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Enantioselective C–S bond formation by iron/Pybox catalyzed Michael addition of thiols to (*E*)-3-crotonoyloxazolidin-2-one

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Abstract—The enantioselective Michael addition of thiols to (*E*)-3-crotonoyloxazolidin-2-one was effectively catalyzed by the $Fe(BF_4)_2{\cdot}6H_2O$/(*S*,*S*)-*ip*-Pybox catalyst, and the addition product was obtained with up to a 95% ee.

Iron is one of the most abundant and environmentally friendly metals on earth. During last two decades, some efficient organic transformations, which were catalyzed by iron salts, were reported.[1] Most of the reports demonstrated carbon–carbon bond formations such as coupling, cycloaddition or polymerization reactions. Our group also reported some iron-catalyzed reactions; that is, cycloaddition reactions and Michael addition-type reactions in organic or an ionic liquid solvent system.[2] However, until recently, iron was relatively underrepresented in the field of asymmetric catalysts[1,3,4] compared to other transition metals for chiral complexes such as palladium, rhodium, ruthenium, etc. Therefore, we believe that the use of iron required for asymmetric organic syntheses, and the enantioselective construction of carbon–heteroatom bond is one of the most challenging topics in this field.

The asymmetric Michael addition reaction is one of the most important reactions in organic synthesis. Recently, such an asymmetric Michael addition of active methylene compounds with α,β-unsaturated carbonyl compounds was attained by some chiral transition metal catalysts.[5,6] On the other hand, the asymmetric Michael addition of thiols to α,β-unsaturated carbonyl compounds is still a difficult process,[7] and to the best of our knowledge, there are only four reports about such reactions with (*E*)-3-crotonoyloxazolidin-2-one.[8] The first example using the Ni catalyst was reported by Kanemasa et al. in 1999.[8a] After their pioneering work, three groups demonstrated this kind of asymmetric reaction using Yb,[8b] Hf,[8b,c] or Sc[8d] catalyst. From this perspective, the iron catalyzed Michael addition of thiols to α,β-unsaturated compounds still remains unresolved. We now report the first example of the iron catalyzed highly enantioselective Michael addition of thiols to (*E*)-3-crotonoyloxazolidin-2-one.

The screening of an effective iron catalyst for the conjugate addition of benzenethiol (**1a**) to (*E*)-3-crotonoyloxazolidin-2-one (**2**) was performed using varying iron salts ($FeCl_2$, $FeCl_3$, $Fe(BF_4)_2$, $Fe(ClO_4)_2$, $Fe(ClO_4)_3$, $Fe(OAc)_2$, $Fe(acac)_2$, etc.), chiral ligands (BINAP, MOP, Phox, Pybox, Box, Jacobsen ligand, etc.[9]) and solvents (toluene, THF, diethyl ether, dioxane, dichloromethane, acetonitrile, dimethylforamide, etc.). We discovered that the iron(II) salt with the bisoxazoline-based chiral ligand in THF exhibited a better reactivity and enantioselectivity than the other iron catalysts and solvents (Scheme 1). For example, iron(II) chloride with the chiral (*S*,*S*)-*ip*-Pybox ligand (**L1**) gave the addition product **3a** in both a higher yield and enantioselectivity than iron(III) chloride with **L1** (Table 1, entries 1 and 2). From these results, it is obvious that iron(II) salts are promising catalysts for the asymmetric Michael addition of benzenethiol (**1a**) to α,β-unsaturated amide **2**. So we attempted to evaluate iron(II) salts; switching the catalyst from $FeCl_2$ to $Fe(ClO_4)_2$ increased the chemical yield of **3a** up to 90%, while the enantioselectivity was significantly dropped to 40% ee (entry 3). Optimization

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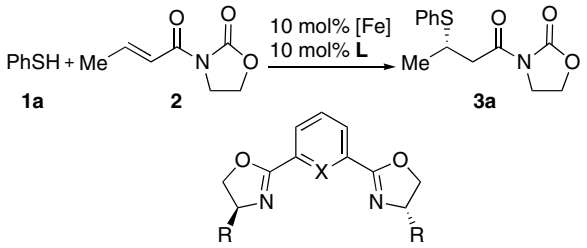


Scheme 1. Iron-catalyzed Michael addition of benzenethiol (**1a**) to (*E*)-3-crotonoyloxazolidin-2-one (**2**).

Table 1. Iron-catalyzed asymmetric Michael addition of benzenethiol (**1a**) to *N*-crotonoyl-2-oxazolidinone (**2**)[a]

Entry	[Fe]	L	Additive	Temperature (°C)/time (h)	Yield[b] (%)	ee[b,c] (%)
1	$FeCl_2$	**L1**	—	rt/24	79	53
2	$FeCl_3$	**L1**	—	rt/24	69	17
3	$Fe(ClO_4)_2$	**L1**	—	rt/24	90	40
4	$Fe(BF_4)_2$	**L1**	—	rt/24	74	66
5	$Fe(BF_4)_2$	**L2**	—	rt/24	92	0
6	$Fe(BF_4)_2$	**L3**	—	rt/24	95	0
7	$Fe(BF_4)_2$	**L1**	—	−20/150	86	86
8	$Fe(BF_4)_2$	**L1**	MS 4A	−20/24	86	90
9[d]	$Fe(BF_4)_2$	**L1**	MS 4A	−20/72	93	90

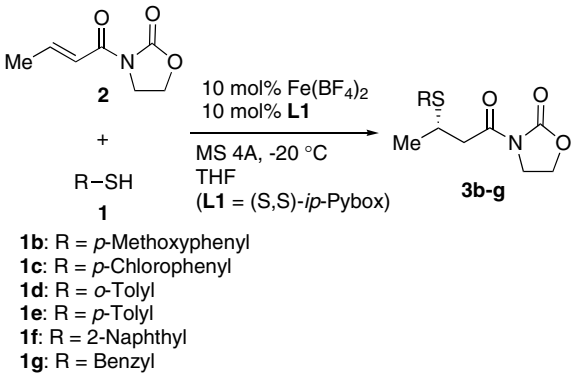
[a] All reactions were carried out with **1a** (0.75 mmol), **2** (0.50 mmol), 10 mol % iron salt, and 10 mol % chiral ligand in 0.8 mL of THF under nitrogen.

[b] Values for ee and yields are for pure, isolated compounds and are an average of two runs.

[c] Values of ee were determined by chiral HPLC using Daicel CHIRALPAK AD–H (hexane/2-propanol = 5/1).

[d] 3 mol % of [Fe] and **L1** were used.

of iron(II) salts concluded that combination of iron(II) tetrafluoroborate [$Fe(BF_4)_2$] with the (*S*,*S*)-*ip*-Pybox ligand (**L1**) was the best catalyst and **3a** was obtained in 74% yield with 66% ee (entry 4).[11] Interestingly, the reaction using other chiral bisoxazoline-based ligands, such as (*S*,*S*)-*phe*-Pybox (**L2**) and (*S*,*S*)-*ip*-Phebox (**L3**), showed no enantioselectivity (entries 5 and 6). These results suggest that both the isopropyl group[10] in the Pybox ligand and pyridyl backbone are essential for realizing high enantioselective reaction. According to these results, we concluded that the chiral iron catalyst with (*S*,*S*)-*ip*-Pybox (**L1**) is the most effective Lewis acid iron catalyst for the asymmetric Michael addition of thiol **1** to α,β-unsaturated amide **2**. The higher enantioselectivity (86% ee) was attained at a lower temperature (−20 °C), while the reaction rate was significantly decreased and it took 150 h to complete the reaction (entry 7). Fortunately great acceleration was obtained when the reaction was conducted in the presence of molecular sieves 4 A, and the enantioselectivity was also slightly increased up to 90% ee (entry 8). Furthermore, it was found that the reaction proceeded with excellent enantioselectivity using only 3 mol % of the catalyst, though a longer reaction time was needed (entry 9).



Scheme 2. Iron/*ip*–Pybox catalyzed asymmetric Michael addition of thiols **1b–g** to **2**.

Results of the asymmetric Michael addition of various types of thiols by this iron/*ip*-Pybox catalyst system (Scheme 2) are summarized in Table 2. All reactions were carried out in the presence of $Fe(BF_4)_2$ (10 mol %), *ip*-Pybox (10 mol %), and MS 4A in THF at −20 °C. The reactions of the aromatic thiols exhibited both high yields and enantiomeric excesses (Table 2. entries 1–5). The highest enantioselectivity (95% ee) was obtained for the reaction of the sterically hindered 2-methylbenzenethiol (**1d**) (entry 3). It should be emphasized that excellent enantioselectivity was obtained even when the reaction was performed using 3 mol % of the chiral iron catalyst, though it required a longer reaction time to complete the reaction (entry 6). Unfortunately, it was found that our catalyst system was not effective for the reaction of an alkyl thiol, such as benzyl mercaptan (**1g**), and it gave **3g** with only 24% ee (entry 7).

In conclusion, we succeeded in demonstrating the first examples of an iron salt-catalyzed asymmetric Michael reaction of thiols with α,β-unsaturated amide; the iron catalyst prepared from $Fe(BF_4)_2$ with the (*S*,*S*)-*ip*-Pybox ligand in situ exhibited excellent enantioselectivity and desired Michael products was obtained in good yield. Further investigation of the scope and limitations of the present iron salt-catalyzed reaction will make it even more valuable.

Table 2. $Fe(BF_4)_2$/*ip*-Pybox catalyzed asymmetric Michael addition of thiols **1b–g** to **2**[a]

Entry	1	Temperature (°C)/time (h)	Yield[b] (%)	ee[b,c] (%)
1	**1b**	−20/24	84	85
2	**1c**	−20/24	99	87
3	**1d**	−20/108	92	95
4	**1e**	−20/24	87	90
5	**1f**	−20/72	96	89
6[d]	**1f**	−20/168	72	91
7	**1g**	−20/48	53	24

[a] All reactions were carried out with **1** (0.75 mmol), **2** (0. 50 mmol), 10 mol % iron salt, 10 mol % chiral ligand, and MS 4A (17 mg) in 0.8 mL of THF under nitrogen.

[b] Values for ee and yields are for pure, isolated compounds and are an average of two runs.

[c] Values of ee were determined by chiral HPLC (for details, see Supplementary data).

[d] 3 mol % of $Fe(BF_4)_2{\cdot}6H_2O$ and (*S*,*S*)-*ip*-Pybox (**L1**) were used.

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Supplementary data

Experimental details and spectral data of all products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.053.

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9. BINAP = (*R*)- or (*S*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. MOP = (*R*)- or (*S*)-2-(Diphenylphosphino)-2′2methoxy-1,1′-binaphthyl, and its analogues. Phox = (*R*)- or (*S*)-2-[2-(Diphenylphosphino)phenyl]-4-(1-methylethyl)-4,5-di-hydrooxazole, and its analogues. Pybox = 2,6-Bis[(4*R*)- or (4*S*)-4-(*i*-propyl)-2-oxazolin-2-yl]pyridine, and its analogues. Box = 2,2-Bis[(4*S*)-4-phenyl-2-oxazolin-2-yl]propane, and its analogues. Jacobsen ligand = (1*R*,2*R*) or (1*S*,2*S*)-1,2-Cycloheanediamino-*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene).
10. Similar results about the difference between isopropyl group and phenyl group in iron–pybox complexes was also reported by Hossain et al., see: Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987–8990.
11. *General procedure of catalytic Michael addition.* The reaction conditions and results are shown in Tables 1 and 2. A typical procedure is given for the reaction of (−)-(*S*)-3-(3-Phenylthiobutanoyl)-2-oxazolidinone (**3a**) (Table 1, entry 4). To a solution of $Fe(BF_4)_2{\cdot}6H_2O$ (16.9 mg, 0.05 mmol), (*S*,*S*)-*ip*-Pybox (15.1 mg, 0.05 mmol), and (*E*)-3-crotonoyl-2-oxazolidinone (**2**) (77.6 mg, 0.50 mmol) in THF (0.3 mL) was added benzenethiol (**1a**) (78 mg, 0.75 mmol), then stirred at room temperature for 24 h. The reaction mixture was quenched with satd NH_4Cl, then extracted with THF (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 7/3) to give 196 mg (74%) of a mixture of conjugate adducts **3a**. The enantiomeric purity was determined by chiral HPLC analysis with a chiral stationary phase column. (−)-(*S*)-3-(3-Phenylthiobutanoyl)-2-oxazolidinone (**3a**):[3] Colorless oil; $[\alpha]_D^{24}$ −12.70 (*c* 1.26, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ −11.05 (*c* 1.23, $CHCl_3$)} {90% ee estimated on the basis of HPLC using a chiral column (Daicel CHIRALPAK AD–H, hexane/*i*-PrOH = 5/1 v/v, flow rate = 1.0 mL/min, $t(R) = 11$ min, $t(S) = 16$)}; ^1H NMR (400 MHz, $CDCl_3$) 1.36 (d, $J = 6.56$ Hz, 3H), 3.14 (dd, $J = 17.24$, 7.36 Hz, 1H), 3.27 (dd, $J = 16.88$, 6.60 Hz, 1H), 3.74–3.82 (m, 1H), 3.90–4.01 (m, 2H), 4.33–4.44 (m, 2H), 7.23–7.33 (m, 3H), 7.44–7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 21.17, 38.86, 42.20, 42.33, 61.98, 127.25, 128.80, 132.68, 134.00,153.27, 170.90.