

Communication

Iron Catalyzed Asymmetric Oxyamination of Olefins

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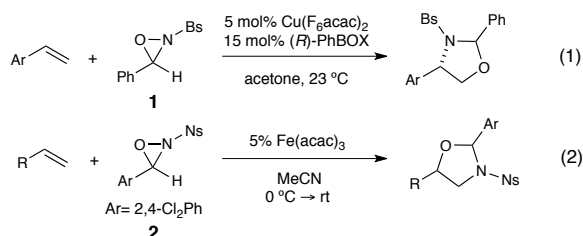
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Supporting Information Placeholder

ABSTRACT: The regioselective and enantioselective oxyamination of alkenes with *N*-sulfonyl oxaziridines is catalyzed by a novel iron(II) bis(oxazoline) complex. This process affords oxazolidine products that can be easily manipulated to yield highly enantioenriched free amino alcohols. The regioselectivity of this process is complementary to that obtained from the analogous copper(II)-catalyzed reaction. Thus, both regioisomers of enantioenriched 1,2-aminoalcohols can be obtained using oxaziridine-mediated oxyamination reactions, and the overall sense of regiochemistry can be controlled using the appropriate choice of inexpensive first-row transition metal catalyst.

The Sharpless asymmetric aminohydroxylation reaction is a powerful method for the stereocontrolled construction of 1,2-aminoalcohols.^{1,2} Nevertheless, the poor regioselectivity of this reaction³ and the requirement for a toxic and precious osmium catalyst has inspired significant efforts over the last decade to design alternative oxyamination processes based on palladium,⁴ platinum,⁵ rhodium,⁶ gold,⁷ copper,⁸ hypervalent iodine,⁹ and radical reactions.¹⁰ Several enantioselective osmium-free oxyaminations have been reported in an intramolecular context.^{8b,11} However, with the exception of a recent report from our laboratory,¹² no enantioselective *intermolecular* oxyaminations have been reported to date. In this communication, we describe the oxaziridine-mediated enantioselective oxyamination of alkenes catalyzed by a novel iron(II) bis(oxazoline) complex. This reaction is highly regioselective and enantioselective for a range of alkenes, and it is a rare example of a highly enantioselective oxidative transformation catalyzed by iron.



For the past several years, our group has been investigating reactions between *N*-sulfonyl oxaziridines¹³ and alkenes in the presence of various transition metal catalysts.¹⁴ Recently, we reported that a copper(II) bis(oxazoline) complex catalyzes the oxaziridine-mediated oxyamination of alkenes with excellent regioselectivity

and good enantioselectivity (eq 1).¹² In a separate study, we also discovered that the opposite regioisomer is accessible using iron salts (eq 2).¹⁵ Recognizing that the ability to control both the stereochemistry and the regiochemistry of intermolecular oxyamination processes with chiral first-row transition metal catalysts would provide an attractive alternative to state-of-the-art osmium-catalyzed aminohydroxylation methods, we initiated a study focused on the development of an enantioselective iron-catalyzed oxyamination.

Table 1. Optimization studies for olefin oxyamination.

entry ^a	Fe(X) ₂ (mol%)	Ligand (mol%)	Yield ^b	ee ^c
1	FeCl ₂ (5)	5a (10)	46%	91%
2	Fe(OTf) ₂ (5)	5a (10)	62%	43%
3	Fe(NTf ₂) ₂ (5)	5a (10)	61%	13%
4	Fe(NTf ₂) ₂ (5)	5b (10)	31%	5%
5	Fe(NTf ₂) ₂ (5)	5c (10)	80%	55%
6	Fe(NTf ₂) ₂ (5)	5d (10)	38%	55%
7	Fe(NTf ₂) ₂ (5)	5e (10)	65%	72%
8	Fe(NTf ₂) ₂ (10)	5e (20)	85%	76%
9	Fe(NTf ₂) ₂ (10)	5f (20)	53%	85%
10 ^d	Fe(NTf ₂) ₂ (10)	5f (20)	76% ^f	92%
11 ^{d,e}	Fe(NTf ₂) ₂ (10)	5f (20)	76% ^f	95%

^a Unless otherwise noted, reactions were performed using 0.2 mmol olefin and 2.5 equiv of oxaziridine in benzene (0.1 M) at 23 °C. ^b Determined by ¹H NMR using TMS₂Ph as an internal standard unless noted. ^c Enantiomeric excess determined by SFC analysis. ^d Performed at 0.05 M with 400 wt% MgO added as drying agent. ^e Reaction started at 0 °C and allowed to warm to room temperature. ^f Isolated yield.

Despite significant interest in the discovery of new catalytic reactions based on iron catalysts,¹⁶ relatively few enantioselective iron-catalyzed processes have been reported to date.¹⁷ In particular, the development of highly enantioselective oxidative transformations catalyzed by iron

has been challenging due to the limited number of effective ligand frameworks that possess good oxidative stability and also provide superior levels of stereocontrol for iron-catalyzed reactions.¹⁸ Based upon Corey's report of asymmetric Diels–Alder reactions catalyzed by an iron bis(oxazoline) complex,¹⁹ and given the success of this ligand class in a variety of oxidative reactions,^{8b,20} we began our own investigations by screening combinations of iron salts and known bis(oxazoline) ligands for their ability to catalyze the reaction between 4-methylstyrene and oxaziridine **2** (Table 1). We quickly found that oxazolidine **3** could be synthesized with excellent enantioselectivity using FeCl₂ and ligand **5a** (entry 1). This system, however, suffered from limited substrate scope and generally poor yields. Upon closer analysis of the reaction byproducts, we found that rapid decomposition of **2** to sulfonylamide **4** occurred at a rate competitive with the desired transformation.²¹

The undesired amide **4** presumably arises from the one-electron reduction and rearrangement of **2**; indeed, the iron(II)-catalyzed radical rearrangement of oxaziridines to amides by this mechanism was described by Emmons in 1957.²² Hypothesizing that a less reducing iron catalyst would retard the formation of this by-product, we elected to investigate catalysts bearing less-coordinating counterions. We were pleased to find that the triflate and triflimide²³ complexes provided higher yields (entries 2 and 3) and that unreacted oxaziridine was still present after the completion of the reaction. Reinvestigation of common bis(oxazoline) ligands showed that the combination of Fe(NTf₂)₂ and 4,5-diphenyl-substituted bis(oxazoline) **5c** provided good yields and reasonable asymmetric induction (entries 3–7). Increasing the loading of the catalyst (entry 8) and using the bulkier naphthalene-substituted ligand **5f** resulted in synthetically useful enantioselectivities (entry 9). Addition of a drying agent and lowering the concentration increased the selectivity and reproducibility of this process (entry 10). Finally, noticing that the reaction warms slightly at the beginning of the reaction, we began the reaction at 0 °C and allowed the reaction to warm slowly to ambient temperature over the course of the reaction (entry 11), which provided optimal levels of stereoinduction.

Table 2 summarizes experiments probing the scope of this oxyamination process. As in our copper chemistry and racemic iron system, styrenes proved to be excellent substrates. Substitution at all positions of the aryl ring is well tolerated (entries 2–4). Styrenes bearing substituents at the α -position of the olefin also provided high enantioselectivities (entry 9), although β -substituted styrenes gave no oxyamination product (entry 10). The reaction is tolerant of electronic perturbation; styrenes bearing electron-withdrawing (entries 5 and 6) and electron-donating substituents (entry 7) react with good yield and high enantioselectivity. Fused polycyclic aromatics (entry 8) are also good substrates for this reaction. The functional group compatibility of the process is good; halides, esters, and protected oxygen and nitrogen moieties were easily tolerated without modification of the reaction conditions (entries 5, 6, 11, and 12). 1,3-Dienes also undergo efficient oxyamination, and we observed exclusive chemoselectivity for the terminal olefin (entries 13 and 14). Notably, the enantioselectivities remained high for these substrates

despite the reduced steric demand of an alkene compared to an arene ring. Aliphatic olefins, however, failed to react under these conditions (entry 15) and are a current limitation of the method.

Table 2. Scope of iron catalyzed aminohydroxylation.

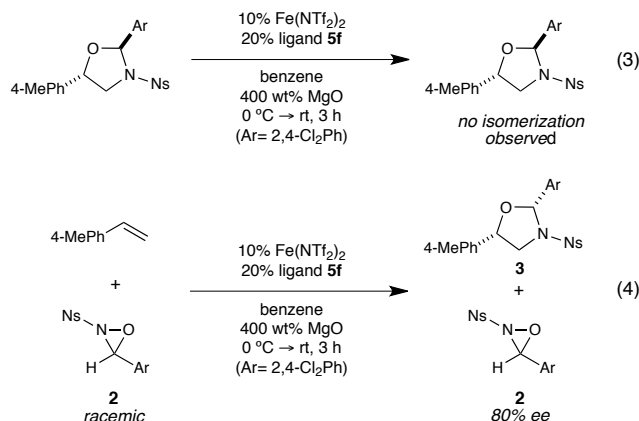
Ar = 2,4-Cl₂Ph
2

entry ^a	olefin	product	time	yield ^{b,c}	ee ^{b,d}
1	R = Ph		3 h	75%	92%
2	R = 4-MePh		3 h	76%	95%
3	R = 3-MePh		4 h	68%	91%
4	R = 2-MePh		5 h	62%	93%
5	R = 4-ClPh		48 h	64%	90%
6	R = 4-BrPh		48 h	63%	85%
7	R = 4-AcOPh		3 h	81%	95%
8	R = 2-Naphth		5 h	71%	91%
9			6 h	52%	88%
10			48 h	--	--
11			8 h	78%	92%
12			10 h	62%	91%
13			3 h	82%	91%
14			4 h	51%	94%
15			48 h	--	--

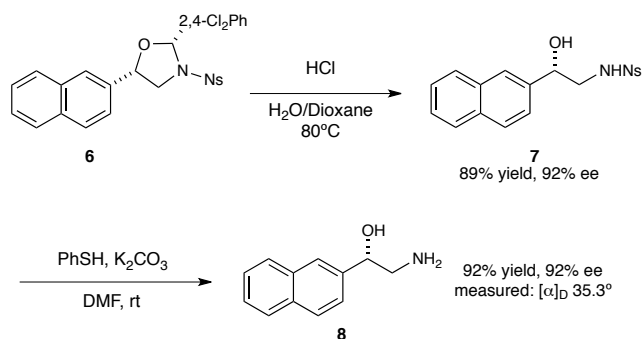
^a Reactions were performed using 0.3 mmol olefin and 2.5 equiv of oxaziridine. ^b Data represent the averaged results of two reproducible experiments. ^c Isolated yield. ^d Enantiomeric excess determined by chiral SFC analysis.

We were intrigued to observe that the oxyamination products in all cases were formed with excellent *cis* diastereoselectivity. In our previously reported copper-catalyzed method for preparation of the regioisomeric amins, we had found that the oxyamination products were isolated as mixtures of amina diastereomers, and that the two diastereomers were generally formed with different ee's. To test whether the high diastereoselectivity of this iron-catalyzed process arises from Lewis acid-catalyzed stereomutation of the amina group, we prepared the *trans* isomer of **3**²⁴ and subjected it to the iron triflimide catalyst (eq 3). After 3 h, no formation of the *cis*

diastereomer was observed. We speculate, therefore, that the high diastereoselectivity observed in this reaction is a consequence of selective reaction of one of the enantiomers of the racemic oxaziridine **2** in a kinetic resolution process. Consistent with this hypothesis, after completion of the oxyamination reaction, we find that the remaining unreacted oxaziridine can be re-isolated with significant optical enrichment (80% ee, eq. 4).²⁵



Finally, we examined the stereochemical integrity of the oxyamination product upon deprotection to reveal the corresponding free amino alcohol (Scheme 1). Subjecting 2-vinylnaphthalene-derived aminal **6** to standard acid-catalyzed hydrolysis conditions cleanly removed the aminal to give the *N*-nosyl protected amino alcohol **7** in 89% yield. Thiol-mediated removal of the nosyl group yielded the free amino alcohol **8** in high yield. Importantly, no erosion of ee was observed in either step. In addition, we were able to confirm the absolute stereochemistry of **8** by comparison of its optical rotation to known values,²⁶ verifying the selectivity of the oxyamination process.



Scheme 1. Deprotection of the amino alcohol.

In conclusion, we have developed a highly enantioselective and regioselective asymmetric oxyamination reaction catalyzed by an iron(II) bis(oxazoline) complex. When used in conjunction with our previously reported copper chemistry, this method allows regio- and stereochemical control in the generation of a variety of 1,2-amino alcohols. Current efforts in our lab are underway to better understand the mechanistic intricacies of this process so that we may improve its scope, reduce the catalyst loading, and apply this reaction towards the synthesis of complex targets.

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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²⁴ The racemic *trans* oxazolidine was isolated from an unselective oxyamination reaction catalyzed by Fe(acac)₃. See ref 15a.

²⁵ At the suggestion of a reviewer, we also examined the stereospecificity of the oxyamination with respect to the olefin by subjecting (*Z*)-β-deuterostyrene to the optimized reaction conditions. The oxazolidine product was obtained as a 1:1.5 ratio of deuterated diastereomers, consistent with a step-wise oxyamination process.

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