Efficient access to unprotected primary amines by iron-catalyzed aminochlorination of alkenes

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Abstract:

Primary amines are essential constituents of biologically active molecules and versatile intermediates in the synthesis of drugs and agrochemicals. However, their preparation from easily accessible alkenes remains challenging. Herein, we report a general strategy to access primary amines from alkenes through an operationally simple iron-catalyzed aminochlorination reaction. A stable hydroxylamine derivative and benign sodium chloride act as the respective nitrogen and chlorine sources. The reaction proceeds at room temperature under air, tolerates a large scope of aliphatic and conjugated alkenes, including densely functionalized substrates, and provides excellent anti-Markovnikov regioselectivity with respect to the amino group. The reactivity of the 2-chloroalkylamine products, an understudied class of amphoteric molecules, enables facile access to linear or branched aliphatic amines, aziridines, aminonitriles, azido amines and homoallylic amines.

Main Text:

Aliphatic primary amines are present in a wide range of important bioactive compounds. They are also among the most versatile synthetic intermediates in the atom-economical construction of secondary amines, tertiary amines and heterocycles (*1*). The synthesis of primary amines traditionally relies on reductive amination (*2*, *3*), dehydrogenative coupling of alcohols (*4*), allylic amination (*5*, *6*), azide or nitrile reduction. These methods rely on the pre-installation of a polar group in the starting material. A complementary and potentially more versatile alternative would employ ubiquitous alkenes, which are commonly encountered in petrochemical feedstocks and synthetic intermediates, as

starting materials (*7*). Although aminofunctionalization reactions, such as hydroamination (*8-13*) and aminohydroxylation (*14-17*) of alkenes and alkene azidation (*18-21*) have played an important role in this area, these reactions are generally limited by the need to protect (and later deprotect) the nitrogen, activate the olefin with an aryl substituent, or generate hazardous azide intermediates (Fig. 1A). Falck and Kürti recently reported the preparation of a wide range of NH-aziridines via rhodium catalysis, a reaction that addresses some important challenges in this area (*22*, *23*). However, the application of this reaction is limited by the challenges associated with the subsequent regioselective opening of the aziridines to reveal the desirable primary amine building blocks, as well as the high cost of rhodium. Thus, the direct catalytic and regioselective synthesis of unprotected amine derivatives from unactivated alkenes remains an unsolved challenge in organic chemistry.

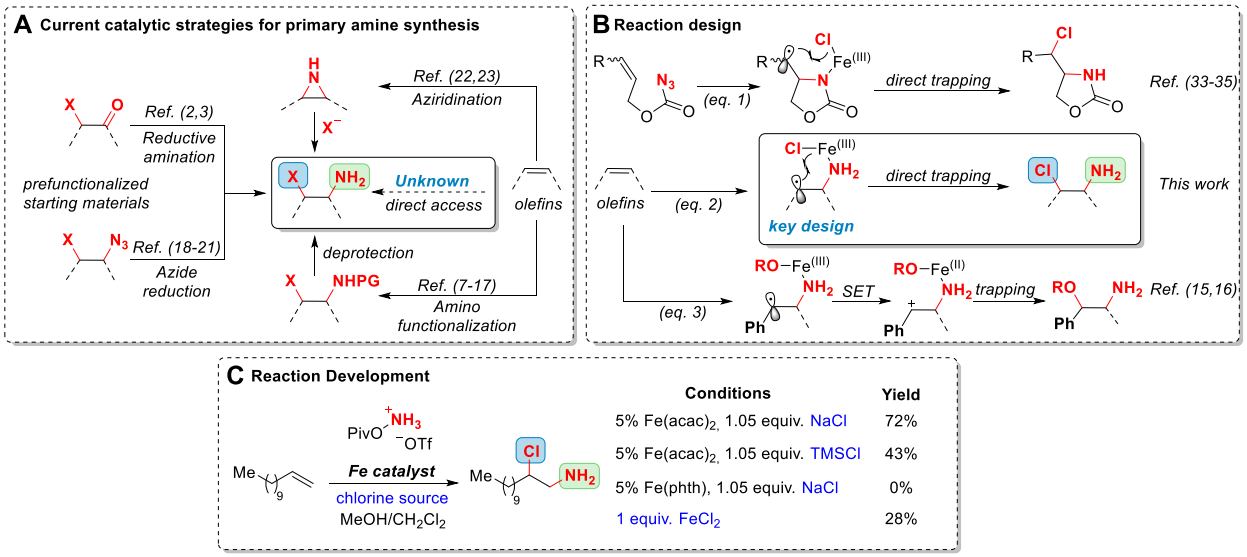

Fig. 1. Development of a strategy for the synthesis of a broad class of unprotected amines. (**A**) Traditional approach for primary amine synthesis. (**B**) Our design for direct radical trapping. (**C**) Reaction development (selected conditions).

A catalytic method to introduce both the desired unprotected amine group, ideally at the more challenging primary position, and a versatile electrophile at the secondary position, would prove particularly useful in the preparation of important compounds because of the complementary reactivity of these functional groups. Ideally, these products could be accessed using a simple protocol, inexpensive reagents and an earth-abundant metal catalyst. Unprotected 2-chloroalkylamines would, in principle, fulfill the role of amphoteric aminated building blocks. These seemingly unstable molecules have rarely been reported in the literature (*24*), and the few viable synthetic methods to access

them have generally relied on the direct chlorination of amino alcohols (*25*) or the ring-opening of *NH*-aziridines (*26*). Alternatively, derivatives protected by a tosyl group, can be occasionally accessed from alkenes using stoichiometric protocols, but these reactions are limited by the challenging selective cleavage of the Ts group in the presence of the chloride, the lack of regioselectivity, as well as poor scope and yield (*27-32*). An intramolecular iron-catalyzed aminochlorination has been reported by Bach, though the products are chloro-substituted oxazolidinones rather than unprotected 2-chloroalkylamines (*33-35*).

In iron-catalyzed amination reactions of alkenes more generally (*11*, *15-17*, *36-41*), the use of specific substituents (e.g. Ts) on the nitrogen atom to control reactivity and the high inefficiency when using inactivated olefins remain limiting factors. In order to collectively address these issues, we reasoned that the use of chloride as a nucleophile in electrophilic amination reactions would not only enable access to versatile 2-chloroalkylamines, but would also provide a strategy to address the lack of reactivity observed with traditionally unreactive alkenes. Related (*15*, *16*) iron-catalyzed amino hydroxylation reactions and etherifications indeed suffer from a limited substrate scope because they rely on a mechanism that involves a single electron transfer mediated oxidation of a carbon centered radical to a carbocation, a process that becomes very challenging when non-benzylic radicals are generated as intermediates (Fig. 1B, eq. 3). Based on Bach's precedent (Fig. 1B, eq. 1) and the well-known propensity of chlorine atom to undergo homolytic substitution reactions (*42*), we hypothesized that the putative unstable radical intermediate generated through the attack of an ammonium radical onto a C=C double bond could instead rapidly undergo chlorine atom transfer from the amine-bound iron(III) complex to form the desired product and regenerate the iron(II) catalyst (Fig. 1B, eq. 2). In this strategy, the facile homolytic substitution reaction of the carbon radical with the iron-bound chlorine atom, a pathway not easily accessible with oxygen-containing ligands, provides a direct route to product formation that does not involve any additional single electron transfer step nor cationic intermediates. Consequently, a broader palette of alkenes should be amenable to this new process.

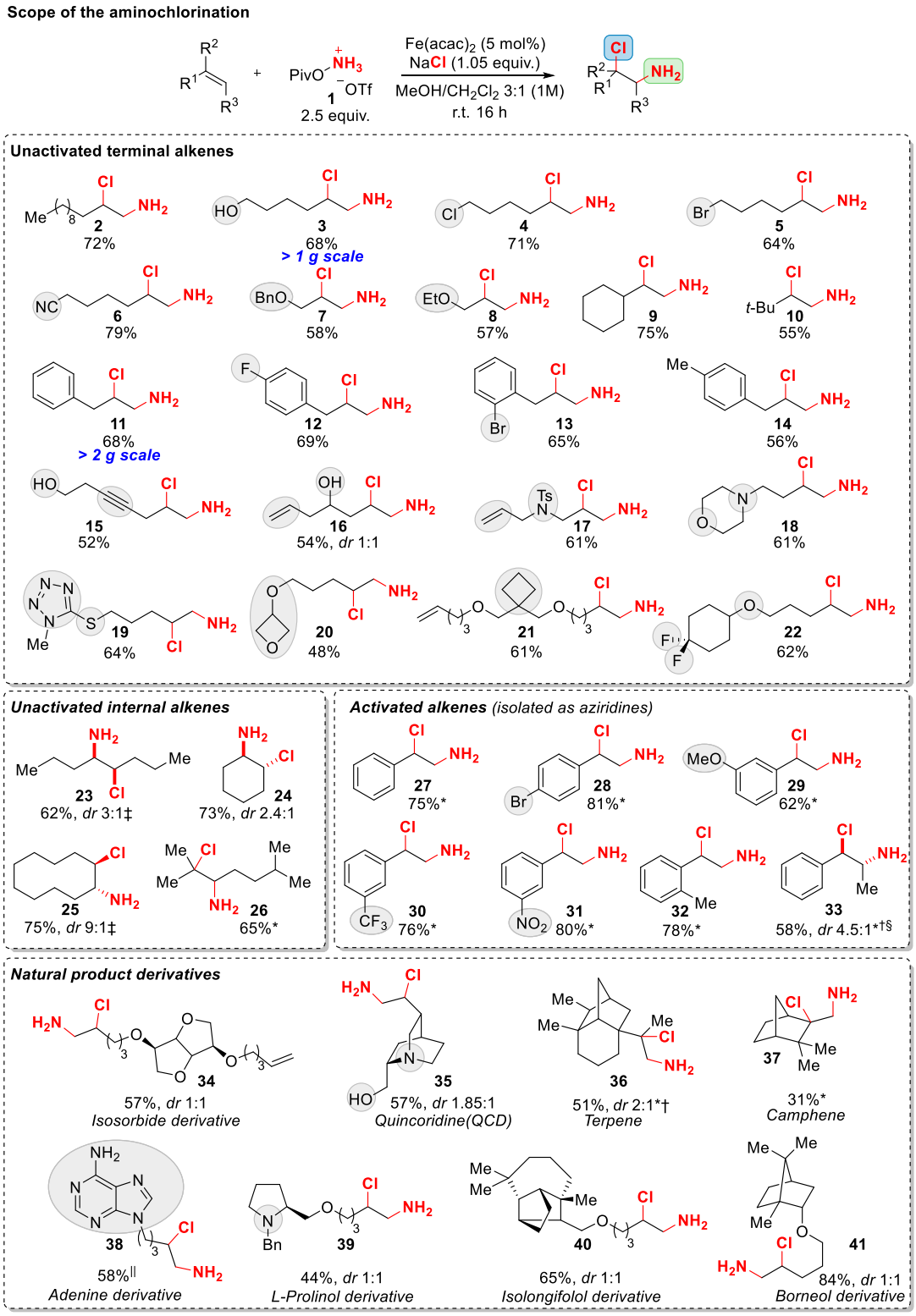

Fig. 2. Scope of the reaction with activated and unactivated alkenes. All yields, unless otherwise noted, are isolated yields of the 2-chloroalkylamine products. *Yields refer to the isolated aziridine products after basic workup. †Diastereomeric ratio of the isolated

aziridine products. ‡(*E*)-alkene isomer used as substrate. §(*Z*)-alkene isomer used as substrate. ||^{1}H-NMR yield, see SM for isolation and characterization. *dr*: diastereomeric ratio; r.t., room temperature.

Herein, we report the iron-catalyzed aminochlorination of a wide range of conjugated and non-conjugated alkenes, including densely functionalized substrates. The reaction proceeds with excellent regioselectivity for the linear amine (the minor branched isomer could not be detected by H-NMR spectroscopy) and leads to the direct formation of unprotected 2-chloroalkylamines under operationally simple conditions.

Initial proof of concept experiments were conducted under air with a stoichiometric amount of $FeCl_2$ added to a solution of 1-dodecene (a traditionally challenging substrate in electrophilic amination reactions) in the presence of a variety of hydroxylamine-derived reagents (Fig 1C and Table S1). A significant conversion to the product was observed, albeit in low yields because of the product's instability in the presence of excess Lewis acidic iron salts. We then explored different stoichiometric chloride sources to move away from the use of stoichiometric amounts of iron salts. Although trimethylsilylchloride, the source used by Bach (*33*-*35*) gave moderate yields of product, we discovered that much more benign and easy-to-handle sodium chloride gave superior results. We believe that the use of a mild, non-Lewis acidic source of chloride is crucial to prevent the undesired decomposition of the relatively unstable amino chlorinated product. Optimal conditions for the reaction employed inexpensive $Fe(acac)_2$ as catalyst, simple sodium chloride as a chlorinating agent and a hydroxylamine derived reagent as amine source at room temperature in a methanol/dichloromethane mixture. The 2-chloro terminal amine was isolated in 72% yield with no detected alternative regioisomers. The aminating reagent is thermally stable up to a temperature of 160°C, as demonstrated by differential scanning calorimetry analysis (Fig S2).

We next explored the alkene substrate scope of this reaction, including two gram-scale demonstrations. A wide range of terminal alkenes, some containing unprotected polar groups that are traditionally problematic in transition metal catalysis (eg cyano substrate **6** and hydroxy substrates **3**, **15** and **16**) gave the corresponding products in good yields (Fig. 2). Basic tertiary nitrogen centers (**35**, **18**, **38** and **39**) were also tolerated, an important prerequisite for the application of any methodology to the discovery of bioactive compounds. Heterocycles commonly used in drug discovery, such as tetrazole (**19**), oxetane (**20**) and purine (**38**) could be readily employed, as could an alkyne (**15**).

Furthermore, aromatic halides (**12**, **13**), which can serve as handles for further functionalization through cross-coupling, gave the desired product in good yields. A striking feature of the reaction was the exclusive formation of the monofunctionalized product even in cases where two alkenes are present in the starting material (**16**, **17**, **34**); the absence of difunctionalization product in the crude reaction mixture suggests that the low solubility of the protonated amine product might prevent over-functionalization. The reaction is not limited to monosubstituted alkenes. Both 1,1 (**36**, **37**) and 1,2-disubstituted (**23**-**25**) alkenes and even a trisubstituted alkene (**26**) also gave the products in high yields with partial retention of stereochemistry. Styrenes (**27**-**33**) could also be employed in this transformation, however, in this case, the instability of the benzylic chlorides prevented the isolation of the products. Instead, the corresponding aziridine was isolated directly after basic work up. With regards to the substrates that failed to produce synthetically useful yields of products (Fig S3), solubility issues encountered with cholesterol derivatives and the lack of chemoselectivity with polyolefin substrates account for most of the limitations observed thus far.

We next probed the range of densely functionalized substrates amenable to the reaction. A derivative of isosorbide (**34**), a renewable feedstock, as well as several structurally complex terpene derivatives (**36, 37, 40, 41**) were aminochlorinated in good yields. More importantly, nitrogen-based bioactive scaffolds, such as quincoridine (**35**), prolinol (**39**) and even unprotected adenine (**38**) delivered the corresponding aminated products. Such substrates would arguably pose a great challenge to the vast majority of other transition-metal catalyzed amination reactions.

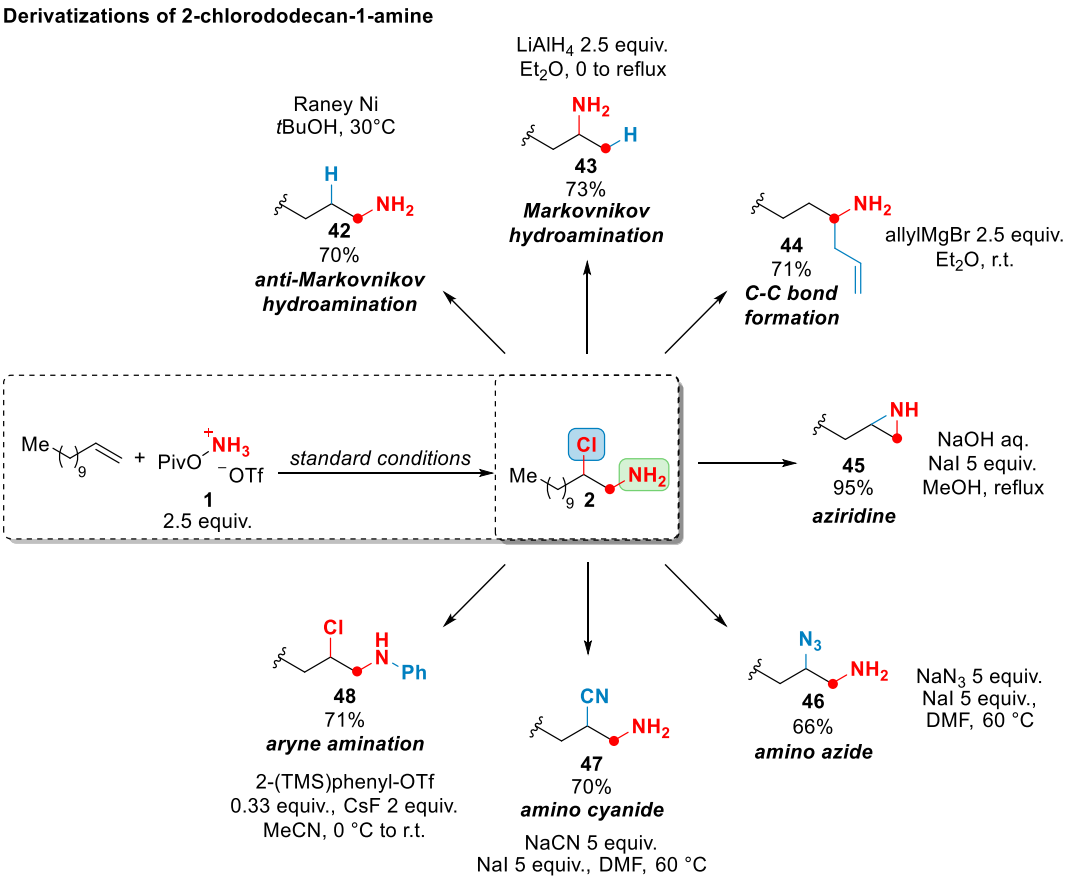

Fig. 3. Synthetic utility of 2-chlorododecan-1-amine. All yields, unless otherwise noted, are isolated yield of the products. Reaction conditions for the derivatizations of 2-chloro-1-amine are specified below the products. DMF, dimethylformamide.

Unprotected 2-chloroalkylamines are rare compounds whose reactivity has not yet been studied extensively. Having a convenient method to access them, we sought to explore their reactivity and synthetic utility (Fig. 3). In particular, it was our goal to address current challenges in amination chemistry through the use of these amphoteric building blocks. The catalytic synthesis of primary amines from terminal olefins has been recognized as one of the top ten challenges in catalysis (*43*). 2-chloroalkylamines can easily be reduced to the corresponding amines (**42**), affording a practical solution to this challenge. Changing the reducing agent and solvent even enables access to the Markovnikov hydroamination product (**43**), a process that probably proceeds through *in situ* generation of an aziridine intermediate followed by reductive ring opening. Common nucleophiles, such as azide (**46**) and cyanide (**47**), led to a practical synthesis of the corresponding products, which are versatile building blocks for diamine and amino acid synthesis, respectively. The corresponding aziridines (**45**) can also be easily accessed upon simple treatment with base, providing

a convenient iron-based alternative to the rhodium method reported by Kürti and Falck. Surprising reactivity was observed with allyl magnesium bromide, as C–C formation occurred at the α-position relative to the amino group, leading to useful unprotected homoallylic amines (**44**). This reaction likely proceeds through initial HCl elimination to form an imine intermediate which can subsequently be attacked by the Grignard reagent.

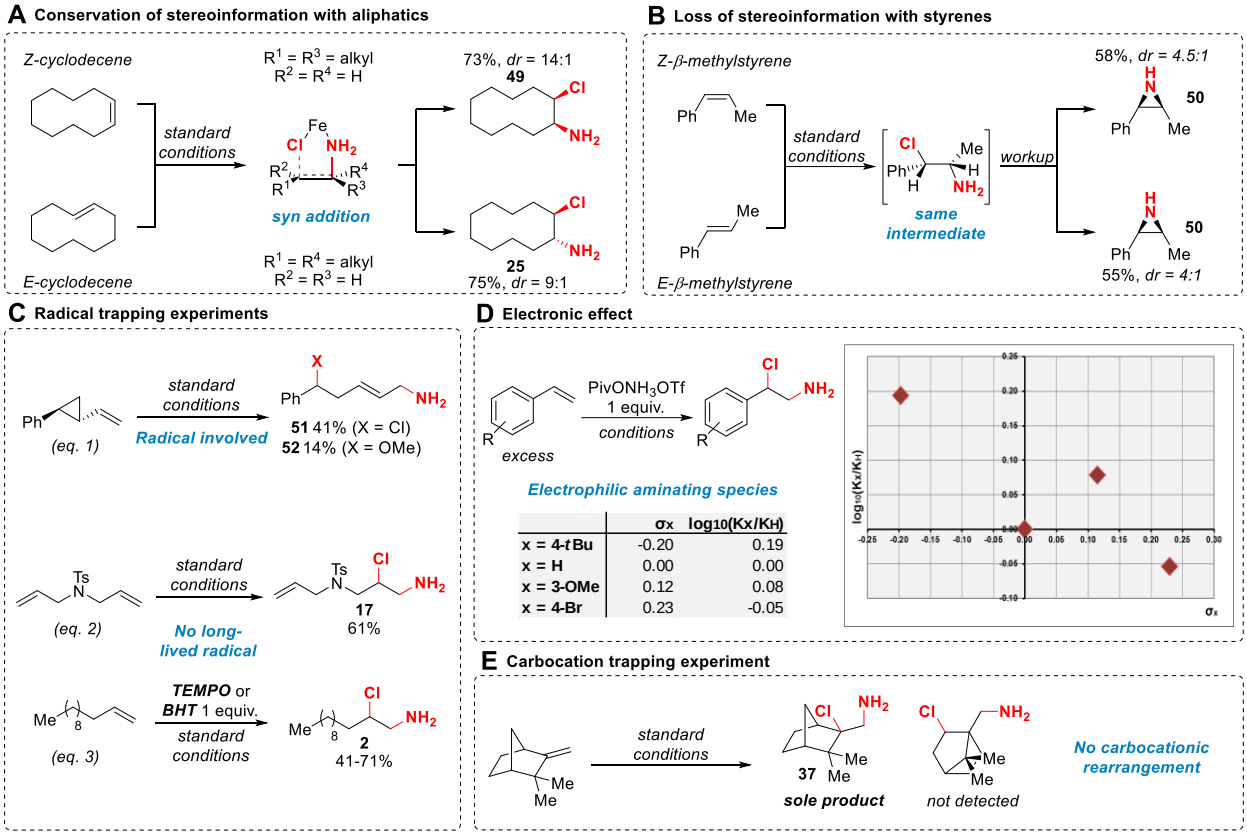

Fig. 4. Preliminary mechanistic experiments. (**A**) Conservation of stereoinformation with cyclodecene substrates indicating a *syn* addition mechanism. (**B**) Loss of stereoinformation with β-Me-styrene substrates showing a stepwise mechanism with this class of substrates. (**C**) Radical experiments proving the intermediacy of a short-lived radical intermediate. (**D**) Preliminary Hammett Study supporting a mechanism involving an electrophilic amination mechanism. (**E**) Lack of backbone rearrangement supporting the absence of carbocationic intermediates.

Preliminary studies were performed to support our initial mechanistic hypothesis (Fig. 1B). The use of *cis* and *trans* cyclodecene led to the isolation of the corresponding products (**49**, **25**) in good yields and, more importantly, with good overall conservation of stereochemistry (Fig. 4A). This result suggests an efficient formal *syn* delivery of the NH_2 and Cl groups. Interestingly, a similar experiment employing both *cis*- and *trans*-β-Me styrene resulted in a

completely different outcome (Fig. 4B). The stereoinformation was completely lost in this case, and both starting materials led to the same stereoisomer of the major product after conversion to the more stable aziridines through stereoinvertive ring-closing (*44*). This divergent outcome between the two classes of substrates is consistent with the proposed model (Fig. 1B), wherein an amine-coordinated iron complex rapidly delivers the chloride from the same face with non-stabilized aliphatic alkenes as substrates, whereas rapid oxidation of the radical intermediate to a stable benzylic cation occurs in styrenes, concomitant with stereochemical randomization.

We next aimed to support experimentally the postulated formation of the radical in the aliphatic alkene reaction. Experiments using one of the fastest radical clocks to detect the intermediacy of short-lived radical species proved the formation of radical intermediates because ring-opening of the cyclopropane could clearly be observed (Fig. 4C, eq. 1). This result, combined with the high stereoretention of the reaction with aliphatic alkenes (Fig. 4A), and the lack of cyclization of another radical clock (Fig. 4C, eq. 2), supports the formation of an extremely short lived carbon-centered radical intermediate. This conclusion was further supported by radical trapping experiments using TEMPO and BHT that did not significantly influence the reactivity (Fig. 4C, eq. 3). Based on those experiments, we believe that the rate constant of the intramolecular chlorine atom transfer is very high, although it cannot exceed the known rate constant of the cyclopropyl radical clock (3×10^{11} s^{-1}) (*45*). A preliminary Hammett study showed a rate increase for electron-rich substrates, a result consistent with a mechanism involving the attack of highly electrophilic aminating species onto the alkene (Fig. 4D). Finally, we performed a simple experiment aiming to trap a possible carbocationic intermediate (Fig. 4E) through a rapid cationic rearrangement. In contrast to previous reports (*15*, *46*), no rearrangement was observed under our reaction conditions, supporting the operation of a distinct mechanistic pathway.

Collectively, these results are best explained by our initially proposed model and support the direct intramolecular trapping of a short lived carbon-centered radical through intramolecular *syn*-chlorine atom transfer from an amine-coordinated iron(III)-Cl complex.

Acknowledgements: We thank Dr. Benjamin Bhawal for critical proofreading of this manuscript and our apprentice, Sophia Begoihn, for the synthesis of some compounds. We also thank Andre Pommerin for the DSC measurements. We kindly thank Prof. Benjamin List for sharing analytical equipment, and the MS-department of the MPI for technical assistance. **Funding:** Generous funding from the Max-Planck-Society, the Max-Planck-Institut für Kohlenforschung, the European Research Commission (grant agreement ShuttleCat 757608), the ETH Zürich and the Fonds der

Chemischen Industrie are acknowledged. **Author contributions:** B. M., L. L and G. P.-C. designed the project. L. L., G. P.-C., T. D. and S. W. performed the experiments and collected the data. All authors analyzed the data and contributed to the writing of the manuscript. L. L. and G. P.-C. contributed equally as first authors. T. D. and S. W. contributed equally as third authors. **Competing interests:** We declare no competing financial interests. **Data and materials availability:** all experimental data are available in the supplemental information. X-ray structures can be accessed free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC-1863481 to CCDC-1863483.

Supplementary Materials:

Materials and methods

Figures S1 to S6

Tables S1 to S4

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NMR spectra

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