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REGIOSELECTIVE 1,4-ADDITION OF NUCLEOPHILES TO 1,3-DIENE MONOEPOXIDES CATALYZED BY PALLADIUM COMPLEX

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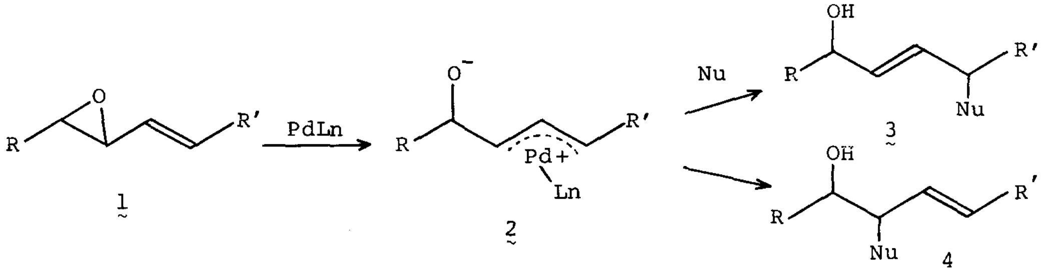
Summary: 1,3-Diene monoepoxides react with nucleophiles in the presence of palladium complex as a catalyst under neutral conditions to give 1,4-adducts selectively. The 1,4-adducts are allylic alcohols and there is a possibility of another nucleophilic attack. Ester of Monarch butterfly pheromone was prepared.

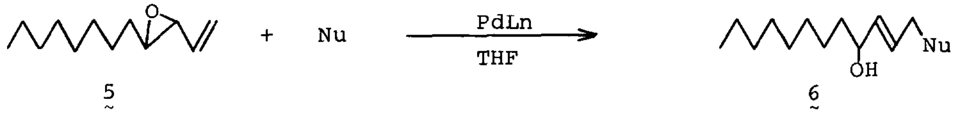
1,3-Diene monoepoxides are useful for synthesis of highly functionalized compounds, particularly when their regioselective transformation is possible. Although a number of reactions of the epoxides are known,$^{1-6)}$ the addition of nucleophiles is scarcely regioselective. Only few nucleophiles such as organocoppers and organoboranes undergo regioselective 1,4-addition to the simple diene epoxides.$^{3-6)}$ In this paper, we wish to report the regioselective nucleophilic attack to the diene monoepoxides catalyzed by palladium complex.

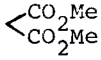
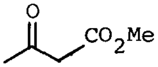
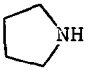
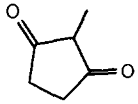
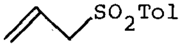
Reactions of allylic compounds with various nucleophiles catalyzed by palladium complexes via π-allylpalladium complexes are well-known.$^{7)}$ We considered the possibility of forming π-allylpalladium complexes **2** from the diene monoepoxides **1**, because **1** can be regarded as an allylic ether. If the complex formation takes place, then the nucleophilic attack should give either **3** or **4**. Actually we found the regioselective reaction under mild conditions to afford synthetically useful (*E*)-allyl alcohols **3** in good yields.



The reaction of (*E*)-3,4-epoxy-1-dodecene (**5**) with various nucleophiles proceeded rapidly under mild conditions with 1-5 mol% of the palladium catalyst. As shown in Table 1, the nucleophilic attack took place selectively at the terminal carbon. No detectable regioisomer of type **4** was formed. Since the π-allylpalladium complexes **2** behave as a base to pick up a proton, this carbon-carbon bond formation proceeds without adding a base (No. 1,2,4,5).

Table 1



Exp.No.	Nucleophile	Catalyst	Conditions		Yield (%)[a)]
1		$Pd(PPh_3)_4$ (7)	r.t.	5h	84[b)]
2		"	r.t.	15min	67
3		"	reflux	12h	92
4		"	reflux	30min	91[c)]
5		$Pd_3(TBAA)_3\cdot CHCl_3$ (8)[8)] + DIPHOS (9)	reflux	30min	64[d)]

a) Isolated yields. b) E : Z = 96 : 4 c) E : Z = 98 : 2

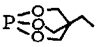
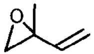
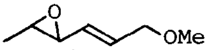
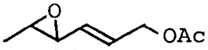
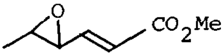
d) Reaction occurred only at α-position, but the olefin isomerization took place (αβ : βγ = 1 : 1).

Then the reactions of various diene monoepoxides with nucleophiles were carried out as shown in Table 2. The reaction of (*E*)-1,2-epoxy-3-nonene (10) was not completely selective when $Pd(PPh_3)_4$ (7) was used as the catalyst. 1,2-Addition took place in some extent (No. 6). We found that ligands and solvents changed the selectivity drastically. Uses of the phosphite 11 and aprotic solvents (CH_3CN, DMSO, HMPA) afforded the 1,4-adduct with high regioselectivity.

Moreover, this reaction shows high chemoselectivity. Formation of π-allylpalladium complexes from allylic acetates and ethers is well-known. But only the diene epoxide moiety reacted selectively even when allylic acetate and ether are present in the same molecules (No. 11,12). Also the presence of an ester group conjugated with double bond showed no effect on the regioselectivity of the reaction (No. 13).

The reaction is useful for regioselective carbon-carbon bond formation. The usefulness is augmented by the fact that the newly produced allyl alcohol moiety in 3 has high synthetic utility.[9)] For example, after acetylation, the palladium-catalyzed nucleophilic substitution can be carried out again. We demonstrated this possibility by the following short synthesis of the dimethyl ester 21b of the Monarch butterfly pheromone 21a[10)] using the palladium-catalyzed reaction twice.

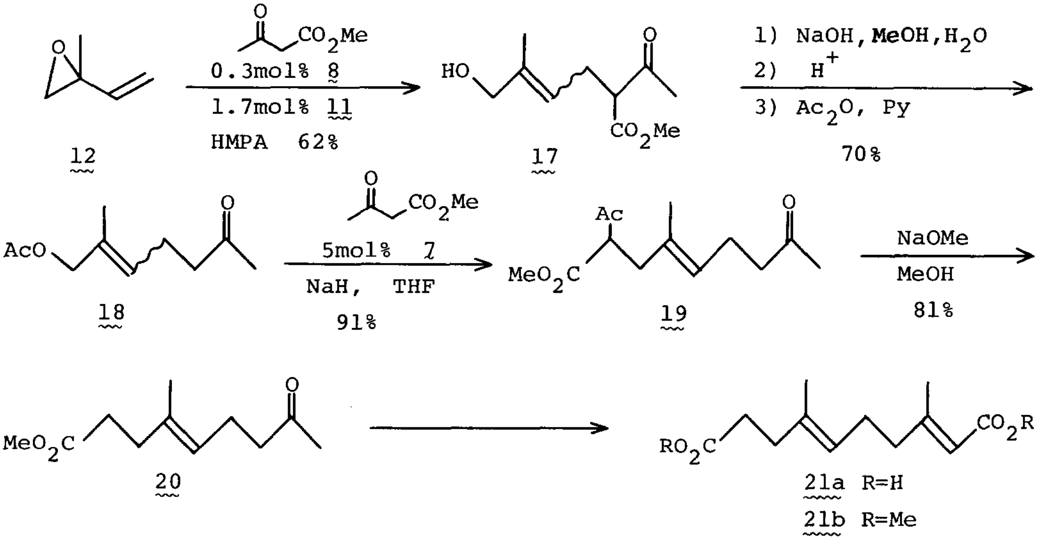
Table 2 The reaction of various diene monoepoxides with methyl acetoacetate

Exp.No.	Substrate	Catalyst	Solvent	Conditions		Ratio$^{a)}$ (1,4:1,2)	Yield(%)$^{b)}$
6	 10	7	THF	r.t.	15min	78:22	67
7	"	8 + 9	"	reflux	30min	85:15	61
8	"	8 +  (11)	"	r.t.	3h	92: 8$^{e)}$	65
9	"	"	CH_3CN	reflux	30min	95: 5	60
10	 12	"	HMPA	r.t.	2.5h	100: 0$^{c)}$	62
11	 13	"	THF	reflux	15min	90:10	90
12	 14	"	"	r.t.	30min	89:11	72
13	 15	"	DMSO	40	1h	90:10$^{d)}$	78

a) Determined from isolated products. b) Isolated yields.
c) E : Z = 5 : 2 d) The olefin isomerization took place (αβ : βγ = 1 : 4).
e) E : Z = 97 : 3

The disubstituted double bonds in the products are mainly E isomers (Exp. No., 1, 4, 8). But a mixture of the E isomers was obtained when the trisubstituted double bond was generated. (Exp. 10).

Isoprene monoepoxide (12) reacted regioselectively with methyl acetoacetate to give the product 17 as a mixture of *E*,*Z*-isomers (*E* : *Z* = 5 : 2). After demethoxycarbonylation of 17 followed by acetylation, the acetate 18 was alkylated again with methyl acetoacetate by using the palladium catalyst. Surprisingly, the product obtained was only the *E*-isomer 19. Transformation of the ester 20 to dimethyl ester of the pheromone 21b has been reported.$^{11)}$ This synthetic methodology is useful for syntheses of terpenoids.



Stereochemistry and application of this reaction to syntheses of more complex natural products are under active investigation.

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