

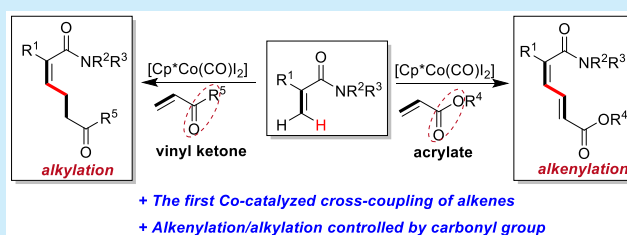
Cobalt-Catalyzed Olefinic C–H Alkenylation/Alkylation Switched by Carbonyl Groups

Tingyan Li, Cong Shen, Yaling Sun, Jian Zhang,*^{1b} Panjie Xiang, Xiunan Lu, and Guofu Zhong*^{1b}

College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China

S Supporting Information

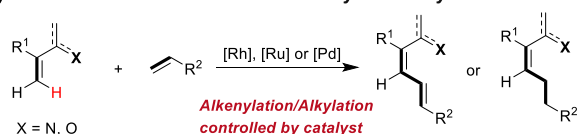
ABSTRACT: The first cobalt-catalyzed cross-couplings between olefins has been demonstrated to provide C(alkenyl)–H alkenylation and alkylation products, using complex $[\text{Cp}^*\text{Co}(\text{CO})\text{I}_2]$. While coupling partner acrylates afforded conjugated dienoates, α,β -unsaturated ketones led to γ -alkenyl ketones completely, representing a switchable C–H functionalization controlled by different carbonyl groups.



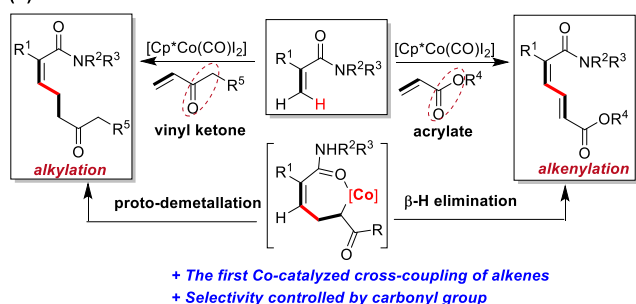
Direct C–H alkenylation such as Heck reaction is a powerful synthetic method to form new carbon–carbon bonds; thus, it is highly desirable in pharmaceutical and materials chemistry.¹ In particular, the oxidative olefinic C–H alkenylation reactions provided an attractive access toward the preparation of conjugated dienes with atomic economy.^{2–4} Two strategies can be used to realize these cross-coupling of alkenes. One is originated by alkenyl–Pd intermediates to form (*E,E*)-conjugated dienes,³ and the other is the functionality-directed olefinic C–H alkenylation to produce (*Z,E*)-butadienes via a cyclometalation event (see Scheme 1a).⁴ However, one limitation is that only noble metals, such as Rh, Ru, and Pd, have been utilized in olefinic C–H alkenylation, and there is still no example by the usage of inexpensive first-row transition-metal catalyst, such as rather environmentally benign cobalt complexes.⁵

Scheme 1. Catalytic C(alkenyl)–H Alkenylation/Alkylation

(a) Chelation-assisted olefinic C–H alkenylation/alkylation



(b) This work



Recently, the addition of a C–H bond across an inert alkene has become an important method to realize direct C–H alkylation, because of attractive features such as byproduct-free properties and greater availability of alkenes than alkyl halides.⁶ Although remarkable progress have been made on aromatic C–H alkylation using alkyl halides or alkenes,⁶ olefinic C–H alkylation has still remained undeveloped,⁷ especially alkenyl C–H alkylation using alkenes.^{6,8} Toste and Bergman previously reported an intramolecular cross-coupling of alkenes mediated by the $[\text{CpCo}(\text{NO})_2]$ complex.^{8a} However, there is still no intermolecular cross-coupling of alkenes via cobalt catalysis (see Scheme 1a).

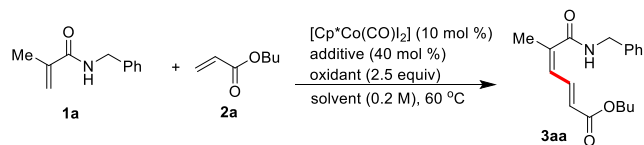
Despite the vast majority of catalyzed $\text{C}(\text{sp}^2)\text{--H}$ functionalizations achieved by precious second- and third-row transition metals, the focus has shifted to the use of inexpensive and Earth-abundant first-row transition metals, such as rather environmentally benign cobalt.^{5,9,10} Remarkable progress has been made in cobalt-catalyzed C–H activation, and it is urgent to extend the olefinic C–H alkenylation/alkylation to cobalt catalysis for the complementary substrate scope and reaction type, as well as new opportunities to develop ligand-controlled and site-selective/stereoselective C–H transformations.^{9–11} Unfortunately, examples on cobalt-catalyzed olefinic C–H activation remain scarce, most of which were restricted to C–H activation/annulations to provide heterocycles.¹¹ Although our group has made progress in transition-metal-catalyzed olefinic C–H activation using Rh, Ir, or Ru complexes,^{4b–j} we are still curious about the reactivity and selectivity of their lighter congeners such as inexpensive cobalt. Herein, we disclose the first Co-catalyzed regioselective and stereoselective cross-coupling of alkenes, leading to dienoates and γ -alkenyl ketones. The carbonyl group, ester or ketone, plays a key role in the switchable C(alkenyl)–H alkenylation and alkylation (see Scheme 1b).

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The amide group has been widely utilized in pharmaceutical chemistry, as well as directed C–H activation, and we tested the cross-coupling between acrylamide **1a** and acrylate **2a**, using robust Cp*Co(III) cobalt complex as a catalyst.^{9,10} Although [Cp*Co(CO)I₂] combined with AgOAc led to no product, the addition of AgSbF₆ (40 mol %) greatly promoted the reaction, producing 1,3-diene **3aa** in 51% yield (see Table 1, entries 1 and 2). Representative silver salts, such as AgOTf,

Table 1. Condition Optimization^a



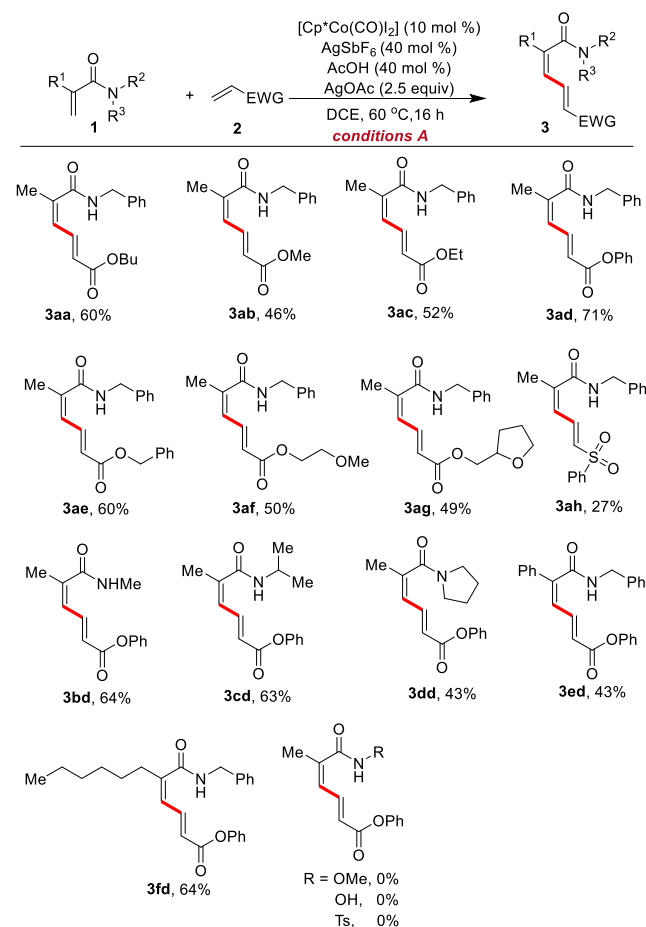
entry	additive	oxidant	solvent	yield ^b (%)
1	–	AgOAc	DCE	0
2	AgSbF ₆	AgOAc	DCE	51
3	AgOTf	AgOAc	DCE	21
4	AgNTf ₂	AgOAc	DCE	49
5	AgBF ₄	AgOAc	DCE	31
6 ^c	AgSbF ₆ /AcOH	AgOAc	DCE	60
7 ^c	AgSbF ₆ /PivOH	AgOAc	DCE	39
8 ^c	AgSbF ₆ /HCOOH	AgOAc	DCE	43
9 ^c	AgSbF ₆ /AcOH	Ag ₂ CO ₃	DCE	15
10 ^c	AgSbF ₆ /AcOH	Cu(OAc) ₂	DCE	44
11 ^c	AgSbF ₆ /AcOH	AgOAc	MeOH	0
12 ^c	AgSbF ₆ /AcOH	AgOAc	MeCN	0
13 ^c	AgSbF ₆ /AcOH	AgOAc	DCM	40
14 ^c	AgSbF ₆ /AcOH	AgOAc	CHCl ₃	58
15 ^c	AgSbF ₆ /AcOH	AgOAc	DME	49
16 ^{c,d}	AgSbF ₆ /AcOH	AgOAc	DCE	0

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cp*Co(CO)I₂] (10 mol %), additive (40 mol %), oxidant (2.5 equiv), in a solvent (1 mL) at 60 °C, 16 h. ^bIsolated yields. ^cCarboxylic acid (40 mol %) and AgSbF₆ (40 mol %) were used. ^dCo(OAc)₂ (10 mol %) was used instead of [Cp*Co(CO)I₂]. [Legend: DME = 1,2-dimethoxyethane, DCE = 1,2-dichloroethane, and DCM = dichloromethane.]

AgNTf₂, and AgBF₄, have been screened, but none of them improved the reaction (see Table 1, entries 3–5). Interestingly, the addition of acetic acid further improved the C–H alkenylation, leading to **3aa** in 60% yield with complete (*Z,E*)-configuration (*Z,E/Z,Z* > 99/1), supporting a chelation-assisted vinylic C–H activation via cyclometalation.^{4,10} (see Table 1, entry 6). However, other carboxylic acids, such as PivOH and HCOOH, exhibited decreased efficacy (see Table 1, entries 7 and 8). Different metal oxidants such as Ag₂CO₃ or Cu(OAc)₂ were examined, but neither of them provided satisfactory results (see Table 1, entries 9 and 10). Moreover, replacing the DCE with other solvents, such as methanol (MeOH), acetonitrile (MeCN), dichloromethane (DCM), CHCl₃, or 1,2-dimethoxyethane (DME) failed to further improve the coupling reaction (see Table 1, entries 11–15). Finally, simple cobalt complexes such as Co(OAc)₂ did not catalyze the cross-coupling (see Table 1, entry 16).

Next, we turned to examining the scope of substrates acrylamides **1** and alkenes **2**. As shown in Scheme 2, a wide variety of acrylates **2** reacted well with *N*-benzyl methacrylamide **1a** to provide conjugated diene derivatives successfully, and phenyl acrylate reacted best (**3aa–3af**). Notably,

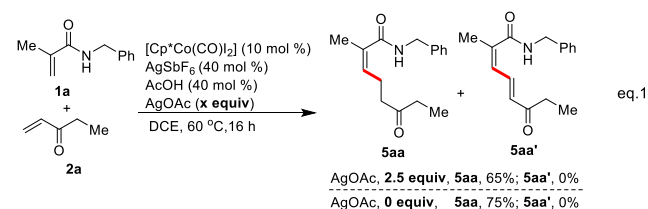
Scheme 2. Scope of Alkenyl C–H Alkenylation^{a,b}



^aReaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), [Cp*Co(CO)I₂] (10 mol %), AgSbF₆ (40 mol %), AcOH (40 mol %), AgOAc (2.5 equiv), in DCE (1 mL) at 60 °C, 16 h. ^bIsolated yields.

tetrahydrofurfuryl alcohol derived acrylate also converted well and led to moderate yield (**3ag**). Unfortunately, phenyl vinyl sulfone only exhibited limited reactivity (**3ah**). Differently *N*-substituted acrylamides were further investigated. While secondary amides bearing methyl or isopropyl produced 1,3-diene in good yields, tertiary amide such as pyrrolidine amide **1d** led to moderate yield. Installation of a phenyl ring and long aliphatic chain to the α-position of acrylamides also reacted, and the corresponding dienes **3ed** and **3fd** were isolated in 43% and 64% yields, respectively. Some other unsuccessful substrates included acrylamides bearing *N*-OH, *N*-OMe, and *N*-Ts substituents.

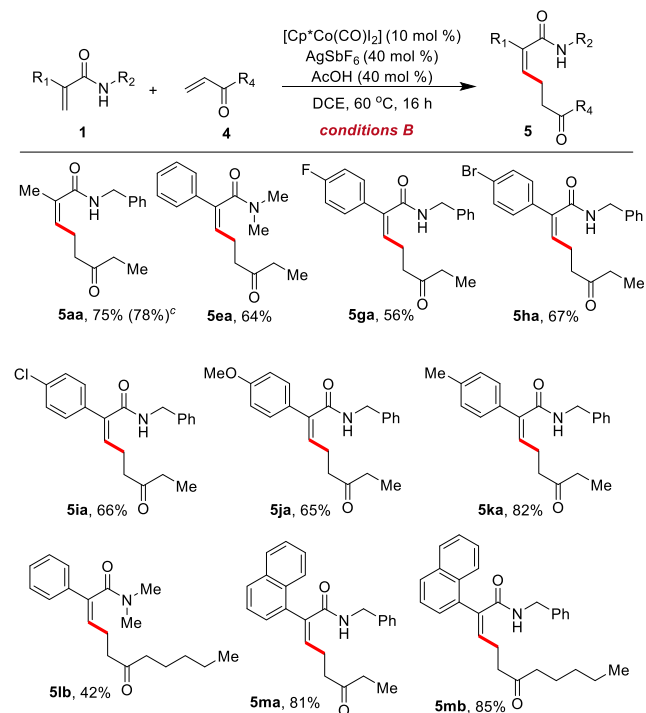
Electron-deficient alkene such as vinyl ketones **4** were also examined as coupling partners. Interestingly, vinyl ethyl ketone **4a** reacted well with acrylamide **1a** to provide alkylation product **5aa** in 65% yield under the optimal conditions (Condition A), without the formation of 1,3-diene **3aa** (eq 1):



The C–H alkylation is redox-neutral and it is supposed to proceed via a proto-demetalation step-involved mechanism. Therefore, the optimization was performed without AgOAc,^{6,7} leading to γ -alkenyl ketone **5aa** in 75% yield (Condition B).

Consequently, various acrylamides were employed to react with unsaturated ketones to construct γ -alkenyl ketones (Scheme 3). Aromatic acrylamides bearing F, Cl, Br, or

Scheme 3. Scope of Alkenyl C–H Alkenylation^{a,b}

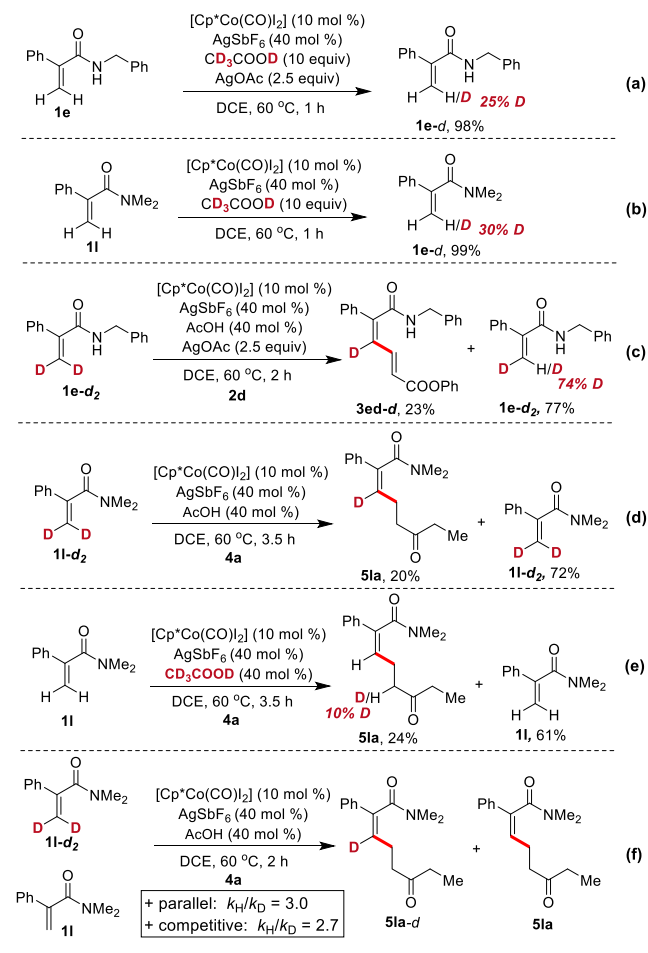


^aReaction conditions: **1** (0.2 mmol), **4** (0.4 mmol), [Cp*Co(CO)₂]₂ (10 mol %), AgSbF₆ (40 mol %), AcOH (40 mol %), in DCE (1 mL) at 60 °C, 16 h. ^bIsolated yields. ^c2.0 mmol scale (**1a**, 0.35 g).

OMe were all well-converted, regardless their electron-donating or electron-withdrawing properties (**5ea**–**5ka**, 64%–82% yields). Tertiary amide **1l** and acrylamide **1m** bearing a larger aromatic naphthalene were proven to be good substrates to react with ketones, including 1-octen-3-one **4b** (**5lb**, **5ma**, and **5mb**). Notably, gram-scale preparation of **5aa** was also successful, leading to a yield of 78%.

Treatment of acrylamides **1e** or **1l** under Condition A or Condition B, in the presence of CD₃COOD (10 equiv), led to significant vinylic deuterium incorporation in both cases, exhibiting reversible cyclometalation events (see Schemes 4a and 4b). The reaction between deuterium-labeling acrylamide **1e-d₂** and acrylate **2a** under Condition A provided only **3ed-d** in 23% yield, exhibiting a complete *cis*-C(alkenyl)-D cleavage and alkenylation. The olefinic H/D exchange in recovered substrate **1l-d₂** supported the hypothesis that the olefin insertion was competitive with the reversibility of the C–H activation step (see Scheme 4c). Deuterium-labeling acrylamide **1e-d₂** was also reacted with ketone **4a** under conditions B, but no olefinic H/D exchange to recovered substrate **1l-d₂** was observed, exhibiting that the alkylation step is much faster to outcompete the reversibility of the C–H cleavage step (see Scheme 4d). If CD₃COOD is used instead, H/D exchange in the α -position of ketone in product **5la** was observed, supporting a keto/enol like isomerization involved mechanism

Scheme 4. Deuterium-Labeled Experiments

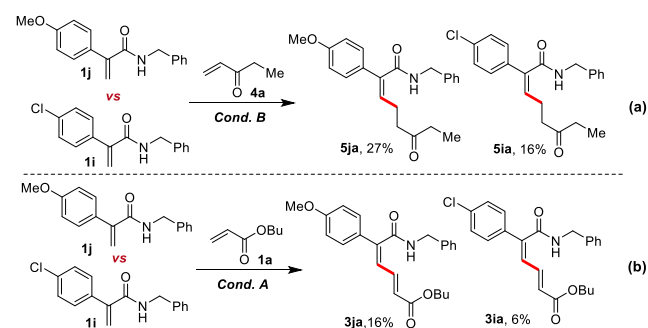


(see Scheme 4e). Parallel and competitive kinetic isotope effect (KIE) experiments confirmed the directed alkenyl C–H activation to be the rate-determining step (see Scheme 4f).¹³

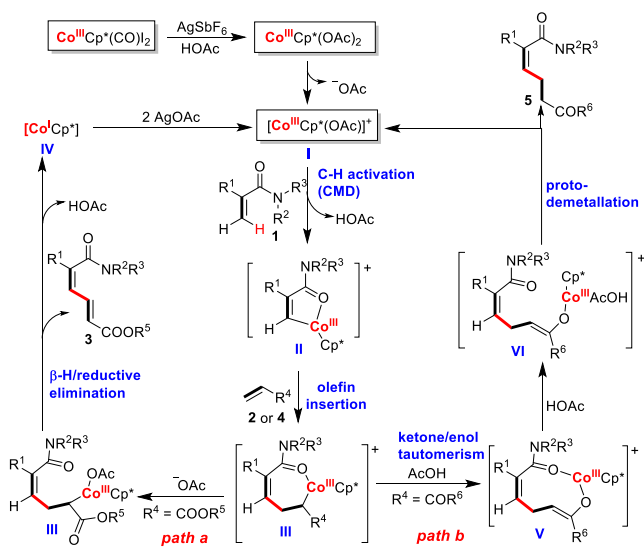
Intermolecular competition experiments between acrylamides **1j** and **1i** under Conditions A and B were performed to gain some preliminary understanding of the reaction mechanisms. Both experiments showed that the electron-rich alkene reacts preferentially, thereby exhibiting an electrophilic C–H activation (see Scheme 5).^{4,14}

Plausible catalytic mechanism is presented in Scheme 6. First, AgSbF₆-abstracted halide from the [CoCp*(CO)₂]₂ complex in the presence of acetate, leading to a monocationic and catalytically active species [Cp*Co(III)(OAc)]⁺ (**I**). Next, Co(III)-O chelation-assisted^{9,10} vinylic C–H bond cleavage

Scheme 5. Competition Experiments



Scheme 6. Proposed Mechanisms



occurred to form metalacycle **II** via acetate assisted concerted metalation-deprotonation (CMD).¹⁵ Olefin insertion, β -hydride elimination, and the following reductive elimination would produce conjugated diene **3** and acetic acid, with the liberation of Co(I)Cp^* (**IV**), which was oxidized by AgOAc to regenerate the active species **I** (path a). In the reaction of ketones, the 7-membered cobaltocyclic intermediate **III** binded an AcOH , underwent a keto/enol-like isomerization and a following “de-chelation isomerization”, would generate an intermediate **VI**. Protonation of **VI** by acetic acid produced **5** and regenerated the $[\text{Cp}^*\text{Co(III)(OAc)}]^+$ species **I** (path b). Herein, the metallo- keto/enol isomerization was considered to be the key step in the C–H alkylation process. However, the use of acrylate significantly destabilized this isomerization, thus driving the reaction toward the C–H alkenylation.^{9–12}

In summary, the first Co-catalyzed cross-couplings between electron-deficient olefins have been developed using cobalt complexes $[\text{Cp}^*\text{Co}(\text{CO})_2]$, leading to regioselective and stereoselective construction of a wide variety of *Z,E*-dienamides, as well as γ -alkenyl ketones, by judiciously choosing of coupling partners. While acrylates led to conjugated dienes via β -hydride elimination, α,β -unsaturated ketones produced C–H alkylation products by proto-demetalation. Further explorations on the cobalt-catalyzed C–H functionalizations are 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.9b02717.

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

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhangjian@hznu.edu.cn (J. Zhang).

*E-mail: zgf@hznu.edu.cn (G. Zhong).

ORCID

Jian Zhang: 0000-0001-8734-3003

Guofu Zhong: 0000-0001-9497-9069

Notes

The authors declare no competing financial interest.

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