Tetrahedron Letters 50 (2009) 3158–3160

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A chiral bidentate phosphoramidite (Me-BIPAM) for Rh-catalyzed asymmetric hydrogenation of α-dehydroamino esters, enamides, and dimethyl itaconate

Kazunori Kurihara, Yasunori Yamamoto *, Norio Miyaura *

Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

ARTICLE INFO

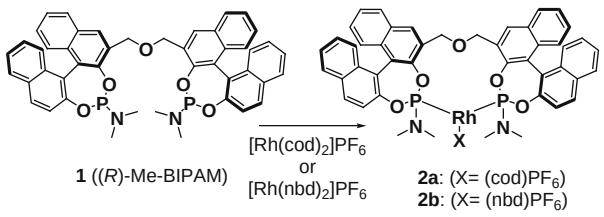
Article history:
Received 17 October 2008
Revised 12 November 2008
Accepted 18 December 2008
Available online 24 December 2008

Keywords:
Bidentate phosphoramidite ligand
Rhodium catalyst
Asymmetric hydrogenation

ABSTRACT

High performance of Me-BIPAM for enantioselective hydrogenation of α-dehydroamino esters, enamides, and dimethyl itaconate was demonstrated. [Rh(Me-BIPAM)(diene)]X (diene = cod, nbd; X = BF_4, PF_6, SbF_6) gave optically active β-aryl α-amino esters up to 99% ee, 1-arylethylamines up to 97% ee, methyl 2-acetylaminobutanoate with 90% ee, and dimethyl 2-methylsuccinate with 97% ee under 0.3–0.8 MPa dihydrogen with 0.1–1 mol % catalyst loading.

Transition metal-catalyzed enantioselective hydrogenation is a powerful strategy to synthesize chiral substances from unsaturated starting materials. In the past three decades, many C_2 symmetric bisphosphines have been developed as the chiral auxiliaries for enantioselective metal-catalyzed hydrogenation of alkenes.[1] Monophosphines,[2] such as phosphoramidite,[3,4] phosphite,[5] and phosphonite,[6] are new entries which are effective for hydrogenation of α-dehydroamino esters, enamides, and dimethyl itaconate. These ligands, which were developed for enantioselective hydrogenation, also worked well for C–C bond-forming reactions with alkenes because the molecular recognition mechanism of alkenes is analogous to that of hydrogenation. Thus, they have been successfully used for palladium-catalyzed allylic substitution[7] and copper- or rhodium-catalyzed conjugate addition of organozinc[7] and arylboronic acids[8,9] to unsaturated carbonyl compounds. Among these chiral auxiliaries for metal-catalyzed hydrogenation and bond-forming reactions, phosphoramidites developed by de Vries and Feringa are unique ligands for which monodentate forms exhibit high enantioselectivity for a large number of enantioselective transformations.[3,10] The enantioselectivities dramatically changed in a series of *N*,*N*-dialkylamino derivatives of phosphoramidites. Among their extensive study, bidentate phosphoramidite ligands have remained unexplored despite of the fact that they have high flexibility in preparation of analogs from commercially available chiral diols.[11] We previously reported the syntheses of bisphosphoramidite ligands (Me-BIPAM and *N*-Me-BIPAM) on the basis of Shibasaki's *O*-linked-BINOL[12] and *N*-linked BINOL[13] for additions of arylboronic acids to α,β-unsaturated carbonyl compounds[14] and *N*-sulfonyl aldimines.[15] In contrast to the excellent performance of monodentate phosphoramidite for cyclic enones, it was not effective for acyclic enones. Due to the rigid structures of bisphosphine complexes, the use of Me-BIPAM and *N*-Me-BIPAM had a wide scope and resulted in high enantioselectivities compared to those of monodentate ligands. Herein, we report the performance of Me-BIPAM for rhodium-catalyzed hydrogenation of α-dehydroamino esters, enamides, and itaconate. Both a rhodium(I) catalyst (**2**) synthesized from **1** and $[Rh(diene)_2]X$ (diene = cod or nbd; X = BF_4, PF_6, SbF_6) or a catalyst prepared in situ by mixing **1** and $[Rh(diene)_2]X$ provided high yields and high enantioselectivities (Eq. 1).[16]



(1)

Hydrogenation of α-dehydroamino esters was carried out at 25 °C in the presence of a rhodium(I)/(*R*)-Me-BIPAM catalyst (1 mol %) (Table 1).[17] 2-Acetamido derivatives of methyl acrylate and ethyl cinnamate were smoothly hydrogenated at room temperature, when $[Rh(cod)_2]PF_6$ or $[Rh(nbd)_2]BF_4$ was used for (*R*)-Me-BIPAM (runs 1–9). Quantitative conversion was also

* Corresponding authors. Tel./fax: +81 11 706 6560 (Y.Y.), tel./fax: +81 11 706 6561 (N.M.).
E-mail addresses: yasuyama@eng.hokudai.ac.jp (Y. Yamamoto), miyaura@eng.hokudai.ac.jp (N. Miyaura).

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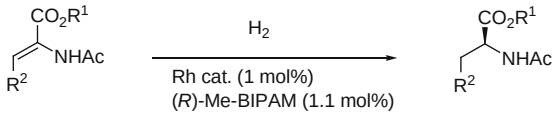
doi:10.1016/j.tetlet.2008.12.086

Table 1
Hydrogenation of α-dehydroamino esters[a]



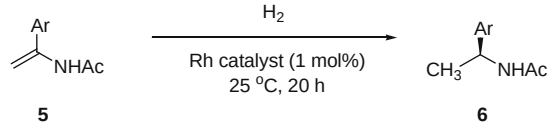
3 **4**

Run	R^1	R^2	Rh catalyst (mol %)	Solvent	H_2 (MPa)	Conv[b] (%)	% ee[c]
1	Me	H	$[Rh(cod)_2]PF_6$/**1** (1)	Toluene	0.3	>99	98 (*S*)
2	Me	H	$[Rh(cod)_2]PF_6$/**1** (1)	CH_2Cl_2	0.3	>99	99.6 (*S*)
3	Me	H	$[Rh(cod)_2]PF_6$/**1** (1)	THF	0.3	>99	99.6 (*S*)
4	Me	H	$[Rh(cod)_2]PF_6$/**1** (1)	AcOEt	0.3	>99	98 (*S*)
5	Me	H	**2a** (0.1)	THF	0.6	>99	99 (*S*)
6	Et	Ph	$[Rh(nbd)_2]BF_4$/**1** (1)	Toluene	0.3	>99	99.4
7	Et	Ph	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2	0.3	>99	94
8	Et	Ph	$[Rh(nbd)_2]BF_4$/**1** (1)	THF	0.3	>99	92
9	Et	Ph	$[Rh(nbd)_2]BF_4$/**1** (1)	AcOEt	0.3	>99	73
10	Me	4-MeC_6H_4	$[Rh(nbd)_2]BF_4$/**1** (1)	Toluene	0.3	<5	—
11	Me	4-MeC_6H_4	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2	0.3	>99	97
12	Me	4-MeC_6H_4	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/3)	0.3	>99	98
13	Et	4-MeC_6H_4	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	99
14	Me	2-MeC_6H_4	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2	0.6	>99	98
15	Me	4-$MeOC_6H_4$	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/3)	0.6	>99	91
16	Et	4-$MeOC_6H_4$	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	97
17	Me	4-ClC_6H_4	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	97
18	Et	4-ClC_6H_4	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	99
19	Me	3-ClC_6H_4	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/3)	0.6	>99	96
20	Me	2-ClC_6H_4	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2	0.6	95	96
21	Me	4-FC_6H_4	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	93
22	Me	4-$CF_3C_6H_4$	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	97
23	Me	3-$CF_3C_6H_4$	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (3/1)	0.6	>99	96
24	Me	4-AcC_6H_4	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	94
25	Me	4-$MeO_2CC_6H_4$	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	95
26	Me	2-Napthyl	$[Rh(cod)_2]BF_4$/**1** (1)	CH_2Cl_2/toluene (1/1)	0.6	>99	99
27	Me	3,4-(Methylenedioxy)C_6H_3	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2	0.3	>99	92
28	Et	3,4-(Methylenedioxy)C_6H_3	$[Rh(nbd)_2]BF_4$/**1** (1)	CH_2Cl_2	0.6	>99	91

[a] Reactions were carried out with 1 mmol of substrate in 2 ml of solvent in the presence of Rh catalyst for 20 h under hydrogen pressure.
[b] Determined by ^1H NMR.
[c] Determined by HPLC.

achieved with 0.1 mol % catalyst loading (run 5). There were no large differences in conversions and enantioselectivities between polar and nonpolar solvents for methyl 2-acetamidoacrylate (runs 1–4), but nonpolar toluene showed higher selectivities for ethyl 2-acetamidocinnamate than those solvents having coordination ability to the catalyst (runs 6–9). Because of the low solubility of

Table 2
Hydrogenation of enamides[a]



5 **6**

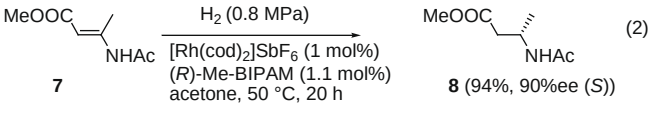
Run	Ar	Rh catalyst (mol %)	Solvent	H_2 (MPa)	Conv[b] (%)	% ee[c]
1	Ph	$[Rh(nbd)_2]PF_6$/**1** (1)	Toluene	0.3	50	95 (*S*)
2	Ph	$[Rh(nbd)_2]PF_6$/**1** (1)	CH_2Cl_2	0.3	>99	80 (*S*)
3	Ph	$[Rh(nbd)_2]PF_6$/**1** (1)	THF	0.3	47	60 (*S*)
4	Ph	$[Rh(nbd)_2]PF_6$/**1** (1)	AcOEt	0.3	92	39 (*S*)
5	Ph	$[Rh(nbd)_2]PF_6$/**1** (2)	Toluene	0.3	>99	95 (*S*)
6	Ph	**2b** (1)	Toluene	0.3	72	93 (*S*)
7	Ph	**2b** (1)	Toluene	0.6	98	97 (*S*)
8	4-MeC_6H_4	**2b** (1)	Toluene	0.6	>99	85
9	3-MeC_6H_4	**2b** (1)	Toluene	0.6	>99	94
10	2-MeC_6H_4	**2b** (1)	Toluene	0.6	0	—
11	4-$MeOC_6H_4$	**2b** (1)	Toluene	0.6	83	77
12	4-BrC_6H_4	**2b** (1)	Toluene	0.6	>99	91
13	4-$CF_3C_6H_4$	**2b** (1)	Toluene	0.6	>99	91
14	4-$MeO_2CC_6H_4$	**2b** (1)	Toluene	0.6	92	86
15	1-Napthyl	**2b** (1)	Toluene	0.6	0	—
16	2-Napthyl	**2b** (1)	Toluene	0.6	>99	94

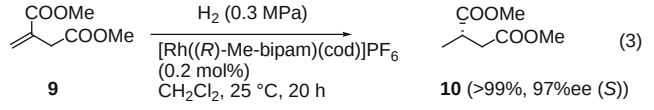
[a] Reactions were carried out with 1 mmol of substrate in 2 ml of solvent in the presence of Rh catalyst for 20 h under hydrogen pressure.
[b] Determined by ^1H NMR.
[c] Determined by HPLC.

methyl or ethyl 2−acetamidocinnamates possessing a substituent at the *para*, *meta*, or *ortho* carbon, hydrogenation of these substrates was carried out in a mixed solvent of toluene and CH_2Cl_2 or in CH_2Cl_2 (runs 12−28). The conversions and selectivities were almost perfect for most substrates, but 4-methoxy, 4-fluoro, 4-acetyl, and 3,4-methylenedioxy cinnamate resulted in selectivities less than 95% ee (runs 15, 21, 24, 27, and 28) and ethyl 2-acetamidocinnamates showed higher selectivities than those of methyl analogs (runs 15/16 and 17/18).

The results of hydrogenation of α-aryl enamides are shown in Table 2. The effects of solvents on enantioselectivities and reaction rates were analogous to those shown in Table 1, but the reaction was significantly slower than that of α-dehydroamino esters. The reaction was completed in CH_2Cl_2 with 1 mol % catalyst loading (run 2), but slow reaction in toluene showed the best enantioselectivity (95% ee, run 1), and the use of such a catalyst prepared in situ resulted in yields and selectivities comparable to those of a rhodium/Me-BIPAM complex (**2b**) (run 6). The conversion in toluene was quantitative when 2 mol % of catalyst was used (run 5), but increase of hydrogen pressure to 0.6 MPa in the presence of a rhodium(I)/Me-BIPAM complex (**2b**) finally achieved practical conversion and selectivity (run 7) without increasing the catalyst loading (run 5). Thus, hydrogenation of other derivatives of α-aryl enamide was conducted under 0.6 MPa hydrogen in the presence of **2b** (1 mol %) (runs 8–16). Although the reaction was highly sensitive to steric hindrance of *ortho-substituents* on the aromatic ring (runs 10 and 15), analogs possessing a para and a meta-substituent were hydrogenated under these conditions in high yields. Aliphatic enamide, such as 2-acetamide-3,3-dimethyl-1-butene, similarly gave low conversion (15%).

Hydrogenation of (*E*)-β-acylamino methyl crotonate (**7**) and that of dimethyl itaconate (**9**) are shown in Eqs. 2 and 3. Hydrogenation of **7** under the optimal conditions shown in Tables 1 and 2 suffered from low conversions and low enantioselectivities (8−57% yields and 35−87% ee). The reaction finally achieved 90% ee with 94% conversion when $[Rh(cod)_2]SbF_6$ (1 mol %) and Me-BIPAM in acetone were used at 50 °C under 0.8 MPa of hydrogen (Eq. 2). On the other hand, hydrogenation of dimethyl itaconate (**9**) took place smoothly at room temperature to yield the corresponding chiral diester with 97% ee (Eq. 3). Under 0.3 MPa hydrogen, the reaction was also completed quantitatively at 25 °C with 0.2 mol % loading of **2a**.





In conclusion, we demonstrated high performance of Me-BIPAM for enantioselective hydrogenation of α-dehydroamino ester, enamides, and itaconate, the results of which are comparable to representative C_2 symmetric chiral auxiliaries reported for hydrogenation of alkenes.[1] Further application of Me-BIPAM to other enantioselective transformations is in progress in our group.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research in Priority Areas (No. 18064001, Synergy of Elements) and the Global COE Program (No. B01, Catalysis as the Basis for Innovation in Materials Science) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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16. To a solution of Me-BIPAM (0.05 mmol) in CD_2Cl_2 was added $[Rh(nbd)_2]BF_4$ (0.05 mmol) under argon atomosphere. The solvent was evaporated in vacuo to give solids of $[Rh(nbd)(Me\text{-}BIPAM)]BF_4$. ^{31}P NMR (CD_2Cl_2) 142.4 (d, J_{Rh-P} = 248.9 Hz); HRMS (FAB) calcd for $C_{53}H_{46}O_5P_2Rh^+$ (M^+-BF_4) 955.1932, found 955.1938.
17. *General procedure for hydrogenation*: A stainless-steel autoclave charged with rhodium catalyst and Me-BIPAM was flushed with nitrogen. Solvent was then added. After being stirred for 1 h at room temperature, alkene was added. The hydrogenation was performed under hydrogen for 20 h. The hydrogen pressure was passed carefully in a hood, and the reaction mixture was evaporated. The conversion and enantiomeric excesses were measured by ^1H NMR and HPLC without purification.