VIP Chiral-at-Iron Catalyst for Highly Enantioselective and Diastereoselective Hetero-Diels-Alder Reaction

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Abstract: This study demonstrates that chiral-at-iron complexes, in which all coordinated ligands are achiral and the overall chirality the consequence of a stereogenic iron center, are capable of catalyzing asymmetric transformations with very high enantioselectivities. The catalyst is based on a previously reported design (*J. Am. Chem. Soc.* **2017**, *139*, 4322), in which iron(II) is surrounded by two configurationally inert achiral bidentate N-(2-pyridyl)-substituted N-heterocyclic carbenes in a C_2-symmetric fashion and complemented by two labile acetonitriles. By replacing mesityl with more bulky 2,6-diisopropylphenyl substituents at the NHC ligands, the steric hindrance at the catalytic site was increased, thereby providing a markedly improved asymmetric induction. The new chiral-at-iron catalyst was applied to the inverse electron demand hetero-Diels-Alder reaction between β,γ-unsaturated α-ketoester and enol ethers provide 3,4-dihydro-2*H*-pyrans in high yields with excellent diastereoselectivities (up to 99:1 *dr*) and excellent enantioselectivities (up to 98% *ee*). Other electron rich dienophiles are also suitable as demonstrated for a reaction with a vinyl azide.

Introduction

The development of homogeneous catalysts from earth-abundant rather than noble metals is an important trend towards the development of more sustainable chemistry. Much current attention is focusing on the metal iron due to its high abundance in the Earth's crust combined with a low toxicity profile.[1] In fact, Nature makes use of iron as a catalytic or redox center in a plethora of enzymes. With respect to asymmetric iron catalysis, a significant variety of chiral iron complexes have been developed to catalyze asymmetric transformations.[2] Despite impressive advancements over the past decade, challenges remain with respect to catalytic performance, new catalytic mechanisms, and the economic synthesis of the chiral iron catalysts.

Over the past 50 years, the development of chiral transition metal catalysts has been centered predominately around the careful design of tailored chiral metal-coordinating ligands. However, since the seminal work of Alfred Werner[3] it is already established that chiral transition metal complexes do not need to contain chiral ligands for achieving optical activity and we have demonstrated over the past few years that chiral transition metal catalysts composed solely of achiral ligands provide untapped opportunities for the design of novel chiral catalyst architectures with potentially novel properties.[4] In such chiral-at-metal catalysts the required chirality is the consequence of an asymmetric coordination of achiral ligands around the central metal, thereby implementing a stereogenic metal center with overall metal-centered chirality. Importantly, in this design the metal serves both as the exclusive stereogenic center and at the same time acts as the reactive center for catalysis. While our initial work was focused on noble metals,[5–8] we recently introduced the first example of a chiral-at-iron complex for asymmetric catalysis (Figure 1a).[9] In this catalyst, iron(II) is *cis*-coordinated by two chelating N-(2-pyridyl)-substituted N-heterocyclic carbene (PyNHC) ligands in a C_2-symmetric fashion and the coordination sphere is further complemented with two coordinating acetonitrile ligands. Depending on the helical twist of the two PyNHC ligands, the metal center adopts either a Λ or Δ absolute configuration. Importantly, the two PyNHC ligands are configurationally inert while the two acetonitriles are labile. This was accomplished by combining a strongly σ-donating NHC moiety with a π-accepting pyridyl moiety in the bidentate PyNHC which maximizes the ligand field stabilization energy and at the same time labilizes the acetonitrile ligands due to a kinetic *trans*-effect of the σ-donating NHC ligands. We demonstrated that such a chiral-at-iron complex is capable of catalyzing an enantioselective intramolecular Cannizzaro reaction and an asymmetric Nazarov cyclization. However, enantioselectivities were only modest and we therefore fell short of demonstrating the merit of this chiral-at-iron catalyst architecture. Here, we report for the first time that such chiral-at-iron catalysts can provide very high asymmetric inductions. We achieved this by increasing the steric bulk of the substituent at the NHC moieties from a previous 2,4,6-trimethylphenyl (Mes, **FeMes**) to a 2,6-diisopropylphenyl (Dipp, **FeDipp**) moiety (Figure 1b). These moieties directly reach into the active site and affect the asymmetric induction. We demonstrate in this work

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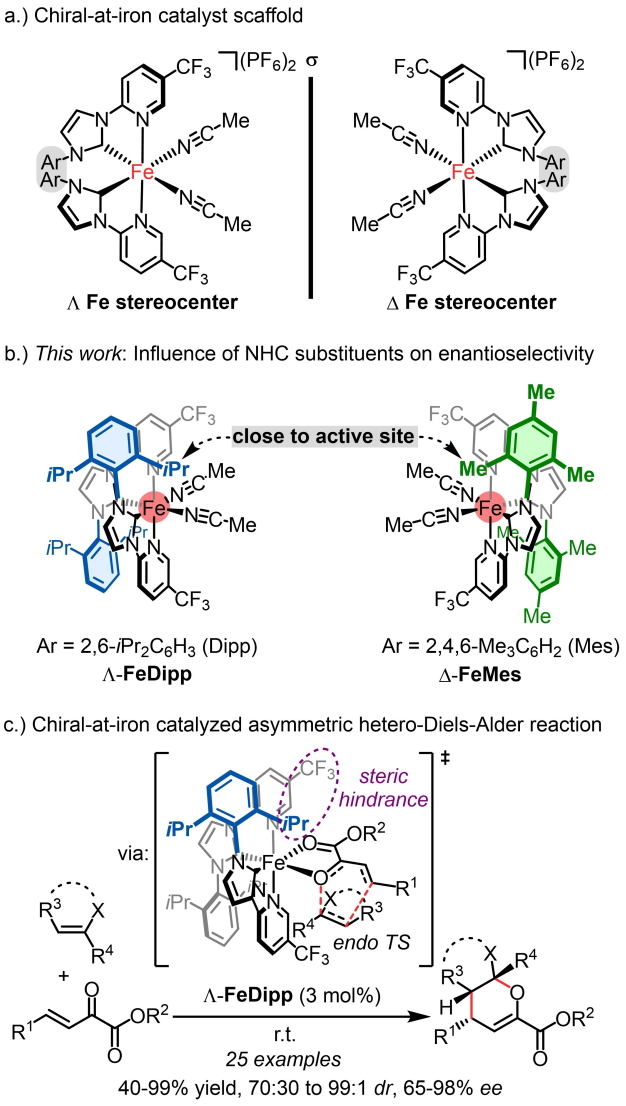


Figure 1. Chiral-at-iron complexes for asymmetric catalysis. a.) Previously developed chiral-at-iron catalyst scaffold. b.) Replacement of 2,4,6-trimethylphenyl (Mes) with 2,6-diisopropylphenyl (Dipp) substituents at the NHC ligands increases steric hindrance at the catalytic site. c.) Application of the sterically more demanding Dipp-functionalized chiral-at-iron catalyst to an asymmetric hetero-Diels-Alder reaction. X = alkoxy or azide.

that the Λ-enantiomer of **FeDipp** catalyzes hetero-Diels-Alder reactions with high diastereoselectivity and up to 98% enantiomeric excess (*ee*) (Figure 1c).

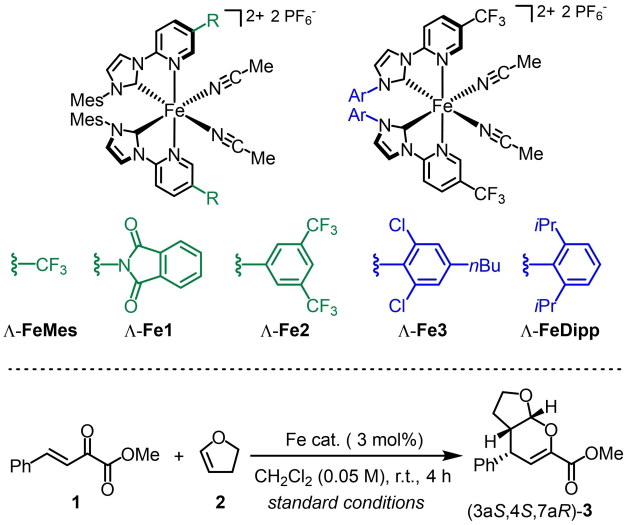
Results and Discussion

We commenced our study by synthesizing a few modified chiral-at-iron complexes (see Supporting Information for the detailed synthesis) (Table 1). Our previously reported catalyst **FeMes**[9] contained a mesityl substituent at the NHC ligand and a CF_3 group at the pyridine ligand. We found that the electron-withdrawing CF_3 group is beneficial for the configurational stability of the chiral-at-iron complex. Since this substituent is in close proximity to the site of catalysis, we aimed at increasing the asymmetric induction by replacing the CF_3 groups with bulkier electron-withdrawing substituents, such as phthalimides (Λ-**Fe1**) and 3,5-bis(trifluoromethyl)phenyl moieties (Λ-**Fe2**). However, when we evaluated the catalytic performance of these new iron catalysts for the inverse electron demand hetero-Diels-Alder reaction[10,11] of the β,γ-unsaturated α-ketoester **1**, serving as a heterodiene, with the dienophile 2,3-dihydrofuran (**2**) to generate the bicyclic compound **3**, we observed a decreased stereoselectivity. Whereas 3 mol% of Λ-**FeMes** provided (3a*S*,4*S*,7a*R*)-**3** with a *dr* of 98:2 and 91% *ee* (Table 1, entry 1), Λ-**Fe1** and Λ-**Fe2** displayed a slightly diminished diastereoselectivity and only 88% ee (entries 2 and 3). We therefore shifted our attention to the mesityl substituent at the NHC ligand, which is involved in inter-ligand π-π-stacking with the pyridyl moiety of the second PyNHC ligand and is therefore in direct proximity of the catalytic site. Replacing the mesityl group with a 2,6-dichloro-4-*n*-butyl group (Λ-**Fe3**) provided the hetero-Diels-Alder product **3** with 98:2 *dr* and 91% *ee* (entry 4), identical to our previous catalyst Λ-**FeMes**. However, gratifyingly, when we introduced the bulkier Dipp group (Λ-**FeDipp**), both catalytic activity and stereocontrol improved markedly. Using 3 mol% of Λ-**FeDipp**, an almost full conversion was observed after 4 hours at room temperature and (3a*S*,4*S*,7a*R*)-**3** was isolated in 98% yield with 97% *ee* and 99:1 *dr* (entry 5). The catalyst loading can be reduced to 2 or 1 mol% with only a slightly decreased performance (entries 6 and 7). We next tested some reaction parameters. Reducing the reaction temperature from room temperature to 5 °C did not increase the stereoselectivity but markedly reduced the catalytic activity. Executing the reaction under air instead of nitrogen reduced somewhat the catalytic activity (93% conversion after 4 hours) and enantioselectivity (94% *ee*, Δ = −3% *ee*) (entry 9). More problematic is the presence of water: the addition of 0.1% water reduced the enantioselectivity to 82% *ee* (Δ = −15% *ee*) (entry 10). The combination of air atmosphere and 0.1% water is most deleterious. While catalytic activity and diastereoselectivity remained satisfactory, the enantioselectivity dropped to just 63% *ee* (Δ = −34% *ee*), which we rationalize with a racemization of the catalyst during the reaction (entry 11). Interestingly, when we added just one equivalent of MeCN, the enantioselectivity recovered but the overall catalytic activity suffered, most likely due to a competition between ketoester substrate and MeCN for binding to the iron catalyst.

Figure 2 shows a crystal structure of the racemic **FeDipp** complex. The Dipp substituents of the individual NHC ligands stack against the pyridyl moieties of the neighboring bidentate ligands with one isopropyl group of each Dipp moiety reaching towards the catalytic site composed of the two labile acetonitrile ligands. This steric hindrance of the Dipp group leading to a more sterically crowded active site can explain the improved asymmetric induction of Λ-**FeDipp** over Λ-**FeMes** for the hetero-Diels-Alder reaction.

Since configurational stability is a key requirement for chiral-at-metal complexes devoid of any achiral ligands, we evaluated the configurational stability of **FeDipp**. For this, Λ-**FeDipp** (>99:1 *er*) was subjected to different conditions and

Table 1. Initial experiments and optimization.



Entry	Catalyst	Conditions[a]	Conversion (%)[b]	dr[c]	ee (%)[d]
1	Λ-**FeMes**	standard	50	98:2	91
2	Λ-**Fe1**	standard	60	93:7	88
3	Λ-**Fe2**	standard	64	94:6	88
4	Λ-**Fe3**	standard	77	98:2	91
5	Λ-**FeDipp**	standard	99 (98)[e]	99:1	97
6	Λ-**FeDipp**	2 mol% Λ-**FeDipp**	99	99:1	96
7	Λ-**FeDipp**	1 mol% Λ-**FeDipp**	89[f]	99:1	95.5
8	Λ-**FeDipp**	5 °C instead of r.t.	32	99:1	97
9	Λ-**FeDipp**	under air	93	99:1	94
10	Λ-**FeDipp**	added H_2O (0.1 %)	99	99:1	82
11	Λ-**FeDipp**	air, H_2O (0.1 %)	97	99:1	63
12	Λ-**FeDipp**	air, H_2O (0.1 %), MeCN[g]	19 (92)[h]	99:1	97 (86)[h]

[a] Standard condition: **1** (0.1 mmol), **2** (0.15 mmol), catalyst (0.003 mmol, 3 mol%) in distilled CH_2Cl_2 (2.0 mL) stirred at r.t. for 4 h under nitrogen. Deviations from these standard conditions are shown. [b] Determined by ^{1}H-NMR of crude products using $Cl_2CHCHCl_2$ as internal standard. [c] Diastereomeric ratios determined by ^{1}H-NMR. [d] Determined with the purified products by HPLC on chiral stationary phase. [e] Isolated yield. [f] Reaction time of 8 h. [g] 1 equivalent of MeCN added. [h] Results in brackets are for extended reaction time of 24 h.

afterwards coordinated to (*R*)-α-methoxyphenylacetate, ((*R*)-**Aux1**, 99% *ee*). Racemization leads to the formation of a diastereomeric mixture of Δ-(*R*)-**Fe4** and Λ-(*R*)-**Fe4**, which can be analyzed by ^{1}H-NMR, allowing a calculation of the degree of racemization. Note, all racemization experiments were performed in the presence of a 5-fold excess of α-ketoester **1** which improved reproducibility for reasons that are not completely clear yet. Nevertheless, since α-ketoester is present in large excess at the beginning of the catalytic reaction, these conditions are representative for the catalytic conditions. Accordingly, dissolving Δ-**FeDipp** in dry CH_2Cl_2 for 4 hours under nitrogen atmosphere demonstrated configurational inertness of Δ-**FeDipp** under these conditions (Δ:Λ = 99:1). However, the same conditions but under an atmosphere of air resulted in a significant racemization (Δ:Λ = 81:19). The presence of 0.1% water under an inert atmosphere resulted in Δ:Λ = 60:40, while the combination of 0.1% water and air atmosphere led to a complete racemization. However, when we added just 0.1% MeCN to the conditions in the presence of 0.1% water under air atmosphere, racemization was completely suppressed (Δ:Λ = 99:1). These experiments demonstrate that **FeDipp** is configurationally robust in the presence of MeCN (Figure 3). In non-coordinating solvents such as CH_2Cl_2 water and air must be omitted which is consistent with results shown in Table 1 (entries 9–11). It is worth noting that Λ- and Δ-**FeDipp** are configurationally stable in the solid state under air for at least several weeks. Analogous racemization experiments with Λ-**FeMes** provided almost identical results (see Supporting Information), revealing that the higher steric crowding of **FeDipp** compared to **FeMes** does not affect its configurational stability.

With an improved chiral-at-iron catalyst for the hetero-Diels-Alder reaction in hand, we next performed a substrate scope (Figure 4). We started with the reaction of modified methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**1**) with the dienophile 2,3-dihydrofuran. Replacing the methyl ester of **1** with an ethyl ester provided the bicyclic product **4** in 96% yield with 96% *ee* as a single diastereomer (99:1 *dr*). An allyl ester afforded the bicyclic product **5** in 96% yield with 97% *ee* and 98:2 *dr*. Substituents in the phenyl moiety were also well tolerated. For example, a *para*-, *meta*- or *ortho*-methyl in the phenyl ring as well as an *ortho*-bromine, *para*-fluorine, or a *para*-trifluoromethyl group provided the bicyclic products **6**–**11** (96–99% yield, 98:1–99:1 *dr*, 96–98% *ee*) with equally high yields and stereoselectivities.

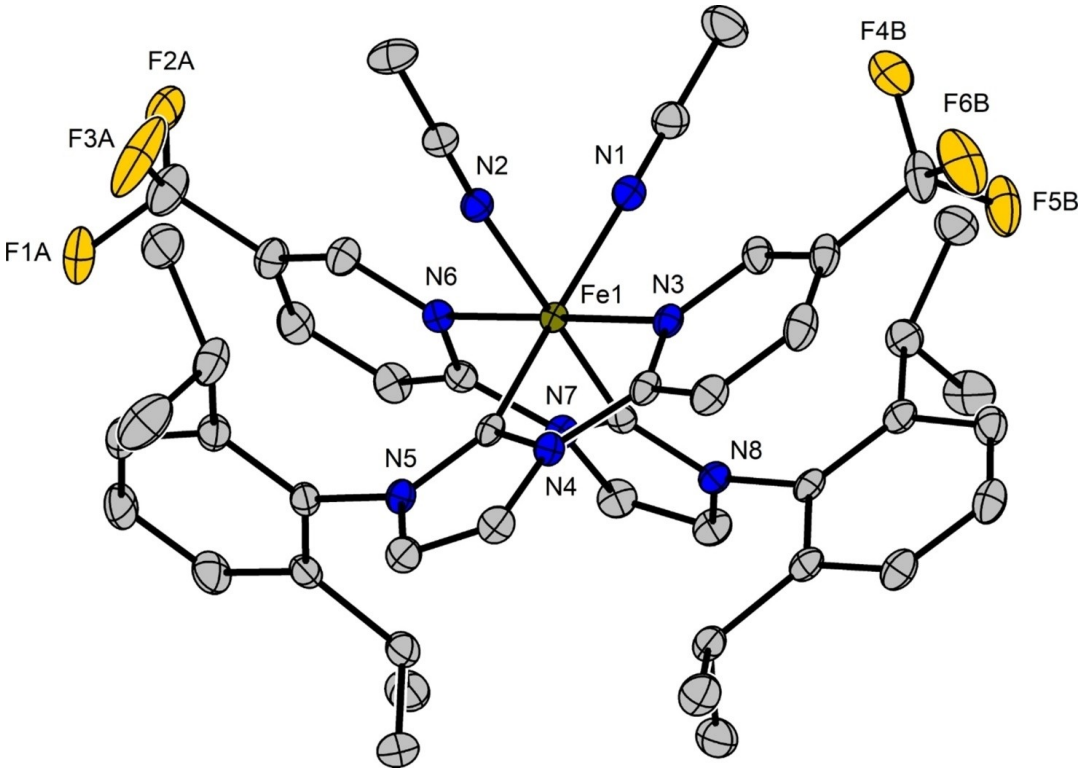
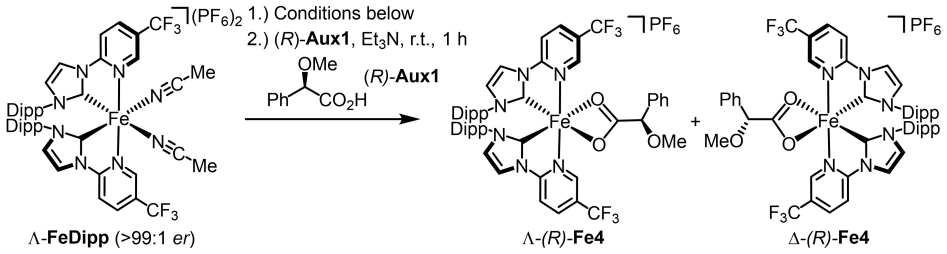


Figure 2. X-ray crystal structure of racemic **FeDipp**. Only one enantiomer is shown. Only one disordered species of the CF_3 groups is shown. The hexafluorophosphate anions, the acetonitrile solvent molecule and the hydrogen atoms are omitted. Displacement ellipsoids are shown at 50% probability level at 100 K.



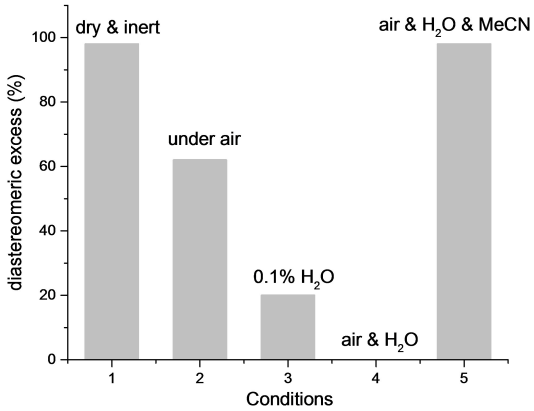


Figure 3. Racemization study. Conditions: All experiments were performed with Δ-**FeDipp** (> 99:1 *er*) in dry CH_2Cl_2 for 4 h in the presence of α-ketoester **1** (5 equivalents). After an incubation time under conditions described below, (*R*)-**Aux1** (0.01 M in CH_2Cl_2, 1.0 equivalent) was added followed by triethylamine (0.01 M in CH_2Cl_2, 1.2 equivalents). The resulting mixture was concentrated to dryness, redissolved in CD_2Cl_2 and analyzed by ^{1}H-NMR spectroscopy. Different reaction conditions for the initial incubation: 1) Under nitrogen atmosphere. 2) Under air atmosphere instead. 3) Under nitrogen atmosphere and addition of 0.1% H_2O. 4) Under air atmosphere and addition of 0.1% H_2O. 5) Under air atmosphere, addition of 0.1% H_2O, and addition of 0.1% MeCN.

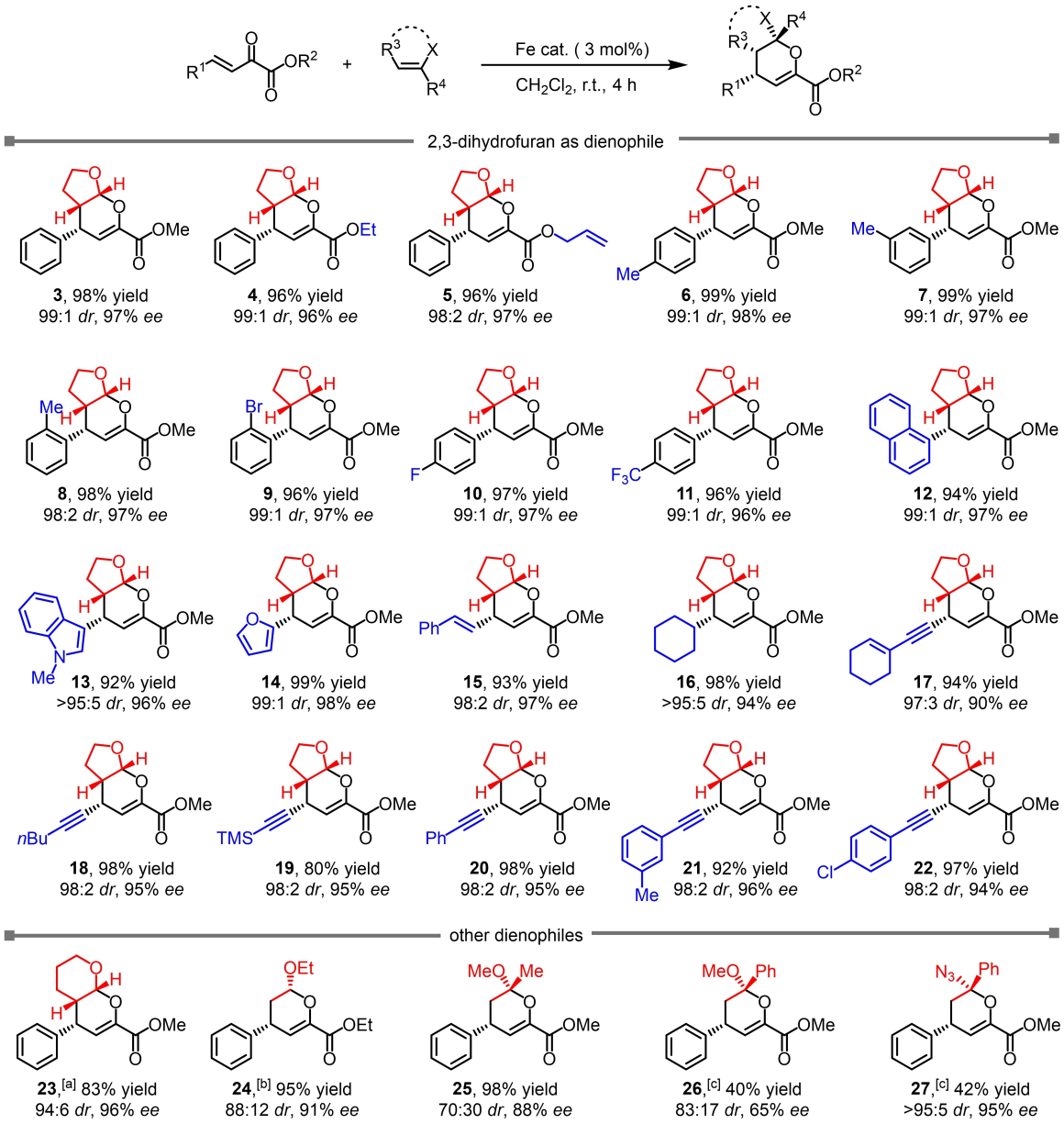


Figure 4. Substrate scope. Reaction conditions: ketoester (0.10 mmol), dienophile (0.15 mmol) and Λ-**FeDipp** (0.003 mmol, 3.0 mol%) in distilled CH_2Cl_2 (2.0 mL) stirred at r.t. for 4 h under nitrogen. [a] Performed with 2 equivalents of dienophile (0.20 mmol). [b] Performed with 5 equivalents of dienophile (0.50 mmol). [c] Reaction time increased to 24 h and scale doubled (0.20 mmol ketoester).

The phenyl moiety can also be replaced with a naphthyl moiety, an indole, and a furane (products **12**–**14**, 92–99% yield, 95:5–99:1 *dr*, 96–98% *ee*). Likewise, bicyclic products with alkenyl, cyclohexyl, and a variety of different alkynyl groups in 4-position are also accessible with very high yields and high stereoselectivities (products **15**–**22**, 80–98% yield, 95:5–98:2 *dr*, 90–97% *ee*). A crystal structure of **22** confirmed the preference for the *endo* stereochemistry (see Supporting Information). We also tested other dienophiles. Accordingly, the reaction of 3,4-dihydro-2*H*-pyran with ketoester **1** afforded the bicyclic product **23** in 83% yield with 94:6 *dr* and 96% *ee*. For optimal results, two equivalents of the dienophile were used. The reaction of ketoester **1** with 5 equivalents of the dienophile ethyl vinyl ether afforded the Diels-Alder product **24** in 95% yield with 88:12 *dr* and 91% *ee*. Using instead 2-methoxypropene as the dienophile provided the dihydropyrane product **25** with 98% yield but a reduce diastereoselectivity of 70:30 *dr* and a modest enantioselectivity of 88% *ee*. 1-Methoxyvinylbenzene is not a suitable dienophile and provided the dihydropyrane **26** in only 40% yield and with 83:17 *dr* and 65% *ee* after an elongated reaction time of 24 hours. 1-Azidoethenylbenzene can also be used as the dienophile and the reaction with ketoester **1** afforded the azidopyrane product **27** with 95:5 *dr* and 95% *ee* but only a modest yield of 42%. Finally, it is worth noting that the chiral-at-iron catalyzed inverse electron demand hetero-Diels-Alder reaction can be

scaled up without any loss in performance: using just 1 mol% of Λ-**FeDipp**, ketoester ester **1** at a scale of 1 mmol reacted with 2,3-dihydrofuran to furnish bicyclic 3,4-dihydro-2*H*-pyran **6** in 99% yield with 99:1 *dr* and 97% *ee*.

Jørgensen et al.[12] and Evans et al.[13] independently set the gold standard for asymmetric inverse demand hetero-Diels-Alder reactions between β,γ-unsaturated α-ketoester and electron-rich dienophiles using readily available copper(II)-bis(oxazoline) catalysts, leading to valuable substituted 3,4-dihydro-2*H*-pyrans. Jørgensen and Evans established the preference of an endo transition state. DFT calculations by Houk and coworkers confirmed the preference for the endo diastereoselectivity due to secondary orbital interactions between the oxadiene and a lone pair of the heteroatom at the dienophile (see transition state in Figure 1c).[14] Xu recently demonstrated that copper(II)-bis(oxazoline) catalysts can also be applied to the reaction of β,γ-unsaturated α-ketoester with vinyl azides.[15] Feng and coworkers introduced chiral N,N'-dioxide/erbium(III) catalyst erbium(III)-N,N'dioxide catalysts for the asymmetric reaction of β,γ-unsaturated α-ketoester with enol ether,[16] while X.-W. Wang, Xia, and Z. Wang recently reported a copper(II)-bis(oxalamide) catalyst for this transformation.[17] However, to the best of our knowledge, our work marks the first example of iron-catalyzed asymmetric hetero-Diels-Alder cycloadditions between β,γ-unsaturated α-ketoester and enol ether, including one example with vinylazide as the dienophile.

Finally, after having established the utility of the new chiral-at-iron catalyst, we improved the synthesis of enantiomerically pure Λ- and Δ-**FeDipp** (Figure 5). Accordingly, starting with the pyridylimidazolium salt **LDipp**, which can be synthesized in a single step from 2,6-diisopropylaniline and 2-bromo-5-trifluoromethylpyridine, conversion to its silver carbene complex followed by electrolysis in MeCN with an iron plate as the sacrificial anode provided the racemic complex *rac*-**FeDipp** in 56% yield.[18] Reaction of the racemic mixture with the salicyloxazoline auxiliary (*S*)-**Aux2** in the presence of Et_3N afforded the complex Λ-(*S*)-**Fe5** in 46% yield as a single diastereomer. Interestingly, no Δ-(*S*)-**Fe5** is formed in this procedure so that Δ-**FeDipp** can be isolated in 44% yield with 94:6 *er*. Reaction of this enantiomerically enriched Δ-**FeDipp** with the matched auxiliary (*R*)-**Aux2** then provided Δ-(*R*)-**Fe5** as a single diastereomer. Treatment of the individual enantiomeric auxiliary complexes Λ-(*S*)-**Fe5** and Δ-(*R*)-**Fe5** with NH_4PF_6 in MeCN at 30 °C provided the enantiomerically pure catalysts Λ-**FeDipp** (92% yield, >99:1 *er*) and Δ-**FeDipp** (77% yield over 2 steps, >99:1 *er*).

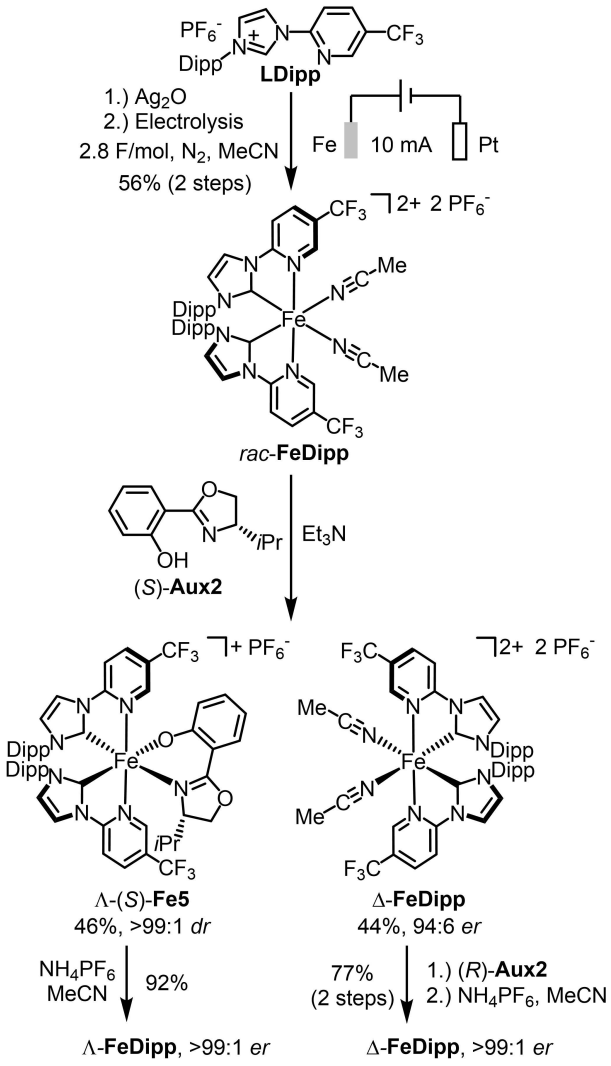


Figure 5. Optimized synthesis of enantiomerically pure Λ- and Δ-**FeDipp**.

Conclusion

We have here demonstrated for the first time that chiral-at-iron complexes, in which all coordinated ligands are achiral and the overall chirality is exclusively due to a stereogenic iron center, are capable of catalyzing asymmetric transformations with very high enantioselectivities. The octahedral chiral-at-iron catalyst contains two configurationally inert achiral bidentate N-(2-pyridyl)-substituted N-heterocyclic carbenes and two labile acetonitriles. By introducing bulky 2,6-diisopropylphenyl substituents at the NHC ligands, the steric hindrance at the catalytic site was increased, thus providing a markedly improved asymmetric induction. The new chiral-at-iron catalyst was applied to the inverse electron demand hetero-Diels-Alder reaction between β,γ-unsaturated α-ketoester and enol ethers provide 3,4-dihydro-2*H*-pyrans in high yields with excellent diastereoselectivities (up to 99:1 *dr*) and excellent enantioselectivities (up to 98% *ee*). Other electron rich dienophiles are also suitable as demonstrated for a reaction with a vinyl azide. Chiral 3,4-dihydro-2*H*-pyrans and their corresponding tetrahydropyrans are frequent motifs in natural products and other bioactive molecules.[19,20]

Experimental Section

Detailed experimental procedures, analytical data, NMR spectra, CD spectra, and HPLC traces are provided in the Supporting Information.

Deposition numbers 2064430 (for **FeDipp**) and 2064431 (for **22**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · chiral-at-metal · hetero-Diels-Alder · iron · stereogenic metal

[1] For reviews on iron catalysis for organic synthesis, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; b) S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321; *Angew. Chem.* **2008**, *120*, 3363–3321; c) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; d) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778–789; e) G. Olivio, O. Cussó, M. Costas, *Chem. Asian J.* **2016**, *11*, 3148–3158; f) R. Shang, L. Ilies, E. Nakamura, *Chem. Rev.* **2017**, *117*, 9086–9139; g) A. Piontek, E. Bisz, M. Szostak, *Angew. Chem. Int. Ed.* **2018**, *57*, 11116–11128; *Angew. Chem.* **2018**, *130*, 11284–11128; h) M. Guo, T. Corona, K. Ray, W. Nam, *ACS Cent. Sci.* **2019**, *5*, 13–28; i) V. F. Batista, D. C. G. A. Pinto, A. M. S. Silva, *ACS Catal.* **2020**, *10*, 10096–10116; j) Q. Liang, D. Song, *Chem. Soc. Rev.* **2020**, *49*, 1209–1232; k) C. Damiano, P. Sonzini, E. Gallo, *Chem. Soc. Rev.* **2020**, *49*, 4867–4905; l) Y. Liu, T. You, H.-X. Wang, Z. Tang, C.-Y. Zhou, C.-M. Che, *Chem. Soc. Rev.* **2020**, *49*, 5310–5358.

[2] For reviews on asymmetric iron catalysis, see: a) R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282; b) K. Gopalaiah, *Chem. Rev.* **2013**, *113*, 3248–3296; c) T. Ollevier, H. Keipour, *Top. Organomet. Chem.* **2015**, *50*, 259–310; d) H. Pellissier, *Coord. Chem. Rev.* **2019**, *386*, 1–31; e) A. Casnati, M. Lanzi, G. Cera, *Molecules* **2020**, *25*, 3889.

[3] A. Werner, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1887–1898.

[4] a) L. Zhang, E. Meggers, *Acc. Chem. Res.* **2017**, *50*, 320–330; b) X. Huang, E. Meggers, *Acc. Chem. Res.* **2019**, *52*, 833–847.

[5] Our first work on reactive chiral-at-iridium catalysts: H. Huo, C. Fu, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2014**, *136*, 2990–2993.

[6] Our first work on chiral-at-rhodium catalysts: C. Wang, L.-A. Chen, H. Huo, X. Shen, K. Harms, L. Gong, E. Meggers, *Chem. Sci.* **2015**, *6*, 1094–1100.

[7] Our first work on chiral-at-ruthenium catalysts: Y. Zheng, Y. Tan, K. Harms, M. Marsch, R. Riedel, L. Zhang, E. Meggers, *J. Am. Chem. Soc.* **2017**, *139*, 4322–4325.

[8] Our first work on chiral-at-osmium catalysts: G. Wang, Z. Zhou, X. Shen, S. Ivlev, E. Meggers, *Chem. Commun.* **2020**, *56*, 7714–7717.

[9] Our first work on chiral-at-iron catalysts: Y. Hong, L. Jarrige, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2019**, *141*, 4569–4572.

[10] X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515–5546.

[11] G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2018**, *118*, 2080–2248.

[12] a) J. Thorhauge, M. Johannsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **1998**, *37*, 2404–2406; *Angew. Chem.* **1998**, *110*, 2543–2406; b) H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 4487–4497.

[13] a) D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey, *Angew. Chem. Int. Ed.* **1998**, *37*, 3372–3375; *Angew. Chem.* **1998**, *110*, 3553–3375; b) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

[14] J. Liu, S. Niwayama, Y. You, K. N. Houk, *J. Org. Chem.* **1998**, *63*, 1064–1073.

[15] N. Thirupathi, F. Wei, C.-H. Tung, Z. Xu, *Nat. Commun.* **2019**, *10*, 3158.

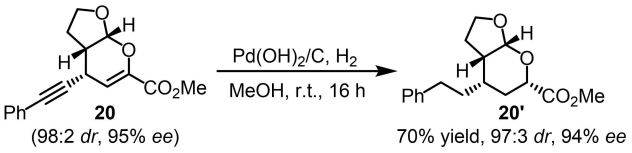
[16] Y. Zhu, M. Xie, S. Dong, X. Zhao, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 8202–8208.

[17] J.-B. Chen, M. Xu, J.-Q. Zhang, B.-B. Sun, J.-M. Hu, J.-Q. Yu, X.-W. Wang, Y. Xia, Z. Wang, *ACS Catal.* **2020**, *10*, 3556–3563.

[18] Compare with: B. Liu, Y. Zhang, D. Xu, W. Chen, *Chem. Commun.* **2011**, *47*, 2883–2885.

[19] For selective bioactive dihydropyrans and tetrahydropyrans, see: a) K. L. Jackson, J. A. Henderson, A. J. Phillips, *Chem. Rev.* **2009**, *109*, 3044–3079; b) R. Jacques, R. Pal, N. A. Parker, C. E. Sear, P. W. Smith, A. Ribaucourt, D. M. Hodgson, *Org. Biomol. Chem.* **2016**, *14*, 5875–5893; c) B. Pande, *ChemistrySelect* **2019**, 9143; d) W. A. Donaldson, *Beilstein J. Org. Chem.* **2020**, *16*, 1991–2006.

[20] The 3,4-dihydropyran can be reduced diastereoselectively to the corresponding tetrahydropyran. See the following example:



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