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Letter

Radical-Mediated *α-tert*-Alkylation of Aldehydes by Consecutive 1,4- and 1,3-(Benzo)thiazolyl Migrations

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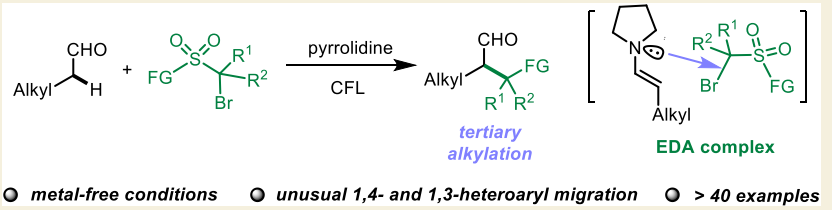


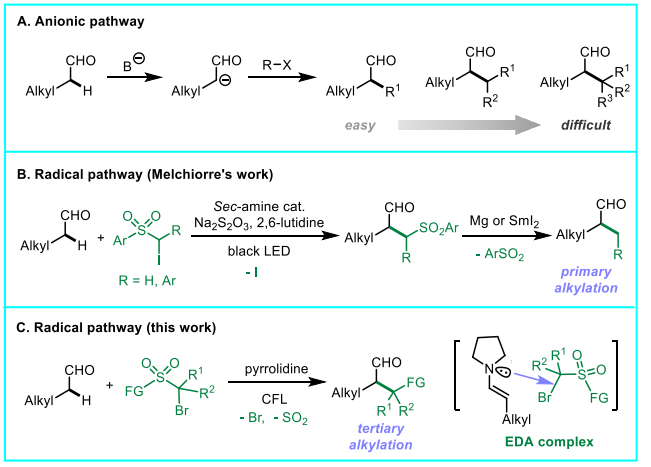
ABSTRACT: The direct alkylation of the α-position of aldehydes is an effective method for accessing a wide range of structurally diverse aldehydes, yet *tert*-alkylation has proven to be a challenging task. In this study, we present a novel radical-mediated *tert*-alkylation approach targeting the α-position of aldehydes, enabling the synthesis of complex aliphatic aldehydes. The transformation is initiated by the interaction between an *in situ* generated enamine intermediate and α-bromo sulfone, forming an electron donor−acceptor (EDA) complex, followed by consecutive 1,4- and 1,3-functional group migrations. This protocol operates under metal-free and mild photochemical conditions, delivering a broad scope of products and providing new mechanistic insights into radical rearrangement reactions.

KEYWORDS: *radical reactions, alkylation, aldehyde, functional group migration, EDA complex*

Aliphatic aldehydes are renowned for their roles as versatile intermediates in organic synthesis, representing a prominent category of compounds that are widely found in numerous natural products and bioactive molecules. The direct functionalization of the α-position in aldehydes provides an expedient route toward the generation of structurally intricate aliphatic aldehydes. Substantial research efforts have been dedicated to the α-alkylation of aliphatic aldehydes.[1] Conventionally, this process involves the electrophilic alkylation of aldehyde α-anions with alkyl halides (Scheme 1A). In this ionic process, the introduction of tertiary alkyl groups is hampered by steric congestion, coupled with the propensity of tertiary alkyl halides to undergo halide elimination. In pursuit of alternative α-alkylation approaches, significant strides have been made through radical-mediated singly occupied molecular orbital (SOMO) catalysis, as elaborated by MacMillan,[2] Melchiorre,[3] and others.[4] A noteworthy contribution by Melchiorre in 2017 featured an asymmetric α-alkylation of aldehydes to affix sulfone-pendent alkyl groups using iodoalkylarylsulfone as the alkylating agent; however, this approach necessitates an extra step to detach the arylsulfonyl group from the final product with the use of potent reducing agents (Scheme 1B).[3c] Furthermore, this method primarily facilitated the incorporation of methyl and benzyl groups.

Radical Smiles−Truce rearrangement has proven to be a powerful strategy for functionalization of alkenes, alkynes, and other functionalities.[5] Herein, we disclose the application of Smiles−Truce rearrangement for the elusive *tert*-alkylation of

Scheme 1. Alkylation of *α*-C(sp^3)-H Bonds of Aldehydes



the α-position in aldehydes. We strategically synthesized α-bromo sulfones to serve as efficient *tert*-alkylating agents. The

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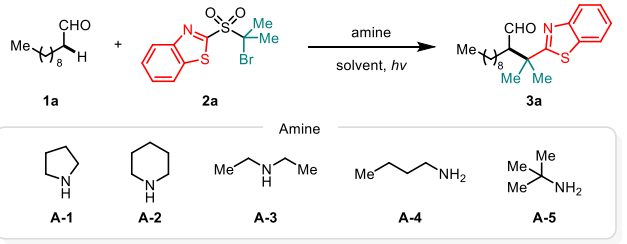
alkylation reaction is initiated through the formation of an electron donor−acceptor (EDA) complex involving the *in situ* generated enamine intermediate and the α-bromo sulfone reactant. The process unfolds via a novel series of 1,4- and 1,3-heteroaryl migration events (Scheme 1C).[6] This approach not only circumvents the challenges associated with traditional methods but also enriches the toolbox for aldehyde alkylation.

The *tert*-alkylation of aldehydes was explored using *n*-undecanal **1a** and α-bromo sulfone **2a** as model substrates for an in-depth investigation into the reaction parameters (Table 1; for details, see the SI). The process was successful with the utilization of stoichiometric quantities of pyrrolidine as the base without the aid of any external photosensitizers. Irradiation by a 45 W compact fluorescent lamp (CFL) resulted in the synthesis of the targeted product **3a** with 75% yield (entry 1). A notable drop in yield was observed when reducing the amount of pyrrolidine to substoichiometry (entry 2), suggesting that an excess of pyrrolidine is required to maintain a high enamine concentration, which acts as the radical acceptor. Subsequent optimization involved the systematic evaluation of organic solvents, wherein dichloromethane emerged as the most favorable medium (entries 3−7). The influence of light sources with different wavelengths and intensities was examined; it was found that these variables produced yields that were relatively consistent (entries 8−10). Preliminary screening of various amines suggested that secondary amines (**A-1** to **A-3**) reliably promote the reaction, whereas primary amines (**A-4** and **A-5**) proved to be ineffectual (entries 11−13). Control experiments reinforced the critical role of both amine and light, as omission of either component abolished the reaction (entries 14−15). Additionally, conducting the reaction in the presence of air massively compromised the yield (entry 16).

With the optimized reaction conditions in hand, we explored the generality of this protocol. First, the scope of aliphatic aldehydes was probed (Scheme 2). Using an excess of the aldehyde improved the reaction's conversion rate, and the aldehyde could be efficiently recovered if necessary. The procedure could be scaled up without compromising the yield, as demonstrated by the gram-scale preparation of compound **3a**. The reaction efficiency appeared to be indifferent to the length of the aliphatic chain in the aldehydes (**3a**−**3c**), yet branched aliphatic aldehydes resulted in diminished yields (**3d**), likely due to the steric hindrance adjacent to the α-position. Phenylacetaldehyde was tolerated in the reaction, enabling transformation of the benzylic site (**3e**). Our

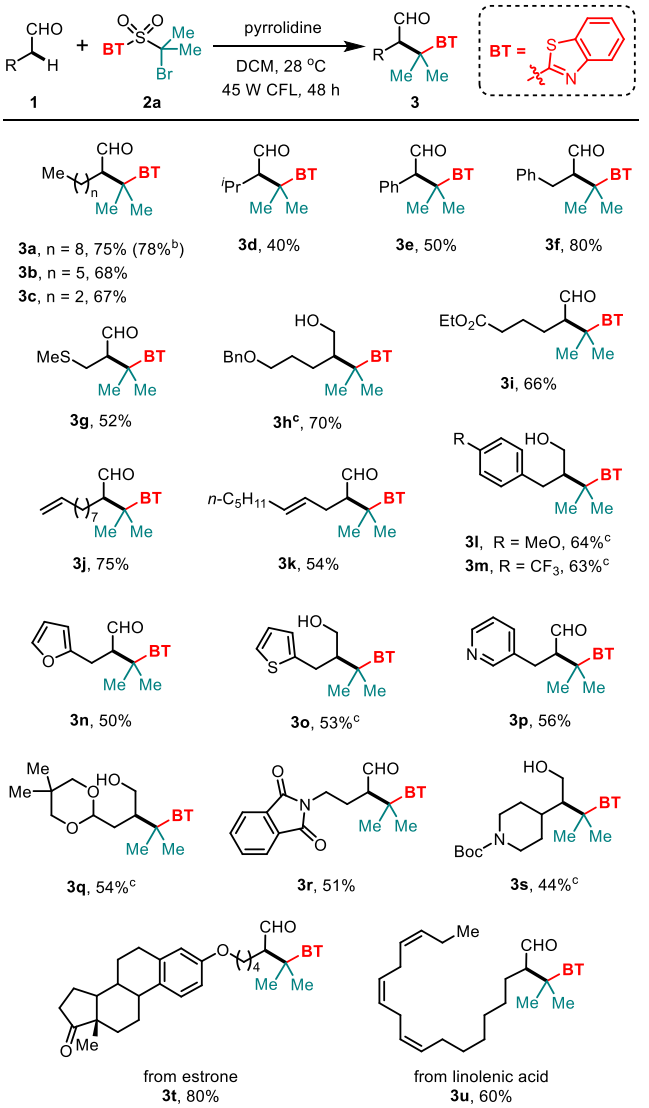
Table 1. Reaction Parameter Survey[a]



Entry	Solvent	Light source	Yield
1	DCM	45 W CFL	75%
2[b]	DCM	45 W CFL	10%
3	THF	45 W CFL	55%
4	Dioxane	45 W CFL	60%
5	DMF	45 W CFL	39%
6	MeOH	45 W CFL	23%
7	MeCN	45 W CFL	29%
8	DCM	40 W 390 nm KL	53%
9	DCM	40 W 427 nm KL	63%
10	DCM	40 W 456 nm KL	65%
11[c]	DCM	45 W CFL	66%
12[d]	DCM	45 W CFL	48%
13[e]	DCM	45 W CFL	ND
14[f]	DCM	45 W CFL	ND
15	DCM	—	ND
16[g]	DCM	45 W CFL	34%

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.1 mmol) and **A-1** (0.3 mmol) in DCM (1 mL), irradiated with light under N_2 at 28 °C for 48 h. Yields of isolated products are given. [b]With 0.05 mol **A-1**. [c]With **A-2**. [d]With **A-3**. [e]With **A-4** or **A-5**. [f]Without **A-1**. [g]Under air. KL = Kessil LED light.

Scheme 2. Scope of Aliphatic Aldehydes[a]



[a]Reaction conditions: **1** (0.6 mmol), **2a** (0.2 mmol) and pyrrolidine (0.6 mmol) in DCM (2 mL), irradiated with 45 W CFL under N_2 at 28 °C. [b]Five mmol scale. [c]Purification after treating the product with $NaBH_4$ in MeOH.

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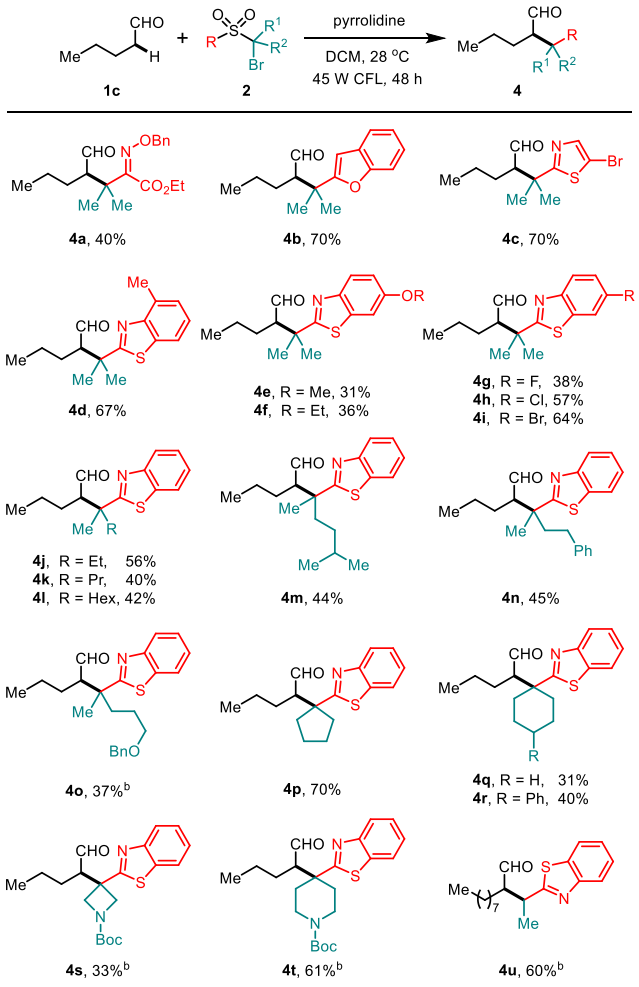
approach proved to be broadly tolerant of various functional groups. Thioethers, ethers, esters, and imides were all compatible with the reaction conditions (**3g**−**3i**, **3r**). Remarkably, alkenyl groups, especially terminal alkenes, which are susceptible to radical conditions, remained intact (**3j** and **3k**). Beside phenyl, heteroaryl (e.g., furyl, thienyl, and pyridyl) substituted aldehydes were also apt to give rise to the corresponding products (**3n**−**3p**). Sensitive groups such as acetal were not affected under the mild photochemical conditions (**3q**). This method was also applied to the modification of complex aldehydes derived from natural products (**3t** and **3u**), thereby demonstrating its practicality in synthesis. In certain instances, the aldehyde was reduced to an alcohol to facilitate product purification.

Subsequent exploration focused on the diversity of *tert*-alkylating agents (Scheme 3). Modifications were readily made to both sides of the sulfone framework. A multifunctionalized aldehyde **4a** was generated by the inclusion of an oxime-ester-substituted isopropyl group. In sulfone **2a**, the benzothiazolyl moiety was successfully replaced with various heteroaryl groups such as benzofuryl and thiazolyl, which resulted in the synthesis of corresponding products with satisfactory yields

Scheme 3. Scope of *tert*-Alkylating Agents[a]



[a]Reaction conditions: **1c** (0.6 mmol), **2** (0.2 mmol), and pyrrolidine (0.6 mmol) in DCM (2 mL), irradiated with 45 W CFL under N_2 at 28 °C. [b]With K_2CO_3 (1 equiv). **4j**: *d.r.* = 2:1; **4k**: *d.r.* = 1.5:1; **4l**: *d.r.* = 2:1; **4m**: *d.r.* = 2:1; **4n**: *d.r.* = 1:1; **4o**: *d.r.* = 2:1; **4u**: *d.r.* = 1.25:1.

(**4b** and **4c**). The introduction of assorted substituents on heteroaryls, ranging from halides to ethers, influenced the reaction efficacies (**4d**−**4i**). Moreover, the method adopted the displacement of *gem*-dimethyl groups by a variety of other alkyl chains. For example, substituting one methyl group with a bulkier counterpart still readily proceeded, yielding the desired *tert*-alkylation products (**4j**−**4o**). Tertiary cycloalkyls, including cyclopentyl and cyclohexyl groups, were also effectively integrated into the parent aldehydes (**4p**−**4r**). The method proved adept at forging complex aldehydes with incorporated *N*-heterocycles, such as azetidine and piperidine, that are otherwise difficult to synthesize (**4s** and **4t**). Furthermore, this approach was extended to achieve the *sec*-alkylation of the α-position in aldehydes (**4u**), highlighting its broad applicability.

The synthesized products can be transformed into a set of valuable compounds featuring proximal tertiary alkyl groups (Scheme 4). For example, the reduction of aldehyde **3a** to the corresponding primary alcohol **5** is accomplished using sodium borohydride, while its oxidation to carboxylic acid **6** is realized through a system coupling NHPI with O_2. The reaction of aldehyde **3a** with a Grignard reagent successfully yields secondary alcohol **7**. The conversion of aldehyde **3c** into primary amine **8** succeeded via reductive amination procedures. Furthermore, the reaction of **3a** with the Bestmann−Ohira reagent results in the synthesis of terminal alkyne **9**, and the construction of alkenes (**10** and **11**) from **3a** is achieved through the Horner−Wadsworth−Emmons (HWE) reaction or the Wittig reaction. Additionally, aldehyde conversion into epoxide **12** is attainable using dibromomethane as a base. Esterification of alcohol **5** with 3,5-dinitrobenzoic acid leads to the formation of ester **13**, whose structure has been corroborated by X-ray single-crystal diffraction.[7] An intriguing spirobicyclic architecture, compound **14**, is synthesized via intramolecular nucleophilic cyclization of **5** with excellent diastereoselectivity. Despite endeavors in asymmetric alkylation reactions employing chiral amines (**A-6** to **A-10**), optimal outcomes have yet to be attained.

Photolytic experiments were carried out to investigate the potential of compound **2a** to autonomously incur radicals through photodecomposition, without the formation of an EDA complex with the enamine intermediate. The lack of decomposition observed unequivocally excludes this mechanism (Scheme 5-1). Furthermore, the addition of a radical scavenger such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) completely suppressed the reaction, signifying that the reaction proceeds via a free radical mechanism (Scheme 5-2). In crossover experiments, where **1a** was employed reacting with two distinct sulfone reagents, the absence of cross-coupled products lends credence to the hypothesis that the reaction proceeds through intramolecular functional group translocation (Scheme 5-3). The emergence of a remarkable redshift in the UV−vis absorption spectra upon combining **1a**, **2a**, and pyrrolidine verifies the formation of an EDA complex (Scheme 5-4).[8] Lastly, the measurement of quantum yield (Φ = 5.2) indicates that a radical chain process is involved in the reaction.[9]

A plausible reaction mechanism is illustrated in Scheme 5-5. The condensation of aldehyde with pyrrolidine generates enamine **Int-I** that assembles with α-bromo sulfone to form an EDA complex. Single-electron transfer in the photoexcited EDA complex generates the radical species **Int-II**. The addition of this electrophilic radical to an enamine via **TS-II** produces

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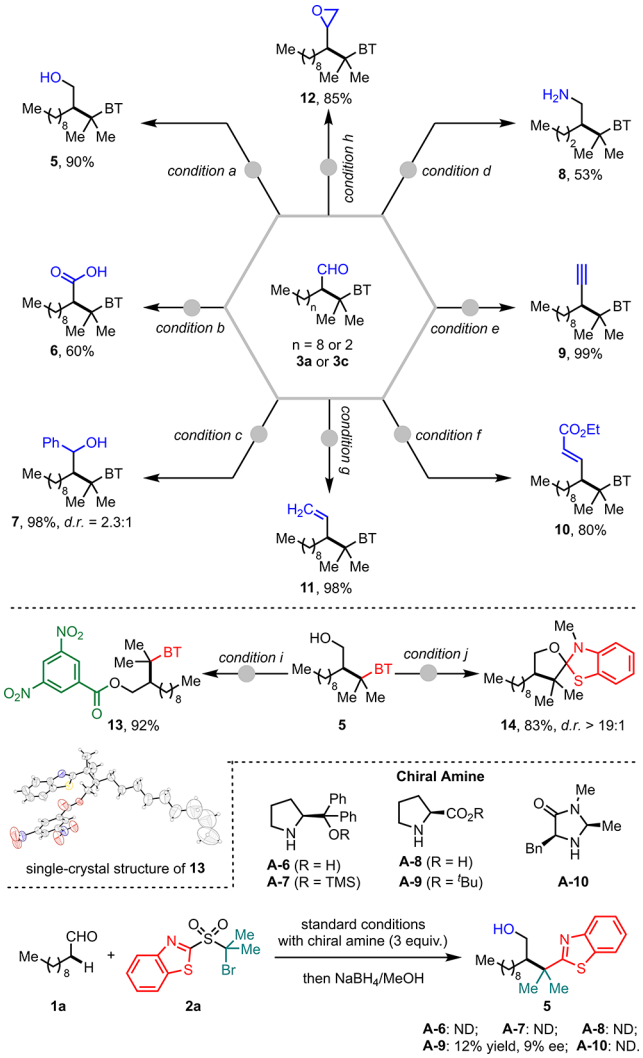
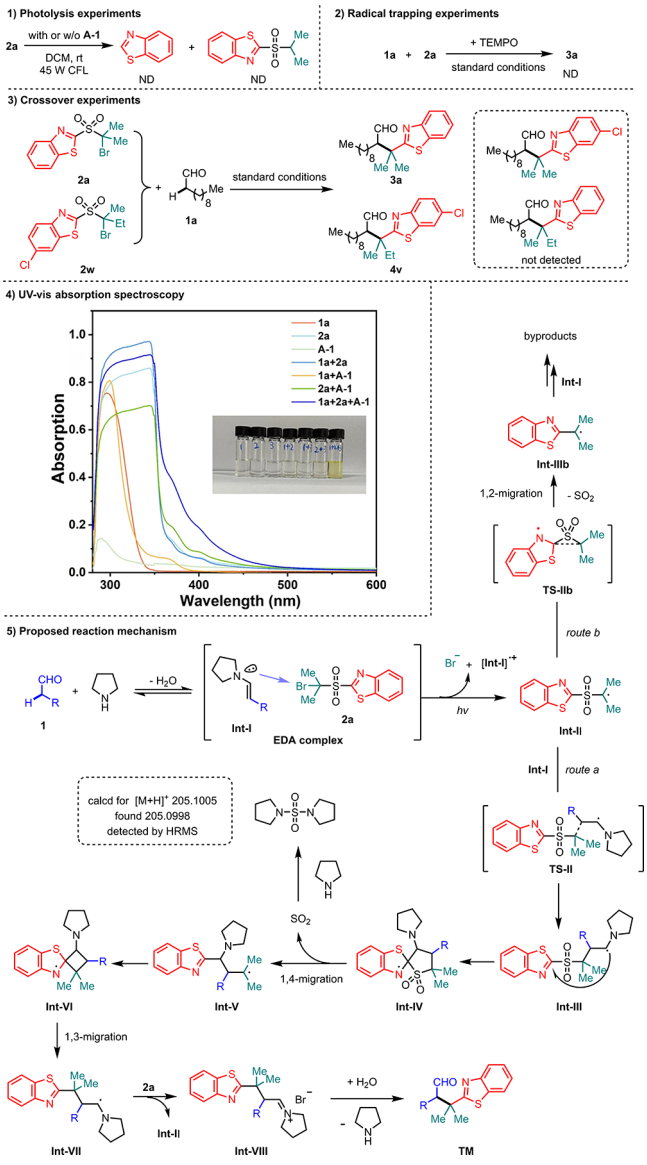
Scheme 4. Product Transformations[a]



[a]Reaction conditions: *Condition a*: $NaBH_4$, MeOH, rt. *Condition b*: NHPI, O_2, 30 °C. *Condition c*: PhMgBr, THF, −78 °C-rt. *Condition d*: *tert*-butylsulfinamide, $Ti(OEt)_4$, THF, rt; $NaBH_4$, MeOH, −50 °C-rt, then 2 N HCl. *Condition e*: dimethyl(1-diazo-2-oxopropyl)-phosphonate, K_2CO_3, MeOH, rt. *Condition f*: $EtO_2CCH_2PO(OEt)_2$, NaH, THF, 0 °C-rt. *Condition g*: Ph_3PMeBr, *n*-BuLi, THF, −78 °C-rt. *Condition h*: CH_2Br_2, *n*-BuLi, THF, −78 °C-rt. *Condition i*: 3,5-dinitrobenzoic acid, DCC, DMAP, DCM, rt. *Condition j*: MeI, NaH, THF, 0 °C-rt.

Scheme 5. Mechanistic Studies and Proposed Mechanism



Int-III (*route a*). Because a high concentration level of enamine intermediate is vital to this step, the use of stoichiometric amounts of pyrrolidine is required. Alternatively, **Int-II** may undergo 1,2-migration via **TS-IIb** to generate **Int-IIIb** after SO_2 extrusion (*route b*). Simultaneously, **Int-III** undergoes 1,4-heteroaryl migration and generates the alkyl radical **Int-V** after SO_2 extrusion. It is found that the extruded SO_2 could be captured by pyrrolidine and thus consumes pyrrolidine, evidenced by HRMS analysis.[10] The densely substituted intermediate **Int-V** undergoes unusual 1,3-heteroaryl migration via four-membered cyclic transition state driven by the Thorpe−Ingold effect,[11] leading to a stable α-amino radical **Int-VII**. The single-electron oxidation of **Int-VII** by α-bromo sulfone leads to a cationic species, which upon subsequent hydrolysis delivers the final product. Meanwhile, **Int-II** is regenerated, perpetuating the radical chain.

To gain a better understanding of the proposed reaction mechanism, density functional theory (DFT) calculations were performed. As shown in Figure 1, in the competing reaction pathway diverting at **Int-II**, the Gibbs free energy barrier is 22.4 kcal/mol to directly form **Int-IIIb** (*route b*). The high barrier possibly arises from the high strain of the three-membered ring in **TS-IIb**. Conversely, the barrier associated with the proposed radical addition pathway through **TS-II** leading to **Int-III** is substantially lower (*route a*), at only 5.5 kcal/mol, indicating that *route a* is kinetically more favored. Furthermore, energy profile calculations reinforce the viability of the suggested reaction mechanism. The cyclization step transforming **Int-V** into an unstable intermediate, **Int-VI**, via **TS-V**, necessitates overcoming a Gibbs free energy barrier of 20.4 kcal/mol. Subsequently, the 1,3-heteroaryl migration to yield **Int-VII** through **TS-VI** is considerably more facile, with a barrier of just 1.6 kcal/mol. The overall Gibbs free energy change from **Int-II** to **Int-VII** is −26.1 kcal/mol, indicating

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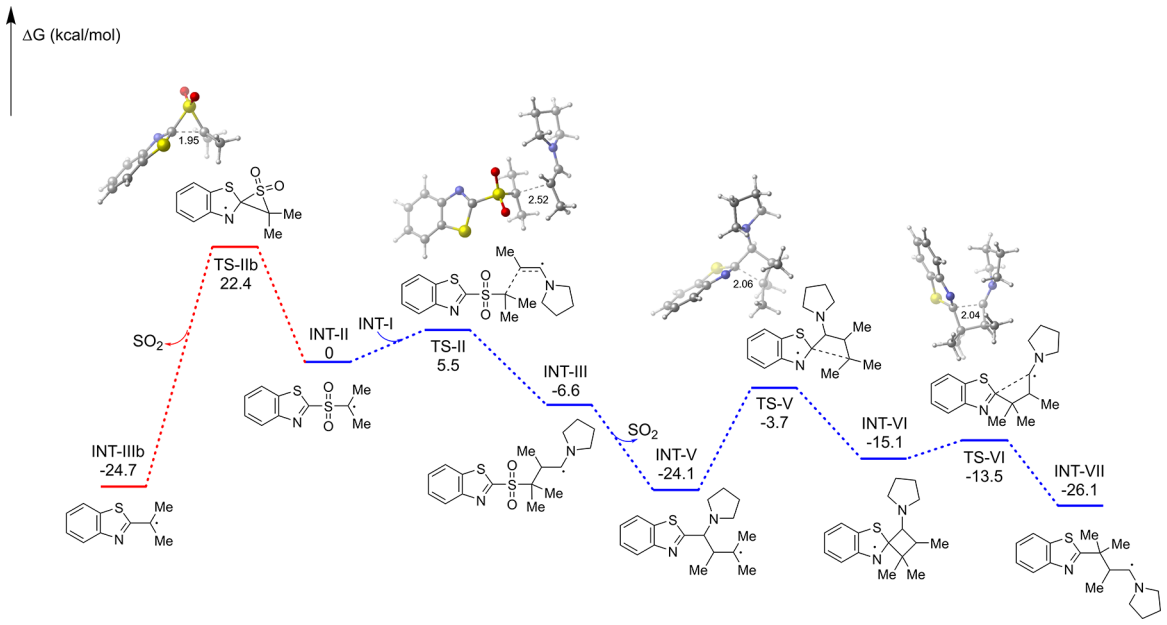

Figure 1. DFT calculations of possible mechanisms.

that *route a* is both kinetically and thermodynamically more favorable.

In summary, this study delineates a radical-mediated tertiary alkylation process targeting the α-position in aliphatic aldehydes. The reaction proceeds through the difunctionalization of an *in situ* formed enamine intermediate with a strategically engineered α-bromo sulfone and undergoes successive 1,4- and 1,3-functional group migrations. The utilization of secondary amines is pivotal, as they promote enamine formation which subsequently interacts with α-bromo sulfone, resulting in an electron-donor-acceptor (EDA) complex. This complex acts as a precursor for radical species under photoirradiation, thereby triggering the chemical transformation. This protocol is distinguished by its metal-free environment and its ability to produce a wide array of complex aliphatic aldehydes and provides a strategic, complementary approach for the challenging *tert*-alkylation at the α-position of aldehydes, a goal not readily attainable via conventional anionic strategies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00322.

Experimental procedures, NMR, HRMS, IR data, and NMR spectra for all new compounds (PDF)

Single-crystal structure of **13** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Jige Liu** data curation, formal analysis, investigation, writing-original draft; **Jiangshan Ma** formal analysis, investigation; **Tongkun Wang** investigation; **Xiao-Song Xue** software, supervision; **Chen Zhu** conceptualization, funding acquisition, supervision, writing-review & editing.

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Notes

The authors declare no competing financial interest.

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