Copper-Mediated Diastereoselective C–H Thiolation of Ferrocenes

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Supporting Information Placeholder

ABSTRACT: The first copper-mediated diastereoselective C–H thiolation of ferrocenes has been developed. A chiral oxazoline directing group with *tert*-butyl substituent is essential to the high diastereoselectivity ratio and the suppression of overreaction of mono-thiolated products. This reaction tolerated various functional groups on arylthoils, implying its potential application in N, S-bidentate planar chiral ligands.

Since the discovery and confirmation of its unique sandwich-like structure in 1950s, ferrocene has been widely investigated in academic and industry community.[1] One of the most prominent features of ferrocene derivatives is their application in asymmetric reactions as planar chiral ligands[2] or catalysis.[3] (**Figure 1.**) Traditionally, the synthesis of planar chiral ferrocenes was realized through diastereoselective directed *ortho*-metalation (DoM),[4] enantioselective DoM,[5] and resolution.[6] However, in these DoM reactions, combustible butyl lithium is needed and must be handled with great care.[7]

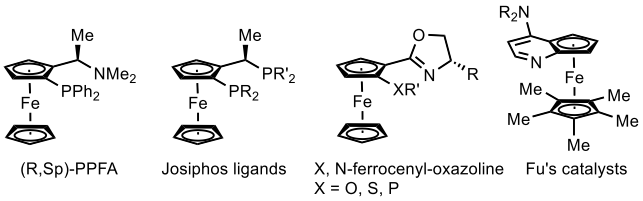
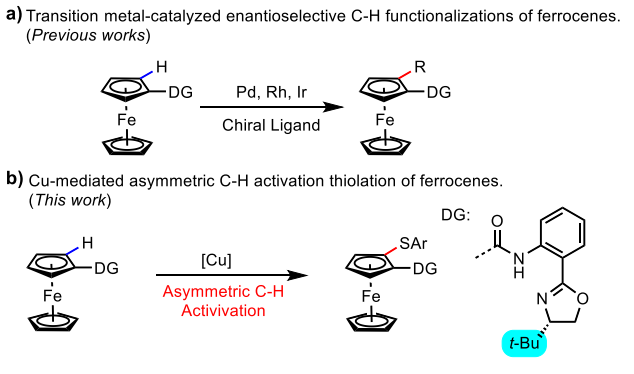


Figure 1. Chiral planar ligands and catalysis based on ferrocene.

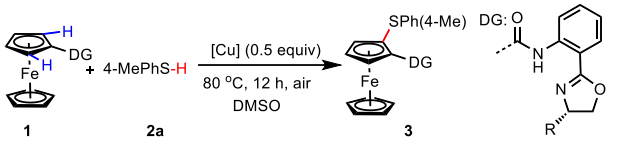
Transition metals-catalyzed C–H functionalizations has seen significant progress in the past two decades and enriched the toolbox in retrosynthesis analysis. One emerging challenge in this field is to realize asymmetric C–H activation and this has inspired chemists to apply it on ferrocenes to construct planar chiral structures (**Scheme 1, *a***).[8] You and other groups have made great progress in palladium-catalyzed enantioselective C–H functionalizations of ferrocene.[9] Shibata and coworkers have reported the first iridium(I)-catalyzed ferrocene C–H activation alkylation reaction to date.[10] Recently, rhodium(I)-catalyzed intramolecular silylation of ferrocene has been reported too.[11] In addition, some examples of transition metal-catalyzed non-asymmetric C–H functionalizations of ferrocene are reported.[12] In contrast to these noble metals, cheap metals such as copper-, iron- and nickel-catalyzed or mediated asymmetric C–H functionalizations of ferrocene are still underdeveloped.[13] To the best of our knowledge, there is no report of copper-catalyzed or -mediated directed asymmetric C–H functionalization to date,[14] except for few examples of copper-catalyzed non-directed C(sp^3)–H functionalizations.[15] Since our group have developed a series of copper catalyzed or mediated transformations of aryl C–H bond with an oxazoline based directing group,[16] we envisioned that with a chiral oxazoline amide as directing group, diastereoselective C–H functionalization might be realized on ferrocene. Here we communicate the first copper-mediated diastereoselective C–H thiolation of ferrocene with a chiral oxazoline directing group (**Scheme 1, *b***).[17]

Scheme 1. Transition Metal-Catalyzed or -Mediated C–H Functionalizations of Ferrocene



We initiated the research with **1a** as substrate, which was tethered a phenyl group on the oxazoline ring and 4-methylbenzenethiol as thiolation reagent. Firstly, different copper complexes were tested, including cupric acetate, copper(II) trifluoromethanesulfonate, copper(II) pivalate and copper(I) halides. The results showed that copper(II) pivalate gave the best result (8% mono-thiolated yield and 41% di-thiolated product). While copper(I) alone could not promote this reaction (see Supporting Information), the combination of copper(II) pivalate and copper(I) bromide could increase the yield of mono-thiolated product remarkably. Then other substituents like isopropyl (**1b**), benzyl (**1c**), methyl (**1d**) and *tert*-butyl (**1e**) groups with different steric size on the oxazoline ring were investigated (entries 6-9, **Table 1**). To our delight, *tert*-butyl group could suppress the overreaction of mono-thiolated product. What is more, with *tert*-butyl group on the oxazoline, the diastereoselectivity ratio was increased to more than 20:1 (entry 9, **Table 1**). When the loadings of both CuBr and $Cu(OPiv)_2$ were increased to 1.5 equivalence, the yield of **3a** was increased to 41% (entry 11, **Table 1**).

Table 1. Optimization of the Reaction Conditions [a]



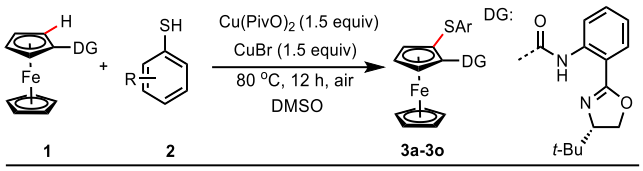
1 2a 3

Entry	R =	Cu(II)	Cu(I)	Mono	Di	dr
1	Ph(**1a**)	$Cu(OAc)_2{\cdot}H_2O$	–	16	–	5:1
2	Ph	$Cu(OTf)_2$	–	–	–	–
3	Ph	$Cu(OPiv)_2$	–	8	41	6:1
4	Ph	–	CuX (Br, Cl, I)	–	–	–
5	Ph	$Cu(OPiv)_2$	CuBr	22	34	10:1
6	*i*-Pr(**1b**)	$Cu(OPiv)_2$	CuBr	17	34	1:1
7	Bn(**1c**)	$Cu(OPiv)_2$	CuBr	12	38	1:1
8	Me(**1d**)	$Cu(OPiv)_2$	CuBr	15	41	6:1
9	*t*-Bu(**1e**)	$Cu(OPiv)_2$	CuBr	22	3	> 20:1
10[b]	*t*-Bu	$Cu(OPiv)_2$	CuBr	30	6	> 20:1
11[c]	*t*-Bu	$Cu(OPiv)_2$	CuBr	41(36%)[d]	9	> 20:1

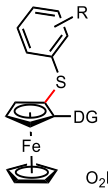
[a] Conditions:**1** (0.1 mmol), **2** (0.2 mmol), [Cu] (0.5 equiv) in DMSO (5.0 mL) under air in a 15 mL sealed tube at 80 °C for 12 h; Yields were determined by ^{1}H-NMR with 1,3,5-trimethoxybenzene as an internal standard. [b] With $Cu(OPiv)_2$ (1.0 equiv) and CuBr (1.0 equiv). [c] With $Cu(OPiv)_2$ (1.5 equiv) and CuBr (1.5 equiv). [d] isolated yield of **3a**.

With the optimized conditions confirmed, the generality of the asymmetric C–H thiolation was explored (**Table 2**). A series of substituted arylthoils were applicable in this reaction to give high diastereoselectivities (> 20:1) and moderate yields (36%-55%). Various substituents on the *para*-position were tolerated in this reaction (**3a**-**3f**). Trifluoromethyl substituted phenylthiol gave the best result of 55% yield (**3e**). The others afforded the corresponding products in yields around 40%. Thiophenols with electronic withdrawing and donating groups at *meta*-position gave the desired products in yields from 40% to 50% with >20:1 dr. This reaction also tolerated a small hindrance on the *ortho*-position. *Ortho*-fluoro substrate gave **3m** in 43% yield. In addition, when substrate bearing an ester group on the other Cp (Cp = cyclopentadienyl) ring is subjected to typical condition, 40% of sulfenylated product **3o** is formed.

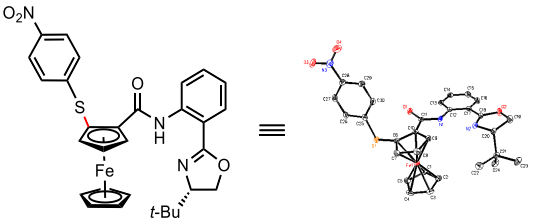
Table 2. Substrates Scope of Cu-Mediated Asymmetric C–H Thiolation of Ferrocene [a]



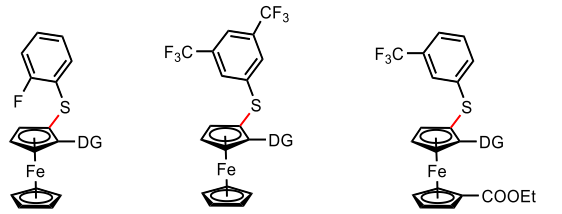
1 2 3a-3o



3a: R = 4-Me, 36%, dr > 20:1
3b: R = 4-H, 42%,[b,c] dr > 20:1
3c: R = 4-OMe, 45%,[b,d] dr > 20:1
3d: R = 4-F, 37%[b], dr > 20:1
3e: R = 4-CF_3, 55%, dr > 20:1
3g: R = 3-Me, 42%,[b] dr > 20:1
3h: R = 3-OMe, 45%,[b] dr > 20:1
3i: R = 3-CF_3, 50%,[b] dr > 20:1
3j: R = 3-Br, 44%,[b] dr > 20:1
3k: R = 3-Cl, 40%, dr > 20:1
3l: R = 3-F, 43%,[b] dr > 20:1



3f, 50%, dr > 20:1



3m, 43%,[b] dr > 20:1 **3n**, 47%,[b,e] dr > 20:1 **3o**, 40%, dr > 20:1

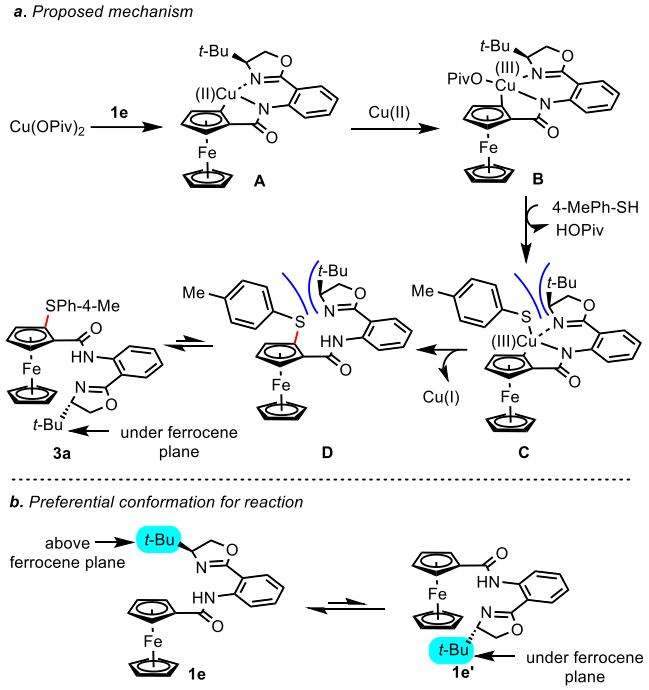
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Cu(PivO)_2$ (1.5 equiv), CuBr (1.5 equiv) in DMSO (5 mL) under air in a 15 mL sealed tube at 80 °C for 12 h; Isolated yield; Disteroselecitivity ratio values were determined by HPLC-MS analysis. [b] With BHT (0.2 equiv).[c] **2b** was diphenyl disulfide (1.0 equiv). [d] With **2** (1.3 equiv). [e] With **2n** (1.0 equiv).

The detailed mechanism of this reaction was still intriguing. Here we proposed a Cu(II)/(III) reaction model to explain the C–H activation thiolation reaction. Firstly, Cu(II) complex coordinated to the bidentate directing group of **1e** and C–H activation of Cp ring take place with the assistant of pivalate anion to give intermediate **A**, which was oxidized by Cu(II) to give Cu(III) complex **B**. Intermediate **C** was formed through anion exchange, followed by reductive elimination to release the desired product **3a** and Cu(I) species (**a, Scheme 2**).

In another aspect, the excellent diastereoselectivity and mono- *vs* di-thiolated product ratio could be rationalized through conformational analysis of the substrate and product. Through the X-ray analysis of product **3f**, we could see that C–H activation take place when the *tert*-butyl group was above the tethered ferrocene plane, which process determined the diastereoselectivity of this reaction. Compared with phenyl, isopropyl, and methyl, *tert*-butyl group is bulkier and the conformational ratio of **1e** :**1e'** (**b, Scheme 2**) is much higher than those of others

statistically (X-ray of **1e**), thus rendering its excellent diastereoselectivity. Once **3a** was formed, directing group was pushed to the other side and *tert*-butyl group was below the tethered Cp ring due to steric repulsion with the installed aryl thioether group. This conformation is unfavorable for further C–H activation at the other side of ferrocene, thus suppressing the formation of di-thiolated product.

Scheme 2. Mechanism Discussion



In summary, we have developed the first copper-mediated diastereoselective C–H thiolation of ferrocenes with a chiral oxazoline directing group. The reaction proceeds with high diastereoselectivity and mono-thiolation selectivity. This new method provides an alternative to the synthesis of chiral planar ligands for asymmetric transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge *via* the Internet at http://pubs.acs.org.

Experimental procedures and spectral data for all new compounds, and details of X-ray crystallographic analysis for **1e** and **3f** (PDF).

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Notes

The authors declare no competing financial interest.

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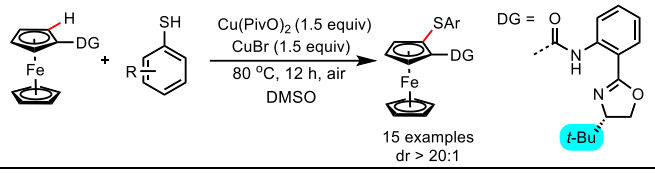
H
DG
Fe
SH
R
Cu(PivO)2 (1.5 equiv)
CuBr (1.5 equiv)
80 °C, 12 h, air
DMSO
SAr
DG
Fe
15 examples
dr > 20:1
DG =
O
N
H
N
O
t-Bu