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Article

Iridium-Catalyzed Intramolecular β-C−H Alkenylation of Ketones with Alkynes via a Hydride-Transfer Approach

Bo Zhou, Shuang Deng, Yin Xu, Xiaotian Qi,* and Guangbin Dong*

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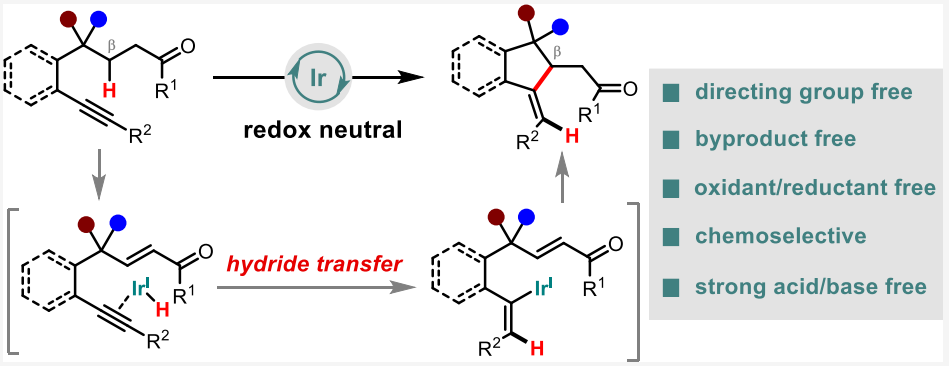

ABSTRACT: Direct functionalization of carbonyl β C−H bonds without using directing groups has not been a trivial task, and it is even more challenging to realize the corresponding atom-economical transformations with common alkenes or alkynes as the coupling partner. Here, we describe the development of an iridium-catalyzed intramolecular direct β-alkenylation of ketones with regular alkynes. The reaction is redox neutral, avoids strong acids or bases, and tolerates various functional groups. The combined experimental and computational mechanistic studies reveal a hydride-transfer pathway, involving ketone α,β-desaturation, iridium-hydride-mediated alkyne insertion, conjugate addition, and α-protonation.

INTRODUCTION

Ketone moieties ubiquitously exist in feedstock chemicals and synthetic intermediates. They have served as important handles for the functionalization of organic molecules.[1] While the ipso and α-positions of ketones are quite reactive, direct functionalization at the inert β position remains a nontrivial task. Classical methods based on conjugate addition of pre-formed α,β-enones have been efficient and broadly used in complex molecule synthesis.[2,3] Elegant modern strategies (Scheme 1A) based on directed C−H metalation or β-radical formation have been realized for site-selectively converting ketone β-C(sp^3)−H bonds to a functional group, although some intrinsic requirements are associated.[4] For example, linear ketones are needed for the directing group (DG)-mediated reactions,[5] and less bulky cyclic ketones or silyl enol ethers are used to generate β-radicals.[6,7] On the other hand, the merger of catalytic α,β-desaturation with in situ or one-pot addition of nucleophiles offers a complementary approach, in which stoichiometric oxidants are necessary to generate the enone intermediates.[8]

To devise redox-neutral β-functionalization of carbonyl compounds, our laboratory has been developing a Pd-catalyzed redox-cascade strategy for direct β-arylation,[9] β-alkylation,[10] and β-alkenylation,[11] employing organohalides as the coupling partners. Considering the issue of forming stoichiometric by-products when using organohalides, it would be more attractive if unsaturated hydrocarbons, such as unactivated alkenes or alkynes, can be used as the β-functionalization reagents. As illustrated in Scheme 1B, we proposed that after α-metalation and β-H elimination, the metal hydride intermediate could be trapped by the unsaturated hydrocarbon via migratory insertion (MI), and the resulting new carbo-metal species could then undergo conjugate addition to the enone intermediate to furnish the β-functionalization, and regenerate the catalyst after protonation. In this proposed process, the metal catalyst remains in the same oxidation state, and no stoichiometric by-product is formed.

Toward this goal, a Pd-catalyzed intramolecular β-alkenylation of cyclohexanones with aryl alkynyl groups has been recently discovered (Scheme 1C).[12] However, the reaction suffers from a limited substrate scope and low efficiency due to several off-cycle side reactions. In addition,

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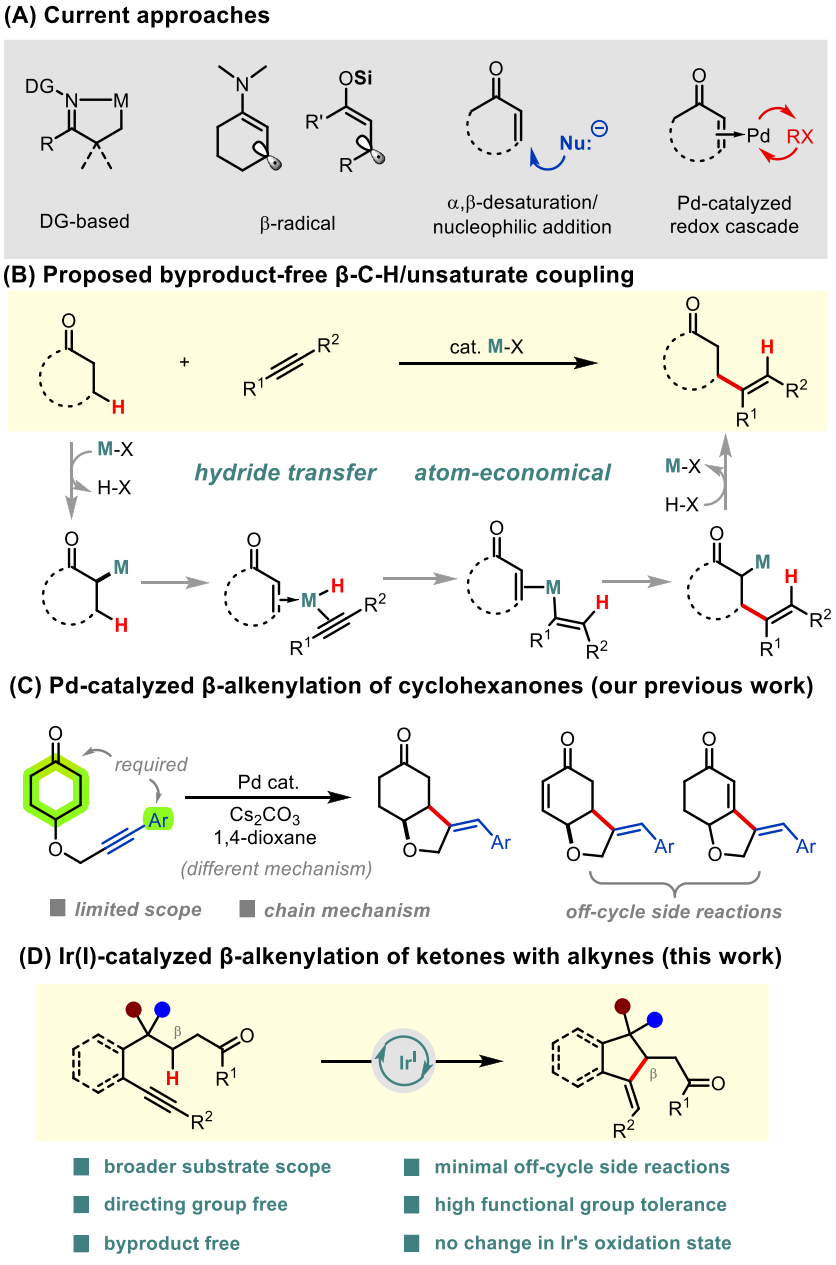
Scheme 1. Catalytic β-Functionalization of Ketones



the detailed mechanistic studies do not support the proposed metal-hydride MI pathway; instead, the reaction involves a cyclometalation and a chain-transfer process. To address these shortcomings, a new catalytic system operated by a different catalytic mechanism would be imperative. Herein, we disclose the development of an Ir-catalyzed intramolecular β-alkenylation of ketones with various alkynyl groups (Scheme 1D). The reaction is DG and oxidant free and works for both acyclic and cyclic ketones. The mechanistic studies support the proposed hydride-transfer pathway.

RESULTS AND DISCUSSION

Reaction Optimization. To examine the feasibility of the proposed strategy, an alkyne-tethered acyclic ketone (**1a**) was selected as the model substrate. After systematic evaluation of various reaction parameters, the desired β-alkenylation product **3a** was obtained in 89% yield (Table 1, entry 1), with 10 mol % $[Ir(COD)_2]BArF$ as the catalyst[13] and 40 mol % LiO*t*-Bu/4-fluorophenol as the additive in DME at 80 °C. Unsurprisingly, the alkene moiety in the initially formed product (**2a**) tends to migrate under the reaction conditions to give a more stable indene compound (**3a**). Simple workup with HCl cleanly afforded **3a** in one pot, and its structure was unambiguously determined by the X-ray crystallography of its hydrazone derivative (vide infra, Scheme 3). With this Ir catalyst system, the potential overoxidation to β-alkenyl enones[12,14] or the competing α-alkenylation[15] was not observed, representing an advantage over the prior Pd system. A set of control experiments were conducted to understand the role of each component. In the absence of the Ir catalyst, the reaction exhibited low conversion, and no β-alkenylation product was obtained (entry 2). The replacement of $[Ir(COD)_2]BArF$ with neutral $[Ir(COD)OMe]_2$ resulted in a somewhat lower yield (entry 3), while $[Rh(COD)_2]BArF$ led to the decomposition

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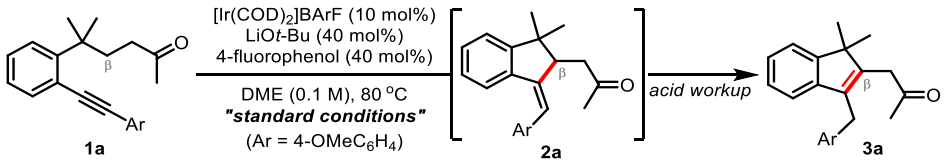
Table 1. Selected Reaction Optimization with Substrate 1a[a]



entry	variation from the "standard conditions"	yield (%)[b]	unreacted **1a** (%)[b]
1	**none**	**89(82**[c]**)**	**<2**
2	w/o $[Ir(COD)_2]BArF$	0	86
3	$[Ir(COD)OMe]_2$ instead of $[Ir(COD)_2]BArF$	79	5
4	$[Rh(COD)_2]BArF$ instead of $[Ir(COD)_2]BArF$	6	18
5	w/o LiO*t*-Bu	3	7
6	NaO*t*-Bu instead of LiO*t*-Bu	82	4
7	KO*t*-Bu instead ofLiO*t*-Bu	74	3
8	Cs_2CO_3 instead of LiO*t*-Bu	22	73
9	w/o 4-fluorophenol	26	16
10	2,2′-biphenol instead of 4-fluorophenol	86	2
11	phenol instead of 4-fluorophenol	85	3
12	benzoic acid instead of 4-fluorophenol	15	83
13	LiOPh instead of LiO*t*-Bu/4-fluorophenol	69	10
14	THF instead of DME	55	38
15	MTBE instead of DME	63	22
16	toluene instead of DME	27	60
17	90 °C instead of 80 °C	78	<1
18	70 °C instead of 80 °C	64	31

[a]Unless otherwise noted, all reactions were run with **1a** (0.1 mmol) in 1.0 mL solvent at 80 °C for 48 h and then worked up with HCl (0.5 M in 1,4-dioxane) under 60 °C for 6 h. [b]Determined by ^1H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield. BArF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, COD = 1,5-cyclooctadiene, DME = 1,2-dimethoxyethane, MTBE = methyl *tert*-butyl ether.

of the substrate (entry 4). Notably, the additives proved to be critical to the reaction efficiency. Without LiO*t*-Bu or 4-fluorophenol, the reaction gave a low yield with severe decomposition of the substrate (entries 5 and 9). A survey of different bases indicated that *t*-BuO^- bases are superb for this transformation (entries 6−8). Simple phenol or 2,2′-biphenol is more effective than more acidic benzoic acid (entries 10−12). It is likely that the phenol additive could serve as an efficient proton shuttle. Given that LiO*t*-Bu can react with phenols, the direct use of LiOPh gave a slightly lower yield and conversion (entry 13). Solvent effects were also surveyed: DME was superior to other ether solvents, such as THF and MTBE, while the less polar toluene results in much lower conversion (entries 14−16). Finally, the reaction could also take place at higher or lower temperatures, albeit with lower mass balance or lower conversion (entries 17 and 18).

Substrate Scope. With the optimized reaction conditions in hand, the scope based on the acyclic ketone scaffold was first investigated (Table 2). In general, substrates containing an electron-rich or -poor arene on the alkyne part can react smoothly to deliver the desired *β*-alkenylation products **3a**−**3t**.[16] In addition, substitutions on the aryl ortho (**3p**, **3q**), meta (**3m**−**3o**), or para (**3a**, **3c**−**3l**) positions were all tolerated, suggesting that the reaction is not sensitive to steric hindrance on the arenes. Owing to the relatively milder reaction conditions, the reaction exhibits excellent functional group compatibility. A broad range of functional groups, including phenyl ether (**3d**), sulfonamides (**3f**, **3t**), trifluoromethyl ether (**3g**), fluoride (**3h**), chloride (**3i**, **3n**), bromide (**3j**, **3q**), trifluoromethyl group (**3k**), nitrile (**3l**), carboxylic ester (**3o**), naphthalene (**3r**), and silyl ether (**3v**), survived due to the redox-neutral reaction conditions. Heterocyclic moieties, such as 1,3-benzodioxole (**3s**) and Ts-protected indole (**3t**), were also well compatible. In addition, the substrates with alkyl-substituted alkynyl groups (**3u**, **3v**) are also competent for this transformation, which was challenging for the prior Pd catalysis system.[12] Besides methyl ketones, other alkyl-substituted ketones (**3w**, **3x**) and phenyl ketones (**3y**) underwent the regioselective *β*-alkenylation to provide the corresponding 1*H*-indene products. Moreover, substrates bearing electron-withdrawing (**3z**) or -donating substituents (**3aa**) on the ortho phenylene linkers worked well. Furthermore, aside from the geminal-dimethyl linkage, other quaternary carbon centers (**3ab**−**3ae**) are also suitable for this transformation. It is noteworthy that in the absence of the quaternary carbon center, the desired cyclization product (**3af**) can still be obtained with a simple methylene, albeit in a lower conversion, implying an important role of the Thorpe−Ingold effect in this reaction.[17]

To retain the originally formed exocyclic alkene moiety, the substrate scope was further explored without an acid workup (Table 3). In the absence of the HCl treatment, the corresponding *γ*,*δ*-enone products **2** can indeed be isolated as the major products after careful isolation. Further exploration shows that the *β*-alkenylation can take place smoothly for the substrates without the orthophenylene linker to afford simple cyclopentane products (**5a**−**5c**). While the Thorpe−Ingold effect is still important for this type of substrates, this method shows the potential to access more diverse cyclic compounds.[18]

In addition to acyclic ketones, preliminary success has been achieved with cyclohexanone-derived substrates (Table 4).[19] After further tuning the reaction parameters, the desired *β*-alkenylation was realized with decent efficiency when 20 mol %

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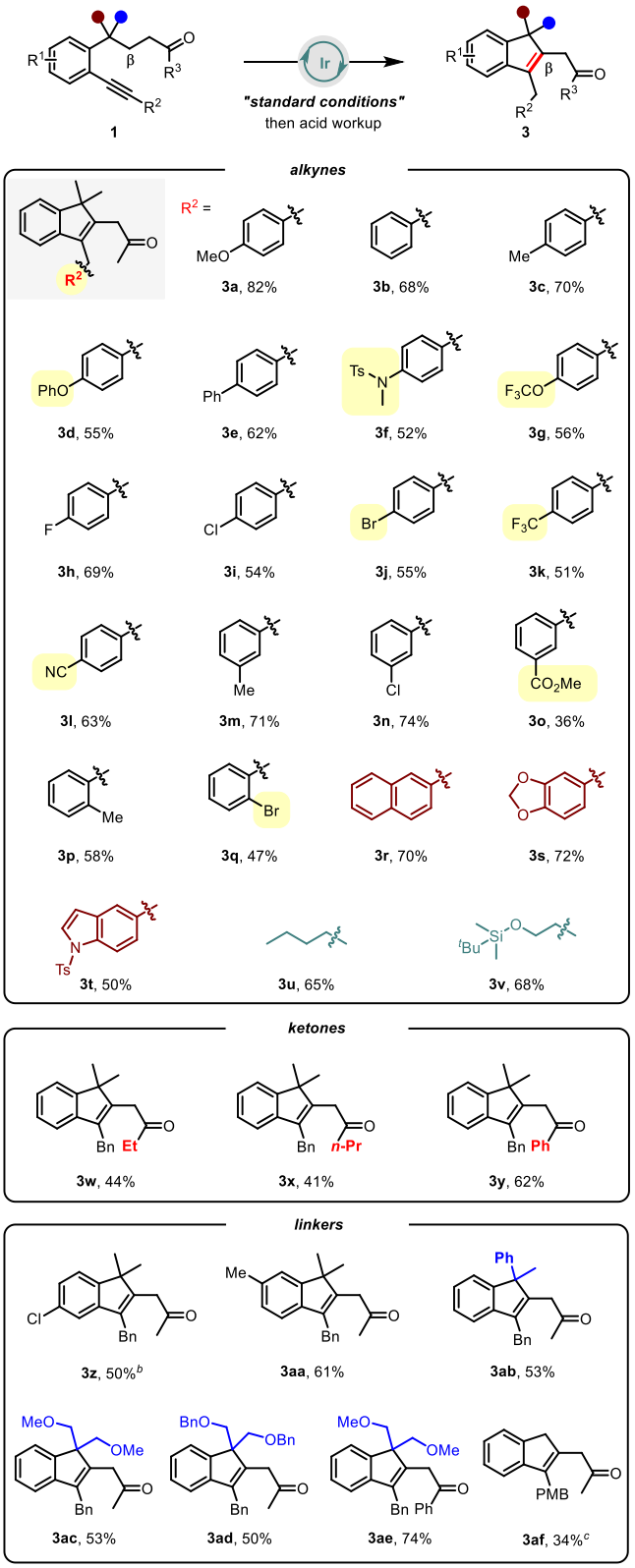
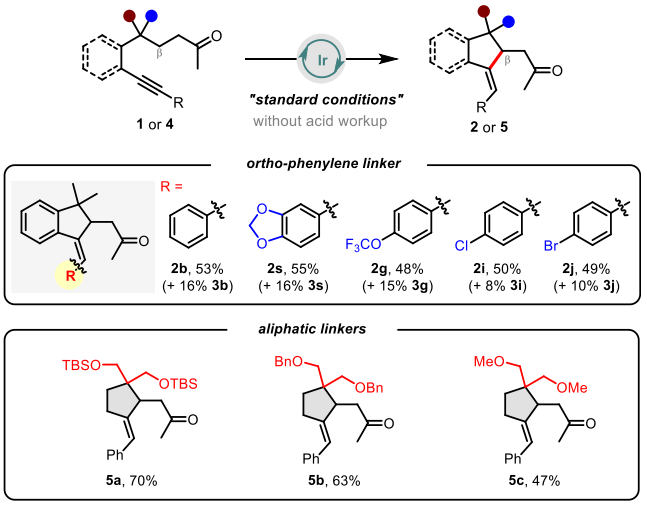
Table 2. Substrate Scope of Acyclic Ketones[a]



[a]All reactions were carried out with 0.1 mmol **1** for 48 h under the standard conditions and then worked up with HCl (0.5 M in 1,4-dioxane) at 60 °C for 6 h. All yields are isolated yields. [b]Workup with HCl (0.5 M in 1,4-dioxane) at 90 °C for 8 h [c]The reaction was carried out at 90 °C for 48 h, and the conversion was 41%. PMB = *p*-methoxybenzyl.

Table 3. Substrate Scope of the Acyclic Ketones without Acid Workup[a]



[a]All reactions were carried out with 0.1 mmol substrate for 48 h under the standard conditions. All yields are isolated yields.

2,4,6-triisopropylbenzoic acid **A1** and 1.2 equiv Cs_2CO_3 were employed as additives along with 1,4-dioxane as the solvent.[20] It is likely that a weaker base (derived from carboxylic acid **A1**) works better for more acidic cyclohexanone substrates. While the conversion with these substrates is generally lower than with acyclic ketones, the reaction also showed high functional group tolerance. In addition, both aryl- and alkyl-substituted alkynyl groups were suitable for this transformation. A slightly higher reaction temperature was needed for alkyl-substituted alkynes. Note that these orthophenylene-linked substrates did not work under the prior Pd catalysis conditions.[12] Finally, an oxygen-tethered cyclohexanone substrate successfully delivered the desired bicyclic product **7v** in 57% yield.

Mechanistic Studies. To gain some insights into the reaction mechanism, several deuterium labeling experiments were conducted. First, the reaction of the *β*-deuterated substrate **4a-D** gave the product **5a-D** under the standard conditions with almost complete deuterium transfer to the alkenyl position, indicating that the alkenyl hydrogen should only come from the *β*-position of the ketone (eq 1). In addition, a crossover experiment between the *β*-deuterated substrate **4a-D** and the non-deuterated substrate **4b** showed that intermolecular hydrogen migration did not take place (eq 2), which suggests that the transfer of the *β* hydrogen must be an intramolecular process. These observations are in sharp contrast to the prior Pd-catalyzed *β*-alkenylation, which involved an intermolecular hydrogen transfer.[12] Moreover, the intermolecular competition experiment revealed a small value (1.3) for the kinetic isotope effect (KIE) at the ketone *β*-position (eq 3), and no primary KIE was observed at the ketone *α*-position with a similar substrate (see the Supporting Information). These results suggest that the cleavage of either the ketone *β* or the *α* C−H bond is not involved in the turnover-limiting step (TLS).

Based on these observations, a plausible reaction mechanism is proposed (Scheme 2). After forming the Ir(I) enolate (**A**/**B**) via a facile base-assisted *α*-deprotonation, the subsequent *β*-hydrogen elimination should also be relatively fast and lead to an Ir(I)−H intermediate (**C**). At this stage, at least two plausible reaction pathways could be possible. **Path a** involves

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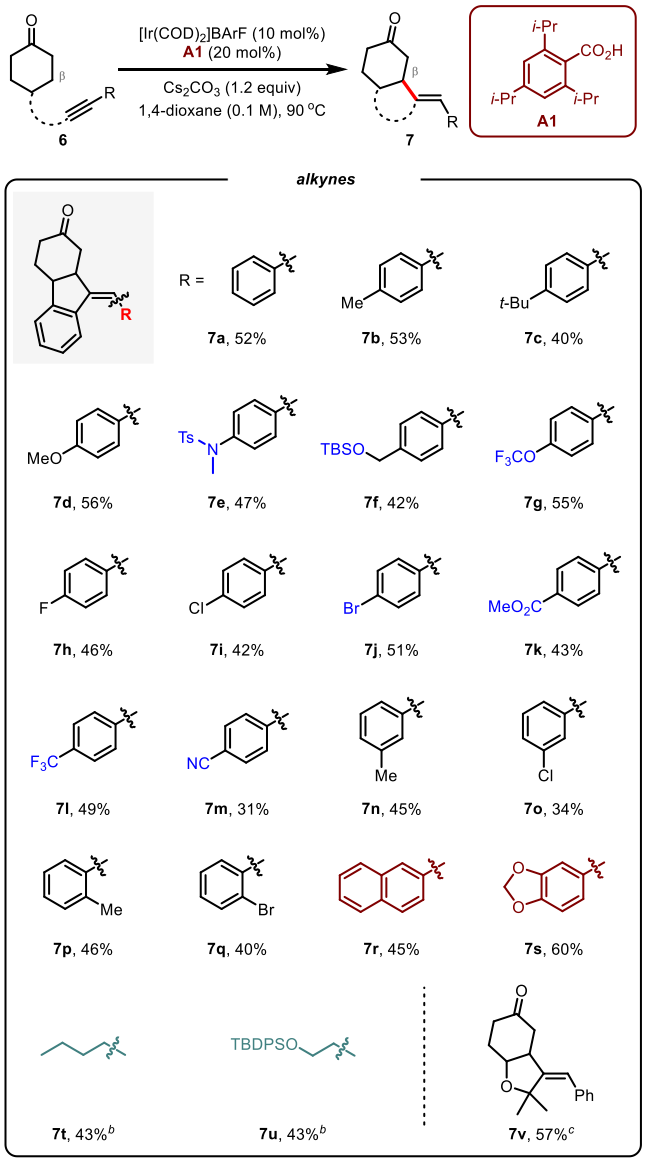
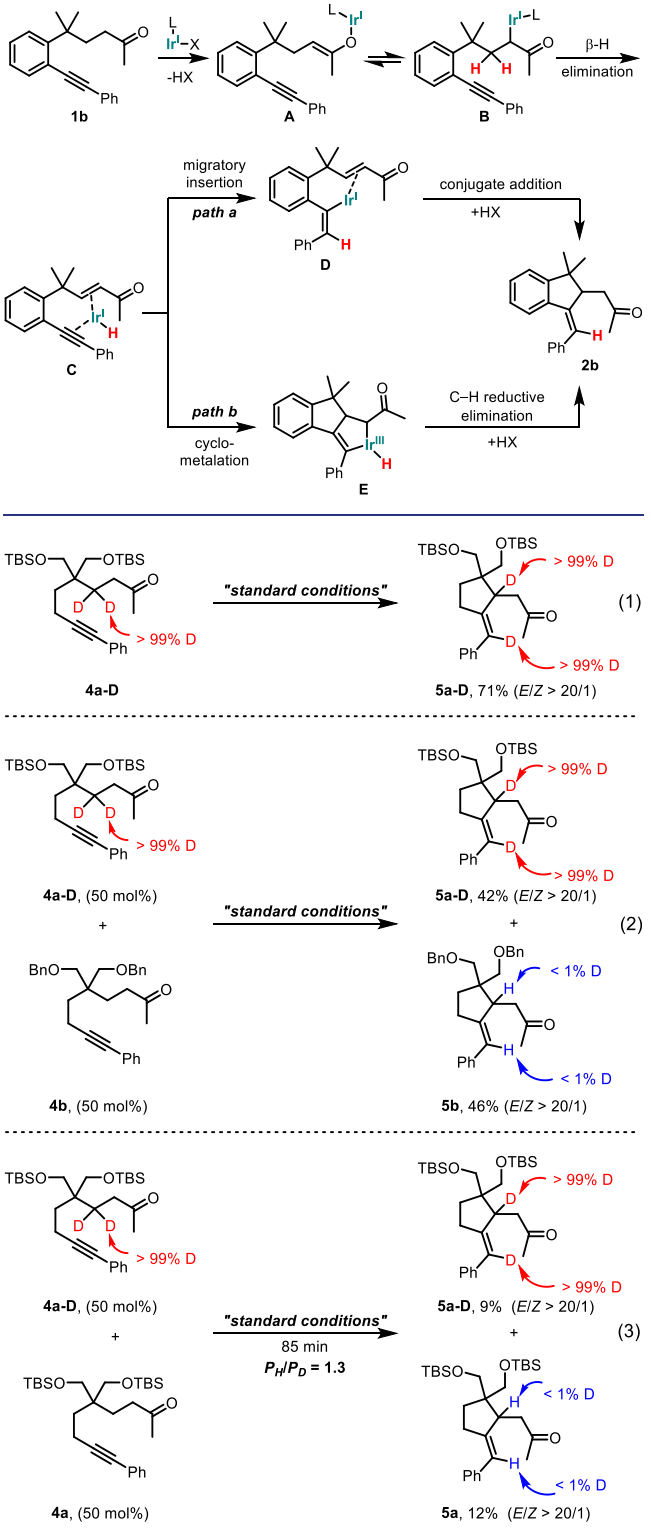
Table 4. Scope of the Cyclohexanone-Derived Substrates without Acid Workup[a]



[a]All reactions were carried out with 0.1 mmol **6** for 48 h under the standard conditions. All yields are isolated yields. [b]The reaction was run at 100 °C. [c]The reaction was run with only 20 mol % Cs_2CO_3. TBDPS = *t*-butyl-diphenylsilyl.

Scheme 2. Proposed Reaction Pathways



an intramolecular Ir(I)−H MI into the alkyne moiety, where the hydride is added on the carbon distal to the ketone moiety (intermediate **D**). The subsequent conjugate addition and *α*-protonation form the *β*-C−C bond[21] and deliver the desired product with the regeneration of the Ir(I) catalyst. Alternatively, as described in **path b**, enyne cyclometalation could take place to give an Ir(III) metallacycle and forge the *β*-C−C bond (intermediate **E**).[22] The following C−H reductive elimination and *α*-protonation can also give the desired product.

To differentiate these two pathways and gain a deeper understanding of the reaction mechanism, density functional theory calculations were performed with ynone **1b** as the model substrate. As shown in Figure 1, the ligand exchange with **1b** generates the intermediate **8**, which contains the coordination of ketone and alkyne moieties to the iridium center. The deprotonation of **1b** followed by the *β*-H elimination (via **TS-1**, Figure 2) leads to the formation of an iridium hydride **11**. The two competitive pathways have been studied for the subsequent cyclization process. Computational results suggest that the Ir(I)−H MI mechanism via **TS-2a** (**path a**) only requires an energy barrier of 5.6 kcal/mol. The formation of the vinyl iridium(I) intermediate **12** is irreversible and is exergonic by 20.0 kcal/mol. The following intra-

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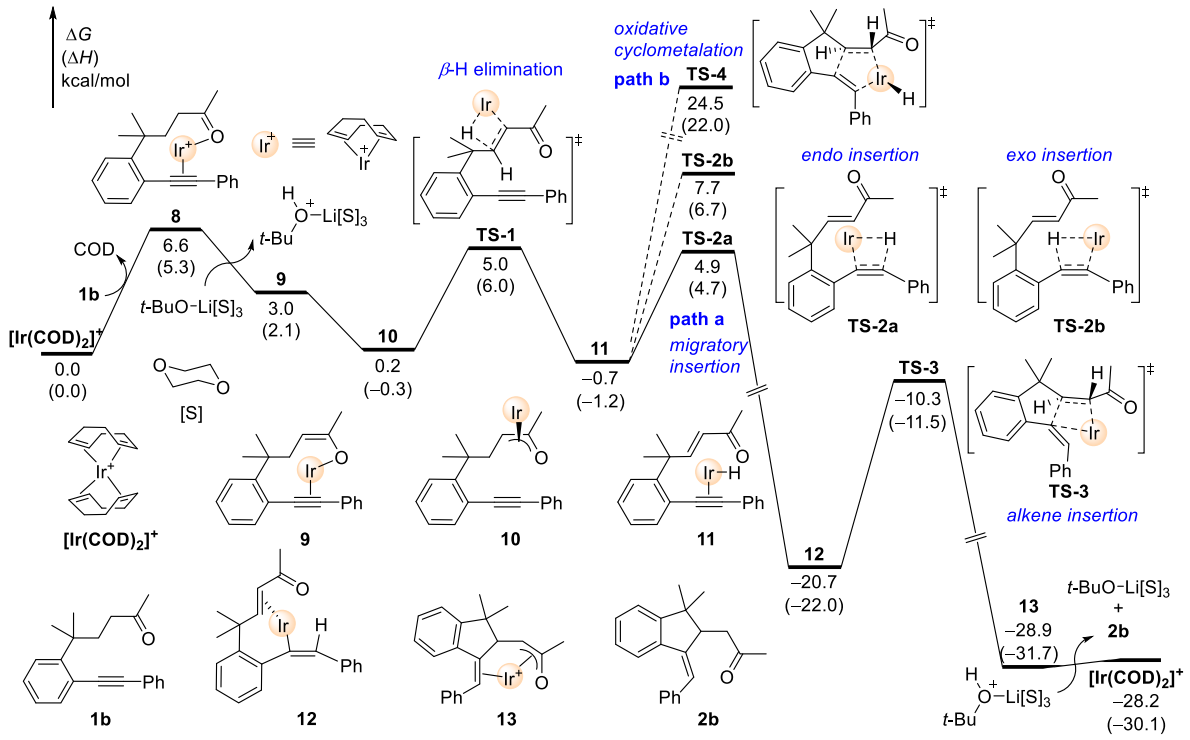

Figure 1. Free energy profile of the Ir-catalyzed intramolecular β-alkenylation of the alkyne-tethered ketone. All energies were calculated at M06/6-311+G(d,p)−SDD/SMD(1,4-dioxane)//B3LYP-D3(BJ)/6-31G(d)−LANL2DZ level of theory.

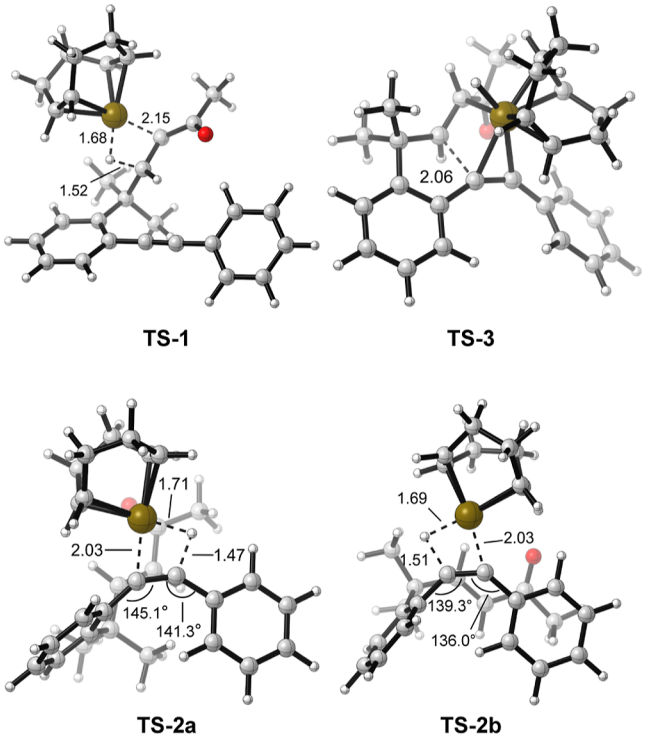

Figure 2. Optimized structures of the key transition states. The bond lengths are in angstrom.

molecular alkene insertion into the Ir(I)−C bond via **TS-3** is demonstrated to be the TLS due to the higher energy barrier of ($\Delta G^{\ddagger}$ = 10.4 kcal/mol). These results are consistent with the deuterium labeling experiments—the deprotonation of the α-H and the β-H elimination are not involved in the TLS. In **path b**, the oxidative cyclometalation transition state **TS-4** requires an energy barrier of 25.2 kcal/mol. The higher energy barrier ($\Delta\Delta G^{\ddagger}$ = 19.6 kcal/mol) compared to the MI mechanism (**path a**) indicates that the formation of an Ir(III) metallacycle is less likely. Besides, the regioselectivity of the alkyne insertion is also investigated. The *exo* alkyne insertion via **TS-2b** is disfavored compared to the *endo* alkyne insertion (**TS-2a**). The greater distortions in **TS-2b** witnessed by the smaller bond angles (139.3 and 136.0° in Figure 2) account for the higher energy barrier. Therefore, the most favorable reaction pathway of the Ir(I)-catalyzed intramolecular β-alkenylation consists of the deprotonation, β-H elimination, alkyne *endo* insertion, alkene insertion, and α-protonation.

Synthetic Utility. To explore the synthetic utility of this method, a gram-scale reaction was first carried out, which provided the β-alkenylation product in 74% yield (Scheme 3A). In addition, the indenylpropanone product **2a** can readily undergo various transformations to access diverse structural motifs (Scheme 3B). For example, the olefin moiety could undergo dihydroxylation with OsO_4 to provide vicinal diol **14**[23] or hydrogenation to deliver the saturated product **15**. Note that these transformations all proceeded with excellent diastereoselectivity. Moreover, the Wittig olefination, Eschenmoser methenylation, and ketone 1,2-reduction successfully functionalized the carbonyl group and efficiently furnished products **16**−**18**. Treatment of **2a** with 2,4-dinitrophenylhydrazine (DNPH) delivered the hydrazone derivative **19**, which was further characterized by X-ray crystallography.

CONCLUSIONS

In summary, the first iridium-catalyzed direct β-alkenylation of ketones with alkyne groups has been developed, which offers a byproduct-free approach to functionalize carbonyl β-positions. This method avoids the use of DGs and shows a broad scope and high functional group tolerance. The mechanistic study

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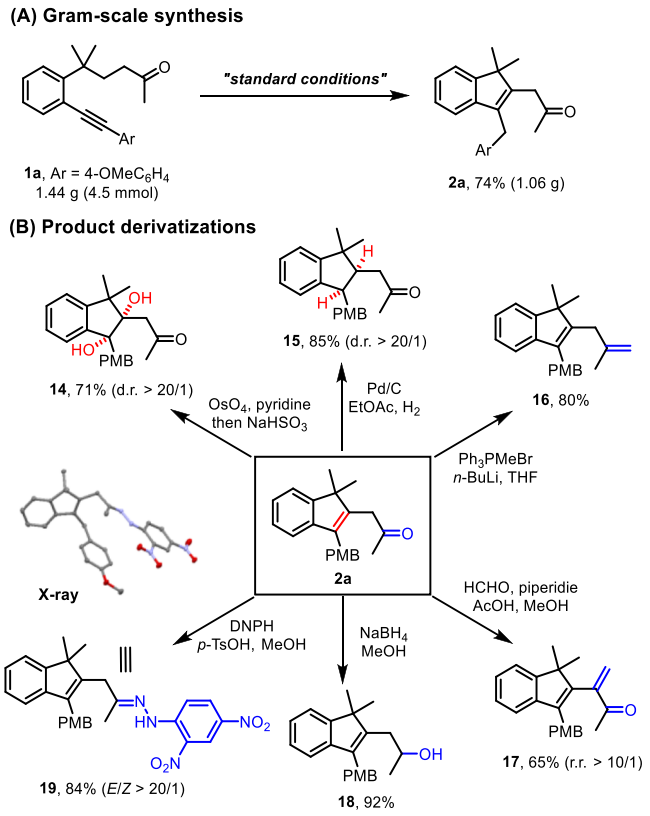
Scheme 3. Synthetic Utility Study



reveals an efficient hydride-transfer pathway involving α-deprotonation, β-H elimination, *endo* alkyne insertion, conjugate addition, and α-protonation. The mechanistic insights gained here should have further implications on developing other desaturation-promoted β-functionalizations. Efforts on developing enantioselective β-alkenylation and expanding the reaction mode to other carbonyl classes are ongoing.[24]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c11505.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2191162 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.

■ AUTHOR INFORMATION

Corresponding Authors

Xiaotian Qi − *College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, China;* orcid.org/0000-0001-5420-5958; Email: qi7xiaotian@whu.edu.cn

Guangbin Dong − *Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States;* orcid.org/0000-0003-1331-6015; Email: gbdong@uchicago.edu

Authors

Bo Zhou − *Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States*

Shuang Deng − *College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, China*

Yin Xu − *Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c11505

Notes

The authors declare no competing financial interest.

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