Asymmetric Catalysis

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Enantioselective Iron-Catalyzed Intramolecular Cyclopropanation Reactions**

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Abstract: *An iron-catalyzed asymmetric intramolecular cyclopropanation was realized in high yields and excellent enantioselectivity (up to 97% ee) by using the iron complexes of chiral spiro-bisoxazoline ligands as catalysts. The superiority of iron catalysts exhibited in this reaction demonstrated the potential abilities of this sustainable metal in asymmetric carbenoid transformation reactions.*

Enantioselective catalysis by chiral transition-metal complexes constitutes one of the most powerful tools for the synthesis of optically active organic compounds on both laboratory and industrial scales,[1] and many chiral catalysts have been developed in recent decades. However, most of these catalysts are based on precious metals, such as palladium, rhodium, ruthenium, iridium, and osmium. The scarcity of precious metals makes them expensive and unsustainable over the long term. In addition, the biological toxicity of heavy metals seriously limits their use in pharmaceutical production. Therefore, the development of sustainable catalysts in which scarce or toxic metals are replaced with abundant and harmless metals is urgently required.[2]

Iron, which is readily available, inexpensive, and environmentally benign, is an ideal alternative to precious metals. However, compared to other transition metals, iron is less developed as a catalyst for organic processes, particularly asymmetric reactions.[3] Only a few iron-catalyzed reactions show good enantioselectivity,[4] and iron catalysts generally exhibit lower enantioselectivity and a narrower substrate scope than precious metal catalysts. In addition, there are a number of important reactions for which iron catalysts have never been reported to show good enantioselectivity, including the asymmetric cyclopropanation reaction between diazo compounds and olefins, which has been extensively studied and widely used in organic synthesis during the past several decades.[5] Several chiral iron porphyrins and analogues with complicated structures have been used in asymmetric intermolecular cyclopropanation reactions of α-diazoacetates with styrenes, but these reactions are only moderately enantioselective (up to 86% *ee*).[6]

Recently, a highly enantioselective (up to 97% *ee*) intermolecular cyclopropanation was realized with an engineered cytochrome P450 enzyme.[7] However, to the best of our knowledge, iron-catalyzed asymmetric intramolecular cyclopropanation remains unknown,[8] although intramolecular cyclopropanation is a powerful tool for the construction of complicated multiple ring systems and has been widely used in organic synthesis.[5] As part of our continuing studies of iron-catalyzed carbenoid transformations,[9] herein we report the first iron-catalyzed asymmetric intramolecular cyclopropanation. Specifically, we used iron catalysts with chiral spiro-bisoxazoline ligands to carry out intramolecular cyclopropanation of diazoesters in high yields and excellent enantioselectivities (up to 97% *ee*), thus providing a convenient method for generating synthetically versatile [3.1.0]bicycloalkanes.[10]

Initially, we performed the cyclopropanation reaction of 2-methylallyl 2-diazo-2-phenylacetate (**1a**) in chloroform at 60 °C in the presence of an iron catalyst generated in situ from 10 mol% $FeCl_3$, 12 mol% of the chiral spiro-bisoxazoline ligand (R_a,*S*,*S*)-**3a**, and 12 mol% $NaBAr_F$ (Table 1). Under these conditions, the cyclopropanation product (1*S*,5*S*)-5-methyl-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (**2a**) was obtained in 67% yield and 71% *ee* (entry 1). The structure and absolute configuration of **2a** were determined by X-ray diffraction of a single crystal.[11] Although there are four possible isomers of **2a**, which has two chiral centers, only the enantiomers (1*S*,5*S*)-**2a** and (1*R*,5*R*)-**2a**, in which the phenyl and methyl groups are *cis* to each other, were detected in the reaction mixture. The *trans* isomers did not form, owing to the highly strained nature of the fused ring system.

Various other iron precursors were then evaluated, and all gave the desired product in moderate to good yield (Table 1, entries 1–8). $FeCl_2$ exhibited higher catalytic activity than $FeCl_3$ (compare entries 1 and 2), and with $FeCl_2{\cdot}4H_2O$, the transformation was complete within 17 hours, and the product was obtained in 77% *ee* (entry 3). Although water was present in this case, no O–H insertion product was detected.[9a] Iron precursors with oxygen ligands, including $[Fe(acac)_2]$, $Fe(OAc)_2$, and $Fe(OTf)_2$, exhibited lower activity and enantioselectivity than $FeCl_2{\cdot}4H_2O$ (entries 4–6). Ferrous salts $Fe(BF_4)_2{\cdot}6H_2O$ and $Fe(ClO_4)_2{\cdot}4H_2O$ proved to be the best catalyst precursors (entries 7 and 8). Both of these iron sources accomplished the intramolecular cyclopropanation reaction in a relatively short time (5 and 7 h, respectively) and generated the desired product in high yields (83% and 94%, respectively) and enantioselectivities (88% and 92% *ee*, respectively). It is noteworthy that the enantioselectivity

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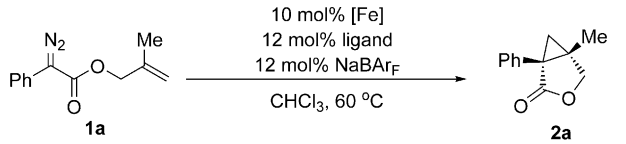
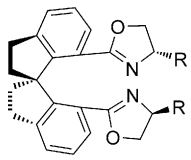
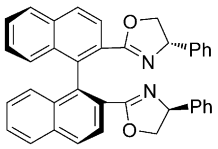
Table 1: Enantioselective iron-catalyzed intramolecular cyclopropanation of **1a**: Optimizing reaction conditions.[a]

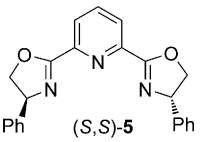




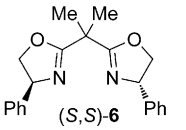
(R_a,*S*,*S*)-**3a**: R = Ph
(R_a,*S*,*S*)-**3b**: R = Bn
(R_a,*S*,*S*)-**3c**: R = Me
(R_a,*S*,*S*)-**3d**: R = *i*Pr



(S_a,*S*,*S*)-**4**



(*S*,*S*)-**5**



(*S*,*S*)-**6**

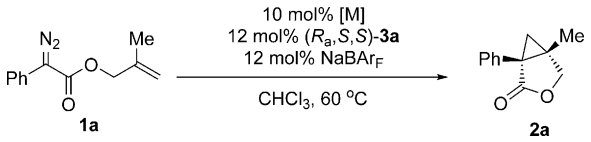
Entry	[Fe]	Ligand	*t* [h]	Yield [%][b]	*ee* [%][c]
1	$FeCl_3$	(R_a,*S*,*S*)-**3a**	30	67	71
2	$FeCl_2$	(R_a,*S*,*S*)-**3a**	24	92	73
3	$FeCl_2{\cdot}4H_2O$	(R_a,*S*,*S*)-**3a**	17	82	77
4	[Fe(acac)$_2$]	(R_a,*S*,*S*)-**3a**	30	83	59
5	Fe(OAc)$_2$	(R_a,*S*,*S*)-**3a**	30	64	69
6	Fe(OTf)$_2$	(R_a,*S*,*S*)-**3a**	30	57	62
7	$Fe(BF_4)_2{\cdot}6H_2O$	(R_a,*S*,*S*)-**3a**	5	83	88
8[d]	$Fe(ClO_4)_2{\cdot}4H_2O$	(R_a,*S*,*S*)-**3a**	7 (17)	94 (83)	92 (82)
9	$Fe(ClO_4)_2{\cdot}4H_2O$	(R_a,*S*,*S*)-**3b**	7	85	55
10	$Fe(ClO_4)_2{\cdot}4H_2O$	(R_a,*S*,*S*)-**3c**	10	87	57
11	$Fe(ClO_4)_2{\cdot}4H_2O$	(R_a,*S*,*S*)-**3d**	30	59	36
12	$Fe(ClO_4)_2{\cdot}4H_2O$	(S_a,*S*,*S*)-**3a**	30	51	44
13	$Fe(ClO_4)_2{\cdot}4H_2O$	(R_a,*S*,*S*)-**4**	24	55	14
14	$Fe(ClO_4)_2{\cdot}4H_2O$	(S_a,*S*,*S*)-**4**	24	78	58
15	$Fe(ClO_4)_2{\cdot}4H_2O$	(*S*,*S*)-**5**	30	66	4
16	$Fe(ClO_4)_2{\cdot}4H_2O$	(*S*,*S*)-**6**	7	82	72

[a] Reaction conditions: [Fe]/ligand/NaBAr$_F$/**1a** = 0.030:0.036:0.036:0.3 (mmol), in 4 mL $CHCl_3$ at 60 °C. [b] Yield of isolated product. [c] Determined by HPLC using a Chiralpak AS column. [d] The data within parentheses were obtained with 5 mol% catalyst. acac = acetylacetonate, NaBAr$_F$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, Tf = trifluoromethanesulfonate.

(92% *ee*) obtained with the iron catalysts in this study is comparable to the best enantioselectivity previously obtained for this reaction using chiral dirhodium catalysts.[12]

The substituents on the oxazoline rings of chiral spirobisoxazoline ligands **3** markedly affected the outcome of the cyclopropanation reaction (Table 1, entries 9–11). Specifically, an alkyl substituent lowered both the activity and the enantioselectivity. The ligand (S_a,*S*,*S*)-**3a** yielded inferior results to those obtained with the diastereomer (R_a,*S*,*S*)-**3a** (entry 12), and clearly indicates that the chirality of the ligand (R_a,*S*,*S*)-**3a** is appropriately matched for this reaction. For comparison, we also evaluated several widely used chiral bisoxazoline ligands with different scaffolds, such as 2,2′-bis(4,5-dihydro-4-phenyloxazol-2-yl)-1,1′-binaphthyl (**4**), 2,6-bis(4,5-dihydro-4-phenyloxazol-2-yl)pyridine (**5**), and 2,2′-bis(4,5-dihydro-4-phenyloxazol-2-yl)propane (**6**), under the standard reaction conditions (entries 13–16) and found that poorer yields and enantioselectivities were obtained. These results demonstrate that the bulky, rigid scaffold of **3** plays a vital role in controlling the activity of the catalyst and the enantioselectivity of the reaction.

Table 2: Enantioselective intramolecular cyclopropanation of **1a**: Comparison of metal precursors.[a]



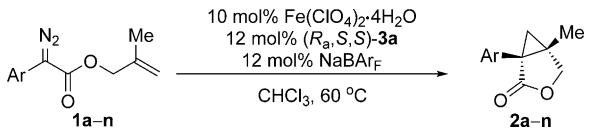
Entry	[M]	*t* [h]	Yield [%]	*ee* [%]
1	$Fe(ClO_4)_2{\cdot}4H_2O$	7	94	92
2	$[Cu(CH_3CN)_4]ClO_4$	0.1	90	48
3	$[\{RhCl(CO)_2\}_2]$	3	82	20
4	$[Pd(PhCN)_2Cl_2]$	3	66	4
5	$[\{RuCl_2(C_6H_6)\}_2]$	0.5	39	3
6	$CoCl_2$	30	64	52
7	$AgClO_4$	7	62	9
8	AuCl	5	59	7

[a] Reaction conditions and analysis are identical to those in Table 1, entry 8, but using the indicated metal precursor.

We also tested various other transition metals, including copper, palladium, rhodium, ruthenium, cobalt, silver, and gold, in the intramolecular cyclopropanation reaction under the standard reaction conditions (Table 2). Although all the tested transition metals afforded the desired product **2a** in moderate to good yields, the enantioselectivities were much lower than those obtained with the iron catalyst under the standard reaction conditions.

Under the optimized reaction conditions, the α-diazoester substrates **1a**–**m**, having various substituents on the phenyl ring were subjected to the asymmetric intramolecular cyclopropanation (Table 3, entries 1–13). All the tested substrates produced the desired cyclopropanation products in high yields (86–96%). Diazoesters with an electron-withdrawing

Table 3: Enantioselective iron-catalyzed intramolecular cyclopropanation of α-diazoesters **1a**–**n**.[a]



Entry	Substrate	Product	*t* [h]	Yield [%]	*ee* [%]
1	C_6H_5 (**1a**)	**2a**	7	94	92
2	2-FC_6H_4 (**1b**)	**2b**	7	93	93
3	2-ClC_6H_4 (**1c**)	**2c**	8	96	94
4	2-MeC_6H_4 (**1d**)	**2d**	10	88	4
5	3-$CF_3C_6H_4$ (**1e**)	**2e**	7	89	96
6	3-ClC_6H_4 (**1f**)	**2f**	10	90	94
7	3-MeC_6H_4 (**1g**)	**2g**	20	86	90
8	3-$MeOC_6H_4$ (**1h**)	**2h**	6	90	93
9	4-FC_6H_4 (**1i**)	**2i**	7	94	91
10	4-ClC_6H_4 (**1j**)	**2j**	10	91	90
11	4-MeC_6H_4 (**1k**)	**2k**	7	90	85
12	4-$MeOC_6H_4$ (**1l**)	**2l**	7	93	44
13	3,4-$Cl_2C_6H_3$ (**1m**)	**2m**	12	94	94
14	2-Naphthyl (**1n**)	**2n**	7	92	93

[a] Reaction conditions and analysis are identical to those in Table 1, entry 8.

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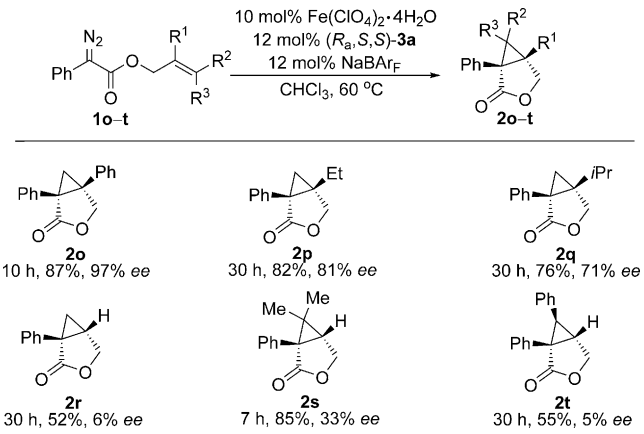
group, such as fluoro (**1b** and **1i**), chloro (**1c**, **1f**, **1j**, and **1m**), or trifluoromethyl (**1e**), on the phenyl ring exhibited higher enantioselectivity (entries 2, 3, 5, 6, 9, 10, and 13), with 3-(trifluoromethyl)phenyl-α-diazoacetate (**1e**) giving the highest enantioselectivity (entry 5). In contrast, a strongly electron-donating methoxy group at the *para* position of the α-diazoester (**1l**) lowered the enantioselectivity to 44% *ee* (entry 12). The enantioselectivity of the reaction was strongly affected by steric hindrance in the α-diazoester: reaction of an α-diazoester having an *ortho*-methyl group on the phenyl ring (**1d**) gave extremely low enantioselectivity (entry 4). In addition, 2-naphthyl diazoester (**1n**) also showed very high enantioselectivity (entry 14).

The effect of the allyl moiety in the substrate was also investigated (Scheme 1). The R^1 group strongly affected the



Scheme 1. The effects of olefin moiety.

enantioselectivity of the reaction. The substrate **1o**, in which R^1 is a phenyl group, gave the highest enantioselectivity (97% *ee*), whereas when R^1 was ethyl (**1p**) or isopropyl (**1q**), the enantioselectivities dropped to 81% and 71% *ee*, respectively. The enantioselectivity of the reaction **1r**, in which R^1 is H, was dramatically lower (6% *ee*). The substrates **1s** (R^1 = H, $R^2 = R^3$ = Me) and **1t** ($R^1 = R^3$ = H, R^2 = Ph), having internal olefin moieties, smoothly underwent the cyclopropanation reaction albeit with poor *ee* values. The *trans* H on the cyclopropane moiety of **2t** implies that the cyclopropanation undergoes a concerted process.

Iron can undergo facile changes in its oxidation state and exhibit distinct Lewis acid character, and could therefore be used to activate diazo compounds in a variety of different ways, which makes the mechanism study difficult.[6a] We cannot identify a clear mechanism of the iron-catalyzed intramolecular cyclopropanation at present, however, the following features are helpful for understanding this reaction. 1) The iron(II) exhibited higher reactivity than iron(III). 2) The by-products are mainly fumarates and maleates, which are generally attributed to the dimerization of carbenes. 3) The reaction exhibits higher reactivity for electron-rich olefins (compare **2a** with **2r**), and thus agrees with the reactivity of electrophilic iron carbenoid species.[13] According to these features, the iron catalysts most likely generate iron carbenoids in this reaction rather than just serve as Lewis acid catalysts. The studies of the detailed mechanism of this reaction are still ongoing.

In summary, we realized an efficient iron-catalyzed asymmetric intramolecular cyclopropanation reaction using iron complexes of chiral spiro-bisoxazoline ligands. This method provides an efficient protocol for the preparation of synthetically useful chiral [3.1.0]bicycloalkanes. The superiority of iron catalysts in this reaction demonstrates the possibility of using environmentally benign iron to replace precious metals in important asymmetric carbenoid transfer reactions through developing suitable chiral ligands.

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