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Merging "*Anti*-Baldwin" 3-*Exo-Dig* Cyclization with 1,2-Alkynyl Migration for Radical Alkylalkynylation of Unactivated Olefins

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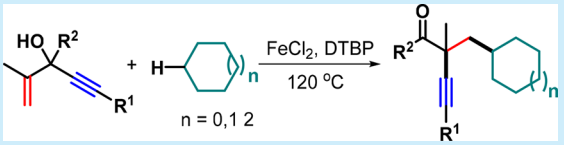
Supporting Information

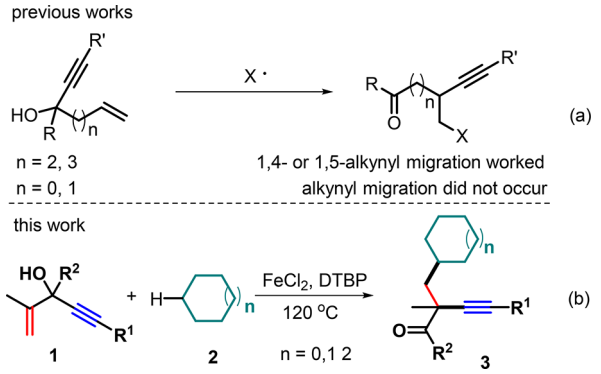
ABSTRACT: A new combination of "*anti*-Baldwin" 3-*exo-dig* cyclization with 1,2-alkynyl migration of 1,4-enynes with simple cycloalkanes was established, enabling C−C breaking and reconstruction to access a wide range of α-alkynyl ketones with generally good yields by $FeCl_2$/di-*tert*-butyl peroxide (DTBP) as a catalytic oxidation system. Radical-induced C(sp^3)−H functionalization of cycloalkanes was realized, leading to the direct formation of C(sp^3)−C(sp^3) and C(sp)−C(sp^3) bonds. The mechanism for forming α-alkynyl ketones was proposed.



Due to low polarity and high bond-dissociation energy (BDE), C(sp^3)−H functionalization has become a challenging and attractive mechanism and has aroused the interest of many chemists. Over the years, substantial significant advances have been achieved in this field,[1] in which the vast majority of efforts had been made on C(sp^3)−H functionalization adjacent to heteroatoms,[2] phenyl,[3] alkenyl,[4] and electron-withdrawing groups.[5] In contrast, research on inert C(sp^3)−H functionalization of simple alkanes has been relatively less popular, but is full of challenge.[6] Recently, oxidative coupling reactions (OCRs) have proven to be a powerful and promising tool for forging carbon−carbon and carbon−heteroatom bonds in the organic community, because of its step and atom economy without prefunctionalizations, therefore providing high-efficient pathways for inert C(sp^3)−H functionalization of simple alkanes.[7] For example, Li's group reported an interesting ruthenium catalyzed oxidative coupling reaction between cycloalkanes and chelating arenes for direct inactive C(sp^3)−H functionalization.[8] Later, our group discovered an unprecedented dual α,α-C(sp^3)−H difunctionalization of cycloalkanes under oxidative conditions.[9] Despite these limited significant advances, the development of a new and facile protocol for inert C(sp^3)−H bond functionalization of cycloalkanes toward functionalized molecules is still highly desirable.

Over the past decade, we have witnessed a growing boom in the radical-induced difunctionalization of alkenes,[10] especially via the functionality migration strategy.[11] Specifically, Zhu and other groups reported the difunctionalization of alkenes by aryl,[12] cyano,[13] formyl,[14] heteroaryl,[15] alkynyl,[16] and alkenyl[17] migration, respectively. Notably, Zhu's group pioneered radical alkynylation of unactivated alkenes through distal 1,4- and 1,5-alkynyl migration, but 1,2- and 1,3-alkynyl migration did not work (Scheme 1a).[16a] They suggested that the migration prefers five- or six-membered cyclic transition states thermodynamically rather than three- or four membered cyclic transition states.[16a] It is well-known that the tertiary carbon radical is more stable than the secondary carbon radical. Thus, we considered preparing the 1,4-enynes with the replacement of an isopropenyl group for the vinyl moiety. In view of the abundance and easily availability of cycloalkanes and the continuation of our efforts on the direct C(sp^3)−H functionalization, we attempted to employ the preformed 1,4-enynes with an isopropenyl unit to react with simple cycloalkanes to evaluate the possibility of 1,2-alkynyl migration. Interestingly, with $FeCl_2$/di-*tert*-butyl peroxide (DTBP) as the catalytic oxidation system, the reaction worked well to afford the corresponding α-alkynyl ketones with generally good yields via radical 3-*exo-dig* cyclization/1,2-alkynyl migration. Notably, in Baldwin's rules, 3-*exo-dig* cyclization is generally considered to be unfavorable. During our reaction process, this reaction involving "*anti*-Baldwin" 3-*exo-dig* cyclization enabled C−C breaking and reconstruction via radical-induced alkylalkynylation of unactivated alkenes under the mild catalytic oxidative conditions. Here, we describe a new and attractive1,2-alkynyl

Scheme 1. Radical-Induced Alkynyl Migration



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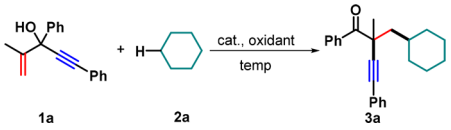
migration of 1,4-enynes via radical relay for achieving the C(sp^3)–H bond alkylation of cycloalkanes. To the best of our knowledge, there is no precedent report on the 1,2-alkynyl migration of 1,4-enynes through radical-triggered "*anti*-Baldwin" 3-*exo*-*dig* cyclization.[18]

Our initial attempts focused on identifying the optimized conditions for the reaction of the preformed 1,4-enyne **1a** and cyclohexane **2a** as both a reaction component and reaction media. With $FeCl_2$ as the catalyst and *tert*-butyl peroxybenzoate (TBPB, 4.0 equiv) as the oxidant, the reaction proceeded readily at 120 °C, leading to the clean formation of the migration product **3a** in 52% yield (Table 1, entry 1). This

Table 1. Optimization of the Reaction Conditions[a]



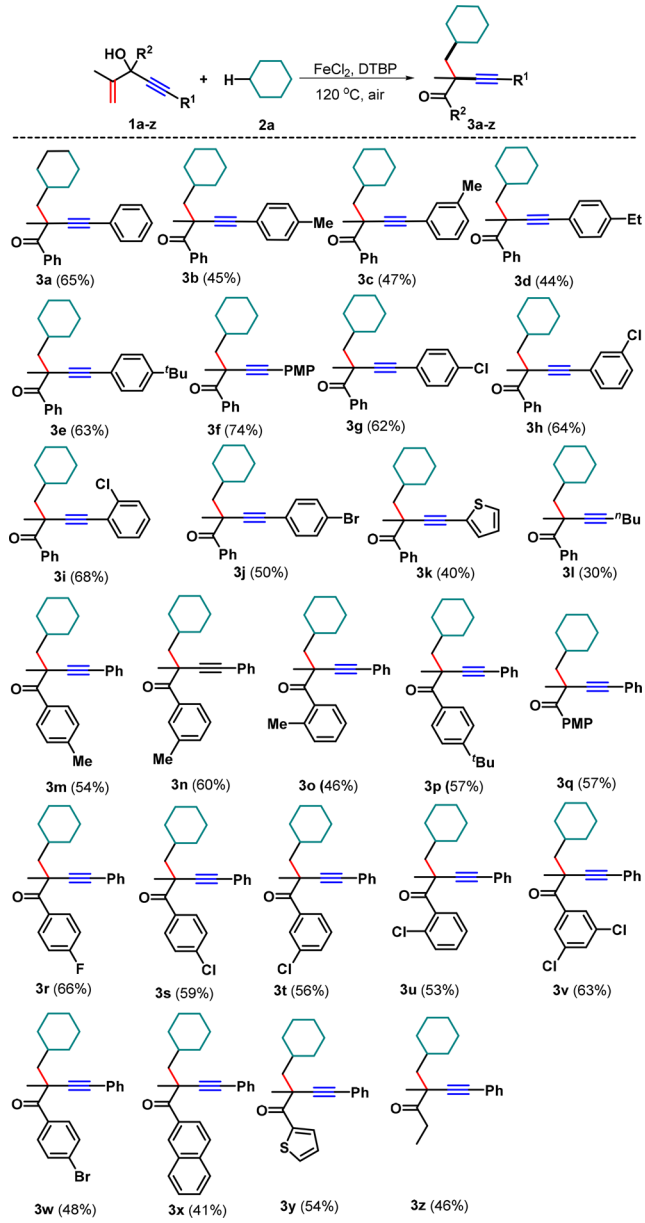
entry	cat. (10 mol %)	oxidant (equiv)	temp (°C)	yield[b] (%)
1	$FeCl_2$	TBPB (4.0)	120	52
2	$FeCl_2$	TBHP (4.0)	120	trace
3	$FeCl_2$	DTBP (4.0)	120	65
4	$FeCl_2$	DTBP (4.0)	110	47
5	$FeCl_2$	DTBP (4.0)	100	37
6	$FeCl_2$	DTBP (3.0)	120	58
7	$FeCl_2$	DTBP (2.0)	120	35
8	–	DTBP (4.0)	120	60
9	$FeCl_3$	DTBP (4.0)	120	49
10	CuI	DTBP (4.0)	120	53
11	Cu_2O	DTBP (4.0)	120	47
12	$Cu(OTf)_2$	DTBP (4.0)	120	trace

[a]Reaction conditions: 1,4-enyne **1a** (0.2 mmol, 1.0 equiv), cyclohexane **2a** (2.0 mL), catalyst (10 mol %), oxidant (*x* equiv), under the air conditions, for 12 h. [b]Isolated yield based on **1a**.

satisfactory result prompted us to further search for the optimal reaction conditions. Changing the oxidant from TBPB to *tert*-butyl hydroperoxide (TBHP) completely suppressed the reaction process (entry 2). The use of di-*tert*-butyl peroxide (DTBP) as the oxidant gave the best outcome as the product **3a** was offered in 65% yield (entry 3). We discovered that the reaction temperature was an important factor in affecting the reaction efficiency. The decrease of the reaction temperature is not beneficial to the transformation, and inferior results were observed (entries 4 and 5). Moreover, the yield of product **3a** dropped remarkably when lowering the amount of DTBP (entries 6 and 7). Without $FeCl_2$, the transformation could give a 60% yield of product, but necessitated the prolonging of the reaction time to 32 h (entry 8). The following screening of metal salts revealed that $FeCl_3$, CuI, Cu_2O, and $Cu(OTf)_2$ were found to be inferior in terms of catalytic performance in the transformation as compared with $FeCl_2$ (entries 9–12).

With the optimized reaction conditions in hand, we set out to investigate the generality of the migration reaction of 1,4-enynes by utilizing cycloalkanes as the solvent and C-radical precursors (Scheme 2). 1,4-Enynes **1** with diverse functionalities were first examined in combination with cyclohexane (**2a**) under the optimal conditions. Both electron-rich and electron-poor groups at different positions of the arylalkynyl moiety (R^1) can all tolerate this radical relay system well, delivering the corresponding products **3b**–**3j** in 30%–74%

Scheme 2. Substrate Scope of 1,2-Alknyl Migration[a,b]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), cyclohexane **2a** (2.0 mL), $FeCl_2$ (10 mol %), DTBP (4.0 equiv), under the air conditions, 12 h. [b]Isolated yield in parentheses based on **1**.

yields. Diverse functionalities, such as methyl (**1b** and **1c**), ethyl (**1d**), *tert*-butyl (**1e**), methoxy (PMP = *p*-methoxyphenyl, **1f**), chloro (**1g**, **1h** and **1i**), and bromo (**1j**), were proven to be favorable for this alkynyl migration. Notably, 1,4-enynes carrying thienyl (**1k**) and *n*-butyl (**1l**) on the alkynyl moiety could be readily transformed into α-alkynyl ketones **3k** and **3l**, respectively, albeit with 40% and 30% yields. The electronic nature of substituents (R^2) attached by a quaternary carbon of 1,4-enynes was then evaluated. The alkynyl migration reaction still worked well with various functional groups, including methyl, *tert*-butyl, methoxy, fluoro, chloro, and bromo, locating at the different positions of the phenyl ring (R^2), enabling radical-induced alkylalkynylation of unactivated alkenes to access the corresponding α-alkynyl ketone products **3m**–**3w** with yields from 46% to 66%. Moreover, a sterically

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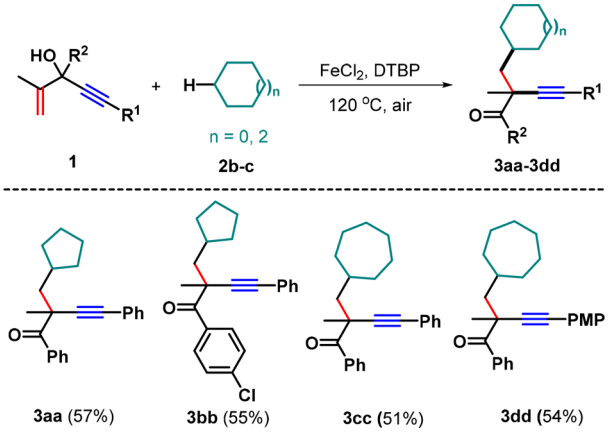
encumbered 2-naphthyl (2-Np) analogue **1x** was an appropriate reaction partner, which underwent the similar radical relay alkynyl migration process toward the corresponding product **3x** in 41% yield. Alternatively, thienyl and ethyl functionalities linked by quaternary carbon (**1y** and **1z**) were found to show high reactivity, resulting in thienyl and ethyl substituted α-alkynyl ketones **3y** and **3z** in 54% and 46% yields, respectively.

Next, the scope with respect to other cycloalkane components as C-radical precursors, such as cyclopentane (**2b**) and cycloheptane (**2c**), was investigated. As anticipated, both of these cycloalkanes were proven to be suitable substrates, thus enabling the C-radical relay approach to furnish the corresponding α-alkynyl ketones **3aa**−**3dd** in moderate yields (Scheme 3). The structures of these α-alkynyl ketones

Scheme 3. Application of 1,2-Alknyl Migration[a,b]

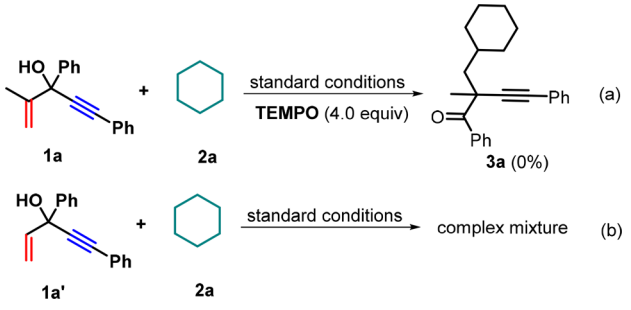


[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), cycloalkanes **2b**−**c** (2.0 mL), $FeCl_2$ (10 mol %), DTBP (4.0 equiv), under the air conditions, 12 h. [b]Isolated yield in parentheses based on **1**.

were fully characterized by their NMR spectroscopy and HRMS data. Furthermore, sulfonyl hydrazone **4a** derived from α-alkynyl ketone **3a** and *p*-tosylhydrazine was confirmed by X-ray diffraction analysis (CCDC 1844500).

To understand the mechanism of this reaction, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[19] as the radical scavenger was subjected to the reaction system under the standard conditions; the desired α-alkynyl ketone **3a** was not observed and the starting materials were recovered, indicating that this transformation may include a radical process (Scheme 4a). When the methyl group on the terminal olefin unit was replaced with hydrogen, the reaction of 1,4-enyne **1a′** gave a complex mixture under the standard conditions, showing that

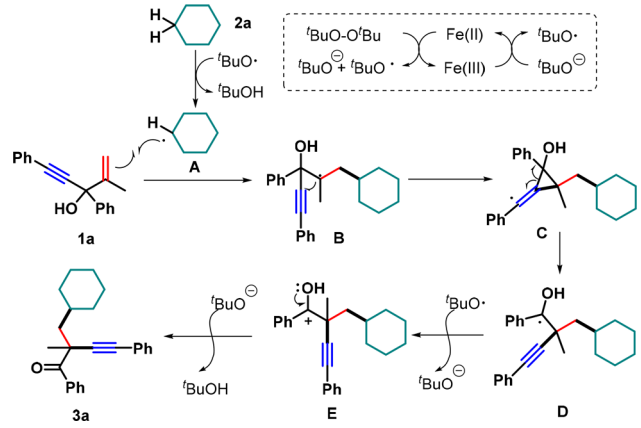
Scheme 4. Control Experiments



the methyl group linked to the terminal olefin unit was the key in the success of this transformation (Scheme 4b).

On the basis of the above results and previous reports,[9,16a] a reasonable mechanism is depicted in Scheme 5. Initially, Fe(II)

Scheme 5. Plausible Reaction Pathways



catalyzes the decomposition of DTBP to afford a *tert*-butoxy radical intermediate and *tert*-butoxy anion, which is further oxidized by Fe(III) to form a *tert*-butoxy radical intermediate and release Fe(II).[9] Then, cyclohexane is converted into cyclohexane radical **A** by H-abstraction of the *tert*-butoxy radical. The addition of cyclohexane radical **A** to the terminal alkene unit of 1,4-enyne **1a** gives radical intermediate **B**, followed by 3-*exo*-*dig* cyclization ("*anti*-Baldwin" rules) and alkynyl migration (the homolysis of the C−C bond) to render hydroxyalkyl radical **D**. Finally, a single electron oxidation of the intermediate **D** leads to the carbon cation **E**, which loses a proton to give the desired product **3a**.

In summary, starting from easily available 1,4-enynes and simple cycloalkanes, we have established a new combination of "*anti*-Baldwin" 3-*exo*-*dig* cyclization with 1,2-alkynyl migration for the practical synthesis of a wide range of α-alkynyl ketones with generally good yields under the catalytic oxidative conditions. The C-centered radical-induced alkylalkynylation of unactivated olefins enabled the direct formation of $C(sp^3)$−$C(sp^3)$ and $C(sp)$−$C(sp^3)$ bonds with simultaneous realization of $C(sp^3)$−H functionalization in one step. This chemistry is very rarely seen in chemical science. Further application of this attractive radical 1,2-alkynyl migration strategy is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01382.

Experimental procedures and spectroscopic data for all new compounds **3a**−**3dd** (PDF)

Accession Codes

CCDC 1844500 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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