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Radical 1,2,3-tricarbofunctionalization of α -vinyl- β -ketoesters enabled by a carbon shift from an all-carbon quaternary center†

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Herein, we report an intermolecular, radical 1,2,3-tricarbofunctionalization of α -vinyl- β -ketoesters to achieve the goal of building molecular complexity *via* the one-pot multifunctionalization of alkenes. This reaction allows the expansion of the carbon ring by a carbon shift from an all-carbon quaternary center, and enables further C–C bond formation on the tertiary carbon intermediate with the aim of reconstructing a new all-carbon quaternary center. The good functional group compatibility ensures diverse synthetic transformations of this method. Experimental and theoretical studies reveal that the excellent diastereoselectivity should be attributed to the hydrogen bonding between the substrates and solvent.

A leading motive for the impressive achievements in the area of assembling molecular complexity is the transformation of simple feedstock chemicals into complex molecular skeletons with superior bioactive properties. In this respect, the direct functionalization of alkenes has been demonstrated as one of the most effective and simple strategies to meet this criterion at a high level. While the difunctionalization of alkenes in a one-pot process is the major theme of considerable interest in this field,¹ the multifunctionalization of alkenes,² for example, a 1,2,3-trifunctionalization of alkenes, has the power to simultaneously incorporate multifunctional groups. Therefore, this multifunctionalization reaction model can be regarded as an efficient and novel strategy to afford molecules with high structural diversity and complexity. However, such methods are elusive.

During the last decades, radical alkene functionalizations have been revealed to be a powerful tool for building complex molecular frameworks by employing a radical initiator, a transition metal catalyst, or a photocatalyst.^{3–5} However, only several successful methods for the radical multifunctionalization of

alkenes have been achieved. For example, the Studer group reported an elegant 1,2-boryl shift-enabled radical 1,2,3-trifunctionalization of allylboronic esters using AIBN as the radical initiator (Fig. 1a).³ Shi *et al.* disclosed an excellent photocatalytic perfluoroalkylation of a vinyl-substituted all-carbon quaternary center through 1,2-aryl migration (Fig. 1b).⁴

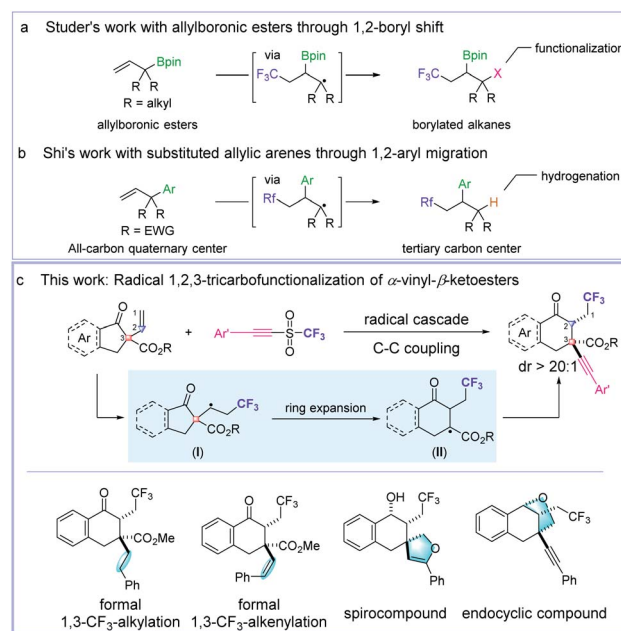


Fig. 1 Radical 1,2,3-trifunctionalization of alkenes. (a) Studer's work; (b) Shi's work; (c) This work.

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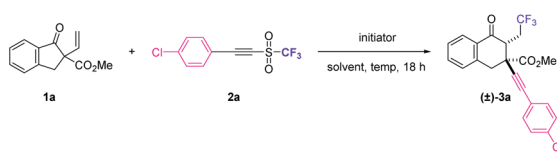
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Herein, we report a new one-pot protocol to realize an intermolecular, radical 1,2,3-tricarbofunctionalization of α -vinyl- β -ketoesters through a cascade process of deconstruction–reconstruction of the all-carbon quaternary center (Fig. 1c).⁵

The direct incorporation of a fluorine atom or fluorinated moieties into organic compounds has been extensively investigated and proved to be an significant synthetic strategy in the field of discovering new pharmaceuticals.⁶ Recently, we are interested in the radical functionalization of alkenes with fluoroalkyl groups,⁷ and we envisioned that, different from the typical Dowd–Beckwith⁸ ring expansion reaction,⁹ the addition of a fluoroalkyl radical to the C=C double bond would generate an adduct radical species **I**, which will transform into the radical intermediate **II** upon ring expansion (Fig. 1c). Finally, the cascade C–C coupling affords the product with a reconstructed all-carbon quaternary center. However, there are several challenging issues that need to be addressed: (1) the carbon shift from an all-carbon quaternary center to afford a tertiary carbon center which is bulkier than the tertiary carbon center formed in a typical Dowd–Beckwith ring expansion reaction; (2) the reconstruction of all-carbon quaternary center from tertiary carbon radical **II** will meet the associated conformational restriction and steric congestion; (3) side reactions, such as 1,2-radical addition to the alkenyl group, homolytic couplings of the carbon radical intermediates **I** and **II**, and direct H-atom abstraction;¹⁰ (4) how to control the diastereomeric ratio of the products. To meet these challenges, we developed a novel method for the 1,2,3-trifunctionalization of alkenes using alkynyl triflones as both the CF₃ (ref. 6) and alkynyl sources, providing the ring-expanded cyclic β -ketoesters with excellent diastereoselectivity and functional group diversity. In addition, good functional group compatibility of this method was observed, which ensures the diverse synthetic transformations. Moreover, hydrogen bonding between the substrates and 2,2,2-trifluoroethanol solvent was revealed to be the key factor for the excellent diastereoselectivity obtained in this reaction, and this result was confirmed by both experimental and theoretical studies.

This study began by surveying radical initiators for 1,2,3-tricarbofunctionalizing α -vinyl- β -ketoester **1a** with alkynyl triflone **2a**¹¹ (Table 1). Although dibenzoyl peroxide (BPO) and lauroyl peroxide (LPO) have been shown as good radical initiators for this radical reaction, the purification of the desired product (\pm)-**3a** turned out to be a great challenge¹² (Table 1, entries 1 and 2). When azodiisobutyronitrile (AIBN) was used as the radical initiator, the complexity of the reaction decreased and product (\pm)-**3a** could be obtained in 63% ¹⁹F NMR yield with a diastereomeric ratio (dr) of 12 : 1 (Table 1, entry 3). The screening of solvents indicates that non-polar solvents such as methyl *tert*-butyl ether (MTBE) and dichloroethane (DCE) cannot improve the performance of the reaction (Table 1, entries 4 and 5). However, the reaction failed when another non-polar solvent, toluene, was used as the solvent, presumably due to the generation of trifluoromethylated toluene (Table 1, entry 6). When the reaction was performed in an aprotic polar solvent DMF or a protic polar solvent MeOH, only a trace amount of the desired product (\pm)-**3a** was detected (Table 1, entries 7 and 8).

Table 1 Reaction conditions of optimization^a



Entry	Solvent	Yield ^b (%)
1	EA	60 (dr = 13 : 1) ^c
2	EA	55 (dr = 11 : 1) ^d
3	EA	63 (dr = 12 : 1)
4	MTBE	45 (dr = 10 : 1)
5	DCE	63 (dr = 15 : 1)
6	Toluene	Trace
7	DMF	Trace
8	MeOH	Trace
9	TFE	63 (dr > 20 : 1)
10 ^e	TFE	60 (dr > 20 : 1)
11 ^f	TFE	56 (dr > 20 : 1)
12 ^g	TFE	70 (dr > 20 : 1)
13 ^h	TFE	76 (65) ⁱ (dr > 20 : 1)
14 ^j	TFE	71 (dr > 20 : 1)
15	TFE	Trace

^a Reaction conditions: alkene **1a** (0.2 mmol, 1 equiv.), **2a** (0.6 mmol, 3.0 equiv.), and AIBN (0.3 equiv.) in 3 mL of solvent at 85 °C for 18 h in a sealed tube under a nitrogen atmosphere. ^b Crude yield and crude diastereomeric ratio were determined by ¹⁹F NMR. ^c LPO was used as the initiator. ^d BPO was used as the initiator. ^e The reaction was performed at 100 °C. ^f The reaction was performed at 120 °C. ^g AIBN (60 mol%) was used. ^h **2a** (3.0 equiv.) and AIBN (60 mol%) were added as two equal portions with an interval of 9 h. ⁱ Isolated yield in parentheses. ^j **2a** (3.0 equiv.) and AIBN (60 mol%) were added as three equal portions with an interval of 6 h.

Interestingly, the use of 2,2,2-trifluoroethanol (TFE)¹³ dramatically increased the diastereoselectivity and (\pm)-**3a** could be obtained in an identical yield with an even higher dr value (dr > 20 : 1) (Table 1, entry 9). Increasing the reaction temperature resulted in a slight loss of yield (Table 1, entries 10 and 11), while increasing the loading amount of AIBN increased the yield of (\pm)-**3a** (Table 1, entry 12). Furthermore, by changing the loading model, the best ¹⁹F NMR yield of (\pm)-**3a** was obtained when alkynyl triflone **2a** and AIBN were added as two equal portions with an interval of 9 h (Table 1, entries 13 vs. 14).¹⁴ Without the addition of a radical initiator, a reaction did not happen (Table 1, entry 15). It is worth mentioning that some amounts of the 1,2-alkynyltrifluoromethylation product (without ring-expansion) were detected in all the cases during the reaction optimization. Under optimal conditions, the desired 1,3-alkynyltrifluoromethylation product (\pm)-**3a** could be isolated in 65% yield as only *syn* diastereoisomers.

Under optimal conditions, a diverse array of α -vinyl- β -ketoesters serve as substrates in this metal-free deconstruction–construction of all-carbon quaternary centers for the synthesis of carbon-ring expanded cyclic β -ketoesters (Fig. 2). In most of the cases, excellent diastereoselectivities (dr > 20 : 1) were observed by crude ¹⁹F NMR analysis. Substrates with the substituents at the 5- or 6-position of the α -vinyl- β -ketoesters



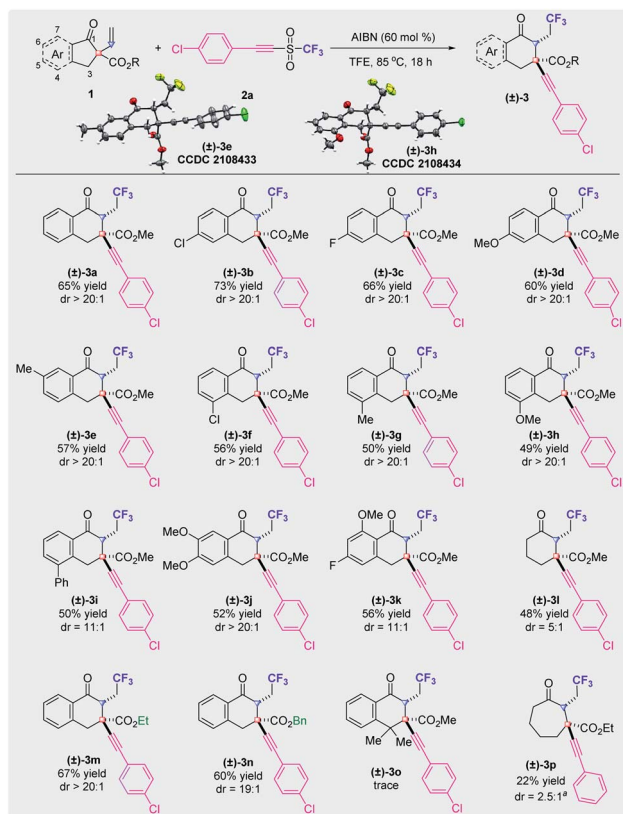


Fig. 2 Substrate scope of α -vinyl- β -ketoesters. ^aThe reaction was performed with **1p** and **2b**.

generally produced the corresponding product (\pm)-**3** in higher yields than those with the substituents at the 4-position. Apart from the carbonyl group and the ester group, functional groups such as chloride ((\pm)-**3b** and (\pm)-**3f**), fluoride ((\pm)-**3c**), a methoxyl group ((\pm)-**3d** and (\pm)-**3h**), a methyl group ((\pm)-**3e** and (\pm)-**3g**) and a phenyl group ((\pm)-**3i**) can be tolerated under the reaction conditions. Notably, the phenyl ring of the core structure with two substituents reacted smoothly to afford the corresponding products ((\pm)-**3j** and (\pm)-**3k**). When substrate **1l** that lacks the fused benzene ring was used for this carbon-ring expansion reaction, a dramatical loss of diastereoselectivity was detected, presumably because of the feasible interconversion of the boat and chair conformations of the intermediate. Substrates with an ethyl ester or a benzyl ester group, as opposed to a methyl ester group, delivered the corresponding products ((\pm)-**3m** and (\pm)-**3n**) with moderate yields and excellent diastereoselectivity. When the CH_2 unit of the six membered-ring was replaced by a CMe_2 group, only a trace amount of the desired product (\pm)-**3o** was detected. A reaction with the purpose of realizing an extension from the six-membered ring was also carried out and (\pm)-**3p** was obtained, although with a low yield and low diastereoselectivity. Notably, the diastereochemistries of products (\pm)-**3e** and (\pm)-**3h** have been confirmed by X-ray crystallography.

The scope with respect to the alkynyl triflates was also investigated and the results are summarized in Fig. 3. Generally,

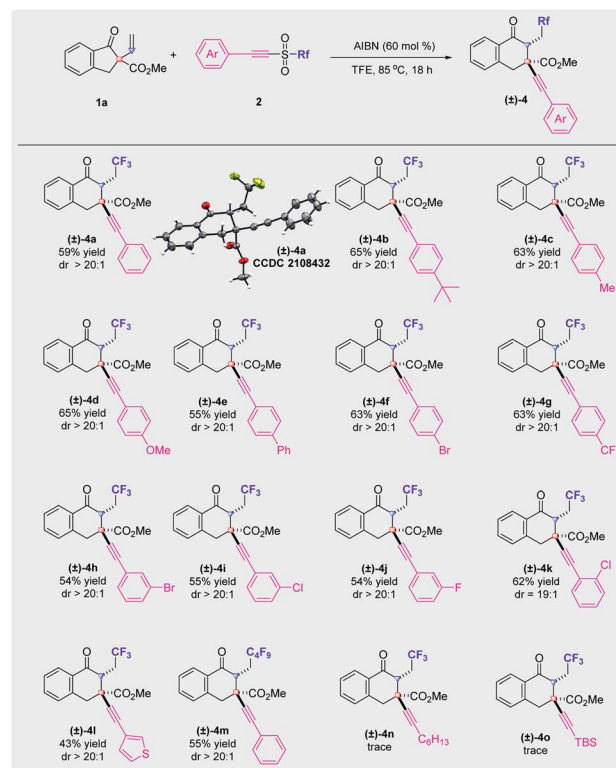


Fig. 3 Substrate scope of alkynyl triflates.

substituents on the phenyl ring of the aryethynyl moiety have little impact on the yields of the corresponding products. The functional groups at the *para*-, *meta*-, or *ortho*-position of the phenyl ring produced the desired products ((\pm)-**4a**–(\pm)-**4k**) with excellent diastereoselectivities. Furthermore, the method is compatible with alkynyl triflates that have a thienyl group or a perfluorobutyl group and the reactions afforded the product ((\pm)-**4l** or (\pm)-**4m**) with an excellent dr value, respectively. However, when the aryethynyl moiety was replaced by an alkylethynyl or a silylethynyl part, the reaction failed to produce the targeted tricarbonyl product ((\pm)-**4n** or (\pm)-**4o**).¹⁵ Moreover, when triflic azide or (*Z*)- $\text{ToI}(\text{CH}=\text{CHSO}_2\text{CF}_3)$ was used in place of the alkynyl triflate, the desired product was not obtained and most of the starting material was recovered. Notably, the diastereochemistry of product (\pm)-**4a** has been confirmed by X-ray crystallography.

This 1,2,3-trifunctionalization reaction not only allows the deconstruction and reconstruction of all-carbon quaternary centers, but features good functional group tolerance and excellent diastereoselectivity. Regarding the diverse reactivities of these functional groups, many valuable synthetic transformations have been successfully achieved (Fig. 4). For example, the C–C triple bond of (\pm)-**4a** can be completely reduced to a CH_2CH_2 unit ((\pm)-**5**) in the presence of hydrogen and a Pd/C catalyst,¹⁶ while the selective reduction of (\pm)-**4a** gives rise to a *Z*-alkene (\pm)-**6** when quinoline is added as an additive for the Lindlar reduction.¹⁷ The diastereochemistry of (\pm)-**6** has been confirmed by X-ray crystallography. The selective reducing methods afford formal approaches for radical 1,3-



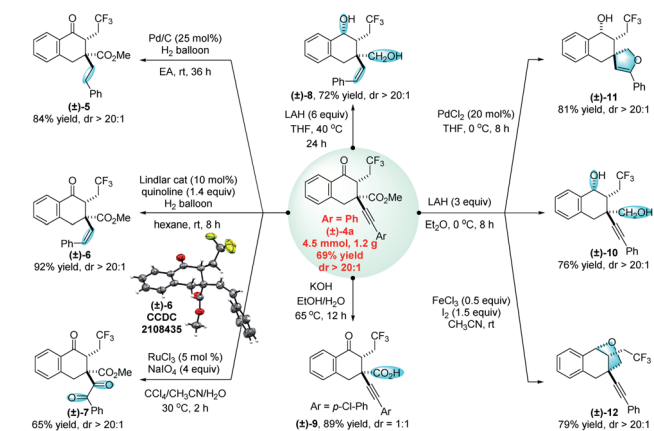
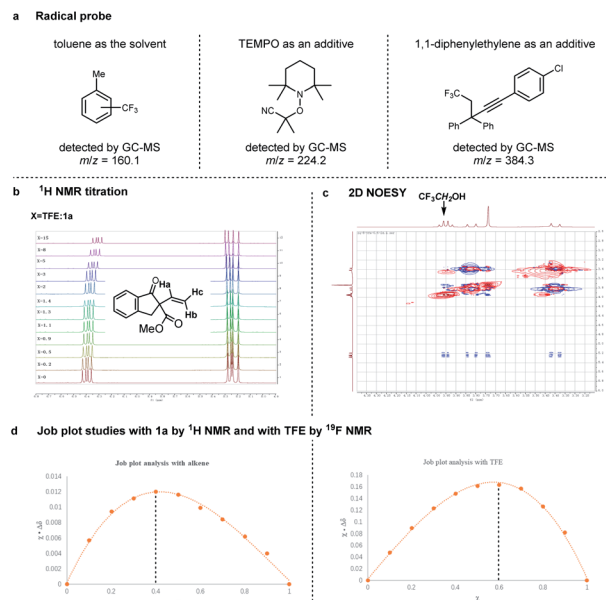


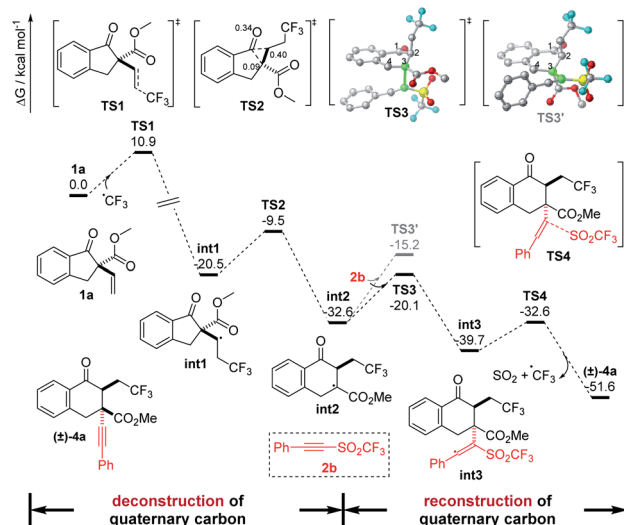
Fig. 4 Synthetic transformations.

trifluoromethylalkylation and 1,3-trifluoromethylalkenylation of α -vinyl- β -ketoesters, respectively, to produce the corresponding products which are otherwise difficult to obtain. In addition, the C–C triple bond can be oxidized under oxidative conditions with $\text{RuCl}_3/\text{NaIO}_4$, and (\pm)-**4a** can be smoothly transformed into the trifluoromethylated triketone (\pm)-**7** in 65% yield.¹⁸ With a large excess amount of reducing agent LiAlH_4 , the carbonyl group and the ester group, together with the C–C triple bond, can be unexpectedly reduced simultaneously, affording the alkenyl diol (\pm)-**8** in excellent regioselectivity. The hydrolysis process under basic conditions provided a reliable method for access to a free carboxylic acid (\pm)-**9**. Interestingly, when the reaction was performed under milder conditions compared to those for the synthesis of (\pm)-**8**, (\pm)-**4a** was successfully converted into an alkynyl diol (\pm)-**10**, which can be cyclized into a spiro compound (\pm)-**11** (ref. 19) and an endocyclic compound (\pm)-**12**,²⁰ respectively. Notably, in the majority of these cases, the excellent diastereoselectivity was reserved. These synthetic applications can demonstrate the significant value of this method.

In order to gain some mechanistic insights into this radical cascade reaction, subsequent efforts have been made (Fig. 5). First, the detection of trifluoromethylated toluene (with toluene as the solvent, Table 1, entry 6), TEMPO– $\text{CMe}_2(\text{CN})$ adduct (with TEMPO additive), and a 1,2-trifluoromethylalkynylation product of 1,1-diphenylethylene (with 1,1-diphenylethylene additive) by GC-MS analysis suggested that the reaction proceeded through a radical pathway (Fig. 5a, see ESI† for details). Second, we were curious about the excellent diastereoselectivity associated with the use of TFE as the solvent. As can be seen in Fig. 5b, ^1H NMR titration of **1a** with increasing amounts of TFE showed a chemical shift of the resonance signal corresponding to protons. The 2D NOESY spectrum indicates the existence of an interaction between **1a** and TFE (Fig. 5c). Moreover, Job plot studies by both ^1H NMR and ^{19}F NMR imply a 1 : 1.5 stoichiometry of the complex adduct resulting from **1a** and TFE (Fig. 5d). These mechanistic studies strongly suggest that the excellent diastereoselectivity of this reaction might be attributed to the hydrogen bonding between TFE and the α -vinyl- β -ketoester.

Fig. 5 Mechanism studies. (a) Radical probe; (b) ^1H NMR titration; (c) 2D NOESY; (d) Job plot studies.

On the other hand, density functional theory (DFT) calculations have also been performed at the B3LYP-D3(SMD)/Def2-TZVP//B3LYP-D3(SMD)/Def2-SVP level of theory in the TFE solvent model to further investigate the reaction pathways (Fig. 6). On the basis of the experimental results, herein, the radical pathway was considered. Initially, the CF_3 radical addition onto **1a** was calculated, and a transition state, **TS1**, was located with a free energy barrier of $10.9 \text{ kcal mol}^{-1}$ to deliver the radical intermediate **int1** with an exergonicity of $20.5 \text{ kcal mol}^{-1}$. Then, a bicyclic transition state, **TS2**,²¹ with a barrier of $11.0 \text{ kcal mol}^{-1}$ through a concerted 1,2-shift route was found to be the lower barrier TS for **int2** formation than that

Fig. 6 Gibbs free energy profile for the synthesis of **4a** in the TFE solvent model.

of the addition to **2b** for the byproduct (see Fig. S5 in ESI†), which is consistent with the experimental results of the mainly hexacyclic products. Moreover, the intrinsic reaction coordinate (IRC) calculations and the root mean square (RMS) gradient of the potential energy surface from **TS2** suggested that no transition state for the formation of the previously proposed strained alkoxy radical was found. Next, the radical intermediate **int2** attacking **2b** was calculated. To understand the diastereoselectivity of this step, the transition states of the addition of **2b** onto the Re and Si faces of C3 in **int2** were located with barriers of 12.5 and 17.4 kcal mol⁻¹ (**TS3** and **TS3'**), respectively. It is noteworthy that the torsion angle of C1–C2–C3–C4 in **TS3'** is –62.3°, larger than that of –40.9° in **int2** and –49.0° in **TS3**, indicating that the distortion factor in **TS3'** is large due to the steric effect from the trifluoroethyl group in **int2** and, therefore, increases the barrier. The transition states of **2b** addition were also optimized in solvents DCE and EA, and the free energy barrier differences between **TS3** and **TS3'** [$\Delta G^\ddagger = G^\ddagger(\text{TS3}') - G^\ddagger(\text{TS3})$] are 3.6 and 3.0 kcal mol⁻¹, respectively, in agreement with the experimental observations. Finally, dissociation of a SO₂ molecule with a CF₃ radical from **int3** to deliver the product was conducted, and a transition state **TS4** with a much lower barrier of only 7.1 kcal mol⁻¹ was located, which led to the major product (\pm)-**4a** with a relative free enthalpy of –51.6 kcal mol⁻¹.

Conclusions

In conclusion, we have developed an intermolecular 1,2,3-tricarbofunctionalization of α -vinyl- β -ketoesters through a radical process of deconstruction and construction of all-carbon quaternary centers. This one-pot reaction allows the expansion of the carbon ring by a carbon shift from the all-carbon quaternary center and enables further C–C bond formation on the tertiary carbon intermediate with the aim to reconstruct a new all-carbon quaternary center. The high level of functional group compatibility ensures the diverse synthetic transformations of this method. The experimental and theoretical studies reveal that the hydrogen bonding between the substrates and trifluoroethanol solvent is beneficial to obtaining the excellent diastereoselectivity.

Data availability

All experimental and characterization data, as well as DFT calculation data are available in the ESI.†

Author contributions

H. Bao and Y. Li directed the investigations. Y. Li prepared the manuscript. Q. Zhang, C. Ye, and X. Yuan performed the synthetic experiments and analyzed the experimental data. M.-F. Chiou conducted the theoretical calculations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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