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Synthesis of a Novel Type of α-Phosphonocyclobutanones Using Rh(II)-Catalyzed C-H Insertion Reaction

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ロジウム（II）触媒下進行する炭素－水素結合挿入反応を用いた新規 α-ホスホノシクロブタン類の合成

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Abstracts: In the rhodium(II)-catalyzed intramolecular C-H insertion of α-diazo β-keto phosphonates bearing 9,10-dihydro-9,10-ethanoanthracene, using dirhodium tetra(N-phthaloyl-(L)-phenylalaninate) featured by a bulky chiral ligand afforded the optically active phosphonocyclobutanones in preference to phosphonocyclopentanones up to 44% ee.

Keyword: rhodium(II) catalyst, C-H Insertion reaction, phosphonocyclobutanone, aminoacid

A variety of cyclobutanone derivatives, which were versatile intermediate reagents for the synthesis of prostaglandin derivatives[1] and chrysanthemic acid derivatives,[2] have been synthesized by [2+2] cycloaddition[3] of ketenes with olefins or the reaction of cyclopropyl- sulfonium salts with ketones.[4] However, the convenient synthesis of cyclobutanone bearing phosphorus residue at α-position have been rarely reported. Although the rhodium(II)-catalyzed intramolecular C-H insertion of α-diazo carbonyl compounds has been useful method to give cyclic compounds, the insertion reaction of α-diazo compounds of ketones,[5] α-diazo β-keto esters[6] and β-keto phosphonates[7] led to ordinarily cyclopentanones with functional groups at α-position.

We describe here the synthesis of α-phosphono-cyclobutanones bearing 9,10-dihydro-9,10-ethanoanthracene using rhodium(II)-catalyzed intramolecular C-H insertion reaction.

Catalytic decomposition of **1b,c** was carried out in 1,2-dichloroethane containing $Rh_2(OAc)_4$ at 80 °C to

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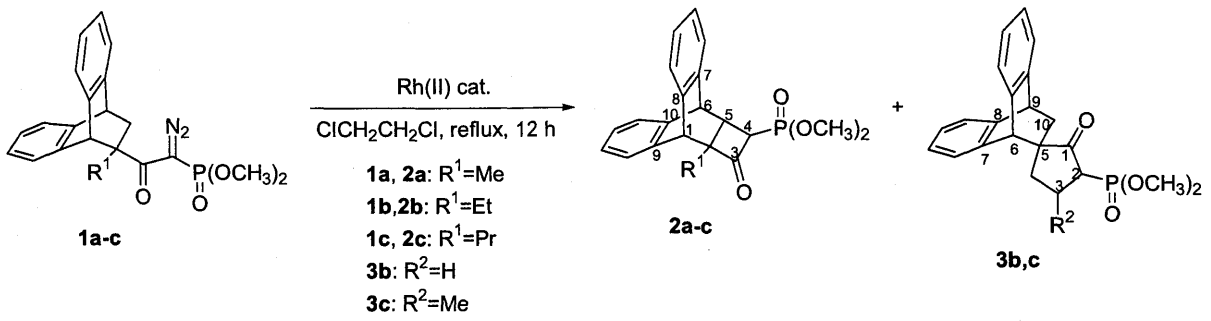

afford the mixtures of cyclobutanones **2b,c** and cyclopentanones **3b,c** in 79% and 40% yield, respectively. Isolation of **2b**[8] and **3c**[9] from the mixtures, although very difficult to separate, was succeeded by the use of preparative TLC with $CHCl_3$-AcOEt (1/1, v/v). The stereochemical assignment of the cyclobutanone **2b** and cyclopentanone **3c** was made on the basis of their ^1H NMR and IR spectral data. That is, the IR spectrum of **2b** shows a peak for carbonyl absorption at 1774.7 cm^{-1} which is characteristic of cyclobutanone (~1800 cm^{-1}), while that of **3c** shows the corresponding peak at 1738.1 cm^{-1} which is characteristic absorption of carbonyl group of cyclopentanone. The NMR spectrum of **2b** shows a signal for methyl (t, J=4.9 Hz, 3H) at δ 1.09, a signal for methine (dd, J=5.4 and 24.4 Hz, 1H) of 4-position at δ 2.61, and a signal for methine (d, J=3.9 Hz, 1H) of 6-position at δ 4.51. Accordingly, the cyclobutanone was exclusively produced *via* insertion into the ethane bridge methylene C-H bonds. The medium coupling constant (5.4 Hz) between methine at 4-posotion and methine at 5-position of **2b** must be a *cis* coupling.[10] On the other hand, that of **3c** shows a signal for

Table 1. Rh(II)-Catalyzed Decomposition of α-Diazo β-Keto Phosphonates Bearing 9,10-Dihydro-9,10-ethanoanthracene (**1a-c**).[a)]

entry	Substrate	Rh(II) cat.	Product (yield, %[b)])			$[\alpha]_D$ (c, $CHCl_3$)	%ee[c)]
			2		**3**	**2**	
1	**1b**	$Rh_2(OAc)_4$	**2b**	+	**3b** (79)		
2	**1c**	$Rh_2(OAc)_4$	**2c**	+	**3c** (40)		
3	**1a**	Rh_2[N-Phth-(D)-Phe]$_4$	**2a** (4)			-46 7 (0.26)	
4	**1b**	Rh_2[N-Phth-(L)-Phe]$_4$	**2b**	+	**3b** (42)	-68.6 (0.54)	
5	**1b**	Rh_2[N-Phth-(D)-Phe]$_4$	**2b**	+	**3b** (63)	+67.9 (1.63)	44
6	**1b**	Rh_2[N-Phth-(L)-Ala]$_4$	**2b**	+	**3b** (12)	-21.5 (0.26)	
7	**1c**	Rh_2[N-Phth-(L)-Phe]$_4$	**2c** (26)[d)]	+	**3c** (9)[d)]	-56.6 (1.36)	43
8	**1c**	Rh_2[N-Phth-(D)-Phe]$_4$	**2c**	+	**3c** (52)[e)]	+47.0 (1.89)[f)]	
9	**1c**	Rh_2[N-Phth-(L)-Ala]$_4$	**2c**	+	**3c** (37)[g)]	+21.3 (1.13)[f)]	32

a) All reactions were carried out in $ClCH_2CH_2Cl$ at reflux for 12 hours in the presence of 5% mol of catalyst.
b) Isolated total yield.
c) Determined by HPLC analysis of α-methylene cyclobutanone derivatives prepared from **2b,c** and paraformaldehyde, with CHIRALCEL OJ (Daicel Chem. Co.).
d) Isolated yield.
e) The **2c**/**3c** ratio was 6.4 which was determined by ^1H NMR analysis of a mixture.
f) For the mixture of **2c** and **3c**.
g) The **2c**/**3c** ratio was 0.3 which was determined by ^1H NMR analysis of a mixture.

methyl (d, *J*=6.3 Hz, 3H) at δ 1.19, a signal for methylene{(dd, *J*=3.1 and 12.5 Hz, 1H) and (dd, *J*=2.4 and 12.5 Hz, 1H)} of 10-position at δ 1.70 and 2.01, and a signal for methine (t, *J*=2.4 Hz, 1H) of 9-position at δ 4.33. Therefore, the cyclopentanone was exclusively produced *via* insertion into the methylene C-H bonds at side chain.

Next, we attempted to apply this synthetic method to the enantioselective synthesis of α-phosphonocycloalkanones. A similar decomposition of **1a-c** with chiral Rh(II)-catalysts[11] afforded the mixture of optically active cyclobutanones **2a-c** and cyclopentanones **3b,c** in 4-63% yields. The optical purities of the obtained cyclobutanones **2a-c** were determined by HPLC analysis of their exocyclic methylene compounds, derived from each of the optically active cyclobutanones and paraformaldehyde, with chiral column (Daicel Chemical Co., CHIRALCEL OJ). The results were summarized in Table 1. The reaction of **1c** using Rh_2[*N*-Phth-(L)-Phe]$_4$ as a catalyst led to cyclobutanone **2c**[9] preferentially, while use of Rh_2[*N*-Phth-(L)-Ala]$_4$ produced predominantly cyclopentanone **3c** (entries 7 and 9). In addition, use of *N*-phthaloylphenylalanine as a ligand resulted in increasing optical yield, regardless of the size of the alkyl side-chain of the diazo compounds (entries 5, 7, and 9). These results indicated that, in this asymmetric C-H insertion reaction, the selectivity in the formation of the cycloalkanone was dependent on the size of the ligand of the catalyst.

Thus, it was found that, in the Rh(II)-catalyzed asymmetric intramolecular C-H insertion reaction of α-diazo β-keto phosphonates bearing 9,10-dihydro-9,10-ethanoanthracene moiety, the use of bigger chiral ligand produced the cyclobutanone preferentially with increasing optical yield.

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8. 7,8:9,10-Dibenzo-2-ethyl-4-(dimethylphosphono)tricyclo[4.2.2.0^{2,5}]dec-7,9-dien-3-one (**2b**): IR (neat) cm^{-1} 1774.7; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.06-1.10 (m, 1H, C$\underline{H}_2$CH$_3$),

1.09 (t, *J*=4.9 Hz, 3H, CH_3), 1.91 (dd, *J*=4.9 and 12.2 Hz, 1H, $C\underline{H}_2CH_3$), 2.53-2.61 (m, 1H, CH), 2.61 (dd, *J*=5.4 and 24.4 Hz, 1H, CHP), 3.70 (d, *J*=11.2 Hz, 3H, OCH_3), 3.73 (d, *J*=11.2 Hz, 3H, OCH_3), 4.42 (s, 1H, CH), 4.51 (d, *J*=3.9 Hz, 1H, CH), 7.12-7.35 (m, 8H, ArH).

7,8:9,10-Dibenzo-2-propyl-4-(dimethylphosphono)tricyclo[4.2.2.$0^{2,5}$]deca-7,9-dien-3-one (**2c**): IR (neat) cm^{-1} 1774.7; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=7.3 Hz, 3H, CH_3), 1.00-1.21 (m, 1H, CH_2CH_3), 1.58 (dd, *J*=7.3 and 16.6 Hz, 2H, $C\underline{H}_2CH_3$), 1.63-1.80 (m, 1H, CH_2CH_3), 2.50-2.62 (m, 1H, CHP), 2.59 (dd, *J*=4.4 and 10.7 Hz, 1H, CH), 3.63 (d, *J*=11.2 Hz, 3H, OCH_3), 3.70 (d, *J*=11.2 Hz, 3H, OCH_3), 4.40 (t, *J*=3.4 Hz, 1H, CH), 4.49 (s, 1H, CH), 7.00-7.34 (m, 8H, ArH)

9. 7,8-Benzo-3-methyl-2-(dimethylphosphono)-6,9-(*o*-phenylene)spiro[4,5]dec-7-en-1-one (**3c**): IR (neat) cm^{-1} 1738.1; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J*=6.3 Hz, 3H, CH_3), 1.29 (dd, *J*=4.9 and 12.7 Hz, 1H, CH_2), 1.44 (t, *J*=11.9 Hz, 1H, CH_2), 1.70 (dd, *J*=3.1 and 12.5 Hz, 1H, CH_2), 2.01 (dd, *J*=2.4 and 12.5 Hz, 1H, CH_2), 2.36-2.54 (m, 1H, CH), 2.51 (d, *J*=10.7 Hz, 1H, CHP), 3.69 (d, *J*=11.2 Hz, 3H, OCH_3), 3.72 (d, *J*=11.2 Hz, 3H, OCH_3), 4.02 (s, 1H, CH), 4.33 (t, *J*=2.4 Hz, 1H,CH), 7.04-7.36 (m, 8H, ArH).

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11. The chiral rhodium(II)-catalysts were prepared by ligand exchange reaction of rhodium acetate in chlorobenzene with *N*-phthaloyl-(L)-phenylalanine [*N*-Phth-(L)-Phe], *N*-phthaloyl-(D)-phenylalanine [*N*-Phth-(D)-Phe], and *N*-phthaloyl-(L)-alanine [*N*-Phth-(L)-Ala], see: H. J. Callot and F. Metz, *Tetrahedron*, **41**, 4495 (1985).