ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2017, **4**, 2139

Phosphine-catalyzed remote α-C–H bond activation of alcohols or amines triggered by the radical trifluoromethylation of alkenes: reaction development and mechanistic insights†

Lei Li,‡[a] Liu Ye,‡[a,b] Shao-Fei Ni,‡[a] Zhong-Liang Li,[a] Su Chen,[a] Yi-Meng Du,[c] Xiao-Hua Li,[a] Li Dang*[d] and Xin-Yuan Liu*[a]

Received 22nd June 2017,
Accepted 19th July 2017

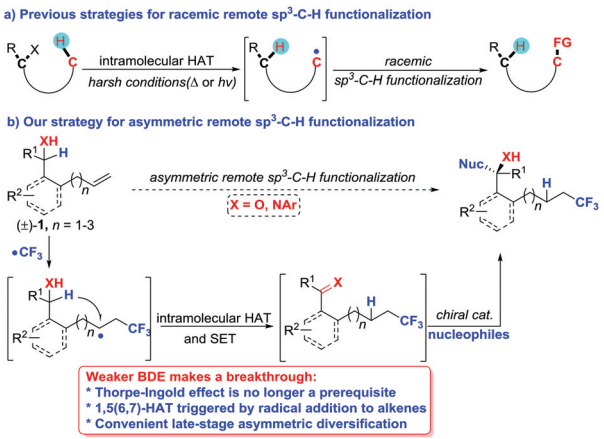
DOI: 10.1039/c7qo00500h

rsc.li/frontiers-organic

Intramolecular hydrogen atom transfer (HAT) for the remote functionalization of C(sp^3)–H bonds has emerged as a powerful strategy, but its asymmetric diversification remains a great challenge because of the requirement of harsh reaction conditions and less enantiotopic discrimination. To overcome this, we described a general and efficient radical protocol for the concomitant functionalization of both alkenes and the remote α-C–H bonds of alcohols or amines *via* 1,5(6,7)-HAT triggered by the addition of a trifluoromethyl radical to alkenes in a highly controlled site-selective manner. Furthermore, such an approach could be developed for late-stage asymmetric diversification at the remote sp^3-hydridized positions of alcohols or amines *via* a cascade sequence for the facile construction of chiral CF_3-containing homoallylic alcohols or secondary amines with good to excellent enantioselectivities. Mechanistic experiments and DFT calculations revealed that 1,5(6,7)-HAT is a kinetically relevant process and provided a rationale for the observed different reactivities between the linear alkenyl alcohol or amine and alkenyl ketone or amide.

Introduction

The intramolecular hydrogen atom transfer (HAT) of an inherently high-energy radical intermediate, especially using oxygen-, nitrogen-, vinyl- and aryl-radical precursors, has emerged as a powerful strategy in organic synthesis for the remote functionalization of unreactive C(sp^3)–H bonds[1] since the pioneering studies including the Hofmann–Löffler–Freytag reaction[2] and Barton's nitrite photolysis.[3] In recent years, the use of HAT of reactive sp^3-carbon-centered radicals has provided an exceptional opportunity for the remote C(sp^3)–H functionalization of complex molecules (Scheme 1a).[4] In spite of these attractive attributes, few asymmetric transformations have been developed to convert the unreactive C(sp^3)–H bonds into useful chiral products with high levels of enantiocontrol. In this scenario, several main obstacles have impeded the development of efficient asymmetric C(sp^3)–H functionalization. They require precious and/or toxic radical metal complexes such as tin hydrides, unfriendly radical initiators



Scheme 1 Strategy for remote sp^3-C–H functionalization *via* intramolecular HAT.

[a]*Department of Chemistry, South University of Science and Technology of China, Shenzhen, 518055, P. R. China. E-mail: liuxy3@sustc.edu.cn; Tel: (+86)755-88018314*
[b]*State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China*
[c]*School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen, 518055, China*
[d]*Department of Chemistry and Key Laboratory for Preparation and Application of Ordered Structural Materials of Guangdong Province, Shantou University, Guangdong 515063, P. R. China. E-mail: ldang@Stu.edu.cn*

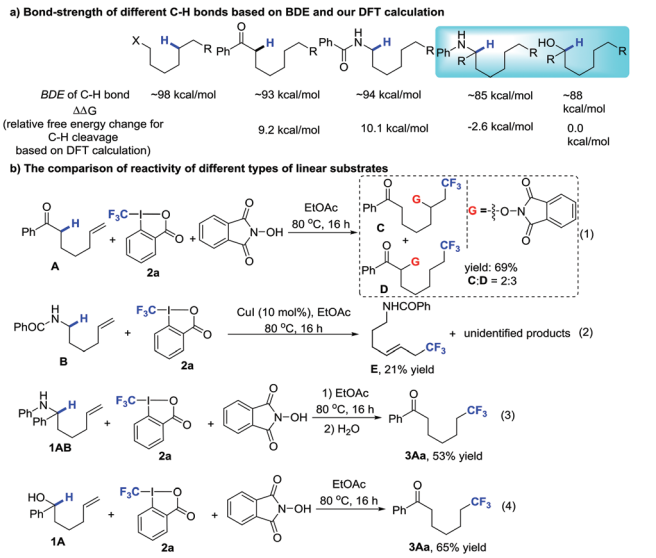
†Electronic supplementary information (ESI) available: NMR and HRMS. See DOI: 10.1039/c7qo00500h

‡These authors contribute equally to this work.

including peroxides or diazines, and harsh reaction conditions at high reaction temperatures or *hv* conditions,[5] therefore leading to the difficult tolerance of the chiral catalysts. Moreover, the *in situ* generated short-lived sp^3-carbon-centered radical species is difficult to provide a handle for enantiotopic discrimination during the catalysis due to the nature of the highly reactive carbon radical intermediates.[6] To overcome such limitations, the development of a practical and mechanistically distinct asymmetric approach under mild conditions still remains a formidable challenge for synthetic chemists.

Among the intensive research studies in alkene chemistry,[7] the difunctionalization of unactivated alkenes, such as the recently developed trifluoromethylation,[8] has attracted considerable attention, providing the simultaneous formation of two vicinal chemical bonds bearing C–CF_3 and C–X (X = C, N, O, X, *etc*.). These approaches have provided powerful tools for the incorporation of the trifluoromethyl group into pharmaceutically and agrochemically relevant molecules, because of fluorine to improve metabolic stability, lipophilicity, and bioavailability.[9] In these reported reactions, sp^3-carbon-centered radical species were generated as the key intermediates under mild reaction conditions.[8] Inspired by these seminal studies and to address the challenges described above, we reasoned that inherently high-energy sp^3-carbon-centered alkyl radicals, which could be *in situ* generated from the addition of the CF_3 radical to unactivated alkenes, would readily abstract the remote α-hydrogen atoms in alcohols or amines to generate transient neutral ketyl or α-amino radicals, which thereafter would undergo single-electron oxidation leading to ketones, aldehydes or imines at remote positions. Given ketones, aldehydes or imines as the valuable and versatile building blocks for the synthetic transformations, we further speculated on the possibility that such approaches could be developed for late-stage asymmetric diversification at the remote sp^3-hydridized position of the alcohol or amine in a one-pot synthetic operation *via* a cascade sequence (Scheme 1b). However, the success of this approach not only requires efficient methods for the site-selective remote α-C–H bond functionalization *via* HAT over competitive 1,2-difunctionalization and β-hydrogen elimination due to the high propensity of these sp^3-carbon-centered alkyl radicals,[8] but also provides the possibility of the combination of two distinct reaction sequences to a one-pot process with minimal extra procedures.

More recently, we have reported an effective approach to realize the remote C–H bond functionalization of amide and carbonyl compounds *via* intramolecular 1,5-HAT by inherently high-energy α-CF_3-alkyl radicals *in situ*-generated from the radical trifluoromethylation of alkenes, thereby enabling the assembly of functionalized chemical structures with remarkable precision and excellent functional-group tolerance *via* controlled activation of C–H bonds.[10] However, these reactions have encountered several restrictions: (1) The key to the success of such a protocol relies heavily upon the Thorpe–Ingold (angle compression) effects of carbonyl or amide substrates bearing only geminal groups, thus preferentially favouring the intramolecular 1,5-HAT process. (2) In the reported systems, only the 1,5-HAT process was involved, probably due to the favoured entropy factor and proximity effects in the six-membered cyclic transition state of such processes.[1a] In the previous studies, the original mechanistic studies revealed that intramolecular 1,5-HAT seemed to be a kinetically relevant process.[10a,c] Based on the reported bond dissociation energies (BDEs)[11] and HAT exchange constants,[12] we speculated that the underlying reason for these limitations of such a method might be attributed to the fact that the BDEs of the α-C–H bond of the carbonyl or amide group (carbonyl α-C–H BDE = ~93 kcal mol^{-1} and amide α-C–H BDE = ~94 kcal mol^{-1}) are only slightly weaker than those of the secondary alkyl C–H bond (alkyl α-C–H BDE = ~98 kcal mol^{-1}) (Scheme 2a),[11] thus rendering a weak driving force for the aforementioned 1,5-HAT.[10] To circumvent these problems and given that the α-C–H bond of alcohols or amines is much weaker than that of the secondary alkyl C–H bond (alcohol α-C–H BDE = ~88 kcal mol^{-1} and amine α-C–H BDE = ~85 kcal mol^{-1}) (Scheme 2a),[11] we reasoned that the remote α-hydrogen atoms of alcohols or amines would be more readily abstracted. Herein, we describe an efficient protocol for the successful implementation of phosphine-catalyzed radical reactions with the CF_3 radical reagent and alkenyl alcohols or racemic amines with or without tethered groups *via* intramolecular 1,5(6,7)-HAT in a highly controlled site-selective manner, delivering remotely functionalized carbonyl compounds in good to excellent yields (Scheme 1b). Furthermore, the convenient and step-economical one-pot synthetic strategy, providing valuable chiral trifluoromethyl homoallylic alcohols and amines with excellent enantioselectivities, was also accomplished. Mechanistic experiments and DFT calculations reveal that 1,5(6,7)-HAT should be a kinetically relevant process and provide a rationale for the observed different reactivities between the linear alkenyl alcohols or racemic amines and alkenyl ketones or amides.



Scheme 2 Reactivities of different types of linear substrates.

Results and discussion

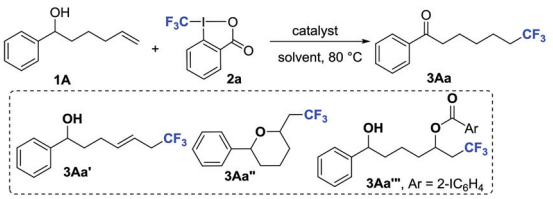
To specifically compare the relative α-C–H bond strength of the alcohol, amine, carbonyl or amide, density functional theory (DFT) calculation was carried out and showed that the free energy changes for the designed eqn (S6)–(S9) in Fig. 1 in the ESI† have the sequence of ΔGS7 (−20.0 kcal mol^{-1}) < ΔGS6 (−17.4 kcal mol^{-1}) < ΔGS8 (−8.2 kcal mol^{-1}) < ΔGS9 (−7.3 kcal mol^{-1}). From these calculated results, we can list the relative energy difference as shown in Scheme 2a, which represents the relative bond dissociation energy of the α-C–H bond of these four compounds. These clearly imply that the α-C–H bond of the alcohol or amine is weaker than that of the carbonyl or amide, which is in concordance with the finding from the reported BDE.[11] To validate our hypothesis that the remote α-hydrogen atoms of alcohols or amines would be more readily abstracted compared with those of the carbonyl or amide due to the weaker strength of their α-C–H bonds, we synthesized linear alkenyl ketone **A**, amide **B**, alcohol **1A** or amine **1AB** and next investigated how these functional groups in the substrate influenced the outcome of the designed reactions (Scheme 2b). Not surprisingly, when linear alkenyl ketone **A** or amide **B** was subjected to the reported standard conditions,[10a,c] poor yields of the desired products with poor selectivities were observed (Scheme 2b, eqn (1) and (2)), implying the difficulty in overriding the conformational bias of these more general types of substituted substrates due to their stronger α-C–H bonds. In sharp contrast, with linear alkenyl alcohol **1A** or amine **1AB** as the substrate under the standard conditions, the expected CF_3-containing ketone **3Aa** was observed in 53% and 65% yield, respectively (Scheme 2b, eqn (3) and (4)). These contrasting experiments clearly imply that the difference in reactivity is likely in line with the strength of the α-C–H bonds of these functional groups.

On the basis of the above preliminary results and to further improve the reaction efficiency, we treated the model reaction of linear alkenyl alcohol **1A** with Togni's reagent **2a**[13] under mild and metal-free conditions, inspired by the success of our recently developed organic base-catalyzed radical trifluoromethylation of alkenes.[10e] In the presence of DABCO (20 mol%), the reaction provided the desired product **3Aa** in 86% yield with excellent chemo- and regioselectivities, while no byproducts resulting from allylic trifluoromethylation (**3Aa′**), intra- or intermolecular 1,2-oxytrifluoromethylation (**3Aa″** or **3Aa‴**)[8] were observed from ^{19}F NMR analysis (entry 1, Table 1). These results suggested that the 1,5-HAT step is much more favourable than other reaction pathways in the current catalytic system. Based on these findings, upon optimizing the reaction conditions through the variation of the organic base catalysts, catalyst loadings, solvents, and the molar ratios of the reactants (Table 1), we identified the following protocol as optimal: reaction of **1A** and **2a** with the molar ratio of 1.0 : 1.5 in the presence of PPh_3 (15 mol%) in DCE at 80 °C for 16 h, **3Aa** was obtained in 89% isolated yield (entry 14).

With the optimal reaction conditions in hand, we set out to explore the scope with respect to various linear alkenyl alcohols (Table 2). A range of diversely functionalized linear alkenols, including those having aryl groups (with electron-donating groups: **1B**, **1C**; with electron-withdrawing groups: **1D–1H** at the different positions) and naphthyl group (**1I**), were found to be suitable substrates to give the corresponding products **3Aa–3Ia** selectively in 60–90% yields. However, the reaction with substrate **1J** bearing a thienyl group gave low yield under the standard conditions. To improve the product yield, we found that the corresponding product **3Ja** was obtained in 63% yield with CuI (10 mol%) as the catalyst. Most importantly, substrates **1K–1M**, with various aliphatic groups, also afforded the expected products **3Ka–3Ma** in 65–71% yields, thus clearly demonstrating that the current reaction was not severely affected by switching the nature of the benzylic carbon to the inactive alkyl group. It should be noted that linear alkenyl alcohols with the geminal-disubstituted alkenyl group (**1N**) or heteroatom-tethered groups, such as oxygen- and sulfonamide-tethered substrates **1O** and **1P**, were also well tolerated to give the trifluoromethylated ketones **3Na–3Pa** in 70–86% yields, respectively.

Comparable to linear alkenyl alcohols, the aryl-tethered substrates **1Q–1W** were also applicable to this process. For examples, a variety of substrates, bearing different aliphatic groups (**1Q–1S**), either electron-donating groups or electron-withdrawing groups on the phenyl ring α to the alcohol group (**1T–1W**), reacted efficiently to afford highly substituted CF_3-containing aryl ketones **3Qa–3Wa** in 61–95% yield. It is noteworthy that the geminal-disubstituted alkene **1X** or **1Y**

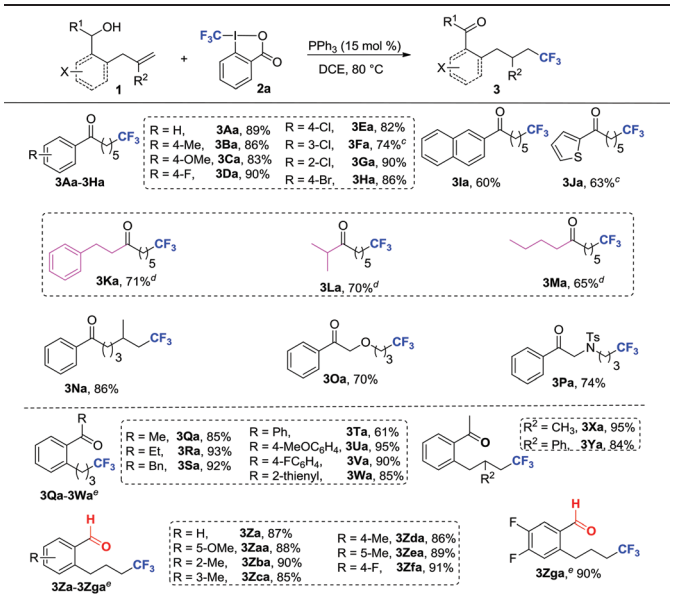
Table 1 Screening results of the reaction conditions[a]



Entry	Catalyst (mol%)	**2a** (*X* equiv.)	Solvent	Yield[b] (%)
1	DABCO (20)	2.0	DCE	86
2	DMAP (20)	2.0	DCE	76
3	Ph_3P (20)	2.0	DCE	90
4	$(PMP)_3P$ (20)	2.0	DCE	83
5	$(4\text{-}CF_3C_6H_4)_3P$ (20)	2.0	DCE	80
6	Ph_3P (20)	2.0	Dioxane	88
7	Ph_3P (20)	2.0	CH_3CN	88
8	Ph_3P (20)	2.0	EtOAc	85
9	Ph_3P (20)	2.0	MeOH	83
10	Ph_3P (20)	2.0	Toluene	4
11	Ph_3P (20)	1.8	DCE	91
12	Ph_3P (20)	1.5	DCE	89
13	Ph_3P (20)	1.2	DCE	83
14	**Ph_3P (15)**	**1.5**	**DCE**	**89**
15	Ph_3P (10)	1.5	DCE	84
16	Ph_3P (5)	1.5	DCE	83
17	None	1.5	DCE	16

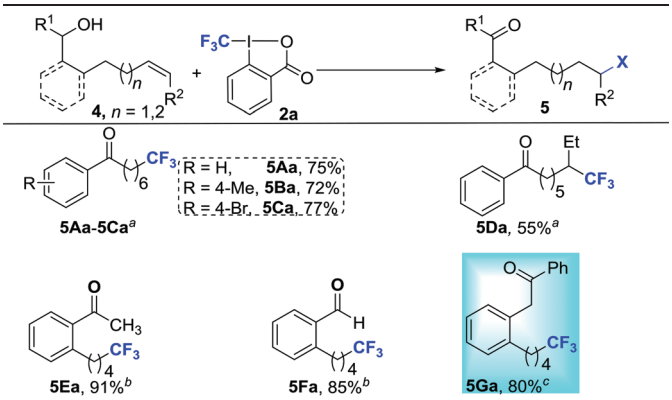
[a] Reaction conditions: **1A** (0.2 mmol), Togni's reagent **2a**, solvent (2.0 mL) at 80 °C for 16 h under argon. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. PMP = *p*-$MeOC_6H_4$.

Table 2 Substrate scope of the trifluoromethylation reaction[a,b]



[a] Reaction conditions: **1** (0.2 mmol), Togni's reagent **2a** (1.5 equiv.), PPh_3 (15 mol%), DCE (2.0 mL) at 80 °C for 16 h under argon. [b] Isolated yield. [c] CuI (10 mol%) in EtOAc. [d] EtOAc as a solvent. [e] PPh_3 (20 mol%) in MeOH at 70 °C for 16 h under argon.

Table 3 Substrate scope of the 1,6(7)-HAT process

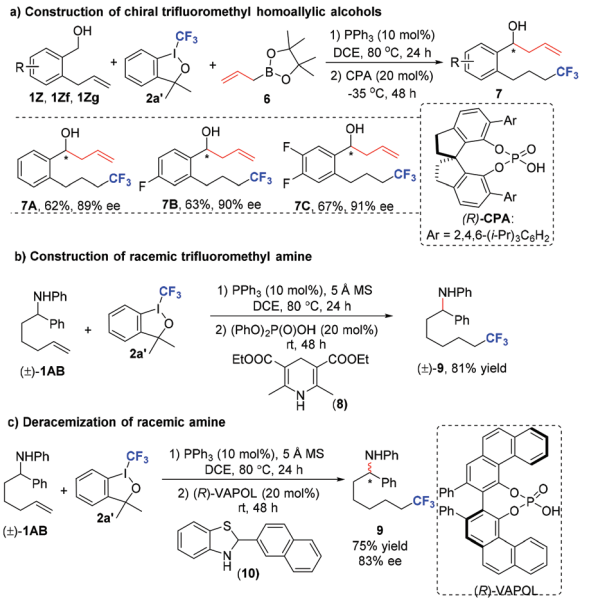


[a] Reaction conditions: **4** (0.2 mmol), Togni's reagent **2a** (1.5 equiv.), PPh_3 (15 mol%), DCE (2.0 mL) at 80 °C for 16 h under argon. [b] PPh_3 (20 mol%), MeOH at 70 °C. [c] Reaction conditions: **4** (0.2 mmol), Togni's reagent **2a** (2.0 equiv.), CuI (10 mol%), DCE (2.0 mL) at 80 °C for 16 h under argon.

bearing either a methyl or a phenyl group was also an excellent substrate and gave the product **3Xa** or **3Ya** in 95% or 84% yield, respectively. Inspired by the above results, we turned our attention to the reactivity of alkenyl primary alcohols. With the modified conditions, we were pleased to find that a series of alkenyl primary alcohols bearing electron-neutral (**1Z**), -rich (**1Za–1Ze**) or -deficient (**1Zf**, **1Zg**) aryl groups proved to be suitable substrates, furnishing the corresponding CF_3-containing aryl aldehydes **3Za–3Zga** in 85–91% yields.

Inspired by the above success in the 1,5-H radical shift process, we thus switched our synthetic targets to the use of alkenols with longer chains to probe whether the more challenging 1,6(7)-H radical shift step *via* higher-energy seven(eight)-membered cyclic transition states[4b] could be realized in the current reaction system. Gratifyingly, under the reaction conditions identical to those of the 1,5-H shift process (Table 2), remotely trifluoromethyl-substituted ketones or aldehydes could be obtained in moderate to good yields from alkenyl alcohols **4A–4G** through remote alcohol α-C–H bond activation *via* the 1,6-H shift triggered by the addition of trifluoromethyl radicals to the unactivated alkenes (Table 3). It should be emphasized that a broad range of substrates including linear alkenyl alcohols containing different substituents at the aromatic ring (**4A–4C**), internal substituted alkene (**4D**) and aryl-tethered secondary or primary alcohols (**4E** and **4F**) were well tolerated in the current reaction system. Notably, remotely trifluoromethyl-substituted ketone **5Ga** was obtained in 80% yield from alkenyl alcohol **4G** through remote alcohol α-C–H bond activation *via* 1,7-HAT.

As previously described, we were hopeful that a one-pot synthetic operation *via* a cascade sequence could be realized for late-stage asymmetric diversification at remote sp^3-hydridized positions of alcohols or amines. More recently, the asymmetric allylboration of carbonyl groups with nontoxic and stable allylboronic acid pinacol ester **6** with chiral phosphoric acid catalysts constitutes one of the most efficient ways to access synthetically and pharmaceutically important chiral homoallylic alcohols.[14] However, convergent one-step or one-pot methods to prepare such important skeletons directly from simple alcohols are rare. To demonstrate the synthetic utility of the methodology, we reasoned that the *in situ* generated aldehydes with the concurrent installation of remotely diverse functional groups would provide an ideal platform to construct a variety of useful chiral homoallylic alcohols *via* a cascade sequence. In order to address this issue, we expected that the two-step sequence could be carried out in the same solvent to obviate the need for changing the solvent for each cycle in spite of two distinct reaction sequences. To our delight, after the systematic optimization of different reaction parameters, including catalysts, solvents and temperature (Table S1 in the ESI†), a simple one-pot procedure for the formation of chiral homoallylic alcohols remotely from the newly formed C–CF_3 bond was successfully realized directly from readily available alkenyl alcohols. Alkenyl alcohols **1Z**, **1Zf** and **1Zg** were efficiently converted into the corresponding aldehyde **3** in the presence of PPh_3 (10 mol%) with Togni's reagent **2a′** in DCE under otherwise identical conditions, followed by the allylboration[14b,c] of the resulting aldehydes with allylboronic acid pinacol ester **6** in the presence of the (*R*)-2,4,6-triisopropylphenyl-SPINOL-derived chiral phosphoric acid catalyst (20 mol%) at −35 °C to afford chiral trifluoromethylated homoallylic alcohols **7A–7C** in 62–67% yields with 89–91% ee (Scheme 3a). It is encouraging to note that the present process is a rather general and efficient protocol for setting a chiral center remotely from the



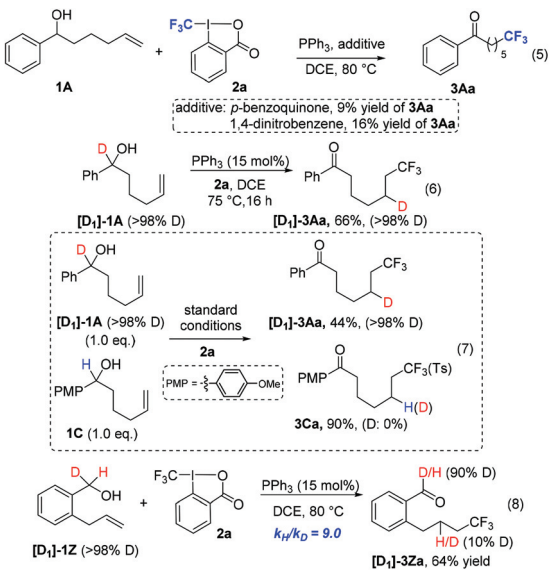
Scheme 3 Versatile transformations *via* a cascade sequence.

newly formed C–CF_3 bond from simple alkenyl alcohols through the simultaneous functionalization of two remotely sequential Csp^2–H, and Csp^3–H bonds and the selective installation of different functional groups with remarkable precision under metal-free conditions.

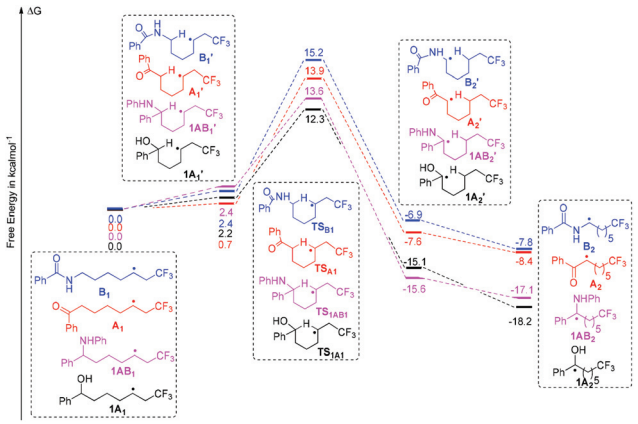
Based on the result with good reactivity of the linear alkenyl amine as described in eqn (3) in Scheme 2b and the particular importance of chiral amines in medicinal chemistry and organic synthesis,[15] we focused on the development of a catalytic enantioselective tandem reaction for the synthesis of chiral diversely functional amines from racemic amines. Considering the possibility of the formation of a ketimine intermediate in the current reaction system, which could further undergo enantioselective transfer hydrogenation in the presence of the hydride source with chiral phosphoric acid catalysts,[16] we envisioned that this one-pot protocol could be realized to form chiral amine derivatives. However, a particular challenge with the development of this cascade sequence is that oxidants (Togni's reagent) and reductants (hydride source) easily and directly quench each other in a single reactor. To ascertain the feasibility of this hypothesis, we first carried out a racemic cascade reaction and found that the expected trifluoromethyl product (±)-**9** could be obtained in 81% yield with 10 mol% of PPh_3 in the presence of 5 Å MS with DCE as a solvent at 80 °C for 24 h, followed by the addition of 20 mol% of diphenyl phosphate and 1.5 equivalents of Hantzsch ester **8** (Scheme 3b). To realize the enantiocontrol, upon optimizing the reaction conditions through the variation of the chiral phosphoric acids and hydride sources, we were pleased to find that the use of (*R*)-VAPOL hydrogen phosphate as a catalyst in the presence of benzothiazoline **10** (1.5 equiv.)[16b,17] resulted in product **9** with 75% yield and 83% ee (Scheme 3c). It is noteworthy that this protocol which provides a concise deracemization of the racemic amine, in particular with the concomitant installation of the functional group at the remote position, is an advantageous alternative to the conventional deracemization of racemic amines.[18]

To gain more insights into the reaction mechanism, we tested the trifluoromethylation reaction in the presence of radical scavengers such as *p*-benzoquinone (BQ) and 1,4-dinitrobenzene under the standard conditions, and found that the reactions were significantly inhibited by these reagents (Scheme 4, eqn (5)), suggesting that a radical process is involved in these reactions. To further investigate the mechanism in detail, the reactions of deuterated substrates **[D_1]-1A** were carried out. The trifluoromethylation reaction of **[D_1]-1A** was performed under the standard conditions and the deuterium at the carbon adjacent to the oxygen atom completely shifted to the β-position of the alkene in **[D_1]-3Aa** (Scheme 4, eqn (6)). Next, a crossover experiment involving equimolar amounts of **[D_1]-1A** and **1C** showed no deuterium incorporation in **[D_1]-3Aa** and **3Ca** (Scheme 4, eqn (7)). Furthermore, the kinetic isotope effect was also examined through the reaction of deuterated **[D_1]-1Z**, and K_H/K_D = 9.0 was observed (Scheme 4, eqn (8)). These observations clearly implied that the current reaction proceeded with an intramolecular 1,5-H radical shift, which should be a kinetically relevant process. All these experimental results are in support of our initial proposal, in which the selective addition of trifluoromethyl radicals to unactivated alkenes could trigger remote alcohol α-C–H bond activation *via* the 1,5- or 1,6(7)-HAT process.

To better understand the mechanism of this kinetically relevant process and to account for the different reactivities between the linear alkenyl alcohol **1A** or amine **1AB** and ketone **A** or amide **B** in the experiment (Scheme 2), DFT calculations were further performed to focus on the relative stability of the possible radical intermediates and the 1,5-HAT process



Scheme 4 Control experiments.



Scheme 5 Energy profiles for the 1,5-HAT process calculated at the M06L/6-311G* level of theory.

by taking the generally assumed alkyl sp^3-carbon-centered radical intermediates $\mathbf{1A_1}$, $\mathbf{1AB_1}$, $\mathbf{A_1}$, or $\mathbf{B_1}$ as the reference energies (Scheme 5).[10] The transformation from $\mathbf{1A_1}$ to $\mathbf{1A_2}$ or $\mathbf{1AB_1}$ to $\mathbf{1AB_2}$ has a barrier of 12.3 and 13.6 kcal mol^{-1} *via* TS_{1A1} or TS_{1AB1}, which are lower in relative energies than those from $\mathbf{A_1}$ to $\mathbf{A_2}$ (13.9 kcal mol^{-1} for TS_{A1}) and $\mathbf{B_1}$ to $\mathbf{B_2}$ (15.2 kcal mol^{-1} for TS_{B1}). This sequence is in agreement with the sequence of calculated free energies in Scheme 2a. Importantly, $\mathbf{A_2}$ and $\mathbf{B_2}$ are relatively more stable than $\mathbf{A_1}$ and $\mathbf{B_1}$ by 7.8 and 8.4 kcal mol^{-1}, respectively, thus rendering the transformation reversibly from $\mathbf{A_2}$ or $\mathbf{B_2}$ to $\mathbf{A_1}$ or $\mathbf{B_1}$ by about 22 kcal mol^{-1} barriers, showing the possibility to undergo competitive β-hydrogen elimination or 1,2-oxytrifluoromethylation[8] from intermediates $\mathbf{A_1}$ or $\mathbf{B_1}$, which is consistent with the experimental observation for carbonyl and amide substrates (Scheme 2b, eqn (1) and (2)). In sharp contrast, it is very difficult for a relatively very stable $\mathbf{1A_2}$ or $\mathbf{1A_{B2}}$, to reversibly go back to $\mathbf{1A_1}$ or $\mathbf{1A_{B1}}$ due to a very high reaction barrier of about 30 kcal mol^{-1}. Therefore, these calculated results show that the 1,5-H radical shift process for linear alkenyl alcohol **1A** or amine **1AB** is both kinetically and thermodynamically favorable, while such a process for carbonyl and amide substrates is kinetically favorable but thermodynamically reversible, thus providing a rationale for the observed different reactivities between the linear alcohol **1A** or amine **1AB** and linear ketone **A** or amide **B**. Our experimental and theoretical findings thus lead us to conclude that both the stability of the radicals generated *via* intramolecular 1,*n*-HAT and the bond dissociation energies of the corresponding C–H bonds play a vital role in controlling the site-selectivity under the current reaction conditions.

Conclusions

In summary, we have successfully developed the general and efficient phosphine-catalyzed radical protocol for the concomitant trifluoromethylation of both the alkene and the remote alcohol or amine α-C–H bond at various distances, which provide valuable trifluoromethyl-substituted ketones or aldehydes through neutral ketyl or α-amino radical intermediates *via* 1,5(6,7)-HAT triggered by the addition of the corresponding CF_3 radical to alkenes in a highly controlled site-selective manner. This versatile method shows a broad substrate scope with a series of alkenyl alcohols or amines with or without tethered groups. Moreover, the newly developed one-pot cascade protocol from simple alkenyl alcohols or racemic secondary amines provides a rapid access to valuable chiral CF_3-containing homoallylic alcohols and secondary amines, thus demonstrating great potential in synthetic and medicinal chemistry. Mechanistic experiments and DFT calculations show that 1,5(6)-HAT is a kinetically relevant process and it provides a rationale for the observed different reactivities between the linear alkenyl alcohol or amine and alkenyl ketone or alkenyl amide. Further studies to expand the scope of this process and to deeply understand the reaction mechanism are underway in our laboratory.

Experimental

General procedure 1 for the catalytic trifluoromethylation reaction system

Under argon, a 25 mL Schlenk tube equipped with a magnetic stir bar was charged with **1** (0.2 mmol, 1.0 equiv.), Togni's reagent **2a** (0.3 mmol, 1.5 equiv.), triphenylphosphine (0.03 mmol, 0.15 equiv.) and 1,2-dichloroethane (DCE, super dry, 2.0 mL). The sealed tube was then stirred at 80 °C for 16 hours. After completion (monitored by TLC), the reaction solution was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to give the desired products **3**.

General procedure 2 for the catalytic trifluoromethylation reaction system

Under argon, a 25 mL Schlenk tube equipped with a magnetic stir bar was charged with **1** (0.2 mmol, 1.0 equiv.), Togni's reagent **2a** (0.3 mmol, 1.5 equiv.), triphenylphosphine (0.03 mmol, 0.15 equiv.) and methanol (super dry, 2.0 mL). The sealed tube was then stirred at 70 °C for 16 hours. After completion (monitored by TLC), the reaction solution was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to give the desired products **3**.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 215722096 and 21573102), the National Key Basic Research Program of China (973 Program 2013CB834802), the Shenzhen overseas high level talents innovation plan of technical innovation project (KQCX20150331101823702), the Shenzhen special funds for

the development of biomedicine, internet, new energy, and new material industries (JCYJ20150430160022517) and the South University of Science and Technology of China is greatly appreciated.

Notes and references

1 For selected examples of the high-energy radical mediated HAT process, see: (*a*) Ž. Čeković, *Tetrahedron*, 2003, **59**, 8073; (*b*) S. Chiba and H. Chen, *Org. Biomol. Chem.*, 2014, **12**, 4051; (*c*) F. Dénès, F. Beaufils and P. Renaud, *Synlett*, 2008, **16**, 2389; (*d*) A. Gansäuer, T. Lauterbach and S. Narayan, *Angew. Chem., Int. Ed.*, 2003, **42**, 5556; (*e*) G. Majetich and K. Wheless, *Tetrahedron*, 1995, **51**, 7095; (*f*) D. P. Curran, A. C. Abraham and H. Liu, *J. Org. Chem.*, 1991, **56**, 4335; (*g*) E. T. Hennessy and T. A. Betley, *Science*, 2013, **340**, 591; (*h*) V. Snieckus, J. C. Cuevas, C. P. Sloan, H. Liu and D. P. Curran, *J. Am. Chem. Soc.*, 1990, **112**, 896; (*i*) A.-F. Voica, A. Mendoza, W. R. Gutekunst, J. O. Fraga and P. S. Baran, *Nat. Chem.*, 2012, **4**, 629.

2 (*a*) A. W. Hofmann, *Chem. Ber.*, 1883, **16**, 558; (*b*) K. Löffler and C. Freytag, *Chem. Ber.*, 1909, **42**, 3427.

3 (*a*) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, 1961, **83**, 4076; (*b*) D. H. R. Barton, *Pure Appl. Chem.*, 1968, **16**, 1.

4 (*a*) Č. Živorad, *J. Serb. Chem. Soc.*, 2005, **70**, 287; (*b*) M. Nechab, S. Mondal and M. P. Bertrand, *Chem. – Eur. J.*, 2014, **20**, 16034; (*c*) G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature*, 2016, **539**, 268; (*d*) J. C. K. Chu and T. Rovis, *Nature*, 2016, **539**, 272; (*e*) W. Shu and C. Nevado, *Angew. Chem., Int. Ed.*, 2017, **56**, 1881; (*f*) R. Wang, Y. Li, R.-X. Jin and X.-S. Wang, *Chem. Sci.*, 2017, **8**, 3838; (*g*) X.-Q. Hu, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 1960.

5 (*a*) D. Crich, S. Sun and J. Brunckova, *J. Org. Chem.*, 1996, **61**, 605; (*b*) J. Cassayre and S. Z. Zard, *J. Organomet. Chem.*, 2001, **624**, 316; (*c*) M. S. Wilson, J. C. S. Woo and G. R. Dake, *J. Org. Chem.*, 2006, **71**, 4237; (*d*) A. Attouche, D. Urban and J.-M. Beau, *Angew. Chem., Int. Ed.*, 2013, **52**, 9572; (*e*) X. Xiao, Z. Xu, Q.-D. Zeng, X.-B. Chen, W.-H. Ji, Y. Han, P. Wu, J. Ren and B.-B. Zeng, *Chem. – Eur. J.*, 2015, **21**, 8351.

6 (*a*) P. Renaud and M. Sibi, in *Radicals in Organic Synthesis*, Wiley, Weinheim, Germany, 2001, vol. 1 and 2; (*b*) A. Baralle, A. Baroudi, M. Daniel, L. Fensterbank, J.-P. Goddard, E. Lacôte, M.-H. Larraufie, G. Maestri, M. Malacria and C. Ollivier, in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, Ltd, 2012; (*c*) R. Zhu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 12655; (*d*) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2015, **137**, 8069; (*e*) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan and X.-Y. Liu, *J. Am. Chem. Soc.*, 2016, **138**, 9357.

7 (*a*) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795; (*b*) Y. Shimizu and M. Kanai, *Tetrahedron Lett.*, 2014, **55**, 3727; (*c*) Y. Deng, H. Wang, Y. Sun and X. Wang, *ACS Catal.*, 2015, **5**, 6828; (*d*) V. Rodriguez-Ruiz, R. Carlino, S. Bezzenine-Lafollée, R. Gil, D. Prim, E. Schulz and J. Hannedouche, *Dalton Trans.*, 2015, **44**, 12029; (*e*) M. D. Greenhalgh, A. S. Jones and S. P. Thomas, *ChemCatChem*, 2015, **7**, 190.

8 For selected recent reviews on the trifluoromethylation of alkenes and alkynes, see: (*a*) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950; (*b*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (*c*) P. Chen and G. Liu, *Synthesis*, 2013, **45**, 2919; (*d*) A. Studer and D. P. Curran, *Nat. Chem.*, 2014, **6**, 765; (*e*) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513; (*f*) T. Koike and M. Akita, *J. Fluorine Chem.*, 2014, **167**, 30; (*g*) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598; (*h*) J. Xu, X. Liu and Y. Fu, *Tetrahedron Lett.*, 2014, **55**, 585; (*i*) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (*j*) S. Barata-Vallejo, B. Lantaño and A. Postigo, *Chem. – Eur. J.*, 2014, **51**, 16806; (*k*) J. Charpentier, N. Fruh and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (*l*) P. Guo, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Chem. – Eur. J.*, 2015, **21**, 7648; (*m*) Y. Zeng, C. Ni and J. Hu, *Chem. – Eur. J.*, 2016, **22**, 3210.

9 For selected recent reviews on fluorine in medicinal chemistry, see: (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*c*) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305; (*d*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*e*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*f*) X.-L. Qiu, X.-H. Xu and F.-L. Qing, *Tetrahedron*, 2010, **66**, 789; (*g*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (*h*) N. Shibata, S. Mizuta and H. Kawai, *Tetrahedron: Asymmetry*, 2008, **19**, 2633; (*i*) V. A. Brunet and D. O'Hagan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1179–1182; (*j*) D. Cahard, X. Xu, C. Couve-Bonnaire and X. Pannecoucke, *Chem. Soc. Rev.*, 2010, **39**, 558; (*k*) Y. Zheng and J.-A. Ma, *Adv. Synth. Catal.*, 2010, **352**, 2745; (*l*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (*m*) G. Valero, X. Companyó and R. Rios, *Chem. – Eur. J.*, 2011, **17**, 2018; (*n*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455; (*o*) X. Yang, T. Wu, R. J. Phipps and F. D. Toste, *Chem. Rev.*, 2015, **115**, 826.

10 (*a*) P. Yu, J.-S. Lin, L. Li, S.-C. Zheng, Y.-P. Xiong, L.-J. Zhao, B. Tan and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 11890; (*b*) L. Huang, J.-S. Lin, B. Tan and X.-Y. Liu, *ACS Catal.*, 2015, **5**, 2826; (*c*) L. Huang, S.-C. Zheng, B. Tan and X.-Y. Liu, *Org. Lett.*, 2015, **17**, 1589; (*d*) L. Huang, S.-C. Zheng, B. Tan and X.-Y. Liu, *Chem. – Eur. J.*, 2015, **21**, 6718; (*e*) P. Yu, S.-C. Zheng, N.-Y. Yang, B. Tan and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2015, **54**, 4041; (*f*) T.-T. Li, P. Yu, J.-S. Lin, Y. Zhi and X.-Y. Liu, *Chin. J. Chem.*, 2016, **34**, 490; (*g*) H. Egami, R. Shimizu, S. Kawamura and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4000.

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

12 J. M. Mayer, *Acc. Chem. Res.*, 2011, **44**, 36.
13 P. Eisenberger, S. Gischig and A. Togni, *Chem. – Eur. J.*, 2006, **12**, 2579.
14 (*a*) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047; (*b*) P. Jain and J. C. Antilla, *J. Am. Chem. Soc.*, 2010, **132**, 11884; (*c*) P. Jain, H. Wang, K. N. Houk and J. C. Antilla, *Angew. Chem., Int. Ed.*, 2012, **51**, 1391; (*d*) C.-H. Xing, Y.-X. Liao, Y. Zhang, D. Sabarova, M. Bassous and Q.-S. Hu, *Eur. J. Org. Chem.*, 2012, 1115.
15 T. C. Nugent, *Chiral Amine Synthesis: Methods, Developments and Applications*, Wiley-VCH, Weinheim, Germany, 2010.
16 (*a*) C. Zheng and S.-L. You, *Chem. Soc. Rev.*, 2012, **41**, 2498; (*b*) C. Zhu, K. Saito, M. Yamanaka and T. Akiyama, *Acc. Chem. Res.*, 2015, **48**, 388.
17 (*a*) A. Henseler, M. Kato, K. Mori and T. Akiyama, *Angew. Chem., Int. Ed.*, 2011, **50**, 8180; (*b*) K. Saito, K. Horiguchi, Y. Shibata, M. Yamanaka and T. Akiyama, *Chem. – Eur. J.*, 2014, **20**, 7616.
18 (*a*) R. Carr, M. Alexeeva, A. Enright, T. S. C. Eve, M. J. Dawson and N. J. Turner, *Angew. Chem., Int. Ed.*, 2003, **42**, 4807; (*b*) A. D. Lackner, A. V. Samant and F. D. Toste, *J. Am. Chem. Soc.*, 2013, **135**, 14090; (*c*) Y. Ji, L. Shi, M.-W. Chen, G.-S. Feng and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2015, **137**, 10496.