ORGANIC
LETTERS

2013
Vol. 15, No. 21
5531–5533

Synthesis of Dienyl Ketones via Palladium(II)-Catalyzed Direct Cross-Coupling Reactions between Simple Alkenes and Vinyl Ketones: Application to the Synthesis of Vitamin A1 and Bornelone

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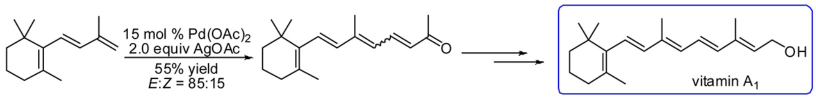
Received September 18, 2013

ABSTRACT



An efficient and general method for the synthesis of conjugated dienyl ketones via palladium(II) acetate catalyzed direct cross-coupling between simple alkenes and vinyl ketones is reported. This method has been successfully applied for the synthesis of Vitamin A1 and bornelone.

Dienyl ketone fragments are basic scaffolds of many natural products and pharmaceutically active molecules.[1] In addition, they are versatile synthetic building blocks in organic synthesis.[2] Traditional methods for the construction of 1,3-dienyl ketone fragments involve the use of carbonyl olefination[3] by a direct Wittig[4] or Horner–Wadsworth–Emmons reaction,[4] transition metal catalyzed classic coupling reactions,[5,6] isomerization of alkynones,[7] and others. Among the methods, palladium and rhodium catalyzed cross-coupling reactions have been widely utilized for the synthesis of dienyl ketones.[5,6] However, a direct C–C bond formation reaction between alkenes avoiding the need to use prefunctionalized olefins has been recognized as a more promising method because of its atom economy and environmentally friendly advantages.[8]

While the homocoupling of two simple alkenes has been reported by Gusevskaya,[9] cross-coupling using simple alkene has rarely been reported. In this context, our group[10] and others[11] have embarked on the search for new and efficient methods for the direct oxidative cross-coupling between different olefins. However, in most cases, only acrylates were suitable to be used as the efficient coupling partners to afford the corresponding dienoate derivatives.

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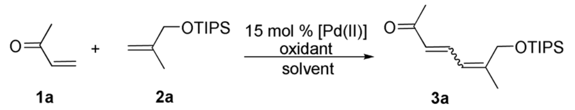
The use of an unsaturated ketone such as methyl vinyl ketones posed a more challenging task due to its potential for polymerization. In this paper, we report an efficient palladium-catalyzed oxidative cross-coupling reaction between simple olefins and vinyl ketone to form 1,3-dienyl ketone derivatives. The synthetic utility of this method has also been demonstrated with the synthesis of Vitamin A1 and bornelone.

Initially, **2a** and methyl vinyl ketone (MVK) were chosen as the model substrates to optimize this reaction (Table 1). Under our previously reported conditions,[10] no desired product was obtained. Diverse oxidants were then examined, and it was found that the desired product could be generated in 34% yield at a temperature of 110 °C in the presence of AgOAc. The yield of the product could be increased to 52% when the amount of AgOAc was increased to 2.0 equiv (entry 4). Other oxidants such as BQ, O$_2$, and Cu(OAc)$_2$ gave the desired product in lower yields (entries 1, 2, 3, and 5). After different palladium catalysts were screened, Pd(OAc)$_2$ was found to be a better choice (entries 6–8). A series of solvents was tested, and it was found that polar solvents such as THF and DMSO were not suitable for this reaction (entries 9, 12, and 13). When toluene was used, a side product from MVK coupled with the solvent was observed (entry 10). Next, 1 mol % BQ was added as the polymerization inhibitor of MVK, but there was no obvious effect. Next when we changed the ratios of the two reactants to 1:2 (**1a**:**2a**), the cross-coupling product was furnished in 56% yield. With the price of these two reactants taken into consideration, a 2:1 ratio of **1a**:**2a** was adopted in this reaction. The yield decreased slightly when the reaction was carried out at lower temperature (80 °C). The control experiment carried out in the absence of the palladium catalyst afforded no desired product. Ultimately, we established the optimized reaction conditions as follows: 15 mol % Pd(OAc)$_2$ as the catalyst and 2.0 equiv of AgOAc as the oxidant in DCE, heated at 110 °C.

With the optimization reaction conditions, we first examined the scope of common olefins for this Pd-catalyzed oxidative cross-coupling reaction by employing MVK. Most of the olefins as shown in Scheme 1 could afford the olefination products in moderate to good yields with different *E*/*Z* selectivities. First, we extended this reaction to 1,1-disubstituted alkenes. The reaction using protected 2-methyl-2-propen-1-ol compounds afforded the desired coupling products in good yields and with acceptable *E*/*Z* selectivities. It is noteworthy that the more bulky triisopropylsilyl (TIPS) group will lead to a better *E*/*Z* selectivity as compared to the acetal or benzoyl protecting group. The olefins with an oxygen-containing substituent

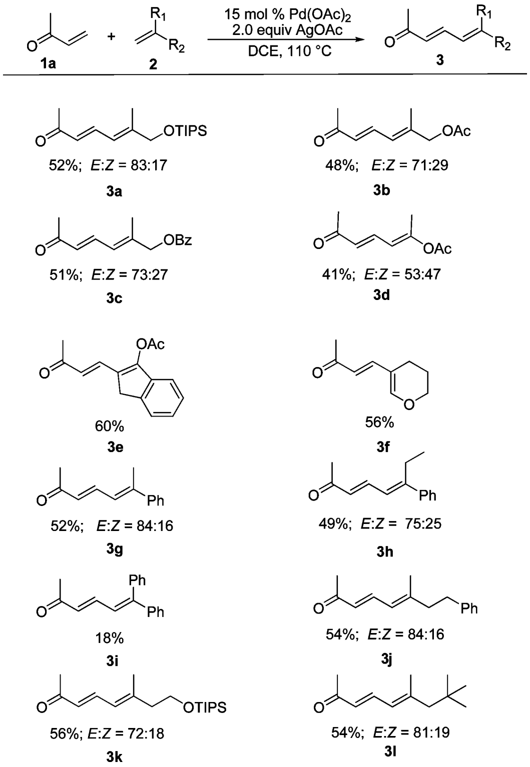
Table 1. Optimization of the Reaction Conditions[a]



entry	t (°C)	cat.	solvent	oxidant	yield (%)[b]
1	110	Pd(OAc)$_2$	DCE	Cu(OAc)$_2$	trace
2	110	Pd(OAc)$_2$	DCE	BQ	NR
3	110	Pd(OAc)$_2$	DCE	PhI(OAc)$_2$	17
4	110	Pd(OAc)$_2$	DCE	AgOAc	52
5	110	Pd(OAc)$_2$	DCE	O$_2$	NR
6	110	PdCl$_2$	DCE	AgOAc	33
7	110	Pd(TFA)$_2$	DCE	AgOAc	26
8	110	PdCl$_2$(PhCN)$_2$	DCE	AgOAc	43
9	110	Pd(AcAc)$_2$	THF	AgOAc	36
10	110	Pd(OAc)$_2$	toluene	AgOAc	16
11	110	Pd(OAc)$_2$	dioxane	AgOAc	33
12	110	Pd(OAc)$_2$	DMSO	AgOAc	trace
13	110	Pd(OAc)$_2$	DCE	AgOAc	56[c]
14	80	Pd(OAc)$_2$	DCE	AgOAc	49

[a] Unless noted otherwise, the reaction was carried out with MVK (1.0 mmol), olefin (0.50 mmol), and 15 mol % of palladium catalyst (0.075 mmol) in the given solvent (3.0 mL). TIPS = triisopropylsilyl. [b] Isolated yield. [c] **1a**:**2a** = 1:2.

Scheme 1. Olefination of Various Alkenes with MVK[a,b]



[a] Reaction conditions: Unless noted otherwise, alkene (0.5 mmol), methyl vinyl ketone (1.0 mmol), AgOAc (2.0 equiv), and Pd(OAc)$_2$ (15 mol %) in DCE (3.0 mL) were heated at 110 °C for 12 h. [b] Isolated yields of the *E*/*Z* isomers.

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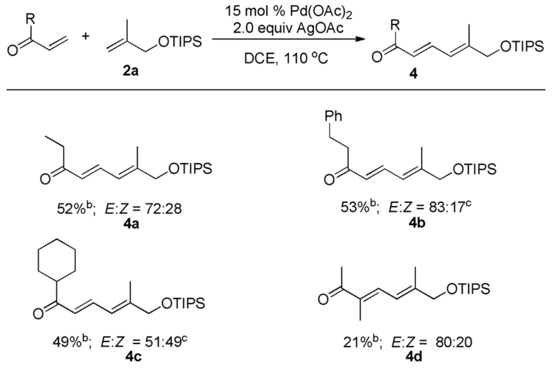
Scheme 2. Olefination of Different Vinyl Ketones with **2a**[a]



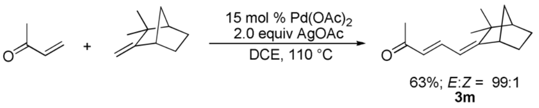
[a] Reaction conditions: Unless noted otherwise, alkene (0.5 mmol), vinyl ketone (1.0 mmol), oxidant (2 equiv), and Pd(OAc)$_2$ (15 mol %) in DCE were heated at 110 °C (3.0 mL) for 12 h. [b] Isolated yields of the *E*/*Z* isomers. [c] 2.0 equiv of olefin were used.

on the double bond also could be used as the reactant. The simple isopropenyl acetate gave the product in 41% yield as a mixture of *E*/*Z* isomers (53:47 *E*/*Z* ratio). On the other hand, a better yield and only a single geometrical isomer could be obtained using cyclic olefins. When the α-methyl styrene was reacted with MVK, the product could be obtained in good yield and regioselectivity, and diminishing yields were observed for **3h** and **3i** which may be caused by steric hindrance. Even a longer carbon chain of the α-methyl substituted terminal olefins afforded the product in a comparably similar yield and regioselectivity to that of **3a**.

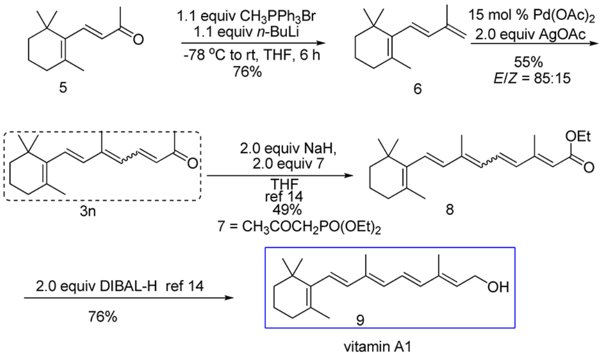
Next we tested different α,*β*-unsaturated ketones as coupling partners to react with **2a**; the results are summarized in Scheme 2. Both ethyl vinyl ketone and phenyl ethyl vinyl ketone could react well with **2a** and give the products in moderate yields and good *E*/*Z* selectivities. However, a slightly lower yield and poorer *E*/*Z* selectivity of the product was observed when cyclohexyl vinyl ketone was used as the coupling partner. The use of α-substituted vinyl ketone such as 3-methyl-3-buten-2-one furnished the product in only 21% yield.

To demonstrate the synthetic usefulness of our developed method, we applied it to the synthesis of bornelone,[12] an ultraviolet protection medicine. The coupling reaction of camphene with methyl vinyl ketone afforded bornelone in 63% yield in one single step (Scheme 3).

Scheme 3. Synthesis of Bornelone



Scheme 4. Synthesis of Vitamin A1



The most impressive part of this reaction is the perfect *E* selectivity observed in this reaction. Next, this method was applied to the total synthesis of Vitamin A1 (Scheme 4).[13]

We noticed that the key trienone fragment of **3n** could be achieved by using this current method. As described in Scheme 3, starting from *β*-ionone, the starting material olefin **6** could be easily obtained via the Wittig reaction. Under the optimized reaction conditions, **3n** was obtained in one step in 55% yield and with 85:15 *E*/*Z* ratio. The target molecule **9** could be easily achieved in a total yield of 16% from **5**.[14] Compared with other reported processes, our method is simple and efficient.[15]

In conclusion, we reported a palladium-catalyzed cross-coupling reaction of vinyl ketones using common alkenes to prepare conjugated dienyl ketones in reasonable yields. The substrate scope of this reaction is broad. Moreover, this method is quite useful as demonstrated with the efficient synthesis of bornelone and Vitamin A1.

Acknowledgment. We are grateful for financial support by the National Science Foundation for Young Scientists of China (21202156), the Research Fund for the Doctoral Program of Higher Education (20123402120019), and the China Postdoctoral Science Foundation (2012M521231). We also thank the Singapore Ministry of Education Academic Research Fund (MOE2011-T2-1-013, NEA1002111 and MOE2010-T2-2-067) for the funding of this research.

Supporting Information Available. Experimental procedures, characterization data, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.