

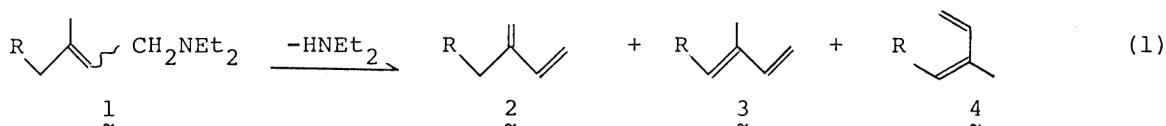
A PRACTICAL SYNTHESIS OF MYRCENOL BY PALLADIUM COMPLEX-  
CATALYZED ELIMINATION REACTION

Hidenori KUMOBAYASHI, Shigeru MITSUHASHI,  
Susumu AKUTAGAWA, and Sei OHTSUKA<sup>†</sup>  
R&D Institute, Takasago Corporation,  
5-36-31, Kamata, Ohta-ku, Tokyo 144

<sup>†</sup>Department of Chemistry, Faculty of Engineering Science,  
Osaka University, Toyonaka, Osaka 560

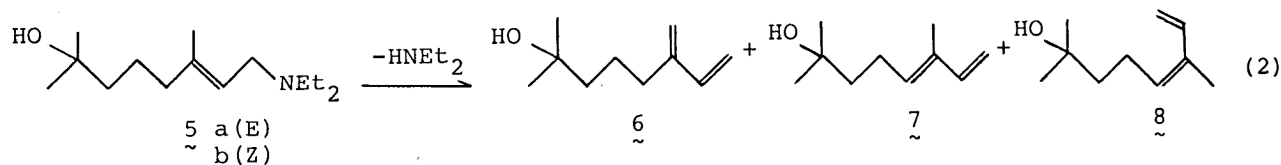
A Palladium complex-catalyzed elimination reaction of allyl amines was studied to establish a practical process for production of myrcenol. The catalytic elimination occurred smoothly with the cationic Pd(II) complexes. Among a variety phosphorous ligands, the tetramethylene and the pentamethylene diphosphine ligands proved to be the best ligand with respects to the catalytic activity and selectivity.

Various types of allylic transformation reaction mediated by  $\eta^3$ -allyl complex formation can be seen in literatures.<sup>1)</sup> In particular, nucleophilic allylic substitution reactions effected with palladium complexes have been extensively studied from both preparative and mechanistic point of view.<sup>2)</sup> In the absence of a nucleophile it is possible, by virtue of a palladium complex, to transform functionalized allylic compounds into dienes. Thus, phenoxy or acetate constitutes a good leaving group in the 1,4-elimination reaction catalyzed by a system Pd(OAc)<sub>2</sub> excess PPh<sub>3</sub>.<sup>3)</sup> This particular Pd system fails to effect the elimination reaction of certain allyl amines, alcohols and alkylethers.<sup>3)</sup> Elimination reaction of certain allyl amines may be effected by conventional base such as n-BuLi, NaNH<sub>2</sub> or KH.<sup>4)</sup> In case of trisubstituted allyl amines of type 1, the reaction with the conventional bases generally results in a non-selective elimination producing a mixture of 2-4 (Eq. 1).



Because of the availability of 1 in large quantity, in addition to the industrial use of the product 2, we have been interested in obtaining 2 selectively. Thus, considerable effort has been placed in search of appropriate ligands to develop appropriate Pd(II)-catalysts. The results are briefly summarized below.

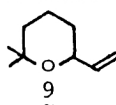
As the representative substrate, 7-hydroxy geranylamine 5 was chosen to see if 6, a fragrance material, can be obtained selectively.



Typically, the reaction was carried out in a flask equipped with a short fractionating column (5 theoretical plates). A mixture of the substrate and catalyst (0.2 mol%) was heated removing the amine and the product diene under vacuum (20 mmHg) through the column. The products collected in an ice-cooled trap was analyzed by GLC.

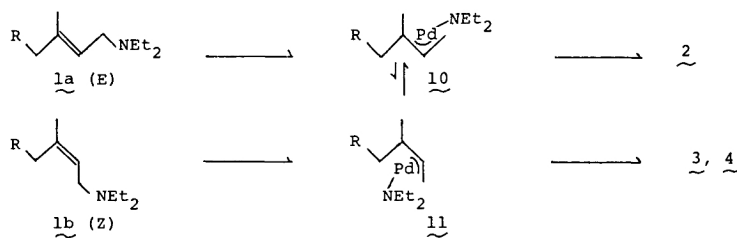
$\text{Pd}(\text{PPh}_3)_4$  or a system  $\text{Pd}(\text{OAc})_2\text{-PPh}_3$  (1:4) was totally inactive to effect reaction (2). Precipitation of palladium metal was observed in both cases. In contrast to  $\text{Pd}(\text{PPh}_3)_4$  the reaction with  $\text{Pd}[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2]_2$  took place to give a mixture of dienes as shown in Table 1 (entry 1). The catalytic rate was slow. In this elimination reaction, the nitrogen atom coordination to the metal center was considered to be a requisite. Accordingly, we tested several cationic Pd(II) complexes. Cationic  $\eta^3$ -allyl diphosphine complex,  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2]^+\text{ClO}_4^-$  was prepared as follows. To a mixture of  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (2.5 mmol) and  $\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$  (5 mmol) in 25 ml of  $\text{CH}_2\text{Cl}_2$  were added an aqueous solution (15 ml) of  $\text{NaClO}_4$  (15 mmol) and subsequently an aqueous solution (5 ml) of  $\text{PhCH}_2\text{NET}_3\text{Br}$  (0.5 mmol) under stirring. After 3 h stirring at ambient temperature, the  $\text{CH}_2\text{Cl}_2$  layer was separated, washed with water, and then dried. The crude ionic complex obtained upon evaporation was recrystallized from a  $\text{CH}_2\text{Cl}_2$ -THF mixture. The purified white complex was dried under high vacuum (1 mmHg) at room temperature, mp 213 °C (dec). Similarly prepared were  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2(\text{CH}_2)_n\text{PPh}_2]^+\text{ClO}_4^-$  ( $n=2,3,5$ ) and  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\text{PPh}_3)_2]^+\text{ClO}_4^-$ .<sup>5)</sup> All these complexes were well characterized by  $^1\text{H}$  and  $^{31}\text{P}$  nmr spectra as well as by elemental analysis. Selected spectroscopic data are summarized in Table 2.

As expected, with these cationic Pd(II) complexes, the catalytic elimination reaction occurs smoothly. The ligands exert dramatic effects on the catalytic rate and selectivity. Thus, (1) although the monodentate phosphine complex shows a fairly high selectivity (87.8%) for **6**, the catalytic activity is low (Table 1 entry 2). (2) The diphosphine analogues exhibit much higher activity (entries 3-6) compared to the  $\text{PPh}_3$  complex. And (3) the chelate ring size of diphosphine affects both the catalytic rate and selectivity (entries 3-7). Among the diphosphine complexes, the tetramethylene and pentamethylene diphosphine compounds proved to be the best catalyst in terms of both respects. The results so far described were obtained with the (E)-allylamine. The corresponding (Z)-amine, 7-hydroxy neryl diethylamine<sup>6)</sup> was also prepared and the catalytic rate and the product selectivity were compared employing  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2]^+$  as catalyst. Under the same condition (130 °C, 3 h, 0.2 mol% catalyst) the elimination of the (Z)-allyl amine underwent with somewhat lower selectivity, viz. 73.4, 16.2, and 6.4% respectively for **6**, **7**, and **8**. A small amount (2.9%) of a cyclized product **9** (Scheme 1) was also formed.



Scheme 1.




These results suggest a mechanism involving an  $\eta^3$ -allyl intermediate. The predominant formation of the diene 2 containing an exo-methylene group can be accounted for with preferential formation of the  $\eta^3$ -allyl species, 10 in which the bulkier substituent occupies the syn-site, and subsequent hydrogen abstraction from the anti-methylene group.



Scheme 2.

The inferior selectivity observed for the (Z)-allyl amine 5b is consistent with this mechanism. Of the two geometrical isomers 10 and 11, the latter should be thermodynamically less stable than the former because of the bulkier substituent at anti-site. The formation of the unstable species 11, by a kinetically controlled process, would be followed by the geometrical isomerization presumably through an  $\eta^3$ -allyl species, to the thermodynamically more stable form 10 (Scheme 2).<sup>7)</sup>

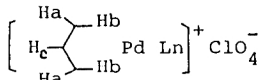
Table 1. Catalytic elimination of amine from 7-hydroxy geranyl diethylamine with palladium complexes

Complexes	Conversion a)	Product %		
		 <u>6</u>	 <u>7</u>	 <u>8</u>
$\text{Pd}[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2]_2$	19	54.5	32.3	13.3
$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\text{PPh}_3)_2]^+\text{ClO}_4^-$	27	87.8	6.7	5.5
$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2(\text{CH}_2)_2\text{PPh}_2]^+\text{ClO}_4^-$	66	84.0	9.1	6.9
$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2]^+\text{ClO}_4^-$	67	86.9	8.9	4.2
$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2]^+\text{ClO}_4^-$	81	93.1	4.8	2.1
$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_5\text{PPh}_2]^+\text{ClO}_4^-$	85	93.5	5.0	1.5
$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_6\text{PPh}_2]^+\text{ClO}_4^-$	16	80.6	11.4	8.0

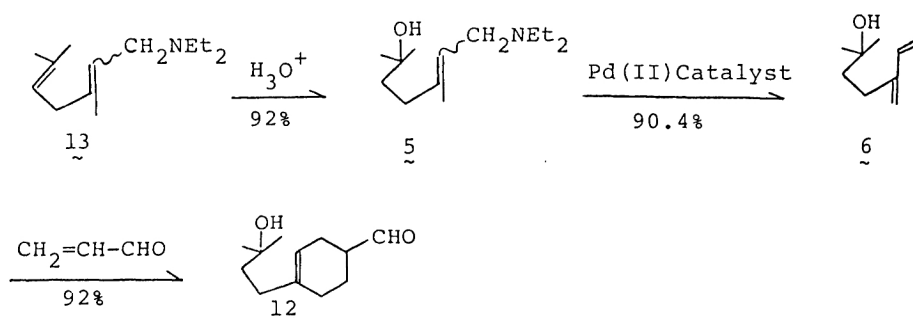
a) All reaction were carried out at 130 °C for 3 h under vacuum (20 mmHg).

Table 2. Selected  $^1\text{H}$  and  $^{31}\text{P}$  NMR data of  $\eta^3$ -allyldiphosphine complexes  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2]^{\text{+a}}$  ( $n=2-5$ )

Ligand	$^1\text{H}$ NMR (ppm) b)			$^{31}\text{P}$ NMR (ppm) c)
	Ha	Hb	Hc	
$\text{PPh}_3$	4.0	3.45	5.86	26.628
$\text{Ph}_2\text{P}(\text{CH}_2)_2\text{PPh}_2$	4.01	3.24	5.80	20.725, 15.59 d)
$\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2$	4.02	3.20	5.70	11.892
$\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$	4.04	3.06	5.65	25.503
$\text{Ph}_2\text{P}(\text{CH}_2)_5\text{PPh}_2$	4.07	3.01	5.54	56.349

a)  b) in  $\text{CD}_2\text{Cl}_2$  c) in  $\text{CD}_2\text{Cl}_2$ ,  $\text{Ph}_3\text{P}$  was used as external standard. d) Two peak were observed and ratio was 1/2.26.

This catalytic reaction can be successfully applied to other type of terpenoid allyl amines. For example, geranyl diethyl amine gave (130 °C, 5 h, 2.2 mol% of  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2]^{\text{+}}$ , 50% conversion) myrcene with virtually perfect chemoselectivity. The success prompted us to apply the process to a practical synthesis of 4-(4'-hydroxy-4'-methylpentyl)-3-cyclohexene carbaldehyde **12**, a fragrance material having a lily-like floral note. The compound was obtained via the route shown in Scheme 3, starting from either geranyl- or neryl diethylamine. The former (E)-amine gave **12** in 76.5% overall yield.



Scheme 3.

#### References

- 1) R. Baker, *Chem. Rev.*, **73**, 487 (1973); R. Huttel, *Synthesis*, **1970**, 225; B. M. Trost, *Acc. Chem. Res.*, **13**, 385 (1983); J. Tsuji, *Yuki Gosei Kagaku*, **41**, 1619 (1983).
- 2) E. Keiman and Z. Roth, *J. Org. Chem.*, **48**, 1769 (1983).
- 3) J. Tsuji, T. Yamanaka, M. Kaito, T. Mandai, *Tetrahedron Lett.*, **1978**, 2075.
- 4) M. Tanaka and G. Hata, *Chem. Ind.*, **1976**, 370.
- 5) An analogous complex  $[\text{Pd}(2\text{-methyl-allyl})(\text{PPh}_3)_2]^{\text{+}}\text{BPh}_4^{\text{-}}$  is known; J. Powell and B. L. Shaw, *J. Chem. Soc., A*, **1968**, 774.
- 6) 7-Hydroxy geranyl diethylamine was prepared by hydration of geranyl diethylamine with 50% of aqueous sulfuric acid at 0 °C for 1 h.
- 7) B. Akermark and A. Vitagliano, *Organometallics*, **4**, 1275 (1985).

( Received October 26, 1985 )