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Heck reaction with an acyl synthon: new coupling reaction between α-halo vinyl ether and alkene☆

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Abstract—α-Halo vinyl ethers were successfully applied to palladium-catalyzed Heck reaction. Reactions of α-halo vinyl ether with alkenes under various Heck conditions form a new carbon–carbon bond along with a vinyl ether functionality, which can be further manipulated. This is the first synthetic methodology for the coupling of an acyl synthon with alkene employing Heck reaction.

Palladium-catalyzed reaction of vinyl or aryl halide with alkene (Heck reaction) has been the subject of much attention by organic chemists since it was first discovered by Heck in the late 1960s.[2] In the last two decades, it has rapidly developed into an important methodology for carbon–carbon bond formation.[3] In addition, the Heck reaction has also been successfully applied to the total synthesis of many biologically active natural products.[4] Despite the tremendous developments in this field, the Heck reaction is still limited to the vinylation or arylation of alkenes. To the best of our knowledge, coupling of an acyl synthon with alkene under Heck reaction conditions has never been reported.

Recently, we reported a general methodology for the highly stereoselective synthesis of α-halo vinyl ethers.[5] We demonstrated that α-halo vinyl ethers can serve as precursors of acyl anion equivalents and can undergo many important organic transformations including palladium-catalyzed Stille coupling,[5,6] and Sonagashira reaction.[5,7] These preliminary results led us to investigate the possibility of the application of α-halo vinyl ethers in the palladium-catalyzed Heck reaction.

We found that α-halo vinyl ethers underwent facile reaction with various alkenes under Heck reaction conditions. Palladium-catalyzed reactions between α-halo vinyl ethers and various alkenes are summarized in Table 1.[8] The first four entries are the Heck reactions between α-bromo vinyl ethers and electron deficient olefins. Due to their high reactivity and relative stability, α-bromo vinyl ethers were chosen as the reaction substrates. Compound **1** reacted with methyl acrylate in the presence of $Pd(PPh_3)_4$ and Et_3N in CH_3CN at reflux to provide conjugated diene ester **3** in 79% yield (entry 1).[9] Under the same reaction conditions, the coupling reaction between vinyl bromide **1** and acrylonitrile **4** gave conjugated diene nitrile **5** in 76% yield (entry 2). It should be noted that the olefin geometry was completely inverted in both compounds **3** and **5** presumably due to the bulkiness of the alkoxy group and the high reaction temperature.[10] The inversion of the geometry of vinyl ethers was also observed in both Stille coupling and palladium-catalyzed carbonylation.[5] Compound **6** underwent a facile intramolecular Heck reaction to afford diene **7** in 73% yield (entry 3).[11] The Heck reaction between vinyl bromide **8** and styrene **9** did not afford any desire product in the presence of $Pd(PPh_3)_4$ and Et_3N in CH_3CN at reflux, but under Jeffery's conditions ($Pd(OAc)_2$, KOAc, and n-Bu_4NCl in DMF),[12] it afforded conjugated diene **10** in moderate yield (entry 4). In contrast, at a reaction temperature of 25 °C for entry 4, the geometry of the vinyl ether double bond was fully retained.

We found that α-halo vinyl ethers also underwent palladium-catalyzed Heck reaction with electron-rich olefins such as 2,3-dihydrofuran **12**.[13] The reaction of compound **11** with 2,3-dihydrofuran **12** under Jeffery's

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Keywords: α-Halo vinyl ether; Heck reaction; Vinyl ether; Masked ketone.

☆ See Ref. 1.

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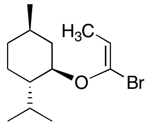
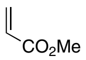
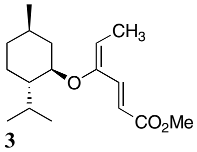
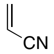
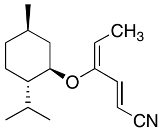
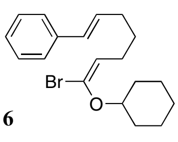
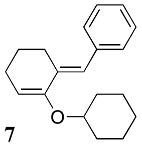
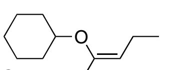
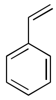
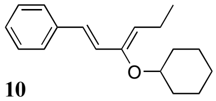
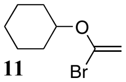
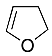
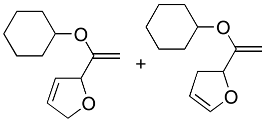
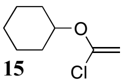
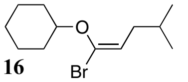
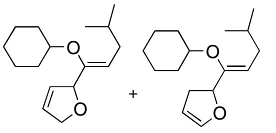
Table 1. Heck reaction between α-halo vinyl ethers and various alkenes

Entry	α-Halo vinyl ether	Olefin	Condition	Products	Yield (%)
1	 **1**	 **2**	A	 **3**	79
2	**1**	 **4**	A	 **5**	76
3	 **6**		A	 **7**	73
4	 **8**	 **9**	B	 **10**	58
5	 **11**	 **12**	B	 **13** (8:1) **14**	79
6	**11**	**12**	C	**13** (17:1) **14**	57
7	 **15**	**12**	B	**13** (10:1) **14**	70
8	 **16**	**12**	B	 **17** (6:1) **18**	92

Conditions: A: α-halo vinyl ether (1 equiv), olefin (10 equiv), Pd(PPh$_3$)$_4$ (5 mol%), Et$_3$N (1.5 equiv), CH$_3$CN, reflux for 6 h. B: α-halo vinyl ether (1 equiv), olefin (10 equiv), Pd(OAc)$_2$ (5 mol%), KOAc (2.5 equiv), *n*-Bu$_4$NCl (2.5 equiv), DMF, 25 °C for 8 h. C: α-halo vinyl ether (1 equiv), olefin (10 equiv), Pd(OAc)$_2$, (5 mol%), *n*-Bu$_4$NOAc (2.5 equiv), DMF, 25 °C for 8 h.

conditions[12] gave compounds **13** and **14** in a combined yield of 79% at a ratio of 8:1 (entry 5). This is the first example of the reaction between an acyl synthon and 2,3-dihydrofuran under Heck reaction conditions. Although it was possible to improve the ratio to 17:1 by employing different phase-transfer catalyst, the yield was reduced to 57% (entry 6). The relatively less reactive α-chloro vinyl ether **15** could also undergo Heck reaction under Jeffery's conditions to provide compounds **13** and **14** in the ratio of 10:1 (entry 7). α-Bromo vinyl ether **16** reacted with **12** afforded the two regioisomers **17** and **18** in a ratio of 6:1 (entry 8). It should be noted that the geometry of the vinyl ether double bond was retained (entry 8).[10]

A typical procedure follows: A mixture of α-bromo vinyl **11** (1.1 mmol), 2,3-dihydrofuran **12** (11 mmol), KOAc (2.8 mmol), *n*-Bu$_4$NCl (2.8 mmol), and Pd(OAc)$_2$ (0.055 mmol) in 4.0 mL DMF was stirred at 25 °C for 8 h. The reaction was monitored by TLC. After the reaction was complete, H$_2$O (10 mL) was added and the reaction solution was extracted with Et$_2$O (3 × 15 mL). The combined organic phase was washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated by rotary evaporation. The products were purified by silica gel flash column chromatography (pretreated with 2.5% v/v of triethylamine/hexane) to afford compounds **13** and **14** in 79% yield with a ratio of 8:1.

In conclusion, we have demonstrated that α-halo vinyl ethers are excellent substrates for palladium-catalyzed Heck reactions. More importantly, since the vinyl ether functionality can be easily converted to ketone in very mild acidic conditions, our methodology has extended the scope of the classic Heck reaction to the acylation of alkenes.

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