Pergamon

Tetrahedron Letters, Vol. 35, No. 31, pp. 5701-5704, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01138-9

Tandem Pd-Catalyzed Carbonylation and Intramolecular Ene Reaction of 1-(2-Methoxycarbonylethynyl)-4-alkenyl Methyl Carbonates

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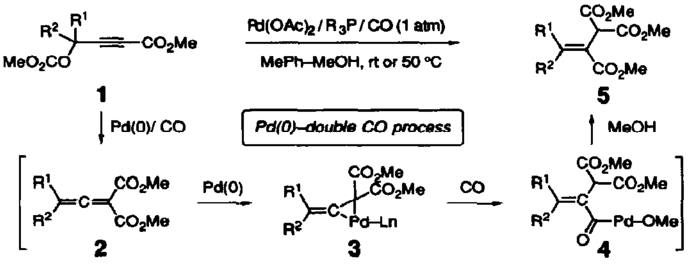
*Summary: The palladium-catalyzed carbonylation of 1-(2-methoxycarbonylethynyl)-4-alkenyl methyl carbonates **6** and **9** provides allenyl geminal diesters as reactive intermediates which induce an intramolecular ene reaction to give 6- and 5-membered products.*

We have reported in the preceding paper[1] that the Pd-catalyzed vicinal carbonylation of 1-substituted-3-methoxycarbonyl-2-propynyl methyl carbonates **1** results in the efficient synthesis of the triesters **5** under *1 atm of CO at room temperature* as illustrated in Scheme I. To the best of our knowledge, such unusually mild carbonylation conditions have not been recorded yet[2] and we are now postulating that the allenyl geminal diesters **2** generated by the first carbonylation process are highly reactive enough for the Pd(0) catalyst to nucleophilically attack the central allenyl sp carbon leading to the palladacycles **3** even at rt. These three-membered alkylidenepalladacycles should be reactive again enough for the second CO insertion to give rise to the acyl complexes **4**, from which the triesters **5** can be released by methanolysis. In our efforts to gain more insight into the postulated intermediates **2**, it turned out that a similar intermediate like **2** became extremely susceptible to an intramolecular ene process[3] so that the second carbonylation process (**2**-**4**) mentioned above virtually disappeared, if **2** involve an olefin function at an appropriate position in its main chain.

Scheme I



For instance the substrates **6** bearing an isopropenyl terminus have proven to undergo palladium-catalyzed carbonylation followed by an intramolecular ene process via **7** and ensuing thermodynamically controlled olefinic isomerization from 1,4- to 1,3-diene to afford **8** in high yields (Scheme II). In sharp contrast, the 2-methyl-1-propenyl terminus version **9** have proven to pattern after the same reaction sequence as **6** but result in the formation of the 5-membered carbocycles **11** having an isopropenyl substituent via the intermediates **10** (Scheme II). In this case, however, no olefinic migration was observed at all.

Scheme II

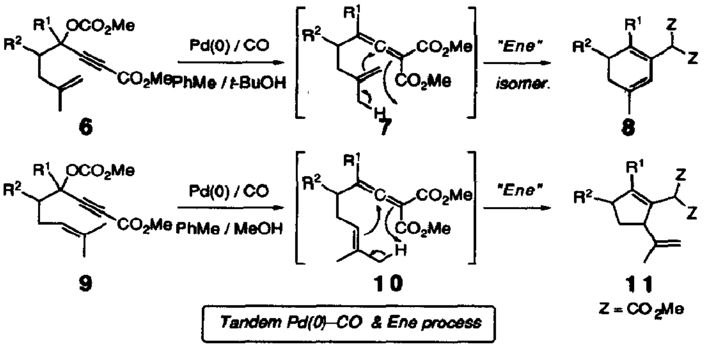
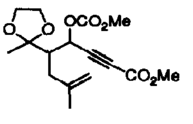
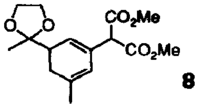
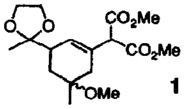
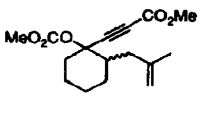
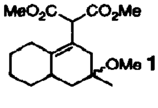
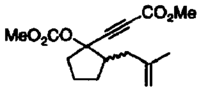
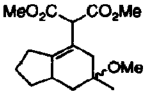
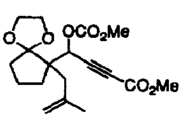
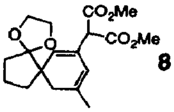
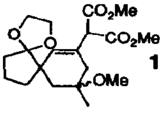
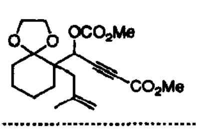
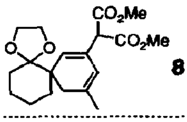
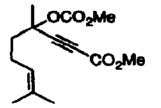
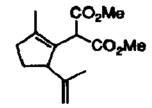
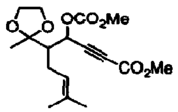
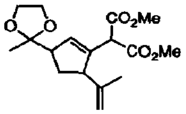
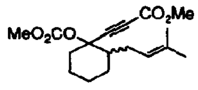
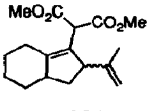
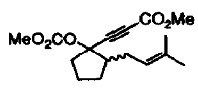
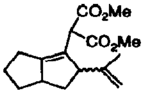
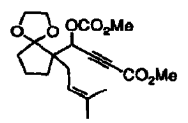
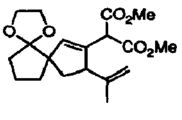


Table 1. The tandem palladium-catalyzed carbonylation and intramolecular ene reaction of 6 and 9

Entry	Carbonates	Catalyst[a]	Solvent	Time/h	Products[b]	Yield/%
	6		→		8 and 13	
1	 **6a**	A	MePh/MeOH	17 (rt)	 **8a**	**8a** 7 **13a** 70
		A	MePh/^{t}BuOH	6	 **13a**	**8a** 78 **13a** 0
		D	MePh/^{t}BuOH	18		–
2	 **6b**	A	MePh/MeOH	3	 **13b**	81
		D	MePh/MeOH	3		68
3	 **6c**	A	MePh/MeOH	3	 **13c**	77
		D	MePh/MeOH	1		85
4	 **6d**	B	MePh/MeOH	4	 **8d**	**8d** 32 **13d** 25
		B	MePh/^{t}BuOH	6	 **13d**	**8d** 76 **13d** 0
		D	MePh/^{t}BuOH	18		–
5	 **6e**	A	MePh/^{t}BuOH	2	 **8e**	65
		D	MePh/^{t}BuOH	2		70

(continued)

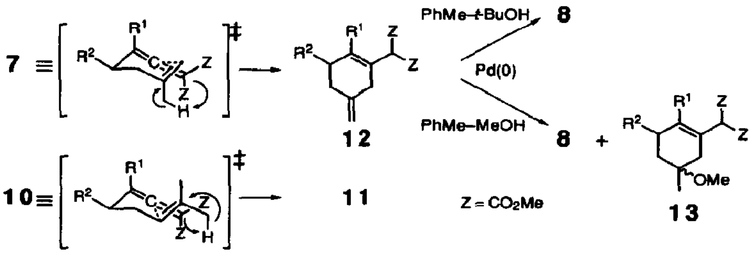
	9			→		11		
6		**9a**	A	MePh/MeOH	4		**11a**	88
			D	MePh/MeOH	2			84
7		**9b**	A	MePh/MeOH	4		**11b**	79
			C	MePh/MeOH	16			52
			D	MePh/MeOH	1			71
8		**9c**	A	MePh/MeOH	2		**11c**	86
			D	MePh/MeOH	2			85
9		**9d**	A	MePh/MeOH	4		**11d**	89
			D	MePh/MeOH	2			84
10		**9e**	A	MePh/MeOH	3		**11e**	70
			D	MePh/MeOH	2			67

(a) Catalyst A: Pd(OAc)$_2$/dppp (5 mol% for each), B: Pd(OAc)$_2$/dppp (5 mol%/10 mol%), C: Pd(OAc)$_2$/PPh$_3$ (5 mol%/15 mol%), D: Pd(OAc)$_2$/dppf (5 mol% for each). (b) All products showed reasonable combustion analyses, ^{1}H and ^{13}C-NMR spectra.

The reactions were carried out by mixing 1-(2-methoxycarbonylethynyl)-4-alkenyl methyl carbonates **6** or **9** with Pd(OAc)$_2$/dppp or dppf and stirring the mixture under 1 atom of CO at 50 °C for several hours. In every case, the indicated bidentate phosphine ligands are more effective than triphenylphosphine. Binary solvent systems such as toluene/MeOH or toluene/*t*-BuOH were found to be a reasonable choice because of the good solubility of the ligands in such solvent systems. The results are summarized in Table I. A typical procedure is as follows (entry 10). A mixture of the carbonate **9e** (183 mg, 0.5 mmol), Pd(OAc)$_2$ (5.6 mg, 0.025 mmol), and dppp (10.3 mg, 0.025 mmol) in toluene/MeOH (1.5 ml/0.3 ml) was heated at 50 °C for 3 h under 1 atm of CO. The reaction mixture was diluted with ethyl acetate and passed through Florisil. Concentration and purification by column chromatography (SiO$_2$) gave **11e** (123 mg, 70%) as a 1:1 mixture of diastereomers.

Thus, depending on whether the substrate involves an isopropenyl or 2-methyl-1-propenyl terminus, **6** (entries 1—5) and **9** (entries 6—10) exclusively led to the 6- and 5-membered carbocyclic products, respectively. In Scheme III are illustrated the hypothetical transition-state structures corresponding to **7** and **10** in which the reasonable ene–enophile assembly is proposed and is essentially the same for both. The only difference between these transition states (Scheme III) is electron-flow triggered by migrating hydrogens which must, however, be crucial for the formation of the 6- (**12**) or 5-membered (**11**) frameworks. The 6-membered 1,4-dienes **12**, though not isolable, should be reasonable initial products of the reaction sequence starting from **6**. The incorporation of a methoxy substituent (**13**) was clearly observed only for the 6-membered products when the solvent was switched from a *t*-BuOH–toluene to a MeOH–toluene system (entries 1—4) and can be explained by the attack of MeOH to the exomethylene part of **12**: the reaction mechanism of methanol addition to the exomethylene group is still ambiguous. In sharp contrast to this, 1,3-cyclohexadienes were provided as a sole product in the reaction of **6** employing *t*-BuOH as a partner of toluene in place of MeOH under the same reaction conditions. This high chemoselectivity can be understood in the following way: the isomerization of the 1,4-diene to the thermodynamically stable 1,3-diene may be promoted by the palladium-catalyst which should be much faster than the addition of *t*-BuOH to the exomethylene part.

Scheme III



Exceptionally, the ene reactions leading to the bicyclic 6-membered rings (entries 2 and 3) smoothly proceeded in a toluene/MeOH system to provide the cyclohexene derivatives (**13b** and **13c**) in high yields, whereas a toluene/*t*-BuOH system, in these cases, resulted in the formation of a complex mixture though expected to give the 1,3-cyclohexadiene derivatives: the reason why these reactions did not afford the product of type **8** remains unsolved. It is noticeable that the present intramolecular ene reaction[4] proceeds even at room temperature (entry 1)[5] without any promoter such as Lewis acid catalyst. This remarkable reactivity would be rationalized by the assumption that the geminal ester groups lower the LUMO level of the allenyl part. In any event, the present palladium-catalyzed carbonylation and intramolecular ene reaction provides a unique way of constructing the 5- and 6-membered carbocycles in a single operation which is otherwise difficult to access and should be of great benefit to organic synthesis.

Acknowledgment: This work was supported by the Grant-in-Aid for Scientific Research (#05453132) from the Ministry of Education, Science and Culture, Japan.

References and Notes

(1) The preceding paper in this issue.

(2) For the vicinal carbonylation under more severe reaction conditions, see (a) Tsuji, J.; Nogi, T. *J. Org. Chem.*, **1966**, *31*, 2641 and (b) Nogi, T.; Tsuji, J. *Tetrahedron* **1969**, *25*, 4099.

(3) Only one example was reported for the tandem palladium-catalyzed carbonylation and ene reaction of 2-alkynyl methyl carbonate, which, however, is not general. See: Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.*, **1986**, *27*, 731.

(4) For example: Snider, B. B. "Ene reactions with alkenes as enophiles", *Comprehensive Organic Synthesis* **1991**, *5*, pp 1-28.

(5) Although not indicated, all the reactions listed in Table 1 proceeded with a practical rate at room temperature.

(*Received in Japan* 10 *May* 1994)