Enantioselective Iron-catalyzed Cross-[4+4]-Cycloaddition of 1,3-Dienes Provides Chiral Cyclooctadienes

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Supporting Information Placeholder

ABSTRACT: Chiral cyclooctadienes are a frequently occurring scaffold in natural products and specialty chemicals, and are used as ligands in asymmetric catalysis. Accessing substituted cyclooctadienes in an efficient asymmetric fashion has been notoriously challenging. We report an iron-catalyzed enantioselective cross-[4+4]-cycloaddition of 1,3-dienes to form substituted cyclooctadienes under very mild conditions. A highly tailored chiral α-diimine (DI) iron complex is key for the success of the transformation providing a balanced performance between reactivity, excellent cross-selectivity and very high enantioselectivity. Steric maps of the complexes help accounting for the observed selectivity. The developed method allows rapid and atom-economic access to novel differently functionalized cyclooctadienes in very high yields and enantioselectivities.

Eight-membered carbocycles are the structural core of several naturally occurring biologically active compounds[1] and specialty chemicals, finding application in the market of fragrances,[2a] fuels,[2b] and polymers[2c] (Figure 1A). Chiral cyclooctadienes have been used as steering ligands for Rh- and Ir-catalyzed enantioselective transformations.[3,4] However, 8-membered systems as prototypical example of medium-sized ring are unquestionably among the most difficult to synthesize *via* classical ring closure strategies, mainly because of unfavorable entropic and transannular penalties.[5] These challenges are partially responsible for the large underrepresentation of medium-sized cycles in marketed drugs and drug discovery programs with respect to their 5- and 6-membered counterparts.[6] Over the past decades, the progress in metal-catalyzed methodologies partially addressed these synthetic challenges.[7] For instance, ring-closing metathesis,[8] radical cascades[9] and ring expansion[10] reactions enabled the construction of natural products with eight-membered rings (Figure 1B). The metal-catalyzed [4+4]-cycloaddition of 1,3-dienes has emerged as a powerful tool for the efficient and atom-economic synthesis of cyclooctadienes.[11] Nickel-catalyzed [4+4]-cyclodimerizations of butadiene yielding 1,5-cyclooctadiene (COD) date back to the work of Ziegler,[12a] Wilke[12b] and Reed[12c] in the 1950s and are nowadays well-established protocols at industrial scale.[13] In contrast, substituted 1,3-dienes are less reactive and lead to unsatisfactory product selectivities.[14] For instance, different [4+4]-isomers arising from competitive cross- and homo- dimerizations, [4+2]-cycloadducts as well as additional oligomers are observed (Scheme 1A).

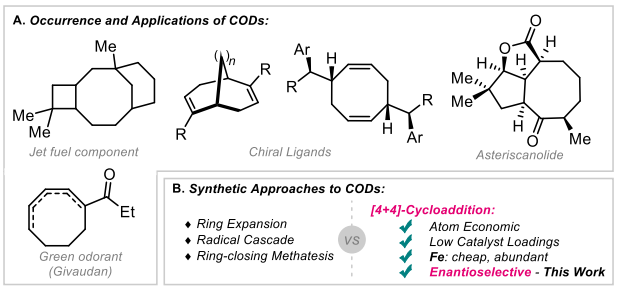
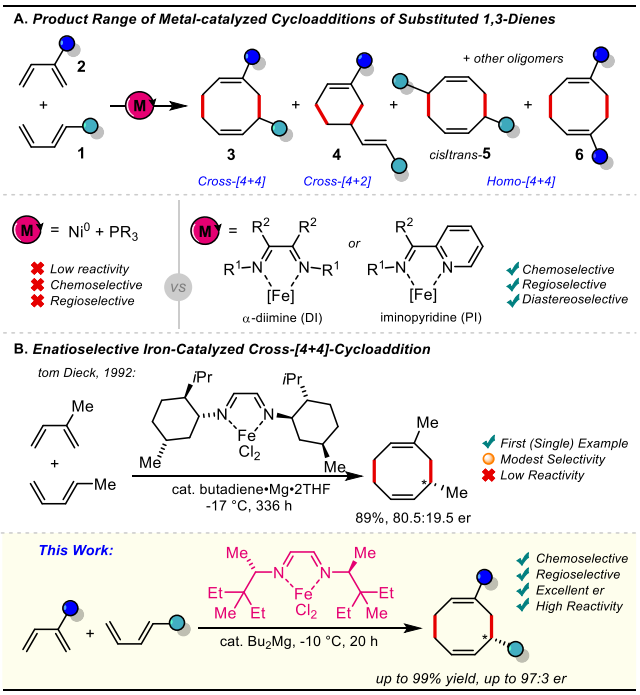


Figure 1. Synthetic approaches to eight-membered carbocycles and their occurrence and applications.

Iron complexes are highly attractive as catalysts in organic synthesis due to their very high abundance, low price and toxicity, paired with the ability to span a broad range of oxidation states.[15] In this respect, tom Dieck described the use of *in situ* reduced α-diimine (DI) iron(II) catalysts in the [4+4]-cyclodimerization of butadiene to COD.[16] Linear **1** and branched **2** 1,3-dienes (poorly reacting under Ni catalysis) underwent regioselective [4+4]-cyclization to the correspondent cross-cycloadducts **3**. Noteworthily, in 1992 tom Dieck reported a menthyl-derived chiral DI-Fe complex able to catalyze the cycloaddition between isoprene and *trans*-1,3-pentadiene, yielding the corresponding [4+4]-cycloadduct in 61% *ee* (Scheme 1B).[17] Despite the long reaction time, the modest enantioinduction observed in this example highlighted the untapped potential of α-diimine iron complexes for asymmetric catalysis. However, the development of more general protocols remained an unsolved and longstanding challenge. Evaluation of the structural and spectroscopic data for α-diimine (DI) and iminopyridine (PI) iron-complexes by Chirik[18] and Ritter[19] revealed that the catalytically active species is likely an iron(I) center antiferromagnetically coupled to a ligand-based radical anion. Very recently, Chirik reported that the ligand backbone controls chemo-, regio- and diastereoselectivity in the [4+4]-cycloaddition of monosubstituted 1,3-dienes.[18b] α-Diimine ligands were shown to favor the cross-[4+4]-cyclization product over other oligomers in the iron-catalyzed cycloaddition of branched and linear dienes.[17,18b] We reasoned that well-de-

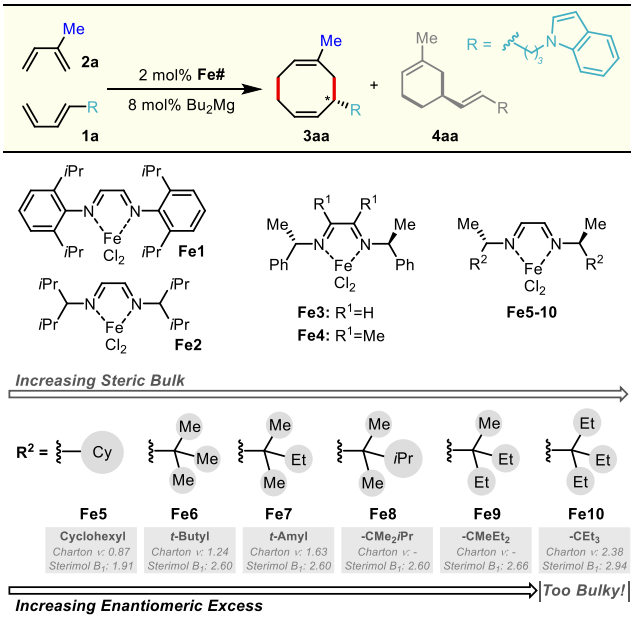
signed and carefully tailored chiral α-diimine (DI) iron complexes could act as efficient catalysts for enantioselective cross-[4+4]-cycloadditions between a broad range of two different substituted 1,3-dienes, overcoming current limitations in reactivity, chemo- and importantly enantioselectivity. Herein, we report a novel α-diimine $FeCl_2$ complex with bulky ligand side-arms enabling access to variously substituted cyclooctadienes in excellent enantioselectivity. Topographic steric maps of the complexes provide insights into the relationship between catalyst structure and regio- and enantioselectivity.

Scheme 1. Metal-catalyzed Cycloaddition of 1,3-Dienes: challenges and existing methods.



We first explored few achiral α-diimine iron(II) complexes to map the general reactivity requirements of the cross-[4+4]-cycloaddition of isoprene **2a** and linear diene **1a** (Table 1). In this respect, complex **Fe1** equipped with a classical 2,6-diisopropyl aniline-derived diimine ligand was activated *in situ* with dibutylmagnesium.[20] The high conversion of starting material together with 16% of [4+2] product **4aa** and just trace amounts of cross-cyclized product **3aa** indicated a poor selectivity (entry 1). In contrast, achiral complex **Fe2** featuring two bulky alkyl side chains displayed high chemoselectivity for the [4+4]-product **3aa** (77% yield) with [4+2]-cycloadduct **4aa** as main side-product in 13 % yield (entry 2). Hence, we started investigating surrogates of **Fe2** with bulky chiral side chains. Complexes **Fe3**,**5** gave unsatisfactory performances, with poor chemo- and enantioselectivity (entries 3,5). Adding methyl substituents in the diimine backbone (**Fe4**, entry 4) did not improve the reaction outcome significantly. Pleasingly, increasing the steric bulk at the ligand side arms improved chemo- as well as enantioselectivity. For instance, **Fe6** having *tert*-butyl units delivered **3aa** in 84% yield and 87:13 er (entry 6). Interestingly, a switch in enantiomeric ratio of **3aa** (entries 3,6) was observed when **Fe6** equipped with aliphatic side arms was used instead of **Fe3** bearing aromatic units, indicating a change in the mechanism of enantioinduction (sterics versus π-stacking).[21] Progressively increasing the bulkiness of the side arms correlated well with improved enantioselectivities. Complex **Fe7** with *tert*-amyl groups (R^2=CMe_2Et) resulted in 90:10 er (entry 7). **Fe8** (R^2=Me_2iPr) increased the selectivity further to 92:8 er, but displayed slightly lower reactivity and chemoselectivity (entry 8). Complex **Fe9** with 3-methyl-3-pentyl units (R^2=$CMeEt_2$), readily accessible in 4 steps (see SI for details), showed the best performance, forming **3aa** in 80 % yield and 93:7 er (entry 9). Noteworthily, a further enhancement in bulk using **Fe10** (R^2=CEt_3) caused a very sharp drop in all parameters (conversion, chemo- and enantioselectivity of 65:35 er) (entry 10). Lowering the reaction temperature to -10 °C improved the performance of **Fe9**, providing **3aa** in 92% yield and 95:5 er (entry 11). Further cooling to -30 °C slightly increased the enantioselectivity, however with a too large trade-off with respect to the conversion (entry 12). The direct relationship between catalyst side-arm size and enantioselectivity was further analyzed using Charton[22] (ν) and Sterimol[23] (B_1) parameters. The *t*-butyl side-arms of **Fe6** (ν=1.24, B_1=2.60) are bulkier than **Fe5** cyclohexyl units (ν=0.87, B_1=1.91), in line with the observed jump in enantioselectivity for **3aa**. Catalyst **Fe9** side-arms (R^2=$CMeEt_2$) possess higher shielding ability (B_1=2.66) than in the **Fe6-8** series (B_1=2.60), leading to an optimal performance. The deviation from the general trend observed for **Fe10** (65:35 er, ν=2.38, B_1=2.94) can be rationalized with a conformational change in the catalyst geometry, giving rise to a congested catalytic pocket.[24]

Table 1. Optimization of the enantioselective Fe-catalyzed cross-[4+4]-cycloaddition.[a]



Entry	Fe#	% Conv.[b]	% **3aa**[b]	er of **3aa**[c]	% **4aa**[b]
1	**Fe1**	80	traces	-	16
2	**Fe2**	91	77	-	13
3	**Fe3**	>95	47	24:76	50
4	**Fe4**	>95	53	22:78	44
5	**Fe5**	>95	45	50:50	50
6	**Fe6**	95	84	87:13	10

7	**Fe7**	90	80	90:10	10
8	**Fe8**	85	68	92:8	15
9	**Fe9**	92	80	93:7	12
10[d]	**Fe10**	72	39	65:35	33
11[e]	**Fe9**	>99	92	95:5	8
12[f]	**Fe9**	21	18	96:4	3

[a] 0.3 mmol **1a**, 0.33 mmol **2a**, 6 µmol **Fe#**, 24 µmol Bu_2Mg (1 M in heptane) at 25 °C for 20 h; [b] determined by ^{1}H-NMR using 1,2-dichloroethane as internal standard; [c] determined by chiral HPLC; [d] 15 µmol **Fe10**, 60 µmol Bu_2Mg (1 M in heptane); [e] at -10 °C; [f] at -30 °C.

To further rationalize the relationship between ligand geometry and enantioselectivity, X-ray crystal structures of complexes **Fe4**, **Fe6** and **Fe9** were obtained (Figure 2).[25] Steric maps of the binding pocket were generated with SambVca Web tool.[26] Complex **Fe4** appears to be sterically more congested (51.1 $\%V_{bur}$) compared to **Fe6** (47.3 $\%V_{bur}$) and **Fe9** (48.0 $\%V_{bur}$). A less accessible iron atom seems to be connected to a much lower chemoselectivity ([4+4] *vs* [4+2]). The steric bulk for **Fe4** is mainly located in the western and the eastern quadrants, while access to the metal center from the northern and southern trajectories seems wide open, eventually explaining the modest 78:22 er for **3aa**. In contrast, steric maps of **Fe6** and **Fe9** display a more pronounced C2-symmetric pocket, with blocked NW and SE quadrants. This arrangement correlates with their improved regio- and enantioselectivities. Both ethyl groups of **Fe9** occupy shielding positions above the diimine-iron plane, with superior protecting properties compared to **Fe6** and without impacting the direct environment at the iron atom. Although an X-ray crystal structure of **Fe10** was not obtained, its poor performances can be rationalized by the third ethyl group perturbing this catalytically relevant sphere.

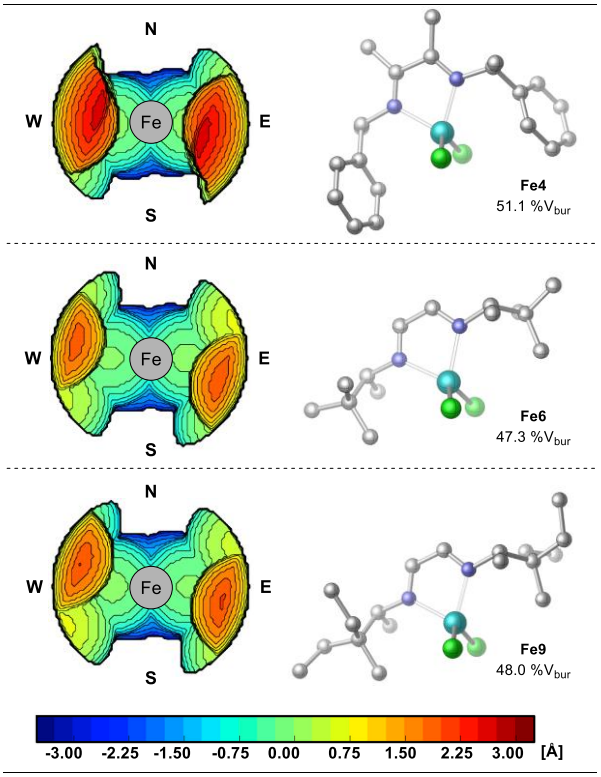
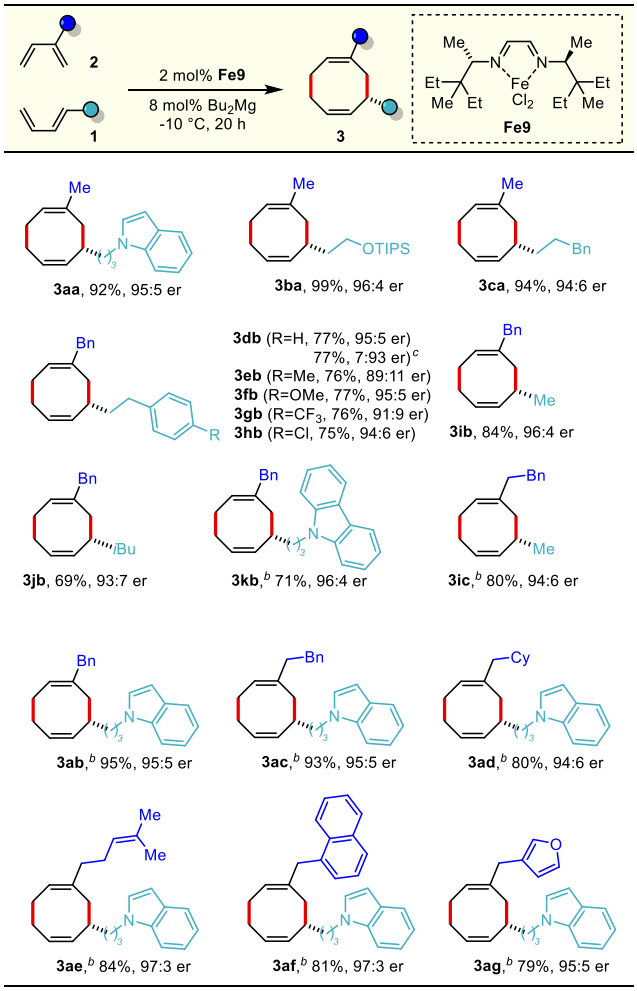


Figure 2. X-ray crystal structures of **Fe4**, **Fe6** and **Fe9**,[25] buried volumes and corresponding steric maps.[26] Bondi radii scaled by 1.17, sphere radius: 3.5 Å, mesh spacing: 0.1 Å.

We next explored the scope of the enantioselective [4+4] cycloaddition (Scheme 2). In this respect, linear dienes bearing decoupled aryl moieties with both electron-rich and electron-poor substituents successfully engaged in the cross-cycloaddition, yielding COD derivatives **3db-3hb** in high yields and excellent enantioselectivities. Cyclooctadienes bearing functional groups such as halogens (**3hb**) and protected alcohols (**3ba**), as well as fluorescent tags like carbazole (**3kb**), were obtained with high enantioselectivity (up to 96:4 er), thus opening up the possibility for further functionalization of the synthesized CODs. Introduction of steric bulk in closer proximity to the forming stereogenic center of the 8-membered ring impacted the reaction outcome. *iso*-Butyl-substituted cyclooctadiene **3jb** was obtained in slightly lower yield and with an enantiomeric ratio of 93:7 compared to methyl substituted compound **3ib** (84%, 96:4 er). The scope of the branched diene was evaluated next. In all cases, cyclooctadienes **3ic-3ag** were obtained in high yields and excellent enantiomeric ratios (up to 97:3). Myrcene (**2e**) with its additional peripheral double bond successfully engaged in the transformation, forming **3ae** as the sole product in 97:3 er. The enantioselective cross-[4+4]-cycloaddition could be successfully extended to branched dienes with heteroaromatic substituents. A 3-furyl derived diene **2g** gave rise to [4+4] product **3ag** in 79% yield and 95:5 er with any observed [4+2]-cycloaddition involving its furan moiety.[27] The transformation is scalable as demonstrated by the synthesis of **3db** on a 1.2 mmol scale (four-fold increase). Cyclooctadiene **3db** was obtained with the identical yield of 77% and 93:7 enantiomeric ratio (Note: *ent*-**3db** was formed as catalyst *ent*-**Fe9** was used).

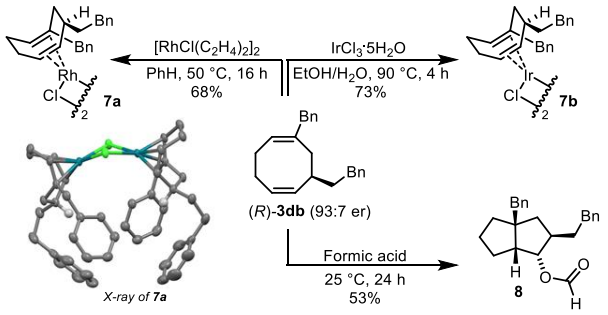
Scheme 2. Scope for the enantioselective Fe-catalyzed cross-[4+4]-cycloaddition.[a]



[a] 0.3 mmol **1**, 0.33 mmol **2**, 6 µmol (*S,*S)-**Fe9**, 24 µmol Bu_2Mg (1 M in heptane) at -10 °C for 20 h; [b] with 12 µmol (*S,*S)-**Fe9**, 48 µmol Bu_2Mg (1 M in heptane) at -10 °C for 40 h; [c] 4-fold scale, with (*R,R*)-**Fe9**.

Very few highly enantioselective syntheses of chiral cyclooctadienes have been reported in literature.[28] Despite the application potential of chiral diene metal complexes for asymmetric catalysis, synthetic methods to access them mostly rely on the chiral pool[29] or require resolution *via* preparative HPLC.[4a,b] The outlined step-economic Fe-catalyzed strategy to chiral cyclooctadienes may facilitate their further application in synthesis and catalysis. In this respect, treatment of COD **3db** with [RhCl(ethylene)]$_2$ provided access to Rh(I)-complex **7a** in 68% yield (Scheme 3).[4b] X-ray analysis of obtained single-crystals of **7a**[24] allowed to unequivocally assign the absolute configuration of the COD obtained from (*R,R*)-**Fe9** as (*R*)-**3db**. Moreover, related Ir(I)-complex **7b** was prepared from (*R*)-**3db** and $IrCl_3{\cdot}5H_2O$. Complex **7a** was preliminary evaluated as catalyst for conjugate addition of phenylboronic acid to cyclohexenone (see SI details),[30] indicating an application potential of the prepared chiral cyclooctadienes in asymmetric catalysis. Moreover, cationic cyclizations of COD-derivatives constitute a concise strategy for the construction of the bicyclo[3.3.0]octane core.[17] In this respect, bicyclo[3.3.0]octane **8** was obtained in moderate yield as a single diastereomer with four contiguous stereogenic centers when exposing (*R*)-**3db** to formic acid at ambient temperature.

Scheme 3. Absolute configuration determination *via* Rh-complex 7a and synthesis of 7b and 8.



In conclusion, we have developed an iron-catalyzed enantioselective cross-[4+4]-cycloaddition of 1,3-dienes to form substituted cyclooctadienes. A highly tailored chiral α-diimine based ligand was essential for the success of the transformation providing a balanced performance with respect to reactivity, excellent cross-selectivity and very high enantioselectivity. Analysis of the steric maps of the microenvironment around the iron center helps account for the observed selectivity. Our method provides a straightforward and step-economic access to a wide variety of differently functionalized cyclooctadienes in high yields and excellent enantioselectivities. Access to substituted cyclooctadienes in an efficient asymmetric fashion has been a notoriously challenging task for synthesis, limiting the exploitation of chiral CODs in asymmetric catalysis. The method fills a long-standing gap in enantioselective iron-catalysis. Moreover, the reported chiral α-diimine (DI) iron complexes are expected to be of general utility for additional iron-catalyzed asymmetric transformations.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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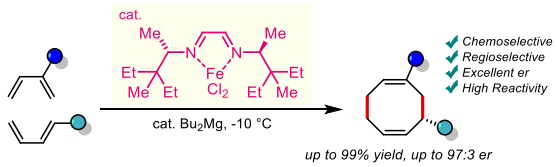

up to 99% yield, up to 97:3 er