Published in final edited form as:

ACS Catal. 2018 June 1; 8(6): 5032–5037. doi:10.1021/acscatal.8b01253.

Iron(II)-Catalyzed Azidotrifluoromethylation of Olefins and N-Heterocycles for Expedient Vicinal Trifluoromethyl Amine Synthesis

Cheng-Liang Zhu[†], Cheng Wang[†], Qi-Xue Qin[†], Sam Yruegas[‡], Caleb D. Martin[‡], and Hao Xu^{*,†}

[†]Department of Chemistry, Georgia State University, 100 Piedmont Avenue SE, Atlanta, Georgia 30303, United States

[‡]Department of Chemistry and Biochemistry, Baylor University, 1 Bear Place, Waco, Texas 76798, United States

Abstract

We report herein an iron-catalyzed azidotrifluoromethylation method for expedient vicinal trifluoromethyl primary-amine synthesis. This method is effective for a broad range of olefins and N-heterocycles, and it facilitates efficient synthesis of a wide variety of vicinal trifluoromethyl primary amines, including those that prove difficult to synthesize with existing approaches. Our preliminary mechanistic studies revealed that the catalyst-promoted azido-group transfer proceeds through a carbo-radical instead of a carbocation species. Characterization of an active iron catalyst through X-ray crystallographic studies suggests that in situ generated, structurally novel iron-azide complexes promote the oxidant activation and selective azido-group transfer.

Graphical Abstract

Keywords

iron catalysis; trifluoromethyl amines; azides; olefins; N-heterocycles

*Corresponding Author: hxu@gsu.edu.

ORCID

Caleb D. Martin: 0000-0001-9681-0160 Hao Xu: 0000-0001-5029-8392

Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b01253.

Experimental procedures, characterization data for all new compounds, and selected NMR spectra (PDF)

INTRODUCTION

Vicinal trifluoromethylated primary amines are valuable building blocks that are often incorporated in pharmaceuticals and biological probes.¹ Although indirect, multistep syntheses have been described,¹ the direct olefin difunctionalization with both a trifluoromethyl and a nitrogen-based group is arguably one of the most straightforward means to afford these high-value chemicals. To address this synthetic challenge, several olefin aminotrifluoromethylation methods have been developed.² Among these methods, Sodeoka reported an intra-molecular method to generate trifluoromethylated *N*-aryl aziridines and pyrrolidines using Togni's Reagent II **2a** (Scheme 1a).^{2a,b} Other existing intermolecular methods are exclusively limited to styrenyl olefins, which afford trifluoromethylated amides and anilines via Ritter-type processes through β -trifluoromethyl carbenium ions.^{2d,e}

Alternatively, olefin azidotrifluoromethylation followed by reduction can afford β -trifluoromethyl primary amines. Liu developed an azidotrifluoromethylation method that is most effective for terminal and cyclic olefins using Togni's Reagent **2b** (Scheme 1b).^{3a} Hartwig reported the efficient iron-catalyzed natural product C–H azidation as well as azido-trifluoromethylation with **2b** (Scheme 1c).^{3b} Other methods through photoredox catalysis for styrenyl olefins, enamides, and enol ethers have been developed; however, moderate yields are observed for aliphatic isolated olefins.^{2d,e,3c}

These existing methods are valuable; however, significant gaps still exist for the development of a general method for vicinal trifluoromethyl primary amine synthesis. First, the synthesis of a variety of medicinally relevant vicinal trifluoromethyl amines has not been fully addressed by the existing olefin amino- and azido-trifluoromethylation methods.¹ These challenging substrates include olefins with labile C–H bonds and the vast majority of N-heterocycles, such as allylic esters and carbamates, indoles, pyrroles, and their derivatives (Scheme 2a). Therefore, a general method has yet to be developed that is effective for a broad range of olefins and N-heterocycles. Next, mechanistic understanding of the oxidant activation and azido-group transfer steps has been limited. In particular, it is ambiguous whether a carbo-radical or a carbocation is involved in the C–N₃ bond-forming step. Furthermore, structural characterization of active catalysts in olefin azidation, especially through X-ray crystallographic analysis, has been under-explored. These insights will likely shed light on the design and discovery of new catalysts for nitrogen-atom-transfer reactions.

Herein, we report an iron-catalyzed azidotrifluoromethylation method for efficient synthesis of a wide variety of vicinal trifluoromethyl primary amines (Scheme 2b). This method is compatible with a broad range of olefins and N-heterocycles, many of which have been difficult substrates via the existing approaches.^{2,3} Compared with our reported iron-catalyzed olefin diazidation,⁴ the mechanistic studies revealed an entirely different oxidant activation mechanism and rate-determining step; therefore, new optimal iron catalysts and ligands have been identified, and enhanced diastereoselectivity for cyclic olefins has been observed. Additionally, crystallographic studies suggest that both the oxidant activation and rapid azido-group transfer steps may proceed through structurally novel iron-azide species that are assembled in situ.

RESULTS AND DISCUSSION

We selected allylbenzene (**1**) as a model substrate for catalyst discovery because **1** is known to undergo facile olefin allylic trifluoromethylation and β -elimination (Table 1).⁵ We observed that the Fe(NTf₂)₂-**L1** complex, an effective catalyst for diastereoselective olefin diazidation,⁴ catalyzed regioselective olefin azidotrifluoromethylation in the presence of both **2a** and TMSN₃, affording **3** in moderate yield (Table 1, entry 1).

We noted that the Fe(OAc)₂-tridentate **L1** complex evidently improved both the conversion and yield (entries 2–3) within 6 h. To our surprise, the Fe(OAc)₂-bidentate **L2** complex catalyzed a rapid reaction which afforded **3** in excellent yield (entry 4, 3 h, 83% yield).⁶ It is worth noting that although the Fe(OAc)₂-tridentate **L1** catalyst promotes a reaction with a similar yield, it is less reactive compared with the Fe(OAc)₂-bidentate **L2** catalyst (entry 2 vs entry 4). Additionally, a structurally simplified Fe(OAc)₂-bidentate **L3** complex also catalyzed the reaction and provided essentially the same efficiency (entry 5 vs entry 4, 3 h, 86% yield). Notably, both the Fe(OAc)₂-**L1** and Fe(OAc)₂-**L3** catalysts promote a less-efficient allylbenzene azidotrifluoromethylation in control experiments when Togni's reagent **2b** was used.⁷ Interestingly, the FeCl₂-**L3** complex proved catalytically active; however, the corresponding β -trifluoromethyl chloride was identified as a side product (entry 6). To the best of our knowledge, no β -elimination product **4** was detected in all of these experiments, presumably due to rapid azido-group transfer (vide infra, Scheme 3).⁷ Moreover, **3** can be readily converted to β -trifluoromethyl aminium salt **5** through a straightforward reduction–protonation sequence (87% yield).

Upon discovery of the new catalyst, we explored a range of olefins to determine the scope and limitation of this method (Table 2). First, we evaluated a variety of olefins with labile allylic C–H bonds that are difficult substrates for the existing olefin azidotrifluoromethylation methods due to facile β -elimination (Table 2, entries 1–5). Allyl silane proved to be an excellent substrate, and no β -elimination product was detected (entry 2). Both allyl acetate and an allyl carbamate are compatible with this method, affording vicinal trifluoromethylated amino alcohol **7** and diamine **8** in excellent yields (entry 3–4). Furthermore, both reactions can be scaled up to gram scale with consistent yields and regioselectivity. Notably, the trifluoromethylated amino alcohol **7** can be applied as a key intermediate for facile synthesis of AAKI kinase inhibitors.^{1b} We also observed that the catalyst was compatible with a silyl dienol, which was converted to a vicinal amino alcohol **9**, exclusively in a 1,4-addition fashion, upon reduction (entry 5).

Subsequently, we evaluated a variety of isolated olefins: Both mono- and 1,1-disubstituted olefins are excellent substrates (entries 6–7). We noted that an aliphatic *trans*-disubstituted olefin could be effectively converted to the corresponding trifluoromethylated carbamate **12** (entry 8). This method can be successfully applied to styrenyl olefins, regardless of electronic character as well as α or β substitution patterns (entries 9–13). Cyclic styrenyl olefins, including indene and dihydronaphthalene,⁸ can be diastereoselectively converted to vicinal trifluoromethylated aminium salts (**19** and **20**) with excellent dr (entries 14–15, dr > 20:1). Interestingly, both an electron-rich enamide and an electron-deficient cinnamate are compatible with this method (entries 16–17). We further observed that the iron catalyst

effectively controlled both the regio- and diastereoselectivity of the addition reaction with 1,3-cyclooctadiene (entry 18, dr > 20:1, 1,4-addition only).⁸ Most notably, cyclooctene, a substrate that was previously difficult to control diastereoselectivity in olefin azido-trifluoromethylation,^{3a} can be converted to a *trans*-trifluoromethylated carbamate **24** as a single diastereomer (entry 19). Moreover, a tertiary allylic alcohol can be directly applied to afford a trifluoromethylated amino alcohol **25** without formation of the competing semipinacol rearrangement product (entry 20).

Trifluoromethylated amino-N-heterocycles are also of interest in medicinal chemistry;¹ however, N-heterocycle amino- or azido-trifluoromethylation has been under-developed, presumably due to the facile elimination and re-aromatization after the trifluoromethylation step using the existing methods. Therefore, we explored this method with indole and pyrrole derivatives (Table 3, entries 1–6). We discovered that the iron catalyst selectively transferred the CF₃ group to the indole 2-position while installing the azido group at the 3-position with excellent dr (entry 1, dr > 20:1). Notably, the 3-methyl substitution neither compromises diastereoselectivity nor diminishes its reactivity (entry 2). The iron catalyst proves sufficiently functional group-tolerant such that both tryptamine carbamate and indole propionic acid are compatible with this method (entries 3–4). The 3-trifluoromethyl-4-amino-pyrrolidine motif has been incorporated into biological probes; however, their known syntheses are lengthy.^{1a} We subsequently evaluated the reactivity of 3,4-dehydro-pyrrolidine, which was converted to the aforementioned target with excellent dr (entry 5, dr > 20:1). Moreover, *N*-Boc-pyrrole is an acceptable substrate, and it can be converted to amino trifluoromethylated 2,3-dihydro-*N*-Boc-pyrrole as a single diastereomer (entry 6, dr > 20:1).

Complex terpenes provide diverse structural motifs with rich stereochemical information; however, complex primary-amine synthesis based upon these readily available natural products has been under-explored. Therefore, we further evaluated this new method with a variety of terpenes (Table 3, entries 7–12). We observed that both (+)-camphene and (+)-3-carene could be selectively functionalized to the corresponding vicinal trifluoromethylated carbamates (**32** and **33**) as a single diastereomer (entries 7–8). Interestingly, two olefinic moieties within (–)-carvone are differentiated, and the azido-group is selectively transferred to the less electron-deficient olefin (entry 9). We also discovered that the labile aldehyde group in (±)-citronellal is compatible with the iron catalyst without detrimental aldehyde oxidation (entry 10). The more electron-rich distal olefin in geranyl acetate is preferentially functionalized in the presence of an allylic acetate moiety (entry 11). To our great surprise, the iron catalyst can selectively 1,2-difunctionalize the exocyclic olefin of (–)- β -pinene, exclusively affording a vicinal trifluoromethylated amine upon reduction (entry 12, **37**, dr > 20:1). Most notably, this reaction can be consistently scaled up to gram scale without detecting the potential β -elimination and rearrangement product **40** (Scheme 3).

The absence of **40** in the iron-catalyzed (–)- β -pinene azido-trifluoromethylation is mechanistically interesting, since the copper-catalyzed method solely affords the rearrangement product (Scheme 3).^{3a} This observation suggests that the rate of azido-group transfer in the iron-catalyzed reaction is rapid such that it outcompetes the rate of reactive intermediate rearrangement. Notably, the potential ring-contraction product **39b**, presumably

through the well-documented rearrangement of a carbocation intermediate generated from the (–)- β -pinene scaffold, was not detected as well.⁹

To gather mechanistic insight about the reactive intermediate involved in the azido-group transfer, we evaluated a fully substituted vinylcyclopropane **41** as a mechanistic probe (Scheme 3).¹⁰ It is known that a cyclopropyl carbanyl radical **42a**, presumably generated through CF₃ radical addition, leads to fragmentation of bond **a** and formation of a benzylic radical species.¹⁰ A cyclopropyl carbanyl cation **42b** will instead rapidly fragment through bond **b** to afford an oxocarbenium ion.¹⁰ Notably, benzylic azide **43** was exclusively observed in the iron-catalyzed azidotrifluoromethylation of **41**, presumably through the intermediacy of a benzylic radical species **42a**. It is possible that SET oxidation of the benzylic radical species **42a** could still occur with the iron catalyst or the Togni reagent II **2a** to afford a carbocation before the C–N₃ bond formation; however, lack of the ring-contraction product **40** in the aforementioned (–)- β -pinene azidotrifluoromethylation suggests that it is less likely. These results suggest that the C–N₃ bond formation proceeds through a carbo-radical instead of a carbocation species.

Next, we compared the reactivity of both *cis*- and *trans*-stilbenes and observed that *trans*-stilbene **45** is more reactive than its *cis*-isomer **44** (Scheme 4).¹¹ Unlike the iron-catalyzed olefin diazidation,⁴ no *cis*–*trans* isomerization was observed during the reaction. This experiment suggests that the C–CF₃ bond forming step is irreversible. Furthermore, we observed that **2a** is inert to either Fe(OAc)₂ catalyst or TMSN₃ (Scheme 4); however, the iron catalyst and TMSN₃ cooperatively promoted rapid decomposition of **2a** to afford *o*-iodobenzoic acid (Scheme 4).¹¹ These results suggest that both Fe(OAc)₂ catalyst and TMSN₃ are necessary to reduce **2a** and that the iron-catalyzed CF₃ radical generation is irreversible.

Based upon the aforementioned mechanistic insights, we suspect that Fe(OAc)₂ may be a precatalyst and it may be activated in situ. We observed that the gray solution of both Fe(OAc)₂–**L1** and Fe(OAc)₂–**L3** complexes turned dark once a superstoichiometric amount of TMSN₃ was introduced. Subsequent ether trituration readily afforded solids **47** and **48**, respectively (eqs 1 and 2).

Interestingly, both **47** and **48** are catalytically active for allylbenzene azidotrifluoromethylation.¹¹ IR analysis revealed strong azido group absorptions shifted to lower energy in comparison to free azide, characteristic of iron-azide complexes.¹²

To obtain further information into the bonding environment about the iron center upon addition of TMSN₃, crystals suitable for an X-ray diffraction study of the complex featuring the tridentate ligand **L1** were obtained at low temperature. The solid-state structure of **47** revealed a novel iron coordination polymer with all iron centers equivalent and generated by

symmetry ($\text{Fe}(\mathbf{L1})(\text{N}_3)_2$)_n (Figure 1). The iron is in distorted octahedral geometry with the rigid tridentate ligand coordinated in a meridional fashion, and the three remaining coordination sites are occupied by three azides with one being terminal and the other two azides *cis* to each other bridging adjacent iron centers to form the coordination polymer.¹²

We further evaluated the reactivity of $\text{Fe}(\mathbf{L1})(\text{N}_3)_2$ (**47**) in allylbenzene azidotrifluoromethylation. Surprisingly, it activates **2a** in the absence of TMSN_3 and affords the desired product **3** with good mass balance (eq 3). In another control experiment, it catalyzes allylbenzene azidotrifluoromethylation in the presence of TMSN_3 and afforded **3** in excellent yield (eq 4). These results suggest that the azido-group transfer may proceed through iron-azide species and TMSN_3 is necessary for catalyst regeneration.

Based upon the collective mechanistic evidence, we propose a mechanistic working hypothesis for the iron-catalyzed olefin azidotrifluoromethylation (Scheme 5). First, the $\text{Fe}(\text{OAc})_2$ -ligand complex can be activated in situ by TMSN_3 and thereby converted to an iron-azide-derived catalyst **A**. Subsequently, **A** may irreversibly reduce Togni's reagent **II** (**2a**) through singleelectron transfer (SET) and thereby generate a CF_3 radical, which is reminiscent of TEMPO Na -promoted radical trifluoromethylation.¹³ The irreversible CF_3 radical addition to an olefin may afford a carbo-radical species **B**, which can be rapidly sequestered by a high-valent iron-azide species through inner-sphere azide-ligand transfer, furnishing the desired product.¹⁴ The iron-azide-derived catalyst **A** can thereby be readily regenerated from its precursor **C** through the TMSN_3 -mediated anion metathesis.

CONCLUSIONS

In conclusion, we have developed a unique iron-catalyzed method for efficient synthesis of vicinal trifluoromethyl primary amines. It is effective for a broad range of olefins and N-heterocycles and readily affords a variety of synthetically valuable trifluoromethyl primary amines that are difficult to prepare with alternative methods. Our mechanistic studies suggest that the in situ generated novel iron-azide complex may facilitate the irreversible oxidant activation and the rapid yet selective azido-group transfer. Our current efforts focus on the mechanistic studies of selective azido-group transfer processes mediated by these novel iron-azide species.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

H.X. is an Alfred P. Sloan Research Fellow. S.Y. is supported by the Welch Foundation (AA-1846) to C.D.M. We thank Professor David Crich for suggesting compound **41** as a probe during our mechanistic studies. This research was supported by the National Institutes of Health (GM110382) and Alfred P. Sloan Foundation (FG-2015-65240).

References

1. For selected references of trifluoromethyl amines in medicinal chemistry, see: Li Q, Wang W, Berst KB, Claiborne A, Hasvold L, Raye KM, Nilius TA, Shen LL, Flamm R, Alder J, Marsh K, Crowell D, Chu DTW, Plattner JJ. Synthesis and Structure-activity Relationships of 2-Pyridones: II. 8-(Fluoro-substituted pyrrolidinyl)-2-Pyridones as Antibacterial Agents. *Bioorg Med Chem Lett*. 1998; 8:1953–1958. [PubMed: 9873465] Vrudahula VM, Senliang P, Rajamani R, Nara SJ, Karatholuvhu MS, Maishal TK, Ditta JL, Dzierba CD, Bronson JJ, Macor JE. Aryl Lactam Kinase Inhibitors. US20160333006 A1. Nov 17.2016
2. For selected references of olefin aminotrifluoromethylation, see: Egami H, Kawamura S, Miyazaki A, Sodeoka M. Trifluoromethylation Reactions for the Synthesis of β -Trifluoromethylamines. *Angew Chem, Int Ed*. 2013; 52:7841–7844. Kawamura S, Egami H, Sodeoka M. Aminotrifluoromethylation of Olefins via Cyclic Amine Formation: Mechanistic Study and Application to Synthesis of Trifluoromethylated Pyrrolidines. *J Am Chem Soc*. 2015; 137:4865–4873. [PubMed: 25798656] Lin JS, Dong XY, Li TT, Jiang NC, Tan B, Liu XY. A Dual-Catalytic Strategy to Direct Asymmetric Radical Aminotrifluoromethylation of Alkenes. *J Am Chem Soc*. 2016; 138:9357–9360. [PubMed: 27414501] Yasu Y, Koike T, Akita M. Intermolecular Aminotrifluoromethylation of Alkenes by Visible-Light-Driven Photoredox Catalysis. *Org Lett*. 2013; 15:2136–2139. [PubMed: 23600821] Dagousset G, Carboni A, Magnier E, Masson G. Photoredox-Induced Three-Component Azido- and Aminotrifluoromethylation of Alkenes. *Org Lett*. 2014; 16:4340–4343. [PubMed: 25102254]
3. For selected references of olefin azidotrifluoromethylation, see: Wang F, Qi X, Liang Z, Chen P, Liu G. Copper-Catalyzed Intermolecular Trifluoromethylazidation of Alkenes: Convenient Access to CF_3 -Containing Alkyl Azides. *Angew Chem, Int Ed*. 2014; 53:1881–1886. Karimov RR, Sharma A, Hartwig JF. Late Stage Azidation of Complex Molecules. *ACS Cent Sci*. 2016; 2:715–724. [PubMed: 27800554] Geng X, Lin F, Wang X, Jiao N. Azidofluoroalkylation of Alkenes with Simple Fluoroalkyl Iodides Enabled by Photoredox Catalysis. *Org Lett*. 2017; 19:4738–4741. and refs 2d and e. A single example of dihydroquinoline azido-trifluoromethylation was reported in ref 3a. [PubMed: 28876952]
4. (a) Yuan YA, Lu DF, Chen YR, Xu H. Iron-Catalyzed Direct Diazidation for a Broad Range of Olefins. *Angew Chem, Int Ed*. 2016; 55:534–538. (b) Zhu HT, Arosio L, Villa R, Nebuloni M, Xu H. Process Safety Assessment of the Iron-Catalyzed Direct Olefin Diazidation for the Expedient Synthesis of Vicinal Primary Diamines. *Org Process Res Dev*. 2017; 21:2068–2072. [PubMed: 29353989]
5. For selected references of olefin allylic trifluoromethylation, see: Parsons AT, Buchwald SL. Copper-Catalyzed Trifluoromethylation of Unactivated Olefins. *Angew Chem, Int Ed*. 2011; 50:9120–9123. Xu J, Fu Y, Luo DF, Jiang YY, Xiao B, Liu ZJ, Gong TJ, Liu L. Copper-Catalyzed Trifluoromethylation of Terminal Alkenes through Allylic C–H Bond Activation. *J Am Chem Soc*. 2011; 133:15300–15303. [PubMed: 21913663] Wang X, Ye Y, Zhang S, Feng J, Xu Y, Zhang Y, Wang J. Copper-Catalyzed $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ Bond Formation Using a Hypervalent Iodine Reagent: An Efficient Allylic Trifluoromethylation. *J Am Chem Soc*. 2011; 133:16410–16413. [PubMed: 21936560]
6. Racemic L2 was used. No significant asymmetric induction was observed (<5% ee) when enantio-pure L2 was applied.
7. A significant amount of allylic trifluoromethylation product was isolated when a copper catalyst was applied in a control experiment. When 2b was used as the oxidant in control experiments, the $\text{Fe}(\text{OAc})_2\text{--L1}$ and $\text{Fe}(\text{OAc})_2\text{--L3}$ catalysts promote the reaction with lower conversion and yield. See SI for details.
8. Regio- and diastereo-selective dihydronaphthalene and cyclic diene azidotrifluoromethylation have not been reported.
9. For selected references of carbocation rearrangements from the β -pinene scaffold, see: Winstein S, Holness NJ. Neighboring Carbon and Hydrogen. XVIII. Solvolysis of the Nopinyl *p*-Bromobenzenesulfonates. *J Am Chem Soc*. 1955; 77:3054–3061. Prakash GKS, Reddy VP, Rasul G, Casanova J, Olah GA. The Search for Persistent Cyclobutylmethyl Cations in Superacidic Media and Observation of the Cyclobutylidicyclopropylmethyl Cation. *J Am Chem Soc*. 1998; 120:13362–13365.

10. Newcomb M, Chestney DL. A Hypersensitive Mechanistic Probe for Distinguishing between Radical and Carbocation Intermediates. *J Am Chem Soc.* 1994; 116:9753–9754.. For a related mechanistic study using the same probe, see: Egami H, Usui Y, Kawamura S, Nagashima S, Sodeoka M. Product Control in Alkene Trifluoromethylation: Hydrotrifluoromethylation, Vinylic Trifluoromethylation, and Iodotrifluoromethylation using Togni Reagent. *Chem - Asian J.* 2015; 10:2190–2199. [PubMed: 25960034]
11. See SI for details. The in situ generated iron-azide complex may activate 2a via SET to generate trifluoromethyl radical, which may initiate decomposition of 2a.
12. For a selected reference of characterized monomeric iron-azide complexes and their IR measurements, see: Grove LE, Hallman JK, Emerson JP, Halfen JA, Brunold TC. Synthesis, X-Ray Crystallographic Characterization, and Electronic Structure Studies of a Di-Azide Iron(III) Complex: Implications for the Azide Adducts of Iron(III) Superoxide Dismutase. *Inorg Chem.* 2008; 47:5762–5774. [PubMed: 18533647]
13. Li Y, Studer A. Transition-Metal-Free Trifluoromethyl-oxylations of Alkenes. *Angew Chem, Int Ed.* 2012; 51:8221–8224.. See also: Zhang B, Mück-Lichtenfeld C, Daniliuc CG, Studer A. 6-Trifluoromethyl-Phenanthridines through Radical Trifluoromethylation of Isonitriles. *Angew Chem, Int Ed.* 2013; 52:10792–10795. Kong W, Casimiro M, Fuentes N, Merino E, Nevado C. Metal-Free Aryltrifluoromethylation of Activated Alkenes. *Angew Chem, Int Ed.* 2013; 52:13086–13090.
14. For a seminal study of metal-catalyzed radical oxidation, see: Kharasch MS, Sosnovsky G. The Reactions of *t*-Butyl Perbenzoate and Olefins-A Stereospecific Reaction. *J Am Chem Soc.* 1958; 80:756–756.

Figure 1.
X-ray crystallographic analysis of a catalytic active polymeric iron-azide complex **47**.

Scheme 1.

Selected Existing Olefin Amino- and Azidotrifluoromethylation Methods

Scheme 2.

(a) Biological Probes as Challenging Targets for the Existing Olefin Azidotrifluoromethylation Methods and (b) the Iron-Catalyzed Azidotrifluoromethylation of Olefins and N-Heterocycles

Scheme 3. Iron-Catalyzed Azidotrifluoromethylation of $(-)\text{-}\beta\text{-Pinene}$ and a Fully Substituted Vinylcyclopropane

$\text{Fe}(\text{OAc})_2\text{-L3}$ (15 mol %), **2a** (1.2 equiv), TMSN_3 (1.5 equiv), $\text{CH}_2\text{Cl}_2/\text{MeCN}$, 0°C , 2 h.

Scheme 4. Control Experiments to Probe for the Rate-Limiting Step

^a $\text{Fe}(\text{OAc})_2\text{-L3}$ (15 mol %), **2a** (1.5 equiv), TMSN_3 (2.0 equiv), $\text{CH}_2\text{Cl}_2/\text{MeCN}$, 22 °C, 3 h.

^b $\text{Fe}(\text{OAc})_2\text{-L3}$ (15 mol %), $\text{CH}_2\text{Cl}_2/\text{MeCN}$, 22 °C, 6 h. ^c TMSN_3 (2.0 equiv), $\text{CH}_2\text{Cl}_2/\text{MeCN}$, 22 °C, 6 h. ^d $\text{Fe}(\text{OAc})_2\text{-L3}$ (15 mol %), TMSN_3 (1.5 equiv), $\text{CH}_2\text{Cl}_2/\text{MeCN}$, 22 °C, 6 h.

Scheme 5.
Mechanistic Working Hypothesis of the Iron-Catalyzed Olefin Azidotrifluoromethylation

Catalyst Discovery for Allylbenzene Azidotrifluoromethylation

Table 1

entry ^a	Fe(X) ₂	ligand	reaction time	conversion ^b	yield (3) ^c
1	Fe(NTf ₂) ₂	L1	6.0 h	71%	64%
2	Fe(OAc) ₂	L1	3.0 h	56%	47%
3	Fe(OAc) ₂	L1	6.0 h	90%	81%
4	Fe(OAc) ₂	L2	3.0 h	>95%	83%
5	Fe(OAc) ₂	L3	3.0 h	>95%	86%
6	FeCl ₂	L3	3.0 h	92%	68%

^aReactions were carried out under N₂ with **2a** (1.2 equiv) and subsequently quenched with saturated Na₂CO₃ solution. Reduction conditions: Pd/C, H₂, MeOH, 22 °C, 2 h, then TsOH·H₂O.

^bConversion was measured by ¹H NMR analysis.

^cIsolated yield. Standard safety precautions about handling TMSN₃ have been taken; see SI for details.

Table 2

Iron-Catalyzed Olefin Azidotrifluoromethylation for Vicinal Trifluoromethyl Primary Amine Synthesis

^a Isolated yield for olefin azidotrifluoromethylation.^b Isolated yield for reduction/derivatization.^c PPh_3 (1.2 equiv), H_2O (10 equiv), then Boc_2O (1.2 equiv).^d $\text{Fe}(\text{OAc})_2\text{-L2}$ (15 mol %).^e PMe_3 (1.5 equiv), H_2O (10 equiv), then Boc_2O (1.2 equiv).

Table 3

Iron-Catalyzed N-Heterocycle and Terpene Azidotrifluoromethylation for Complex Vicinal Trifluoromethyl Primary Amine Synthesis

$\text{N-heterocycles or terpenes} + \text{2a} + \text{TMSN}_3 \xrightarrow[\text{b) reduction protection}]{\text{a) Fe}^{\text{II}} \text{ catalyst ligand}}$			vicinal aminotrifluoromethylated N-heterocycles or terpenes
	1.5 equiv	2.0 equiv	
1	2	3	
26	27	28	
72%, <i>dr</i> >20:1 ^{a,c}	83%, <i>dr</i> >20:1 ^{a,c}	74%, <i>dr</i> >20:1 ^{a,c}	
86% ^{b,d}	91% ^{b,d}	63% ^{b,e}	
4	5	6	
29	30	31	
73%, <i>dr</i> >20:1 ^{a,c}	53%, <i>dr</i> >20:1 ^{a,c}	51%, <i>dr</i> >20:1	
	88% ^{b,d}	over two steps ^{b,c,e}	
7	8	9	
32	33	34	
73%, <i>dr</i> >20:1 ^{a,f}	78%, <i>dr</i> >20:1 ^{a,f}	86%, <i>dr</i> : 1:1 ^{a,f}	
76% ^{b,e}	85% ^{b,d}	92% ^{b,h}	
10	11	12	
35	36	37	
70%, <i>dr</i> : 1:1 ^{a,f}	63% ^{a,c}	82%, <i>dr</i> >20:1 ^{a,f}	
93% ^{b,g}	81% ^{b,h}	87% ^{b,d}	

^a Isolated yield for olefin azidotrifluoromethylation.

^b Isolated yield for reduction/derivatization.

^c Fe(OAc)₂-L2 (10–15 mol %).

d Pd/C (10 wt %), H₂, then Boc₂O (1.2 equiv) or Et₃N (2.0 equiv), CbzCl (1.5 equiv).

e PMe₃ (1.5 equiv), H₂O (10 equiv), then Boc₂O (1.2 equiv) or Et₃N (2.0 equiv), CbzCl (1.5 equiv).

f Fe(OAc)₂–**L3** (10–15 mol %).

g LAH (2.0 equiv).

h PPh₃ (1.2 equiv) or PMe₃ (1.5 equiv), H₂O (10 equiv).