

Asymmetric Fe^{II}-Catalyzed Thia-Michael Addition Reaction to α,β -Unsaturated Oxazolidin-2-one Derivatives

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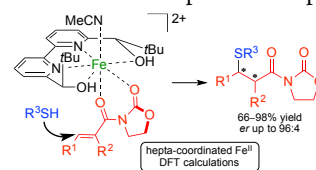
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Supporting Information

ABSTRACT: A highly enantioselective Fe^{II}-catalyzed thia-Michael addition to α,β -unsaturated carbonyl derivatives was developed. The scope of the reaction was demonstrated with a selection of aromatic, heterocyclic, and aliphatic thiols, and various Michael acceptors. The corresponding β -thioethers were obtained in good to excellent yields (up to 98%) and moderate to excellent enantioselectivities (up to 96:4 *er*). Unusual hepta-coordination of the metal and chelation to α,β -unsaturated oxazolidin-2-one derivatives allowed the construction of a coherent model rationalizing the enantioselective event. DFT calculations support the proposed model for observed stereoselectivities.

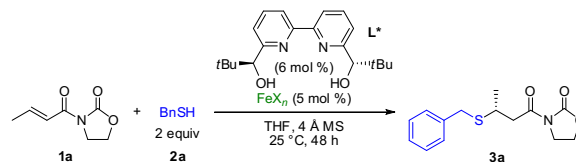


The use of iron complexes as catalysts has arisen from traditional transition metal catalysis in various synthetic transformations of modern organic chemistry.¹ Many catalysts are originally derived from rare metals such as palladium, ruthenium, platinum, and iridium. Their low availability, toxicity, and high market prices encourage their replacement by alternative metals.² From a sustainable chemistry perspective, developing new synthetic methods using iron, which is abundant, inexpensive, environmentally benign, and relatively nontoxic in comparison with other metals, is a major advantage.^{2b,3} The ability to use iron in homogeneous asymmetric catalysis is promising for the development of greener synthetic methods,⁴ contributing to major improvements for both academia and pharmaceutical industries.⁵ The 1,4-addition on α,β -unsaturated carbonyl derivatives is one of the most powerful and efficient ways to create new C–C bonds and various heteroatom-carbon bonds, such as N–C, O–C, and S–C bonds.⁶ Sulfur-containing compounds, which are essential building blocks for biologically active pharmaceutical agents, are important targets.⁷ Chiral Brønsted acids and bases,⁸ thiourea and squaramide *cinchona* alkaloid derivatives,⁹ and a non-covalent NHC,¹⁰ have been reported to be efficient catalysts for the thia-Michael addition reaction. Previous work has been disclosed using chiral Lewis acid catalysts derived from Ni^{II},¹¹ Hf^{IV},¹² Sc^{III},¹³ and Co^{II}¹⁴ salts for the asymmetric 1,4-addition of thiols to α,β -unsaturated oxazolidin-2-ones. Chiral Fe^{II} and Fe^{III} complexes afforded β -thioethers with excellent yields and enantioselectivities.¹⁵ However, most of the methods use costly transition metals, high catalytic loadings or chlorinated solvents.

In our continuing studies in asymmetric catalysis using iron salts, *i.e.*, Mukaiyama aldol, *meso*-epoxide opening, and aromatic sulfide oxidation reactions, Fe^{II}/chiral bipyridine complexes have proven to

be efficient enantioselective catalysts.¹⁶ A simple and highly asymmetric thia-Michael addition on acyclic α,β -unsaturated derivatives using iron salts as environmentally benign chiral catalysts is disclosed herein. Experimental insights into the influence of the nucleophile on the stereoselectivity control, together with DFT calculations, are also presented.

Table 1. Iron-Catalyzed Thia-Michael Addition to (*E*)-3-Crotonoyloxazolidin-2-one–Catalyst Optimization^a

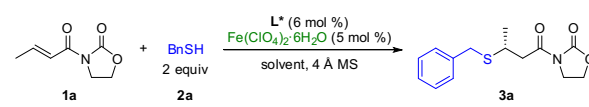


entry	FeX _n	yield (%) ^b	<i>er</i> ^c
1	FeCl ₂	14	63:37
2	Fe(BF ₄) ₂ ·6H ₂ O	50	91:9
3 ^d	Fe(OTf) ₂	42	93:7
4	Fe(ClO ₄) ₂ ·6H ₂ O	77	95:5
5	FeCl ₃	20	62:38
6	Fe(acac) ₃	64	55:45
7	Fe(OTf) ₃	19	88:12
8	Fe(ClO ₄) ₃ ·6H ₂ O	28	89:11

^aConditions: FeX_n (5 mol %), L* (6 mol %), 4 Å MS, **1a** (0.5 mmol), and **2a** (1 mmol), THF. ^bConversion by ¹H NMR. ^cDetermined by chiral HPLC (OD–H column). ^dReaction stopped after 72 h.

Asymmetric Michael addition of benzylthiol **2a** to (*E*)-3-crotonoyloxazolidin-2-one **1a**, run in THF, was initially selected as the model reaction for the screening of various iron salts with (*S,S*)-Bolm's ligand **L***¹⁸ (Table 1). FeCl₂ showed a moderate chiral induction in a low conversion (entry 1). Fe(BF₄)₂·6H₂O, Fe(OTf)₂, and Fe(ClO₄)₂·6H₂O afforded (3*R*)-**3a** with good enantioselectivities and moderate to good conversions (entries 2–4). Fe^{III} salts, such as FeCl₃ and Fe(acac)₃, allowed the formation of thioether (3*R*)-**3a** with low chiral inductions (entries 5 and 6). Fe(OTf)₃ and Fe(ClO₄)₃·6H₂O led to good *er*'s with low conversions (entries 7 and 8). Overall, both conversions and enantioselectivities were higher when using Fe^{II} vs. Fe^{III} salts. An optimum 95:5 *er* was obtained, together with high conversion, when using Fe(ClO₄)₂·6H₂O, and thereby, this system was used as a chiral catalyst in our study (entry 4). It is noteworthy to mention that the addition of 4 Å molecular sieves, known as attractive additive in asymmetric reactions,¹⁹ enhanced the enantioselectivity, but extended the reaction time.²⁰ Since 4 Å MS were advantageous in terms of *er*, they were used as an additive in the *thia*-Michael addition reaction.

Table 2. Fe^{II}-Catalyzed Thia-Michael Addition to (*E*)-3-Crotonoyloxazolidin-2-one–Solvent Optimization^a



entry	solvent	<i>t</i> (°C)	time (h)	yield (%) ^b	<i>er</i> ^d
1	THF	25	24	88	95:5
2	Et ₂ O	25	24	82	84:16
3	CH ₂ Cl ₂	25	24	77	82:18
4	PhMe	25	72	89	89:11
5	MeCN	25	24	94	96:4
6	MeCN	−10	48	67 ^c	98:2
7 ^e	MeCN	−20	144	36 ^c	97:3
8 ^f	MeCN	25	144	51 ^c	94:6
9 ^g	MeCN	25	24	94	51:49

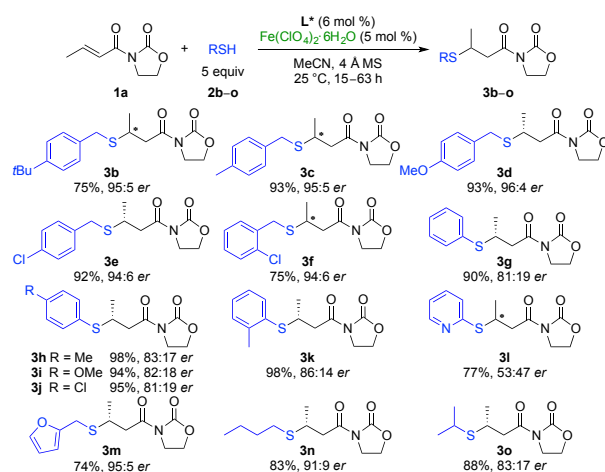
^aConditions: Fe(ClO₄)₂·6H₂O (5 mol %), **L*** (6 mol %), 4 Å MS, **1a** (0.5 mmol), **2a** (1 mmol), solvent. ^bYield of isolated product. ^cConversion by ¹H NMR. ^dDetermined by chiral HPLC (OD–H column). ^eWith 7.5 mol % of Fe(ClO₄)₂·6H₂O and 9 mol % of **L***. ^fWith 1 equiv of **2a**. ^g6 mol % of **L*** used in the absence of Fe(ClO₄)₂·6H₂O.

The optimization study was first performed using various solvents (Table 2). An increase of the substrate concentration from 0.5 M to 1 M in THF led to a higher conversion and shorter reaction time, but unchanged *er* (entry 1 vs. Table 1, entry 4). Et₂O and CH₂Cl₂ led to good yields with lower enantioselectivities (entries 2 and 3). Using PhMe as a solvent afforded a good *er*, albeit in an extended reaction time (entry 4). A coordinating and polar solvent, such as MeCN, afforded (3*R*)-**3a** in high yield and excellent enantioselectivity (entry 5). Considering the azaphilicity of iron,^{21a,21b} the binding of MeCN in the coordination sphere of Fe^{II} increased the transition state stability, which affected both the rate and selectivity.^{21c} These optimized catalytic conditions involving Fe(ClO₄)₂·6H₂O/**L*** in MeCN were chosen for further studies.²² The temperature was then decreased from 25 °C to −10 °C, and then −20 °C, and up to 98:2 *er*'s were obtained, whereas conversions were low (entries 6 and 7).

However, pursuing this study at 25 °C appeared to be the most practical alternative inducing minor *er* variations. When a stoichiometric quantity of thiol **2a** was used, a similar *er* was obtained, in a prolonged reaction time (entry 8). Virtually no enantioselectivity was obtained when using (*S,S*)-Bolm's ligand in the absence of an Fe^{II} salt (entry 9).

To demonstrate the scope of the Fe(ClO₄)₂·6H₂O catalyzed asymmetric Michael addition, a range of thiols was studied. Substituted aromatic, heterocyclic, and aliphatic thiols were used. As previously shown, the stereoselectivity does not depend on thiol concentration. Consequently, five equivalents of thiol were used to promote the conversion.²³ Michael addition reactions of various substituted thiols (**2b–o**) on (*E*)-3-crotonoyloxazolidin-2-one **1a** were run under the optimal reaction conditions (Scheme 1).

Scheme 1. Fe^{II}-Catalyzed Conjugate Addition of Different Thiols to (*E*)-3-Crotonoyloxazolidin-2-one^{a–c}

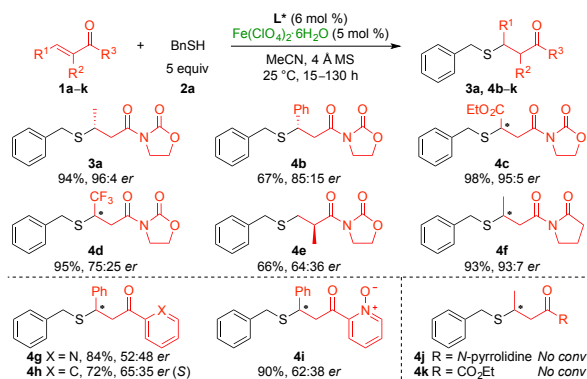


^aConditions: Fe(ClO₄)₂·6H₂O (5 mol %), **L*** (6 mol %), 4 Å MS, **1a** (0.5 mmol), **2b–o** (2.5 mmol), MeCN. ^bDetermined by chiral HPLC. ^cAbsolute configurations assigned from the literature, except for optically active **3b**, **3c**, **3f**, and **3l** (unknown absolute configurations).

The Fe^{II}-catalyzed Michael addition of various thiols to (*E*)-3-crotonoyloxazolidin-2-one **1a** surprisingly led to a wide range of enantioselectivities. Up to 96:4 *er*'s were obtained using *para*- and *ortho*-substituted benzylthiols (**3b–3f**). In comparison, lower stereoselectivity control was observed using *para*- and *ortho*-substituted phenylthiols ((3*R*)-**3h–(3R)-3k**). The same observation was made when using unsubstituted thiophenol **2g** ((3*R*)-**3g** vs. (3*R*)-**3a**). Electron-rich and -deficient groups in the *para* position of the thiol aromatic ring had negligible influence on the enantioselectivity in both the benzyl and phenyl series (**3b–3e** and (3*R*)-**3h–(3R)-3j**). These groups changed the thiol reactivity, but with no influence on the stereoselectivity control. *o*-Methyl substitution of the aryl thiol induced an increased *er*, which was not observed using thiol **2f** ((3*R*)-**3k** vs. **3f**). No enantioselectivity was obtained using 2-mercaptopyridine (**3l**). Furfuryl thiol, as a heterocyclic nucleophile, led to an excellent *er* ((3*R*)-**3m**). Butyl and isopropyl thiols led to good and moderate enantioselectivities, respectively ((3*R*)-**3n** and (3*R*)-**3o**). Finally, all β-thioethers in this study were obtained in good to excellent yields (up to 98%).

A variety of α,β-unsaturated carbonyl compounds (**1a–i**) were examined as substrates for the 1,4-addition of benzylthiol **2a**, under the optimal reaction conditions (Scheme 2). The electronic and steric

Scheme 2. Fe^{II}-Catalyzed Conjugate Addition of Benzylthiol to α,β -Unsaturated Carbonyl Compounds^{a-c}



^aConditions: $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (5 mol %), L^* (6 mol %), 4 Å MS, **1a–k** (0.5 mmol), **2a** (2.5 mmol), MeCN. ^bDetermined by chiral HPLC. ^cAbsolute configurations assigned from the literature, except for optically active **4c**, **4d**, **4f**, **4g**, and **4i** (unknown absolute configurations).

effects of various R¹ groups on the enantioselectivity was studied. Among a small chosen set of α,β -unsaturated oxazolidin-2-ones, comprising electron-donating (**1a**, **1b**) and electron-withdrawing (**1c**, **1d**) groups, the highest *er* was obtained with R¹ = Me ((3*R*)-**3a**). A major decrease of the enantioselectivity was observed when increasing the electron-withdrawing ability of R¹ from CH₃ to CF₃ ((3*R*)-**3a** vs. **4d**), albeit a high level of *er* was maintained with R¹ = CO₂Et (**3c**). Introducing a Me group at the α -position (R²) instead of the β -position (R¹) caused the enantioselectivity to no longer be dependent on the *Re* addition face, but rather on the later protonation step. A low enantioselective α -protonation step by the chiral catalyst was highlighted by the 64:36 *er* obtained with (2*R*)-**4e**. A slightly reduced *er* was afforded using a 2-pyrrolidinone 5-membered cycle (**4f**). The nature of the chelating properties of R³ was also examined. Pyridyl, phenyl, and pyridyl *N*-oxide as R³ substituents were studied in regard to their different chelating structures; the enantioselectivity dropped dramatically in comparison with the oxazolidin-2-one analogue (**4g–4i** vs. (3*S*)-**4b**). The absence of a dicarbonyl chelating system did not lead to any reaction using α,β -unsaturated amide **1j** and ester **1k** (0% of **4j** and **4k**, recovered starting materials). Indeed, the dicarbonyl core of the Michael acceptor appeared to be essential for maintaining high levels of stereocontrol in the asymmetric 1,4-addition of thiols using Fe^{II}/ L^* system.

A catalytic cycle was postulated based on precedents gained on the coordination of Fe^{II} salt with L^* (Figure 1).^{16a-c} The bipyridine ligand is coordinated to the metal center in a tetradentate fashion, *via* the coordination of two O and N atoms in the four equatorial sites of the octahedral d^6 Fe^{II} center. MeCN molecules (noted as S) are coordinated to the axial sites as shown in **I**. As observed from previous crystallographic studies using Fe^{II} and L^* ,^{16a} the appearance of a fifth labile equatorial substituent arisen from electrostatic interactions, reveals the pentagonal bipyramidal geometry adopted by the chiral catalyst. After ligand exchange with substrate **1a**, both carbonyl groups chelated Fe^{II} to form complex **II**. This hypothesized structure of complex **II** is similar to the previously reported C₂-symmetrical Fe^{III}/bis(oxazoline) complex by Corey.²⁴ Then, the thiol would attack the more accessible *Re* face of the β -carbon of the α,β -

unsaturated carbonyl compound to give **III**. Enantioselectivities were induced by the steric hindrance of the *t*Bu group of the ligand, which blocks the nucleophilic attack on the *Si* face of the substrate **1a**. Finally, a low enantioselective protonation on **III** (as noted with **4e**) generates the expected thioether adducts. The high enantioselectivities arising from the chiral induction in the β -position are in agreement with this speculated mechanism.

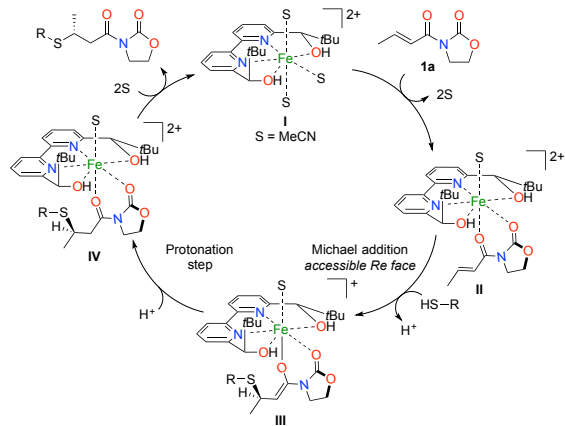


Figure 1. Postulated mechanism

In the *endo* complex **II** depicted above, the C=C bond of **1a** is oriented towards the bipyridine backbone, making its *Re* face the most accessible one for the thiol. Exchanging the equatorial and apical carbonyls would place the C=C bond in the opposite direction, with the *Si* face being more accessible. Thus, the *endo/exo* orientation of the substrate is a critical feature, as it determines the absolute configuration of the product. To validate the *endo* configuration as the preferred one, DFT computations were carried out at the B3LYP/SDD(Fe)-cc-pVTZ (other elements) // B3LYP/SDD(Fe)-6-31+G(d) (other elements), as recently described for the mechanism of Fe^{II}-catalyzed asymmetric Mukaiyama aldol reaction.²⁵ Using MeCN as axial ligand, three isomers **IIa–c** could be optimized (Figure 2). In the *exo* complexes **IIa** and **IIb**, the oxazolidin-2-one carbonyl occupies the apical position. The second carbonyl is located at the equatorial position in **IIa**. In **IIb**, the second carbonyl is actually H-bonded to a hydroxyl group. In the *endo* series, no H-bonded isomers could be modelled, as they irretrievably collapse to **IIc** exhibiting the oxazolidin-2-one carbonyl at the equatorial position and the second carbonyl at the apical position. In agreement with the observed stereoselectivity of the title reaction, the *endo* complex **IIc** is the most stable of the three (ΔG_{298} **IIc** (0.0); **IIa** (3.0); **IIb** (3.5)).

In summary, we have successfully developed an efficient asymmetric Michael addition of thiols. An $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ conjointly used with Bolm's ligand has been shown to be an effective catalyst for the asymmetric Michael addition of thiols to α,β -unsaturated oxazolidin-2-ones. The Fe^{II}/*(S,S)*- L^* catalytic system was suitable to catalyze asymmetric thia-Michael addition giving yields up to 98% and *er*'s up to 96:4. The method is practical and cost-effective, and high enantioselectivities were obtained at room temperature. The chiral bipyridine ligand can be easily prepared and recycled in the purification process. A model has been proposed to support the high levels of stereoinduction observed at the β -position. DFT calculations are in agreement with the postulated model. Further developments will be reported in due course.

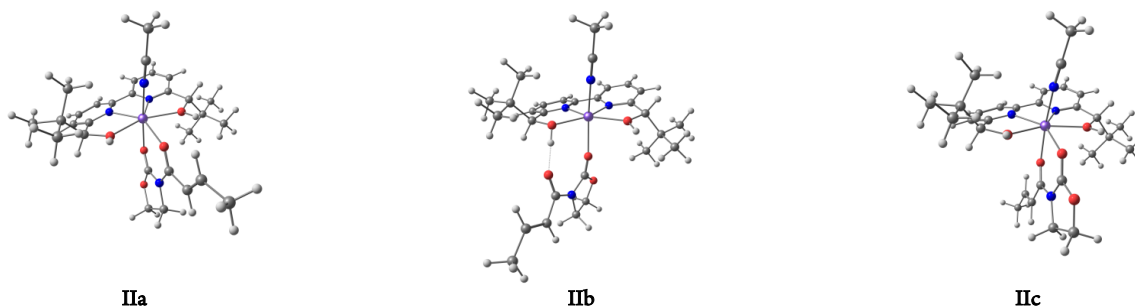


Figure 2. Geometries of the computed complexes IIa

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx. Experimental details, characterization date, NMR spectra, and chromatograms (PDF)

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- (20) Fe(OTf)₂: 93:7 *er*, 42% conv, 72 h vs. 89:11 *er*, 40% conv, 48 h.
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- (22) MeCN was also more effective using Fe(OTf)₂: 95:5 *er*, 72% conv of **3a**. 12 mol % L*/10 mol % Fe(ClO₄)₂·6H₂O: 91:9 *er*, 96% of **3a**. The *er* decreased using 20 mol % Pyr (34% conv, 75:25 *er*, 48 h) or 200 mol % K₂HPO₄ (95% conv, 51:49 *er*, 24 h).
- (23) Reaction times using **2o**: two equiv, >130 h vs. five equiv, 43 h.
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