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PALLADIUM(0) CATALYZED SUBSTITUTION REACTIONS OF CYCLOPROPYL GROUP CONTAINING ALLYLIC ESTERS[1]

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Abstract: Complete regioselectivity is observed in palladium(0) catalyzed allylic substitution reactions of 1-vinylcyclopropyl **3** and cyclopropylideneethyl esters **6** with a series of soft carbon nucleophiles to give γ-cyclopropylidene-1,3-dicarbonyl and 1-carbonyl-2-sulfonyl compounds. Highly functionalized methylenecyclopropanes are thus obtained in good to excellent yields from easily accessible 1-vinylcyclopropyl tosylates **3d**.

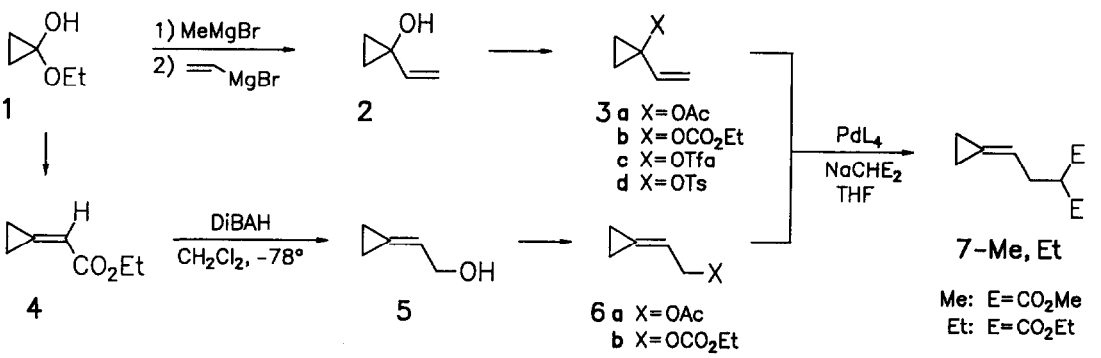
Transition metal catalyzed reactions with carbon carbon bond formation have gained a wide applicability in organic synthesis.[3] Especially a great number of allylic substitution reactions with various nucleophiles are now possible under mild conditions.[4] The underlying mechanism of these mostly palladium-catalyzed transformations of allylic substrates with rather poor leaving groups is reasonably well understood.[5] Allylic acetates or carbonates react with Pd(0) complexes to form (η^3-allyl)palladium complexes, which in situ react with soft carbon nucleophiles. This methodology permits elegant transformations with a high degree of regio-[5a] and diastereoselectivity[6] as well as enantioselectivity with appropriate chiral auxiliaries.[7]

A wide variety of acyclic and cyclic allylic substrates have been subjected to this type of substitution. 1-Vinylcycloalkyl[8] except for 1-vinylcyclopropyl derivatives[9] have been reported to generally react at the terminal vinylic position to give cycloalkylideneethyl products. In view of our efforts to develop new methodology for the preparation of cyclopropyl building blocks and their use in organic synthesis,[10,11] we investigated the possibilities of applying 1-vinylcyclopropanol **3** and cyclopropylideneethanol esters **6** as substrates in Pd(0) catalyzed substitution reactions, although S_N reactions on a cyclopropane with retention of the ring[12] are quite rare and normally only occur with neighboring group participation[13] or extremely good leaving groups.[14]

The readily available cyclopropanone ethyl hemiacetal[15] **1** served as the precursor to both types of allylic esters **3** and **6**. 1-Vinylcyclopropanol[16] **2** was converted to its acetate[16] **3a** (67% yield), ethyl carbonate[17] **3b** (60%), and trifluoroacetate[17] **3c** (57%) by treatment with 1 equiv. of methylmagnesium bromide followed by acetyl chloride, ethyl chloroformate and trifluoroacetic anhydride at 0°C, respectively. The tosylate[18] **3d** was obtained in 83% yield from **2** with p-toluenesulfonyl chloride in pyridine (Scheme 1). Ethyl cyclopropylideneacetate[19] **4** upon reduction with diisobutylaluminum hydride (DIBAH, n-hexane/CH_2Cl_2 (1:1), -78°C)[20] provided cyclopropylideneethanol (**5**) in 91% yield, which was transformed into its acetate[17] **6a** with acetic anhydride/triethylamine in ether (75%) and its ethyl carbonate[17] **6b** with ethyl chloroformate in CH_2Cl_2/pyridine (86%).

Under typical conditions used for other allylic acetates[5a] the cyclopropylideneethyl acetate **6a** in the presence of tetrakis-(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$[21]) as catalyst gave diethyl cyclopropylideneethylmalonate **7-Et**[22] in good yield, while **3a** showed no reaction (entries 2 and 1 in Table 1). With the catalyst $Pd(dba)_2$ /dppe[23,24] **6a** and the ethyl carbonate **6b** gave even higher yields under milder conditions,[25] while the ethyl carbonate **3b** did not react at all. With its better leaving group trifluoroacetate, however, **3c** was converted to the same product **7-Et/7-Me** in yields up to 55%

Scheme 1



(entries 6, 7 in Table 1). Eventually the 1-vinylcyclopropyl tosylate (**3d**) was tested and found to react quantitatively within 5 min at ambient temperature in the presence of $Pd(dba)_2$/dppe(1:1)[23] to give **7-Me** in 86% yield (entries 8,9 in Table 1). In all cases, in which the yields were higher than 80%, the di(2'-cyclopropylideneethyl)propanedioic acid dialkylester **8-Et/8-Me** was observed from further reaction of **7-Et/7-Me** with the π-allyl complex **11**, in fractions up to 11%. Control experiments with acetates **3a**, **6a** and the tosylate **3d** without added Pd(0) catalyst showed no reaction at ambient temperature and at elevated temperatures led to unselective reactions after prior or with concomitant ring opening.

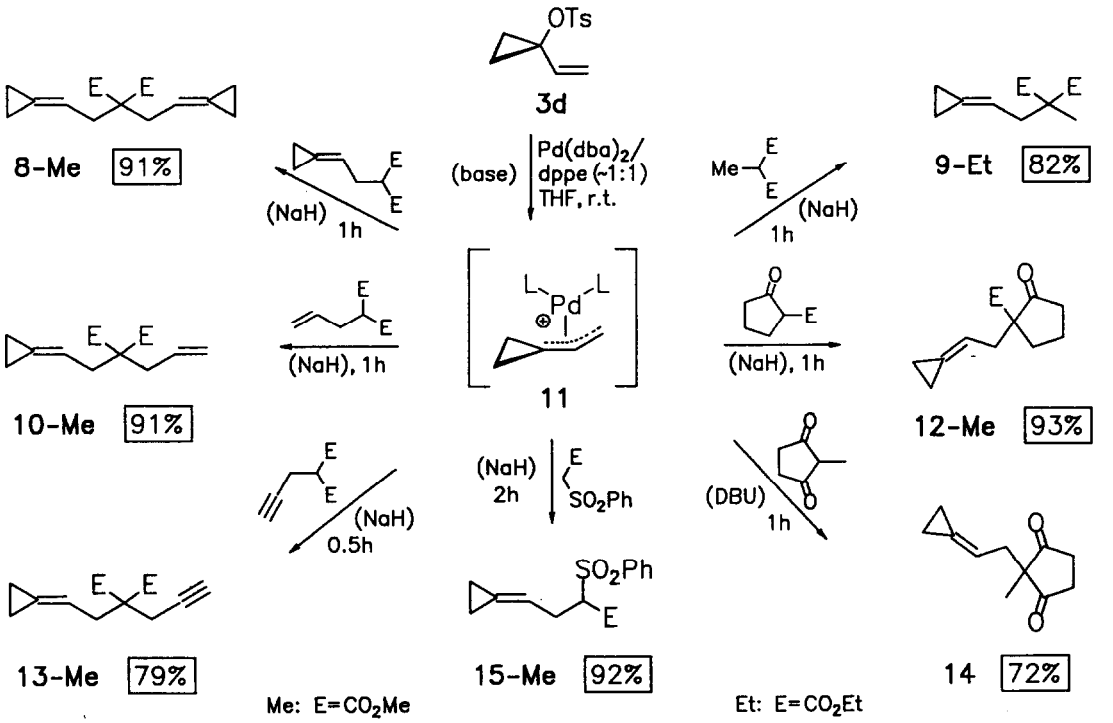
Table 1. Palladium catalyzed nucleophilic substitution of 1-vinylcyclopropanol **3** and cyclopropylideneethanol **6** allylic esters with sodium dialkyl malonate in THF.[a]

Entry	Substrate	Catalyst (mol%)	Conditions Time/Temp. [h]/[°C]	Product	(Byproduct)	Yield [%][b]
1	**3a**	$Pd(PPh_3)_4$ (5)	120 / 65	**7-Et**		0
2	**6a**	$Pd(PPh_3)_4$ (5)	36 / 65	**7-Et**	**(8-Et)**	80 (trace)
3	**6a**	$Pd(dba)_2$/dppe 1:1 (2)[23]	48 / 22	**7-Me**	**(8-Me)**	85 (8)
4	**3b**	$Pd(dba)_2$/dppe 1:1 (2)	48 / 65	**7-Me**		0
5	**6b**	$Pd(dba)_2$/dppe 1:4 (2)	4 / 22[c]	**7-Me**	**(8-Me)**	88 (11)
6	**3c**	$Pd(PPh_3)_4$ (5)	36 / 65	**7-Et**		23
7	**3c**	$Pd(dba)_2$/dppe 1:1.3 (8)[d]	48 / 22	**7-Me**		55
8	**3d**	$Pd(dba)_2$/dppe 1:1.3 (2)	1 / 22	**7-Me**	**(8-Me)**	85 (9)
9	**3d**	$Pd(dba)_2$/dppe 1:1 (0.5)	5 min / 22[c]	**7-Me**	**(8-Me)**	86 (5)
10	**3d**	$Pd(dba)_2$/dppe 1:2 (2)	6 / 22[c]	**7-Me**		-[e]

[a] 100-200 mg allylic ester and 3 equiv. of sodium dialkyl malonate were used in each run. - [b] Yield of isolated product after chromatography. - [c] Reaction was carried out until TLC or GC showed no more starting material. - [d] A 2 mol% portion of the catalyst mixture was added to the reaction mixture every 12h. - [e] Yield not determined in this control experiment.

A competition experiment between 1-vinylcyclopropyl tosylate (**3d**) and 1,1-dimethylallyl acetate with sodium dimethyl malonate revealed a 19:1 selectivity for the cyclopropyl tosylate **3d**. In the corresponding competition between cyclopropylideneethyl acetate (**6a**) and 3,3-dimethylallyl acetate the product **7-Me** from **6a** prevailed even more (>99:1).

Scheme 2. (Cyclopropylideneethyl)malonates and related products from 1-vinylcyclopropyl tosylate (**3d**).



Good to excellent yields (72% - 93%) of substitution products **8-10**, **12-15**[17] were obtained from **3d** and a variety of carbon nucleophiles (Scheme 2). All reactions were practically over within 1 - 2 h at ambient temperature, and the products in all cases arose from nucleophilic attack at the primary vinylic carbon of **3d**. Under the same conditions, 1,1-dimethylallyl acetate gave a 3:7 mixture of primary and tertiary substitution products with sodium dimethyl malonate.

The high selectivity for primary substitution on the π–allyl palladium complex intermediate **11** from **3d** not only arises from a steric preference, but also from the unsymmetrical charge distribution in **11**. As a semiempirical calculation with the MNDO method[26] discloses the net positive charge on the primary carbon of a cyclopropylideneethyl cation is about twice as high as on the tertiary center, while in 1,1-dimethylallyl cation the net charge is higher on the tertiary center.[27]

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