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RESEARCH ARTICLE

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Development and Mechanistic Studies of the Iridium-catalyzed C−H Alkenylation of Enamides with Vinyl Acetates: A Versatile Approach for Ketone Functionalization

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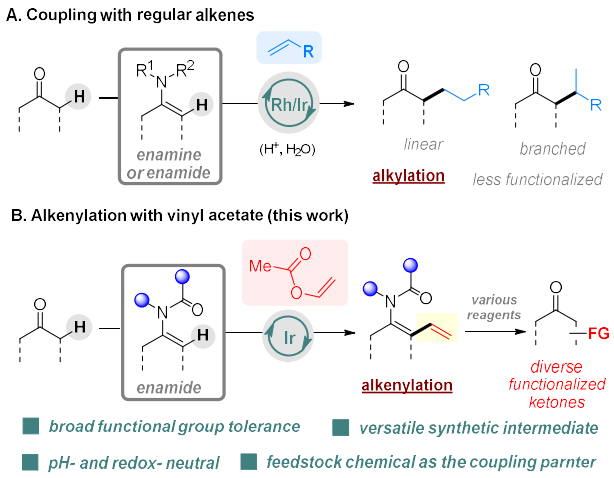
Abstract: Ketone functionalization has been a cornerstone in organic synthesis. Herein, we describe the development of an intermolecular C−H alkenylation of enamides with feedstock chemical vinyl acetate to access diverse functionalized ketones. Enamides derived from various cyclic and acyclic ketones react efficiently and a number of sensitive functional groups are tolerated. In this Ir-catalyzed transformation two structurally and electronically similar alkenes—enamide and vinyl acetate—are selectively cross-coupled through C−H activation. The reaction does not need any partner used in large excess. In addition, it is pH- and redox-neutral with HOAc as the only stoichiometric byproduct. Detailed experimental and computational studies of the reaction mechanism reveal a pathway involving a 1,2-Ir−C migratory insertion followed by a *syn*-β-acetoxyl elimination, which is different from the prior vinyl acetate-mediated C−H activation reactions. Finally, the alkenylation product can serve as a versatile intermediate to deliver a variety of structurally modified ketones.

Introduction

Preparation and derivatization of ketones, one of the basic and prevalent functional groups, have been a cornerstone in organic synthesis.[1] In particular, C−C bond forming reactions with readily available feedstock chemicals, such as alkenes or alkynes, represent attractive methods for ketone functionalization.[2,3] Compared to conventional organohalide-based reactions, the coupling with alkene and alkyne feedstocks hold significant economic advantages and avoid forming halogen-containing byproducts.[4] Towards this goal, our laboratory has been engaged in systematic development of enamine or enamide-based approaches for ketone functionalization through catalytic C−H coupling with alkenes and alkynes (Scheme 1A).[5] For example, the coupling with olefins can provide either linear or branched C−H alkylation products by tuning the bite-angles of the ligands.[5f,h]

Beyond simple olefins, vinyl acetate, with an annual global production of about 7 million metric tons, has been one of the key industry feedstock chemicals. We were fascinated by the question of whether vinyl acetate can be employed as the coupling partner in the enamide-based ketone functionalization strategy, which, if successful, should provide more functionalized ketone products. Compared to regular alkenes, vinyl acetate has not been commonly used in C−H activation reactions.[6] Since the seminal work of Kakiuchi,[6a,b] only a handful examples have been reported on vinyl acetate-mediated C−H functionalization of arenes catalyzed by Ru,[6a,b] Rh[6c,e,f,g] and Co.[6d,h] In particular, their use as a coupling partner for *alkene-based substrates* has not been described yet. One potential concern of using alkene substrates, such as enamides, is that they have similar structural and electronic properties as vinyl acetate. Hence, it is uncertain if such a selective C−H cross coupling can be achieved between these two alkenyl substrates. In this article, we report the development of an Ir-catalyzed C−H alkenylation of enamides derived from various ketones with vinyl acetates (Scheme 1B), which offers a versatile entry to access diverse functionalization of ketones. In this transformation, vinyl acetate serves as a convenient vinylation reagent with HOAc formed as the only stoichiometric byproduct.[6c] Detailed mechanistic studies disclose a pathway involving 1,2-Ir-C migratory insertion, followed by β-acetoxyl elimination; this represents a different mechanistic feature from the prior vinyl acetate-mediated C−H activation reactions.

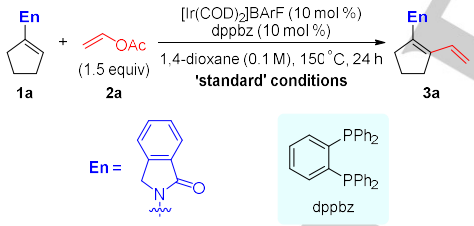


Scheme 1. Enamine/enamide-mediated ketone functionalization.

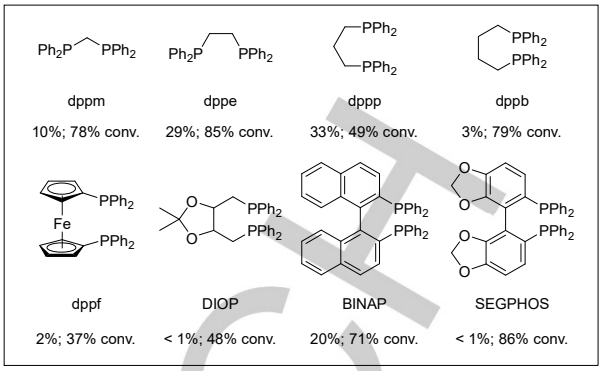
Results and Discussion

Reaction discovery and optimization. To explore the proposed C−H alkenylation with vinyl acetate (**2a**), cyclopentanone-derived enamide **1a** was employed as the model substrate (Table 1). After careful evaluation of various reaction parameters, the desired C−H vinylation product **3a** was ultimately obtained in 91% yield, with $Ir(COD)_2BArF$[7]/dppbz as catalyst, 1,4-dioxane as solvent at 150 °C under N_2 (entry 1). Notably, only 1.5 equivalent of vinyl acetate was needed as the coupling partner, which is in sharp contrast to the regular alkene-mediated C−H coupling reactions[8-10] with enamides.[5f–h] The enhanced efficiency is likely due to the higher binding affinity of vinyl acetate. Control experiments showed that, almost no conversion of substrate **1a** in the absence of the iridium catalyst (entry 2), and replacing Ir with the corresponding $Rh(COD)_2BArF$ only led to decomposition of the substrate (entry 3), suggesting the essential role of Ir in this reaction. The phosphine ligand also proved to be critical, as without the bidentate ligand no desired product was formed with most **1a** decomposed (entry 4). A survey of the ligand effect (entry 5) indicates that dppbz was a superb ligand for this transformation. Among other bidentate phosphine ligands examined, dppe and dppp gave relatively higher yield (29% and 33%, respectively), while the rest exhibited much lower reactivity or selectivity. It appears that the combination of high rigidity and a suitable bite-angle, as seen in dppbz, was important for this alkenylation reaction. The reaction can also take place at a lower temperature albeit in lower yield (entry 6). Finally, 1,4-dioxane proved to be better solvent than less polar toluene or other ethers, such as THF and CPME (entries 7-9).

Table 1. Selected optimization for the C−H alkenylation.[a]



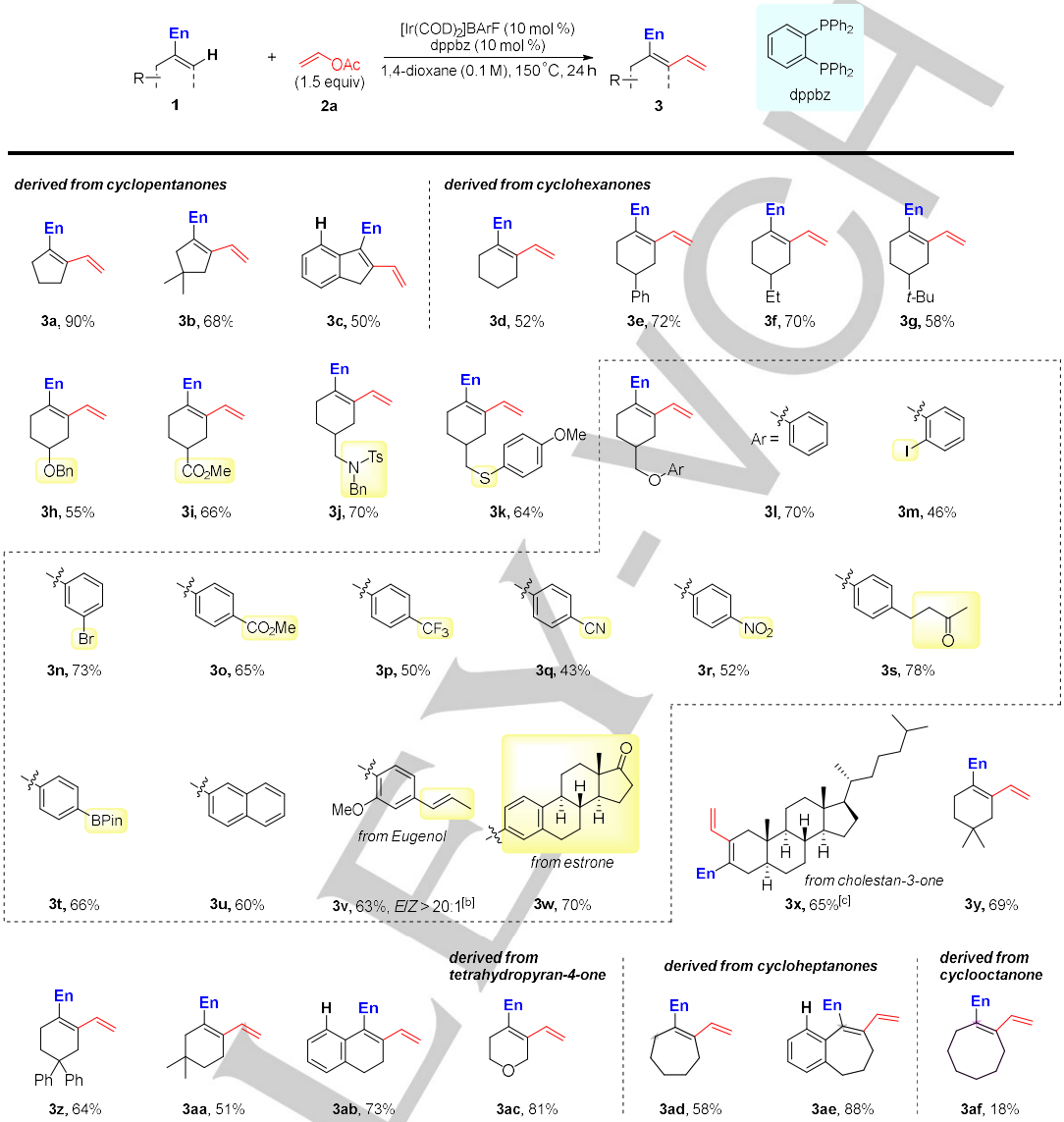
Entry	Variation from the 'standard' condition	Yield of 3a (%)[b]	Conv. (%)[b]
1	**none**	**91**	**> 99**
2	w/o $[Ir(COD)_2]BArF$	< 1	< 5
3	$[Rh(COD)_2]BArF$ as catalyst	< 1	94
4	w/o dppbz	< 1	92
5	other L instead of dppbz	see below	see below
6	130 °C instead of 150 °C	51	94
7	toluene instead of 1,4-dioxane	17	55
8	THF instead of 1,4-dioxane	63	75
9	CPME instead of 1,4-dioxane	6	89



[a] The reaction was performed with **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (0.01 mmol), L (0.01 mmol), in solvent (1 mL) under a N_2 atmosphere at corresponding temperature for 24 h. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard. BArF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; COD = 1,5-cyclooctadiene; CPME = cyclopentyl methyl ether; THF = tetrahydrofuran.

Substrate scope. With the optimized reaction conditions in hand, the scope of cyclic ketone-derived substrates was first investigated (Table 2). In general, enamides with different ring sizes, e.g., from five- to eight-membered rings, can all react to give the desired C−H vinylation products. Comparing to our prior work on the C−H alkylation with regular alkenes,[5f–h] the use of vinyl acetate gave a much broader substrate scope. Besides simple cyclopentanone-derived emamide (**3a**), the one bearing 3,3-dimethyl substituents exclusively underwent the C−H vinylation at the less sterically hindered position in good yield (**3b**). In addition, 1-indanone-based substrate also worked. The six-membered enamides used to be problematic substrates due to the ease of aromatization under the Ir-catalyzed reaction conditions.[5f–h] However, with vinyl acetate as the coupling partner and the use of dppbz ligand, the desired C−H functionalization outcompeted the dehydrogenation side-reaction. This reaction not only gave good yields, but also exhibited excellent functional group compatibility. For example, benzyl ether (**3h**), ester (**3i**), amide (**3j**), thioether (**3k**), iodide (**3m**), bromide (**3n**), trifluoromethyl (**3p**), nitrile (**3q**), nitro (**3r**), ketone (**3s**), pinacolboronate (**3t**) and naphthalene (**3u**) were all tolerated. The terminal alkene moiety from the eugenol-derived substrate underwent complete isomerization to the conjugated product (**3v**), which is consistent with the involvement of metal-hydride species in the reaction (vide infra). Gratifyingly, estrone-derived (**3w**) and cholestan-3-one-based (**3x**) substrates also successfully produced the corresponding vinylation products, showing the potential utility for late-stage modification of complex molecules (vide infra). Moreover, *geminal*-disubstituted six-membered enamides, e.g., 4,4-dimethyl (**3y**), 4,4-diphenyl (**3z**) and 3,3-dimethyl (**3aa**), all worked smoothly. The α-tetralone-derived substrate gave the desired product in 73% yield without touching the aromatic *ortho* C−H bond.[11] Finally, good to excellent yields have been obtained with cycloheptanone- and benzocycloheptenone-derived substrates (**3ad**, **3ae**); promising preliminary success has also been achieved with the more challenging eight-membered-ring enamide (**3af**).

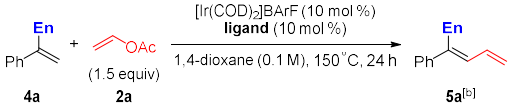
Table 2. Scope of cyclic ketone-derived enamides.[a]



[a] Unless otherwise noted, reactions were run on a 0.2 mmol scale in a 8 mL vial under the standard conditions; All yields are isolated yields. [b] E/Z ratio was determined by ^{1}H NMR analysis of the reaction crude. [c] 48 h.

Compared to cyclic substrates, enamides derived from linear ketones proved to be much less reactive, which is likely due to slower C−H oxidative addition and migratory insertion into vinyl acetate (see Supporting Information, Figure S5). For example, under the standard condition developed in Table 1, enamide **4a** only gave 47% conversion and 28% yield of the C−H vinylation product (**5a**) (Table 3, entry 1). As the ligand plays a critical role in this transformation, the ligand effect was then investigated using linear enamide **4a** as the substrate. Among varies of bidentate phosphine ligands tested, dppp showed the best conversion and yield (entry 5). Other ligands with either small bite-angles, such as dppm and dppe (entries 3 and 4), or larger bite angles, such as DIOP, dppb, dppf, BINAP and SEGPHOS (entry 2 and entries 6-9), gave much lower reactivity. Finally, after extending the reaction time to 48 h, the desired C−H vinylation product **5a** can be obtained in 58% yield (entry 10). It is noteworthy that product **5a** exhibits complete *Z* geometry, which is consistent with a directed C−H activation pathway (vide infra).

Table 3. Selected optimization for acyclic enamides.[a]

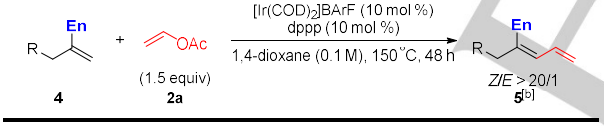


Entry	Ligand	Yield of **5a** (%)[c]	Conv. (%)[c]
1	dppbz	28	47
2	DIOP	< 1	10
3	dppm	8	14
4	dppe	7	11
5	dppp	43	60
6	dppb	20	25
7	dppf	< 1	< 5
8	BINAP	15	20
9	SEGPHOS	< 1	9
10[d]	**dppp**	**58**	**> 95**

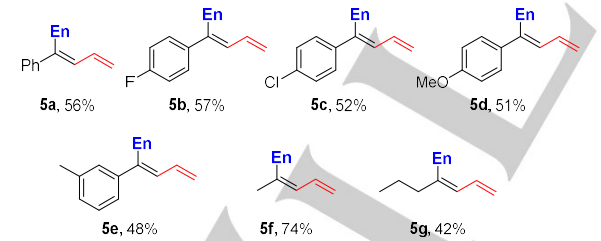
[a] The reaction was performed with **4a** (0.1 mmol), **2a** (0.15 mmol), [Ir(COD)$_2$]BArF (0.01 mmol), L (0.01 mmol), in 1,4-dioxane (1 mL) under a N_2 atmosphere at corresponding temperature for 24 h. [b] *Z*/*E* > 20/1 in all cases. [c] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [d] reaction time 48 h.

The scope of acyclic substrates was then explored (Table 4). Enamides derived from various acetophenones can all be converted to the desired vinylation products **5a**–**e** in moderate yields. Of note, no C−H vinylation at arene *ortho* positions was observed in all these cases, revealing the higher preference of the α-enamide C−H bond. Besides aryl-substituted substrates, enamides derived from simple ketones, such as acetone and 2-pentanone, also worked smoothly (**5f**, **g**).

Table 4. Scope of acyclic ketone derivatives.[a]

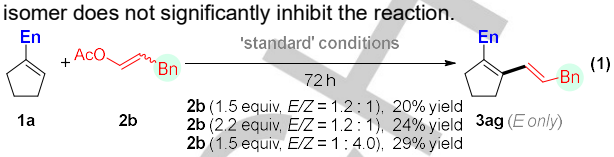


derived from acyclic ketones



[a] Unless otherwise noted, reactions were run on a 0.2 mmol scale in a 8 mL vial under the standard conditions; All yields are isolated yields. [b] *Z*/*E* ratio was determined by ^{1}H NMR analysis of the reaction crude.

Mechanistic study. To explore the reaction mechanism, substituted vinyl acetate was first examined in this reaction to elucidate the regioselectivity of the reaction [Eq. (1)]. When benzyl-substituted vinyl acetate (**2b**) was employed as the coupling partner, the desired alkenylation product (**3ag**) was indeed formed and isolated under the standard condition. Interesting, product **3ag** was isolated as a single *E* isomer despite that **2b** was used as a mixture of *E*/*Z* isomers. The position of the benzyl group in the product suggests that the C−C bond was formed at the position where the OAc group was located, which is opposite from the pathway of the Rh-catalyzed C−H vinylation with vinyl acetate.[6e] In addition, increasing the loading of **2b** to 2.2 equiv boosted the yield from 20% to 24%, while the use of **2b** with a higher Z/E ratio showed a more obvious improvement. These results suggested that the *Z* isomer of **2b** is responsible for the desired coupling and the *E* isomer does not significantly inhibit the reaction.



Based on the observed regioselectivity, at least two possible reaction pathways are possible to explain the formation of the alkenylation products (Figure 1). **Path a** involves a directed oxidative addition of the low-valent Ir(I) into the alkenyl C−H bond, followed by Ir−H migratory insertion into vinyl acetate, where the hydride is added on the carbon containing the OAc substituent.[12] The subsequent β-acetoxy elimination generates an Ir-olefin complex, which undergoes vinyl migratory insertion and β-hydrogen elimination to give the alkenylation product. This pathway is analogous to the one previously proposed by Kakiuchi and co-workers in the Ru-catalyzed vinylation reactions.[6a,b] Alternatively, as illustrated in **path b**, after C−H activation, the Ir−C migratory insertion takes place instead;[5f–h,13] the resulting alkyl-Ir intermediate then undergoes β-acetoxy elimination to give the product.

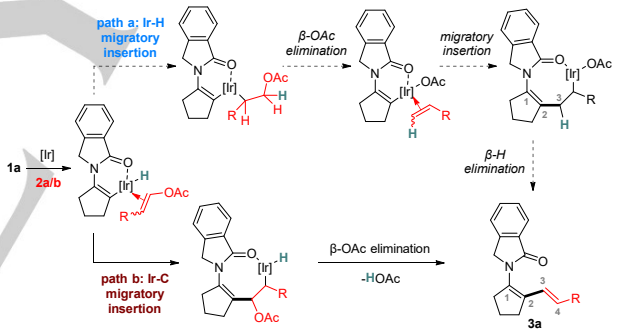
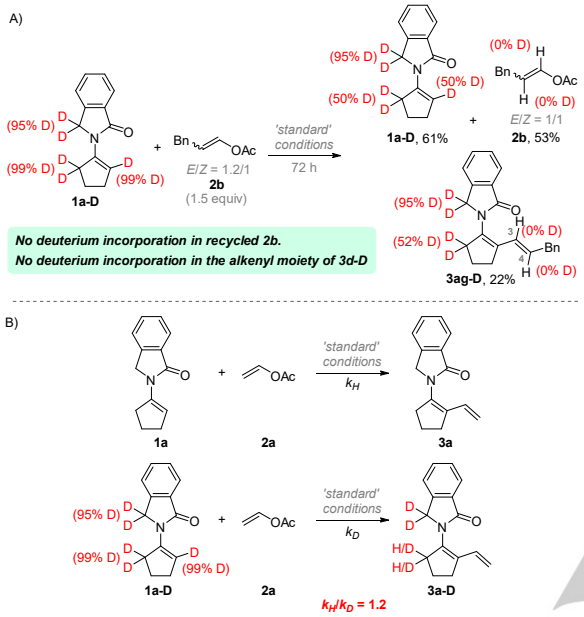


Figure 1. Proposed reaction pathways.

To gain some insights into the reaction mechanism, several deuterium-labelling experiments were conducted. First, when deuterated enamide **1a-D** reacted with vinyl acetate **2b** under the standard conditions except for 72 h, no incorporation of deuterium was observed on either the recovered vinyl acetate **2b** or the alkenyl moiety in the product (**3ag-D**) (Scheme 2A). This result is in sharp contrast to the Ru-catalyzed C−H vinylation reaction.[6b] The lack of deuterium incorporation in the alkenyl moiety of the product can exclude **path a** where deuteration at the C3 position is expected. The lack of deuterium incorporation in the recycled **2b** indicates that the Ir−H migratory insertion into vinyl acetate either did not occur or occurred in a reversible and stereo-retentive way (vide infra, Figure 4). On the other hand, this observation is consistent with **path b**, as through the Ir-C migratory insertion pathway the deuterium does not add to the product (instead, it is eliminated with the OAc group). In addition, erosion of deuterium incorporation at the α-positions of recycled **1a** and the product was observed, which

was likely due to D/H exchange with adventitious water or other proton source in the reaction. Meanwhile, the kinetic isotope effect (KIE) of the parallel reactions was measured (Scheme 2B), and a small KIE value was obtained (k_H/k_D = 1.2). This result suggests that oxidative addition of Ir(I) into the enamide alkenyl C−H bond is not involved in the rate-determining step (RDS). Finally, a control experiment was carried out using a 1:1 ratio of regular **2b** and d_5-allylbenzene (**2c**) as the coupling partners (Scheme 2C). If an olefin-coordinated iridium intermediate is generated as shown in Kakiuchi's system,[6b] it would likely undergo ligand exchange with the more abundant alkene **2c**, which is anticipated to result in deuterium incorporation into the vinylation product (**3ag**). The lack of deuterium incorporation in product **3ag** can further exclude **path a**.

Scheme 2. Deuterium labelling studies.



To obtain deeper understanding of the reaction mechanism, density functional theory (DFT) calculations were performed.[13] All energies were calculated at the M06/6-311+G(d,p)−SDD/SMD(1,4-dioxane)//B3LYP-D3/6-31G(d)−SDD level of theory. First, to investigate the proposed Ir−C migratory insertion/β-acetoxy elimination pathway (**path b**), the Ir-catalyzed C−H alkenylation of enamide **1a** with vinyl acetate **2a** was computed (Figure 2). The oxidative addition of the C(sp^2)−H bond to Ir(I) (via **7-TS**) has a low energy barrier with respect to the reactant complex **6**. The low barrier and the small endergonicity to form Ir(III) hydride **8** are consistent with the deuterium labelling experiment (*vide supra*, Scheme 2B) that suggests oxidative addition with the enamide vinyl C−H bond is reversible and is not the RDS. Subsequent Ir−C migratory insertion via transition state **10-TS** is irreversible. The β-acetoxy elimination step, which delivers product **3a**, prefers to occur through a six-membered cyclic transition state **13-TS**. The corresponding four-membered cyclic transition state **13-TS'** has a higher energy barrier. The *anti*-elimination via transition state **14-TS** also requires a higher barrier than the syn-elimination pathway. The optimized structure of **13-TS** (Figure 3) shows a nearly perpendicular geometry between the plane of the forming alkenyl C=C bond and the OAc group, which allows good orbital alignment in the *syn*-elimination. The catalytic cycle is closed by the AcO−H reductive elimination (**16-TS**) and the enamide coordination to the Ir(I) catalyst. In this catalytic cycle, the β-acetoxy elimination via **13-TS** is the RDS ($\Delta G^{\ddagger}$ = 22.7 kcal/mol with respect to **11**).

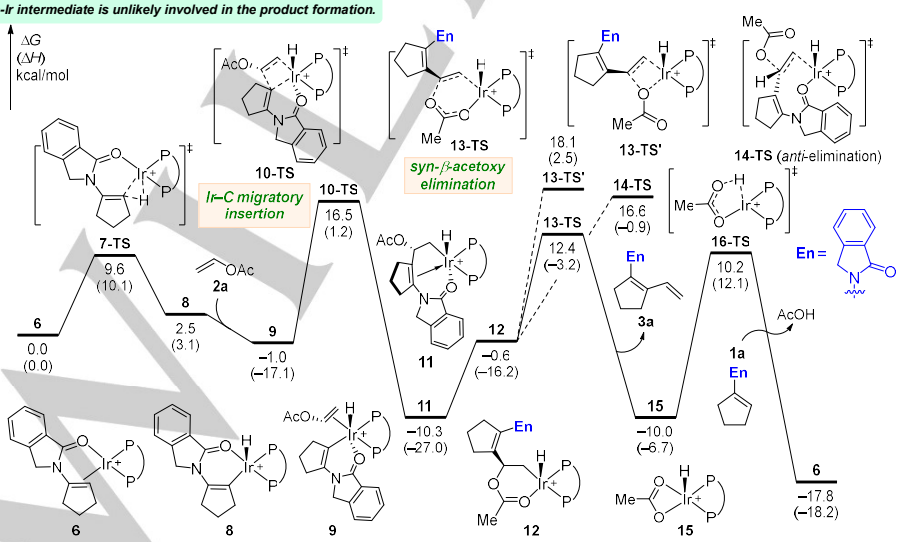


Figure 2. Free energy profile of the Ir−C migratory insertion/*syn*-β-acetoxy elimination pathway of the Ir-catalyzed C−H alkenylation of enamide **1a** with vinyl acetate. Dppbz was used as the ligand.

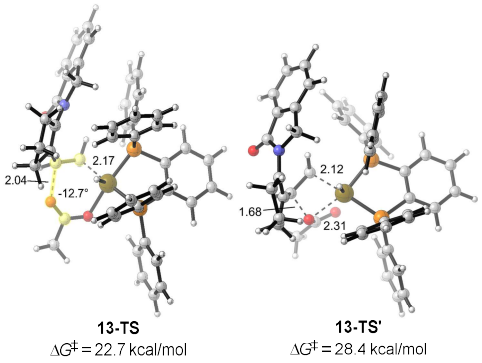


Figure 3. Optimized structures of syn-β-acetoxy elimination transition states **13-TS** and **13-TS'**.

Next, we considered the Ir−H migratory insertion/β-acetoxy elimination pathway (**path a**). In the π-alkene Ir(III) hydride complex **9**, the hydride is *cis* to the vinyl acetate and *trans* to the carbonyl of the enamide. From this complex, several Ir−H migratory insertion pathways were computed, including the direct insertion into the Ir−H bond in **9** (Figure 4) and the isomerization of **9** to a less stable isomer **9b**, in which the hydride is *trans* to a phosphorus on the dppbz ligand (Figure 5).[14] Due to the stronger *trans* effect of phosphines, the migratory insertion with **9b** is expected to be more favorable than the direct insertion with **9**.[15] Indeed, the reaction with **9b** (via **17b-TS**) only requires a very small barrier of 1.5 kcal/mol with respect to **9b**. On the other hand, after multiple attempts, we cannot locate the geometry of the direct alkene insertion transition state (**17-TS**) with **9** or the five-coordinated alkyl iridium intermediate after the alkene insertion (**18**), presumably due to their instability.[16] Constrained geometry optimization by fixing the β-C−H bond distances suggests that **18** is 16.8 kcal/mol less stable than **9**. Because the alkene insertion transition state **17-TS** is higher in energy than **18**, this Ir−H migratory insertion step will require a higher activation barrier than the Ir−C migratory insertion (via **10-TS**). Furthermore, a subsequent step in this pathway, the β-H elimination via transition state **24-TS**, requires an activation free energy of 24.2 kcal/mol, which is 1.5 kcal/mol higher than that of β-acetoxy elimination transition states **13-TS**. Therefore, the direct Ir−H migratory insertion from intermediate **9** as shown in Figure 4 can be ruled out.

In the alternative Ir−H migratory insertion pathway via **9b** (Figure 5), although the Ir−H migratory insertion via **17b-TS** is feasible because of the low activation free energy, the subsequent β-acetoxy elimination via **27-TS** requires a high energy barrier ($\Delta G^{\ddagger}$ = 28.9 kcal/mol with respect to **26**). The distortion of **27-TS** evidenced by the non-planar six-membered ring [θ(C-C-O-C) = 58.7°] is responsible for the high barrier that disfavors this pathway. This distortion is caused by the sterically congested iridium center in **27-TS**. In contrast, the β-acetoxy elimination transition state in the Ir−C migratory insertion pathway (**13-TS**) is not distorted because of the less crowded steric environment around the iridium center.

Although the low barrier to **17b-TS** suggests the Ir−H migratory insertion is reversible, scrambling of the enamide C−H (H^1) and the vinyl acetate C−H (H^2) cannot take place. This is because, after **26** is formed, the β-H^2 elimination via **17c-TS** has a 2.9 kcal/mol higher energy barrier than the β-H^1 elimination via **17b-TS**, which indicates that the reversible Ir−H migratory insertion is stereo-retentive due to the much faster rate to eliminate the same β-H bond formed in the migratory insertion than eliminating the other β-H originated from the vinyl acetate. This observation is consistent with the lack of deuterium incorporation in the recycled vinyl acetate or the installed alkenyl moiety (*vide supra*, Scheme 2A). Besides, a third mechanism that initiates from the C−O oxidative addition[17] of the vinyl acetate to Ir(I) can also be ruled out due to the higher energy barrier of the C(sp^2)−O oxidative addition transition state ($\Delta G^{\ddagger}$ = 32.0 kcal/mol, see Supporting Information, Figure S6). Taken together, the computational results and the experimental mechanistic studies both support the Ir−C migratory insertion over the Ir−H migratory insertion mechanism.

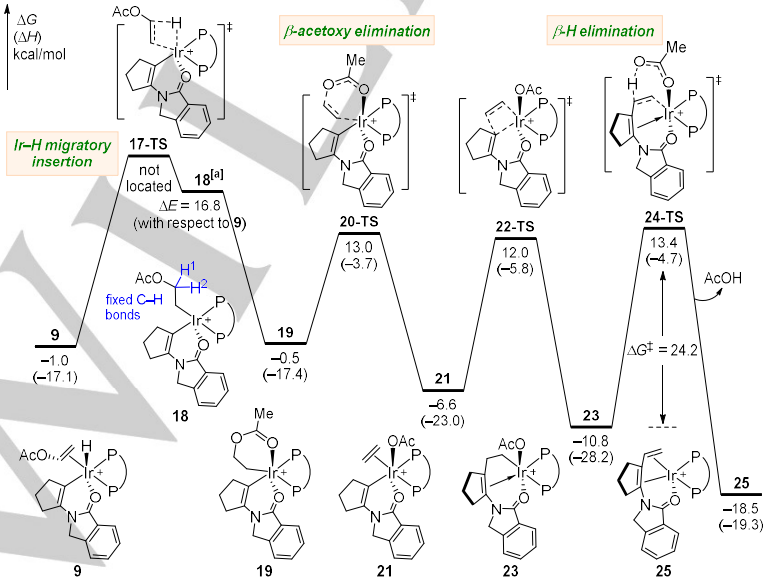


Figure 4. Free energy profile of the Ir−H migratory insertion/β-acetoxy elimination pathway of the Ir-catalyzed C−H alkenylation of enamide **1a** with vinyl acetate. Dppbz was used as the ligand. [a] The structure of **18** was optimized by fixing the C−H^1 and C−H^2 bond distances

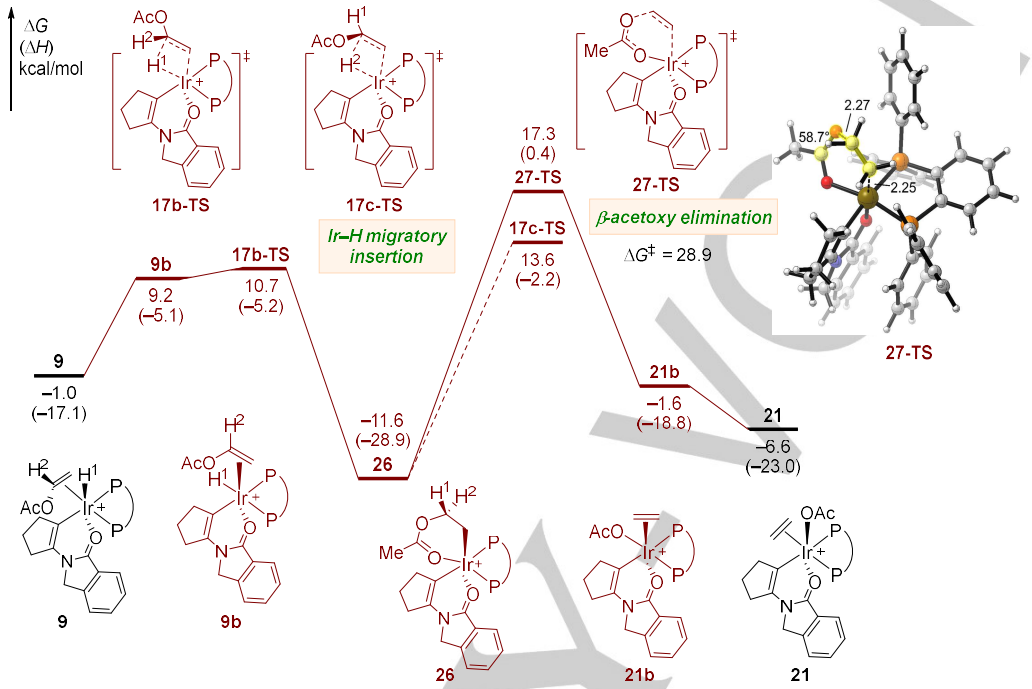
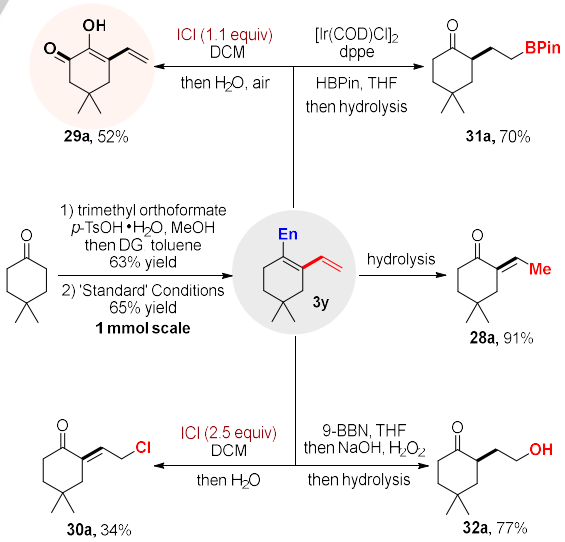
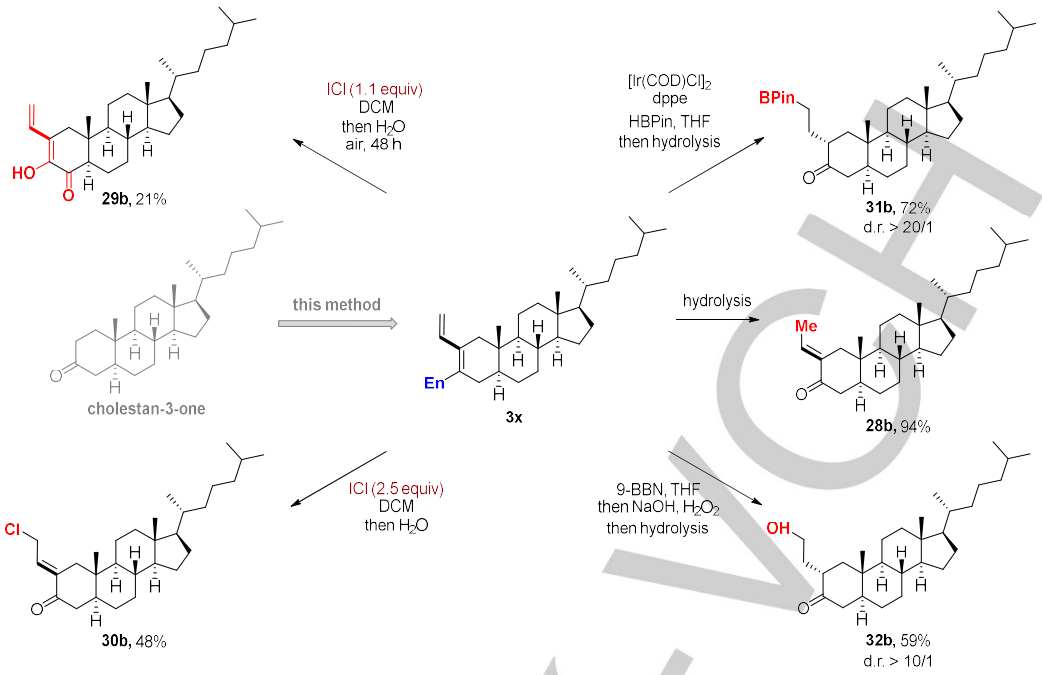


Figure 5. An alternative Ir−H migratory insertion/β-acetoxy elimination pathway from iridium hydride intermediate **9b**. Dppbz was used as the ligand.

Synthetic applications. To show the synthetic utility of this C−H alkenylation method, a series of transformations have been developed for versatile ketone functionalization (Scheme 3). Notably, a larger scale C−H vinylation reaction can be carried out with cyclohexanone-derived enamide substrate **1y**, which was prepared via a one-pot procedure from commercially available 4,4-dimethylcyclohexanone. From the conjugated enamide **3y**, diverse transformations have been achieved. For example, direct hydrolysis of the enamide moiety produced α,β-enone **28a** with excellent yield and *E*/*Z* (> 20/1) selectivity. Coupled with another Ir-catalyzed process[18] followed by hydrolysis, the γ-Bpin-substituted ketone (**31a**) was isolated in good yield. The conventional hydroboration-oxidation and then hydrolysis delivered the γ-hydroxyl ketone (**32a**). Due to the unique electron-rich conjugated diene moiety in product **3y**, its reactions with electrophiles have been explored. Interesting transformations have been observed with ICl as the electrophile. By changing the equivalency of ICl, vastly different products were obtained. When 1.1 equiv ICl was added to a solution of **3y** in DCM at room temperature followed by water quench in the air, 1,2-diketone **29a** with a diosphenol moiety was isolated in 52% yield (see Supporting Information for the tentatively proposed reaction pathway). However, when 2.5 equiv of ICl was used instead, an allyl chloride (**30a**) was formed as the major product. These transformations can be further adopted for derivatization of a more complex natural product (Scheme 4). Diverse functionalized cholestan-3-one derivatives **28b**–**32b** can be conveniently prepared in a regio- and diastereoselective manner.



Scheme 3. Synthetic utility study to access diverse functionalized ketones.



Scheme 4. Late-stage modification of the cholestan-3-one derivatives.

Conclusion

In summary, an iridium-catalyzed enamide C−H alkenylation with feedstock chemical vinyl acetate has been developed, which provides a convenient entry to access diverse functionalized ketones. Various cyclic and more challenging acyclic substrates are suitable for the transformation. Stoichiometric base or oxidant is avoided in this reaction. The tolerance of a variety of reactive functional groups (such as Bpin, I, Br, and carbonyl moieties) could make this method attractive for complex molecule modification or late-stage functionalization. Finally, the mechanistic studies reveal a new reaction mode for the coupling with vinyl acetate, which involves a reversible enamide C−H oxidative addition, followed by an Ir−C migratory insertion and an unusual *syn*-β-acetoxy elimination. The selective cross coupling between two similar alkenyl substrates, i.e., enamide and vinyl acetate, could have implications beyond this work.

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Keywords: enamide • C−H alkenylation • ketones • iridium catalysis • mechanistic study

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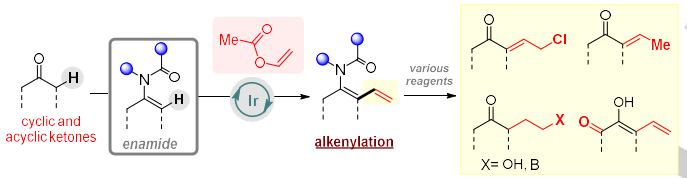

An Ir-catalyzed C−H alkenylation of enamides with vinyl acetates have been developed, which provides a versatile approach for diverse ketone functionalization. The method exhibits a broad substrate scope and high chemoselectivity. It also features a reaction pathway involving 1,2-Ir−C migratory insertion and *syn*-β-acetoxyl elimination.