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Iron(II)-Catalyzed Intramolecular Aminohydroxylation of Olefins with Functionalized Hydroxylamines

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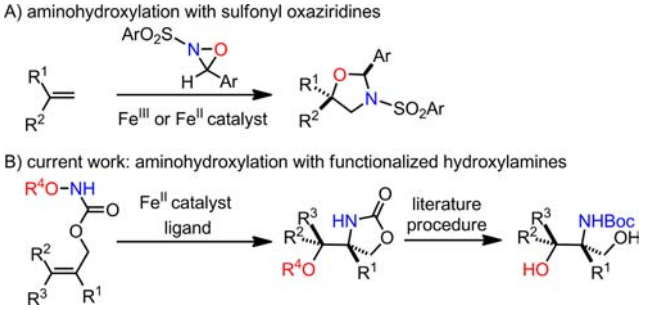
Supporting Information

ABSTRACT: A diastereoselective aminohydroxylation of olefins with a functionalized hydroxylamine is catalyzed by new iron(II) complexes. This efficient intramolecular process readily affords synthetically useful amino alcohols with excellent selectivity (*dr* up to > 20:1). Asymmetric catalysis with chiral iron(II) complexes and preliminary mechanistic studies reveal an iron nitrenoid is a possible intermediate that can undergo either aminohydroxylation or aziridination, and the selectivity can be controlled by careful selection of counteranion/ligand combinations.

Numerous biologically active alkaloids and pharmaceuticals contain chiral amino alcohols, and therefore direct aminohydroxylation of olefins is among the most utilized methods to introduce stereogenic nitrogen atoms in organic synthesis. The pioneering Sharpless asymmetric aminohydroxylation (AA)[1] remains a powerful method for the synthesis of enantioenriched *syn*-vicinal amino alcohols. This reaction has also inspired extensive efforts to discover alternative approaches to address its inherent limitations. Those discoveries include aminohydroxylations mediated by copper,[2] palladium,[3] platinum,[4] rhodium,[5] gold,[6] hypervalent iodine,[7] *N*-phenyl hydroxamic acids,[8] and through electrochemistry.[9] Among those discoveries, Yoon[2b−g] reported that copper is able to catalyze aminohydroxylation of an olefin with a sulfonyl oxaziridine; Chemler[2h−k] discovered copper can catalyze intramolecular olefin aminohydroxylation in the presence of TEMPO; Göttlich[2a] disclosed copper can cocatalyze intramolecular olefin aminohydroxylation with a stoichiometric amount of $BF_3{\cdot}Et_2O$; and Donohoe[10] developed an Os-based tethered strategy to solve the regioselectivity problem in racemic olefin aminohydroxylation.

Despite these important achievements, the direct conversion of a *trans*-olefin to an 1,2 *anti*-amino alcohol remains as an unsolved synthetic problem. In addition, the iron-catalyzed aminohydroxylation is a less-explored process.[11] Recently, Yoon discovered an iron-catalyzed olefin aminohydroxylation with sulfonyl oxaziridines[12a] and a highly enantioselective oxaziridine-based aminohydroxylation of terminal olefins was disclosed by the same author.[12b] We are interested in discovering new iron-catalyzed olefin amination methods that are unique in synthetic utility. Herein, we describe an iron(II)-catalyzed diastereoselective aminohydroxylation of an olefin to afford a 1,2 *anti*-amino alcohol with a functionalized hydroxylamine, possibly via an iron nitrenoid[13] intermediate. The catalysts are able to transfer both the *N* and *O* groups of the hydroxylamine intramolecularly to a variety of olefins, affording amino alcohols with a stereochemical array that is difficult to access with other known methods[10] (Scheme 1). We envision this discovery offers an appealing alternative for existing aminohydroxylation methods.

Scheme 1. Iron Catalyzed Aminohydroxylation



We initiated the catalyst discovery with a cinnamyl alcohol-derived substrate **1** that incorporates both a *trans*-disubstituted olefin and a functionalized hydroxylamine. Preliminary inspection revealed that Fe^{II} salts alone are unable to catalyze the reaction at room temperature; however, the reaction is greatly accelerated by a variety of nitrogen-based bidentate and tridentate ligands (Table 1): ligands **3** and **4** (with π-acceptor character) facilitate more efficient reactions than TMEDA and sparteine (entries 1−4). While Fe^{II}/**3** complexes are able to catalyze the aminohydroxylation, Fe^{III}/**3** complexes are inactive (entry 5). In addition, we observed a significant counterion effect: cyanide (entries 9 and 10) with strong π-acceptor character proves to be superior to bromide (entries 3 and 4), triflate (entry 6), carboxylate (entry 7), and triflimide (entry 8). Re-examination of Fe^{II} cyanide/ligand combinations revealed that $K_4Fe(CN)_6$/**3** can catalyze a highly diastereoselective aminohydroxylation,[14] delivering an *anti*-amino alcohol with a stereochemistry complementary to the one obtained through Os-based methods. We discovered that acyl hydroxyl carbamates prove uniquely effective for the desired reaction: both alkyl and sulfonyl hydroxyl carbamates are not viable substrates.[15]

To explore the scope and limitation of this reaction, we have applied the method to a variety of olefins (Table 2). *trans*-Disubstituted styrenyl olefins are excellent substrates (*dr* > 20:1) (entries 1−4). Unlike Os-based methods that are not

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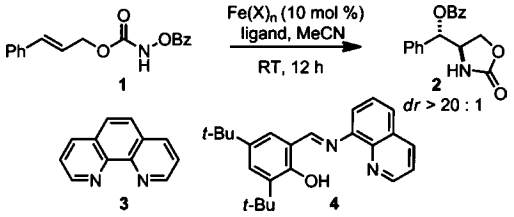
Table 1. Catalyst Discovery for the Aminohydroxylation



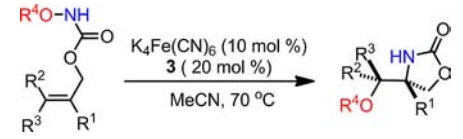
entry[a]	$Fe(X)_n$	ligand (mol %)	conversion[b]	yield[c]
1	$FeBr_2$	none	<10%	<5%
2	$FeBr_2$	sparteine/TMEDA	<40%	<5%
3	$FeBr_2$	**3** (20)	100%	8%
4[d]	$FeBr_2$	**4** (10)	100%	56%
5[e]	$FeBr_3$	**3** (20)	<10%	NA
6	$Fe(OTf)_2$	**3** (20)	50%	5%
7[f]	$Fe(OAc)_2$	**3** (20)	76%	50%
8	$Fe(NTf_2)_2$	**3** (20)	90%	57%
9[d,g,h]	$K_4Fe(CN)_6$	**4** (10)	100%	78%
10[g,h]	$K_4Fe(CN)_6$	**3** (20)	100%	89%

[a]Reactions were carried out under argon at 23 °C, unless stated otherwise. [b]Conversions were determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]Catalyst was prepared in situ by stirring $FeBr_2$ or $K_4Fe(CN)_6$ with freshly prepared potassium salt of the ligand **4**. [e]The reaction was performed at 45 °C. [f]An aziridine was isolated. [g]The reaction was performed at 70 °C for 4 h. [h]Conversion was less than 5% without ligands. TMEDA = tetramethylethylenediamine, OTf = trifluoromethanesulfonate, NTf_2 = trifluoromethanesulfonimide.

tolerant to basic-nitrogen functional groups,[16] the olefin containing a pyridine ring is a viable substrate (entry 4). A *para*-methyl-styrenyl substrate suffers from a total loss of *dr* (entry 5); however, electronic tuning on the benzoyl group increased the *dr* to 3.1:1 (entry 6).[17] *trans*-Disubstituted olefins with 1-naphthyl, alkyl, and alkynyl substituents can participate in the reaction with acceptable yields but diminished diastereoselectivity (entries 7–9, *dr* varies from 2.5:1 to 5:1). We note that the *cis*-disubstituted olefins also afford *anti*-amino alcohols in this reaction (entries 10–11). The stereochemical convergence (entries 1 and 10) and a related crossover experiment[18] suggest the stepwise nature of the amino-hydroxylation. In addition, trisubstituted olefins (entries 12–13) are suitable substrates (*dr* varies from 2.2:1 to > 20:1). Disubstituted terminal olefins are decent substrates (entry 14), while monosubstituted olefins (entry 15) suffer from lower yields.[19] We also discovered a cyclohexanol-derived substrate (entry 16) readily participates in the reaction to afford an *anti*-hydroxyl oxazolidinone that was difficult to access with Os-based strategies.[10f] Further investigation reveals that nonallylic alcohol based substrates, including an olefin containing hydroxamate, can also undergo smooth reactions (entry 17).

Since the asymmetric synthesis of hydroxyl oxazolidinones by catalytic aminohydroxylation has not been reported, we explored the asymmetric induction with Fe^{II}–chiral bisoxazoline (BOX)[20] complexes (Scheme 2A). Extensive optimization[21] revealed that $Fe(NTf_2)_2$[20e]–chiral BOX ligand **10** is effective for enantioinduction. It converts both **9a** and **9b** to *syn*-hydroxyl oxazolidinone **11** with the same *ee* and *dr* (82% *ee*, *dr* > 20:1).[22] A more synthetically useful amino alcohol triad **13** was subsequently obtained without stereochemistry erosion with a known method.[23] To our surprise, the diastereoselectivity observed here is different from the one in the

Table 2. Substrate Scope of Iron Catalyzed Aminohydroxylation



entry	olefin	product	T (h)	yield[a]	dr[b]
1	R^3 = Ph, R^4 = Bz		4	89%	> 20 : 1
2	R^3 = 4-CO_2MePh, R^4 = Bz		10	75%	> 20 : 1
3	R^3 = 3-ClPh, R^4 = Bz		8	74%	> 20 : 1
4	R^3 = 3-Py, R^4 = Bz		12	80%	> 20 : 1
5	R^3 = 4-MePh, R^4 = Bz		4	85%	1 : 1
6	R^3 = 4-MePh, R^4 = 4-CN-benzoyl		4	81%	3.1 : 1
7	R^3 = 1-Naphth, R^4 = Bz		5	81%	5 : 1
8	R^3 = Ph-C≡C, R^4 = Bz		4	92%	5 : 1
9	R^3 = Me, R^4 = Bz		4	85%	2.5 : 1
10	R^2 = Ph		4	75%	>20 : 1
11	R^2 = Ph-C≡C		4	90%	5 : 1
12			12	81%	> 20 : 1
13			12	71%	2.2: 1
14		R^4 = *p*-CO_2Me-benzoyl	12	72%	NA
15[c]			12	40%	>20 : 1
16			7	75%	>20 : 1
17		R^4 = *p*-CO_2Me-benzoyl	12	76%	NA

[a]Combined isolated yield. [b]Determined by ^{1}H NMR. [c]Phenyl vinyl ketone was also isolated as a side product.

$K_4Fe(CN)_6$-catalyzed reaction (Table 2). We also observed that the $Fe(OAc)_2$–chiral BOX ligand **10** complex catalyzes a convergent aminohydroxylation of both **9a** and **9b**, affording **11** with diminished selectivities (71% *ee*, *dr* = 5:1). In addition to **11**, a chiral aziridine **12** (65% *ee*, *dr* > 20:1) was obtained from

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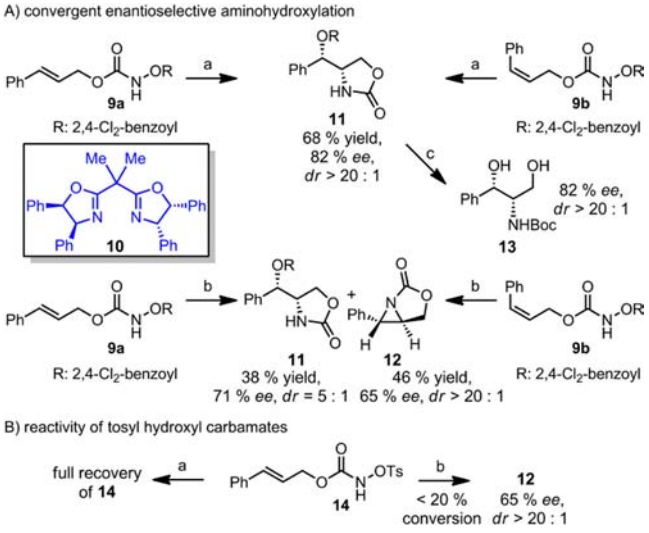
Scheme 2. Iron Catalyzed Asymmetric Intramolecular Olefin Aminohydroxylation

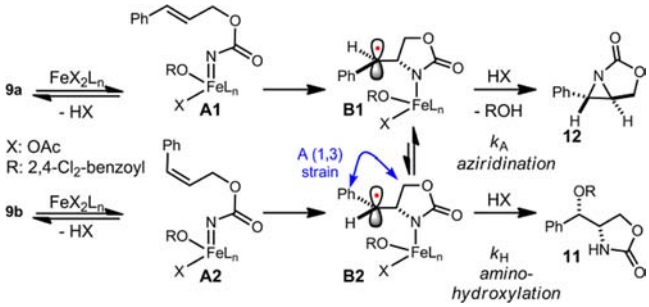


[a]$Fe(NTf_2)_2$ (10 mol %), **10** (20 mol %), MeCN, 0 °C, 8 h. [b]$Fe(OAc)_2$ (10 mol %), **10** (20 mol %), toluene/MeCN = 4:1, 0 °C, 4 h. [c]Boc_2O, Et_3N, DCM, rt, 3 h, then LiOH, dioxane, rt, 4 h, 75% in two steps. Boc_2O = Di-*tert*-butyl dicarbonate.

both **9a** and **9b**.[21] It is important to note that the sense of enantioinduction for **11** and **12** is the same, and they cannot interconvert under reaction conditions.[24] We were curious about this reactivity divergence and explored a series of ligands, discovering that the counteranion effect over the product distribution is general.[21] In literature, Bolm[13i] demonstrated that $Fe(OTf)_2$–chiral BOX can mediate asymmetric styrene aziridination (up to 40% *ee*). Lebel[13j,k] also reported a copper-catalyzed racemic aziridination from tosyl hydroxyl carbamate **14**. To gain further mechanistic insight, we explored the reactivity of **14** under the optimized conditions (Scheme 2B): $Fe(NTf_2)_2$ is unable to catalyze the cyclization of **14**; $Fe(OAc)_2$ can mediate the aziridination of **14**, affording **12** (the same *ee* with the one obtained from **9a** and **9b**), albeit in a low conversion. These results indicate that the $Fe(OAc)_2$-catalyzed aziridination of **9a**, **9b**, and **14** likely go through the same intermediate.

The successful asymmetric induction provides further mechanistic insights: (a) Fe^{II}–chiral ligand complexes are involved in both rate- and enantioselectivity-determining steps; (b) olefin aziridination is likely a competing pathway from the same intermediate. Presumably, two distinct types of mechanistic pathways might operate: (a) Kharasch-type atom transfer radical addition[25] or (b) pathways involving iron nitrenoid[26] species. Based on the collected mechanistic evidence, a working hypothesis that best corroborates the $Fe(OAc)_2$-catalzyed enantioselective reaction is shown in Scheme 3. First, the $Fe(OAc)_2$–ligand complex can reductively cleave the N–O σ-bond and possibly convert the isomeric *cis*- and *trans*-styrenyl substrates **9a** and **9b** to iron nitrenoids **A1** and **A2**, respectively. Then, a stepwise cycloamination (from **A1** and **A2**) will presumably occur, affording two carbo-radical species, **B1** and **B2** that are in a fast equilibrium. In principle, the intramolecular aziridination should occur much slower than the ligand (OR) transfer[27] from **B2**, because of the unfavorable A (1,3) interaction encountered in the transition state leading to aziridines. In contrast, aziridination can effectively compete

Scheme 3. Mechanistic Working Hypothesis of $Fe(OAc)_2$ Catalyzed Asymmetric Aminohydroxylation



with the ligand transfer from **B1**, since the A (1,3) interaction is absent in this conformation. Therefore, the aminohydroxylation should occur predominately from intermediate **B2**, leading to an amino alcohol **11**, while the cyclization from intermediate **B1** will mostly lead to a *trans*-aziridine **12**. It is possible that the mechanistic intricacy will vary with different counterion/ligand combinations, which will influence the relative stability of **B1** vs **B2**, as well as the rates of aziridination (k_A) vs amino-hydroxylation (k_H). Since the diastereoselectivity of $K_4Fe(CN)_6$-catalyzed reactions is very different from the ones catalyzed by $Fe(NTf_2)_2$ and $Fe(OAc)_2$, it is less likely this working hypothesis applies for the $K_4Fe(CN)_6$-catalyzed racemic reactions.

In conclusion, we have discovered a new Fe^{II}-catalyzed intramolecular olefin aminohydroxylation with functionalized hydroxylamines, where both the *N* and *O* functional groups are efficiently transferred for olefin aminohydroxylation. Preliminary mechanistic studies revealed that an iron nitrenoid is possibly an intermediate that can undergo either olefin aziridination or aminohydroxylation. This discovery opens up the possibility of developing a unique and general approach for stereoselective olefin amination. Our current effort focuses on better understanding the mechanistic details of this process and its application in complex-molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data for all new compounds, selected NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) We combined equal moles of two structurally similar substrates and subjected them to a $K_4Fe(CN)_6$-catalyzed reaction. Both HPLC and NMR analysis revealed the presence of two crossover products along with two intramolecular cyclization products. See Supporting Information for details.

(19) Phenyl vinyl ketone was isolated as a side product.

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(21) See Supporting Information for detailed catalyst, ligand, temperature, solvent, and concentration optimization, as well as counterion effect and ligand effect on *dr* and chemoselectivity.

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