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Rhodium-Catalyzed Asymmetric Conjugate Additions of Boronic Acids to Enones Using DIPHONANE: A Novel Chiral Bisphosphine Ligand

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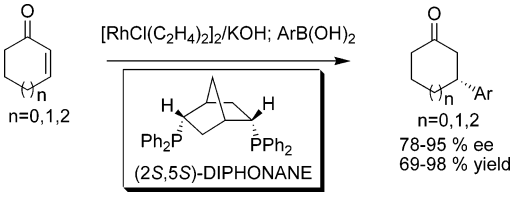
ABSTRACT



The synthesis of a novel enantiopure C_2-symmetric bisphosphine, DIPHONANE, was accomplished starting from 2,5-norbornadione, utilizing (*R*,*R*)- and/or (*S*,*S*)-(2,3-*O*-di[(phenylamino)carbonyl]tartaric acid for the resolution of an intermediate phosphineoxide. The application of this ligand in the rhodium-catalyzed asymmetric conjugate addition of boronic acids to cyclic enones provides the 1,4-addition products in good yields (69–98%) and high ee's (78–95% ee). A byproduct arising from a consecutive 1,4-addition and 1,2-addition was also observed.

The 1,4-addition of aryl or alkenyl groups to electron-deficient double bonds constitutes an interesting approach for C−C bond formation.[1] Therefore, the asymmetric rhodium-catalyzed 1,4-addition to α,β-unsaturated enones has recently received a lot of attention applying various ligands such as biaryl bisphosphines,[2] phosphoramidites,[3a,b] BINOL-based diphosphonites,[3c] amidomonophosphines,[3d] N-heterocyclic carbenes,[3e] ferrocenyl-based bisphosphines,[2c] a P-chiral phosphine,[3f] and dienes.[3g−k] Some other bisphosphine ligands, although efficient in the Rh(I)-catalyzed hydrogenation, fail

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to induce high reactivity and/or selectivity in the rhodium-catalyzed 1,4-addition to α,β-unsaturated enones.[1,2a,c] Within our interest for the design of new ligand architectures[4] and stimulated by the synthesis of DIANANE[5] (Figure 1), we

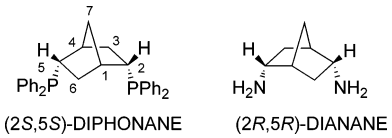
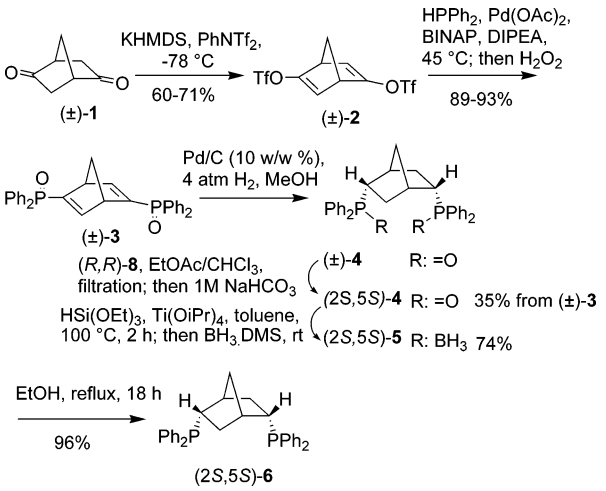


Figure 1.

wish to present our results concerning the synthesis and application of a novel C_2-symmetric bisphosphine, DIPHONANE.

Our approach started with the known 2,5-norbornadione (±)-**1**[6] (Scheme 1). Dienolization/alkylation of this interme-

Scheme 1. Synthesis and Resolution of DIPHONANE



diate is usually addressed in two separate steps,[3h,j,7] but nevertheless the dienolization with KHMDS followed by treatment with $PhNTf_2$ gave a satisfactory yield of the bistriflate (±)-**2**. Pd(0)-catalyzed coupling of **2** with $HPPh_2$ and subsequent oxidation resulted in the racemic vinylic bisphosphineoxide (±)-**3**.[8,9] This intermediate was preferred over its phosphino-borane complex because it allows resolution by applying the hydrogen bonding capacity of the phosphineoxide and BH_3-protected phosphines tend to act as a catalyst poison for heterogeneous hydrogenation.[10] Hydrogenation with Pd on charcoal (10 w/w %) resulted stereoselectively in *endo*-bisphosphine-oxide (±)-**4**.

The bis-*endo* configuration of (±)-**4** could be deduced from the $^3J_{PC}$ coupling in the ^{31}P NMR spectrum of P with C_7 being 15.2 Hz (expected *endo* = 12−16.8 Hz, *exo* ≈ 0 Hz).[11] Nevertheless, resolutions applying commercial (*R*,*R*)-(−)-di-*O*,*O*-benzoyltartaric acid (DBTA) **7**, *R*-(−)-mandelic acid **9**, or (1*R*)-(−)-camphorsulfonic acid (CSA) **10** (Figure 2) were unsuccessful. Fortunately, when (*R*,*R*)-(2,3-di-

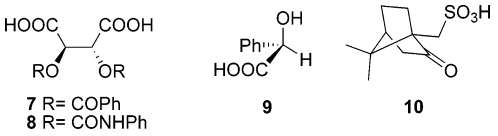


Figure 2. Chiral acids tested for the resolution of (±)-**4**.

[(phenylamino)carbonyl]tartaric acid **8** or its enantiomer was applied (both obtained in three steps from the corresponding tartaric acid[12]), bis-phosphineoxide (±)-**4** was resolved with high enantiomeric excess (>98% ee), as determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD-H). In this way, enantiomerically pure (2*S*,5*S*)-**4** could be obtained in 35% yield in two steps from (±)-**3**. Reduction of the phosphineoxide ($HSi(OEt)_3$, $Ti(OiPr)_4$)[13] was followed by reprotection with BH_3 to ensure easy purification of the phosphine precursor, resulting in the isolation of **5**. Again, the $^3J_{PC}$ coupling with C_7 appeared to be large (12.8 Hz), proving that no epimerization had occurred. The absolute configuration of **5**, being (+)-(1*S*,2*S*,4*S*,5*S*) was established by single-crystal X-ray diffraction (Figure 3).[8] By refluxing the phosphine-borane in EtOH, an efficient procedure recently applied in our group for mild deprotection of phosphines,[14] DIPHONANE **6** was obtained.

The efficiency of our new ligand was tested in the rhodium-catalyzed 1,4-addition of arylboronic acids to enones (Table 1).[1−3] We first examined the addition of phenylboronic acid **12a** to cyclohexenone **11A**. In accordance

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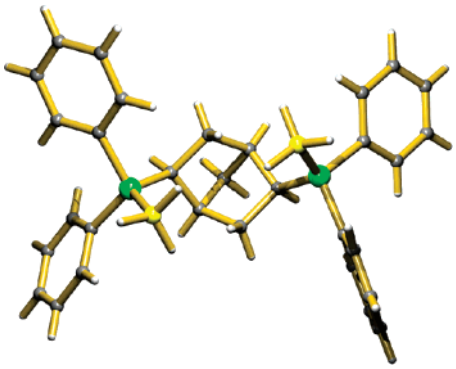


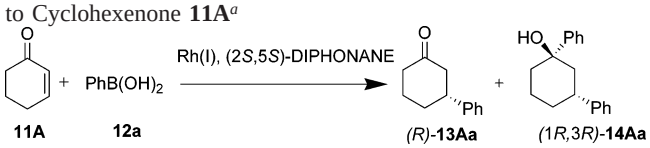
Figure 3. X-ray crystal structure of (2*S*,5*S*)-**5**.

with earlier findings,[15] we observed that the generation of the catalyst from $[RhCl(C_2H_4)_2]_2$ in the presence of KOH and (*S*,*S*)-DIPHONANE (entry 1) resulted in a more active catalyst than in the case of (*S*,*S*)-DIPHONANE with $Rh(acac)(C_2H_4)_2$ (entries 2 and 3), whereas the 1,4-addition product was produced with comparable enantiomeric excess (85% and 86% ee, respectively). The use of 3 mol % of catalyst (entry 4) instead of 1 mol % (entry 1) resulted in an equal enantiomeric excess (85%). The $[RhCl(C_2H_4)_2]_2$/KOH/DIPHONANE system allowed lowering the reaction temperature to 50 °C (entries 5 and 6), affording the product with an enantiomeric excess of 91%. Changing the base from KOH to NEt_3 (entry 7) or changing the solvent (entries 8−13) did not lead to better results.

As a byproduct, resulting from the asymmetric 1,4-addition and a consecutive 1,2-addition, (1*R*,3*R*)-1,3-diphenyl-cyclohexanol **14Aa** could be isolated.[16] The Rh(I)-catalyzed 1,2-arylation of ketones is usually limited to strained ketones as acceptor or to intramolecular additions, whereas arylation of aldehydes or aldimines has been described to a much larger extent.[1,17] The 1,2-addition showed a high level of diastereoselectivity (95% de, entry 14), whereas the resulting product **14Aa** showed a comparable enantiomeric excess as the initial 1,4-adduct **13Aa** (entries 5, 6, and 14). At higher concentration (0.91 M **11A**) **14Aa** was formed in up to 32%, applying only 2 equiv **12a** at 45 °C.

Extending the Rh(I)/DIPHONANE-catalyzed addition to a variety of boronic acids **12a**−**f** and a range of acceptors **11A**−**E** (Table 2) revealed high selectivity in the addition of 4-CF_3-Ph (**12b**) and 1-naphthyl boronic acid (**12d**) to cyclohexenone (**11A**, 92% ee, entry 1, and 95% ee, entry 3, respectively). The hindered *o*-tolyl boronic acid (**12e**) gave

Table 1. Asymmetric 1,4-Addition of Phenylboronic Acid **12a** to Cyclohexenone **11A**[a]

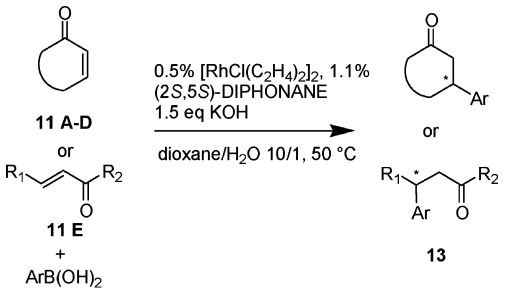


11A **12a** (*R*)-**13Aa** (1*R*,3*R*)-**14Aa**

entry	temp (°C)	solvent	time (h)	**13Aa** (%)[b]	ee (%)[c]	**14Aa** [%] (ee [%])[d]
1	100	dioxane/H_2O 10/1	2	66	85	5
2[e]	100	dioxane/H_2O 10/1	5	43	86	1
3[e]	80	dioxane/H_2O 10/1	21	50	87	1
4[f]	100	dioxane/H_2O 10/1	3	72	85	7
5	60	dioxane/H_2O 10/1	4	83	90	6 (88)
6	50	dioxane/H_2O 10/1	4	78	91	12 (89)
7[g]	50	dioxane/H_2O 10/1	16	65	87	<1
8	50	DME/H_2O 10/1	16	69	90	<1
9	50	EtOH/H_2O 10/1	16	76	91	4
10	50	toluene/H_2O 10/1	21	9	nd	<1
11	50	dioxane/H_2O 5/1	4	63	90	3
12	50	ethyleneglycol/ dioxane 3/1	6	67	89	6
13	50	2-ethoxyethanol	21	74	90	10
14[h]	45	dioxane/H_2O 10/1	19	50	91	32 (89)[i]

[a] Standard conditions $[RhCl(C_2H_4)_2]_2$/DIPHONANE/cyclohexenone 0.5/1.1/100, ~0.35 M **11A**, 1.5 equiv KOH, 5 equiv $PhB(OH)_2$. [b] Isolated as a mixture with **14Aa**. [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel AD-H). [d] Determined from ^1H NMR ratio with (*R*)-**13Aa** based on **11A**, enantiomeric excess determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H). [e] 1% $Rh(acac)(C_2H_4)_2$ was used as catalyst precursor without the addition of base. [f] 1.5% $[RhCl(C_2H_4)_2]_2$ was used. [g] 1.5 equiv NEt_3 was applied as a base. [h] 0.91 M **11A**, 2 equiv $PhB(OH)_2$. [i] ~95% de.

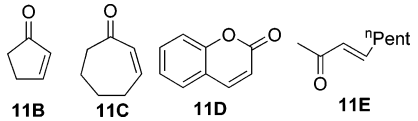
Table 2. Asymmetric 1,4-Addition of Arylboronic Acids **12a**−**f** to α,β-Unsaturated Enones **11A**−**E**



11 A-D or **11 E** + $ArB(OH)_2$ **12 a-f** → **13**

12a Ar= Ph
12b Ar= 4-CF_3-Ph
12c Ar= 4-MeO-Ph
12d Ar= 1-Naphthyl
12e Ar= 2-CH_3-Ph
12f Ar= 2,6-$(CH_3)_2$-Ph

entry	**11**	**12**	time (h)	yield (%)[a] of **13**	ee [%][b] (config)
1	**11A**	**12b**	19	78 (**13Ab**)	92 (*R*)
2	**11A**	**12c**	4	73 (**13Ac**)	79 (*R*)
3	**11A**	**12d**	4	95 (**13Ad**)	95 (*R*)
4	**11A**	**12e**	20	69 (**13Ae**)	78 (*R*)
5	**11A**	**12f**	20	nc (**13Af**)	
6	**11B**	**12a**	4	96 (**13Ba**)	83 (*R*)
7	**11C**	**12a**	4	98 (**13Ca**)	86 (*R*)
8	**11C**	**12d**	4	96 (**13Cd**)	95 (+)
9[c]	**11D**	**12a**	17	nc (**13Da**)	
10	**11E**	**12a**	19	96 (**13Ea**)	31 (*S*)



11B **11C** **11D** **11E**

[a] Isolated yield. nc = no conversion. [b] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD-H or Chiralcel OD-H). [c] 3% $Rh(acac)(CH_2CH_2)_2$, 3.3% (2*S*,5*S*)-**6**, dioxane/H_2O 10/1, 100 °C.

a lower selectivity and yield (69% yield, 78% ee, entry 4), whereas no reaction was observed for 2,6-dimethylphenyl boronic acid (**12f**, entry *5*). A lower selectivity also was observed with the electron-rich 4-MeO-Ph boronic acid (79% ee, 73% yield, entry 2).

The Rh(I)/DIPHONANE-catalyzed addition was also applied to cyclopentenone **11B** and cycloheptenone **11C** as acceptors. The addition to **11B** resulted in the phenyl adduct **13Ba** with good selectivity and excellent yield (entry 6, 83% ee, 96% yield). Addition to **11C** with both phenylboronic acid (**12a**) and 1-naphthylboronic acid (**12d**) resulted in the corresponding 1,4-adducts with high yield and good stereoselectivity (**13Ca**, entry 7, 98% yield, 86% ee and **13Cd**, entry 8, 96% yield and 95% ee, respectively.)

No reactivity was observed in the addition of **12a** to coumarin **11D** (entry 9).[3q] Although the catalyst showed good reactivity in the addition of **12a** to the linear enone **11E** (92% yield, entry 10), the enantioselectivity dropped remarkably (31% ee) Noteworthy is the fact that 1,2-addition was only observed in minor amounts (<3%) in the case of **13Ad** and **13Ab.**

In conclusion, the Rh(I) complex derived from the new bisdiphenylphosphine DIPHONANE catalyses the asymmetric 1,4-addition of boronic acids to enones with ee's up to 95% ee. The intermediate **2** should allow elaboration of a broader range of 2,5-norbornane bisphosphines, both C_2- and C_1-symmetric.

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Supporting Information Available: Experimental procedures and characterization of compounds **2**−**6**, **14Aa** and its epimer **15Aa**, and **13Cd**. X-ray crystal structure of (±)-**3** and (1*S*,2*S*,4*S*,5*S*)-**5** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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