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Iron(II)-catalyzed asymmetric intramolecular olefin aminochlorination using chloride ion†

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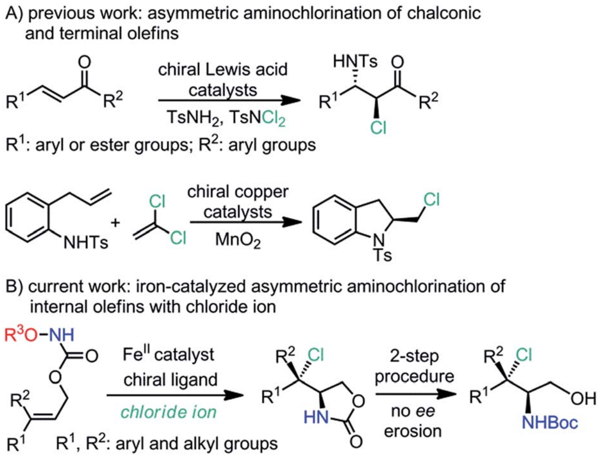
An iron-catalyzed enantioselective and diastereoselective intramolecular olefin aminochlorination reaction is reported (ee up to 92%, dr up to 15 : 1). In this reaction, a functionalized hydroxylamine and chloride ion are utilized as nitrogen and chlorine sources, respectively. This new method tolerates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

Introduction

Enantioselective olefin halo-functionalization reactions constitute 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 the 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 would readily provide vicinal amino chlorides, a class of important chiral building blocks. Moreover, asymmetric olefin aminochlorination that proceeds through an iron-nitrenoid intermediate has not yet been reported.[5]

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 chloride ion were utilized as nitrogen and chlorine sources, respectively. This method tolerates a range of synthetically valuable internal olefins that are all incompatible with existing asymmetric olefin aminochlorination approaches; it also provides a new approach that is complementary to known methods for the asymmetric synthesis of amino chlorides with contiguous stereogenic centers.

Prior to this research, Bach reported an $FeCl_2$-catalyzed racemic intramolecular olefin aminochlorination method using acyl azides, TMSCl, and EtOH under ligand-free conditions.[7]



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

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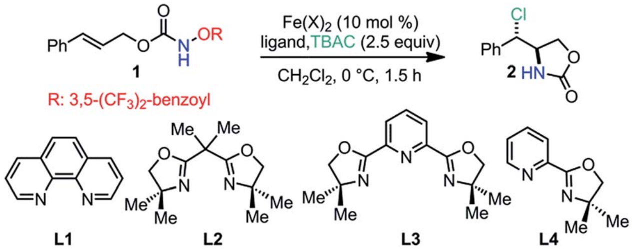
Table 1 Catalyst discovery for the iron-catalyzed diastereoselective olefin aminochlorination reaction



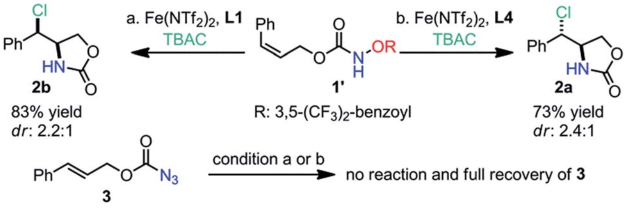
Entry[a]	Fe(X)$_2$	Ligand (mol%)	Conversion[b]	Yield[c]	dr[b] (anti : syn)
1	FeCl$_2$	None	62%	45%	2 : 1
2	FeCl$_2$	**L1** (20)	>95%	80%	>20 : 1
3	Fe(NTf$_2$)$_2$	**L1** (20)	>95%	86%	>20 : 1
4	Fe(NTf$_2$)$_2$	**L2** (10)	>95%	82%	0.83 : 1
5	Fe(NTf$_2$)$_2$	**L3** (10)	61%	34%	0.25 : 1
6	Fe(NTf$_2$)$_2$	**L4** (20)	>95%	75%	1.8 : 1

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

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. Second, 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 conditions (*vide infra*), which suggests that iron-nitrenoid generation may proceed *via* different pathways compared with the known azide activation pathway.

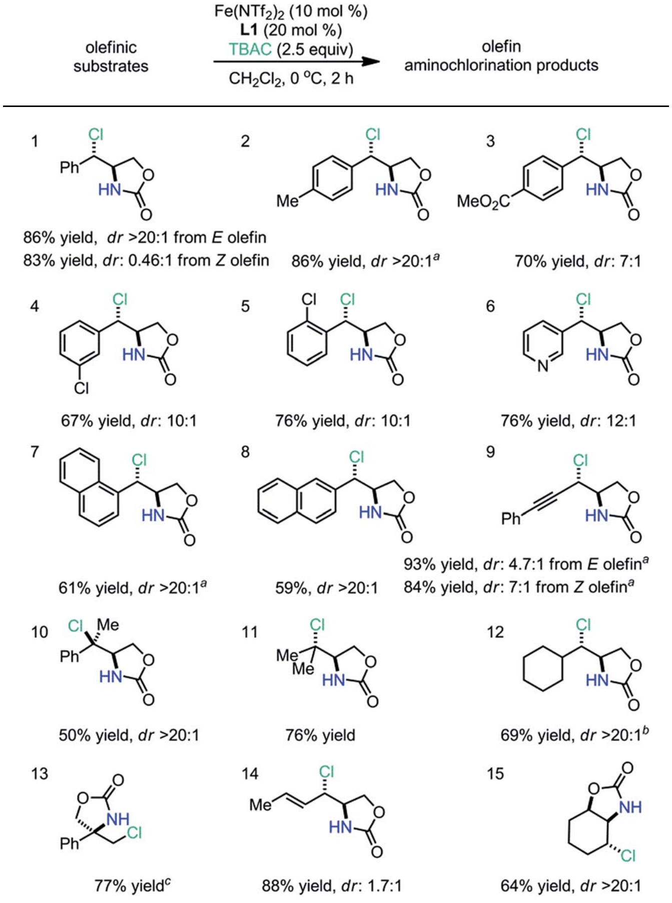
Results and discussion

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 ligand-free conditions (entry 1, 45% yield, dr: 2 : 1).[9] However, the FeCl$_2$–phenanthroline (**L1**) complex catalyzed the anti-



Scheme 2 Iron-catalyzed aminochlorination with a *cis* olefin and an acyl azide. [a]Reaction conditions: Fe(NTf$_2$)$_2$ (10 mol%), **L1** (20 mol%), TBAC (2.5 equiv.), CH$_2$Cl$_2$, 0 °C, 2 h. [b]Reaction conditions: Fe(NTf$_2$)$_2$ (10 mol%), **L4** (20 mol%), TBAC (2.5 equiv.), CH$_2$Cl$_2$, 0 °C, 2 h.

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



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

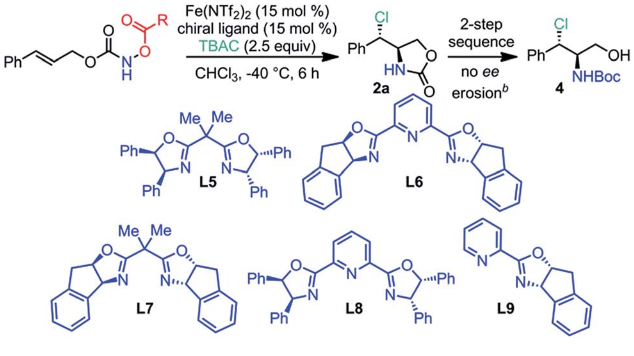
aminochlorination with significantly improved yield and dr (entry 2, 80% yield, dr > 20 : 1). We also noted that the $Fe(NTf_2)_2$–**L1** complex provided essentially the same reactivity and diastereoselectivity (entry 3, 86% yield, dr > 20 : 1). Interestingly, the $Fe(NTf_2)_2$–bisoxazoline (**L2**) complex resulted in a loss of diastereoselectivity (entry 4, 82% yield, dr: 0.83 : 1). Furthermore, 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, an iron–**L4** complex resulted 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 provide excellent opportunities for diastereo-control.

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 a control experiment. 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 *via* different pathways compared with the known azide activation pathway.[7]

We subsequently explored a range of olefins under the 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 electron-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, isomeric ene–ynes are both excellent substrates for the stereo-convergent and anti-selective method (entry 9). Additionally, we observed that both styrenyl and non-styrenyl tri-substituted olefins undergo 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 regioselectivity (entries 13–14). Most notably, a cyclic olefin could also undergo highly diastereoselective anti-aminochlorination (entry 15, dr > 20 : 1), yielding 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 for the iron-catalyzed asymmetric olefin aminochlorination reaction



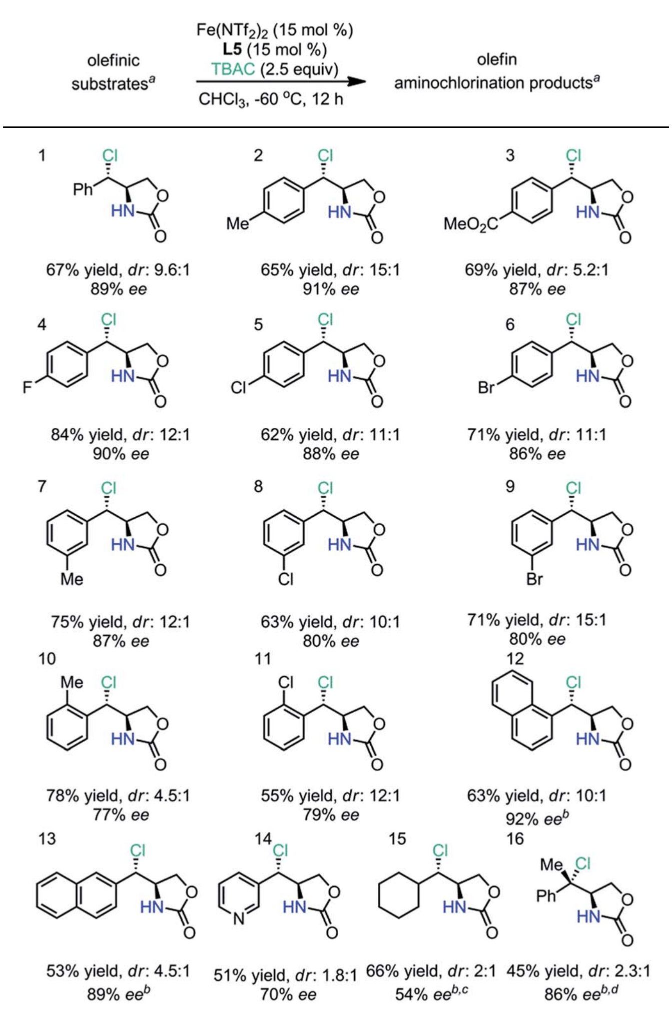
Entry[a]	R	Ligand	Conversion[c]	Yield[d]	dr[c] (anti : syn)	ee[e] (anti)	ee[e] (syn)
1	3,5-$(CF_3)_2$-Ph	**L5**	>95%	53%	9.9 : 1	84%	<5%
2	3,5-$(CF_3)_2$-Ph	**L6**	>95%	68%	0.5 : 1	24%	79%
3	3,5-$(CF_3)_2$-Ph	**L7**	88%	61%	1.7 : 1	<5%	<5%
4	3,5-$(CF_3)_2$-Ph	**L8**	>95%	32%	2.5 : 1	47%	30%
5	3,5-$(CF_3)_2$-Ph	**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 a nitrogen atmosphere with 4 Å molecular sieves. [b] Reaction conditions: Boc_2O, Et_3N, DMAP; then Cs_2CO_3, MeOH, 85% over two steps; see ESI 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 used.

In order to fulfil the need for 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 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 a 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 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 that they are less effective for asymmetric induction (entries 3–4). Additionally, chiral ligand **L9** induced 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 was found to benefit 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 enhanced 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 induced 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 a lower yield (entry 9, 58% yield, dr: 9.0 : 1 and 83% ee for **2a**).

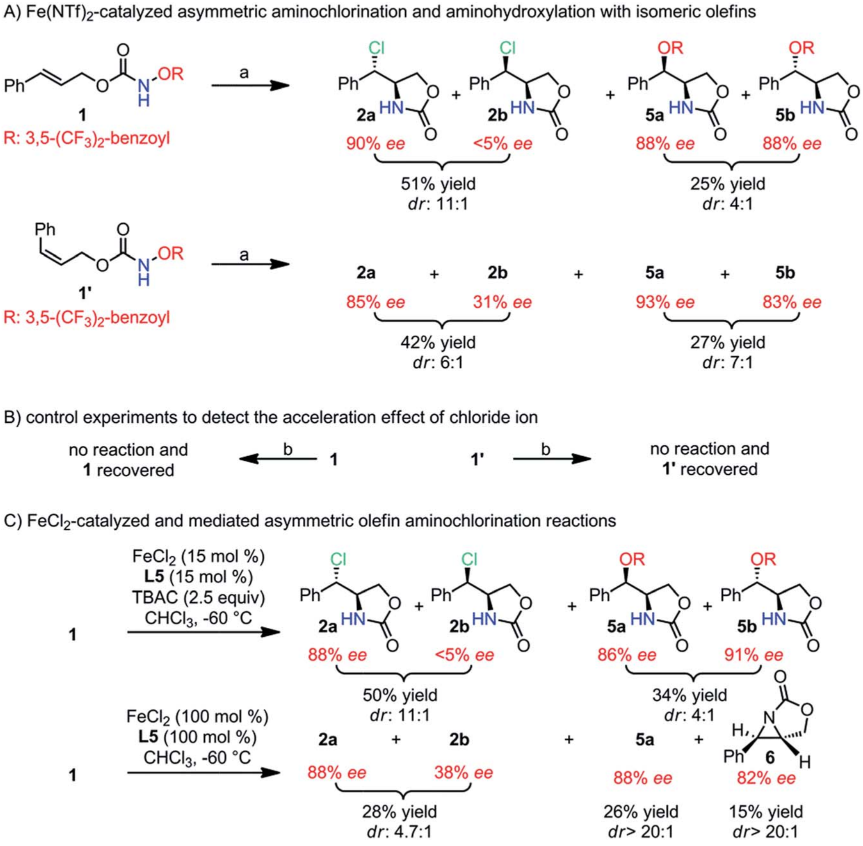
In order to evaluate the scope of this asymmetric method, we explored the asymmetric induction with a range of internal olefins (Table 4). The chiral catalyst provides excellent asymmetric induction with styrenyl olefins. A range of *para*-substituted styrenyl olefins with different electronic properties 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 of 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 delight, 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: 54% for the anti-diastereomer). To our surprise, the iron–**L6** complex proved to be uniquely effective for the asymmetric induction with tri-substituted olefins, while the iron–**L5** complex was less effective (entry 16, dr: 2.3 : 1, ee: 86% for the anti-diastereomer).[16]

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



[a] Unless stated otherwise, mono-chloroacetyl was selected as the activating group for asymmetric catalysis; the ee for all syn-aminochlorination products was less than 5%. [b] Bis(trifluoromethyl)-benzoyl was selected as the activating group. [c] The ee for the syn-addition product was 12%. [d] **L6** was used as the ligand for asymmetric induction; the ee for the syn-addition product was 50%.

During the exploration of substrate scope, it was surprising to observe completely different ee values for 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 greater mechanistic insights, we carried out ee analysis for all isolable products using 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, diastereomers **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:



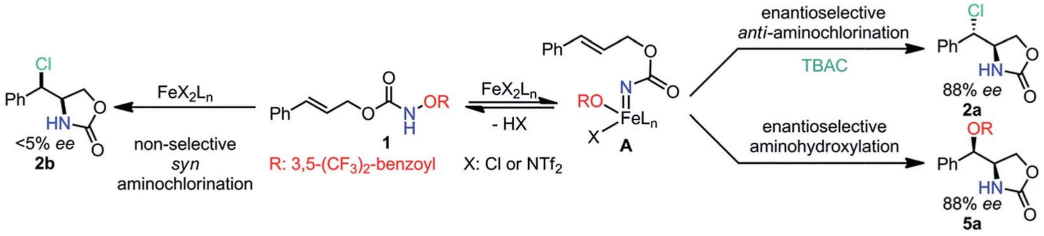
Scheme 3 Control experiments to probe the mechanism. ^{a}Reaction conditions: $Fe(NTf_2)_2$ (15 mol%), **L1** (15 mol%), TBAC (2.5 equiv.), $CHCl_3$, −60 °C, 12 h. ^{b}Reaction conditions: $Fe(NTf_2)_2$ (15 mol%), **L1** (15 mol%), $CHCl_3$, −60 °C, 12 h.

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 conditions.

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] Second, the lack of complete stereo-convergence between the 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 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 a 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, 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 as that obtained under the standard conditions (88% ee for **2a** and <5%



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

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**, Scheme 3C). Under these conditions, $FeCl_2$ is the only available chlorine source. Surprisingly, we discovered that **2a** was obtained with essentially the same ee compared with the 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 conditions.

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 reversibly cleaves the N–O bond in the acyloxyl carbamate **1**, generating iron-nitrenoid **A** with chloride as a counter ion. From there, **A** may participate in enantioselective and diastereoselective aminochlorination and aminohydroxylation 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 as **5a**. At the same time, **1** may be converted to **2b** *via* 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 the 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 existing asymmetric olefin aminochlorination methods. It also provides a complementary approach for the asymmetric synthesis of amino chlorides 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 stereoselective chlorine atom-transfer. Our current efforts are focused on the mechanistic investigation of this new reaction and method development for the enantioselective intermolecular olefin aminochlorination.

Acknowledgements

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8 See ESI† for details of substrate synthesis. Acyloxyl carbamates are reactive, while tosyloxyl and alkoxyl carbamates are non-reactive and fully recovered under the reaction conditions.

9 The relative stereochemistry of **2a** was determined by comparison of the experimental NMR data with those reported in ref. 7. It was further corroborated by ^{1}H NMR and X-ray crystallographic analysis of a structural analog of **2a**. See ESI† 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 ESI† 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 a chiral catalyst, the complex $\mathrm{Fe(NTf_2)_2}$–**L5**. Both the starting material and product were isolated as racemates.

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14 For detailed procedure and HPLC traces of **4**, see ESI.†

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 was 60% and ee for the syn-addition product was <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 ESI† for details.

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

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