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COMPLETE RETENTION OF CHIRALITY IN THE PALLADIUM CATALYZED CYCLIZATION OF METHYL (*R*)-3-OXO-7-(METHOXYCARBONYLOXY)-8-NONENOATE[1)]

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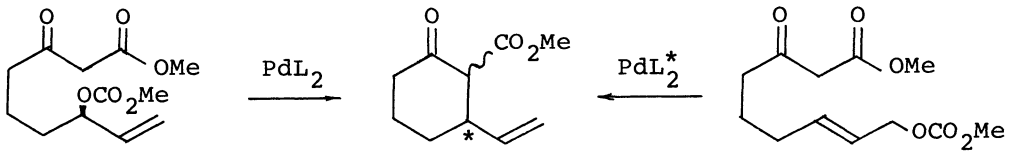
Optically active methyl (*R*)-3-oxo-7-(methoxycarbonyloxy)-8-nonenoate (1) underwent intramolecular allylation catalyzed by $Pd(OAc)_2$-dppe in THF at room temperature to give racemic 3-vinyl-2-methoxycarbonylcyclohexanone (3), whereas similar palladium-catalyzed cyclization of a sodium salt of 1 proceeded very rapidly at 0 °C to form optically active 3, indicative of complete retention of the original chiral center.

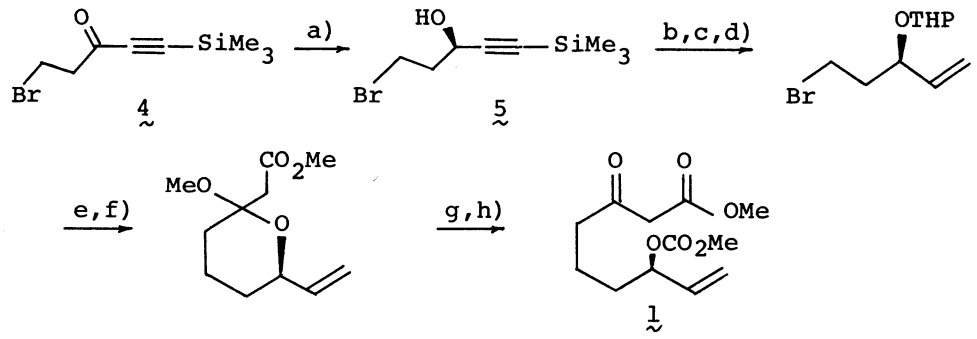
Palladium catalyzed allylation of carbon nucleophiles with a variety of allylic esters is of significant use for organic synthesis.[2,3)] Among these allylic esters, use of allylic carbonates has been extensively studied in our laboratories owing to their high reactivity in the oxidative addition step and in situ formation of an alkoxide ion which acts as a base to generate required carbanions under mild conditions.[4)]

We have recently reported an asymmetric cyclization of prochiral methyl (*E*)-3-oxo-9-(methoxycarbonyloxy)-7-nonenoate (2), in 48% ee, in the presence of certain chiral palladium-diphosphine catalyst.[5)] In our continuing study trying to identify the factors governing this enantioface-differentiation, it is necessary to examine whether a chiral π-allyl palladium intermediate from compound 1, an allylic regioisomer of 2, retains its chirality under the conditions employed for the cyclization as depicted in Scheme 1.



1 3 2

Scheme 1. (L_2 : dppe, L_2^* : chiral diphosphine)



Scheme 2. a) LAH-Darvon/Et_2O, b) cat. Bu_4NF/aq THF, c) DHP/cat. p-TsOH, d) H_2/Pd-$BaSO_4$/quinoline/hexane, e) $AcCH_2CO_2Me$/NaH/BuLi/THF, f) MeOH/cat. p-TsOH, g) aq HCl, h) $ClCO_2Me$/pyridine.

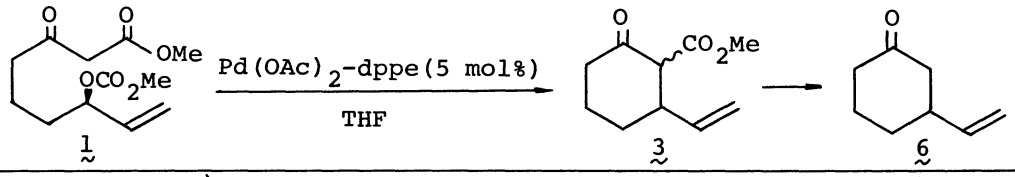
The requisite methyl (*R*)-3-oxo-7-(methoxycarbonyloxy)-8-nonenoate (1) was prepared according to the procedures shown in Scheme 2. With the ketone 4, prepared from β-bromopropionyl chloride and bis(trimethylsilyl)acetylene in the presence of $AlCl_3$, 5 was prepared as a key chiral compound via Darvon alcohol-LAH reduction (50-53% ee)[6] and in turn 1 was obtained in 30% overall yield in seven steps.[8]

Catalytic cyclization of 1 (1.0 mmol) was carried out in the presence of Pd-$(OAc)_2$-dppe (1:2, 5 mol% as PdL_4) in refluxing THF (10 mL). Decarboxylation took place smoothly and the resulting methoxide ion as a base dictated intramolecular allylation at an active methylene moiety to give selectively a six-membered ring compound, 3-vinyl-2-methoxycarbonylcyclohexanone (3), in 80% yield. No optical activity of 3 was detected, i. e., complete racemization of intermediate monosubstituted π-allyl species resulted (see Table 1, Entry 1). The reaction proceeded slower under the same conditions as above except the reaction temperature at 25 °C, and 3 obtained in 79% yield was again racemic (Entry 2).

However, it was found that the cyclization of 1 was markedly accelerated by the addition of NaH (1.2 equiv.) to 1 prior to mixing with the catalyst solution. The palladium-catalyzed cyclization of the sodium salt of 1 proceeded very rapidly even at 0 °C in THF, yielding optically active 3. By a duplicated run, the reaction was confirmed to be exactly reproducible (Entries 3 and 4). The product 3 was decarboxylated by hydrolysis to (*S*)-3-vinylcyclohexanone (6).[5] All results with the optical data are summarized in Table 1.

As is seen from the Table, the striking features of the present cyclization of (*R*)-1 are twofold. (1) As far as a preformed resonance-stabilyzed (soft) carbanion is available, it attacks intramolecularly the chiral monosubstituted π-allyl palladium moiety, which is formed by oxidative addition of the catalyst with inversion

Table 1. Palladium-catalyzed Cyclization of (*R*)-3-Oxo-7-(methoxycarbonyloxy)-8-nonenoate (1).

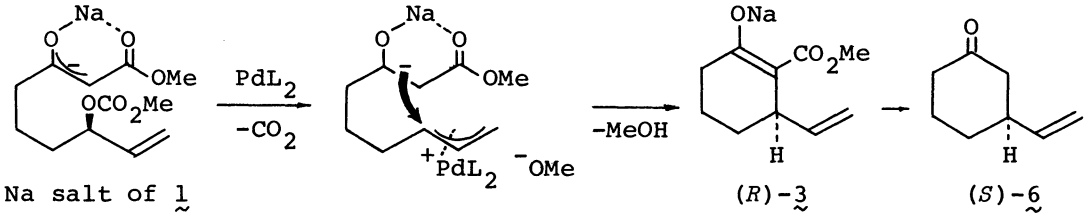


1 3 6

Entry	Opt. purity[a] of 1 /% ee	Base	Temp/°C	Time/min	Yield of 3 %	3, $[\alpha]_D$[b] ($CHCl_3$)	6, $[\alpha]_D$[c] ($CHCl_3$)	% ee (Confgn)
1	53	none	55	30	80	0.0	0.0	racemic
2	50	none	25	45	79	0.0	——	racemic
3	50	NaH[d]	0	10	70	-31.0	——	49 (*S*)
4	50	NaH[d]	0	10	64	——	-10.3	50 (*S*)
5	racemic[e]	none	25	90	72	——	+ 6.0	29 (*R*)

a) As of compound 5. b) $[\alpha]_D$-20.95° ($CHCl_3$) of 3 (33% ee) (Ref.5).
c) *R*-6, $[\alpha]_{D\ max}$+20.6° ($CHCl_3$). d) 1.2 equiv.
e) $Pd(OAc)_2$-(*S*)-(*R*)-BPPFA (1:2, 5 mol%) was used as catalyst.

of the chiral center, from an opposite side of the palladium to form (*R*)-3; The cyclization proceeds with complete overall retention at the original chiral center as depicted in Scheme 3. (2) Consequently, while the chiral π-allyl palladium re-



Na salt of 1 (*R*)-3 (*S*)-6

Scheme 3. (L_2 : dppe)

tains its configurational integrity at least around 0 °C, the methoxide ion formed in situ at 25 °C in THF, as mentioned above, can only abstract an active hydrogen at a rate comparative to racemization of the monosubstituted π-allyl palladium.

In this connection, the asymmetric cyclization of racemic 1 in the presence of $Pd(OAc)_2$-(*S*)-(*R*)-BPPFA as catalyst was carried out, being found to give (*R*)-6, after hydrolysis, in 29% ee (Entry 5). On the other hand, when prochiral 2 was used for the cyclization under exactly the same conditions as above, (*R*)-6 was obtained in nearly the same optical yield (32% ee). These results may be explained by the facile epimerization of the intermediate monosubstituted π-allyl palladium to take place at room temperature without added base.

Bosnich and Mackenzie[9] have also discussed the rapid racemization (or epimerization) of monosubstituted π-allyl systems via π-σ-π mechanism,[10] suggesting dif-

ficulties in asymmetric allylation with these simple systems. Nevertheless, the present study cleanly demonstrates that the racemization is not always too rapid to detect chiral integrity in one of the simplest substitution pattern of coordinated π-allyls, especially in the case of an intramolecular version of catalytic allylation. Very recently, Hiroi and collaborators[11] have reported high degree of chirality transfer (83%) by the palladium-catalyzed alkylation of chiral allylic sulfinates, the simplest π-1-methylallyl palladium being found to retain its chirality in refluxing THF.

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6) (*R*)-5-Bromo-1-(trimethylsilyl)-1-heptyn-3-ol (5); bp 63-65 °C/10 Torr. $[\alpha]_D$ -6.08° (c 3.95, PhH) (53% ee). ^{1}H NMR(90 MHz, $CDCl_3$, TMS) δ0.18(s, 9H), 2.14(br s, 1H), 2.24(q, *J*=6.6 Hz, 2H), 3.54(t, *J*=6.6 Hz, 2H), and 4.59 ppm(t, *J*=6.6 Hz, 1H). IR(film) 3335, 2115, and 1250 cm^{-1}. Optical purity of 5 was determined by an optishift [$Eu(dpm)_3$] method. The *R* configuration is tentatively assigned according to the general trend of the reduction.[7]
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8) (*R*)-1; $[\alpha]_D$ +2.75° (c 1.82, $CHCl_3$). ^{1}H NMR($CDCl_3$) δ1.12-1.92(m, 4H), 2.36-2.76 (m, 2H), 3.44(s, 2H), 3.74(s, 3H), 3.77(s, 3H), 5.15-5.40(m, 2H), and 5.62-5.81 ppm(m, 1H).
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