Chiral Bis-phosphoramidites Based on Linked-BINOL for Rhodium-catalyzed 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Carbonyl Compounds

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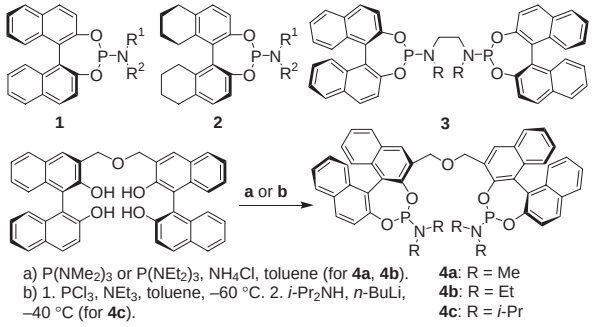
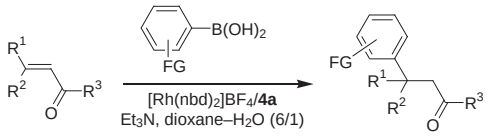
Cationic rhodium(I) complex prepared from Shibasaki's linked-BINOL and $[Rh(nbd)_2]BF_4$ catalyzed asymmetric 1,4-addition of arylboronic acids to enones at room temperature with high enantioselectivities up to 99.8%ee.

Metal-catalyzed conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are the most widely used method for asymmetric carbon–carbon bond formation.[1] The reactions catalyzed by copper,[2] rhodium,[3] and palladium[4] complexes are of great value for asymmetric syntheses because of the availability of chiral ligands. Rhodium(I)–binap catalysts were found to be excellent catalysts for 1,4-addition reactions of aryl- and 1-alkenylboronic acids to electron-deficient alkenes.[3,5] Other catalysts that are effective for arylboronic acids are rhodium(I) complexes of mono-phosphoramidites,[6] chiral P–P ligands such as chiraphos[7] and diphosphonites,[8] P–N ligands of amidomonophosphines,[9] bis(alkene) ligands based on a norbornadiene skeleton,[10] and carbene ligands derived from biscyclophane imidazolium salts.[11] Among these chiral auxiliaries for metal-catalyzed conjugate additions, phosphoramidites developed by Feringa (**1** and **2**),[6,12] are the only ligands for which monodentate form exhibit high enantioselectivity for a large number of asymmetric transformations, including rhodium-catalyzed 1,4-addition of organoboron compounds, though the efficiency of a bidentate ligand (**3**)[12a] was reported in copper-catalyzed addition of diethylzinc to cyclic enones (Scheme 1).

Herein we report bidentate bisphosphoramidites **4** newly synthesized based on Shibasaki's linked-BINOL.[13] **4a** was found to be highly effective for the rhodium-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds (Scheme 2). Both mono- and bisphosphoramidites resulted in excellent enantioselectivities for cyclic carbonyl compounds; however, the use of the rigid bidentate ligand was critical to achieve high enantioselectivity for flexible acyclic substrates.



Scheme 1. Phosphoramidites for asymmetric 1,4-addition.



Scheme 2. Asymmetric 1,4-addition catalyzed by [Rh(I)/**4a**]BF_4.

A mixture of $P(NMe_2)_3$ or $P(NEt_2)_3$ and a (*R*,*R*)-O-linked-BINOL[13] was refluxed in toluene in the presence of a catalytic amount of NH_4Cl to give bisphosphoroamidite **4a** (74%) and **4b** (56%).[14] *N*,*N*-Diisopropyl derivative (**4c**) was obtained in 11% yield by chlorophosphonylation–amidation of the linked-BINOL.[12c] The reaction of **4a** with $[Rh(nbd)_2]BF_4$ in CD_2Cl_2 gave desired [Rh(**4a**)(nbd)]BF_4 (**5a**). ^{31}P NMR exhibited a single signal at 142.4 ppm (d, $J_{Rh-P} = 248.9$ Hz), thus suggesting the intramolecular complexation of two phosphorous atoms to a rhodium metal center (Scheme 1). The formation of a 1:1 complex was also confirmed by mass spectroscopy (FAB), which showed a molecular weight of 955.1938 ($M^+ - BF_4$).

The performance of these ligands for asymmetric syntheses was demonstrated by rhodium-catalyzed 1,4-addition of arylboronic acids to unsaturated carbonyl compounds. The effects of rhodium catalysts and bases in the reaction of 2-cyclohexenone and phenylboronic acid in aqueous 1,4-dioxane are shown in Table 1.

The catalysts were prepared by mixing a rhodium precursor and 10% excess of **4** since it resulted in yields and enantioselectivities that were the same as those of isolated complexes. The neutral complex thus prepared from $[RhCl(coe)]_2$ and **4a** did not catalyze the reaction (Entry 1), but the reaction smoothly took place in the presence of KOH, as was previously demonstrated in analogous conjugated addition catalyzed by neutral Rh(I)–phosphine complexes (Entries 2 and 3). A dramatic rate-acceleration resulting in completion within 0.5 h at room temperature was found when $[Rh(nbd)_2]BF_4$ and **4a** were used in the presence of Et_3N[5c] (Entries 4 and 5). Use of the cationic

Table 1. Reaction Conditions[a]

Entry	Rhodium complex	Base	°C/h	Yield/%	%ee
1	1/2[RhCl(coe)]$_2$/**4a**	none	50/16	0	—
2	1/2[RhCl(coe)]$_2$/**4a**	Et_3N	50/16	46	97 (R)
3	1/2[RhCl(coe)]$_2$/**4a**	KOH	50/16	84	98 (R)
4	[Rh(nbd)$_2$]BF_4/**4a**	Et_3N	50/16	94	99 (R)
5	[Rh(nbd)$_2$]BF_4/**4a**	Et_3N	25/0.5	99	99.6 (R)
6	[Rh(nbd)$_2$]BF_4/**4b**	Et_3N	25/2	62	83 (R)
7	[Rh(nbd)$_2$]BF_4/**4c**	Et_3N	25/2	trace	—

[a]All reactions were carried out in the presence of 2-cyclohexenone (1 mmol), phenylboronic acid (1.5 mmol), rhodium(I) catalyst (3 mol %), ligand (3.3 mol %), and base (if used, 1 mmol) in dioxane–H_2O (6/1).

Table 2. 1,4-Addition of arylboronic acid to α,β-unsaturated carbonyl compounds[a]

Entry	Carbonyl compound	$ArB(OH)_2$, X=	Temp /h	Yield %[b]	%ee[c]
1	2-Cyclopentenone	3-Cl	25/2	99	96
2	2-Cyclohexenone	H	25/0.5	99	99.6 (*R*)
3	2-Cyclohexenone	3-MeO	25/2	90	99.5 (*R*)
4	2-Cyclohexenone	4-MeO	25/2	99	99.8
5	2-Cyclohexenone	3-Cl	25/2	86	99.8
6	2-Cycloheptenone	H	25/2	90	98
7	(*E*)-$C_5H_{11}CH{=}CHCOCH_3$	H	25/2	87	74
8	(*E*)-$C_5H_{11}CH{=}CHCOCH_3$	H	5/48	42	84
9	(*E*)-$C_5H_{11}CH{=}CHCOCH_3$	3-MeO	25/2	98	80
10	(*E*)-$C_5H_{11}CH{=}CHCOCH_3$	3-F	25/2	97	81
11	(*E*)-$C_5H_{11}CH{=}CHCOPh$	3-MeO	25/2	91	85
12	(*E*)-$(CH_3)_2CHCH{=}CHCOCH_3$	H	25/6	80	92 (*R*)
13	(*E*)-$(CH_3)_2CHCH{=}CHCOCH_3$	3-MeO	25/16	78	94
14	(*E*)-$(CH_3)_2CHCH{=}CHCOCH_3$	3-F	25/16	71	90
15	(*E*)-$(CH_3)_2CHCH{=}CHCOC_6H_{11}$	3-MeO	25/2	62	81
16	(*E*)-$(CH_3)_2CHCH{=}CHCOPh$	3-MeO	25/6	98	85
17[d]	(*E*)-*cyclo*-$C_6H_{11}CH{=}CHCOCH_3$	3-MeO	25/10	81	86
18	(*E*)-$PhCH{=}CHCOCH_3$	3-MeO	25/2	99	78
19	(*E*)-$PhCH{=}CHCOPh$	3-MeO	25/6	98	66
20	(*E*)-2-NaphthylCH=CHCOCH$_3$	3-MeO	25/3	93	89
21	(*E*)-$CH_3CH{=}CHCO_2CH_3$	3-MeO	25/24	57	75
22	5*H*-Furan-2-one	3-MeO	25/6	68	77
23	5,6-Dihydro-2*H*-pyran-2-one	3-MeO	25/12	61	91

[a]All reactions were carried out in the presence of enone (1 mmol), arylboronic acid (1.5 mmol), $[Rh(nbd)_2]BF_4$ (0.03 mmol, 3 mol %), **4a** (0.033 mmol) and Et_3N (1 mmol) in dioxane (2.6 mL) and H_2O (0.43 mL). [b]Isolated yields. [c]Enantiomer excess determined by a chiral stationary column. [d]Arylboronic acid (2.5 mmol) was used.

catalyst $[Rh(nbd)_2]BF_4$/**4a** resulted in higher enantioselectivities than $[RhCl(coe)]_2$/**4a**. The mildness of Et_3N to common functional groups is also advantageous over the former combination using KOH. On the other hand, *N*,*N*-diethyl and *N*,*N*-diisopropyl derivatives (**4b** and **4c**) were not effective (Entries 6 and 7). ^{31}P NMR spectrum of a mixture of $[Rh(nbd)_2]BF_4$ and **4b** gave a single signal (142.3 ppm, d, $J_{Rh-P} = 248.9$ Hz) analogous to **5a**, but **4c** did not provide a single complex. ^{31}P NMR exhibited several signals at 24.8, 111.0, and 134.1 ppm, presumably due to intra- and intermolecular coordination of two phosphine atoms.

With these optimized conditions, the scope of the catalyst $[Rh(nbd)_2]BF_4$/**4a** was investigated using representative arylboronic acids and α,β-unsaturated carbonyl compounds (Table 2). There was no difficulty in obtaining high chemical yields and high enantioselectivities for cyclic enones within 2 h at room temperature (Entries 1–6). These selectivities were comparable to or even higher than those of previously reported mono-phosphoramidites **1** or bisphosphine ligands.[5–11]

The enantioselectivities for acyclic (*E*)-enones were dependent on the β-substituent (R^1) and a substituent on ketone carbonyls (R^3). The effect of R^1 increased in the order of Ph < *n*-C_5H_{11} < cyclohexyl ~ 2-naphthyl < isopropyl for a series of methyl ketones (Entries 9, 13, 17, 18, and 20). Steric balance between R^1 and R^3 also can be an important factor affecting on the selectivity. The selectivities were improved by increasing the bulkiness of R^3 for enones having a primary alkyl group at the β-carbon (Entries 9 and 11), but those possessing a hindered substituent (R^1 = isopropyl and phenyl) reduced the selectivity by increasing the bulkiness of R^3 groups (CH_3 > Ph > cyclohexyl) (Entries 13, 15, 16, 18, and 19).

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