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Palladium-catalyzed addition of ketones to alkylidenecyclopropanes

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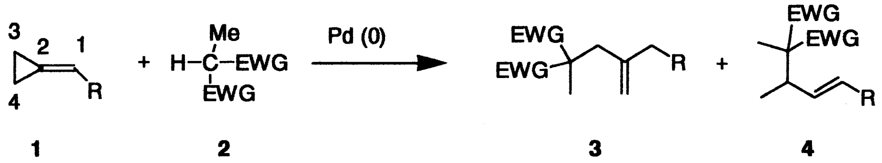
Abstract—Alkylidenecyclopropanes react with ketones under neutral conditions, in the presence of a catalytic amount of $Pd(PPh_3)_4$ to afford the corresponding α-allylated ketone products, in moderate to good yields. © 2002 Elsevier Science Ltd. All rights reserved.

The formation of carbon–carbon bonds is an important process in organic synthesis. The addition of a C–H bond to unactivated C–C multiple bonds to form a new carbon–carbon bond, i.e. hydrocarbonation, is a desirable method since it is ecologically efficient with a high atom economy. Transition metals have been shown to be effective catalysts in promoting the addition of C–H bonds of various carbon pronucleophiles,[1] such as active methyne compounds,[2] terminal alkynes,[3] aldehydes[4] and functionalized aromatic rings,[5] to unsaturated systems.

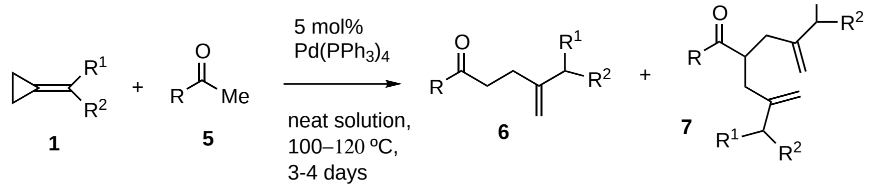
Alkylidenecyclopropanes **1** have been shown to be interesting substrates for various types of transition metal-catalyzed reactions[6] because the strained cyclopropane component can undergo proximal (C2–C3) or distal (C3–C4) bond cleavage. Recently, we reported an efficient hydrocarbonation of alkylidenecyclopropanes with doubly activated carbon pronucleophiles.[7] The strongly activated methyne **2** adds to the double bond of alkylidenecyclopropane **1**, to afford **3** and/or **4** (Eq. (1)) via distal and/or proximal bond cleavage of **1**.

We also disclosed the unprecedented direct addition of furan to alkylidenecyclopropanes, where the C–H bond at the 2-position of furan, which is less acidic than the activated methynes **2**, adds selectively to alkylidenecyclopropanes **1**.[8] In our continuing search for hydrocarbonation reactions, we observed that the C–H bond of simple methyl ketones **5**, adds effectively to the double bond of alkylidenecyclopropanes **1** to give the α-allylated keto adducts via a Pd-catalyzed hydrocarbonation process under neutral conditions.

In the presence of 5 mol% $Pd(PPh_3)_4$ at 100–120°C for 3–4 days, the reaction of alkylidenecyclopropanes **1** with methyl ketones **5** in neat solution afforded the corresponding adducts **6** in good to high yields (Eq. (2)). The double allylation of **5** to give the product **7** was observed in trace amounts.



(1)



(2)

Keywords: alkylidenecyclopropanes; hydrocarbonation; ketones; palladium catalysts.

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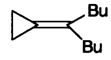
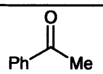
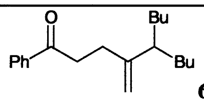
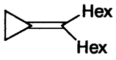
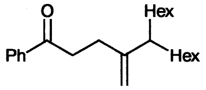
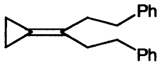
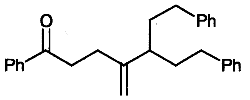
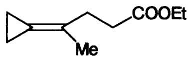
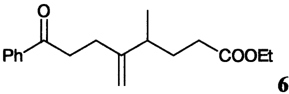
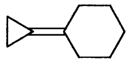
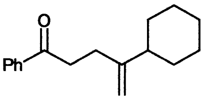
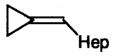
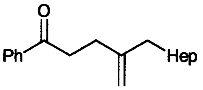
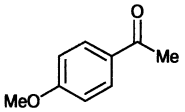
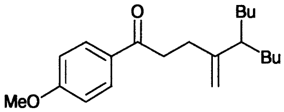
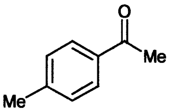
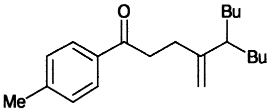
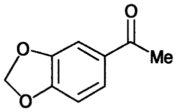
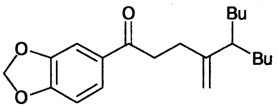
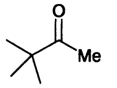
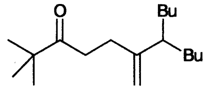
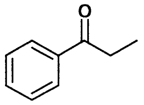
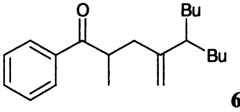
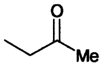
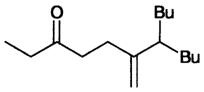
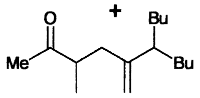
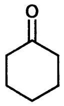
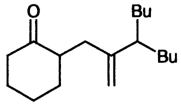
Table 1. Palladium-catalyzed addition of ketones **5** to alkylidenecyclopropanes **1**[a]

Entry	1	5	6	Yield (%) of **6**[b]
1	 **1a**	 **5a**	 **6a**	79 (78)
2	 **1b**	**5a**	 **6b**	70 (65)
3	 **1c**	**5a**	 **6c**	64
4	 **1d**	**5a**	 **6d**	52
5	 **1e**	**5a**	 **6e**	58
6	 **1f**	**5a**	 **6f**	30
7	**1a**	 **5b**	 **6g**	71[c]
8	**1a**	 **5c**	 **6h**	63[c]
9	**1a**	 **5d**	 **6i**	67[c]
10	**1a**	 **5e**	 **6j**	65[c]
11	**1a**	 **5f**	 **6k**	72[c]
12	**1a**	 **5g**	 **6l** +  **6m**	27[c] 30
13	**1a**	 **5h**	 **6n**	45[c]

[a] The reaction of **1** (0.5 mmol) with an excess of **5** (5 eq) in neat solution was carried out in the presence of 5 mol% of $Pd(PPh_3)_4$ at 100 °C for 3-4 days unless otherwise specified. The reaction was monitored by GC.

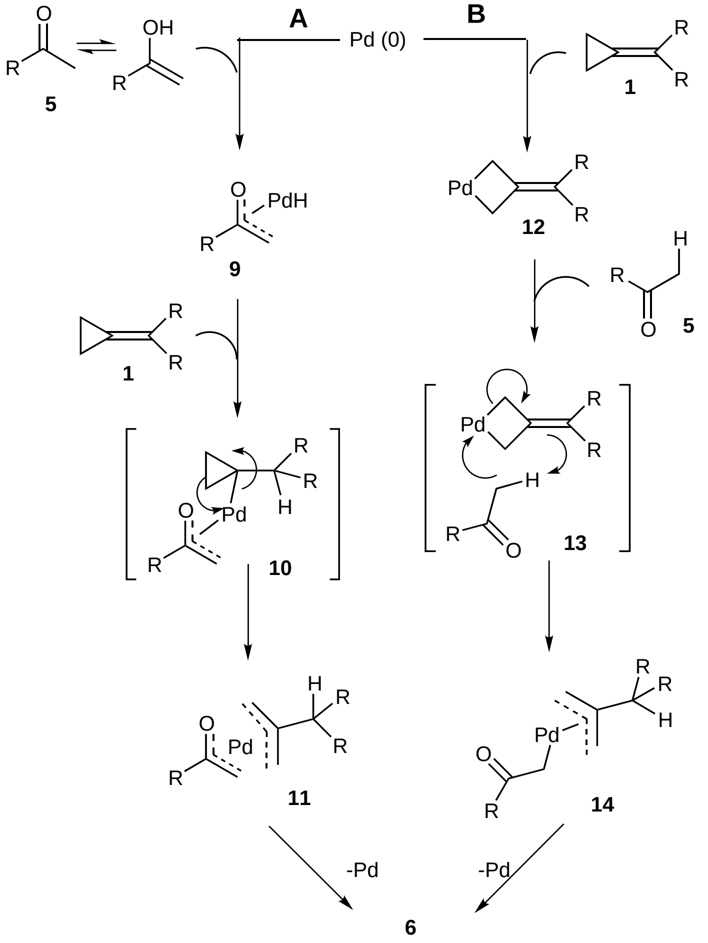
[b] NMR yields based on **1** using 1,4-dioxane as internal standard. Yields using THF as solvent are shown in parentheses. The yields for **7** are usually between 1-12%.

[c] The reaction was carried out at 120 °C and 10 mol% of $P(Bu)_3$ was added.

The results are summarized in Table 1. In the presence of catalytic amounts of $Pd(PPh_3)_4$ (5 mol%), the reaction of 2-butylpentylidenecyclopropane **1a** (0.5 mmol) and acetophenone **5a** (2.5 mmol) at 100°C for 3 days gave the corresponding adducts **6a** in 79% yield (entry 1) and **7a** in 8% yield (not shown). Employing THF as solvent, the reaction also went well to give 78% yield of **6a**. The use of other solvents, such as 1,4-dioxane, toluene and DMF, gave the addition product **6a** in poor yields, while the use of CH_2Cl_2 as a solvent did not afford the addition product. Without a palladium catalyst, the reaction of **5a** and **1a** did not proceed at all. The catalytic systems $Pd_2(dba)_3{\cdot}CHCl_3$, $PdCl_2$ or $Pd(OAc)_2$ did not promote the reaction of **5a** and **1a**. The combination of $Pd(PPh_3)_4$ with phosphine ligands such as PPh_3, P(*o*-tolyl)$_3$, 1,2-bis(diphenylphosphanyl)ethane (dppe), and 1,1′-bis-(diphenylphosphanyl)ferrocene (dppf) gave **6a** in poor yields.

The reactions of 2-hexylheptylidenecyclopropane **1b** and 2-(3-phenylethyl)-4-phenylbutylidenecyclopropane **1c** with **5a**, afforded **6b** and **6c** in yields of 70% and 64%, respectively (entries 2 and 3). The reaction of alkylidenecyclopropane **1d**, having a remote ester substituent, with **5a** also proceeded smoothly to afford the product **6d** in 52% yield (entry 4). Likewise the cyclic substituted alkylidenecyclopropane **1e** gave the corresponding adduct in 58% yield (entry 5). The octylidenecyclopropane **1f** afforded the product **6f** in 30% yield. The low yield is consistent with the observation that an H substituent in the exomethylenecyclopropane position promotes ring opening leading to a diene side product. The substituted acetophenones **5b**–**5d** also undergo smooth addition to **1a** to give the respective products **6g**–**6i** in good yields. The addition of a tributylphosphine ligand increases the yield significantly. The *tert*-butyl methyl ketone **5e** likewise reacted smoothly with **1a** to give the product **6j** in 65% yield. The ethyl phenyl ketone **5f** also undergoes addition reaction at the α-carbon to give **6k** in 72% yield. In the case of 2-butanone **5g**, the expected addition products at the two α-carbons occurred to give **6l** and **6m**, in 27 and 30% yields, respectively. Moreover, the cyclic ketone **5h** likewise undergoes reaction with **1a** to afford **6n** in moderate yield. Double allylation of **5h** was likewise observed. In most cases, the yields of the side product **7** are in the range 1–12%. The major side product of all of these reactions is the diene **8**, which is formed via the Pd-catalyzed ring opening of **1** (vide infra).

Plausible mechanisms for this reaction are shown in Scheme 1. Oxidative addition of Pd(0) to the keto-enol system (route A) would give the Pd-hydride species **9** which then could undergo hydropalladation to give **10**. Rearrangement via distal bond opening of the cyclopropyl ring would give **11** and reductive elimination

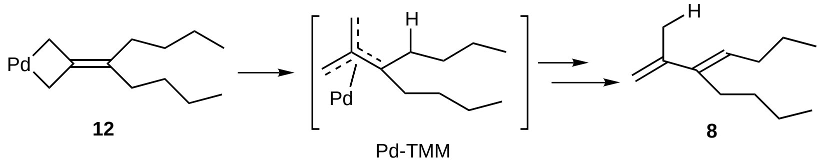


Scheme 1. Plausible mechanisms.

would give the product **6** regenerating the Pd(0). Alternatively, Pd(0) could insert in the distal bond of **1** (route B) to form the palladacyclobutane complex **12**.[9] A pallada-ene type of reaction with **5** may take place as shown in **13** to give the π-allyl palladium species **14**. Reductive elimination would then give **6** and regenerate the Pd(0).

The formation of the diene side product **8** can be explained via facile rearrangement of the palladacyclobutane **12** to the Pd-TMM species followed by β-hydride migration. The diene is not an intermediate in the reaction since independent reaction of **8** or dienes with **5a** did not afford any adduct.

α-Allylated ketones are important synthons for synthesis; for example, they can be easily converted to the corresponding 1,4-diketones whose synthesis requires the use of an unnatural synthon. The usual protocol for C–C bond formation at the α-position of a ketone requires stoichiometric addition of a base, which sometimes makes it difficult to introduce a base labile functional group. Allylation of simple ketones under neutral conditions is therefore desirable. The palladium-catalyzed α-allylation of ketones usually requires preconversion of ketone to its enolate. The α-allylation reactions of masked ketones in the form of Li,[10] tin,[11] boron,[12] acetyl[13] or silyl[14] enolates illustrate the necessity of converting the ketone moieties to the more reactive species. Direct allylation or alkylation of ketones under neutral conditions, however, is not a straightforward process[15] except for Inoue's[15c] and Shibasaki's procedures.[15d] The present hydrocarbonation process proceeds easily using simple methyl ketones and alkylidenecyclopropanes under neutral conditions to give the α-allylated keto adducts.



In conclusion, we have developed a new method for the α-allylation of ketones under essentially neutral conditions.[16] The reaction contrasts the [3+2] cyclization of alkylidenecyclopropanes with aldehydes[17] and imines,[18] which gives the corresponding cycloadducts.

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