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Catalytic Asymmetric Elimination Forming Chiral 1,3-Dienes via π-Allylpalladium Intermediate

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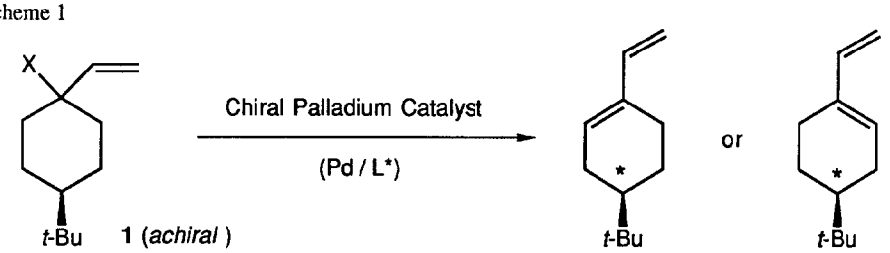
Abstract: Achiral 4-*tert*-butyl-1-vinylcyclohexyl esters underwent asymmetric elimination in the presence of a chiral palladium catalyst coordinated with an optically active ferrocenylbisphosphine ligand to give optically active 4-*tert*-butyl-1-vinylcyclohexene of up to 44% ee.

Enantioselective catalysis via π-allylpalladium intermediates is recognized to be a powerful methodology for the synthesis of optically active compounds.[1,2] In most cases so far reported, new chiral carbon centers are formed upon attack of nucleophiles on the π-allyl carbon of the palladium complexes coordinated with chiral phosphine ligands.[3] We report here a new type of catalytic asymmetric transformation where asymmetric β-hydrogen elimination from π-allylpalladium intermediates produces optically active 1,3-dienes.

Achiral esters of 4-*tert*-butyl-1-vinylcyclohexanol **1** were subjected to the catalytic elimination reaction[4] in the presence of chiral phosphine-palladium complexes,[5] where enantiotopos selective elimination would form optically active 1,3-diene, either (*R*)-**2** or (*S*)-**2** preferentially (Scheme 1).

Scheme 1



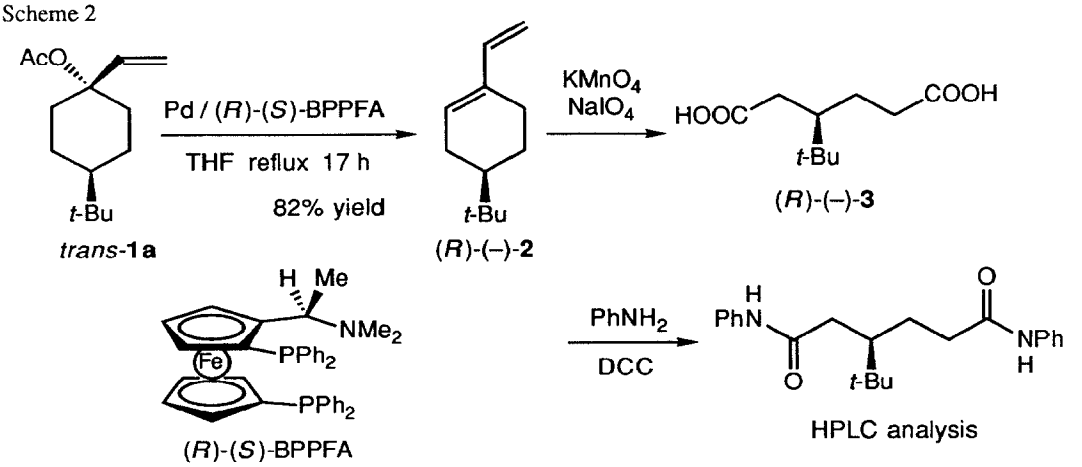
1 (*achiral*)

1a: R = MeCOO
1b: R = $MeCOCH_2COO$
1c: R = EtOCOO

(*R*)-**2** (*S*)-**2**

Treatment of acetate ester *trans*-**1a** with a catalytic amount (2 mol %) of chiral palladium(0) catalyst, generated by mixing $Pd_2(dba)_3$•$CHCl_3$ and ferrocenylbisphosphine ligand (*R*)-(*S*)-BPPFA,[6] in refluxing THF for 17 h gave 82% yield of the desired optically active diene, 4-*tert*-butyl-1-vinylcyclohexene (**2**) ($[\alpha]^{21}_D$ –23.4 (*c* 1.0, chloroform)),[7] which turned out to be an *R* isomer by correlation with known (*R*)-(–)-3-*tert*-butylhexanedioic acid[8] (**3**) obtained by oxidative cleavage of the double bonds in **2** with $KMnO_4/NaIO_4$. The enantiomeric purity was determined to be 21% ee by HPLC analysis of dianilide of **3** with a chiral stationary phase column (Sumichiral OA-3100, hexane/dichloroethane/ethanol = 60/6/1) (Scheme 2).

Scheme 2



The THF reflux temperature was required to complete the elimination reaction of acetate ester *trans*-**1a** in a reasonable reaction time. Acetoacetate ester **1b** and carbonate ester **1c** of *trans*-4-*tert*-butyl-1-vinylcyclohexanol were found to undergo the catalytic elimination under milder conditions than acetate **1a**. It is likely that acetone enolate and ethoxide anions which are generated by decarboxylation of the leaving groups, acetoacetate and ethyl carbonate, respectively, participate as base in the β-hydrogen elimination. The asymmetric elimination of **1b** and **1c** catalyzed by the Pd/(*R*)-(*S*)-BPPFA complex proceeded at room temperature in THF or benzene solution to give diene **2** of higher enantiomeric purity, the highest (44% ee (*R*)) being obtained in the reaction of *trans*-**1b** in benzene. Palladium complexes of other phosphine ligands including BINAP and DIOP were less

Table 1. Palladium-Catalyzed Asymmetric Elimination of Allylic Esters **1**.[a]

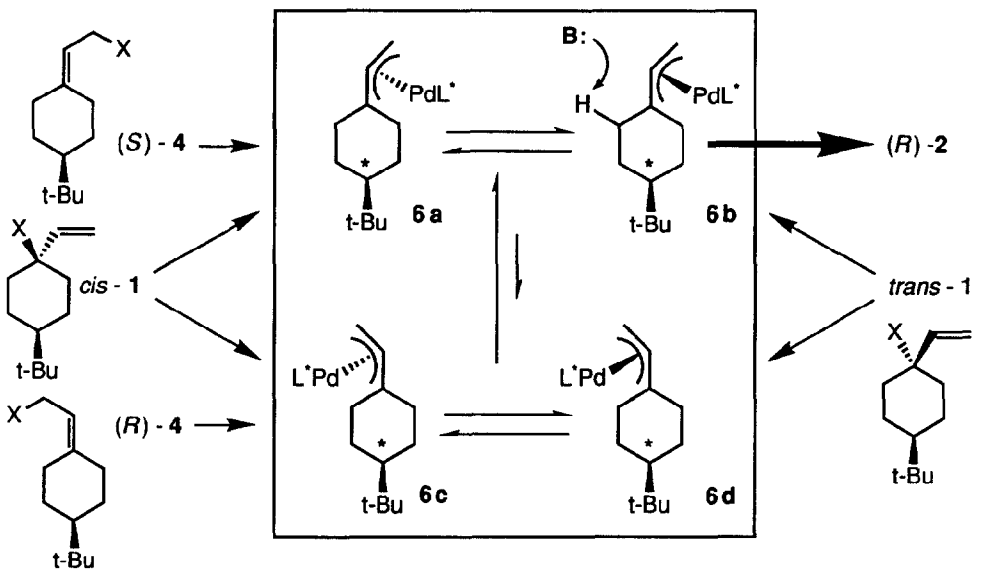
entry	substrate	solvent	temp	time	yield[b] (%)	% ee[c] (config)
1	*trans*-**1a**	THF	reflux	17 h	82	21 (*R*)
2	*trans*-**1b**	THF	r.t.	22 h	65	39 (*R*)
3	*trans*-**1b**	THF	reflux	1 h	75	29 (*R*)
4	*trans*-**1b**	PhH	r.t.	16 h	60	44 (*R*)
5	*trans*-**1c**	THF	r.t.	16 h	82	39 (*R*)
6[d]	*trans*-**1b**	THF	reflux	86 h	67	22 (*S*)
7	*cis*-**1a**	THF	reflux	5 h	63	28 (*R*)
8	*cis*-**1b**	THF	r.t.	47 h	51	39 (*R*)
9	*dl*-**4**	THF	reflux	15 h	66	27 (*R*)
10[e]	*trans*-**5**[f]	PhH	30 °C	3 d	38[g]	32 (*S*)

[a] All reactions were carried out in the presence of 2 mol % of $Pd_2(dba)_3$•$CHCl_3$/(*R*)-(*S*)-BPPFA (L*/Pd = 2/1) unless otherwise noted. [b] Isolated yield by medium-pressure column (silica gel) chromatography. [c] Determined by HPLC analysis of dianilide of **3** (see text). [d] (*R*)-BINAP was used. [e] (*R*)-(*S*)-BPPFNMeCH(CH_2OH)$_2$ (ref 9) was used. [f] *trans*-**5** = Ethyl *trans*-4-*tert*-butyl-1-(1-phenylethenyl)cyclohexyl carbonate. [g] Product is 4-*tert*-butyl-1-(1-phenylethenyl)cyclohexene.

catalytically active or less stereoselective. The results are summarized in Table 1, which also contains data obtained for the reaction of *cis* isomers of **1a** and **1b** and the regioisomeric allylic ester, *dl*-2-(4-*tert*-butylcyclohexylidene)ethyl acetoacetate (**4**).

As can be seen from the Table, almost the same enantioselectivity was observed in the elimination reaction of a set of stereo- and regioisomeric esters. Thus, all the reactions of *trans*-**1b**, *trans*-**1c**, and *cis*-**1b** in THF at room temperature gave (*R*)-**2** of 39% ee (entries 2, 5, and 8), and those in refluxing THF gave (*R*)-**2** in the range of 21% to 29% ee starting with *trans*-**1a**, *trans*-**1b**, *cis*-**1a**, and *dl*-**4** (entries 1, 3, 7, and 9). A mechanism of the stereocontrol for the present asymmetric reaction may be illustrated in Scheme 3, which is proposed based on the result that the stereochemical outcome was not dependent on the relative configuration (*cis* or *trans*) or variation of leaving group (acetate, acetylacetate, or carbonate) of the starting allyl esters.

Scheme 3



It is probable that the catalytic elimination proceeds via π-allylpalladium complex **6**.[4] Diene **2** of *R* configuration will be formed from **6a** or **6b**, provided that one of the protons on *syn* methylene group is abstracted.[10] Oxidative addition of *trans*-**1** to palladium(0) leads to π-allylpalladium **6b** or **6d** and that of *cis*-**1** leads to **6a** or **6c**, since palladium(0) attacks the double bond from the side opposite to leaving group (inversion of configuration).[11] The experimental results that essentially the same stereoselectivity was obtained from *trans* and *cis* isomers indicate that the enantioselectivity in the oxidative addition step forming π-allylpalladium is not important for the overall stereochemistry[12] and the optically active diene (*R*)-**2** is formed after equilibrium of the diastereomeric π-allylpalladium complexes is attained by the isomerization through σ-allyl intermediates (η^3-η^1-η^3 process).[1] The elimination after the equilibration is also demonstrated by the asymmetric induction observed with *dl*-**4**, which otherwise would produce racemic diene **2**.

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7 ^{1}H NMR ($CDCl_3$) for **2**: δ 0.85 (s, 9 H), 1.02-1.34 (m, 2 H), 1.76-2.33 (m, 5 H), 4.86 (dd, J = 11 and 1 Hz, 1 H), 5.02 (dd, J = 18 and 1 Hz, 1 H), 5.64-5.80 (broad m, 1 H), 6.34 (ddd, J = 18, 11, and 1 Hz, 1 H). The maximum rotation of (*R*)-(–)-**2** is calculated to be $[\alpha]^{21}_D$ 113 (*c* 0.9-1.1, chloroform).

8 The optical rotation of **3** obtained here is $[\alpha]_D^{20}$ –3.2 (acetone): Tichy, M.; Malon, P.; Fric, I.; Blaha, K. *Collect. Czech. Chem. Commun.* **1977**, *42*, 3591.

9 (*R*)-*N*-Methyl-*N*-[bis(hydroxymethyl)methyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (ref 3b).

10 A palladium-catalyzed reaction where geranyl acetate and neryl acetate undergo regioselective elimination to produce ocimene and myrcene, respectively, has been reported by Negishi (ref 4b). See also, Åkermark, B.; Vitagliano, A. *Organometallics* **1985**, *4*, 1275.

11 Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767, and references cited therein.

12 This is in striking contrast to the allylic substitution reaction of 4-alkyl-1-vinylcyclohexyl esters reported by Fiaud where the enantioselective step is the oxidative addition of the allylic esters (ref 5a).