EDGE ARTICLE

Check for updates

Iron-catalyzed remote functionalization of inert C(sp³)−H bonds of alkenes *via* 1,*n*-hydrogen-atom-transfer by C-centered radical relay†

Kang-Jie Bian,‡ Yan Li,‡ Kai-Fan Zhang, Yan He, Tian-Rui Wu, Cheng-Yu Wang and Xi-Sheng Wang [ID] *

As an alternative approach to traditional C−H activation that often involved harsh conditions, and vicinal or primary C−H functionalization, radical relay offers a solution to these long-held problems. Enabled by 1,*n* (*n* = 5, 6)-hydrogen atom transfer (HAT), we use a most prevalent moiety, alkene, as the precursor to an sp³ C-centered radical to promote selective cleavage of inert C(sp³)−H bonds for the generation of azidotrifluoromethylated molecules. Mild conditions, broad scope and excellent regioselective control (>20 : 1) are observed in the reactions. Deuterium labelling studies disclose the kinetic characteristics of the transformations and verify a direct 1,*n*-HAT pathway. The key to this C-centered radical relay is that iron plays a dual role as a radical initiator and terminator to incorporate the azide functionality through radical oxidation *via* azido−ligand−transfer. The methods and the later derivatization promise expeditious synthesis of CF₃-containing organic azides, γ-lactam and triazoles that are widely used in designing new fluorescent tags and functional materials.

Introduction

The facile construction of complex functional molecules in a straightforward, efficient and practical manner from easily available materials is a major target and challenge in organic synthesis. Transition-metal-catalyzed C–H functionalization is a highly step- and atom-economic tactic to synthesise target molecules with structural complexity and diversity and it has been developed as one of the most ideal methods meeting the requirements of synthetic chemistry.[1] Indeed, the direct functionalization of C–H bonds is emerging as a powerful strategy for retrosynthetic disconnection in the total synthesis of complex molecules, especially for the omnipresent inert C(sp³)–H bonds in basic chemical raw materials.[2] As an alternative approach to traditional C(sp³)–H activation, where metallacycles are usually formed in five-, six-membered rings and restricted mostly for vicinal functionalization of primary C(sp³)–H bonds, hydrogen-atom-transfer (HAT) through a radical pathway has been used as an efficient tool to activate the remote C(sp³)–H bond selectively.[3] Of note is that, as the target inert C(sp³)–H bond is almost impossible to distinguish from ubiquitous C–H bonds on the alkyl chain, 1,*n* (normally 1,5)-

Hefei National Laboratory for Physical Sciences at the Microscale, Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, China. E-mail: xswang77@ustc.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc03987j

‡ These authors contributed equally to this work.

hydrogen-atom-transfer (HAT) offers a reliable solution for selective cleavage of remote C(sp³)–H bonds in a highly chemo- and site-selective fashion. In addition, the radical relay strategy offers a complementary path to direct functionalization of steric-hindered tertiary C(sp³)–H bonds, which still remains a significant challenge in traditional transition-metal-catalyzed C–H activation reactions.

Very recently, a 'directing-group strategy'[3g] has been introduced through a 1,5-HAT process for direct functionalization of remote C(sp³)–H bonds on alkyl chains. Actually, in retrospect, this type of 'directed-functionalization' can be traced back to 1883. The pioneering work, the Hofmann–Löffler–Freytag (HLF)[4] reaction, has been well documented as a highly efficient and site-selective strategy for remote C(sp³)–H amination, where a pre-decorated *N*-haloamine was required to serve as the precursor to a N-centered radical.

Furthermore, heteroatom-containing groups, such as amides, amines and alcohols, have been widely used as 'directing-groups' to generate the heteroatom-centered radical to initiate the radical relay process due to their intrinsic high reactivity, in which the directing group could be 'recovered' by abstraction of the hydrogen atom from C(sp³)–H bonds. Reasonably, it could be inferred that the carbon radical, likewise, should offer an alternative solution to initiate the 1,*n*-HAT process and promote *in situ* generation of more stable carbon radicals on the alkyl chain for diverse functionalization. Compared with the highly reactive heteroatom-centered radical that can easily undergo hydrogen abstraction, 1,*n*-HAT initiated by the C-centered radical was more difficult with

regard to bond dissociation energies (BDEs)[5] and the HAT rate constant,[6] which led to a weaker driving force for remote functionalization. Actually, to efficiently produce a carbon radical for promotion of following radical relay,[7] one of the most facile and direct methods is through the radical addition to unsaturated C=C bonds, which is also a major method that is known for enhancing molecular complexity in a single step.[8] Using this strategy, several pioneering examples were reported on copper-catalyzed[9] or visible-light-mediated[10] 1,6-difunctionalizations of alkenes recently; however, among these studies, remote functionalization can only be achieved on relatively active C(sp³)–H bonds, requiring an adjacent heteroatom functionality such as a nitrogen or oxygen atom,[9b,d] and carbonyl group,[9c] or on benzylic C–H bonds abutting electron-donating, neutral or weakly-withdrawing arenes.[10] It was proposed that the carbocation was likely to be involved in the catalytic cycle,[9c,10a] where the *in situ* generated carbon radical underwent oxidation through single electron transfer (SET) leading to the corresponding carbocation and then was quenched by nucleophiles (Fig. 1a). In contrast, we envisioned that by using metal-catalyzed radical oxidation,[11] the rapid capture of the carbon radical *via* a ligand-transfer process could offer a solution to the long-held unresolved issue of remote functionalization of *inert/unactivated*[12] C(sp³)–H bonds (Fig. 1b).

Herein, we described the first example of iron-catalyzed remote azidation of an inert C–H bond through radical relay using an sp³ C-centered radical, in which a selective cleavage of the remote C(sp³)–H bond took place, enabled by a direct 1,n-HAT process, furnishing 1,6- and 1,7-azidotrifluoromethylated molecules. The key to success is the radical oxidation of the *in situ* generated carbon radical by iron^III–azide species.[13] This azidotrifluoromethylation was achieved in an iron-catalyzed system, demonstrating high catalytic reactivity, mild conditions, and excellent regioselective control (mostly >20 : 1). The deuterium labeling reactions, for the first time indicate that an entropically less favored 1,6-HAT[3i,14] follows a direct C(sp³)–H bond cleavage pathway.
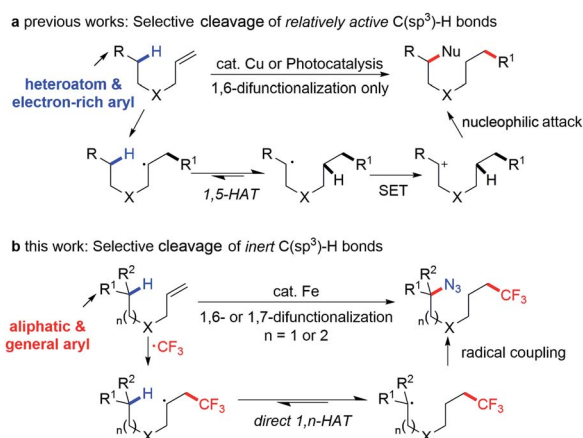

Fig. 1 Remote difunctionalization of alkenes enabled by the 1,n-HAT strategy.

Results and discussion

Iron is widely known as an efficient catalyst for diverse organic transformations due to its low price, non-toxicity and environmentally benign character. Our study commenced with diethyl 2-allyl-2-isobutylmalonate **S1** as the pilot substrate, Togni-II agent as the trifluoroalkylating reagent and TMSN₃ as the azide source in the presence of a catalytic amount of iron salts (entries 1–21, Table 1). To our delight, the desired remote difunctionalized product **1** was obtained in 75% of yield when Fe(acac)₃ was used as the catalyst and **L1** as the ligand (entry 1, Table 1).

A number of phenanthroline and bipyridine ligands were next examined carefully (entries 1–6, Table 1). Even though the reaction yields were slightly improved, the regioselective control

Table 1 Optimization of reaction conditions[a]

Entry	Cat.	Ligand	Solvent	Yield (%)
1	Fe(acac)₃	**L1**	DCM	75
2	Fe(acac)₃	**L2**	DCM	68
3	Fe(acac)₃	**L3**	DCM	79
4	Fe(acac)₃	**L4**	DCM	71
5	Fe(acac)₃	**L5**	DCM	72
6	Fe(acac)₃	**L6**	DCM	70
7	Fe(acac)₃	—	DCM	84 (82)
8[b]	Fe(acac)₃	—	DCM	73
9[c]	Fe(acac)₃	—	DCM	71
10	Fe(acac)₃	—	DCE	82
11	Fe(acac)₃	—	MeCN	73
12	Fe(acac)₃	—	Toluene	55
13	Fe(acac)₃	—	MeOH	Trace
14	Fe(acac)₃	—	DMA	57
15	Fe(acac)₃	—	1,4-Dioxane	59
16	Fe(OTf)₂	—	DCM	18
17	Fe₂(SO₄)₃	—	DCM	57
18	Fe(acac)₂	—	DCM	55
19	Fe(OAc)₂	—	DCM	50
20	FeCl₂	—	DCM	42
21	FeF₂	—	DCM	72
22	—	—	DCM	0
23[d]	CuI	—	DCE	45
24[e]	CuTc	—	DCM/1,4-dioxane	30

[a] Reaction condition: **S1** (0.1 mmol), TMSN₃ (0.3 mmol), Togni-II (0.125 mmol), catalyst (10 mol%), solvent (1.0 mL), 60 °C, N₂, 12 h. ¹H NMR yield using CH₂Br₂ as the internal standard. Isolated yield in parentheses. [b] 40 °C. [c] 60 °C. [d] Liu's condition (ref. 9c). The ratio of 1,6- and 1,2-azidotrifluoromethylation was 4.5 : 1. [e] 1,6 : 1,2 = 5 : 1.

(1,6- *vs.* 1,2-) under these ligand-addition conditions was lacking. Surprisingly, the removal of the ligand from the reaction system could affect the reactivity of the metal center furnishing the desired product **2a** in 82% of isolated yield (in parentheses) with regioselectivity up to 139 : 1 (determined by ^{19}F NMR, entry

7, Table 1). While increasing or decreasing the reaction temperature would reduce almost 10% of the yield (entries 8 and 9, Table 1), the investigation of the solvent effect indicated that the halogenated solvent (entry 10, Table 1) could offer comparable yield, but protonic solvent was not suitable in this

Table 2 Scope of iron-catalyzed 1,6-azidotrifluoromethylation

Reaction conditions (scheme): R$_1$R$_2$CH–X–allyl (S1-45), Fe(acac)$_3$ (10 mol%), Togni-II (1.25 equiv), TMSN$_3$ (3 equiv), DCM, N$_2$, 50 °C, 12h → product with N$_3$ and CF$_3$ (1-45).

aliphatic

1, 82% (30%)[a]; 2, 81%; 3, 78%; 4, 74%; 5, 74%[b]; 6, 72%[b]; 7, 56%[b]; 8, 69%[b]; 9, 80%[b]; 10, 75%[b]; 11, 49%[b]; 12, 58%[b]

aryl-adjacent

13, 85%; 14, 87%; 15, 72%; 16, 72%; 17, 82%; 18, 73%; 19, 69%; 20, 71%; 21, 59% (30%)[a]; 22, 72% (24%)[a]; 23, 67% (28%)[a]; 24, 62% (12%)[a]; 25, 68%; 26, 70%; 27, 65%; 28, 64%; 29, 70%; 30, 54%; 31, 52%; 32, 73%; 33, 65% (32%)[a]; 34, 78%; 35, 59%; 36, 73%; 37, 65% (8%)[a]; 38, 70%; 39, 65% (1.1:1)[c]; 40, 57%[d]; 41, 61%

heteroatom-adjacent

42, 68%; 43, 54%

1,7-azidotrifluoromethylation

44, 59%; 45, 54%; 46, 52%; 47, 61%

Reaction conditions: substrate (0.2 mmol), TMSN$_3$ (3 equiv.), Togni-II (1.25 equiv.), Fe(acac)$_3$ (10 mol%), DCM (2.0 mL), N$_2$, 50 °C, 12 h. Isolated yields. [a] With CuTc (10 mol%), DCM/1,4-dioxane (1 : 1) (2.0 mL), N$_2$, 30 °C, 12 h. [b] 10 mol% of FeF$_2$ was used. [c] 1,6- : 1,2- = 1.1 : 1. [d] 1,4-Dioxane was used as solvent.

reaction (entry 13, Table 1). Next, a careful screening of iron salts was then carried out. Except for the most lewis-acidic Fe(OTf)$_2$ (entry 16), other Fe(II) or Fe(III) catalysts could also furnish **1** in moderate to good yield (entries 17–21, Table 1), but the best result was still for Fe(acac)$_3$. Finally, control experiments indicated that the presence of the iron catalyst was indispensable (entry 22).

It should be noted that not only was the photocatalytic system not capable of activating remote *inert* C–H bonds,[10a] but also only moderate yield of the difunctionalized product (with poor site-selectivity) could be obtained by the replacement of the iron catalyst with a copper catalyst (entries 23 and 24, Table 1) (for more details, see the ESI†).

With the optimized conditions in hand, we next explored the substrate scope of this protocol for azidotrifluoromethylation. As shown in Table 2, the remote azidation of the inert C(sp^3)–H site on the aliphatic chains was achieved smoothly, giving corresponding products in moderate to excellent yields (**1–12**). Of note is that, we also listed the yield (in parentheses) of the representative products using the optimal copper-catalyzed system to show the distinct contrast in efficiency between the two systems. Firstly, functionalization on the acyclic chain including the gem-dimethyl (**1**) and the elongated chains (**2–4**) was successful with high regioselective control (>20 : 1). Cyclic substrates were tested next and the products **5–11** were afforded in moderate to good yields. Interestingly, when using Fe(acac)$_3$ as the catalyst, it was found that a significant amount of 1,2-difunctionlizational byproducts was generated (indicated by ^{19}F NMR) and thus circumscribed the site-selectivity of this transformation; while using FeF$_2$ as the catalyst, the remote azidated products were obtained in almost one isomer (regioselectivity > 20 : 1). In these tests, the functionalization of the bulkier tertiary C(sp^3)–H such as tetrahydropyran (**5**), and N-tethered substrates such as N-Ts (**6**) and N-Boc (**7**) was also compatible with the iron-catalyzed system. Moreover, we then synthesized a series of cycloalkyl substrates and to our excitement, using FeF$_2$, the functionalization at this remote C(sp^3)–H site on four-membered rings to seven-membered rings (**8–10**) proceeded very well (69–80%) to give the corresponding 1,6-azidotrifluoromethylated products. Also, we examined the feasibility of this transformation at a more sterically congested site, where the remote functionalization could be achieved on the tricyclic ring and the tertiary azides (**11**) were furnished in moderate yield. Remarkably, we turned our attention to the more challenging aspect of this reaction-the hydrogen abstraction at the less reactive secondary C(sp^3)–H sites. Of note is that there was almost no energy difference between the initiating carbon radical and the *in situ* generated secondary carbon radical and this interesting case (**12**) gave the corresponding product in 58% of yield. Another type of substrate that is equally difficult to apply, in comparison to the remote functionalization of C(sp^3)–H adjacent to the hetero-atom containing functionality,[9b-d] is the remote functionalization of the benzylic C(sp^3)–H site. Even though there were pioneer reports on the 1,6-difunctionalization on this type of unactivated alkenes, the substrate scope was largely confined to aryl rings bearing electron-donating (OMe and Me) and weak electron-withdrawing groups (halides) in

previous systems.[10] Satisfyingly, when using this iron-catalyzed system, a number of alkenes bearing a range of *para-*, *meta-*, and *ortho-*substituted aryl rings were smoothly azidotrifluoromethylized and gave the corresponding products in moderate to excellent yields (52–87%). Meanwhile, both electron-donating groups such as methyl (**14**, **25**, and **28**), phenyl (**16**), and methoxy (**17**, **26**, and **29**), and weak electron-withdrawing groups such as fluoro (**18**, and **30**), chloro (**19**), and bromo (**20**, **27**, and **31**) can all be tolerated which enabled further synthetic elaboration of the products *via* transition-metal-catalyzed cross-coupling reactions. Of note is that, the previously problematic alkenes bearing strong electron-withdrawing groups such as trifluoromethyl (**21**), esters (**22**), cyano (**23**), and nitro (**24**) could also be compatible with our standard conditions. The protocol was also effective for alkenes bearing di-substituted aryl rings including di-trifluoromethylated (**33**) and di-cholorinated (**34**) alkenes. Furthermore, alkenes bearing fused-/hetero-arenes such as 2-naphthalene (**35**), 2*H*-benzofuran (**32**), thiophene (**36**), and pyridine (**37**) were also well difunctionalized under the standard conditions. Substrates with different substituents on the aliphatic chain (**38–41**) were also studied and accommodated in the reaction including the previously reported problematic N-Ts tethered alkenes,[10a] albeit in relatively lower yields (**40**). Another challenging substrate 1-allyl-2-ethylbenzene was tested and obtained in synthetically useful yield (**41**). Besides C–H bonds on aliphatic chains and at the benzylic site, the protocol also worked well for azidation of C(sp^3)–H abutting a heteroatom (N or O). **42** and **43** could be afforded with high regioselective control in 68% and 54% of yield, respectively.

Compared with 1,5-HAT, 1,6-HAT is less reported due to multiple factors including the rigid structure of intermediates that precludes the formation of six-membered rings.[3i,14] To our great delight, not only remote 1,7-difunctionalization could be achieved on alkenes bearing aryl rings (**45–47**), remote functionalization at the unactivated C–H site on the aliphatic alkene (**44**) can also be smoothly realized with high regioselective control. Even though 1,6-HAT was often considered to be entropy less-favored compared with other competitive side reactions, the facile transformation under this system can furnish the products in synthetically useful yields.
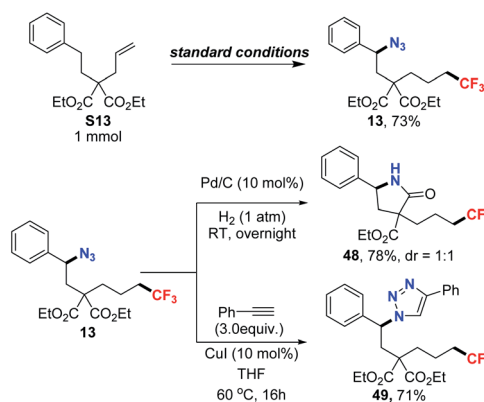
**Scheme 1** Scale-up reaction and derivative studies.

To demonstrate the synthetic potential of these transformations, scale-up reactions and further derivatization studies were then carried out. As depicted in Scheme 1, the scale-up reaction was performed affording the desired product in 73% of yield. Accordingly, the reduction of the azide group was complete under 1 atm H_2 and the reduced product swiftly underwent an intramolecular cyclization, giving the γ-lactam **48** in 78% of yield. Furthermore, Huisgen cyclization was next tested. With the addition of phenylacetylene, 71% yield of cycloaddition product **49** was obtained from the azidotrifluoromethylated product.

To gain some insights into the mechanism of the transformations, elementary mechanistic studies were then carried out. Firstly, the subjection of some known radical scavengers, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and butylated hydroxytoluene (BHT), to the standard conditions afforded no desired product **50** where alkene could be fully recovered. The corresponding coupling (TEMPO-CF_3) could be detected by ^{19}F NMR analysis with 82% yield (eqn (1), Scheme 2). Moreover, a radical clock experiment using alkenyl cyclopropane was conducted, affording the cyclization product **51** in 52% yield (eqn (2), Scheme 2). These radical-trapping experiments confirmed that a free CF_3 radical was generated to initiate the radical relay in the catalytic cycle.

Next, a series of deuterium labeling studies[15] were performed to reveal the kinetic characteristics of the reaction and whether 1,n-HAT undergoes a direct or two-step pathway.

First of all, deuterium-transferred product **13-d$_2$** and 1,2-difunctionalized product **13′-d$_2$** were obtained in the yields of 47% and 26%, respectively (1.8 : 1) (Scheme 3a), which correlated with the direct 1,5-HAT process. For the generation of **13′-d$_2$**, more difficulty was observed in C–D bond cleavage than than in C–H bond cleavage, which resulted in the generation of the competitive 1,2-difunctionalized product. Secondly, the intramolecular and intermolecular kinetic isotope effect (KIE) was then investigated. In the intramolecular competition reaction, **S13-d** yielded a KIE value of 2.6 (Scheme 3b). The observation of the kinetic isotope effect doesn't indicate that C–H cleavage occurs during RDS but demonstrates irreversibility of C–H cleavage *via* the 1,5-HAT process. In the intermolecular competition reactions, one-pot experiments and parallel experiments gave KIE values of 1.3 and 1.27 respectively (for more details, see the ESI†). Collectively, these results demonstrated that the C–H cleavage through HAT is not reversible (primary KIE in intramolecular experiments) and this step is not
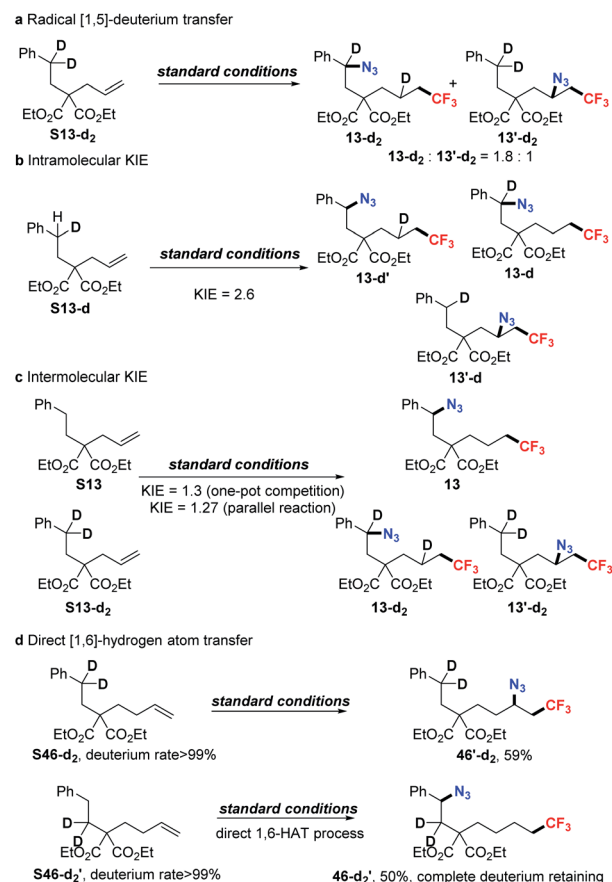

Scheme 3 Deuterium labelling experiments.

the rate determining step (no primary KIE in intermolecular experiments, Scheme 3c).[10a]

To understand the process of 1,7-difunctionalization, in which two possible pathways including direct 1,6-HAT or 1,5-HAT followed by subsequent 1,2-HAT were both likely to be involved, two more deuterium-labeled substrates were designed and studied under standard conditions. Interestingly, benzylic dideuterium-substituted alkene **S46-d$_2$** afforded 1,2-difunctionalized product **46-d$_2$** alone, possibly due to the united effects of more difficult C–D cleavage and less favored 1,6-HAT. Alternatively, we designed another β-dideuterium-labeled (in regard to arene) analogue **S46-d$_2$′**. Supposedly, if the reaction underwent a prior 1,5-HAT followed by 1,2-HAT, the deuterium would shift to the benzylic position; in contrast, no deuterium shifting would be observed through a direct 1,6-HAT process. To our great satisfaction, the desired product **46-d$_2$** was obtained in 50% yield with complete deuterium retention (Scheme 3d). These results suggested that the direct 1,6-HAT process is more feasible for 1,7-difunctionalization.

Based upon the collective mechanistic evidence and previous reports,[11,13,16] a possible mechanistic cycle was suggested, as shown in Fig. 2. The CF_3 radical, generated from the Togni reagent through single electron transfer (SET) between Togni-II and an active Fe catalyst, is captured by alkene to generate a secondary carbon radical B, followed by the direct 1,n-HAT process affording the tertiary/secondary radical C *in situ*.
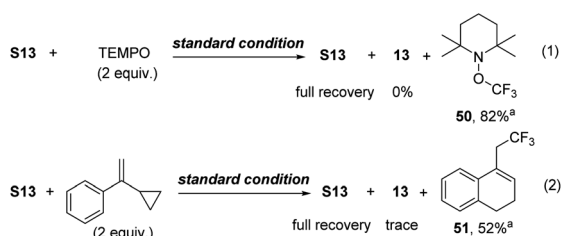
Scheme 2 Elementary mechanistic studies. [a]Using PhCF$_3$ as the internal standard.
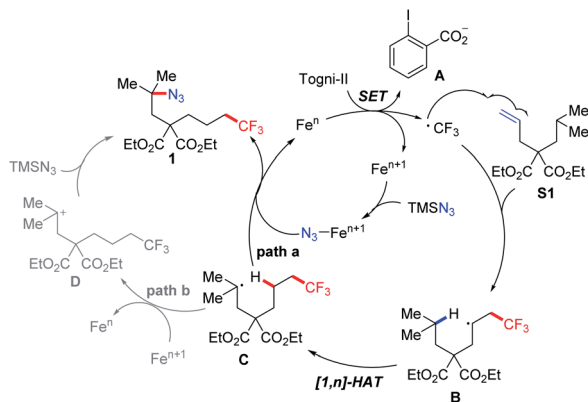
Fig. 2 Possible reaction pathway.

Meanwhile, the higher-valent iron–azide ($Fe^{III}–N_3$) species will swiftly sequester the intermediate C to give the 1,6- (or 1,7-) difunctionalized product **1** *via* azido–ligand-transfer, with concurrent regeneration of the low-valent iron catalyst (path a). Alternatively, we speculated whether the tertiary/secondary carbocation is involved in the reaction, which would disclose a totally different reaction pathway (nucleophilic substitution instead of radical oxidation) (path b).

First of all, the suspected coupling between acid anion A and the tertiary cation D was not detected.[9a] Meanwhile, as has been shown in Table 2, **12** can be afforded without the rearrangement byproduct, which otherwise would be often obtained if the carbocation is generated adjacent to the *tert*-butyl group. These collective results made us inclined towards path a.

Conclusions

In summary, we have developed the first example of iron-catalyzed remote azidation of *inert* $C(sp^3)$–H bonds by sp^3 C-centered radical relay; remote 1,6- and 1,7-azidotrifluoromethylation of alkenes were successfully achieved. This method demonstrates high catalytic reactivity, mild conditions, excellent functional group tolerance and great regioselectivity. The key to the transformation is that iron plays the dual role of a radical initiator to promote the generation of $CF_3^{\cdot}$ and a terminator where iron[III]–azide can oxidize the *in situ* generated remote carbon radical and incorporate the azide functionality *via* azido–ligand-transfer. Deuterium studies revealed the direct 1,n- (n = 5, 6) HAT process. Further investigation of functionalization on fully linear chains and utilization of this strategy to construct potentially bioactive molecules is still underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 (*a*) R. Giri, B. F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (*b*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*c*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*d*) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362; (*e*) B. Liu, F. Hu and B.-F. Shi, *ACS Catal.*, 2015, **5**, 186; (*f*) Y.-F. Liang and N. Jiao, *Acc. Chem. Res.*, 2017, **50**, 1640; (*g*) T. Gensch, M. J. James, T. Dalton and F. Glorius, *Angew. Chem., Int. Ed.*, 2018, **57**, 2296.

2 (*a*) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; (*b*) J. F. Hartwig and M. A. Larsen, *ACS Cent. Sci.*, 2016, **2**, 281; (*c*) X. Huang and J. T. Groves, *ACS Catal.*, 2016, **6**, 751; (*d*) H. M. L. Davies and D. Morton, *ACS Cent. Sci.*, 2017, **3**, 936; (*e*) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754.

3 For reviews on remote C–H functionalization: (*a*) J. Robertson, J. Pillai and R. K. Lush, *Chem. Soc. Rev.*, 2001, **30**, 94; (*b*) Ž. Čeković, *Tetrahedron*, 2003, **59**, 8073; (*c*) S. Z. Zard, *Chem. Soc. Rev.*, 2008, **37**, 1603; (*d*) J. L. Jeffrey and R. Sarpong, *Chem. Sci.*, 2013, **4**, 4092; (*e*) S. Chiba and H. Chen, *Org. Biomol. Chem.*, 2014, **12**, 4051; (*f*) J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Chem. Soc. Rev.*, 2016, **45**, 2044; (*g*) J. C. K. Chu and T. Rovis, *Angew. Chem., Int. Ed.*, 2018, **57**, 62; (*h*) L. M. Stateman, K. M. Nakafuku and D. A. Nagib, *Synthesis*, 2018, **50**, 1569; (*i*) M. A. Short, J. M. Blackburn and J. L. Roizen, *Synlett*, 2019, **31**, 102; (*j*) X. Wu and C. Zhu, *Chinese Chemical Society Chemistry*, 2020, **2**, 813; Recent examples of remote C–H functionalization *via* the HAT strategy: (*k*) N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2010, **132**, 5568; (*l*) A.-F. Voica, A. Mendoza, W. R. Gutekunst, J. O. Fraga and P. S. Baran, *Nat. Chem.*, 2012, **4**, 629; (*m*) G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature*, 2016, **539**, 268; (*n*) B. J. Groendyke, D. I. AbuSalim and S. P. Cook, *J. Am. Chem. Soc.*, 2016, **138**, 12771; (*o*) H. Lu, K. Lang, H. Jiang, L. Wojtas and X. P. Zhang, *Chem. Sci.*, 2016, **7**, 6934; (*p*) E. A. Wappes, K. M. Nakafuku and D. A. Nagib, *J. Am. Chem. Soc.*, 2017, **139**, 10204; (*q*) Y. Xia, L. Wang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 12940; (*r*) Y. Zhu, K. Huang, J. Pan, X. Qiu, X. Luo, Q. Qin, J. Wei, X. Wen, L. Zhang and N. Jiao, *Nat. Commun.*, 2018, **9**, 2625; (*s*) X. Wu, H. Zhang, N. Tang, Z. Wu, D. Wang, M. Ji, Y. Xu, M. Wang and C. Zhu, *Nat. Commun.*, 2018, **9**, 3343; (*t*) C. G. Na and E. J. Alexanian, *Angew. Chem., Int. Ed.*, 2018, **57**, 13106; (*u*) D. Bafaluy, J. M. Muñoz-Molina, I. Funes-Ardroiz, S. Herold, A. J. de Aguirre, H. Zhang, F. Maseras, T. R. Belderrain, P. J. Pérez and K. Muñiz, *Angew. Chem., Int. Ed.*, 2019, **58**, 8912; (*v*) Z. Liu, H. Xiao, B. Zhang, H. Shen, L. Zhu and C. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 2510; (*w*) R. O. Torres-Ochoa, A. Leclair, Q. Wang and

J. Zhu, *Chem.–Eur. J.*, 2019, **25**, 9477; (*x*) Z. Li, R. O. Torres-Ochoa, Q. Wang and J. Zhu, *Nat. Commun.*, 2020, **11**, 403.

4 (*a*) A. W. Hofman, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 558; (*b*) K. Löffler and C. Freytag, *Ber. Dtsch. Chem. Ges.*, 1909, **42**, 3427.

5 Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, 2007.

6 J. M. Mayer, *Acc. Chem. Res.*, 2011, **44**, 36.

7 For selective examples on sp^2 C-radical initiated remote functionalization: (*a*) D. P. Curran, D. Kim, H. T. Liu and W. Shen, *J. Am. Chem. Soc.*, 1988, **110**, 5900; (*b*) M. Murakami, M. Hayashi and Y. Ito, *J. Org. Chem.*, 1992, **57**, 793; (*c*) S. E. Booth, T. Benneche and K. Undheim, *Tetrahedron*, 1995, **51**, 3665; (*d*) G. Han, M. G. LaPorte, M. C. McIntosh, S. M. Weinreb and M. Parvez, *J. Org. Chem.*, 1996, **61**, 9483; (*e*) G. W. Gribble, H. L. Fraser and J. C. Badenock, *Chem. Commun.*, 2001, 805; (*f*) A. L. J. Beckwith, V. W. Bowry, W. R. Bowman, E. Mann, J. Parr and J. M. D. Storey, *Angew. Chem., Int. Ed.*, 2004, **43**, 95; (*g*) F. Dénès, F. Beaufils and P. Renaud, *Synlett*, 2008, 2389; (*h*) N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2010, **132**, 5568; (*i*) J. K. Vellucci and C. M. Beaudry, *Org. Lett.*, 2015, **17**, 4558; (*j*) M. Parasram, P. Chuentragool, D. Sarkar and V. Gevorgyan, *J. Am. Chem. Soc.*, 2016, **138**, 6340; (*k*) J.-Q. Chen, Y.-L. Wei, G.-Q. Xu, Y.-M. Liang and P.-F. Xu, *Chem. Commun.*, 2016, **52**, 6455; (*l*) F.-Q. Huang, X. Dong, L.-W. Qi and B. Zhang, *Tetrahedron Lett.*, 2016, **57**, 1600; (*m*) S. Wu, X. Wu and C. Zhu, *Angew. Chem., Int. Ed.*, 2019, **58**, 1499; (*n*) S. Wu, X. Wu and C. Zhu, *Sci. China: Chem.*, 2019, **62**, 1507; (*o*) S. Yang, X. Wu, S. Wu and C. Zhu, *Org. Lett.*, 2019, **21**, 4837; (*p*) T. Shang, J. Zhang, Y. Zhang, F. Zhang, X.-S. Li and G. Zhu, *Org. Lett.*, 2020, **22**, 3667. For selective examples on sp^3 C-radical initiated remote functionalization: (*q*) D. Crich, S. Sun and J. Brunckova, *J. Org. Chem.*, 1996, **61**, 605; (*r*) Y. Ueno, K. Chino, M. Watanabe, O. Moriya and M. Okawara, *J. Am. Chem. Soc.*, 1982, **104**, 5564; (*s*) G. Stork, R. Mook, S. A. Biller and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1983, **105**, 3741; (*t*) H. Nishiyama, T. Kitajima, M. Matsumoto and K. Itoh, *J. Org. Chem.*, 1984, **49**, 2298; (*u*) M. Masnyk, *Tetrahedron Lett.*, 1997, **38**, 879; (*v*) M. Parasram, P. Chuentragool, Y. Wang, Y. Shi and V. Gevorgyan, *J. Am. Chem. Soc.*, 2017, **139**, 14857.

8 For reviews on alkene difunctionalization: (*a*) R. M. Romero, T. H. Wöste and K. Muñiz, *Chem.–Asian J.*, 2014, **9**, 972; (*b*) T. Courant and G. Masson, *J. Org. Chem.*, 2016, **81**, 6945; (*c*) T. Koike and M. Akita, *Org. Chem. Front.*, 2016, **3**, 1345; (*d*) G. Yin, X. Mu and G. Liu, *Acc. Chem. Res.*, 2016, **49**, 2413; (*e*) M. Yan, J. C. Lo, J. T. Edwards and P. S. Baran, *J. Am. Chem. Soc.*, 2016, **138**, 12692.

9 (*a*) H. Egami, R. Shimizu, S. Kawamura and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4000; (*b*) P. Yu, J.-S. Lin, S.-C. Zheng, Y.-P. Xiong, L.-J. Zhao, B. Tan and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 11890; (*c*) L. Huang, J.-S. Lin, B. Tan and X.-Y. Liu, *ACS Catal.*, 2015, **5**, 2826; (*d*) T. Li, P. Yu, Y.-M. Du, J.-S. Lin, Y. Zhi and X.-Y. Liu, *J. Fluorine Chem.*, 2017, **203**, 210.

10 (*a*) W. Shu, E. Merino and C. Nevado, *ACS Catal.*, 2018, **8**, 6401; (*b*) L. Li, H. Luo, Z. Zhao, Y. Li, Q. Zhou, J. Xu, J. Li and Y.-N. Ma, *Org. Lett.*, 2019, **21**, 9228.

11 (*a*) M. S. Kharasch and G. Sosnovsky, *J. Am. Chem. Soc.*, 1958, **80**, 756; (*b*) J. K. Kochi, *Science*, 1967, **155**, 415.

12 The definition of inert C(sp^3)–H bonds was introduced in ref. 3*g*, 7*r* and D. M. Peacock, C. B. Roos and J. F. Hartwig, *ACS Cent. Sci.*, 2016, **2**, 647.

13 C.-L. Zhu, C. Wang, Q.-X. Qin, S. Yruegas, C. D. Martin and H. Xu, *ACS Catal.*, 2018, **8**, 5032.

14 M. Nechab, S. Mondal and M. P. Bertrand, *Chem.–Eur. J.*, 2014, **20**, 16034.

15 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066.

16 P. Eisenberger, S. Gischig and A. Togni, *Chem.–Eur. J.*, 2006, **12**, 2579.