

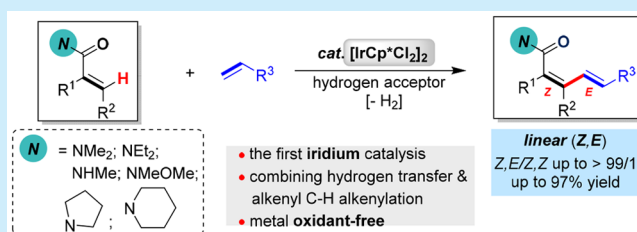
Iridium-Catalyzed Cross-Coupling Reactions of Alkenes by Hydrogen Transfer

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S Supporting Information

ABSTRACT: A range of Ru-, Rh-, or Pd-catalyzed vinylic C–H/C–H cross-coupling reactions of olefins have been demonstrated to provide 1,3-dienes, using a quantitative amount of metal oxidants. Although transfer hydrogenation and C–H alkenylation are two important areas that evolved independently, we herein report the first iridium-catalyzed cross-coupling reactions of alkenes by integration of directed C(alkenyl)–H alkenylation and transfer hydrogenation to obviate the usage of a metal oxidant, employing a hydrogen acceptor such as inexpensive chloranil.

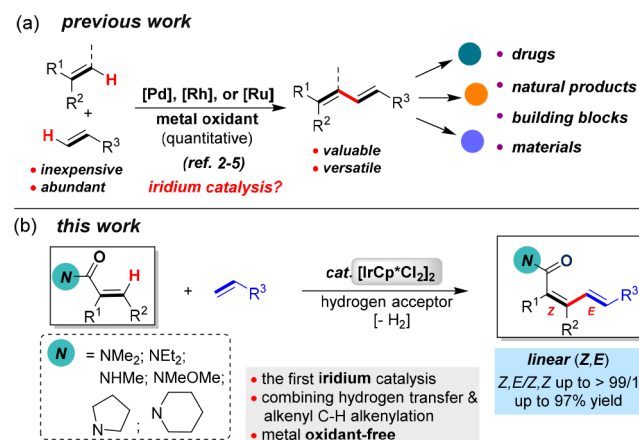


Cross-couplings such as Heck reaction are powerful synthetic methods to construct carbon–carbon bonds in materials and pharmaceutical chemistry.¹ In particular, combining two metal-catalyzed C(alkenyl)–H activations into a single vinylic C–C bond-forming reaction represents one of the most robust and versatile methodologies due to high atomic and step economy, which can be divided into two general categories.^{2–5} One is nondirected cross-coupling of olefins via alkenyl-Pd intermediates, usually leading to *E,E*-configured 1,3-dienes.³ The other one is the Pd-, Ru-, or Rh-catalyzed olefinic C–H alkenylation, which proceeded by metallacycle intermediates formed from directed *syn* C(alkenyl)-H activation.^{4,5} However, a drawback of these strategies is that an excess amount of silver or copper salt was commonly used as an oxidant, leading to high cost, undesired metal waste, and potential side reactions, thus the synthetic utility might be significantly compromised. Moreover, it is still highly attractive to develop novel cross-coupling reactions using other transition-metal catalysts due to their potential to complement the substrate scope and reaction type. To the best of our knowledge, general methods for the iridium-catalyzed cross-coupling reactions between olefins still remain elusive yet highly desirable (Scheme 1a).

Transfer hydrogenation⁶ and C–H alkenylation⁷ are two important areas that evolved independently, and C(alkenyl)–H/C(alkenyl)–H cross-coupling integration of these two areas still remains challenging due to ready olefin isomerization, hydrogenation of double bond, and so on, although hydrogen-evolving aromatic C–H olefination has been disclosed sporadically.⁸ Jeganmohan and co-workers reported an *ortho* C–H olefination of aromatic amides using acrylates by ruthenium catalysis, with the liberation of hydrogen gas.^{8b} However, there is still no report on cross-coupling reactions of olefins by hydrogen transfer to provide conjugated dienes.⁹

Although great efforts have been made on iridium-catalyzed C–H transformations of arenes and alkanes,^{10,11} reports on

Scheme 1. Transition-Metal-Catalyzed Cross-Couplings of Alkenes



olefinic C–H activation continue to be limited due to the lability of olefins.¹² Furthermore, there are several challenges associated with the iridium-catalyzed cross-coupling of olefins by hydrogen transfer, including (1) potential olefin isomerization via π -allyliridium or hydrido-iridium species,^{12,13} (2) competitive vinylic and allyl C–H cleavage sites,^{12,14} and (3) the possible hydrogen transfer to the olefin moiety.^{6,15} Although the organophosphorus and organosulfur compounds served as crucial compounds in the area of pharmaceutical and agricultural chemistry,¹⁶ their employment in catalyzed C–H functionalization has been much less studied.¹⁷ Given our continued interest in directed alkenyl C–H activation,⁵ we report an iridium-catalyzed regio- and stereoselective cross-coupling using structurally diverse acrylamides and vinyl-

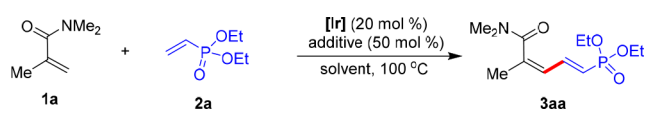
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phosphonate as well as vinyl sulfone, leading to *Z,E*-conjugated dienes (Scheme 1b).

Our objective in alkene–alkene coupling was to integrate C–H activation and hydrogen transfer, thus obviating the usage of an excess amount of a metal oxidant. So, a suitable hydrogen acceptor and olefin substrates had to be identified to be compatible with the C–H alkenylation step. At the beginning of our study, a series of *N*-coordinating (including acidic NHTs) acrylamides were tested as the substrate, but failed under a variety of catalytic conditions. So, we turned to examine relatively soft *O*-coordinating amide **1a**, using diethyl vinylphosphonate **2a** as a coupling partner (Table 1).

Table 1. Optimization of Catalytic Conditions^a



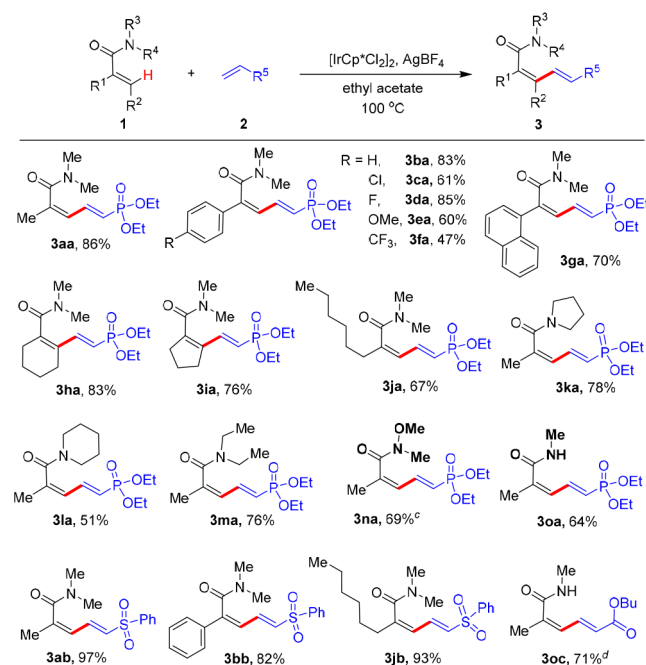
entry	catalyst	additive	solvent	yield (%) ^b
1	[Ir(OMe)(cod)] ₂	AgBF ₄	EA	18
2	[IrCl(cod)] ₂	AgBF ₄	EA	17
3	[IrCp*Cl ₂] ₂	AgBF ₄	EA	86
4	[IrCp*Cl ₂] ₂	AgSbF ₆	EA	80
5	[IrCp*Cl ₂] ₂	AgOTf	EA	62
6	[IrCp*Cl ₂] ₂	Ag ₂ O	EA	9
7	[IrCp*Cl ₂] ₂	–	EA	0
8	[IrCp*Cl ₂] ₂	AgBF ₄	toluene	43
9	[IrCp*Cl ₂] ₂	AgBF ₄	DCE	51
10	[IrCp*Cl ₂] ₂	AgBF ₄	hexane	84
11	[IrCp*Cl ₂] ₂	AgBF ₄	MeOH	24
12	[IrCp*Cl ₂] ₂	AgBF ₄	MeCN	0
13 ^c	[IrCp*Cl ₂] ₂	AgBF ₄	EA	67
14 ^d	[IrCp*Cl ₂] ₂	AgBF ₄	EA	69

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Ir] (20 mol %), Ag salt (50 mol %), in a solvent (1 mL) at 100 °C for 6 h. ^bIsolated yields. ^c1.0 equiv of **2a** used. ^d5 mol % [IrCp*Cl₂]₂ used. EA = ethyl acetate; DCE = 1,2-dichloroethane.

Unfortunately, iridium complexes chelated by a cyclooctadiene ligand were inefficient (entries 1–2). As Cp*/Ir(III) complexes have been extensively utilized in C–H functionalization¹⁰ as well as hydrogen transfer and hydrogen borrowing reactions,⁶ we turned to examine the catalytic reactivity of the Cp*/Ir(III) complex. To our delight, [IrCp*Cl₂]₂ combined with 50 mol % AgBF₄ produced **3aa** in 86% yield with excellent *Z,E*-selectivity (*Z,E/Z,Z* > 99/1) (entry 3). A 2 equiv amount of vinylphosphonate **2a** was required because it also served as a sacrificial hydrogen acceptor in the stoichiometric formation of the diethyl ethylphosphonate.¹⁸ The silver additive is crucial for the cross-coupling, and other silver salts such as AgSbF₆, AgOTf, and Ag₂O led to less satisfactory results (entries 4–7). Representative solvents such as MeOH, DCE, toluene, and hexane were examined, but none of them could improve the reaction (entries 8–11). Notably, MeCN totally blocked the reaction due to its strong coordination to the metal center (entry 12). If 1.0 equiv of **2a** was used, the product yield decreased to 67% (entry 13). If the catalyst loading decreased to 5 mol %, **3aa** was still obtained in 69% yield (entry 14).

Next, we turned to investigate the substrate scope of Ir-catalyzed alkene–alkene cross-coupling reactions (Scheme 2). Phenyl rings bearing F, Cl, CF₃, and OMe were all well tolerated, delivering the 1,3-dienes in up to 85% yields with excellent stereoselectivity (**3ba–3fa**). Installation of naphtha-

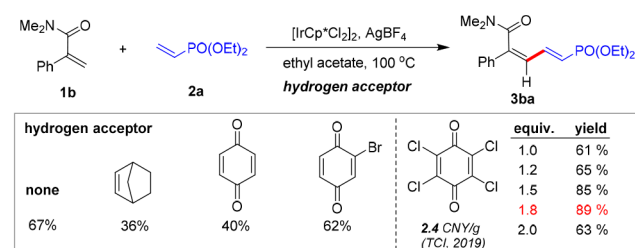
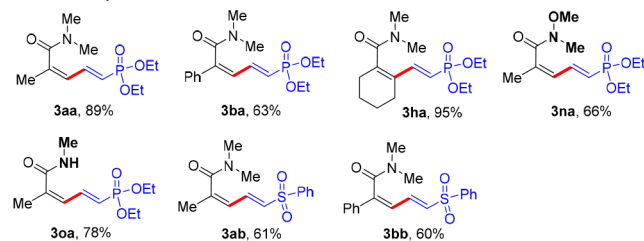
Scheme 2. Substrate Scope of Alkenes^a



^aReaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), [IrCp*Cl₂]₂ (10 mol %), AgBF₄ (50 mol %), in ethyl acetate (1 mL) at 100 °C for 6 h. ^bIsolated yields. ^c*Z,E/Z,Z* = 90/10. ^dAgNTf₂ (2.0 equiv), at 120 °C for 6 h.

lene showed limited influence on the reaction, and the corresponding diene **3ga** was obtained in 70% yield without any decrease in selectivity. Cyclic acrylamides embedded with a cyclohexenyl or cyclopentene moiety led to good yields (**3ha** and **3ia**), as well as the reaction of acrylamide **1j** bearing a long alkyl group. Differently *N*-substituted acrylamides **1** were also converted smoothly (**3ka**, **3la**, and **3ma**). The good reactivity of the Weinreb amide highlighted the great synthetic usage for further elaborations of the products, although with a slight decrease in stereoselectivity (**3na**). Although a primary amide led to trace product, a secondary amide still led to good results (**3oa**). Moreover, phenyl vinyl sulfone also proved to be a good coupling partner in the reactions with various acrylamides, leading to 82–97% yields (**3ab**, **3bb**, and **3jb**). Finally, acrylate also led to satisfactory results by using AgNTf₂ salt instead (**3oc**, 71% yield, *Z,E/Z,Z* > 99/1).

To our knowledge, benzoquinone and norbornene have been demonstrated to be excellent hydrogen acceptors in Ir–H chemistry. Herein, benzoquinone derivatives or norbornene was investigated to understand the hydrogen transfer step, by using 1 equiv of diethyl vinylphosphonate **2a** (Scheme 3). While employment of 1,4-benzoquinone and norbornene retarded the reaction, addition of 2-bromo-1,4-benzoquinone exhibited comparable results. Then, inexpensive chloranil (tetrachloro-*p*-benzoquinone) (1.0 equiv) was examined as a hydrogen acceptor, leading to **3ba** in 61% yield. Interestingly, the cross-coupling was further improved using an increased amount of chloranil (89% yield, 1.8 equiv). The improved catalytic conditions using inexpensive chloranil as a hydrogen acceptor not only led to a much lower cost but also obviated the production of an excess amount of undesired metal oxidant waste; thus, the synthetic utility should be further promoted. Examination of the substrate scope led to satisfactory results, as

Scheme 3. Screening of Hydrogen Acceptor and Substrate Scope^aSubstrate scope^b

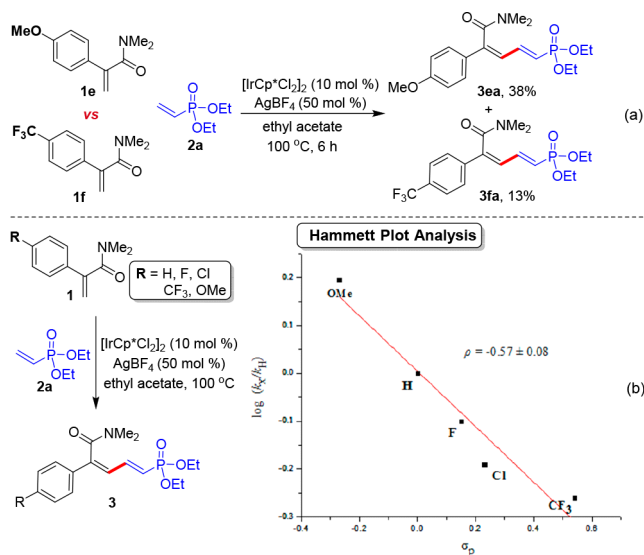
^aReaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), [IrCp*Cl₂]₂ (10 mol %), AgBF₄ (50 mol %), hydrogen acceptor (1.0 equiv), in ethyl acetate (1 mL) at 100 °C for 6 h; the yields are isolated yields.
^bChloranil (1.8 equiv) used as hydrogen acceptor.

illustrated by the preparation of **3aa** to **3bb** to further demonstrate the robustness of the improved protocol.

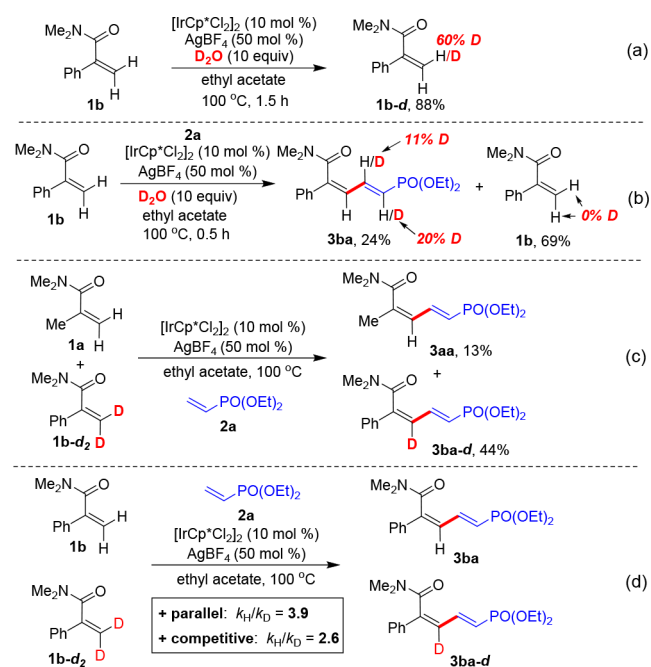
Given the high efficacy of the protocol, some mechanistic experiments were conducted to delineate the mode of action. An intermolecular competition experiment between substrates **1e** and **1f** showed that the electron-rich one to react preferentially, thus exhibiting an electrophilic C–H bond activation (Scheme 4a).⁵ The results were further illustrated by a Hammett plot analysis, which indicated a linear fit with a negative slope of $\rho = -0.57$ (Scheme 4b).

If acrylamide **1b** was treated with 10 equiv of D₂O under optimal conditions in the absence of vinylphosphonate **2a**, significant *cis* vinylic H/D exchange was observed, thus exhibiting a reversible cyclometalation mode (Scheme 5a).

Scheme 4. Intermolecular Competition Experiments and Hammett Plot Analysis



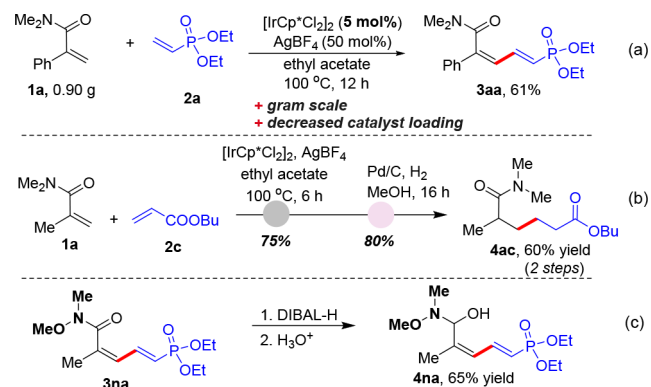
Scheme 5. Deuterium-Labeled Experiments



The excellent site- and stereoselective deuterium incorporation excluded the formation of alkyliridium via hydrido-iridium insertion.^{10,12e,19a} If the same reaction was conducted with alkene **2a**, no deuterium would be incorporated to the recovered **1b**, supporting that the alkene insertion is much faster than the reversibility of the C–H activation step. Moreover, the deuterium incorporation to diene **3ba** showed a sufficiently fast H/D exchange on the hydrido-iridium intermediate to allow the H/D exchange of the vinyl moiety in **2a** by an insertion/ β -elimination pathway (Scheme 5b).^{19b} Furthermore, there was no deuterium scrambling in the crossover experiment using **1a** and **1b-d₂** (Scheme 5c). Finally, vinylic C–H bond cleavage was confirmed to be the rate-determining step by kinetic isotope effect (KIE) experiments (Scheme 5d).²⁰

The robustness of the protocol has been demonstrated by scaling up the reaction up to gram scale using a decreased catalyst loading (Scheme 6a). Conjugated diene was successfully reduced to adipic acid derivative **4ac** under catalytic hydrogenation (Scheme 6b). The Weinreb dienamide **3na** could be smoothly reduced to hemiaminal **4na** by simply

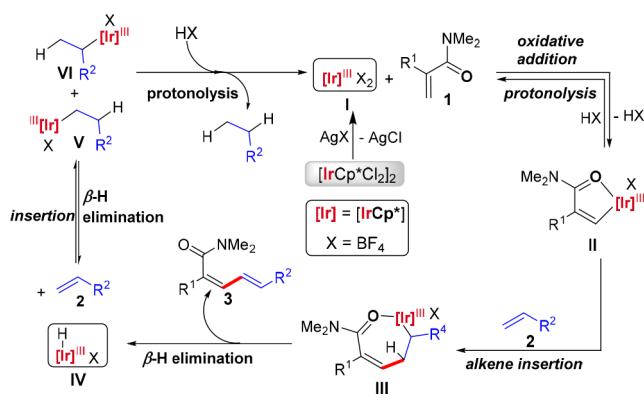
Scheme 6. Synthetic Applications



using DIBAL-H, with the phosphonate group intact (Scheme 6c).

Plausible mechanisms are illustrated in Scheme 7. First, a cationic species I is generated by the aid of silver salt, and the

Scheme 7. Proposed Mechanism



reversible C–H bond cleavage affords II, followed by alkene coordination and insertion, leading to a seven-membered iridacycle III. Next, β -H elimination occurred to provide diene 3 and [Ir]–H complex IV, and the latter reduced the electron-deficient alkene 2 by insertion to afford alkyridium species V and VI. Although the formation of V and VI is reversible, the following protonolysis provided an alkane and regenerated the catalytic species I.

In conclusion, for the first time, an iridium-catalyzed cross-coupling between electron-deficient olefins has been demonstrated, leading to site- and stereoselective preparation of (*Z,E*)-configured dienamides. By judicious choice of complex $[\text{IrCp}^*\text{Cl}_2]_2$ as the catalyst, the reaction led to a much lower cost by using inexpensive chloranil as the hydrogen acceptor. The operationally simple protocol exhibited a broad substrate scope of various di- and trisubstituted cyclic/acyclic acrylamides. Additionally, we have also examined the possible mechanism to gain insights into the directed olefinic C–H alkenylation by hydrogen transfer. Efforts to further understand the mechanism and apply the hydrogen transfer to the novel C–H transformation are currently underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02935.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) Jeganmohan's conditions have been examined in a cross-coupling reaction between acrylamides and alkenes, leading to a messy result.

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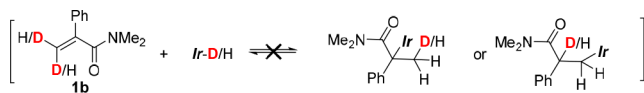
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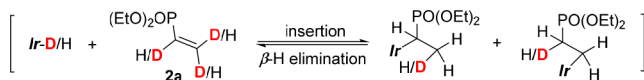
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(b) If diethyl vinylphosphonate **2a** was treated with D₂O (10 equiv) under optimal conditions without acrylamide, significant deuterium incorporation to the olefin moiety was observed. An insertion/ β -H elimination mechanism by a hydrido-iridium intermediate is likely to occur:



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