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Selectivities in organic reactions via π-allylpalladium complexes

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Abstract - Palladium-catalyzed reactions of allylic compounds are important synthetic methods. In order to enhance their usefulness, studies on regio- and stereoselectivities in the reactions of allylic carbonates and 2-vinyloxiranes with various nucleophiles were carried out. It was found that the introduction of trimethylsilyl group to allyl systems showed a profound effect on the regioselectivity.

INTRODUCTION

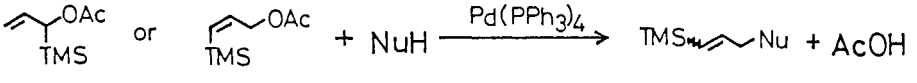
Palladium-catalyzed reactions of various allylic compounds have been studied extensively and they are regarded as important synthetic methods. Their usefulness will be greatly expanded if the reactions have high selectivity. For example, although the attack of nucleophiles on π-allylpalladium system is known to take place at the less substituted side, no regioselectivity is observed with allyl systems bearing substituents at the both sides. Also different selectivity is observed with π-allyl systems of different metals. Thus it is important to control the regiochemistry of the reaction. We found that the introduction of trimethylsilyl group has a profound effect on the regiochemistry of the substitution reactions with various nucleophiles.

REACTIONS OF ALLYLIC CARBONATES AND 2-VINYLOXIRANES BEARING TRIMETHYLSILYL GROUP WITH VARIOUS NUCLEOPHILES UNDER NEUTRAL CONDITIONS

The palladium-catalyzed substitution reaction of allylic compounds via π-allylpalladium complexes with various nuclephiles is a well-established synthetic method, and used extensively in organic synthesis (ref. 1). Nucleophilic substitution of monosubstituted allylic compounds takes place regioselectively at unsubstituted side of allylic system. On the other hand, reaction of α,γ-disubstituted allylic compounds gives a mixture of regioisomers of α- or γ-substituted products. The ratios depend on steric size of the substituents, and it is difficult to achieve high regioselectivity. We found highly regioselective substitution reaction of allylic compounds substituted with trimethylsilyl (TMS) group at the γ-side to give vinylsilane derivatives.

Facile synthesis of α-substituted γ-silylated allylic alcohols is now possible particularly in optically active forms (ref. 2). We investigated the effect of the silyl group on the palladium-catalyzed substitution reactions after converting them to allylic carbonates. Palladium-catalyzed reaction of allyl acetate substituted by TMS at α or γ carbon with carbonucleophiles is known to give vinylsilane derivatives regioselectively as expected (Scheme 1)(ref. 3,4). But no studies on regioselectivity has been carried out with allyl esters substituted at both α and γ carbons.

Scheme 1



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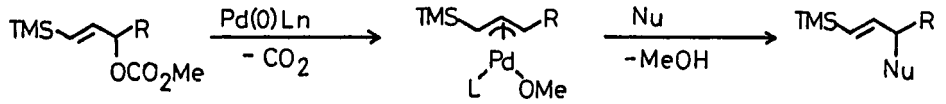
As shown in Scheme 2, we found that it is possible to synthesize vinylsilanes via regioselective substitution of trimethylsilylallyl methyl carbonates (**1a,b**) with nucleophiles (ref. 5).

Scheme 2



1a; R= Am(pentyl)
1b; R=Ph

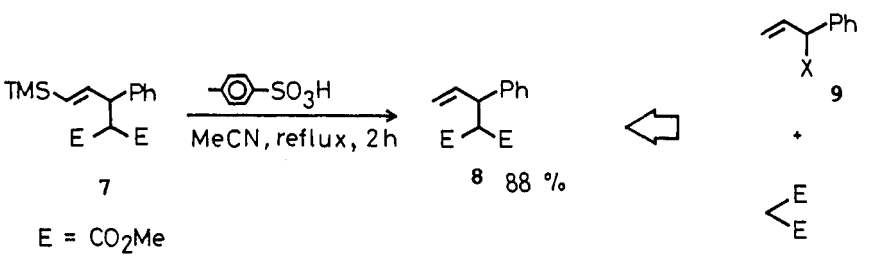
Results of the palladium-catalyzed reactions of trimethylsilylallyl carbonates with some soft carbonucleophiles are summarized in Table 1. The allylic carbonate **1a** (R=pentyl) smoothly reacted with acetoacetate and malonate in the presence of 5 mol% of palladium catalyst to afford the vinylsilanes **2** and **4** in 81 % and 65 % yields respectively (runs 1 & 3). In this reaction, PBu_3 and dppe were suitable phosphine ligands. When PPh_3 was employed, β-elimination of π-allyl intermediate took place to give a considerable amount of the diene **3** (run 2). Also cyclic β-keto esters (runs 4,5), cyanoacetate (run 6), and nitroacetate (run 7) reacted with **1a** similarly to give the corresponding vinylsilanes in satisfactory yields.

The carbonate **1b** (R=Ph) reacted with acetoacetate to afford the vinylsilane **5** in a good yield. But with malonate, a similar substitution did not take place under neutral conditions and the product was the desilylated compound **6** (run 9) (ref. 6). But when sodiomalonate is used, the vinylsilane **7** was obtained (run 10).

These regioselectivities cannot be explained by simple comparison of steric bulkiness of the substituents. Because when the carbonate **1b**, which has a bulky phenyl group was employed, nucleophiles attacked the carbon close to the phenyl group exclusively. Considering the completely controlled regioselectivity, electronic factors seem to play an important role in the π-allylpalladium complex. Thus in the nucleophilic substitution of 1,3-disubstituted π-allylpalladium intermediate, introduction of trimethylsilyl group apparently resulted in the excellent regioselectivity.

Furthermore, the treatment of the vinylsilane **7** with p-toluenesulphonic acid in refluxing CH_3CN gave the desilylated product **8** in 88 % yield (ref. 7), which is equivalent to the product obtained from the monosubstituted allylic compound **9** with malonate. This means that nucleophilic substitution at more substituted side of π-allylpalladium intermediate can be achieved indirectly by these reactions.

Scheme 3



It is well-known that very high regioselectivity is observed in the reaction of 2-vinyloxiranes via π-allylpalladium complexes with soft carbonucleophiles under neutral conditions to give 1,4-adducts. In other words, the nucleophiles attack the carbon which is far from the hydroxy group (ref. 8,9).

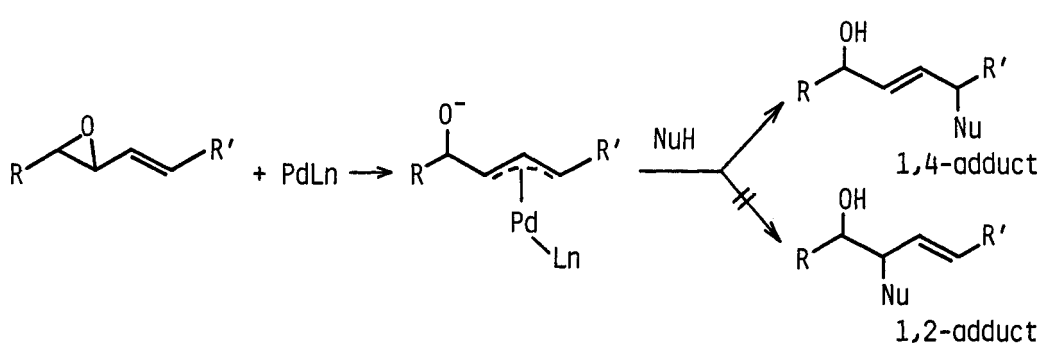
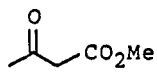
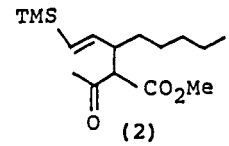
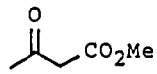
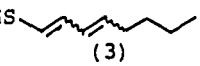
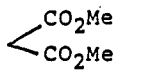
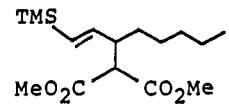
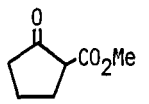
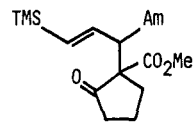
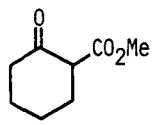
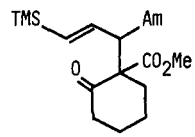
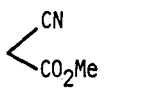
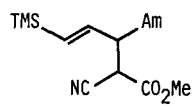
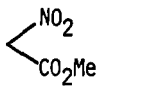
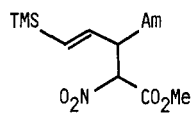
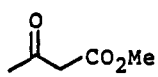
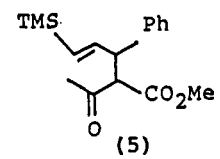
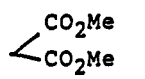
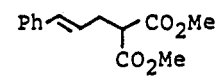
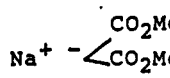
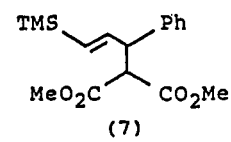
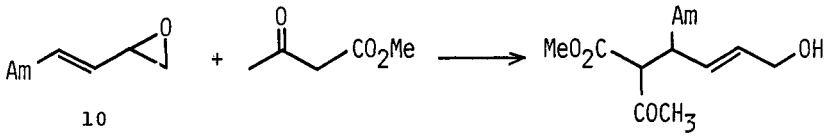


TABLE 1. Palladium-Catalyzed Substitution of Trimethylsilylallyl Carbonates with Nucleophiles [a]

Run	R	Nucleophile	Ligand	Temp (°C)	Time (h)	Product & Yield [b]
1	Am (1a)		PBu_3 dppe	65	0.5	 (2) 81%
2	1a		PPh_3	65	1	2 +  (3) (2.5 : 1)
3	1a		PBu_3	65	0.5	 + 3 (4) 65% (5.7 : 1)
4	1a		PBu_3	65	0.5	 76%
5	1a		PBu_3	65	0.5	 73%
6	1a		PBu_3	65	0.5	 76%
7	1a		PBu_3	65	0.5	 72%
8	Ph (1b)		PBu_3	20-25	2	 (5) 83%
9	1b		PBu_3	20-25	5	 (6) 56%
10	1b		PBu_3	20-25	2	 (7) 80%

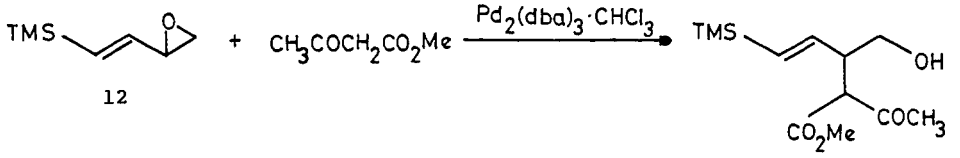
[a] Reactions were carried out using allylic carbonate (1 mmol), nucleophile (1 mmol), $Pd_2(dba)_3CHCl_3$ (0.05 mmol) and phosphine ligand (0.20 mmol) in dry THF (5 mmol) under Ar atmosphere.
[b] Isolated yields.

For example, 2(1-heptenyl)oxirane (**10**) reacted with methyl acetoacetate to give the following 1,4-adduct **11** as a major product.



10 11

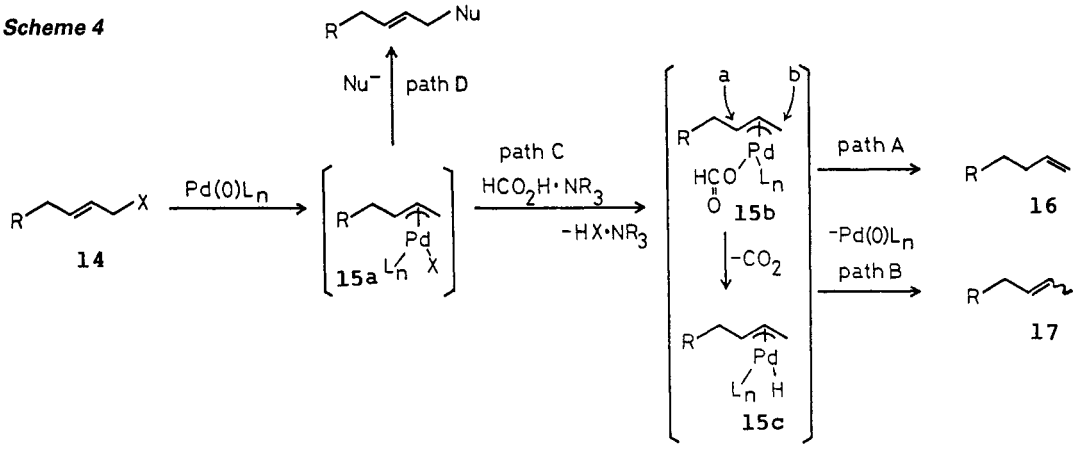
In order to investigate the effect of TMS group on the regioselectivity of this reaction, we carried out the reaction of 2(2-trimethylsilylvinyl)oxirane (**12**) with methyl acetoacetate at room temperature. A single product was obtained in 76% yield, which was found to be the 1,2-adduct **13**. Thus the presence of TMS group again changed the regioselectivity.



12 13

Several years ago, we have reported that various terminal allylic acetates **14** can be converted to 1-alkenes **16** with high regioselectivity by the palladium catalyzed reaction with ammonium formate (ref. 10). The key step of this reaction is reduction of π-allylpalladium intermediates **15** with the hydride generated from ammonium formate by decarboxylation (Scheme 3, path A).

Scheme 4

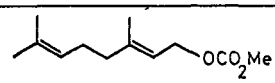
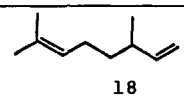
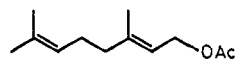
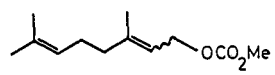
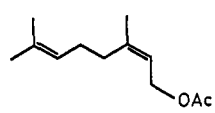
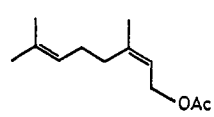
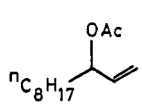
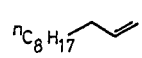
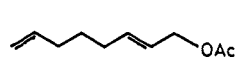
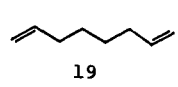
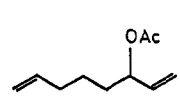
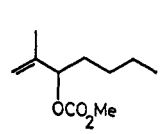
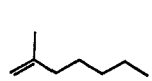
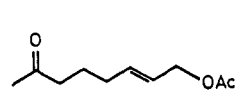
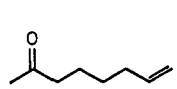
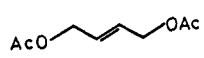
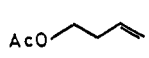


Reaction of allylic compounds with hydride as a nucleophile to form alkenes is known. So far, various hydride sources such as $LiAlH_4$ (ref. 11), Bu_3SnH (ref. 12), $NaBH_4$ (ref. 13), $NaBH_3CN$ (ref. 13), $LiBHEt_3$ (ref. 14), silicon hydrides (ref. 15), alkyl zinc reagents (ref. 16), formic acid (ref. 17), N-propyl-1,4-dihydronicotinamide (ref. 18), and SmI_2 (ref. 19) have been reported to react with the π-allylpalladium intermediates **15** to give alkenes **16** and **17**.

When monosubstituted allylic compounds **14** are subjected to the reaction with nucleophiles, usually carbonucleophiles attack the less substituted side of the intermediate, π-allylpalladium complex **15** (path D). Similarly, if hydride attacks the less substituted side, 2-alkenes **17** are formed (path B). 1-Alkenes should be formed by the attack of hydride at the more substituted side of the π-allyl system (path A). However, hydride generated from various sources gives 2-alkenes with 50-95% selectivity (ref. 11-19). As we have reported previously, only the hydride generated from formates gave 1-alkenes as a major product in 80-95% selectivity with the Pd-PPh_3 catalyst (ref. 10). In other words, unlike carbonucleophiles, the hydride from formate attacks the more substituted side of the π-allylpalladium system. Later we found that the selectivity depends strongly on the kind of phosphine ligands, and 1-alkenes are obtained exclusively by using P^nBu_3, rather than PPh_3 (ref. 20). Furthermore, we found that HCO_2H-Et_3N is an efficient reductant, especially in a preparative scale (ref. 21,22). It is soluble in THF at room temperature. In addition, the reaction with HCO_2H-Et_3N procceds smoothly even at room temperature in THF with 5 mol% of the palladium catalyst. Also selectivity for 1-alkenes is satisfactory with HCO_2H-Et_3N.

We prepared various 1-alkenes from terminal allylic carbonates and acetates. Results are shown in Table 2. Reactions were carried out in 50-200 mmol scales. In all cases, purity of

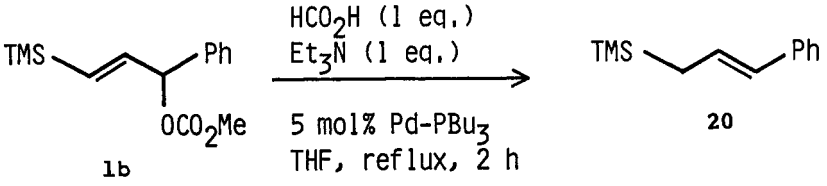
TABLE 2. Preparation of 1-Olefins

Run	Substrate	Time (h)	Product	Yield (%)
1		2	 **18**	83
2		3	**18**	83
3		7	**18**	92
4		2	**18**	69
5		4	**18**	73
6		1.5		77
7		2	 **19**	67
8		4	**19**	76
9		1.5		53
10		2		81
11		2		60

distilled products was calculated to be higher than 98% by GLC analysis. The contents of the by-products, dienes and 2-alkenes, were less than 1-2%. Ketones and esters are not reduced under these conditions (runs 10 and 11). Allylic carbonates which are good precursors of π-allylpalladium intermediates gave better results than allylic acetates. For example, geranyl and neryl carbonates were converted to **18** with 0.05-0.1 mol% of the catalyst. However, corresponding acetates required 0.2 mol% of the catalyst to obtain the same yield (runs 1-5).

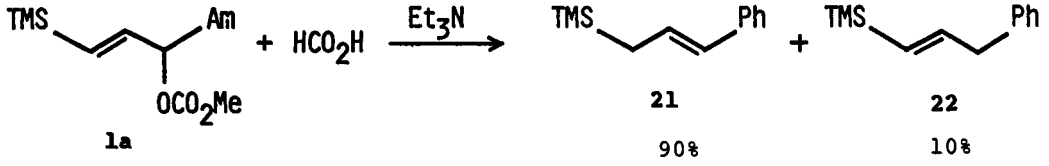
The ligand, P^nBu_3 has to be purified with care. Contaminated impurity (mainly, tributylphosphine oxide) seems to cause side reactions. As for the reagents and solvents, anhydrous, oxygen-free ones should be used. Otherwise, palladium catalyst is gradually deactivated during the reaction. We have established that 1-alkenes can be obtained with high selectivity by the reaction of terminal allylic carbonates and acetates with HCO_2H-Et_3N in boiling THF using Pd(0)-P^nBu_3 as a catalyst. Since these allylic compounds can be synthesized easily by a number of methods, this reaction offers a very useful preparative method for 1-alkenes. Particularly formic acid is the most cheaply available reductant.

Then we carried out the reaction of HCO_2H-Et_3N with allylic carbonate substituted by trimethylsilyl group in order to find out the effect of TMS group (ref. 5). When the carbonate 1b was treated with a 1:1 mixture of formic acid (1 eq) and triethylamine in the presence of palladium catalyst, the allylsilane **20** was obtained as a major product (81% GLC, 58% isolated yield). This means that the hydride derived from formate selectively attacked the carbon attached to TMS group, and the TMS group again showed an interesting effect. In other words, the hydride derived from formate shows behavior different from that of carbonucleophiles.



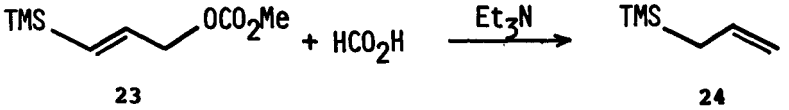
1b **20**

Also the reaction of 1a with formate afforded the allylsilane 21 and vinylsilane 22 in a ratio of 9:1.



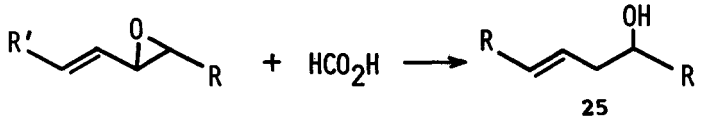
1a **21** 90% **22** 10%

Allylsilane (24) was obtained selectively in 80% yield from the unsubstituted allyl carbonate 23. In this reaction, the TMS group behaves similar to alkyl group to give the terminal olefin.



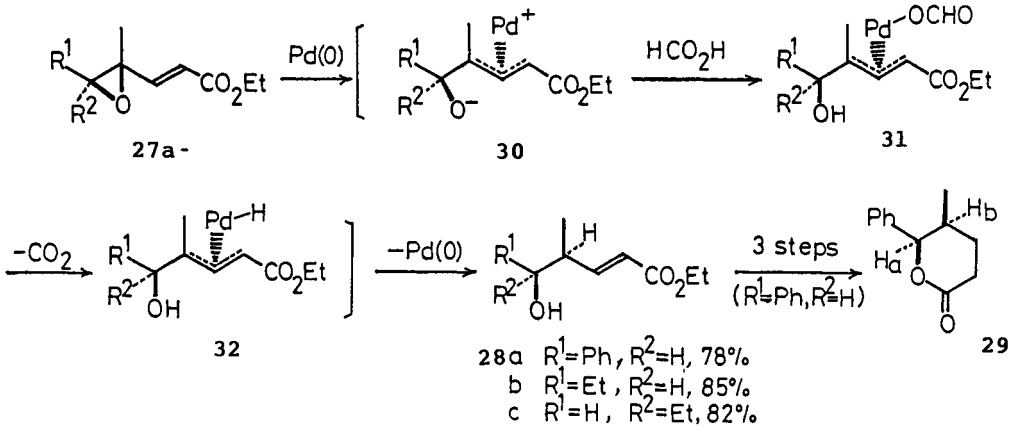
23 **24**

It is known that 2-vinyloxiranes undergo 1,4-addition reaction with carbonucleophiles (ref. 8,9). On the other hand, the hydride from formate afforded homoallylic alcohols 25 by the 1,2-addition exclusively.



25

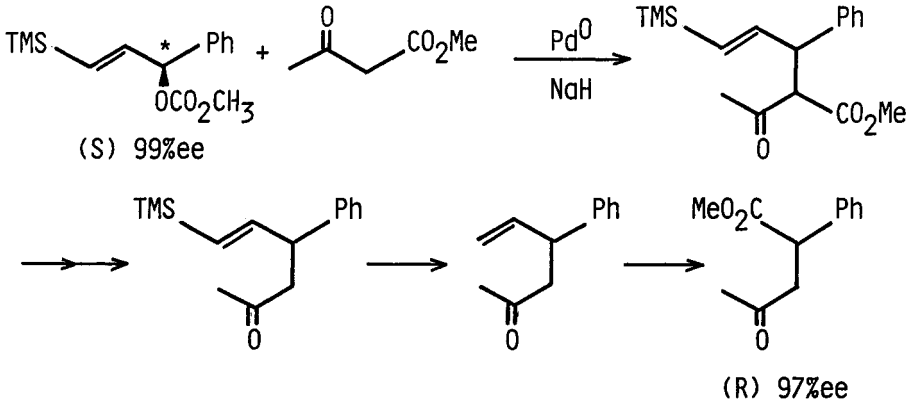
We examined both regio- and stereoselectivity of the hydrogenolysis of (E)-4,5-epoxy-4-methyl-2-alkenoates (**27**) and found a facile stereoselective synthesis of (E)-5-hydroxy-4-methyl-2-alkenoates (**28**) by palladium-catalyzed reaction of **27** with HCO_2H-Et_3N under mild conditions (ref. 23).



(E)-(4S*,5S*)-4,5-Epoxy-4-methyl-5-phenyl-2-pentenoate (**27a**) (2 mmol) was added to a solution of $Pd_2(dba)_3CHCl_3$ (0.05 mmol)-PBu_3 (0.05 mmol), Et_3N (0.3 cm^3) and HCO_2H (0.2 cm^3) in dioxane (10 cm^3). The mixture was stirred for four hours at room temperature to give the hydroxy ester **28a** in 78% yield. The hydroxy ester **28a** was hydrogenated (H_2, Pd/C), followed by subsequent hydrolysis and lactonization to give the cis-lactone **29a**, which proved the syn stereochemistry of **28a**. Similarly, **27b** was converted to the syn-alcohol **28b** in 85% yield. On the contrary, reaction of **27c** (as a 5:1 mixture of **27c** and **27b**) gave the anti-alcohol **28c** (**28c**:**28b**=5:1) in 82% yield. Thus, the reaction was all stereospecific with inversion of the stereochemistry.

The reaction can be explained as follows. At first, Pd(0)-phosphine complexes coordinate the olefin **27** and displace the oxide of **27** with inversion to form π-allylpalladium alkoxide complex **30**. Addition of the formic acid to the palladium complex **30** gives the π-allylpalladium formate **31**, which decarboxylates to give π-allylpalladium hydride complex **32**. Internal attack of the hydride to the more substituted carbon of the π-allylpalladium **32** gives the homoallyl alcohol **28**, and Pd(0) is reproduced.

Optically active allylic compounds are now easily available, and these compounds are useful for the synthesis of highly functionalized optically active compounds, if efficient chirality transfer from C-O chirality to C-C by the palladium catalyzed reactions can be achieved. We have reported the highly efficient chirality transfer in the palladium catalyzed cyclization via π-allylpalladium complexes under certain conditions, and discussed mechanism of the racemization (ref. 24). Trimethylsilyl substituted allylic alcohols in an optically active form is now easily available (ref. 2), and we carried out the studies on chirality transfer in the palladium catalyzed reaction with carbonucleophiles. The reaction of optically active 1b with acetoacetate showed 97% retention of the chirality when the reaction was carried out in the presence of sodium hydride. In the absence of sodium hydride, it was 64% and racemization took place in a considerable extent. The extent of the racemization was different depending on the concentration of the palladium catalyst. The higher concentration tends to give lower efficiency of chirality transfer. Thus the same mechanism discussed in our previous paper can be applied to this case too.



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