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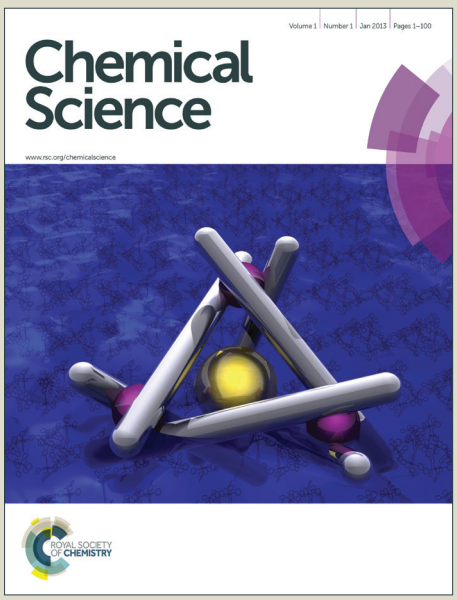

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EDGE ARTICLE

Iron(II)-Catalyzed Asymmetric Intramolecular Olefin Aminochlorination with Chloride Ion

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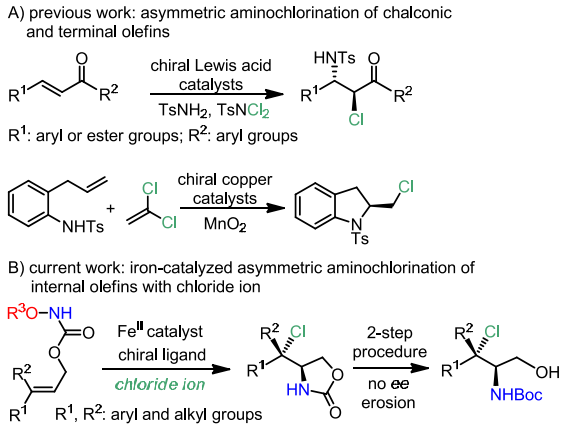
An iron-catalyzed enantioselective and diastereoselective intramolecular olefin aminochlorination reaction is reported (*ee* up to 92%, *dr* up to 15:1). In this reaction, a functionalized hydroxylamine and chloride ion were utilized as the nitrogen and chlorine source. This new method tolerates a range of synthetically valuable internal olefins that are all incompatible with the existing asymmetric olefin aminochlorination methods.

Introduction

Enantioselective olefin halo-functionalization reactions are a range of synthetically valuable yet challenging transformations.[1] Although a variety of excellent asymmetric olefin halo-oxygenation reactions have been discovered,[2] there are much fewer asymmetric olefin aminohalogenation methods available.[3] In particular, there have been just a few reported catalytic asymmetric olefin *aminochlorination* reactions.[4] In one instance, Feng discovered chiral Lewis-acid-catalyzed aminochlorination of chalconic and other α,β-unsaturated olefins.[4a,c] Also, Chemler reported copper-catalyzed aminochlorination of terminal olefins with chlorine radical donors in the presence of MnO_2 (Scheme 1A).[4b] Despite these and other important discoveries, catalytic asymmetric aminochlorination methods for internal, non-chalconic olefins have yet to be developed. These methods would be synthetically valuable because they readily provide vicinal amino chloride, a class of important chiral building blocks. Moreover, asymmetric olefin aminochlorination that proceeds through an iron-nitrenoid intermediate has not been reported.[5]



Scheme 1. Catalytic asymmetric olefin aminochlorination: summary of this work and other existing asymmetric methods

We previously discovered $Fe(BF_4)_2$-based catalysts for both diastereoselective and enantioselective intramolecular olefin aminofluorination reactions.[6] Our initial attempts to apply these catalysts to olefin aminochlorination reactions led to either low diastereoselectivity or low yield, presumably due to the reason that chlorine and fluorine atom-transfer may proceed through distinct mechanisms. Therefore, we explored a range of activating group–ligand combinations and discovered entirely new catalytic conditions for asymmetric olefin aminochlorination. Herein, we describe iron-catalyzed, enantioselective and diastereoselective intramolecular aminochlorination for a range of internal, non-chalconic olefins (*ee* up to 92%, *dr* up to 15:1). In these reactions, a functionalized hydroxylamine and a chloride ion were utilized as the nitrogen and chlorine source. This method tolerates a range of synthetically valuable internal olefins that are all incompatible with the existing asymmetric olefin aminochlorination approaches; it also provides a new approach that is complementary to known methods for the asymmetric synthesis of amino chloride with contiguous stereogenic centers.

Prior to this research, Bach reported an $FeCl_2$-catalyzed racemic intramolecular olefin aminochlorination method with an acyl azide, TMSCl, and EtOH under ligand-free conditions.[7] Excellent *syn*-selectivity was observed with styrenyl olefins (*dr* up to >20:1). However, poor diastereoselectivity was recorded with non-styrenyl acyclic olefins (*dr*: 1:1). The new method presented here has a few unique features which complement the existing iron-catalyzed olefin aminochlorination method. First, excellent *anti*-selectivity has been observed across a wide range of styrenyl and non-styrenyl olefins. Next, good to excellent enantioselectivity has been achieved with a variety of internal, non-chalconic olefins (*ee* up to 92%). Finally, acyl azides are non-reactive under the described reaction condition (vide infra), which suggests that iron-nitrenoid generation may proceed through different pathways compared with the known azide activation pathway.

Results and discussions

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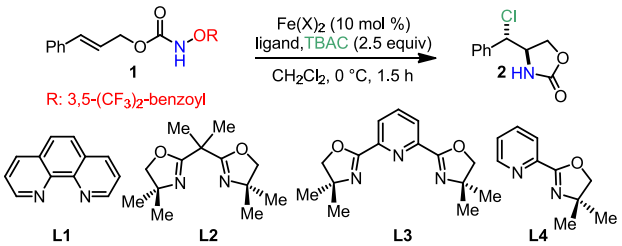
A cinnamyl alcohol-derived acyloxyl carbamate **1** was selected as the model substrate for catalyst discovery (Table 1).[8] In the presence of tetra-*n*-butylammonium chloride (TBAC), we observed that $FeCl_2$ alone catalyzed a sluggish reaction under the ligand-free condition (entry 1, 45% yield, *dr*: 2:1).[9] However, the $FeCl_2$–phenanthroline **L1** complex catalyzed the *anti*-aminochlorination with significantly improved yield and *dr* (entry 2, 80% yield, *dr* >20:1). We also noted that the $Fe(NTf_2)_2$–**L1** complex provided essentially the same reactivity and diastereoselectivity (entry 3, 86% yield, *dr* >20:1). Interestingly, the $Fe(NTf_2)_2$–bisoxazoline **L2** complex resulted in the loss of diastereoselectivity (entry 4, 82% yield, *dr*: 0.83:1). Additionally, the $Fe(NTf_2)_2$–**L3** complex promoted the *syn*-aminochlorination with moderate yield and *dr* (entry 5, 34% yield, *dr*: 0.25:1). We also observed that the $Fe(NTf_2)_2$–**L4** complex catalyzed the *anti*-aminochlorination with a modest *dr* (entry 6, 75% yield, *dr*: 1.8:1). Notably, the iron–**L4** complex results in high *dr* and reaction rate in the previously reported olefin aminofluorination reaction.[6] These observations suggest that ligands are involved in the diastereoselectivity-determining step and they provide excellent opportunities for diastereo-control.

Table 1. Catalyst discovery for the iron-catalyzed diastereoselective olefin aminochlorination reaction

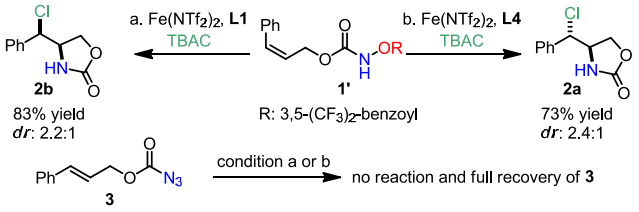


entry[a]	$Fe(X)_2$	ligand (mol %)	conversion[b]	yield[c]	*dr*[b] (*anti*:*syn*)
1	$FeCl_2$	none	62%	45%	2:1
2	$FeCl_2$	**L1** (20)	>95%	80%	>20:1
3	$Fe(NTf_2)_2$	**L1** (20)	>95%	86%	>20:1
4	$Fe(NTf_2)_2$	**L2** (10)	>95%	82%	0.83:1
5	$Fe(NTf_2)_2$	**L3** (10)	61%	34%	0.25:1
6	$Fe(NTf_2)_2$	**L4** (20)	>95%	75%	1.8:1

[a]Unless stated otherwise, the reactions were carried out under nitrogen atmosphere. [b]Conversion and *dr* were determined by ^1H NMR. [c]Isolated yield. TBAC: tetra-*n*-butylammonium chloride.

The observed ligand-enabled diastereo-control with *trans*-olefin **1** prompted us to evaluate *cis*-olefin **1′** (Scheme 2). To our surprise, the $Fe(NTf_2)_2$–**L1** complex catalyzed *syn*-aminochlorination, while the $Fe(NTf_2)_2$–**L4** complex promoted *anti*-aminochlorination with essentially the same *dr* (Scheme 2). The different reaction profiles for isomeric olefins **1** and **1′** suggest that the aminochlorination reaction is neither stereospecific nor fully stereo-convergent, which is significantly different from the iron-catalyzed olefin aminofluorination reaction.[6]

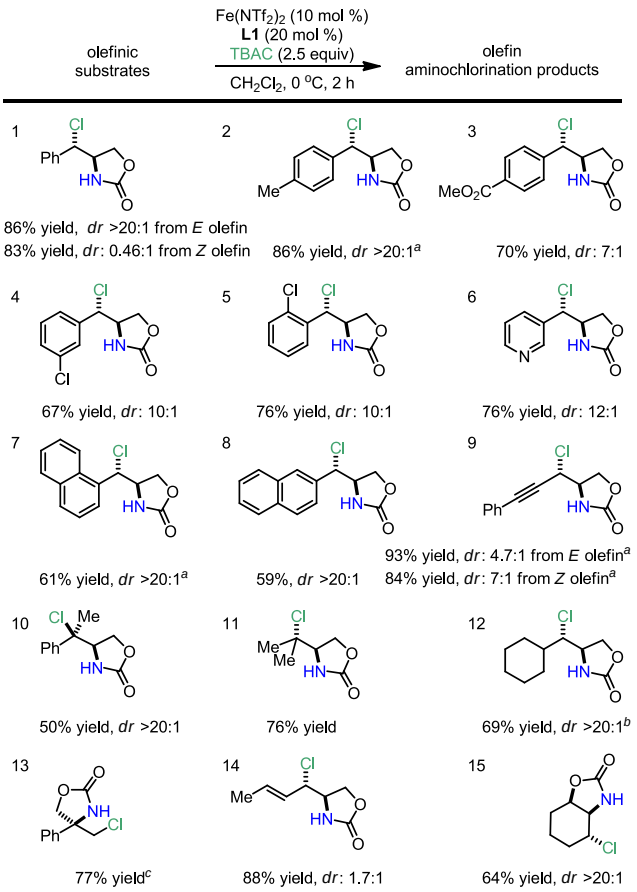
Furthermore, an acyl azide **3** was evaluated under the reaction conditions as control experiments. Interestingly, the acyl azide **3** was fully recovered and no aminochlorination product was detected. These results suggest that the activation of acyloxyl carbamates (**1** and **1′**) may proceed through different pathways compared with the known azide activation pathway.[7]



[a]Reaction condition: $Fe(NTf_2)_2$ (10 mol %), **L1** (20 mol %), TBAC (2.5 equiv), CH_2Cl_2, 0 °C, 2 h. [b]Reaction condition: $Fe(NTf_2)_2$ (10 mol %), **L4** (20 mol %), TBAC (2.5 equiv), CH_2Cl_2, 0 °C, 2 h.

Scheme 2. Iron-catalyzed aminochlorination with a *cis* olefin and an acyl azide

Table 2. Substrate scope of the iron-catalyzed diastereoselective olefin aminochlorination reaction



[a]Reaction condition: -15 °C, 2 h. [b]Reaction condition: 0 °C, 5 h. [c]Reaction condition: 0 °C, 12 h.

We subsequently explored a range of olefins under optimized conditions to evaluate the scope and limitations of this *anti*-aminochlorination method (Table 2). We discovered that di-substituted styrenyl olefins are generally good substrates; both electron-donating and withdrawing substituents are compatible with this method (entries 1–4). Importantly, *ortho*-substituents and pyridyl groups are both tolerated (entries 5–6). Furthermore, extended aromatics, including naphthyl olefins, are reasonable substrates (entries 7–8). Moreover, both isomeric ene-ynes are

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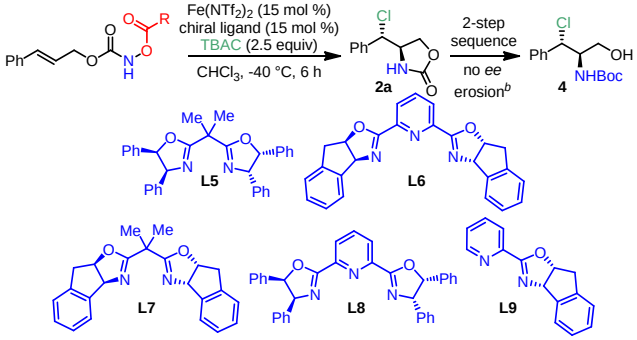
excellent substrates for the stereo-convergent and *anti*-selective method (entry 9). Additionally, we observed that both styrenyl and non-styrenyl tri-substituted olefins underwent aminochlorination smoothly with excellent *dr* (entries 10–11).[10] We also discovered that a cyclohexyl-substituted olefin was an excellent substrate (entry 12, *dr* >20:1). Further exploration revealed that both 1,1-disubstituted olefins and dienes are viable substrates with excellent regio-selectivity (entries 13–14). Most notably, a cyclic olefin could also undergo highly diastereoselective *anti*-aminochlorination (entry 15, *dr* >20:1), a product which is difficult to obtain with known methods.[11] Since the $FeCl_2$–**L1** complex provides essentially the same *dr* and yield in these diastereoselective reactions, $FeCl_2$ can be a convenient substitute for $Fe(NTf_2)_2$ in racemic reactions.

Table 3. Catalyst discovery of the iron-catalyzed asymmetric olefin aminochlorination reaction

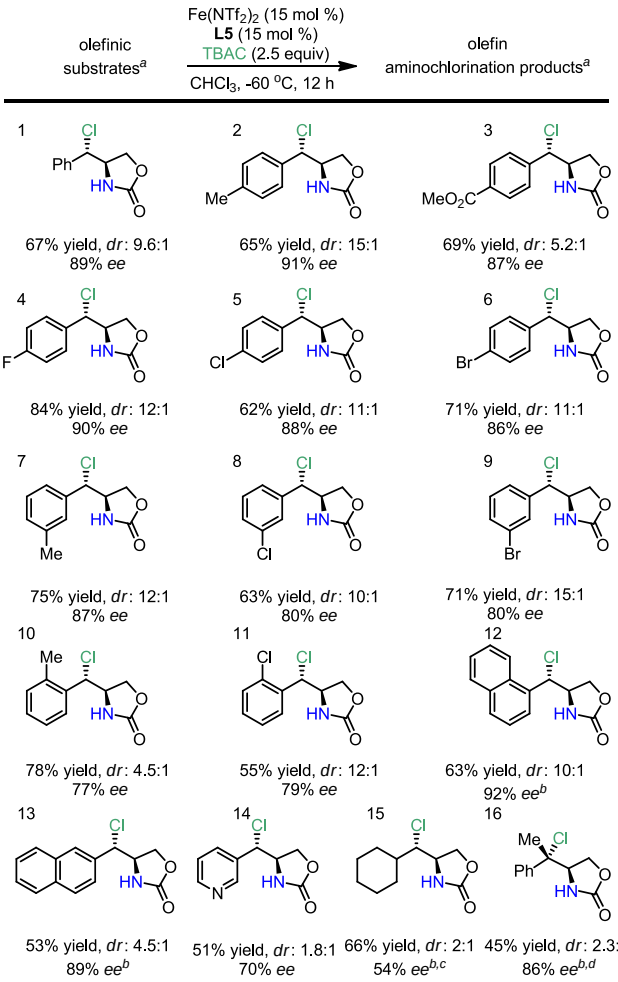


entry[a]	R	ligand	conversion[c]	yield[d]	*dr*[c] (*anti*:*syn*)	*ee*[e] (*anti*)	*ee*[e] (*syn*)
1	3,5-$(CF_3)_2$-Ph	**L5**	>95%	53%	9.9:1	84%	<5%
2	3,5-$(CF_3)_2$-Ph	**L6**	>95%	68%	0.5:1	24%	79%
3	3,5-$(CF_3)_2$-Ph	**L7**	88%	61%	1.7:1	<5%	<5%
4	3,5-$(CF_3)_2$-Ph	**L8**	>95%	32%	2.5:1	47%	30%
5	3,5-$(CF_3)_2$-Ph	**L9**	>95%	82%	0.5:1	8%	24%
6[f]	3,5-$(CF_3)_2$-Ph	**L5**	>95%	51%	11.0:1	90%	<5%
7[f]	CH_3	**L5**	>95%	42%	1.1:1	97%	<5%
8[f]	CH_2Cl	**L5**	>95%	67%	9.6:1	89%	<5%
9[f,g]	CH_2Cl	**L5**	>95%	58%	9.0:1	83%	<5%

[a]Unless stated otherwise, the reactions were carried out under nitrogen atmosphere with 4 Å molecular sieves. [b]Reaction condition: Boc_2O, Et_3N, DMAP; then Cs_2CO_3, MeOH, 85% over two steps; see Supporting Information for details. [c]Conversion and *dr* were determined by ^1H NMR. [d]Isolated yield. [e]Enantiomeric excess (*ee*) was measured by HPLC with chiral columns; the absolute stereochemistry was determined by X-ray crystallographic analysis of an analog of **2a**. [f]The reaction was carried out at -60 °C for 12 h. [g]The $FeCl_2$–**L5** complex was applied.

In order to fill the gap in catalytic asymmetric olefin aminochlorination, we further explored asymmetric induction for internal, non-chalconic olefins with a variety of iron–chiral ligand complexes (Table 3).[12] First, we discovered that the iron–**L5** complex induced a diastereoselective and enantioselective *anti*-aminochlorination, albeit with a low yield, mostly due to the competing aminohydroxylation reaction (entry 1, 53% yield, *dr*: 9.9:1). Interestingly, the *anti*-addition product **2a** was obtained with excellent *ee* (84% *ee*), while the *syn*-addition product **2b** was obtained essentially as racemate (<5% *ee*).[13] Additionally, a two-step procedure can convert **2a** to a chlorinated amino alcohol triad **4** without *ee* erosion.[14] Next, we observed that the iron–**L6** complex induced a moderately diastereoselective *syn*-aminochlorination (entry 2, 68% yield, *dr*: 0.48:1). To our surprise, the *anti*-addition product **2a** was obtained with moderate *ee* (24% *ee*), while the *syn*-addition product **2b** was isolated with significant *ee* (79% *ee*). Furthermore, we evaluated chiral ligands **L7** and **L8** and determined they are less effective for asymmetric induction (entries 3–4). Additionally, chiral ligand **L9** induced a fast yet non-selective aminochlorination with a high overall yield (entry 5).[15] With the iron–**L5** complex in hand, we subsequently explored other reaction parameters. First, a decreased reaction temperature benefits both *dr* and *ee* (entry 6, *dr*: 11:1 and 90% *ee* for **2a** at -60 °C). Next, replacing the 3,5-bis(trifluoromethyl)benzoyl activating group with a smaller acetyl group further enhances the *ee* (entry 7, 97% *ee* for **2a**); however, much lower *dr* and yield were obtained (entry 7, *dr*: 1.1:1, 42% yield). Finally, a chloroacetyl activating group induces an effective balance between overall yield and stereoselectivity (entry 8, 67% yield, *dr*: 9.6:1 and 89% *ee* for **2a**). We also observed that the $FeCl_2$–**L5** complex induced a slightly less selective reaction with lower yield (entry 9, 58% yield, *dr*: 9.0:1 and 83% *ee* for **2a**).

Table 4. Substrate scope for the iron-catalyzed asymmetric olefin aminochlorination reaction



[a]Unless stated otherwise, mono-chloroacetyl group was selected as the activing group in asymmetric catalysis; the *ee* for all *syn*-aminochlorination product is less than 5%. [b]Bis(trifluoromethyl)-benzoyl

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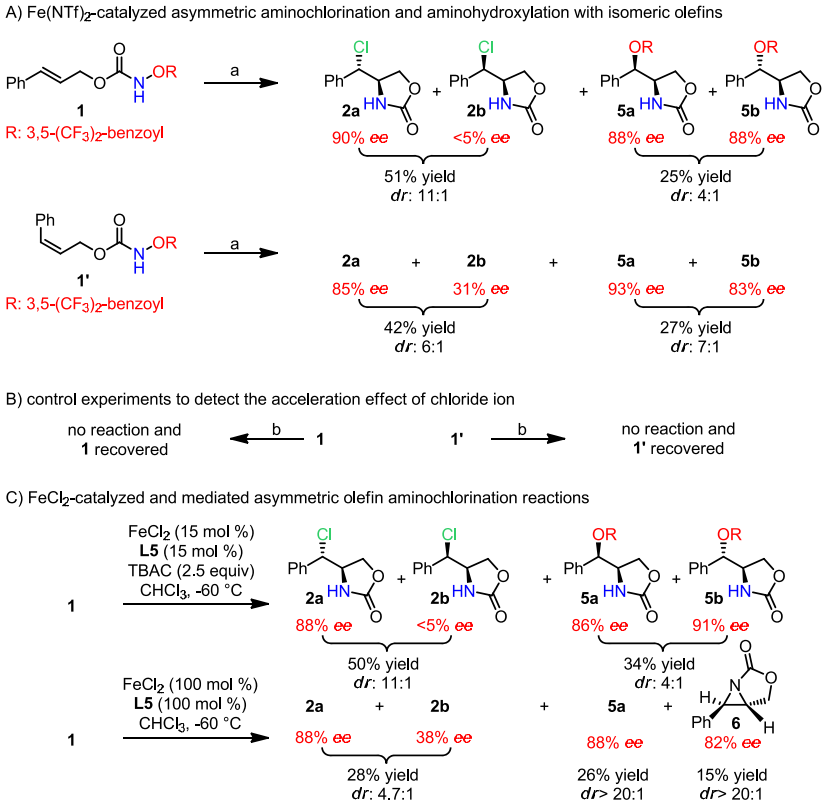
group was selected as the activating group. [c]The *ee* for *syn*-addition product is 12%. [d]**L6** is used as the ligand for asymmetric induction; the *ee* for the *syn*-addition product is 50%.

In order to evaluate the scope of this asymmetric method, we explored the asymmetric induction of a range of internal olefins (Table 4). The chiral catalyst provides excellent asymmetric induction with styrenyl olefins. A range of *para*-substituted styrenyl olefins with different electronic properties were converted to the corresponding aminochlorination products with high *dr* and *ee* (entries 1–6, *dr*: 9.6–15:1, *ee*: 86–91%). Additionally, *meta*-substituted styrenyl olefins are also good substrates but with slightly decreased *ee* (entries 7–9, *dr*: 10–15:1, *ee*: 80–87%). However, we discovered that *ortho*-substitution on styrenes has a deleterious effect on *ee* (entries 10–11, *dr*: 4.5–12:1, *ee*: 77–79%). Interestingly, both α and β-naphthyl olefins are excellent substrates (entries 12–13, *dr*: 4.5–10:1, *ee*: 89–92%). To our pleasure, a 3-pyridyl olefin with a basic nitrogen atom is a reasonable substrate for the asymmetric aminochlorination (entry 14, *dr*: 1.8:1, *ee*: 70% for the *anti*-diastereomer). Moreover, we observed that the iron–**L5** complex can induce significant *ee* in the aminochlorination with non-styrenyl olefins (entry 15, *dr*: 2:1, *ee*: 52% for the *anti*-diastereomer). To our surprise, the iron–**L6** complex proves uniquely effective for the asymmetric induction with tri-substituted olefins while the iron–**L5** complex becomes less effective (entry 16, *dr*: 2.3:1, *ee*: 84% for the *anti*-diastereomer).[16]



[a]Reaction condition: $Fe(NTf_2)_2$ (15 mol %), **L1** (15 mol %), TBAC (2.5 equiv), $CHCl_3$, -60 °C, 12 h. [b]Reaction condition: $Fe(NTf_2)_2$ (15 mol %), **L1** (15 mol %), $CHCl_3$, -60 °C, 12 h.

Scheme 3. Control experiments to probe for a plausible mechanism

During the exploration of substrate scope, it is surprising to observe completely different *ee* for the *anti*- and *syn*-diastereomers (e.g. **2a** and **2b**). In contrast, exactly the same *ee* for both diastereomeric products was observed in the iron-catalyzed aminofluorination of **1**.[6] In order to obtain more mechanistic insights, we carried out *ee* analysis for all isolable products in several control experiments (Scheme 3). First, in an $Fe(NTf_2)_2$-catalyzed reaction with *trans*-olefin **1**, two aminochlorination products were obtained (Scheme 3A, 90% *ee* for **2a**, <5% *ee* for **2b**, *dr*: 11:1).[17] Simultaneously, diastereomeric **5a** and **5b** were also isolated with the same *ee* as two competing olefin aminohydroxylation products (Scheme 3A, 88% *ee* for **5a** and **5b**, *dr*: 4:1). However, completely different selectivity (both *dr* and *ee*) was observed in an $Fe(NTf_2)_2$-catalyzed reaction with *cis*-olefin **1′** (Scheme 3A, 85% *ee* for **2a** and 31% *ee* for **2b**, *dr*: 6:1; 93% *ee* for **5a** and 83% *ee* for **5b**, *dr*: 7:1). In both cases, **5a** and **5b** cannot be converted to **2a** under the reaction condition.

These observations provide several important mechanistic insights. First, the non-stereospecificity observed in the iron-catalyzed olefin aminochlorination suggests that the formation of C–N and C–Cl bonds occurs in a stepwise fashion.[18] Next, the lack of complete stereo-convergence between reaction profiles of isomeric olefins (**1** and **1′**) suggests that C–N bond formation may be the rate- and *ee*-determining step.[18] Furthermore, since

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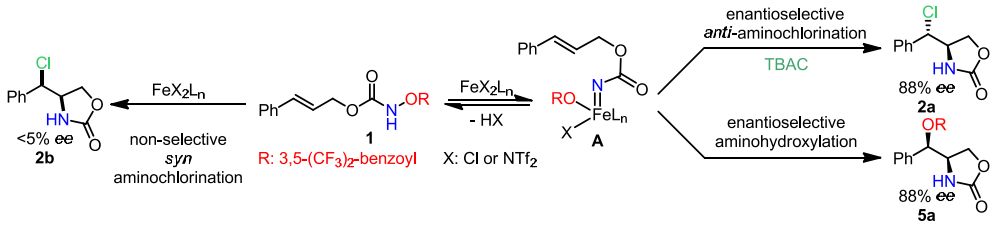
essentially the same *ee* was observed for **2a**, **5a**, and **5b** from the reaction with *trans*-olefin **1**, it is likely that these products are derived from the same intermediate after the *ee*-determining step. Additionally, the fact that the *syn*-aminochlorination product **2b** was isolated as racemate suggests that **2b** may be derived from non-stereoselective pathways which are distinct from the one leading to the formation of **2a**, **5a**, and **5b**.

The product divergence (**2a** vs **5a**/**b**) after the *ee*-determining step is mechanistically interesting. Therefore, we studied the effect of external chloride ion. To our surprise, in the absence of TBAC, the $Fe(NTf_2)_2$–**L5** complex alone was ineffective for the nitrogen atom-transfer at -60 °C; **1** and **1′** were both fully recovered (Scheme 3B). However, the aminochlorination occurred as soon as a stoichiometric amount of TBAC was introduced. This observation suggests that the $Fe(NTf_2)_2$–**L5** complex may serve as a pre-catalyst and it may be activated by chloride ion in situ.

In order to test this hypothesis, we further carried out the $FeCl_2$-catalyzed reaction in the presence of TBAC (Scheme 3C). Notably, **2a** was isolated with essentially the same *ee* compared with the one obtained under the standard condition (88% *ee* for **2a** and <5% *ee* for **2b**). This result suggests that the catalytically relevant species may also be generated from the $FeCl_2$–**L5** complex.

To probe for more mechanistic details, we subsequently carried out the $FeCl_2$-promoted olefin aminochlorination in the absence of TBAC (100 mol % $FeCl_2$, 100 mol % **L5** in Scheme 3C). Under this condition, $FeCl_2$ is the only available chlorine source. Surprisingly, we discovered that **2a** was obtained with essentially the same *ee* compared with two previous control experiments (88% *ee* for **2a**). Furthermore, a *syn*-aminohydroxylation product **5a** was isolated with excellent *dr* and *ee* (*dr* >20:1, 88% *ee*). These observations suggest that Fe–Cl bond cleavage may be relevant for the chlorine atom-transfer step during the enantioselective *anti*-aminochlorination.[19] In addition, we also identified a small amount of aziridine **6** (15% yield, 82% *ee*) and further discovered that it could not be converted to either **2a** or **5a** under the reaction condition.



Scheme 4. Proposed mechanistic working hypothesis for the iron-catalyzed asymmetric aminochlorination of *trans*-olefin **1**.

With the accumulated mechanistic evidence, we propose a plausible mechanistic working hypothesis for the iron-catalyzed asymmetric aminochlorination of *trans*-olefin **1** (Scheme 4). First, the iron catalyst could reversibly cleave the N–O bond in acyloxyl carbamate **1**, generating iron-nitrenoid **A** with chloride as a counter ion. From there, **A** may participate in the enantioselective and diastereoselective aminohydroxylation and aminochlorination to afford **2a** and **5a** respectively. Since the aminochlorination–aminohydroxylation competition occurs after the *ee*-determining step, **2a** is obtained with essentially the same *ee* compared with **5a**. At the same time, **1** may also be converted to **2b** through a non-stereoselective pathway which is distinct from the one leading to the formation of **2a** and **5a**. Further mechanistic studies are required to elucidate details.

Conclusions

In conclusion, we have described an iron-catalyzed enantioselective and diastereoselective aminochlorination method for internal, non-chalconic olefins. This method tolerates a range of synthetically valuable olefins that are all incompatible with the existing asymmetric olefin aminochlorination methods. It also provides a complementary approach for the asymmetric synthesis of amino chloride with contiguous stereogenic centers. Our preliminary mechanistic studies revealed that an $FeCl_2$-derived nitrenoid may be a feasible reactive intermediate and that Fe–Cl bond cleavage may be relevant for the stereoselective chlorine atom-transfer. Our current effort focuses on the mechanistic investigation of this new reaction and method development for the enantioselective intermolecular olefin aminochlorination.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data for all new compounds, selected NMR spectra and HPLC traces. See DOI: 10.1039/b000000x/
‡ These authors contributed equally.

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8 For substrate synthesis, see Supporting Information for details. Acyloxyl carbamates are reactive, while tosyloxyl and alkoxyl carbmates are nonreactive and fully recovered under the reaction condition.

9 The relative stereochemistry of **2a** was determined by comparison of the experimental NMR data with the ones reported in ref. 7. It was further corroborated by ^{1}H NMR and X-ray crystallographic analysis of a structural analog of **2a**. See Supporting Information for details.

10 The relative stereochemistry was assigned based on the ^{1}H NMR and X-ray crystallographic analysis of a structural analog described in ref. 6; see Supporting Information for details.

11 Complementary stereochemistry was achieved (in entry 15 of Table 2), compared with the known method reported in ref. 7, where the *syn*-aminochlorination product was isolated. This substrate did not undergo kinetic resolution with chiral catalyst, the $Fe(NTf_2)_2$–**L5** complex. Both the starting material and product were isolated as racemate.

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13 The absolute stereochemistry of **2a** was determined by X-ray crystallographic analysis of a structural analog of **2a**. See Supporting Information for details.

14 For detailed procedure and HPLC traces of **4**, see Supporting Information.

15 For the synthesis of **L9**, see ref. 6.

16 The iron–**L5** complex catalyzed the reaction favoring the *syn*-addition product: *dr*(*anti*/*syn*): 0.47:1; *ee* for the *anti*-addition product is 60% and *ee* for the *syn*-addition product is <5%. The relative stereochemistry was assigned based on the ^{1}H NMR and X-ray crystallographic analysis of a structural analog described in ref. 6; see Supporting Information for details.

17 When chloroacetyl group is used as the activating group, different result was obtained. For details, see entry 8 of Table 3.

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