

EDGE ARTICLE

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Iron^{III}-catalyzed asymmetric inverse-electron-demand hetero-Diels–Alder reaction of dioxopyrrolidines with simple olefins†

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The asymmetric catalytic inverse-electron-demand hetero-Diels–Alder reaction of dioxopyrrolidines with a variety of simple olefins has been accomplished, significantly expanding the applicability of this cyclization to both cyclic hetero-dienes and dienophiles. A new type of strong Lewis acid catalyst of ferric salt enables the LUMO activation of dioxopyrrolidines *via* formation of cationic species, this method yields a range of bicyclic dihydropyran derivatives with exceptional outcomes, including high yields (up to 99%), diastereoselectivity (up to 99:1) and enantioselectivity (up to 99% ee) under mild conditions. This facile protocol was available for the late-stage modification of several bioactive molecules and transformation into macrocycle molecules as well. The origins of enantioselectivity were elucidated based on control experiments.

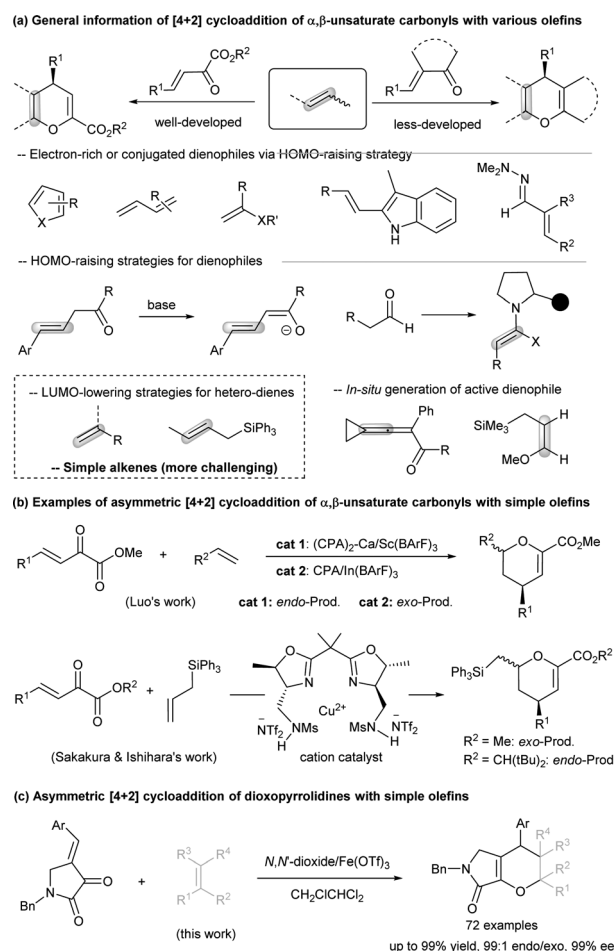
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Introduction

The synthesis of novel heterocyclic scaffolds continues to capture the attention of the organic chemistry community owing to their potential pharmaceutical activities.¹ The inverse-electron-demand hetero-Diels–Alder (IEDHDA) reaction, a significant variant of Diels–Alder reactions, proves adept at incorporating functional groups into hetero-rings (Scheme 1a). Particularly noteworthy is its asymmetric catalytic version, enabling the construction of optically enriched six-membered rings.² Mechanistically, this reaction unfolds through the interaction between the LUMO of an electron-deficient hetero-diene and the HOMO of electron-rich dienophiles. In this context, the use of chiral Lewis acids or organocatalysts becomes instrumental in expediting enantioselective transformations, employing three primary strategies: elevating the HOMO of dienophiles, lowering the LUMO energy of dienes, or concurrently activating both through dual modulation.³ As evidenced in Scheme 1a, the asymmetric catalytic IEDHDA reactions involving α,β -unsaturated carbonyls with electron-rich dienophiles, such as cyclic or acyclic 1,3-dienes,⁴ vinyl ethers⁵ and the related,⁶ or hydrazone conjugated carbon-carbon double bond,⁷ have been well demonstrated. HOMO-raising strategies, employing enamine⁸ or enolate activation⁹



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Scheme 1 General information about the catalytic asymmetric IEDHDA reaction.

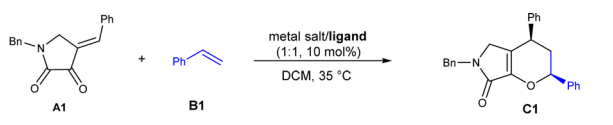
with organocatalysts, further broaden the scope of dienophiles. The generation of active dienophiles *in situ*, exemplified by the conversion of 3-cyclopropylideneprop-2-enone into cyclobutene-fused furans¹⁰ or the oxidation of ethers,¹¹ facilitates rapid and alternative access to cycloaddition products. In contrast, IEDHDA reaction of simple alkenes is generally challenging^{12,14} and achievable only by lowering the LUMO of hetero-dienes. Two successful examples involve the asymmetric [4 + 2] cycloaddition of β,γ -unsaturated α -ketoesters into chiral oxanes (Scheme 1b), as illustrated in Scheme 1b. Luo's approach employs a chiral binary acid complex that synergistically combines a chiral phosphoric acid with a metal salt (In^{III} or Sc^{III}).¹³ Sakakura and Ishihara's report features an *n*-cation copper complex.¹⁴ Critically, both processes aim to enhance the cationic nature of the metal centers for the LUMO activation of dienes. Despite these advancements, further exploration of diene species, such as cyclic enones instead of linear unsaturated α -ketoesters, for the asymmetric catalytic IEDHDA reaction of unactivated alkenes, which may suffer partial polymerization, remains a challenging frontier in current research.

Bicyclic dihydropyrans fused with a γ -lactam or pyrrolidine moiety constitute core structures in bioactive molecules and natural products.¹⁵ The asymmetric IEDHDA reaction of γ -lactam-derived cyclic enones offers an efficient pathway for constructing these valuable backbones (Scheme 1c).¹⁶ We propose that chiral Lewis acid catalysts, specifically those employing *N,N'*-dioxide ligands, may expedite the cycloaddition by LUMO-activating dioxopyrrolidine¹⁷ for cyclization with simple olefins. This rationale is grounded in the observation that chelation of these tetra-oxygen ligands allows the counterion of the metal precursor to delocalize from the metal center to extend, generating *n*-cation-characterized stronger Lewis acid catalysts.¹⁸ Concerning stereoselectivity, challenges extend beyond enantioselectivity to include the *endo/exo* ratio influenced by orbital-favored transition states and a stepwise 1,4-addition/cyclization process.¹⁹ In this context, we present a chiral iron-complex catalyzed asymmetric IEDHDA reaction of dioxopyrrolidines with simple alkenes, yielding various optically active bicyclic dihydropyran derivatives with outstanding results: up to 99% yield, 99:1 diastereoselectivity, and up to 99% enantioselectivity, all achieved under mild conditions.

Results and discussion

Our investigation of the IEDHDA reaction began with dioxopyrrolidine **A1** and styrene **B1** as model substrates to optimize the reaction conditions (Table 1). We identified the critical parameters to the reactivity and found that Lewis acidity of the metal salts played a decisive role in whether the reaction occurs (see ESI† for details), which is in consistent with the mechanism of LUMO-activation of hetero-diene. The reaction performed only in the presence of stronger Lewis acids, such as In(OTf)₃, Fe(OTf)₃, or Al(OTf)₃, to give the desired product **C1** in low diastereoselectivity. The comparison with the reaction of heterosubstituted alkenes which could be performed with Ni^{II} complexes manifested critical of the Lewis acidity of the

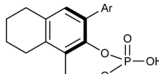
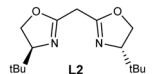
Table 1 Optimization of the reaction conditions^a



$\text{A1} + \text{B1} \xrightarrow[\text{DCM, 35 } ^\circ\text{C}]{\text{metal salt/ligand (1:1, 10 mol\%)}} \text{C1}$

L₃-TQMe₂: X = Me, Y = H
 L₃-TQEt₂: X = Et, Y = H
 L₃-TQEt₂Me: X = Et, Y = Me
 L₃-TQEt₂Br: X = Et, Y = Br
 L₃-TQEt₂Ad: X = Et, Y = 1-adamantyl

L₃-PrEt₂Ad: n = 1
 L₃-PiEt₂Ad: n = 2

L1: Ar = 2,4,6-*i*-Pr₃C₆H₂
 L2: 
 L3: 

Entry	M(OTf) ₃	Ligand	Yield ^b (%)	<i>endo/exo</i> ^c	ee ^c (%)
1	In(OTf) ₃	L ₃ -TQMe ₂	84	56 : 44	43/44
2	In(OTf) ₃	L ₃ -TQEt ₂	99	68 : 32	59/40
3	In(OTf) ₃	L ₃ -TQEt ₂ Me	98	73 : 27	75/53
4 ^d	In(OTf) ₃	L ₃ -TQEt ₂ Me	91	73 : 27	84/59
5 ^d	Fe(OTf) ₃	L ₃ -TQEt ₂ Me	87	83 : 17	93/19
6 ^d	Fe(OTf) ₃	L ₃ -TQEt ₂ Br	29	78 : 22	65/0
7 ^d	Fe(OTf) ₃	L ₃ -TQEt ₂ Ad	95	90 : 10	97/72
8 ^{d,e}	Fe(OTf) ₃	L ₃ -TQEt ₂ Ad	93	90 : 10	97/73
9 ^{d,e}	Fe(OTf) ₃	L ₃ -PrEt ₂ Ad	44	77 : 23	39/31
10 ^{d,e}	Fe(OTf) ₃	L ₃ -PiEt ₂ Ad	36	87/13	92/69
11 ^{d,e}	Fe(OTf) ₃	L1	NR	—	—
12 ^{d,e}	Fe(OTf) ₃	L2	Trace	—	—
13 ^{d,e}	Fe(OTf) ₃	L3	Trace	—	—

^a The reactions were carried out with **A1** (0.1 mmol), **B1** (1.0 mmol) and ligand/metal (1 : 1, 10 mol%) in CH₂Cl₂ (1.0 mL) at 35 °C for 24 h. ^b Yield of isolated product. ^c Determined by chiral UPC² on a chiral stationary phase. ^d CH₂ClCHCl₂ as solvent. ^e With 0.5 mmol **B1** for 48 h. NR, no reaction.

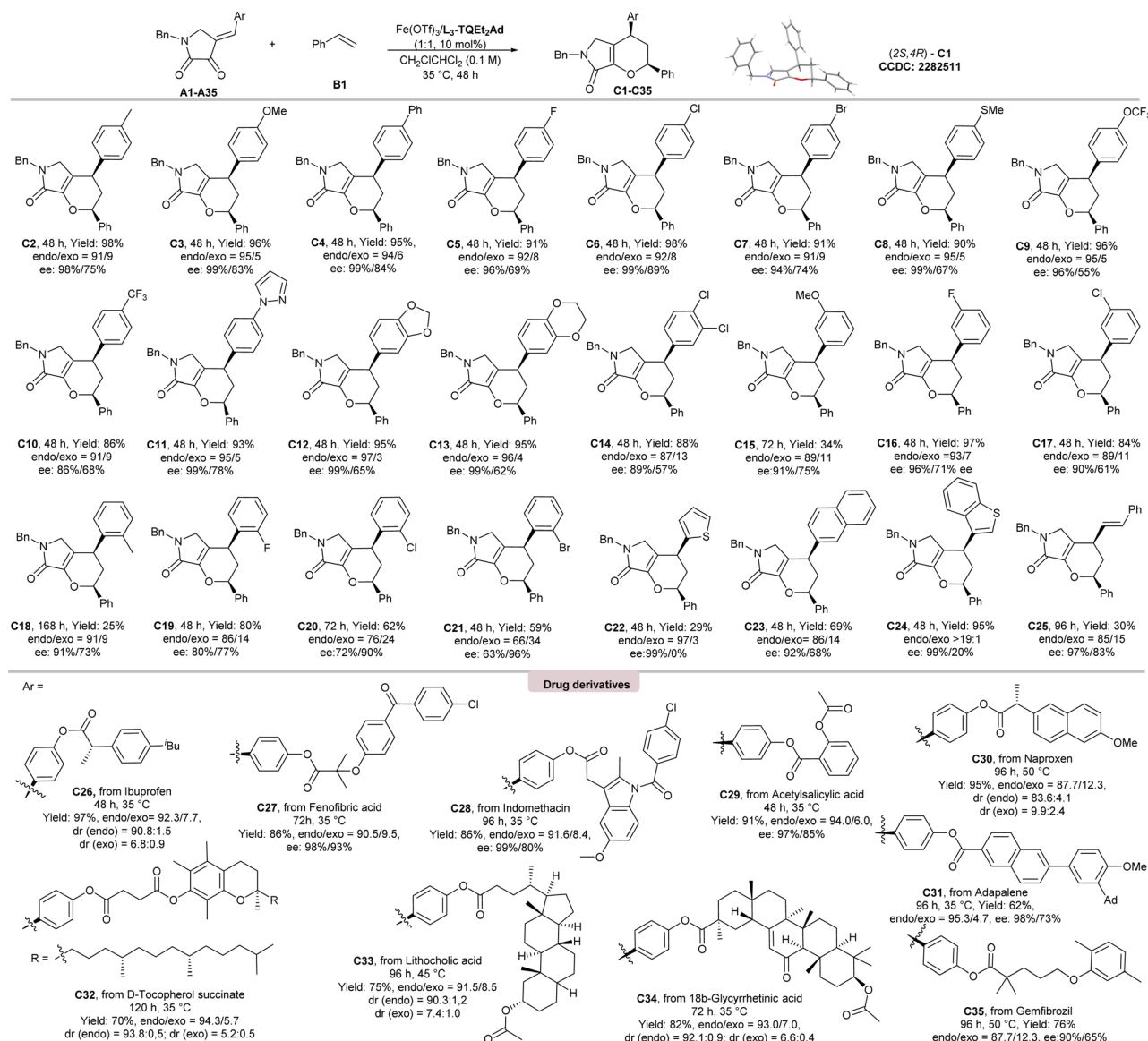
catalyst.²⁰ Using 10 mol% of In(OTf)₃ in CH₂Cl₂ at 35 °C, the cycloaddition product was isolated in 84% yield and 48 : 52 *endo* : *exo*, which is selected to identify optimal chiral ligands to control the stereoselectivity. Noteworthy, the diastereoselectivity is poor, differing from the preferred *endo*-selectivity of achiral Lewis acid-promoted IEDHDA of β,γ -unsaturated α -ketoesters.²¹ Investigating asymmetric catalytic reaction showed that the substituents of chiral *N,N'*-dioxide ligands at the anilines affected the diastereo- and enantioselectivity a lot (Table 1, entries 1–3). The reaction catalyzed by In(OTf)₃/L₃-TQEt₂Me delivered the product in 91% yield with 73 : 27 *endo* : *exo*, and 84% ee for *endo*-isomer when 1,1,2-trichloroethane was used as the solvent (entry 4). The use of Fe(OTf)₃ instead led to slightly increased *endo*-diastereoselectivity (entry 5). Further modification of *para*-substitutions at the aniline units of the ligands was carried out (entries 5–7), and it was observed that by introduction of steric hindered 1-adamantyl group into the *para*-position (L₃-TQEt₂Ad) lead to a slightly higher diastereoselectivity and enantioselectivity, and the product **C1** was isolated in 95% ee with 90 : 10 *endo* : *exo*



ratio and 97% ee (entry 7). Reducing the usage of styrene to 5 equivalents led to no disadvantage to the outcomes (entry 8). Reinvestigation of the amino backbone of *N,N'*-dioxide ligands showed that the reactivity dropped a lot when *L*-proline or *L*-piperidine based ones were employed (entries 9 and 10). Comparatively, other representative chiral ligands, such as chiral phosphoric acid **L1**, bisoxazoline **L2** and pyridine-oxazoline **L3** resulted in poor reactivity (entries 11–13), which manifests the importance of ligand-acceleration in asymmetric Lewis acid catalysis.²² In these cases, the minor *exo*-product was obtained in lower ee value than the *endo*-product. The absolute configuration of *endo*-product **C1** was determined to be (2*S*, 4*R*) by X-ray crystallography analysis²³ (see ESI† for details).

Under the optimal conditions, the substrate scope of IEDHDA reaction of dioxopyrrolidines with styrene were

evaluated as listed in Scheme 2. Most of the desired products could be obtained in excellent total yields (84–98%) and enantioselectivities (86–99% ees) for the *endo*-isomers (**C2–C14**, **C16**, and **C17**). But those with *ortho*-substituted phenyl groups (25–80% yields; **C18–C21**) and *meta*-methoxyl substituted **C15** (34% yield) were exceptions, especially 2-Cl and 2-Br-containing ones whose *endo*-selectivity dropped a lot, and ee value of the *exo*-isomers are higher than *endo*-isomers (**C19–C20**). It is also interesting to found that the *endo*:*exo* ratio of the tetrahydropyranopyrrolones with electron-donating aryls (95 : 5 to 97 : 3) is higher than the electron-deficient ones (87 : 13 to 92 : 8), manifesting the influence of a concert or stepwise pathway. The phenyl ring could be replaced by 2-thiophene (**C22**), 2-naphthyl (**C23**), 2-benzothiophene (**C24**), and phenylallyl substituents (**C25**), which were also suitable.

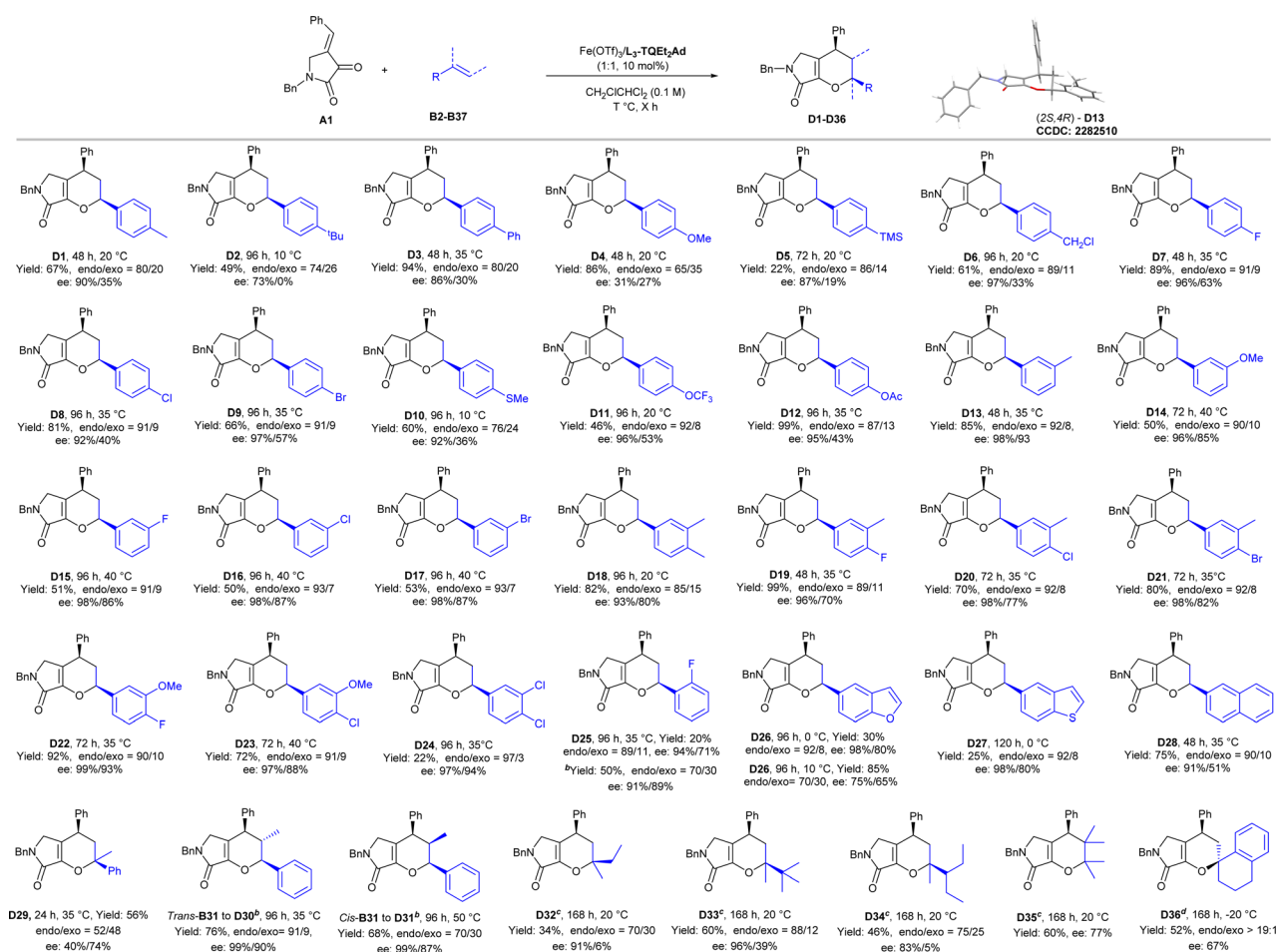


Scheme 2 The substrate scope of dioxopyrrolidines. ^a Unless otherwise noted, all reactions were performed with **A** (0.1 mmol), styrene **B1** (0.5 mmol) and Fe(OTf)₃/L₃-TQEt₂Ad (1 : 1, 10 mol%) in CH₂ClCHCl₂ (1.0 mL) at 35 °C. The yield is isolated yield. The *endo* : *exo* ratio was determined by ¹H NMR analysis and the ee value was determined by UPC² or HPLC on a chiral stationary phase.

To our delight, the current method could be used in the late-stage modification of complex and bioactive compounds. As illustrated in Scheme 2, the reaction of ibuprofen, fenofibric acid, indomethacin, acetylsalicylic acid, naproxen, adapalene, D-tocopherol succinate, as well as gemfibrozil derived dioxopyrrolidines with styrene **B1** underwent smoothly, affording the desired bicyclic dihydropyranes (**C26–C35**) in excellent yields (62–97%), *endo* : *exo* ratio (88 : 12–94 : 6) and enantioselectivities (90–99% ees). Complex terpenoid derivatives underwent smoothly, affording the desired products (**C33–C34**) in good yields (75–82%), and excellent enantioselectivities (98% ee). Nevertheless, the current catalytic system is not fit for the cyclization of acyclic hetero-diene (see ESI† for details).

Subsequently, we turned our attention to the substrate scope of alkenes (Scheme 3) to illustrate the IEDHDA reaction. A series of styrenes **B** (**B2–B37**), regardless of the substituent pattern and the electronic property of the aryl moiety, reacted with dioxopyrrolidine **A1** smoothly, providing the desired bicyclic dihydropyranes **D1–D36** in moderate to good yields and high enantioselectivities. The position of substitution at phenyl group displayed a significant effect on the stereocontrol of [4 +

2] cycloaddition. Styrenes with different functional groups at *para*-position were tolerated well to deliver the corresponding products. Generally, electron-withdrawing groups, as 4-fluor (**D7**) or 4-chloro (**D8**) substitutions, gave better diastereo- and enantioselectivity than electron-donating groups (**D1–D6**). However, if the steric hindrance of *para*-position of the aryl group increased, the reactivity dropped obviously and displayed a negligible effect on the stereocontrol (**D7–D9**). Lower diastereo- and enantioselectivity were given for 4-methoxyphenyl substituted **D4** (86% yield, *endo* : *exo* = 65 : 35, 31%/27% ee), implying the disfavored competition of stepwise 1,4-addition/cyclization process. In contrast, electron-withdrawing groups or weak electron-donating groups at 3- or 3,4- substituted substrates were found to be suitable in the reaction (**D10–D23**; 46–99% yields, 76 : 24–93 : 7 *endo* : *exo*, 81–99% ees). The absolute configuration of product **D13** was determined to be (2*S*, 4*R*) by X-ray crystallography analysis (see ESI† for details).²³ 3,4-Dichloro, and 2-fluoro substituted styrenes could be achieved in good selectivity, unfortunately, the reactivity is lower (**C24–C25**). Moreover, the phenyl ring could be replaced by 2-benzofuran (**D26**), 2-benzothiophene (**D27**), 2-naphthyl (**D28**), but the



Scheme 3 The substrate scope of olefins.^a Unless otherwise noted, all reactions were performed with dioxopyrrolidine **A1** (0.1 mmol), olefin (0.5 mmol) and Fe(OTf)₃/L₃-TQEt₂Ad (1 : 1, 10 mol%) in CH₂ClCHCl₂ (1.0 mL). Isolated yield. The *endo* : *exo* ratio was determined by ¹H NMR analysis and the ee value was determined by UPC² or HPLC on a chiral stationary phase. ^b NaBAR₄ (50 mol%). ^c In CH₃CN with In(OTf)₃/L₃-TQEt₂ (1 : 1, 20 mol%). ^d Fe(OTf)₃/L₂-TQEt₂Ad (1 : 1, 10 mol%).

reaction temperature had to be rationalized in order to balance the enantioselectivity and yield. Propen-2-ylbenzene participated in the cyclization in moderate yield and dropped stereoselectivity (**D29**). Both *trans*- and *cis*-propen-1-ylbenzene could perform the reaction in good *endo*-selectivity and excellent enantioselectivity but the yields were moderate (**D30–D31**) after the addition of NaBAR₄^F. Similarly, when *trans*-methylstyrene bearing 3,4-dimethoxyl substituents was subjected, only moderate stereoselectivity was obtained (see ESI† for details). Although the *trans*-configuration of olefine delivered into the product without change, and no obverse intermediate was detected, stepwise pathway or a concerted asynchronous could not be ruled out. Moreover, when α,α -dialkyl olefins or 2,3-dimethylbut-2-ene were used as the dienophiles (**D32–D35**), good enantioselectivity could be given after reinvestigation of the chiral catalyst as In(OTf)₃/L₃-TQEt₂ combination. The reaction of tetrahydronaphthalene bearing an exocyclic double bond worked in the presence of Fe(OTf)₃/L₂-TQEt₂Ad to afford only *endo*-**D36** in 52% yield with 67% ee.

To illustrate the potential synthetic utility of the current catalytic system, a scale-up synthesis of **C1** were performed. As shown in Scheme 4a, under the optimized reaction condition, dioxypyrrolidine **A1** (3.2 mmol) reacted smoothly with styrene **B1** (5.0 equiv.), affording the desired product **C1** in 94% yield (1.15 g) with 90 : 10 *endo/exo* ratio and 99% and 71% ee separately. Under the oxidation of RuCl₃ with NaIO₄, the double bond of dihydropyrrolone ring of *endo*-**C1** broke to give O,N-based macrocycle **E1** in good yield with slight loss of stereoselectivity.²³ Alternatively, reduction reaction mediated by H₂ in the presence of Pd/C in methanol led to the ring-opening reaction to yield **E2** in nearly completely yield but the optical purity decreased a little (Scheme 4b).

UV-vis absorption spectra were carried out to show the interaction of chiral ferric iron catalyst with the diene (Fig. 1a). There was obvious hyperchromic effect upon mixing Fe(OTf)₃ with dioxypyrrolidine **A1**, especially in the presence of the L₃-TQEt₂Ad ligand. In addition, the investigation of relationship between ee value of L₃-TQEt₂Ad and that of **C1** showed a self-evident linear effect,²⁴ implying catalytically active species was likely to be the monomeric complex of Fe(OTf)₃ and L₃-TQEt₂Ad (Fig. 1b).

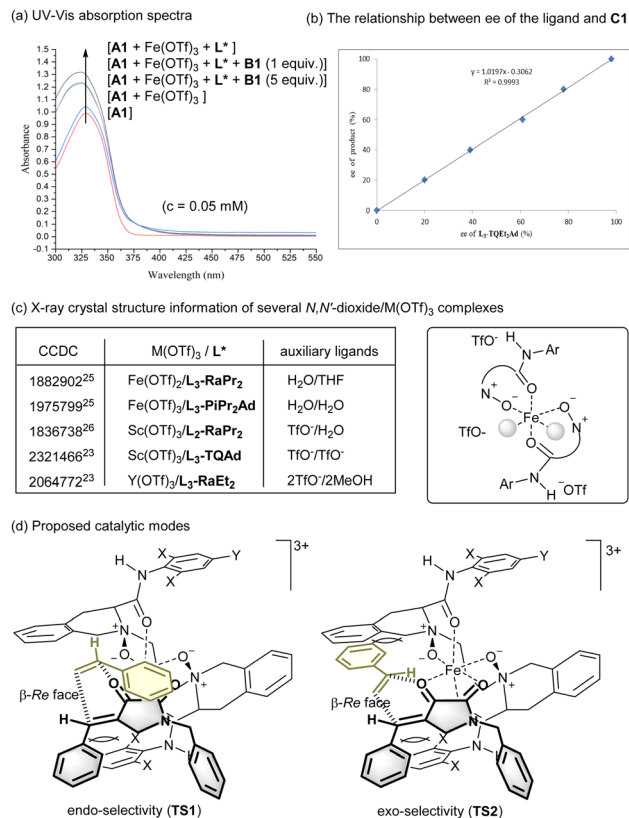
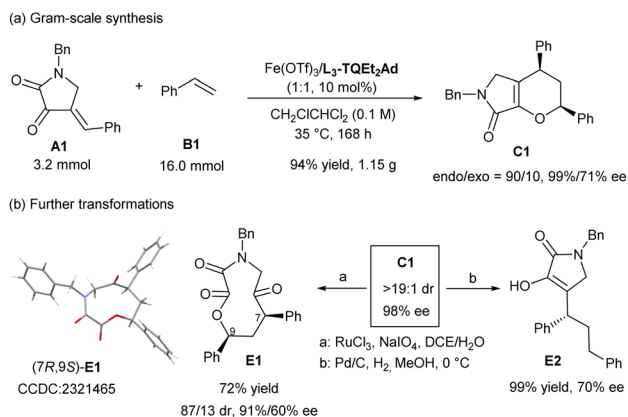


Fig. 1 Reaction mechanism consideration.

Chiral *N,N'*-dioxide rare-earth metal complexes, such as Sc(OTf)₃ or Y(OTf)₃, which are usually rationalized as good Lewis acid candidates, were found to sluggish in accelerating the cycloaddition (see ESI† for details). Analysis of several crystal structures of *N,N'*-dioxide-M(OTf)₃ complexes provide interesting cooperation priority (Fig. 1c). It was found that the Fe(OTf)₃ complexes of *N,N'*-dioxides were more likely to form trication characterized complexes although the whole structures are neutral overall.²⁵ However, there are at least one anion coordinating to the Sc(III) center as showing in the related structures.²⁶ In most cases, the counter ions locate around the complexes, having interaction *via* H-bonds with the outwards amide subunits.¹⁴ In addition, other rare-earth metal complexes with larger ion radii are prone to form metal complexes with coordination number beyond six,^{18,27} which exhibited different configuration geometry from the octahedral complexes of iron. Thus, the chiral ferric iron complexes are capable to efficiently lower the LUMO energy of the dienophile upon coordination.

Based on the observed stereoselectivity and the previous works,²⁰ possible catalytic modes were proposed (Fig. 1d). Initially, the tetradentate L₃-TQEt₂Ad coordinates to Fe(III) to form an octahedral trication species. The substrate **A1** bonds to the ferric iron center with the two carbonyls *via* bidentate manner, which leads to its β -Si face blocking by one of the amide subunits of the ligand. The free styrene **B1** prefers to undergo cyclization from β -Re face of **A1** in *endo*- or *exo*-selectivity (**TS1** or **TS2**). The *exo*-product is the minor one which is in



Scheme 4 Gram-scale synthesis and further transformations.



line with the disfavoured steric hindrance between the aryl substituent of olefin and tetrahydroisoquinoline backbone of the ligand as shown in TS2. As a result, the preferred *endo*- β -*Re* face selective cyclization gives rise to the formation of (2*S*,4*R*)-**C1** as the major one. Additionally, the *exo*-cyclization may occur in a step-wise conjugate addition manner.

Conclusions

In summary, we have developed a highly enantioselective [4 + 2] cycloaddition of a number of simple olefins with cyclic heterodiene of dioxopyrrolidines. The reaction proceeded well in the assistance of chiral *N,N'*-dioxide/Fe^{III} complex catalysts, which could form cationic Lewis acid species to lower the LUMO energy of dioxopyrrolidines. It effectively delivered various optically active bicyclic dihydropyranes derivatives with excellent yield (up to 99%), diastereoselectivity (up to 99:1) and enantioselectivity (up to 99% ee) under mild conditions, including of late-stage modification of drug-molecular-based dienes. Mechanistic studies support the strategy and transition states were proposed to elucidate stereo-induction. Further investigations of asymmetric transformations of simple olefins are currently ongoing in our laboratory.

Data availability

Further details of experimental procedure, ¹H, ¹³C{¹H} and ¹⁹F {¹H} NMR, HPLC spectra, X-ray crystallographic data for **C1**, **D13** and **E1** are available in the ESI.†

Author contributions

T. Y. Z. performed experiments and prepared the ESI† and paper. L. Z. repeated some experiments. Y. Q. Z. for X-ray crystal analysis. B. Q. Y. participated in structure characterization and discussion. X. H. L. and helped with modifying the paper and ESI.† X. H. L. and X. M. F. conceived and directed the project.

Conflicts of interest

There are no conflicts to declare.

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