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# Palladium-Catalyzed Oxidative Heck-Type Allylation of β,β-Disubstituted Enones with Allyl Carbonates

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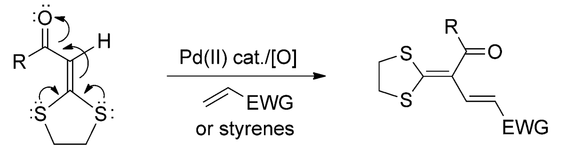
**Abstract:** The palladium-catalyzed oxidative Heck-type allylation of β,β-disubstituted enones, i.e., α-oxoketene dithioacetals, was efficiently realized with allyl carbonates, providing a concise route to highly functionalized dienes. The present synthetic methodology utilizes the substrate activation strategy to activate the C–H bond of β,β-disubstituted enones by introduction of a 1,2-dithiolane functionality to make the enone substrate highly polarized and thus increase its reactivity, demonstrating rare examples for transition metal-catalyzed allylic substitution of ß,ß-disubstituted enones through a Heck-type allylation process.

**Keywords:** allyl carbonates; allylation; C–H activation; enones; ketene dithioacetals; palladium

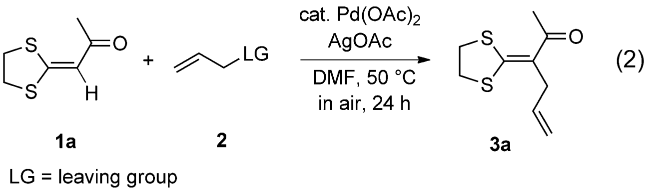
Functionalized olefins are important building blocks in many natural products, pharmaceuticals, and organic functionalized materials.[1] Over the past few decades, the transition metal-catalyzed Heck reaction has emerged as one of the most powerful and straightforward tools for the construction of new C–C bonds in the synthesis of functionalized olefins.[2] In recent years, nickel-[3] and iridium-catalyzed[4] Heck-type allylic substitution reactions by means of simple alkenes as nucleophiles and allylating reagents as electrophiles to prepare functionalized olefins have been well developed. An asymmetric version of the iridium-catalyzed allyl-Heck-type substitution reaction which employed racemic allylic alcohols and simple alkenes as coupling partners was also documented for the enantioselective generation of allyl-functionalized olefin products.[5]

Although enone compounds usually serve as the terminal alkenes, and have been widely demonstrated in transition metal-catalyzed Heck reactions at the β-position to deliver linear olefin products,[2,6] the catalytic cross-coupling of enones which act as the internal alkenes to afford highly branched olefins has attracted less attention. Hirama et al. reported the palladium-catalyzed intramolecular Heck arylation of β,β-disubstituted enones to synthesize the congested benzylic quaternary center.[7] Notably, a pioneer work of intramolecular allylic substitution at the α-position of enones *via* the merging of palladium catalysis and phosphine organocatalysis was realized by Krische and co-workers.[8] In 2010, our group realized the direct oxidative cross-coupling between internal and terminal olefins, successfully synthesizing multifunctionalized conjugated dienes through Pd(II)-catalyzed oxidative C–H bond olefination of the internal olefin units of α-oxoketene dithioacetals with terminal olefins such as acrylates and styrenes.[9] We reasonably attached both the electron-donating cyclic dithioalkyl[10] and an electron-withdrawing carbonyl to the two ends of the C=C bond of an internal alkene to tune it into a highly polarized state and thus increase the reactivity of its C–H bond [Eq. (1)]. During our continuing investigation of α-oxoketene dithioacetals, we envisioned that α-oxoketene dithioacetals, the nature of which is a variant of β,β-disubstituted enones, might be applied for the synthesis of highly functionalized olefins by employing such a substrate activation strategy in allyl-Heck-type reactions.[11,12] Herein, we report a Pd(II)-catalyzed intermolecular oxidative allylation of α-oxoketene dithioacetals with allyl carbonates.



(1)[9]

**Table 1.** Examination of allylating reagents for the allylation of **1a**.[a]



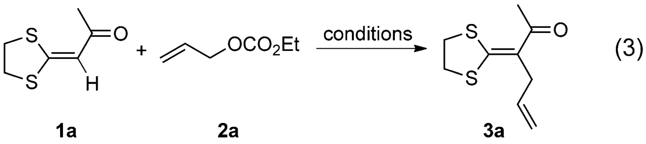
| Entry | LG in **2** | Yield [%][b] | Entry | LG in **2** | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | Br | 2 | 5 | $OCO_2Me$ | 72 |
| 2 | Bpin | 0 | 6 | $OCO_2Et$ | 81 |
| 3 | $P(O)(OEt)_2$ | 0 | 7 | $OCO_2Ph$ | 51 |
| 4 | OAc | 73 | 8 | OBoc | 64 |

[a] *Reaction conditions:* **1a** (0.3 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (0.6 mmol), DMF (2 mL), air atmosphere, 50 °C, 24 h. The reactions were carried out in a sealed 15-mL Pyrex glass screw-cap tube.

[b] Determined by GC analysis using mesitylene as the internal standard; pin = pinacolato, Boc = *t*-BuOCO.

Initially, we tested the reactions of α-oxoketene dithioacetal (**1a**) with the allylating reagents bearing various leaving groups under the typical conditions used for the direct olefination of **1a** with terminal olefins.[9] It was found that the leaving groups had a remarkable effect on the reactivity of the allylating reagents. Allyl bromide, allylboronic acid pinacol ester, and diethyl allylphosphonate exhibited very poor reactivity (Table 1, entries 1–3), while allyl acetate and carbonates showed good reactivity to yield the desired product. This is presumably attributed to the relatively strong basicity of acetate and carbonate anions which serve as the bases to facilitate the C–H bond cleavage and the catalyst dissociation process.[13] Allyl ethyl carbonate behaved as the most effective allylating reagent to form **3a** in 81% yield (Table 1, entries 4–8). It has been well known that allyl carbonates can be utilized as decarboxylative allylation reagents.[14]

**Table 2.** Screening of conditions for the reaction of **1a** and **2a**.[a]



| Entry | Catalyst | Oxidant | Solvent | Time [h] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | AgOAc | DMF | 12 | 56 |
| 2 | $PdCl_2(MeCN)_2$ | AgOAc | DMF | 12 | 59 |
| 3 | $Pd(TFA)_2$ | AgOAc | DMF | 12 | 43 |
| 4 | $[PdCl(allyl)]_2$ | AgOAc | DMF | 12 | 18 |
| 5 | $Pd(OAc)_2$ | AgOAc | DMF | 12 | 72 |
| 6 | $Pd(OAc)_2$ | $Ag_2CO_3$ | DMF | 12 | 9 |
| 7 | $Pd(OAc)_2$ | $Cu(OAc)_2$ | DMF | 12 | 41 |
| 8 | $Pd(OAc)_2$ | BQ | DMF | 12 | 35 |
| 9 | $Pd(OAc)_2$ | $PhI(OAc)_2$ | DMF | 12 | 32 |
| 10 | $Pd(OAc)_2$ | TBHP | DMF | 12 | 13 |
| 11 | $Pd(OAc)_2$ | TEMPO | DMF | 12 | 40 |
| 12 | $Pd(OAc)_2$ | AgOAc | DMA | 12 | 65 |
| 13 | $Pd(OAc)_2$ | AgOAc | THF | 12 | 35 |
| 14 | $Pd(OAc)_2$ | AgOAc | DMSO | 24 | 17 |
| 15[c] | $Pd(OAc)_2$ | AgOAc | DMF/ DMSO | 24 | 95 (70)[d] |
| 16[c] | $Pd(OAc)_2$[e] | AgOAc | DMF/ DMSO | 24 | 54 |
| 17[c] | – | AgOAc | DMF/ DMSO | 24 | 0 |
| 18[c] | $Pd(OAc)_2$ | – | DMF/ DMSO | 24 | 23 |

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst (20 mol%), oxidant (0.6 mmol), solvent (2 mL), air atmosphere.

[b] Determined by GC analysis using mesitylene as the internal standard.

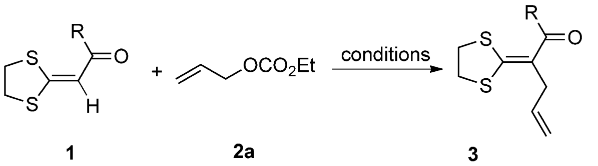
[c] DMF/DMSO = 20:1 (v/v).

[d] Isolated yield given in parentheses.

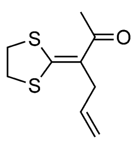
[e] $Pd(OAc)_2$ (10 mol%); TFA = trifluoroacetic acetate, BQ = benzoquinone, TBHP = *tert*-butyl hydroperoxide, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl, DMA = *N*,*N*-dimethylacetamide.

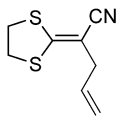
Next, the cross-coupling reaction of **1a** with allyl ethyl carbonate (**2a**) was employed as the model reaction to optimize the reaction conditions [Eq. (3), Table 2]. Examination of the palladium sources revealed that $Pd(OAc)_2$ was the most effective catalyst for the reaction in DMF at 50 °C, leading to the desired product **3a** in 72% yield within 12 h (Table 2, entries 1–5). AgOAc acted as the most efficient oxidant among the screened oxidizing reagents, i.e., AgOAc, $Ag_2CO_3$, $Cu(OAc)_2$, benzoquinone (BQ), $PhI(OAc)_2$, *tert*-butyl hydroperoxide (TBHP), and TEMPO (Table 2, entries 5–11). The desired product was also formed in a moderate yield (65%) in DMA (Table 2, entry 12). To our delight, the reaction proceeded more efficiently in a mixed solvent of DMF and DMSO (v/v, 20/1), reaching 95% yield (70% isolated yield) for **3a** over a period of 24 h (Table 2, entry 15). DMSO may function as a ligand to stabilize the catalytically active species in the catalytic cycle,[15] enhancing the reaction efficiency. Both lowering and elevating the reaction temperature deteriorated the reaction efficiency (see the Supporting Information for details). Reducing the catalyst loading to 10 mol% resulted in **3a** in a lower yield (54%), and the reaction did not occur without $Pd(OAc)_2$ catalyst (Table 2, entries 16 and 17). It should be noted that direct oxidative coupling of internal olefins is very difficult, and in general a relatively high catalyst loading should be applied.[9] Without an added oxidant, the reaction proceeded only slowly in air (Table 2, entry 18). The

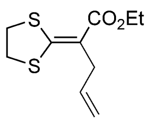
**Table 3.** Oxidative allylation of β,β-disubstituted enones **1** with allyl carbonate **2a**.[a,b]

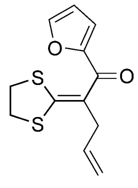


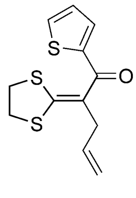
(4)

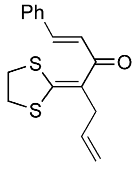

**3a**, 70%

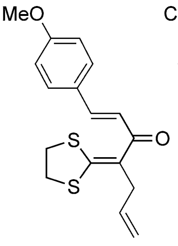

**3b**, 64%

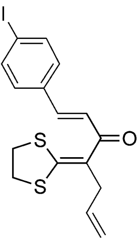

**3c**, 65%

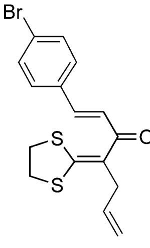

**3d**, 63%

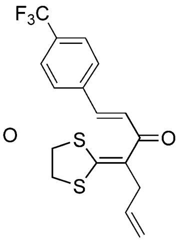

**3e**, 60%

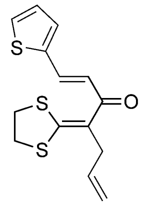

**3f**, 67%

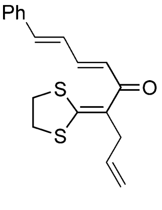

**3g**, 69%


**3h**, 62%


**3i**, 65%


**3j**, 69%


**3k**, 57%


**3l**, 55%

[a] *Reaction conditions:* **1** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (1.0 mmol), DMF/DMSO (2 mL, v/v = 20/1), air atmosphere, 50 °C, 24 h.

[b] Isolated yields.

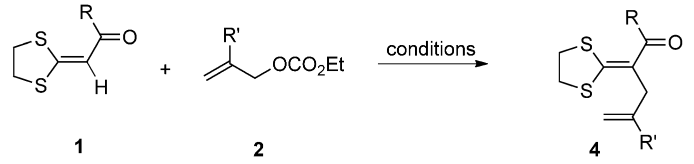
reaction conditions were thus optimized as those for entry 15 in Table 2.

With the optimized reaction conditions in hand, the substrate scope of α-oxoketene dithioacetals **1** was then investigated (Table 3). α-Cyanoketene dithioacetal (**1b**) and α-ester ketene dithioacetal (**1c**) reacted with **2a** to afford the desired olefin products **3b** and **3c** in 64% and 65% yields (Table 3), respectively. The cyano (latent carbonyl) and ester groups exist as two important convertible functionalities for the potential utilitization of the products in organic synthesis. Treatment of heteroaryl α-oxoketene dithioacetals with **2a** exclusively afforded product **3d** (63%) and **3e** (60%), respectively, and no double allylation occurred at the 5-positions of the furyl and thienyl rings. However, during the olefination of the same α-oxoketene dithioacetal substrates with electron-deficient olefins, double olefination products could be obtained.[9] Unexpectedly, α-aroylketene dithioacetals only exhibited very low reactivity under the same conditions, which may be attributed to the steric hindrance from the bulky aryl groups attached to the α-oxo moiety. These results have demonstrated that the direct allylation of **1** is much more difficult than their olefination under similar conditions.[8] As expected, decreasing the steric hindrance of the α-oxoketene dithioacetals by altering α-aroyl groups to α-cinnamoyls made the allylation reactions proceed smoothly to form products **3f**–**3j** in 62–69% yields. The electronic effect of the substituents on the cinnamoyl aryls had little influence on the reaction efficiency. Methoxy, chloro, bromo and trifluoromethyl groups were tolerated, suggesting potential applications of the present synthetic protocol due to the easy transformations of these functionalities in organic synthesis. Surprisingly, tetraene product **3l** was also obtained in 55% yield. The substrates of type **1** exhibited an obvious substituent effect of the alkylthio groups. Under the same conditions, only trace amounts of the desired product could be detected when an α-oxoketene 1,3-dithioacetal was used as the starting material.

Under the same conditions as shown in Table 3, 2-substituted allyl ethyl carbonates were employed to explore the generality of the direct oxidative allylation methodology (Table 4). A notable steric effect was observed from the substituted allyl carbonate substrates. As the steric hindrance of the aryl moieties in the substituted substrates **2** gradually decreased from 2-Me, 3-Me, to 4-Me, the yields of products **4b**–**4d** were increased from 35%, 62%, to 71%, and **4a** was also obtained in a good yield (Table 4, entries 1–4). Electron-donating and electron-withdrawing substituents were tolerated on the aryl groups of **2** (Table 4, entries 2–7). It is noteworthy that 2-alkyl-substituted allyl ethyl carbonates **2i** and **2j** underwent the allylation reactions to furnish the desired products **4i** and **4j** in moderate yields (Table 4, entries 8 and 9). However, 2-naphthyl-substituted allyl ethyl carbonate showed very poor reactivity due to the high steric hindrance from the naphthyl substituent. α-Heteroaroyl- and cinnamoyl-ketene dithioacetals reacted well with 2-aryl-substituted allyl ethyl carbonates to afford the the desired products in 55–68% yields (Table 4, entries 10–13).

The mechanism is unclear at the present stage. Based upon our previous work[8] and observations, a plausible mechanism is proposed (Scheme 1). The initial reaction of α-oxoketene dithioacetal **1** with $Pd(OAc)_2$ leads to the palladated ketene species **A** and acetic acid by electrophilic attack of the catalyst precursor at the C–H bond of olefins. Species **A** reacts with allyl carbonate **2** to form π-allyl-Pd(II) intermediate **B**. A following reductive elimination from

**Table 4.** Oxidative allylation of β,β-disubstituted enones **1** with substituted allyl ethyl carbonates **2**.[a]



(5)

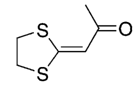
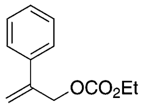
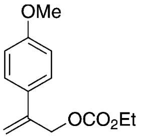
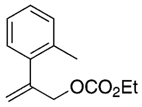
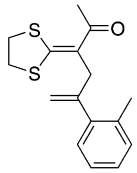
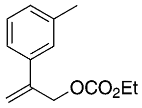
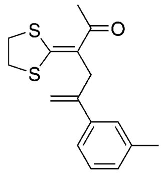
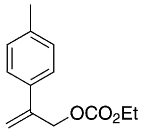
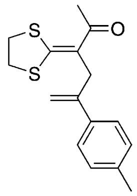
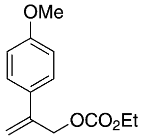
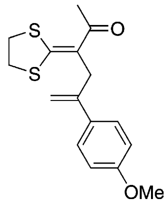
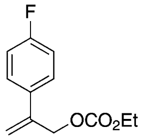
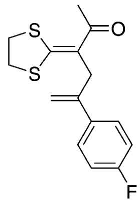
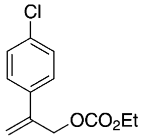
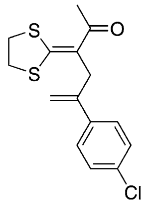
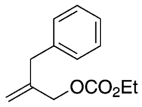
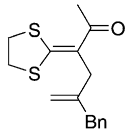
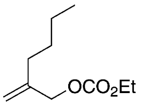
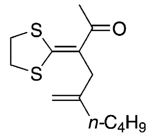
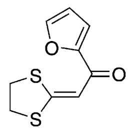
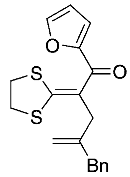
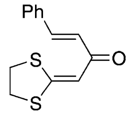
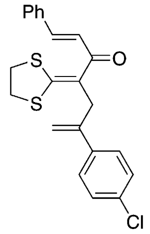
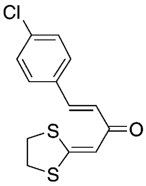
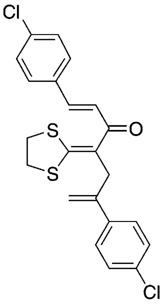
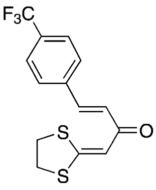
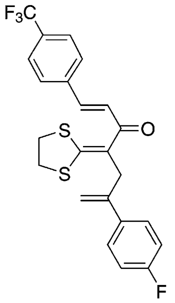
| Entry | | **1** | | **2** | | Product **4** | Yield [%][b] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** |  | **2b** |  | **4a** |  | 69 |
| 2 | **1a** | | **2c** |  | **4b** |  | 35 |
| 3 | **1a** | | **2d** |  | **4c** |  | 62 |
| 4 | **1a** | | **2e** |  | **4d** |  | 71 |
| 5 | **1a** | | **2f** |  | **4e** |  | 65 |
| 6 | **1a** | | **2g** |  | **4f** |  | 70 |
| 7 | **1a** | | **2h** |  | **4g** |  | 75 |
| 8 | **1a** | | **2i** |  | **4h** |  | 58 |

**Table 4.** (Continued)

| Entry | 1 | 2 | Product 4 | Yield [%][b] |
|---|---|---|---|---|
| 9 | **1a** | **2j**  | **4i**  | 40 |
| 10 | **1d**  | **2i** | **4j**  | 55 |
| 11 | **1f**  | **2h** | **4k**  | 65 |
| 12 | **1h**  | **2h** | **4l**  | 68 |
| 13 | **1j**  | **2g** | **4m**  | 65 |

[a] *Reaction conditions:* **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (1.0 mmol), DMF/DMSO (2 mL, v/v = 20/1), 50 °C, air atmosphere, 24 h.

[b] Isolated yields.

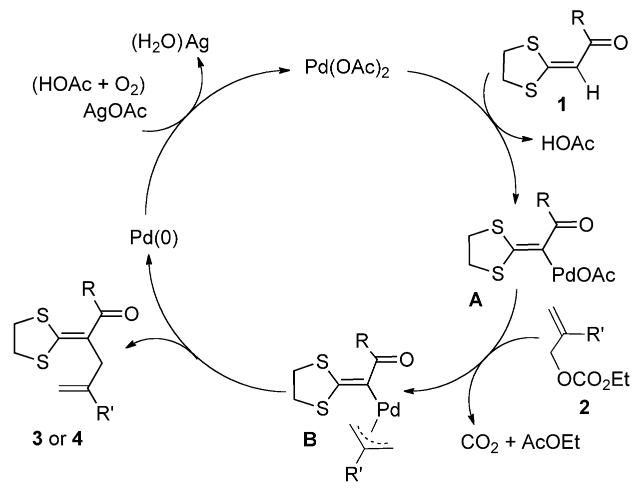
**B** produces the desired product **3** or **4** as well as the Pd(0) species. Oxidation of the Pd(0) species by AgOAc regenerates the $Pd(OAc)_2$ catalyst, and an air atmosphere (oxygen) facilitates the catalyst regeneration. Alternatively, the Heck-type pathway involving oxidative addition of Pd(0) to allyl carbonate **2** and with subsequent carbopalladation and reductive elimination,[2] and the Tsuji–Trost-type process facilitating formation of a π-allyl intermediate for nucleophilic attack cannot be ruled out.[7]

In summary, palladium-catalyzed oxidative Heck-type allylation of α-oxoketene dithioacetals with allyl carbonates has been efficiently realized, providing a concise route to highly functionalized olefins. The present synthetic methodology has demonstrated rare examples for catalytic intermolecular allylic substitution of β,β-disubstituted enones.

## Experimental Section

### Typical Procedure for the Synthesis of 3 and 4: Synthesis of 3a

A mixture of **1a** (80 mg, 0.5 mmol), **2a** (130 mg, 1.0 mmol), $Pd(OAc)_2$ (23 mg, 0.1 mmol) and AgOAc (167 mg,



**Scheme 1.** A proposed mechanism.

1.0 mmol) in 2 mL DMSO/DMF (1/20, v/v) was stirred at 50 °C for 24 h. After being cooled to ambient temperature, the resulting mixture was filtered through a short pad of celite and rinsed with 10 mL of diethyl ether. Brine (30 mL) was added and the mixture extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and all the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography [eluent: petroleum ether (60–90 °C)/diethyl ether = 30:1, v/v] to afford **3a** as a yellow oil; yield: 100 mg (70%).

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**7**