A New Stereocontrolled Approach to 1β-Methylcarbapenem: Asymmetric Hydroformylation of 4-Vinyl β-Lactams Catalyzed by Rh(I) Complexes of Chiral Phosphine−Phosphites and Phosphine−Phosphinites

Kyoko Nozaki,* Wen-ge Li, Toshihide Horiuchi, and Hidemasa Takaya*,†

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-01, Japan

Takao Saito,* Akifumi Yoshida, Kazuhiko Matsumura, Yasushi Kato, Takashi Imai, Takashi Miura, and Hidenori Kumobayashi

Takasago International Corporation, Central Research Laboratory, Nishi-Yawata, Hiratsuka 254, Japan

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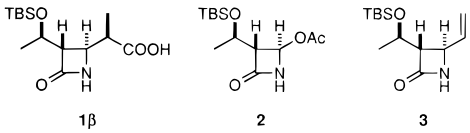
Since the discovery of 1β-methylcarbapenem antibiotics,[1] which possess an excellent antibacterial profile as well as enhanced chemical and metabolic stability, intensive studies have been reported on the stereoselective synthesis of a 1β-methyl intermediate **1**β. Many of these syntheses include the nucleophilic addition of an ester enolate or its derivative to 4-acetoxy-2-azetidinone **2** as a key step.[2,3] On the other hand, we have recently developed a highly enantioselective hydroformylation of various olefins using a rhodium complex of a chiral phosphine−phosphite ligand, (*R,S*)-BINAPHOS [= (*R*)-2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl (*S*)-1,1′-binaphthalene-2,2′-diyl phosphite], as a catalyst.[4] The highest stereoselectivity and the versatility obtained by this hydroformylation prompted us to apply this reaction to the 1β-methylcarbapenem synthesis. We describe here the first example of the synthesis of the key intermediate **1**β *via* rhodium-catalyzed asymmetric hydroformylation. In addition to the phosphine−phosphite, a new class of chiral ligands, phosphine−phosphinites, have been synthesized and used for this purpose. A 4-vinyl-β-lactam, (3*S*,4*R*)-3-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-vinyl-2-azetidinone (**3**),[5] was the substrate of choice.[6]

Hydroformylation of the 4-vinyl β-lactam **3** catalyzed by the Rh(I) complexes of chiral bidentate phosphorus



ligands was carried out under the conditions shown in eq 1. The representative results are summarized in

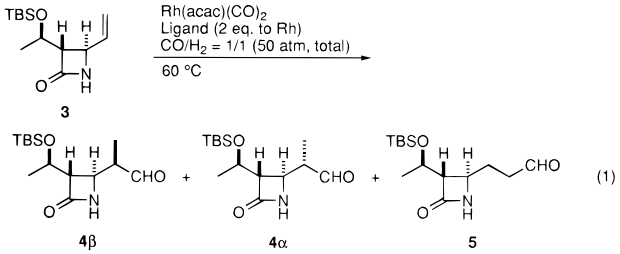
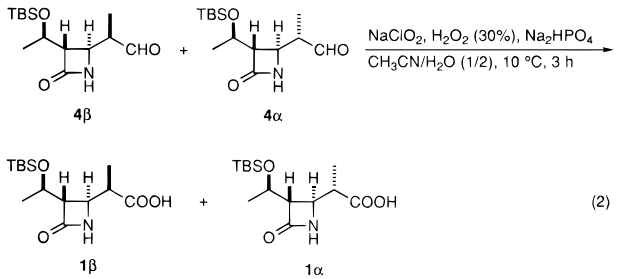


Table 1. The ligands used for this reaction are drawn in Chart 1 along with their abbreviations. As shown in run 1, the desired product **4**β, its epimer **4**α, and their linear isomer **5** were obtained using Rh(I)−PPh_3 as a catalyst. The *iso*/*normal* (**4**/**5**) and the β/α (**4**β/**4**α) selectivities were 51/49 and 45/55, respectively. The use of a conventional bidentate bisphosphine ligand, (*R*)-BINAP, gave **4**β, **4**α, and **5** in the lower total yield (run 2). The **4**β/4α selectivity was slightly improved. When a phosphine−phosphite (*R,S*)-BINAPHOS was employed as a ligand, a higher catalytic activity was observed. Satisfactory β/α selectivity, 93/7, was obtained, and the *i*/*n* ratio was comparable to (*R*)-BINAP (run 3). With another phosphine−phosphite ligand, (*R*)-BIPPHOS, the *i*/*n* ratio was improved but the β/α selectivity was rather low (run 4). The use of a phosphine−phosphinite, (*R*)-BIPNITE, resulted in a slightly higher *i*/*n* than that of (*R,S*)-BINAPHOS, while the high level of β/α was maintained (run 5). The low catalytic activity of (*R*)-BIPNITE was overcome by changing the phenyl groups in the phosphine site to 2-naphthyls (run 6). As shown in run 7, the catalytic activity was remarkably advanced by the introduction of an electron-withdrawing fluoro group into the phosphinite moiety of 2-Nap-BIPNITE. In this case, the electronic properties did not affect on the selectivities. Hence, the best result, a 95% total yield, *i*/*n* = 74/26, and β/α = 96/4, has been achieved using 2-Nap-BIPNITE-*p*-F (run 7). The last ligand shows high crystallinity, which is convenient for industrial treatment.

The oxidation of the aldehydes **4**β and **4**α proceeded without epimerization to produce the corresponding carboxylic acids **1**β and **1**α in excellent yields. Thus, a new synthetic route toward 1β-methylcarbapenem antibiotics has been developed.



The *i*/*n* ratio observed in the hydroformylation of **3** is much higher than simple olefins, such as 1-hexene (*i*/*n* = 26/74, 75% ee for the *iso*-aldehyde)[4a] and 3-methyl-1-

† Deceased on Oct 4, 1995.

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(2) Recent references for this approach: (a) Shirai, F.; Nakai, T. *J. Org. Chem.* **1987**, *52*, 5491 and references cited therein. (b) Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunage, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.* **1992**, *57*, 4243 and references cited therein.

(3) Other recent approaches: Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143 and references cited therein.

(4) (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. (b) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395. (c) Higashizima, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron Lett.* **1994**, *35*, 2023. (d) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2583. (e) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *Chem. Commun.* **1996**, 155.

(5) The 4-vinyl-β-lactam **3** was prepared from 4-acetoxy-2-azetidinone **2** by addition of vinyl Grignard reagent. Kobayashi, T.; Ishida, N.; Hiraoka, T. *J. Chem. Soc., Chem. Commun.* **1980**, 736.

(6) We previously reported the synthesis of **2** using asymmetric hydrogenation as a key step. Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.

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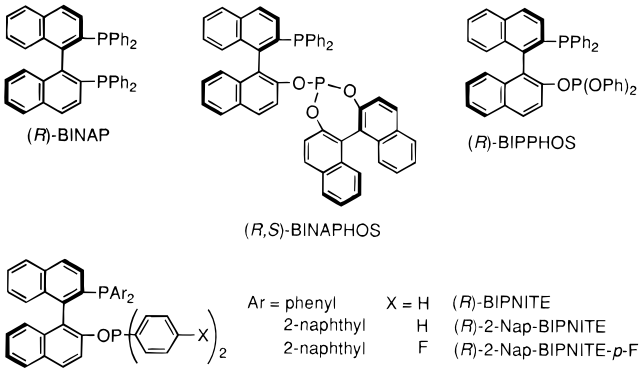
Table 1. Asymmetric Hydroformylation of 4-Vinyl β-Lactam 3 Catalyzed by Rh(I)−Chiral Ligands[a]

run	ligand	S/C[b]	time (h)	total CHO yield[c] (%)	*i*/*n*[c] (**4**β + **4**α)/**5**	β/α[c] **4**β/**4**α
1	PPh_3	200	48	86	51/49	45/55
2	(*R*)-BINAP	200	17	24[d]	52/48	67/33
3	(*R*,*S*)-BINAPHOS	1000	6	95	55/45	93/7
4	(*R*)-BIPPHOS	200	6	92	71/29	60/40
5	(*R*)-BIPNITE	500	6	58[d]	64/36	95/5
6	(*R*)-2-Nap-BIPNITE	500	6	76	74/26	95/5
7	(*R*)-2-Nap-BIPNITE-*p*-F	500	6	95	74/26	96/4

[a] In decane, substrate/solvent = 2 g/mL. [b] Substrate/catalyst. [c] The yield and the (**4**β + **4**α)/**5** and **4**β/**4**α ratios were determined by HPLC using 4-acetoxy-2-azetidinone **2** as an internal standard (Inertsil ODS-2, CH_3CN/H_2O = 65/35). [d] Starting material was recovered. Low conversion is the reason for the low yield.

Chart 1



butene (8/92, 84% ee).[7] This result may be attributed to (1) the β-lactam framework itself, (2) the absolute configuration of the 4-carbon, or (3) the substituent at the 3-position. In order to investigate the factors that induced the high *i*/*n* ratio as well as the high β-methyl selectivity obtained above, 4-vinyl-2-azetidinone (**6**), an unsubstituted analog of **3**, was prepared and then subjected to hydroformylation. A racemic mixture of **6** was treated under the same conditions as **3**.

The regio- and stereoselectivity from each enantiomer was calculated from the product distribution.[8] The general features are as follows: (1) much high *i*/*n* ratio was observed with (*S*)-**6** (76/24-92/8) than with (*R*)-**6** (48/52-56/44) when (*R*,*S*)-BINAPHOS or (*R*)-2-Nap-BIPNITE was used as a ligand, and (2) the absolute configuration of the newly formed chiral center was *R* from both enantiomers, but the selectivity was higher with (*S*)-**6**. From these results, it is manifested that the absolute configuration at the 4-carbon of **3** is essential for the high regioselectivity, (**4**α + **4**β)/**5**. In addition, the *i*/*n* ratios with (*R*)-**6**, which is still higher than with simiple olefins, suggests that the high *i*/*n* with **3** (52/48-74/26) may also be attributed to the β-lactam framework itself. In other words, the electron-withdrawing nature of the β-lactam, which can be effectively transmitted through the 4-membered ring sp^3 carbon to the adjacent alkene, probably does play an important role in favoring the branched regioselectivity. The fact that (*S*)-**6** resulted in higher *i*/*n* than **3** proves that the substituent at the 3-carbon of **3** was unfavorable for the isoaldehyde formation probably due to some steric repulsion. The matching of the chiral ligands with the *S* configuration at the 4-carbons of **3** should have elevated the β-methyl selectivity.

In our previous study, we proposed that the hydride and the phosphite occupy the apical sites of Rh in trigonal-bipyramidal $RhH(CO)_2$[(*R*,*S*)-BINAPHOS] based on the magnitude of $J\{P-H\}$ (21.3 Hz for phosphine and 158.7 Hz for phosphite).[4a,8] With (*R*)-BIPNITE, the ^1H and ^{31}P NMR of the corresponding complex showed a similar trend of $J\{P-H\}$ with BINAPHOS complex (12.0 Hz for phosphine and 135.0 Hz for phosphinite).[9] Thus, it is probable to assume that the $RhH(CO)_2$(ligand) complexes have similar structures between (*R*,*S*)-BINAPHOS and (*R*)-BIPNITEs. Further mechanistic studies are now in progress.

Supporting Information Available: Detailed results on hydroformylation of **6**, experimental procedures, and references for the experiments (6 pages).

JO961689M

(7) Sakai, N. *Highly stereoselective organic synthesis by use of transition-metal catalyzed reactions of carbon monoxide and olefins*, Kyoto University, 1994.

(8) Detailed results on hydroformylation of **6** are given in the supporting information.

(9) Merkin, P.; Muetterties, E. L.; Jesson, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 5271.

(10) $^{31}P[^1H]$ NMR ($CDCl_3$) data for (*R*)-BIPNITE are as follows. Free ligand: δ −13.0 (d, J_{P-P} = 6 Hz, for phosphine), 111.3 (d, for phosphinite). $RhH(CO)_2$[(*R*)-BIPNITE]: δ 23.7 (dd, J_{P-Rh} = 127.0 Hz, J_{P-P} = 28.0 Hz, for phosphine), 163.0 (J_{P-Rh} = 40.0 Hz, for phosphinite).