic approaches have emerged for producing enantiopure planar chiral pCp and ferrocene derivatives. These methodologies range from stoichiometric resolution methods to chromatographic separation employing chiral stationary phases as well as catalytic asymmetric processes. Given the prevalent utilization of pCp and ferrocene derivatives, exploring novel catalytic asymmetric processes holds substantial importance in efficiently synthesizing planar chiral pCp and ferrocene derivatives.

Recently, we have introduced a dynamic kinetic resolution (DKR)[6] process using N-heterocyclic carbene (NHC)[7]

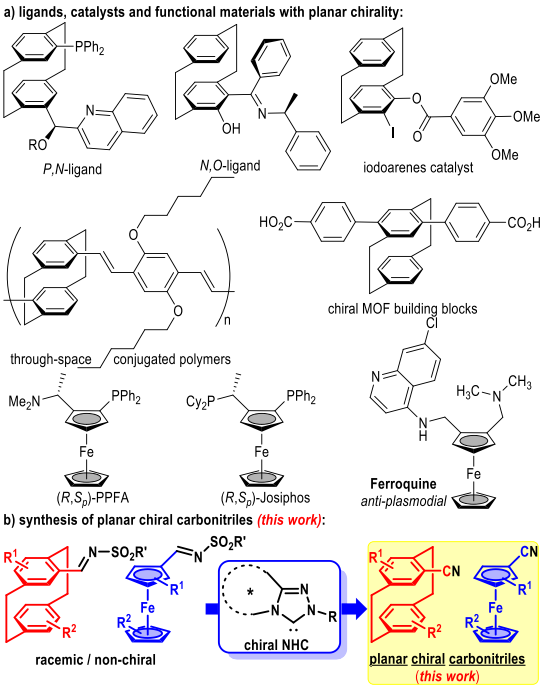
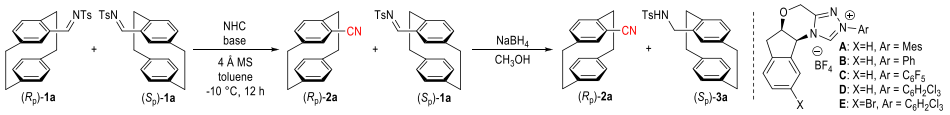


Figure 1. Applications and Syntheses of Planar chiral pCps and ferrocenes.

Received: December 25, 2023
Revised: February 11, 2024
Accepted: February 19, 2024

Table 1. Optimization of Reaction Conditions for the KR Process of 1a[a]



Entry	NHC	Base	Solvent	Yield (%);[b] Er (%)[c] (R_p)-**2a**	(S_p)-**3a**	s[d]
1	A	$(C_2H_5)_2NH$	toluene	0	n.d.	n.d.
2	B	$(C_2H_5)_2NH$	toluene	0	n.d.	n.d.
3	C	$(C_2H_5)_2NH$	toluene	35; 81:19	42; 75:25	7
4	D	$(C_2H_5)_2NH$	toluene	21; 91:9	42; 85:15	21
5	**E**	**$(C_2H_5)_2NH$**	**toluene**	**48; 96:4**	**46; 95:5**	**74**
6	E	$(C_2H_5)_3N$	toluene	21; 89:11	68; 56:44	10
7	E	$^iPr_2NH$	toluene	58; 86:14	40; 98:2	23
8	E	DMAP	toluene	54; 89:11	45; 92:8	21
9	E	DABCO	toluene	53; 91:9	46; 90:10	25
10	E	$(C_2H_5)_2NH$	PhCl	49; 95:5	50; 91:9	48
11	E	$(C_2H_5)_2NH$	CH_2Cl_2	32; 93:7	65; 60:40	16
12	E	$(C_2H_5)_2NH$	THF	52; 90:10	46; 81:19	17

[a]General conditions (unless otherwise specified): racemic **1a** (0.20 mmol), NHC (0.04 mmol), base (0.10 mmol), 4 Å MS (100 mg), and solvent (2.0 mL) at −10 °C for 12 h, then CH_3OH (0.5 mL) and $NaBH_4$ (0.40 mmol) were added successively. [b]Isolated yields. [c]The er values of (R_p)-**2a** and (S_p)-**3a** were determined by HPLC using a chiral stationary phase. [d]Calculated selectivity factors: C= ee of **3a**/(ee of **2a** + ee of **3a**), $s = \ln[(1 - C)(1 - \text{ee of } \mathbf{2a})]/\ln[(1 - C)(1 + \text{ee of } \mathbf{2a})]$.

organocatalysis to synthesize axially chiral benzonitriles from racemic 2-arylbenzaldehydes and readily available toluenesulfonamide. These advancements in easily creating optically pure benzonitriles with axial chiralities offer promising prospects for applications in organic synthesis and biological research.[8] Herein, as part of our ongoing research, we present an asymmetric catalytic approach to synthesize multifunctional planar chiral carbonitriles through NHC organocatalytic kinetic resolution (KR).[9] In addition, we also showcase in this study the potential applications of enantiomerically pure planar chiral molecules through further synthetic transformations and bioactive assessments for pesticides.

Our explorations into the construction of planar chiral carbonitriles start with the KR of the racemic mixture of pCp-derived imine substrate **1a** under NHC organocatalytic conditions (Table 1). Chiral NHC catalysts derived from aminoindanol scaffolds were assessed for this asymmetric transformation with a substoichiometric amount of diethylamine in toluene at −10 °C (entries 1 to 5). The chiral NHC catalysts with electron-donating *N*-substituents proved inefficient for this KR process. (e.g., **A**[10] and **B**,[11] entries 1 to 2). The aminoindanol-derived NHC catalyst **C**,[12] featuring a potent electron-withdrawing *N*-pentafluorophenyl (N-C_6F_5) group, exhibited notable selectivity in activating the two enantiomers of planar chiral imine substrates. Specifically, the (R_p)-configured imine **1a** was preferentially converted into the pCp-carbonitrile product (R_p)-**2a** with a moderate yield and optical purity (entry 3). Technically, since the remaining starting material of (S_p)-**1a** was not stable during purification processes, the mild reducing reagent of $NaBH_4$ was therefore added into the reaction system after completion of the KR process to transform the enantioenriched **1a** into the toluenesulfonamide **3a** for a more accurate evaluation of the reaction outcome. Switching the N-C_6F_5 group on the NHC catalyst into an electron-deficient *N*-2,4,6-trichlorophenyl group led to dramatic improvements on the enantioselectivities of both the products (R_p)-**2a** and (S_p)-**3a** (entry 4). To our great delight, installing an additional bromide group on the NHC catalyst **D**[13] (to afford **E**)[14] can give both of the KR products (R_p)-**2a** and (S_p)-**3a** in excellent yields and optical purities, with the *s* value of the KR process increased to 74 (entry 5). Switching the basic additives from diethylamine into other organic or inorganic bases led to obvious drops in the *s* values of the KR process, although the optical purity of (S_p)-**3a** could occasionally reach 98:2 (entries 6 to 9). Chlorobenzene can also be used as a suitable solvent for this NHC-catalyzed KR process, although the optical purities obtained in the remaining (S_p)-**3a** were slightly dropped (entries 10). Non-aromatic solvents we tested were not good for this asymmetric KR reaction with only moderate *s* values obtained (entries 11 to 12).

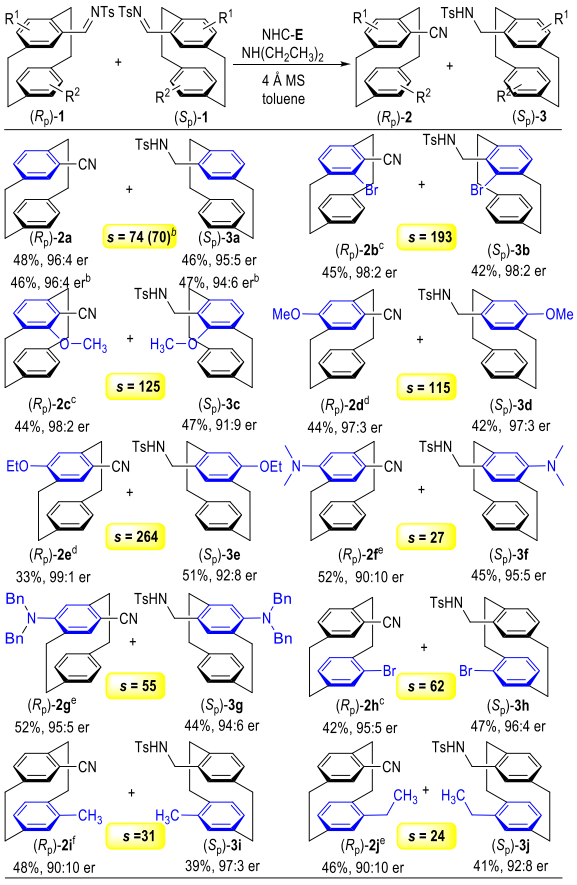
Therefore, we explored the reaction scope for asymmetrically synthesizing planar chiral aryl carbonitriles using the NHC catalyst **E**, along with 4 Å molecular sieves and a substoichiometric quantity of diethylamine in toluene (Table 1, entry 5 and Scheme 1). Subtle adjustments to the reaction conditions may be necessary when preparing various substituted planar chiral benzonitriles to achieve optimal product yields and optical purities.

Both electron-donating and -withdrawing substituents at the *o*- and *p*-positions of the imine group on the pCp ring were effectively tolerated. This resulted in the synthesis of planar chiral pCp-derived carbonitriles and sulfonamides with high yields and exceptional enantioselectivity (Scheme 1, **2b** to **2g**, and **3b** to **3g**). The pCp-derived imine substrate with a pseudogeminal substituent performed effectively in the NHC-catalyzed KR process. However, the obtained planar chiral carbonitrile products exhibited moderate to good optical purities, albeit with decreased *s* values (**2h** to **2j**, **3h** to **3j**). Furthermore, the reaction can be scaled up without significant reductions in yields or enantioselectivity (e.g., Scheme 1, **1a** on a 1 mmol scale).

The *p*-toly group of the toluenesulfonimide moiety on reaction substrate **1a** can be switched into aryl or alkyl groups with various substitution patterns (Scheme 2). The enantioenriched planar chiral sulfonamides (S_p)-**3** bearing different

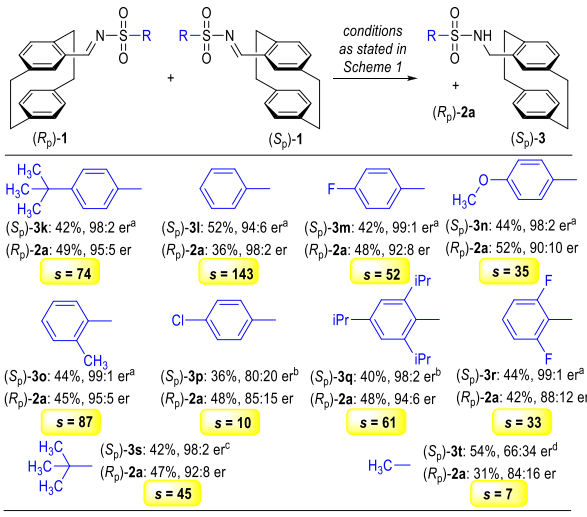
https://doi.org/10.1021/acs.orglett.3c04342
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Substitution Patterns on the Cycloparaphane Rings of the Substrate 1[a]



[a]Reaction conditions as stated in Table 1, entry 5. Isolated yields. Er values were determined via HPLC on chiral stationary phase; [b]The reaction was carried out at 1.0 mmol scale based on **1a**. [c]40 °C for 24 h. [d]−10 °C for 5 h. [e]30 °C for 12 h. [f]40 °C for 12 h.

Scheme 2. Substitution Patterns on the Sulfonyl Group of the Substrate 1

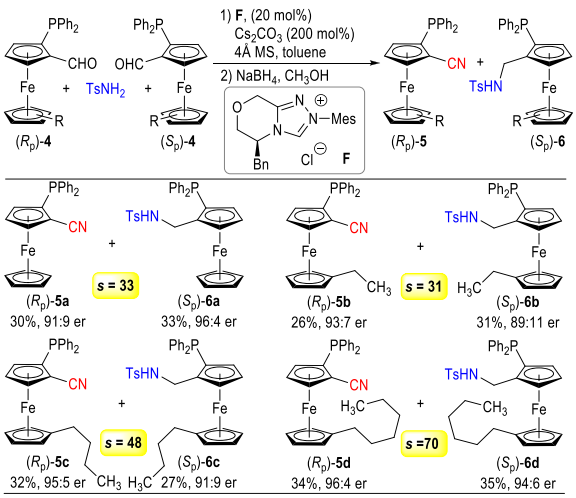


[a]Reaction performed at −10 °C for 5 h. [b]−10 °C for 8 h. [c]40 °C for 48 h. [d]−10 °C for 24 h.

functionalities were obtained with the simultaneous formation of the planar chiral carbonitrile product (R_p)-**2a**. Phenyl groups, with either electron-donating or electron-withdrawing substituents, effectively replaced the *p*-toly group in sulfonimide substrate **1a**. This led to the formation of enantioenriched planar chiral sulfonamide and carbonitrile products with consistently high yields and optical purities (Scheme 2, **3k** to **3r**). The aromatic *p*-tolyl group in substrate **1a** can be replaced with an aliphatic *tert*-butyl group with minimal impact on reaction yields and enantioselectivity (**3s**). However, when the methylsulfonyl imine was used as the reaction substrate, only a moderate yield and er value could be obtained in the final products (**3t**) and **2a** under the current catalytic condition.

Ferrocene-based systems represent one class of the most versatile and commonly used planar chiral structures in both organic synthesis and human medicine development. We therefore tested the applicability of the multifunctional ferrocene-based aldehyde substrates in the asymmetric synthesis of planar chiral carbonitrile molecules through NHC-catalyzed dehydration processes (Schemes 3). We are pleased

Scheme 3. Scope of the Ferrocene-Based Phosphine-Carbaldehyde 4[a]



[a]Reaction conditions: **4** (0.20 mmol), $TsNH_2$ (0.4 mmol), **F** (0.02 mmol), Cs_2CO_3 (0.20 mmol), toluene (2.0 mL), 80 °C, 12 h.

to report that the racemic mixture of ferrocene-derived phosphine aldehyde substrate **4** can undergo direct dehydrogenation/asymmetric N−S bond cleavage cascade reaction with toluenesulfonamide ($TsNH_2$) catalyzed by chiral NHC catalyst **F**.[15] This process yields both ferrocene-derived phosphine carbonitrile **5** and phosphine sulfonamide **6** in good yields and enantioselectivities. Alkyl groups can be added to the unsubstituted cyclopentadiene ring of ferrocene aldehyde substrates, yielding enantioenriched planar chiral sulfonamide and carbonitrile products in generally high yields and optical purities (e.g., **6b** to **6d**).

The optically pure planar chiral molecules derived from the NHC-catalyzed KR process are versatile in various transformations (Figure 2). For example, the cyanide group on the pCp ring of (R_p)-**2a** can be converted into thioamide (**7**) and amide (**8**) in a single step, yielding good results while maintaining an excellent optical purity (Figure 2a). It can also be quantitatively reduced by $LiAlH_4$ to give the free primary

https://doi.org/10.1021/acs.orglett.3c04342
Org. Lett. XXXX, XXX, XXX−XXX

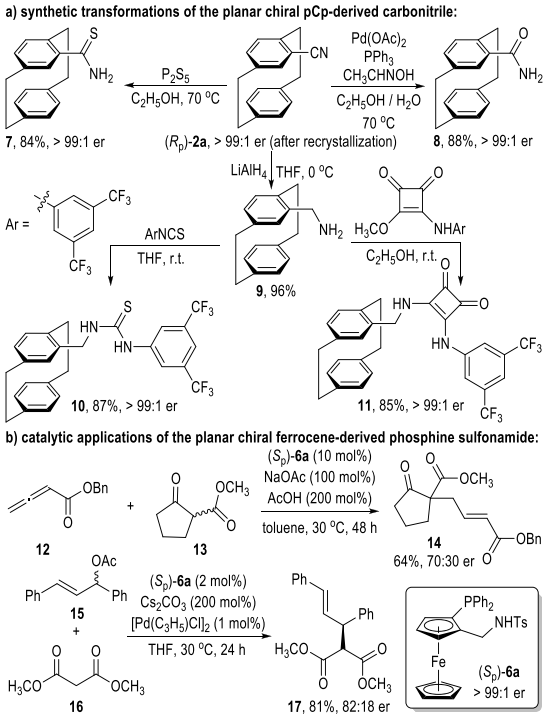


Figure 2. Synthetic applications of planar chiral products.

amine (**9**), which can be further transformed into the optically pure planar chiral thiourea (**10**) and squaramide (**11**) in good yields.

Remarkably, the optically pure ferrocene-based phosphine-sulfonamide bifunctional molecule (S_p)-**6a** obtained from this NHC-catalyzed KR reaction can be used as an effective organic catalyst or ligand to promote asymmetric transformations (Figure 2b). For instance, it efficiently activates allenoate (**12**) as an electrophile, enabling its enantioselective reaction with β-ketoester (**13**) to yield the adduct (**14**) with moderate yield and optical purity. The (S_p)-**6a** can also be used as an efficient chiral ligand in the Pd-catalyzed asymmetric substitution reaction between **15** and **16**, and the product (**17**) was given in a good yield and optical purity.

Our innovative approach produces pCp- and ferrocene-derived planar chiral multifunctional molecules with unique bioactivities, enhancing our research in plant protection pesticides (Table 2). Notably, several of our optically enriched compounds show promising antibacterial effects against *Xanthomonas oryzae* pv *Oryzae* (*Xoo*),[16] a prevalent bacterium causing leaf blight and substantial economic losses in agriculture. Notably, compared to the commercial pesticide thiodiazole copper (TC) commonly used for bacterial control, five of our planar chiral products exhibit superior activity against *Xoo* (Table 2).

Table 2. Inhibitive Activities of the Planar Chiral Compounds against *Xoo*

	Xoo Inhibition Rate (%)[a]	
Compounds	100 μg/mL	50 μg/mL
(R_p)-**2h**	70.6 ± 2.5	50.9 ± 4.3
(S_p)-**3a**	78.6 ± 2.1	61.4 ± 1.3
(S_p)-**3e**	79.4 ± 4.3	72.5 ± 2.3
(S_p)-**3i**	83.6 ± 6.0	51.7 ± 3.8
11	69.1 ± 2.3	55.5 ± 3.4
TC[b]	65.3 ± 0.7	40.4 ± 1.4

[a]Average of three replicates. [b]TC = thiodiazole copper.

In summary, we have presented an efficient method for asymmetrically synthesizing a variety of planar chiral carbonitriles and sulfonamides. This approach involves NHC-catalyzed dehydrative reactions, facilitating the formation of cyanide groups through enantioselective N−S cleavage processes. The planar chiral carbonitrile and sulfonamide products are achieved in high yields and optical purities using KR processes. These optically pure, multifunctional planar chiral molecules hold promising applications in synthetic chemistry and antibacterial pesticide development. Ongoing investigations in our laboratory aim to develop facile methods for constructing planar chiral molecules and exploring their applications with future reports to follow.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c04342.

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

■ AUTHOR INFORMATION

Corresponding Authors

Zhichao Jin − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*; Email: zcjin@gzu.edu.cn

Yonggui Robin Chi − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China; School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore*; orcid.org/0000-0003-0573-257X; Email: robinchi@ntu.edu.sg

Authors

Ya Lv − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*

Chengli Mou − *School of Pharmacy, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China*

Qian Liu − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*; orcid.org/0000-0002-2899-7362

Liangzhen Shu − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*

Yuanlin Cai − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural*

https://doi.org/10.1021/acs.orglett.3c04342
Org. Lett. XXXX, XXX, XXX−XXX

Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China

Xiaokang Lv − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c04342

Author Contributions

Y.L. and C.M. conducted most of the experiments. Q.L., L.S., Y.C., and X.L. conducted some experiments. Z.J. and Y.R.C. conceptualized and directed the project and drafted the manuscript with assistance from all coauthors. All authors contributed to part of the experiments and/or discussions.

Author Contributions

[‖]Y.L. and C.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge funding supports from the National Key Research and Development Program of China (2022YFD-1700300); National Natural Science Foundation of China (21732002, 21961006, 32172459, 22061007, 22071036), Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY number (2020)004], the Science and Technology Department of Guizhou Province (Qiankehejichu-ZK[2021]Key033), Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University, Guizhou University of Traditional Chinese Medicine, and Guizhou University (China). Singapore National Research Foundation under its NRF Investigatorship (NRF-NRFI2016-06) and Competitive Research Program (NRF-CRP22-2019-0002); the Singapore Ministry of Education under its MOE AcRF Tier 1 Award (RG7/20, RG5/19), MOE AcRF Tier 2 Award (MOE2019-T2-2-117), and MOE AcRF Tier 3 Award (MOE2018-T3-1-003), and Nanyang Technological University.

■ REFERENCES

(1) For selected reviews, see: (a) Hassan, Z.; Spuling, E.; Knoll, D. M.; Lahann, J.; Bräse, S. Planar Chiral [2.2]Paracyclophanes: from Synthetic Curiosity to Applications in Asymmetric Synthesis and Materials. *Chem. Soc. Rev.* **2018**, *47*, 6947−6963. (b) Hassan, Z.; Spuling, E.; Knoll, D. M.; Bräse, S. Regioselective Functionalization of [2.2]Paracyclophanes: Recent Synthetic Progress and Perspectives. *Angew. Chem., Int. Ed.* **2020**, *59*, 2156−2170.

(2) For selected examples, see: (a) Zheng, Y.; Qin, T.; Zi, W. Enantioselective Inverse Electron Demand (3 + 2) Cycloaddition of Palladium-Oxyallyl Enabled by a Hydrogen-Bond-Donating Ligand. *J. Am. Chem. Soc.* **2021**, *143*, 1038−1045. (b) Wang, F.; Chen, Y.; Yu, P.; Chen, G. Q.; Zhang, X. Asymmetric Hydrogenation of Oximes Synergistically Assisted by Lewis and Bronsted Acids. *J. Am. Chem. Soc.* **2022**, *144*, 17763−17768.

(3) For selected examples, see: (a) Dahmen, S.; Bräse, S. The Asymmetric Dialkylzinc Addition to Imines Catalyzed by [2.2]-Paracyclophane-Based *N*,*O*-Ligands. *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941. (b) Wang, Y.; Yuan, H.; Lu, H.; Zheng, W. H. Development of Planar Chiral Iodoarenes Based on [2.2]-Paracyclophane and Their Application in Catalytic Enantioselective Fluorination of *β*-Ketoesters. *Org. Lett.* **2018**, *20*, 2555−2558. (c) Xie, E.; Huang, S.; Lin, X. Design of Planar Chiral Phosphoric Acids with a [2.2]Paracyclophanyl Backbone as Organocatalysts for the Highly Enantioselective Aza-Friedel-Crafts Reaction. *Org. Lett.* **2019**, *21*, 3682−3686. (d) Ji, W.; Wu, H.-H.; Zhang, J. Axially Chiral Biaryl Monophosphine Oxides Enabled by Palladium/WJ-Phos-Catalyzed Asymmetric Suzuki−Miyaura Cross-coupling. *ACS Catal.* **2020**, *10*, 1548−1554.

(4) (a) Cakici, M.; Gu, Z.-G.; Nieger, M.; Bürck, J.; Heinke, L.; Bräse, S. Planar-Chiral Building Blocks for Metal−Organic Frameworks. *Chem. Commun.* **2015**, *51*, 4796−4798. (b) Henderson, W. R.; Liu, G.; Abboud, K. A.; Castellano, R. K. Tuning Supramolecular Polymer Assembly through Stereoelectronic Interactions. *J. Am. Chem. Soc.* **2021**, *143*, 12688−12698. (c) Chen, C.-H.; Zheng, W.-H. Planar Chiral Boron Difluoride Complexes showing Circularly Polarized Luminescence. *Org. Chem. Front.* **2021**, *8*, 6622−6627.

(5) Sharma, B.; Kumar, V. Has Ferrocene Really Delivered Its Role in Accentuating the Bioactivity of Organic Scaffolds? *J. Med. Chem.* **2021**, *64*, 16865−16921.

(6) (a) DeHovitz, J. S.; Loh, Y. Y.; Kautzky, J. A.; Nagao, K.; Meichan, A. J.; Yamauchi, M.; MacMillan, D. W. C.; Hyster, T. K. Static to Inducibly Dynamic Stereocontrol: The Convergent use of Racemic *β*-Substituted Ketones. *Science* **2020**, *369*, 1113−1118. (b) Liu, L.-X.; Huang, W.-J.; Xie, Q.-X.; Wu, B.; Yu, C.-B.; Zhou, Y.-G. Dynamic Kinetic Resolution of Flavonoids *via* Asymmetric Allylic Alkylation: Construction of Two Contiguous Stereogenic Centers on Nucleophiles. *ACS Catal.* **2021**, *11*, 12859−12863.

(7) For selected reviews, see: (a) Li, T.; Jin, Z.; Chi, Y. R. N-Heterocyclic Carbene-Catalyzed Arene Formation Reactions. *Sci. China Chem.* **2022**, *65*, 210−223. (b) Zhang, Y.; Cai, H.; Gan, X.; Jin, Z. N-Heterocyclic Carbene-Catalyzed Enantioselective (Dynamic) Kinetic Resolutions and Desymmetrizations. *Sci. China Chem.* **2024**, *67*, 482.

(8) Lv, Y.; Luo, G.; Liu, Q.; Jin, Z.; Zhang, X.; Chi, Y. R. Catalytic Atroposelective Synthesis of Axially Chiral Benzonitriles via Chirality Control during Bond Dissociation and CN Group Formation. *Nat. Commun.* **2022**, *13*, 36.

(9) (a) Das, S.; Majumdar, N.; De, C. K.; Kundu, D. S.; Dohring, A.; Garczynski, A.; List, B. Asymmetric Catalysis of the Carbonyl-Amine Condensation: Kinetic Resolution of Primary Amines. *J. Am. Chem. Soc.* **2017**, *139*, 1357−1359. (b) Tu, H. F.; Yang, P.; Lin, Z. H.; Zheng, C.; You, S. L. Time-Dependent Enantiodivergent Synthesis *via* Sequential Kinetic Resolution. *Nat. Chem.* **2020**, *12*, 838−844.

(10) 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.

(11) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. A Highly Enantioselective Catalytic Intramolecular Stetter Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299.

(12) Enders, D.; Balensiefer, T. Nucleophilic Carbenes in Asymmetric Organocatalysis. *J. Am. Chem. Soc.* **2004**, *37*, 534−541.

(13) 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.

(14) Liu, Y.; Chen, Q.; Mou, C.; Pan, L.; Duan, X.; Chen, X.; Chen, H.; Zhao, Y.; Lu, Y.; Jin, Z.; Chi, Y. R. Catalytic Asymmetric Acetalization of Carboxylic Acids for Access to Chiral Phthalidyl Ester Prodrugs. *Nat. Commun.* **2019**, *10*, 1675.

(15) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. Hoch Asymmetrische NHC-Katalysierte Hydroacylierung Nichtaktivierter Alkene. *Angew. Chem., Int. Ed.* **2011**, *123*, 5087−5091.

(16) Nino-Liu, D. O.; Ronald, P. C.; Bogdanove, A. J. Xanthomonas Oryzae Pathovars: Model Pathogens of a Model Crop. *Mol. Plant Pathol.* **2006**, *7*, 303−324.