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Iron(II)-Catalyzed Asymmetric Intramolecular Aminohydroxylation of Indoles

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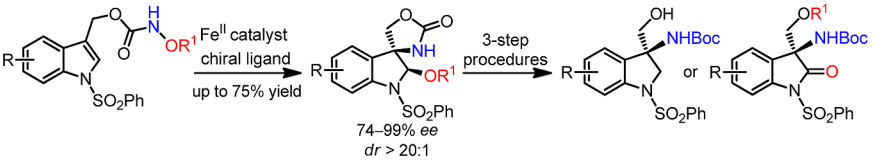
ABSTRACT



An enantioselective intramolecular indole aminohydroxylation reaction is catalyzed by iron(II)−chiral bisoxazoline (BOX) complexes (ee up to 99%, dr > 20:1). This discovery enables expedient asymmetric synthesis of a series of biologically active 3-amino oxindoles and 3-amino indolanes.

Both amino oxindoles and amino indolanes are structural motifs present in numerous medicinal agents and biologically active natural products, such as AG-041R, a gastrin/CCK-B receptor agonist, SSR-149415, a medicine for the treatment of anxiety and depression,[1] and natural products psychotrimine, kapakahines, and chaetomin.[2] Therefore, extensive research effort has been devoted to development of methods for enantioselective synthesis of amino oxindoles and amino indolanes. Chiral substrate-controlled indole−aniline coupling and stereospecific functional group manipulation are among the strategies that have been applied to the asymmetric synthesis of 3-amino indolanes;[2c,d] however, strategies based on asymmetric catalysis still remain highly desirable. There recently has been exciting progress in catalytic asymmetric synthesis of 3-amino oxindoles including (a) organic molecules and Lewis acid-catalyzed addition of oxindoles to azodicarboxylates;[3]

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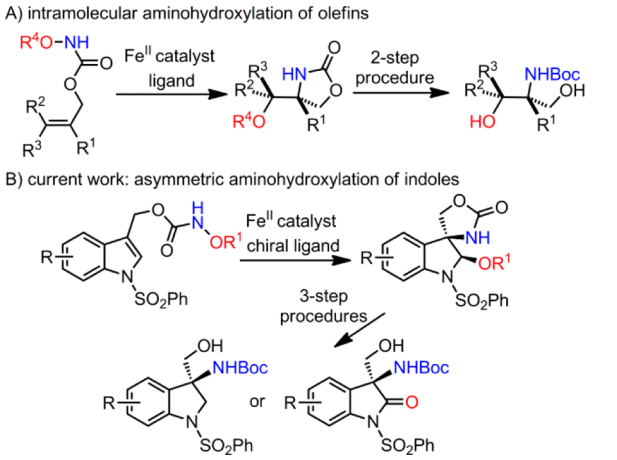
(b) intramolecular α-arylation of amides;[4] and (c) organic molecule-catalyzed addition to isatin-derived ketoimines.[5] Despite these key discoveries, a method that can provide both amino oxindoles and amino indolanes with synthetically useful ee through catalytic asymmetric indole aminohydroxylation has yet to be discovered.

Inspired by the pioneering Sharpless asymmetric aminohydroxylation,[6] there has been significant progress in the development of methods for selective olefin aminohydroxylation.[7] Nonetheless, direct aminohydroxylation of indoles has largely remained unexplored, with a few exceptions: Padwa, Che, Du Bois, and Iwabuchi independently reported rhodium-catalyzed intramolecular aminohydroxylation of indoles or pyrroles;[8] Yoon discovered a copper-catalyzed intermolecular indole aminohydroxylation with oxaziridines;[9] and Dauban disclosed a rhodium-catalyzed intermolecular indole aminohydroxylation.[10] Despite these important achievements, the catalytic asymmetric aminohydroxylation of indoles with synthetically useful ee has remained a challenge.[11] Likewise, iron-catalyzed olefin aminohydroxylation is also a less-explored process;[12] however, Yoon recently discovered an iron-catalyzed olefin aminohydroxylation with sulfonyl oxaziridines.[13] We have recently reported an iron-catalyzed intramolecular olefin aminohydroxylation and the mechanistic studies revealed that an iron-nitrenoid is a possible intermediate in the selective atom transfer reaction (Scheme 1A).[14] Herein, we describe our latest discovery: an iron(II)-catalyzed asymmetric intramolecular aminohydroxylation of indoles. In this reaction, the iron catalyst diastereo- and enantioselectively transfers the *N* and *O* groups of the hydroxylamine to a variety of indoles (dr > 20:1, ee up to 99%). Simple product derivatization provides both amino oxindoles and amino indolanes in their enantioenriched forms (Scheme 1B).

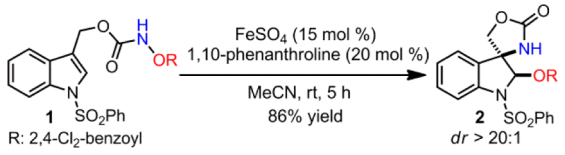
We initiated the catalyst discovery with a model substrate **1** and extensive optimization revealed that the

Scheme 1. Iron(II)-Catalyzed Intramolecular Aminohydroxylation of Olefins and Indoles



$FeSO_4$−1,10-phenanthroline complex catalyzes an efficient racemic indole aminohydroxylation reaction affording product **2** as a single diastereomer (Scheme 2).[15]

Scheme 2. Iron(II)-Catalyzed Racemic Intramolecular Indole Aminohydroxylation



With the optimized racemic reaction in hand, we set out to search for chiral ligands that effectively promote enantioselective indole aminohydroxylation with iron(II) complexes (Table 1). Since $FeSO_4$ is poorly soluble in nonpolar solvents such as toluene, we selected $Fe(OTf)_2$ as the iron salt for chiral ligand discovery. Extensive experimentation revealed that a toluene−MeCN (50:1) mixture is crucial for high enantioselectivity.[16] Under these conditions, we systematically inspected a series of chiral bisoxazoline (BOX and PyBOX) and pyridine−oxazoline hybrid ligands.[17]

We observed that the $Fe(OTf)_2$−^{i}PrBOX **L1** complex fails to induce any enantioselectivity (entry 1); however, the

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(16) This is the optimized result from the screening. A decreased ee was observed in toluene. See the Supporting Information for temperature, solvent, and concentration optimization in details.

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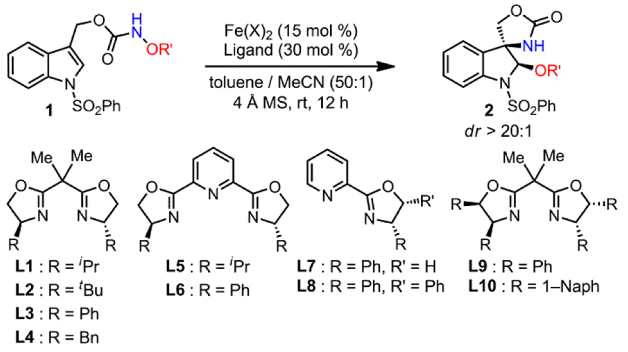
Table 1. Catalyst Discovery for Iron(II)-Catalyzed Asymmetric Indole Aminohydroxylation



entry[a]	$Fe(X)_2$	ligand	R′	yield[b] (%)	ee[c] (%)
1	$Fe(OTf)_2$	**L1**	2,4-Cl_2-benzoyl	22	0
2	$Fe(OTf)_2$	**L2**	2,4-Cl_2-benzoyl	25	31
3	$Fe(OTf)_2$	**L3**	2,4-Cl_2-benzoyl	58	77
4[d]	$Fe(OTf)_2$	**L4**	2,4-Cl_2-benzoyl	48	−86
5	$Fe(OTf)_2$	**L5**	2,4-Cl_2-benzoyl	15	32
6	$Fe(OTf)_2$	**L6**	2,4-Cl_2-benzoyl	33	22
7	$Fe(OTf)_2$	**L7**	2,4-Cl_2-benzoyl	21	37
8	$Fe(OTf)_2$	**L8**	2,4-Cl_2-benzoyl	25	61
9	$Fe(OTf)_2$	**L9**	2,4-Cl_2-benzoyl	65	87
10	$Fe(OTf)_2$	**L10**	2,4-Cl_2-benzoyl	50	81
11	$Fe(OTf)_2$	**L9**	4-CO_2-Me-benzoyl	62	87
12	$Fe(OTf)_2$	**L9**	4-CF_3-benzoyl	65	77
13	$Fe(OTf)_2$	**L9**	4-Cl-benzoyl	58	78
14	$Fe(OTf)_2$	**L9**	3,5-$(CF_3)_2$-benzoyl	75	75
15	$Fe(NTf_2)_2$	**L9**	2,4-Cl_2-benzoyl	67	79
16	$FeCl_2$	**L9**	2,4-Cl_2-benzoyl	63	86
17	$FeBr_2$	**L9**	2,4-Cl_2-benzoyl	52	75
18	$Fe(OAc)_2$	**L9**	2,4-Cl_2-benzoyl	67	90

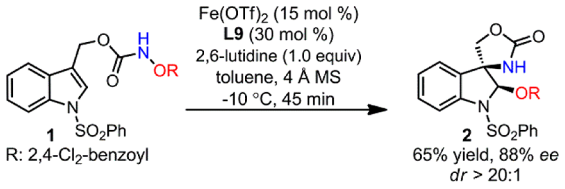
[a] Reactions were carried out under argon in 0.025 M toluene/MeCN (50:1) mixture; catalyst complexes were formed by premixing $Fe(X)_2$ and ligands for 40 min. [b] Isolated yield. [c] ee was measured by HPLC analysis with chiral stationary phase. [d] The sense of enantioinduction in entry 4 is the opposite to that of other entries.

$Fe(OTf)_2$–^{t}BuBOX **L2** complex is capable of asymmetric induction (entry 2, 31% ee). The change from **L2** to PhBOX **L3** correlates with both enhanced reactivity and enantioselectivity (entry 3, 58% yield, 77% ee).[18] Surprisingly, a relatively minor modification to the ligand's structure (from PhBOX **L3** to BnBOX **L4**) leads to asymmetric induction in the opposite sense (entry 4, 48% yield, −86% ee). We therefore tested PyBOX and pyridine-oxazoline hybrid ligands **L5**–**L8** and determined that they are inferior to **L3** and **L4** (entries 5–8, ee up to 61%). Further screening of tetrasubstituted chiral BOX ligands (**L9**–**L10**) revealed that the $Fe(OTf)_2$–**L9** complex catalyzes the indole aminohydroxylation with further enhanced ee (entry 9, 65% yield, 87% ee).

Knowing that aromatic interactions may be important for asymmetric induction,[19] we carried out electronic tuning experiments on the benzoyl protecting group. We discovered that the 4-Cl, 4-CF_3, and 3,5-$(CF_3)_2$ substituents result in decreased ee while the 4-CO_2Me group maintains the similar ee (entries 11–14 compared with entry 9). We also observed that hydrolytically more robust $Fe(NTf_2)_2$[20] promotes the reaction with a slightly increased yield yet decreased ee (entry 15, 67% yield, 79% ee). Concordantly, we discovered that both $FeCl_2$ and $FeBr_2$ promote less selective reactions with **L9** (entries 16–17); however, the $Fe(OAc)_2$–**L9** complex manages to increase the ee to 90% in 12 h (entry 18).

In order to search for a more reactive yet highly selective catalyst, we inspected a variety of additives with bulky *N*-donor ability.[21] Extensive optimization revealed that 2,6-lutidine (1.0 equiv) significantly accelerates the $Fe(OTf_2)$–**L9** catalyzed reaction in toluene with a slight increase in enantioselectivity (Scheme 3, full conversion in 45 min at −10 °C, 65% yield, 88% ee). This discovery offers us an opportunity to expand substrate scope and include substrates that have low reactivity in $Fe(OAc)_2$-catalyzed reactions.

Scheme 3. Iron(II)-Catalyzed Indole Aminohydroxylation Accelerated by 2,6-Lutidine



To explore the scope and limitation of the aforementioned method, we applied the optimized reaction conditions to a variety of substituted indoles (Table 2). We observed that 5-methylindole is an excellent substrate for $Fe(OAc)_2$-catalyzed asymmetric aminohydroxylation (AA) (entry 2, 94% ee). Likewise, the $Fe(OTf)_2$–**L9**–lutidine complex enantioselectively converts a 5-methoxy indole to its corresponding hydroxyl oxazolidinone (entry 3, 93% ee). We also discovered that 6-methyl-, bromo-, and chloro-substituents are all well-tolerated in the $Fe(OAc)_2$-catalyzed indole AA, which thereby offers versatile handles for further transformation (entries 4–6, 91–99% ee). Further exploration revealed that 6-phenyl indole is an excellent substrate for $Fe(OTf)_2$-catalyzed AA (entry 7, 91% ee) and that 7-methyl indole participates in the $Fe(OAc)_2$-catalyzed AA with acceptable ee (entry 8, 88% ee). However, we observed that the ee for aminohydroxylation of 4-bromo indole is significantly lower than other substrates (entry 9, 74% ee), which suggests that 4-H may be important for asymmetric induction.

The enantio-enriched hydroxyl oxazolidinone **2** can be readily converted to either amino indolane **3** or amino

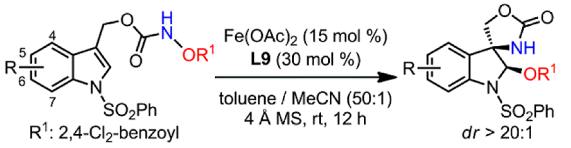
(18) The absolute stereochemistry of the product was determined by X-ray crystallographic analysis; see the Supporting Information for details.

(19) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678.

(20) $Fe(NTf_2)_2$ was prepared in aqueous solvent. For its preparation, see: Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2879.

(21) For the effect of additives with bulky *N*-donor ability in iron-catalyzed oxidation reactions, see: (a) Lee, D.; Lippard, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12153. (b) Hagadorn, J. R.; Que, L.; Tolman, W. B. *J. Am. Chem. Soc.* **1998**, *120*, 13531.

Table 2. Substrate Scope for the Iron(II)-Catalyzed Asymmetric Intramolecular Aminohydroxylation of Indoles



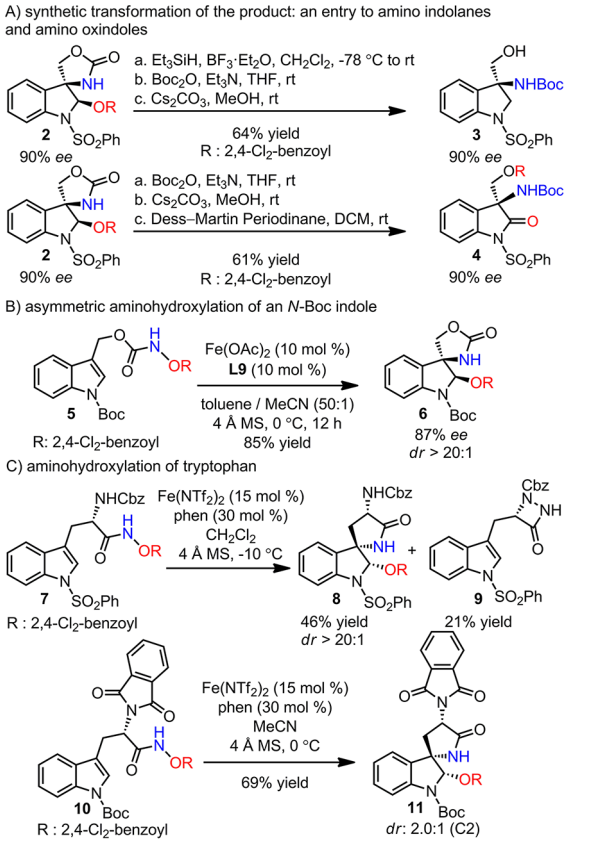
entry[a]	R	yield[b] (%)	ee[c] (%)
1	H	67	90
2[d]	5-Me	72	94
3[d,e]	5-OMe	75	93
4	6-Me	65	95
5	6-Br	64	91
6	6-Cl	70	99
7[e]	7-Ph	65	91
8[d]	7-Me	62	85
9	4-Br	67	74

[a] Reactions were carried out under argon in 0.025 M toluene/MeCN (50:1) mixture, unless stated otherwise. [b] Isolated yield, and 3-indole aldehydes were isolated (ca. 15%) as the side product. [c] ee was measured by HPLC analysis with chiral stationary phase. [d] R^1 = 4-CO_2Me-benzoyl. [e] Reactions were carried out under argon at 0.025 M toluene at −10 °C for 4 h. $Fe(OTf)_2$ (15 mol %) and **L9** (30 mol %) were applied as the catalyst and 2,6-lutidine (1.0 equiv) was used as the additive.

oxindole **4** without erosion of the ee with three-step procedures (Scheme 4A). The *N*-sulfonyl protected amino oxindole motif is of interest in medicinal chemistry because it is present in SSR-149415, a medicine for the treatment of anxiety and depression.[1] In order to develop an easy entry to both unprotected amino indolanes and oxindoles, we explored the aminohydroxylation of an *N*-Boc protected indole **5** (Scheme 4B). We observed that $Fe(OAc)_2$−**L9** complex catalyzes the efficient aminohydroxylation of **5** with an even lower catalyst loading, affording product **6** with excellent yield (10 mol % catalyst, 85% yield, dr > 20:1, 87% ee).[22]

We further observed that the $Fe(NTf_2)_2$−phenanthroline complex catalyzes the aminohydroxylation of a protected tryptophan **7** to afford a single diastereomeric hydroxyl oxazolidinone **8** (full conversion, 46% yield, Scheme 4C); interestingly, the aminohydroxylation occurs from the α face of tryptophan.[23] In addition, we also isolated diazetidinone **9** (25% yield), a side product that is possibly derived

Scheme 4. Synthetic Transformation of the Product and the Iron(II)-Catalyzed Aminohydroxylation of Tryptophan



from an N−H insertion reaction of the putative iron-nitrenoid intermediate.[24] We therefore applied the same catalyst to another fully protected tryptophan **10** and observed the efficient aminohydroxylation to afford **11**.[25]

In conclusion, we have discovered an asymmetric intramolecular indole aminohydroxylation catalyzed by iron(II)−chiral BOX complexes. This enantioselective process enables the facile asymmetric synthesis of biologically relevant 3-amino oxindoles and 3-amino indolanes. Our current research focuses on the application of this method in medicinal agent synthesis and better understanding of the origin for asymmetric induction.

Acknowledgment. This work was supported by Georgia State University and the American Chemical Society Petroleum Research Fund (ACS PRF 51571-DNI1).

Supporting Information Available. Experimental procedure, characterization data for all new compounds, selected NMR spectra, HPLC traces, and X-ray crystallographic analysis data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) The protected hydroxyl oxazolidinone **6** has been converted to the unprotected amino indolane and oxindole follwing the same procedure. See the Supporting Information for details.

(23) The absolute stereochemistry of the product was determined by X-ray crystallographic analysis; see the Supporting Information for details.

(24) When either $Fe(NTf_2)_2$−**L9** or $Fe(NTf_2)_2$−*ent*-**L9** was applied as the catalyst, we only isolated diazetidinone **9** (78−81% yield); see the Supporting Information for details.

(25) $Fe(NTf_2)_2$−**L9** and $Fe(NTf_2)_2$−*ent*-**L9** are less-efficient catalysts to afford **11**: 37−43% yield, 1.0−1.2 dr at the C2 position. The low yield of **11** is due to starting material **10** decomposition. We did not observe significant rate difference with different handed chiral catalysts. See the Supporting Information for details.