Access to Planar Chiral Ferrocenes via N-Heterocyclic Carbene-Catalyzed Enantioselective Desymmetrization Reactions

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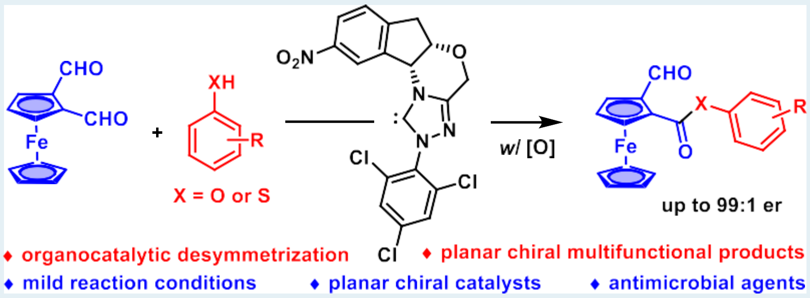


ABSTRACT: Ferrocene-derived dicarbaldehydes bearing pro-chiral planes are desymmetrized under the catalysis of chiral N-heterocyclic carbene organic catalysts. The reaction features selective activation and reaction of one of the aldehyde moieties of the ferrocene derivative while leaving the other aldehyde unit untouched. Our reaction affords enantiomerically enriched planar chiral ferrocene products obtained that are amenable for further transformations. Preliminary application studies show encouraging results when our products are explored for catalysis in chemical synthesis and for antimicrobial utilities in pesticide development.

KEYWORDS: *planar chiral molecule synthesis, N-heterocyclic carbene, organocatalysis, ferrocene derivatives, antibacterial activity*

Ferrocene and its derivatives bear sandwich structures[1] and can create planar chirality once two or more different functional groups are introduced onto one of their cyclopentadienyl rings. To date, planar chiral ferrocene derivatives have been explored in both synthetic chemistry[2] and medicinal research[3] (Figure 1a). For instance, the (R,S_p)-Xyliphos has been used as the ligand in the production of the chiral herbicide (S)-metolachlor.[4] Ferroquine bearing a stereogenic plane is an antimalarial reagent and has been advanced in the Phase II clinical trials for the treatment of malaria in a combination therapy.[5] Ferrocene-based polymers are also attractive because of their switchable polarity, modified electric potentials, electrochromic properties, and good thermal stabilities.[6] Therefore, the development of efficient and stereoselective methods for access to planar chiral ferrocene derivatives continues to attract much interest.

Planar chiral ferrocenes can nowadays be achieved via transition-metal-catalyzed cross-coupling reactions[7] (Figure 1b, left side). With the assistance of a central-chiral directing group (DG) installed on the ferrocene structure, an external functional group (FG) can be effectively introduced via a diastereoselective directed *ortho*-metalation (D*o*M) process.[8] An enantioselective D*o*M can also be achieved with the assistance of a nonchiral DG using a transition metal/chiral ligand catalytic system.[9] Chiral resolution strategies are also widely used for the enantioselective syntheses of vairous planar chiral ferrocene derivatives.[10] Only limited examples have been reported on the preparation of optically enriched ferrocene molecules through desymmetrization reactions[11] (Figure 1b, right side). For instance, Ogasawara, Takahashi, and co-workers have reported in 2010 an asymmetric interannular metathesis reaction for the enantioselective preparation of planar-chiral phosphaferrocene derivatives via a Molybdenum-promoted desymmetrization process.[11a] They also applied this method in the asymmetric intraannular ring-closing metathesis reaction in the desymmetrization of 1,2,3-triallylic ferrocene derivatives.[11b] Stephenson and co-workers have used the "click" reaction in the desymmetrization of 1,3-bisalkynyl ferrocenes with the assisstance of the CuCl/(R,R)-Ph-Pybox catalytic system.[11c] To the best of our knowledge, the use of mild and organocatalytic approaches for ferrocene desymmetrization reactions has remained underdeveloped.

Herein, we report an organocatalytic approach for asymmetric synthesis of ferrocene-based planar chiral multifunctional molecules (Figure 1c). N-Heterocyclic carbene (NHC)[12] is used as the sole organic catalyst for the

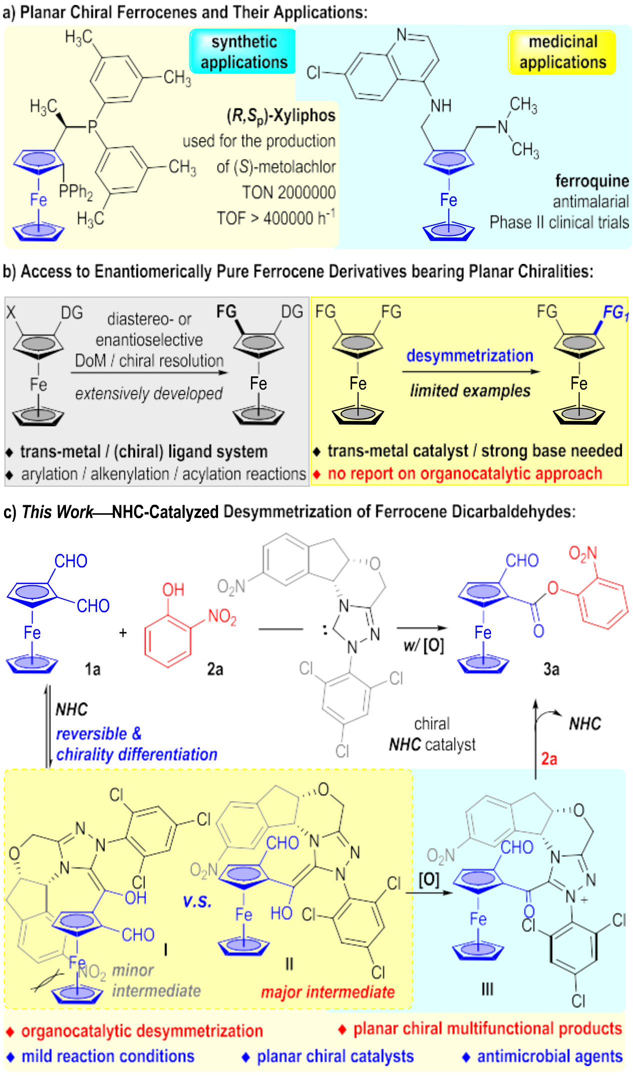


Figure 1. Planar chiral ferrocenes and their syntheses.

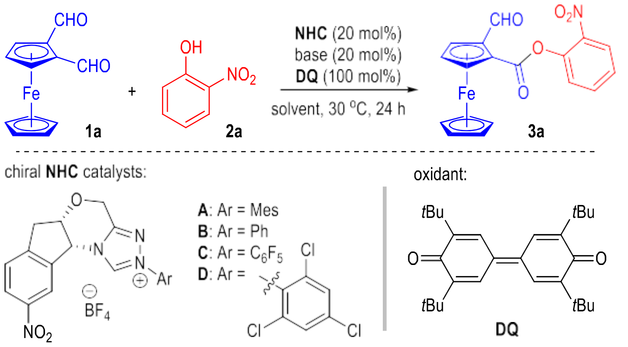
enantioselective desymmetrization of the pro-chiral ferrocene dicarbaldehyde 1a. After addition of the chiral NHC catalyst, two diastereoisomeric Breslow intermediates I and II are formed in reversible fashion. The intermediate II is much more easily formed than intermediate I because of steric reasons and can be oxidized under mild conditions to give the chiral acylazolium intermediate III. 2-Nitrophenol 2a is used as the esterification reagent to react with intermediate III to give the final planar chiral ester product 3a with regeneration of the free NHC catalyst.

As a special note, the optically enriched planar chiral products from our reaction (such as 3a) bear multiple functionalities and can be transformed to a diverse set of chiral molecules bearing stereogenic planes. These planar chiral molecules can be used as catalysts for various asymmetric reactions. They also provide new scaffolds as antimicrobial agents for the development of agrochemicals in plant protections.

It is also worth noting that although NHCs have been extensively used as effective catalysts for enantioselective acylation reactions,[13] NHC organocatalytic reactions have not been used in the synthesis of planar chiral molecules in any form. We hope our present study to stimulate further investigations into planar chiral molecule synthesis via organocatalytic approaches.

We started to search for a suitable reaction condition for the enantioselective desymmetrization of the ferrocene dicarbaldehyde 1a with the 2-nitrophenol 2a using different NHC organic catalysts in the presence of the DQ oxidant[14] (Table 1, entries 1 to 4). The NHC precatalyst A[15] bearing an electron-rich N-Mes group was not effective for this process (entry 1), while the NHC precatalysts bearing electron-neutral or electron-poor N-aryl substituents could give the desired planar chiral monoesterificated product 3a in moderate yields[16] (entries 2 to 4). Rovis, Bode, Berkessel, and others have demonstrated that the electron-withdrawing N-substituents on the NHC catalysts are beneficial to aldehyde esterification reactions under oxidative conditions,[17] since the NHC catalysts with low basicity can form the Breslow intermediates in reversible fashion and are easily oxidized to form the acylazolium intermediates for esterification reactions. To our delight, the NHC precatalyst D bearing an N-2,4,6-trichlorophenyl group gave the target product 3a in a promising 93:7 er value (entry 4). We therefore used the NHC precatalyst D for the examination of different bases in this protocol (entries 5 to 7). Switching the basic additive from Cs_2CO_3 into $PhCO_2Na$ resulted in a dramatic improvement in both the reaction yield and the enantioselectivity (entry 5).

Table 1. Condition Optimization[a]



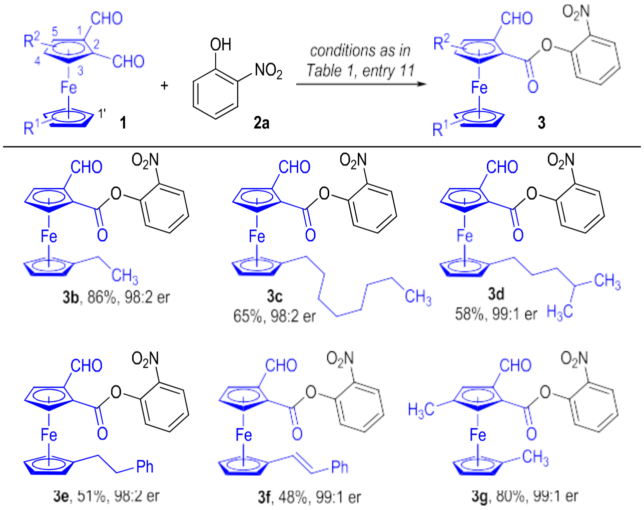
entry	NHC	base	solvent	yield (%)[b]	er (%)[c]
1	A	Cs_2CO_3	THF	0	
2	B	Cs_2CO_3	THF	47	58:42
3	C	Cs_2CO_3	THF	79	73:27
4	D	Cs_2CO_3	THF	58	93:7
5	D	PhCOONa	THF	79	95:5
6	D	Et_3N	THF	75	90:10
7	D	DBU	THF	70	85:15
8	D	PhCOONa	CH_2Cl_2	74	78:22
9	D	PhCOONa	toluene	61	85:15
10	D	PhCOONa	CH_3CN	76	64:36
11[d]	D	PhCOONa	THF	81	96:4
12[e]	D	PhCOONa	THF	79	96:4
13[d,f]	D	PhCOONa	THF	60	96:4
14[d,g]	D	PhCOONa	THF	25	96:4

[a] Unless otherwise specified, the reactions were carried using 1a (0.20 mmol), 2a (0.10 mmol), DQ (0.10 mmol), NHC (0.02 mmol), base (0.02 mmol), solvent (1.0 mL) at 30 °C for 24 h. [b] Isolated yield of 3a. [c] The er values were determined via HPLC on chiral stationary phase. [d] 6.0 mL of THF was used as the solvent at −20 °C for 48 h. [e] The reaction was carried at 10.0 mmol based on 1a. [f] 1a (0.15 mmol) was used. [g] 1a (0.10 mmol) was used.

The use of organic bases led to drops of the reaction outcome (entries 6 to 7). The reaction also turned out to be sensitive to the solvent we used (entries 8 to 10). Both nonpolar (entries 8 to 9) and highly polar (entry 10) organic solvents other than THF we used gave the target product 3a in much decreased optical purities, although the yields of 3a were still moderate. Finally, the er value of the planar chiral monoester 3a could be further increased to 96:4 when carrying out the reaction in a diluted system at −20 °C, with the yield of 3a also improved to 81% after an extended reaction period (entry 11). It is pleasing to find that the reaction can also be carried out at large scale without obvious erosion on either the product yield or optical purity (entry 12). Noteworthily, reducing the amount of the dialdehyde substrate 1a resulted in an obvious drop in the yield of 3a, with the nonchiral diester byproduct afforded in 10% to 30% yields in these cases (entries 13 to 14). In contrast to our previous studies with *o*-phthaladehyde substrates,[18] no formation of the lactol acylation products was observed. This is probably because the formation of the monoesterificated product 3a is both kinetically and thermodynamically favored.

With an optimal reaction condition at hand (Table 1, entry 11), we then examined the substrate scope of this enantioselective desymmetrization reaction using ferrocene-based dicarbaldehydes 1 bearing different substitution patterns (Scheme 1). Various alkyl groups are well tolerated on the 1′-position of the ferrocene moieties of the substrates 1, with the planar chiral monoesterificated products afforded in moderate to good yields and excellent enantioselectivities (3b to 3e). The 1′-alkyl group can also be switched to a *trans*-styryl group, and the planar chiral product 3f was given in a moderate yield with excellent enantioselectivity. Noteworthily, a methyl group can be introduced onto the 4-position of the ferrocene structure, with the optically pure monoesterified product 3g afforded in a good yield.

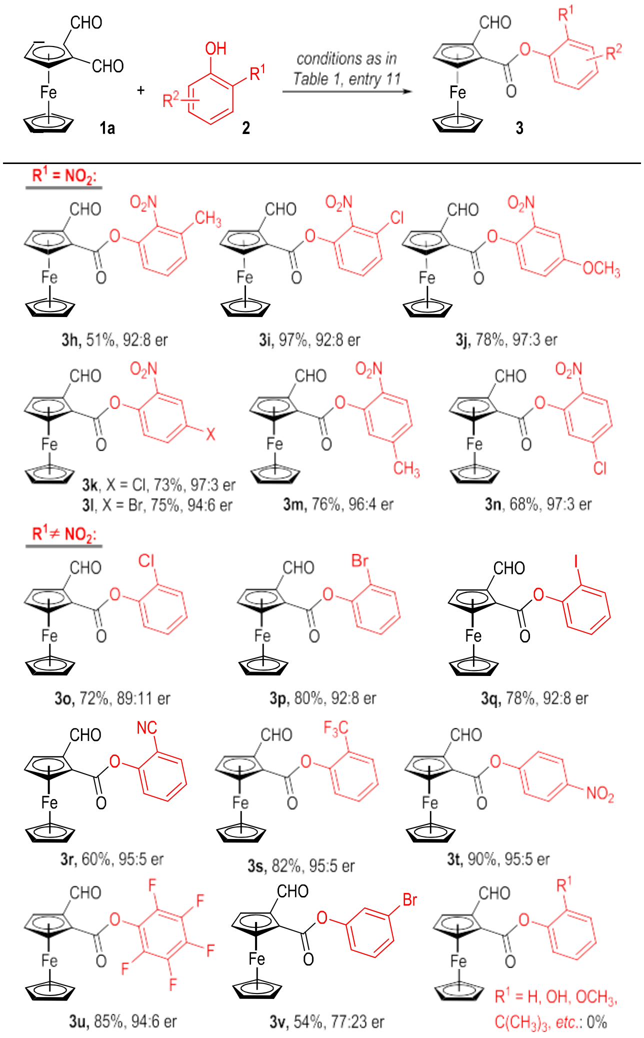
Scheme 1. Scope of Ferrocene Dicarbaldehydes 1[a]



[a] Reaction conditions as stated in Table 1, entry 11. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on chiral stationary phase.

Having examined the substrate scope of the ferrocene dicarbaldehydes 1, we then studied the effects of the substitution patterns on the phenol substrates 2 (Scheme 2). Both electron-donating and electron-withdrawing substituents can be introduced onto the 3- and 4-positions of the 2-nitrophenol moiety, with the target planar chiral ferrocene products afforded in moderate to excellent yields and good to excellent enantioselectivities (3h to 3n). Substitutions on the 5-position of the 2-nitrophenol substrate resulted in no reaction under the current catalytic condition. This is probably due to the fairly increased steric hindrance caused by the two adjacent substituents to the phenol OH group.

Scheme 2. Scope of the Phenols 2[a]

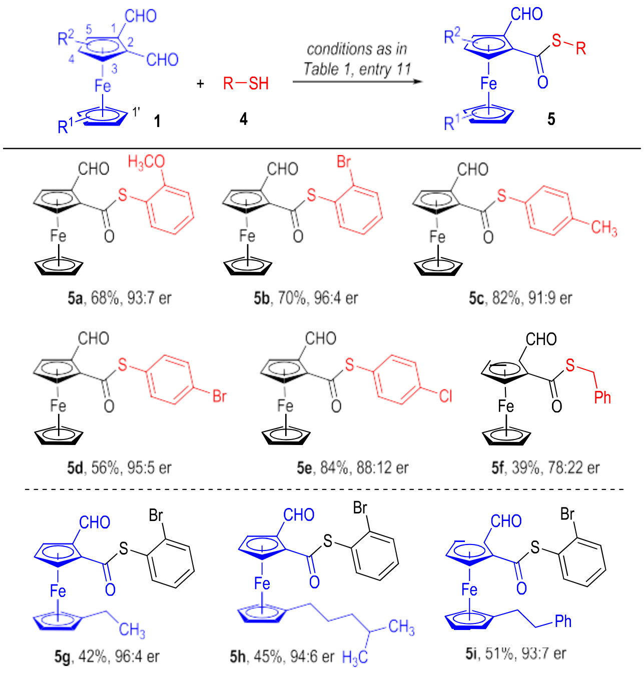


[a] Reaction conditions as stated in Table 1, entry 11. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on chiral stationary phase.

Gratifyingly, the 2-nitro group on the phenol moieties of the products can also be switched into various electron-withdrawing groups to give the corresponding planar chiral monoester products in good yields and optical purities (3o to 3s). Both of the 4-nitrophenol and the pentafluorophenol can be used as effective esterification reactants for this NHC-catalyzed desymmetrization process, with the desired mono-esterificated aldehyde products afforded in good to excellent yields and enantioselectivities (3t and 3u). However, the introduction of a three-electron-withdrawing Br group on the phenol substrate resulted in significant drops of the product yield and er value (3v). It is worthwhile to note that no reaction occurred when using electron-rich phenols as the esterification reagents in this process under the current optimized reaction condition. This is probably because the pK_a values of the phenol molecules bearing electron-donating substituents are very high and the deprotonation processes of the electron-rich phenols are difficult even with stronger bases (e.g., DBU, NaOH, LHMDS) under the otherwise identical conditions.

To our great delight, thiols 4 also worked well as the esterification reagent for the face-selective desymmetrizations of the ferrocene dicarbaldehydes 1 (Scheme 3). Thioesters 5 bearing both electron-donating and electron-withdrawing groups at the 2- and 4-positions of the aromatic thiol moieties were afforded in moderate to good yields and optical purities (5a to 5e). Benzyl mercaptan could also be used as the nucleophile in this reaction, although the product yield and er value were not satisfactory under the current reaction condition (5f). The ferrocene dicarbaldehyde 1 bearing different alkyl substituents could give the corresponding planar chiral 2-bromophenylthioesters in moderate yields with good to excellent enantioselectivities (5g to 5i).

Scheme 3. Reactions between Ferrocene Dicarbaldehydes 1 and Thiols 4[a]



[a]Reaction conditions as stated in Table 1, entry 11. Yields are isolated yields after purification by column chromatography. Er values were determined via HPLC on chiral stationary phase

The optically enriched planar chiral multifunctional products obtained from this approach are amenable in various transformations via simple protocols (Figure 2). For example, the 2-nitrophenol ester moiety of 3a can be hydrolyzed under basic conditions to give the bifunctional planar chiral ferrocene 6 containing both an aldehyde and a carboxylic acid group. The carboxylic acid group of 6 can react with phenylamine and afford the planar chiral amide 7 with retention of the optical purity. Both of the aldehyde groups on 3a and 6 can be protected by alcohols or thiols via simple protocols, with the target products of the acetal 8 and the dithioacetals 9 to 12 (which can be esterificated to give 13 to 16 in excellent yields) afforded in moderate to good yields without obvious erosions on the optical purities.

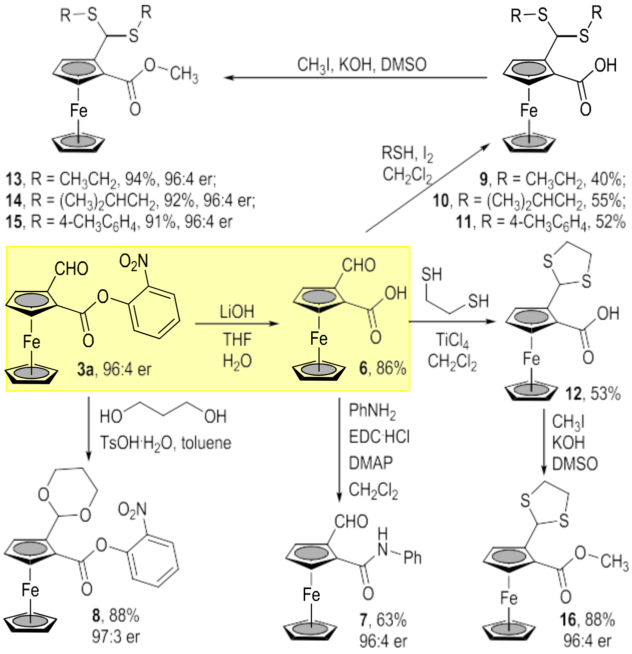


Figure 2. Synthetic derivatizations of the planar chiral ferrocene 3a.

Although carbaldehydes[19] and carboxylic acids[20] bearing stereogenic centers and axes have been extensively studied in various aspects, the application of planar chiral carbaldehydes and acids in either organic synthesis or biological research has been rarely reported. This is probably due to the lack of efficient method for asymmetric preparation of such functional molecules bearing stereogenic planes.

Having obtained a diversity of planar chiral ferrocene-derived aldehydes and carboxylic acids, we were able to apply these functional molecules as catalysts/ligands in asymmetric catalytic reactions (Figure 3). For example, the monoesterificated ferrocene carbaldehyde 3b can catalyze the S_N1 substitution reaction between the amine 17 and the indole phenyl methanol 18 in the presence of a catalytic amount of the acid DNBA, with the chiral indole derivative 19 afforded in a moderate yield and enantioselectivity (eq 1).[21] The bifunctional ferrocene 7 bearing both a carbaldehyde and a carboxylic acid group can promote the cycloaddition reaction of the α, β-unsaturated ester 20 and the α-amino acid ester 21 in enantioselective fashion (eq 2).[22] Both of the *trans*- and *cis*-γ-lactam isomers of the product 22 can be afforded with good er values. Additionally, the planar chiral carboxylic acid 12 can be used as the chiral ligand for the Co-catatyzed enantioselective C(sp3)-H amination reaction between thioamide 23 and the dioxazolone 24, although the optical purity of the product 25 was only moderate at the current stage (eq 3).[23]

The planar chiral ferrocene derivatives obtained from our approach also exhibit interesting bioactivitites in our research on novel pesticide development for plant protections (Table 2). For example, many of our optically enriched ferocene-derived multifunctional molecules show excellent antibacterial activities against *Xanthomonas axonopodis* pv. *citri* (*Xac*)[24] that can cause citrus canker and result in huge economic loss in the production of lemons, oranges, and grapefruits. Compared with the thiodiazole copper (TC) that has been widely used as

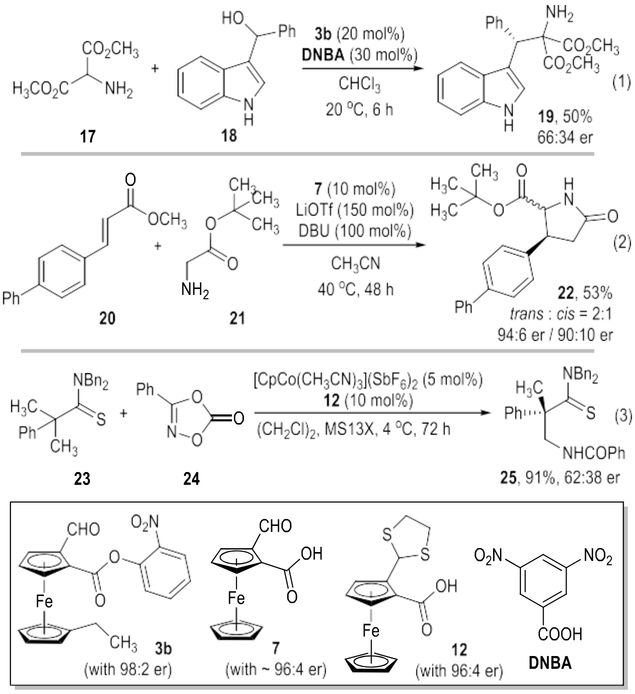


Figure 3. Asymmetric catalytic reactions promoted by the planar chiral ferrocene product derivatives.

Table 2. *In Vitro* Inhibitive Activities of the Planar Chiral Compounds against *Xanthomonas axonopodis* pv. citri (*Xac*)[a]

compounds	100 μg/mL	50 μg/mL
3b	65.75 ± 4.80	61.08 ± 3.32
3j	73.87 ± 1.66	68.28 ± 2.39
3k	68.66 ± 2.16	41.67 ± 0.64
3l	84.19 ± 0.75	71.29 ± 2.21
3m	69.25 ± 0.46	25.91 ± 4.25
3n	72.04 ± 0.49	58.17 ± 2.63
3s	85.86 ± 0.65	74.35 ± 3.22
3v	66.88 ± 5.83	58.49 ± 2.60
5b	76.94 ± 4.48	61.40 ± 4.61
5d	68.44 ± 2.54	59.09 ± 0.83
5e	73.39 ± 1.25	56.56 ± 5.23
5g	65.59 ± 4.52	64.30 ± 2.85
5h	66.34 ± 6.30	64.41 ± 2.70
8	76.24 ± 1.04	87.90 ± 2.45
TC[b]	46.08 ± 3.91	33.17 ± 4.01

[a] All data were average data of three replicates. [b] TC = thiodiazole copper.

a commercially available antibacterial agrichemical, 14 of the chiral prodcuts afforded from our method have shown obviously superior antibacterial activities and can be regarded as promising candidates in the search for new pesticide structures.

In summary, we have disclosed an NHC-catalyzed enantioselective desymmetrization reaction for the synthesis of optically enriched planar chiral ferrocenes. It represents an alternative strategy for the preparation of planar chiral functional molecules under mild and transition-metal-free conditions. The pro-chiral planes existing in the ferrocene dicarbaldehyde substrate can be efficiently discriminated by a single chiral NHC organic catalyst, with one of the two carbaldehyde groups oxidized and esterificated in enantioselective fashion. Both of the ferrocene dicarbaldehyde and the nucleophilic esterification reactants can tolerate a diversity of substitutents, with the planar chiral monoesterificated products afforded in moderate to excellent yields and optical purities. The multifunctional planar chiral ferrocene derivatives obtained from this approach have shown broad applications in both synthetic and biological research. Further investigations into the synthesis of planar chiral functional molecules via simple and metal-free organocatalytic reactions and their applications in novel pesticide development are in progress in our laboratories.

ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at

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

X-ray data for 8 (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge financial support from the National Natural Science Foundation of China (21961006, 32172459, 22071036), The 10 Talent Plan (Shicengci) of Guizhou Province ([2016]5649), the Science and Technology Department of Guizhou Province ([2019]1020, Qiankehejichu-ZK[2021]Key033), the Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University, Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY (2020)004], the Guizhou Province First-Class Disciplines Project [(Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008], 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 Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG7/20, RG5/19), MOE AcRF Tier 2 (MOE2019-T2-2-117), MOE AcRF Tier 3 Award (MOE2018-T3-1-003); Nanyang Research Award Grant, Chair Professorship Grant, Nanyang Technological University.

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