Vaulted Biaryls as Chiral Ligands for Asymmetric Catalytic Diels–Alder Reactions

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The asymmetry associated with the chiral axis in binaphthols has been exploited in asymmetric inductions in both chemical reactivity and chemical associations.[1-3] Early applications of 1,1′-binaphth-2-ol (**1**) (BINOL) include hydride reductions[4a] and chiral building blocks for crown ethers.[4b] Complexes of **1** and derivatives of **1** with Lewis acids have been utilized as chiral auxiliaries and/or catalysts in Diels–Alder reactions,[5] heteroatom Diels–Alder reactions,[6] ene reactions,[7] carbonyl additions reactions,[8,4a] kinetic resolution of epoxide opening,[9] Claisen rearrangements,[10] Ullman coupling,[11a] C–H insertions reactions,[11b] hydrocyanation reactions,[5b,12] Michael additions,[13] akylations,[14] aldol reactions,[5b,15] epoxidation with porphyrin derivatives,[16] host–guest chemistry,[4b,17] and molecular recognition.[18]

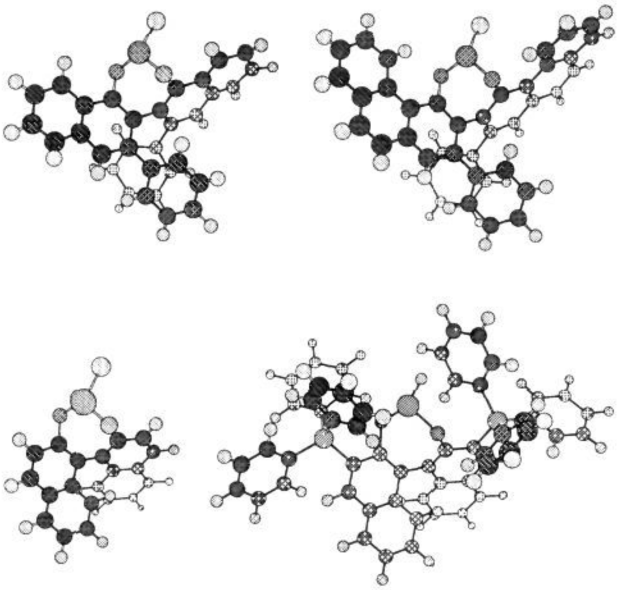
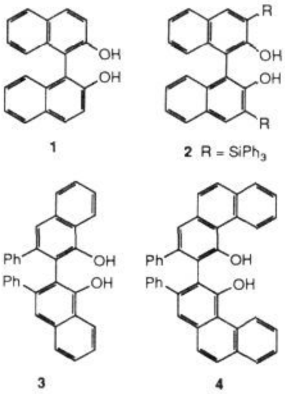


Figure 1. (Top) Chloroaluminum adducts of **3** (left) and **4** (right). (Bottom) Chloroaluminum adducts of **1** (left) and **2** (right).

Chart I



We introduce here the vaulted biaryl ligands **3** and **4** (Chart I) which were previously unknown compounds but whose synthesis and evaluation were undertaken as a result of two main criteria that were considered to be key in the design of new chiral ligands with improved performance over the linear biaryls **1** and **2**.[19,21] The first is that the bulk of the space that is asymmetrically discriminated should be on the same side of the chiral axis as the metal center that is bound to the phenol functions.[22] The differences in the depths of the chiral pockets for linear and vaulted biaryls are evident from the 3-D drawings of the ligands **1**, **3**, and **4** in Figure 1, which are illustrated as their chloroaluminum

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(18) For leading references, see: Ohki, A.; Miyashita, R.; Naka, K.; Maeda, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2714.

(19) The biaryls **3** and **4** were prepared by an oxidative phenolic coupling of the monomers in 80–89% yield. The resolutions of **3** and **4** were effected with procedures related to those described for **1**, and material of greater than 99% optical purity could be obtained as determined by HPLC with a Pirkle D-phenylglycine column.[20] The absolute configuration of (+)-**4** was determined by an X-ray analysis of compound **8** obtained from sequential treatment of (+)-**4** with phosphorus oxychloride and (*S*)-(–)-α-methylbenzylamine. The absolute configuration of the (+)-isomer of **3** has not yet been assigned. No detectable racemization of (+)-**3** was observed upon heating in octane at 180 °C for 2 h. A 95:5 mixture of enantiomers of **3** was observed after heating (+)-**3** for 3 h at 200 °C, and after 12 h an 85:15 mixture was observed.

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(21) The only example of a chiral 2,2′-binaphthol used in asymmetric synthesis is 9,9′-(bi-10-phenanthracenol) which is both a 1,1′-binaphthol and a 2,2′-binaphthol. For leading references, see: Toda, F.; Tanaka, K.; Marks, D.; Goldberg, I. *J. Org. Chem.* **1991**, *56*, 7332.

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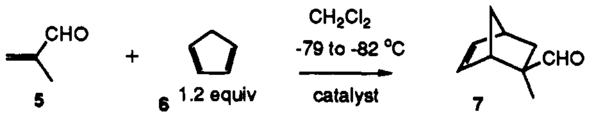
Table I. Asymmetric Induction in a Diels–Alder Reaction Catalyzed by Catalysts Generated from Biaryls **1–4**



entry	ligand	concn of dienophile	mmol dienophile	mol % catalyst[a]	reaction time (h)	exo/endo[b]	% ee[c] exo	(−) 7[c]/(+)-7	yield[b] endo + exo	config **7** [(−) shown]
1	(+)-*S*-**4**	1.0	2.0	10	16	98:2	91.4	22.3:1	100	(−)
2	(+)-*S*-**4**	1.0	2.0	10	0.25	98:2	92.0 (81)[d]	23.9:1	100	(−)
3	(+)-*S*-**4**	0.2	2.0	10	21	98:2	94.7	36.4:1	99	(−)
4	(+)-*S*-**4**	0.05	2.1	10	24	98:2	97.8	88.0:1	100	(−)
5	(+)-*S*-**4**	0.02	2.0	10	24	97:2	97.3	73.0:1	96	(−)
6	(+)-*S*-**4**	1.0	2.0	10	16	98:2	91.4	22.3:1	100	(−)
7	(+)-*S*-**4**	1.0	40.8	0.5	3	97:3	87.7	15.2:1	98 (86)[e]	(−)
8	(+)-*S*-**4**	1.0	40.8	0.5	0.25	92:8	81.0	9.5:1	30	(−)
9	(+)-*S*-**4**	1.0 (slow)[f]	40.9	0.5	4	97:3	97.7	84.9:1	100	(−)
10	(−)-*R*-**4**	1.0 (slow)[f]	40.5	0.5	4	98:2	97.0[i]	65:3:1	100	(+)
11	(−)-*S*-**1**	1.0	2.2	10	20	97:3	23[g]	1.6:1	99	(−)
12	(−)-*S*-**1**	0.05	2.0	10	24	95:5	13[g]	1.3:1	45	(−)
13	(+)-*R*-**1**	1.0 (slow)[f]	42.6	0.5	4	95:5	41[g]	1:2.4	5	(+)
14	(−)-**3**	1.0	2.0	10	22	93:7	5[g]	1.1:1	84	(−)
15	(+)-**3**	0.05	2.0	10	23	92:8	17[g]	1:1.4	85	(+)
16	(+)-**3**	1.0 (slow)[f]	39.9	0.5	4	96:4	29[g]	1:1.8	100	(+)
17	(+)-*R*-**2**	1.0	2.0	10	24	92:8	20	1.5:1	69	(−)
18	(+)-*R*-**2**	0.05	2.0	10	24	93:7	23	1.6:1	78[h]	(−)
19	(+)-*R*-**2**	1.0 (slow)[f]	40.7	0.5	4	93:7	17	1.4:1	100	(−)

[a] Catalyst prepared from **1–4** and 0.85–1.0 equiv of Et_2AlCl in CH_2Cl_2 at 25 °C for 30 min, except for **2** which was 5 h. [b] Unless otherwise specified, the exo/endo ratio and the total yield were determined by ^1H NMR on the crude reaction mixture. [c] Unless otherwise specified, the % ee was determined by capillary GC after conversion of **7** in the crude reaction mixture to a mixture of acetals with (2*R*,4*R*)-(−)-2,4-pentanediol. [d] % ee determined by rotation on **7** after it was separated by silica gel chromatography from the endo isomer; $[\alpha] = -18.85°$ [*c* 0.48, EtOH], which corresponds to an 81% ee on the basis of the rotation reported by Koga.[24a] [e] Isolated yield by distillation. [f] 10% of the dienophile was first added and the rest added by syringe pump over 3 h. [g] Determined by ^1H NMR with chiral shift reagent Eu(hfc)$_3$. [h] Isolated yield by chromatography. [i] A different solution of Et_2AlCl was used than with entry **9** and evidence suggests it was not the same titer. Both (+)-*S*-**4** and (−)-*R*-**4** were ≥99.9% optically pure by HPLC.

complexes. The previous solution to increasing the asymmetry around the active site in the linear binaphthol **1** was the introduction of substituents in the 3 and 3′ positions, and one of the more successful derivatives is the bis(triphenylsilyl) derivative **2**.[5l,6] Since these substituents are appended by a single bond, the effect in these ligands is to buttress the active site with two hemispherical objects. The second main criterion in the design of the valuted biaryls is that the use of aromatic rings to construct the walls of the chiral pocket not only gives a deeper chiral pocket when the walls are extended (i.e., **4** vs **3**) but at the same time gives a high definition to the asymmetry of possible approaches to the active site.

Success has been achieved with 1,1′-binaphthols as chiral auxiliaries in Diels–Alder reactions under stoichiometric conditions;[5] however, there is only a single report of high induction (90% ee) in a catalytic reaction.[5f] Therefore, initially we have examined catalysts generated from the vaulted biaryls **3** and **4** and diethylaluminum chloride for Diels–Alder reactions of methacrolein and cyclopentadiene.[23] The first five entries in Table I reveal that the induction with **4** increases with decreasing concentration from 91.4% ee at 1.0 M to 97.8% ee at 0.05 M.[29] Furthermore the asymmetric induction with **4** decreases with increasing ratios of dienophile to catalyst as indicated in entries **6** and **7** and also in entries **7** and **8** where it is revealed that the induction is lower in the earlier stages of the reaction than at the end suggesting an autoinduction mechanism.[30] This reaction is best be carried out with slow addition of dienophile to give **7** in 97.7% ee with 200 turnovers in 4 h at −80 °C (entry 9).[28] This is the highest induction ever reported for this Diels–Alder reaction with a chiral catalyst[5b,f,k,24,25a] and the lowest catalyst loading ever reported for any asymmetric Diels–Alder reaction with any catalyst.[5,24,25]

The vaulted 2,2′-binaphthol **3** provides a catalyst that is unselective relative to that derived from the vaulted 3,3′-biphenanthrol **4**, and this is also true for catalysts generated from both of the linear biaryls **1** and **2**, as well. It was also found that under the conditions in entry 1 in Table I, the reaction of acrolein with cyclopentadiene in 1.5 h gives a 28% ee for the endo Diels–Alder adduct (endo/exo = 92:8, 100% yield), whereas the same reaction with methyl acrylate under the same conditons in 23 h gives an 86% ee for the endo adduct (endo/exo = 243:1, 93% yield).[27]

We do not know at this time whether the criteria used in the design of vaulted biphenanthrol **4** (VAPOL) are actually responsible for the high induction observed. This will need await the determination of the structure of the active catalyst.[5f,26]

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Supplementary Material Available: Spectral data for **3**, **4**, **8**, and the acetals of (−)-**7** and (+)-**7** with (2R,4R)-(−)-2,4-pentanediol; X-ray data for compound **8** (11 pages); listing of observed and calculated structure factors (10 pages). Ordering information is given on any current masthead.

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(23) The aging time for catalyst formation is important.[24c] The reaction with a catalyst generated from the reaction of **4** and Et_2AlCl for only 5 min at 25 °C gave only 75% ee under the conditions in entry 1 in Table I. Aging times longer than 30 min for catalyst formation did not result in improved induction under the conditions described in entries 1, 10, and 13 for ligands **1**, **3**, and **4**. The optimal aging time for ligand **2** is 5 h, and under the conditions in entry 16, the same induction was observed with an aging time of 24 h.

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(27) The carbon at the α-position of the dienophile has an *R*-configuration in the cycloadduct from the reaction with acrolein and an *S*-configuration from the reaction with methyl acrylate.

(28) There is no detectable loss of the ligand **4** in these reactions since it can be recovered in quantitative yield by silica gel chromatography.

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