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Polystyrene-bound *cyclo*-BINOLs. New heterogeneous ligands for asymmetric catalysis[†]

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Abstract

BINOL and substituted BINOLs, which have been tethered between the 7 and 7′ sites (i.e. 'cyclo-BINOLs'), can be attached via this linkage to polystyrene resins using a simple acetalization. Efficacy associated with these new ligands is demonstrated in heterogeneous asymmetric catalysis (e.g. aryl alkyl sulfide oxidations, and 1,2-additions of Et_2Zn to aryl aldehydes).

Nonracemic BINOL, first recognized by Noyori[1] as a ligand for metal-mediated homogeneous asymmetric synthesis,[2] has spawned an impressive array of applications and continues to serve as the focal point of many new technologies. Issues associated with this nonracemic biaryl, such as catalyst recovery and re-use, simplification of reaction workup, and product purification, have fostered many efforts in search of heterogeneous equivalents.[3–5] In this report, we describe the first examples of 3-mono and 3,3′-unsymmetrically disubstituted BINOLs in their *cyclo*-BINOL form, which are covalently bound to polystyrene resins.

Our modular route to substituted, nonracemic *cyclo*-BINOLs[6] provided us with an entry to BINOL arrays possessing oxygen functionality in the form of an acetonide at a distal site relative to that of eventual metal complexation (**1**, Scheme 1). Removal of the diol protecting group (aq. HCl, MeOH, rt) in **1** led to diol species **3** that was smoothly attached to formylated polystyrene (PS) beads **2** (either 1 or 2% cross-linked polystyrene, prepared from the corresponding chloromethylated material[7] via oxidation with $NaHCO_3$/DMSO; Scheme 2).[8] Traditional Kagan acetalization conditions (benzene or toluene, cat TsOH, reflux, Dean–Stark trap, 1 day)[9] sufficed to arrive at acetals **4**. A series of polymer-supported *cyclo*-BINOLs has been prepared (Table 1), which includes the parent system (**4A**), a 3-monosubstituted case (**4B**), 3,3′-symmetri-cally disubstituted examples (**4C**, **4D**), and two 3,3′-unsymmetrically disubstituted derivatives (**4E**, **4F**).

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[†] Warmly dedicated to Professor Harry H. Wasserman on this most special birthday occasion. For almost three decades he continues to be an incredible inspiration to this PI; indeed, he is a model teacher, an exceptional researcher, an especially valued advisor, and a great friend.

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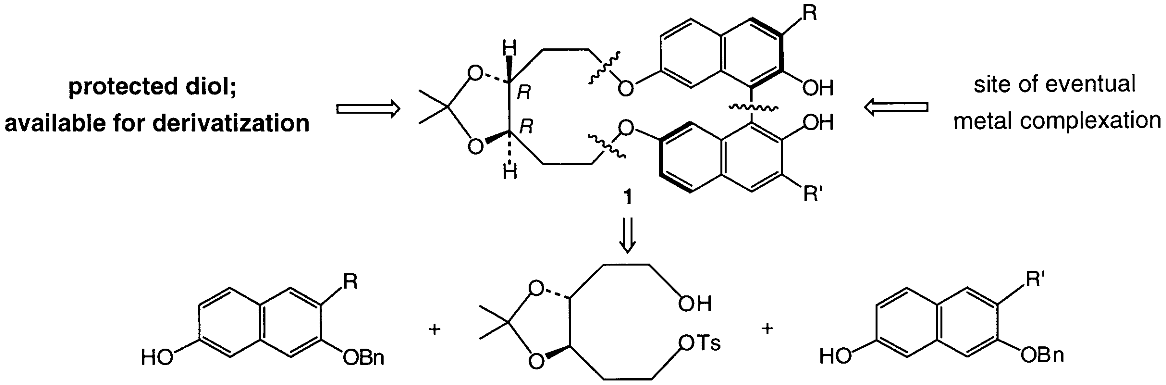
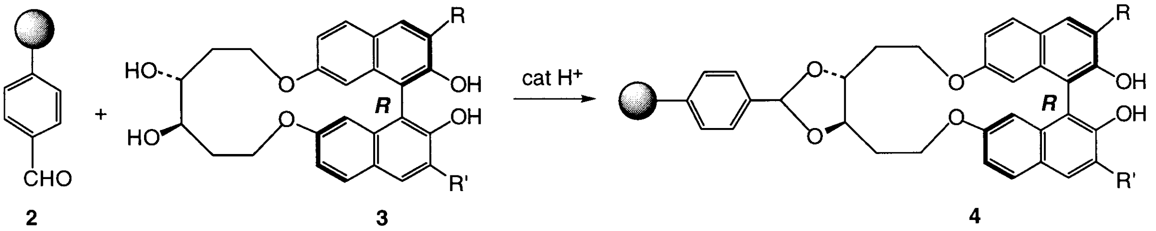


Scheme 1.



Scheme 2.

To test these novel ligands in their capacity as heterogeneous equivalents of known solution-based BINOLs, two sequences were studied: (1) the oxidation of aryl sulfides to nonracemic sulfoxides;[10] and (2) the 1,2-addition of Et_2Zn to aryl aldehydes.[11] Pre-treatment of **4** (R, R′ = H; 1% cross-linked polystyrene) with $Ti(O\text{-}i\text{-}Pr)_4$ in THF at reflux for 1.5 h leads to orange beads presumably composed of in situ generated complex **5** (R = *i*-Pr). Reaction of methyl *p*-tolyl sulfide **6** with *t*-BuOOH in THF at 0°C for 60 h in the presence of catalyst **5** (25 mol%) afforded (*R*)-sulfoxide **8** [67% yield; 78% ee; $[\alpha]_D^{25} = 112$ ($c = 1.1$, acetone); Scheme 3].[10] Methyl phenyl sulfide **7**, under similar conditions (72 h, 50 mol% **5**) gave sulfoxide **9** [65% yield; 88% ee; $[\alpha]_D^{25} = 129$ ($c = 2.1$, acetone)].[10] Both results compare favorably with literature methods involving homogeneous conditions in THF.[12] Isolation of what was anticipated to be ligand **4** (R, R′ = H) was actually material which had retained complexed titanium (i.e. catalyst **5** (R″ = *i*-Pr), or possibly a derivative such as R″ = H). Re-exposure of the reclaimed Ti-complexed catalyst (from each experiment) to sulfide **7** in two additional trials led to essentially the same results in terms of chemical yields and ee's (cf. Scheme 3).

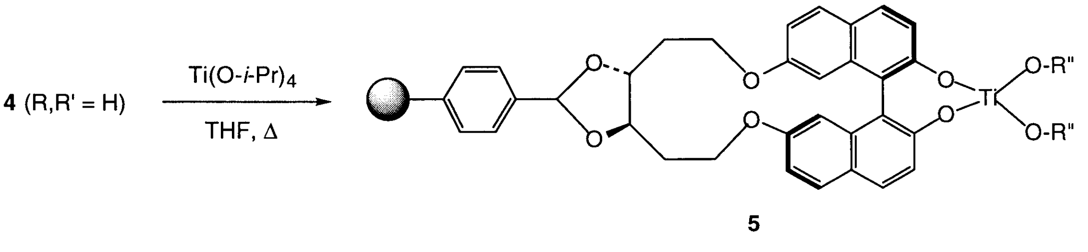
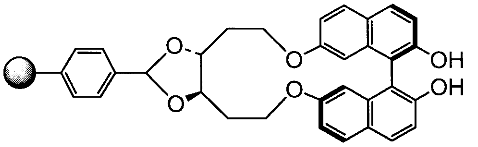
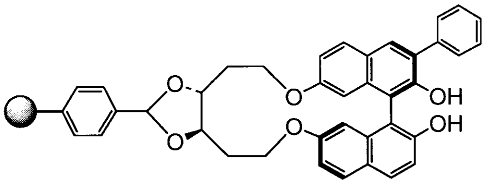


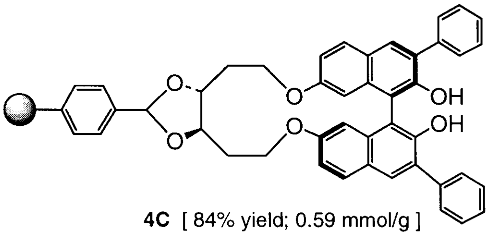
Table 1
Preparation of 1% cross-linked polystyrene-supported (*R*)-*cyclo*-BINOLs



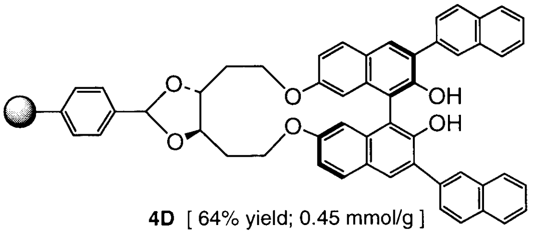
4A [95% yield; 0.68 mmol/g]



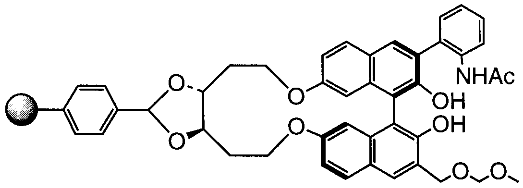
4B [77% yield; 0.55 mmol/g]



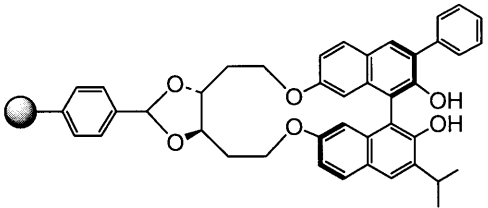
4C [84% yield; 0.59 mmol/g]



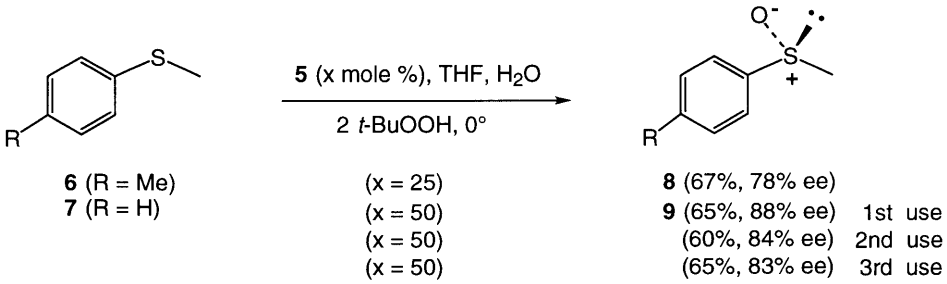
4D [64% yield; 0.45 mmol/g]



4E [86% yield; 0.57 mmol/g]



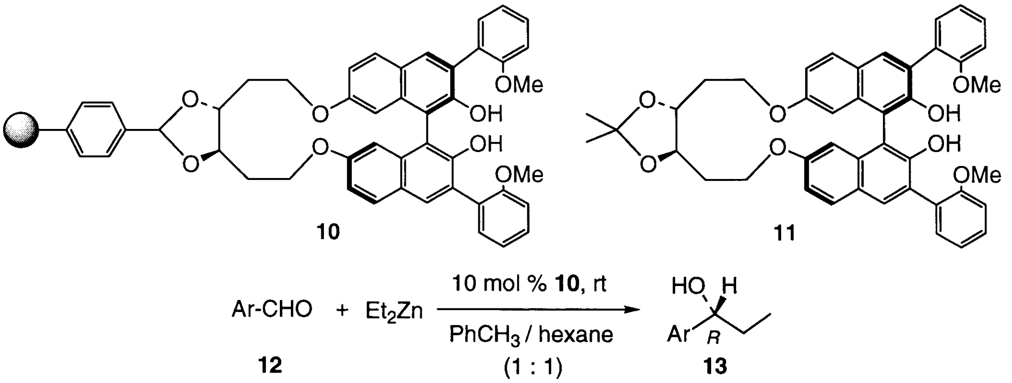
4F [87% yield; 0.64 mmol/g]

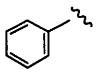
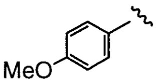
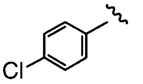


Scheme 3.

Employing an identical modular strategy,[6] 2% cross-linked polystyrene-mounted 3,3′-symmetrically substituted (*R*)-*cyclo*-BINOL **10** was prepared, as was the corresponding *homogeneous* catalyst **11**.[13] Results from a series of 1,2-additions of Et_2Zn to aryl aldehydes **12** in toluene/hexane at room temperature in the presence of 10 mol% **10** are summarized in Table 2.[3a] Benzaldehyde afforded *R* product alcohol **13** in 89% yield with an ee of 96%. Resubmission of this isolated ligand to fresh starting materials and reagents led to essentially the same results over three additional cycles (entries 1a–d). Increasing the amount of catalyst **10** to 20 mol% decreased the reaction time somewhat (8 h versus 12 h), but did not significantly impact the yield

Table 2
1,2-Additions of Et_2Zn to aldehydes catalyzed by **10**



Entry	Ar in **12**	Yield of **13** (%)	% ee	Comments
1 (a)		89	96[a]	1st use
(b)		92	92[b]	2nd use
(c)		90	90[b]	3rd use
(d)		83	93[b]	4th use
(e)		94	93[c]	
2		90	95[d]	
3		84	98[e]	
4	$PhCH_2CH_2$—	56	84[f]	
		69	82[c]	

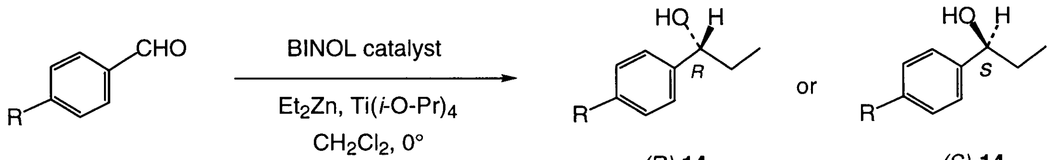
[a] $[\alpha]_D^{25}=43.5$ (*c* 5.2, $CHCl_3$).[17]
[b] Results from recycled **10**.
[c] Results from 10 mol% **11**.
[d] $[\alpha]_D^{25}=31.8$ (*c* 3.5, PhH).[17]
[e] $[\alpha]_D^{25}=25.1$ (*c* 2.0, PhH).[18]
[f] $[\alpha]_D^{25}=-22.6$ (*c* 6.9, PhH).[19]

or product alcohol ee (92% yield; 96% ee). As a control experiment, non-polymer-bound *cyclo*-BINOL **11** reacted faster (3.5 h), but with an otherwise similar outcome (94% yield; 93% ee; entry 1e). Other aryl aldehydes likewise led to aryl carbinols of good ee's. The one case examined of an alkyl aldehyde, under either hetero- or homogeneous conditions, was not as high yielding nor as responsive in terms of observed ee (entry 4), to be expected based on literature precedent for polystyrene-supported catalysts.[3b] Thus, other than affecting to a minor degree the rate of 1,2-addition, the overall effectiveness of this ligand under heterogeneous conditions at delivering the ethyl group in a highly stereocontrolled fashion is comparable to that seen under homogeneous conditions. These results are also competitive with the corresponding polybinaphthyls extensively developed by Pu,[3] with the exception of attempts to apply our heterogeneous conditions to 1,2-additions of Ph_2Zn which did not afford synthetically useful levels of induction (20–40% ee's).[4,5]

Lastly, the potential for unsymmetrical polystyrene-bound *cyclo*-BINOLs to enhance the level of stereoinduction relative to the parent BINOL was demonstrated in comparison reactions of related Et_2Zn additions to aryl aldehydes in the presence of Ti(O-*i*-Pr)$_4$ (Table 3).[5] Under homogeneous conditions, Ti-precomplexed (*S*)-BINOL catalyzes the 1,2-addition of Et_2Zn to benzaldehyde to afford the *S* alcohol (*S*)-**14** with 92% ee. The corresponding polymer-supported (*R*)-*cyclo*-BINOL (**4A**) gives an identical level of enantiomeric excess in product (*R*)-**14**. With *para*-anisaldehyde, both (*S*)-BINOL and PS-(*R*)-*cyclo*-BINOL gave inferior results (<79% ee's). However, the 3-phenyl-substituted PS-*cyclo*-BINOL **4B** led to the desired products (*R*)-**14** not only in high isolated yields (>92%), but most notably, with >95% ee for both aldehydes.

Table 3

Catalysis by an unsymmetrical, heterogeneous, 3-substituted (*R*)-*cyclo*-BINOL (**4B**)



(*R*)-**14** (*S*)-**14**

	BINOL catalyst	Yield of **14** (%)	% ee
(R = H; benzaldehyde)	(*S*)-BINOL	---	92 (*S*)
	PS-(*R*)-*cyclo*-BINOL (**4A**)	87	92 (*R*)
	PS-(*R*)-3-phenyl-*cyclo*-BINOL (4B)	**92**	**95 (*R*)**
(R = MeO; *p*-anisaldehyde)	(*S*)-BINOL	---	79 (*S*)
	PS-(*R*)-*cyclo*-BINOL (**4A**)	91	73 (*R*)
	PS-(*R*)-3-phenyl-*cyclo*-BINOL (4B)	**95**	**96 (*R*)**

In summary, a modular approach has been utilized to arrive at variously substituted polystyrene-bound *cyclo*-BINOLs via attachment of precursor ligands to formylated commercial samples of (1 and 2% cross-linked) polystyrene beads. Efficacy has been demonstrated for conversions of sulfides to nonracemic sulfoxides, as well as in 1,2-additions of Et_2Zn to aryl aldehydes. The ligands are easily handled, are reusable without significant loss of efficiency, and provide for very simple workup procedures which minimize losses of material.[14] With these results in hand, we can now focus on the corresponding polymer-supported (substituted) *cyclo*-NOBIN[15] and *cyclo*-BINAP[16] systems, reports on which will be submitted in due course.

Acknowledgements

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14. Typical procedure for the synthesis of polystyrene-bound *cyclo*-BINOLs (e.g. **4B**). To a well-dried 100 mL round bottom flask was added formylated resin (1.82 g, 1.83 mmol) and the *cyclo*-BINOL **3** ($R=Ph$, $R'=H$; 1.0 g, 1.82 mmol). Benzene (50 mL) and *p*-toluenesulfonic acid (7 mg) were added to the reaction flask and the mixture was refluxed with continuous removal of water with a Dean–Stark trap. After 24 h, the reaction flask was cooled. The resin was collected on a glass filter and washed with dioxane, acetone, *N*,*N*-dimethylformamide, dichloromethane, and finally methanol. There was obtained 2.97 g (91%) of polystyrene-bound (*R*)-*cyclo*-BINOL **4B** after drying at 60°C under high vacuum for 10 h.

   Typical procedure for asymmetric oxidation of aryl alkyl sulfides (e.g. **7** to **9**). Polystyrene-bound (*R*)-*cyclo*-

BINOL **4A** (1.15 g, 0.78 mmol) was suspended in anhydrous tetrahydrofuran (15 mL). To the suspension was added Ti(O-*i*-Pr)$_4$ (1 M in toluene, 319 μL, 0.39 mmol) at rt. The reaction mixture was refluxed for 1.5 h. After cooling to rt, H_2O (105 μL) was added and the mixture was stirred for 2 h at rt. Methyl phenyl sulfide (229 μL, 1.96 mmol) was added and the reaction mixture cooled to 0°C. TBHP (*t*-butylhydroperoxide) in water (70%, 541 μL, 3.91 mmol) was then added dropwise. After stirring for 72 h at the same temperature, the solid was filtered and washed with dichloromethane. The solution was concentrated in vacuo, absorbed onto silica gel and the product sulfoxide isolated by column chromatography with ether as eluent ($R_f=0.32$) to afford a white crystalline solid (178 mg, 65%, 88% ee), $[\alpha]_D^{25}=+129.2°$ (*c* 2.18, acetone).

Typical procedure for the asymmetric addition of diethylzinc to an aryl aldehyde (Table 2, entry 1a). Polystyrene-bound *cyclo*-BINOL **10** (196 mg, 0.10 mmol) was suspended in dichloromethane (15 mL) and stirred for 1 h at rt. To the suspension was slowly added diethylzinc (405 μL, 3.94 mmol) followed by continued stirring for 15 min. The reaction mixture was then cooled to 0°C and benzaldehyde (100 μL, 0.98 mmol) was added. After stirring for 7 h at 0°C, saturated aqueous NH_4Cl (5 mL) was introduced and the mixture stirred for an additional 20 min. The solid was then filtered and the resulting solution was extracted with dichloromethane (15 mL). The combined organic solvents were dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by column chromatography (petroleum ether/ethyl acetate = 7/1, $R_f=0.43$) to afford the product as a colorless liquid (119 mg, 89%), $[\alpha]_D^{25}=+43.5$ (*c* 5.20, acetone). The solid material was transferred into a 50 mL beaker and treated with 15 mL of 2N NaOH. After stirring for 2 h, the solid was filtered and washed with H_2O, dioxane, *N*,*N*-dimethylformamide, dichloromethane and methanol. 320 mg of polystyrene-bound *cyclo*-BINOL **4B** was recovered and showed no decrease in activity after drying at 60°C under vacuum (ca. 10 mmHg) for 10 h.

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