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A Modular Approach to Nonracemic *cyclo*-BINOLs. Preparation of Symmetrically & Unsymmetrically Substituted Ligands

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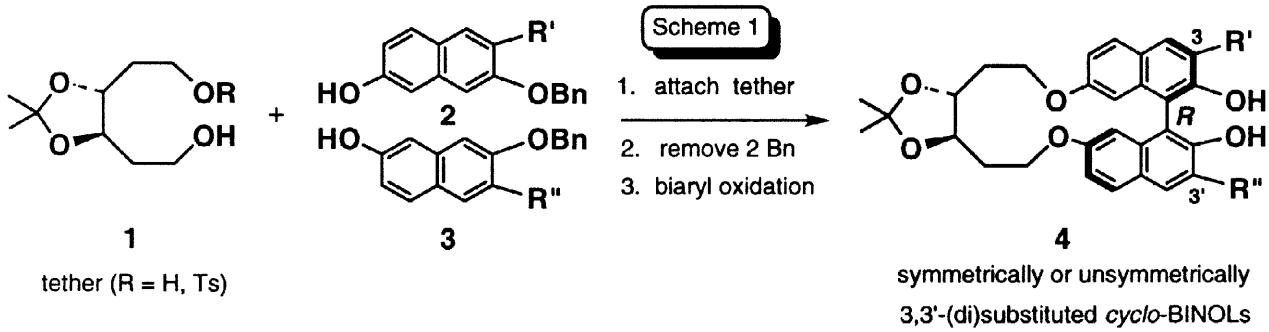
Abstract. *A new series of substituted cyclo-BINOLs is described, constructed using individually fashioned naphthol units which are tethered and oxidized to arrive at nonracemic materials.* © 1998 Elsevier Science Ltd. All rights reserved.

Since being introduced by Noyori in 1979,[1] BINOL continues to enjoy enormous success within the domain of asymmetric synthesis and, in particular, as a ligand in asymmetric catalysis.[2] In this latter capacity, it is known that enhancements in the effectiveness of nonracemic BINOL (*i.e.*, the extent of chiral induction as measured by ee's) may be realized when the environment around the metal-BINOL complex is modified. Such changes are usually localized at the 3- and/or 3' sites,[3] and result from substituents that impact the catalyst *via* steric, stereoelectronic, and/or chelation phenomena. Relatively few 3-mono- or 3,3'-disubstituted BINOLs are known, and to our knowledge, not one in the *unsymmetrically* disubstituted series exists. We now describe a short, convergent sequence based on modular components **1**, **2** and **3** that allows for the preparation of BINOLs, in tethered form (*i.e. cyclo*-BINOLs,[4] **4**), bearing various substituents at the 3 and 3' positions (Scheme 1).



1
tether (R = H, Ts)

3

4
symmetrically or unsymmetrically 3,3'-(di)substituted *cyclo*-BINOLs

Nonracemic tether **1** is prepared in quantity (Scheme 2) starting with esterified commercially available *E*-β-hydromuconic acid, **5**. Reduction and benzoylation sets the stage for a Sharpless AD,[5] affording diol **6** in what appears to be enantiomerically pure form.[6] Acetonide formation followed by

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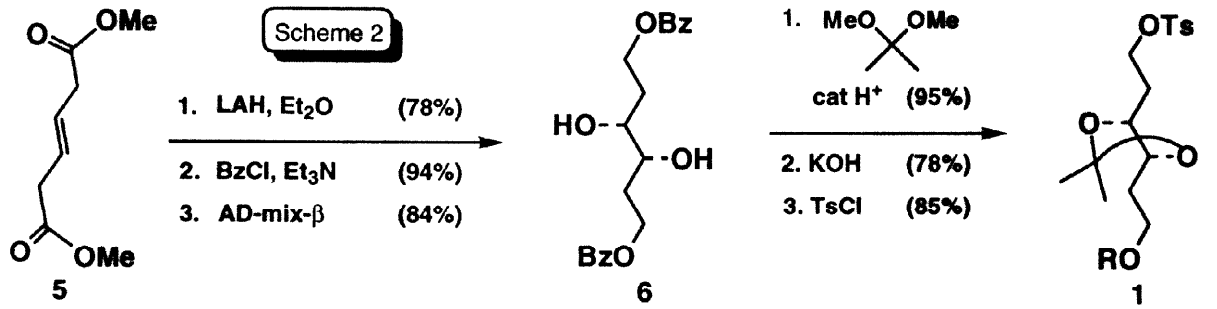
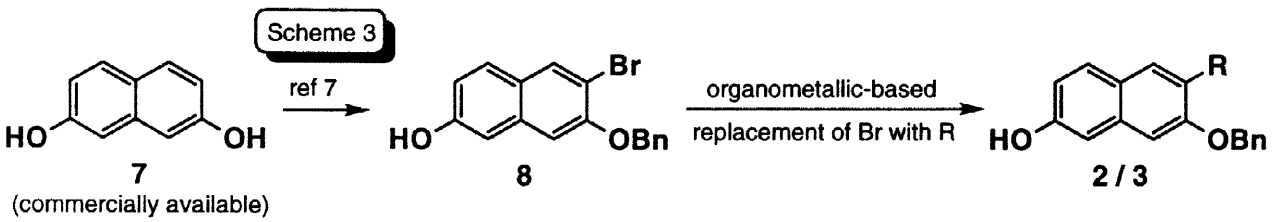
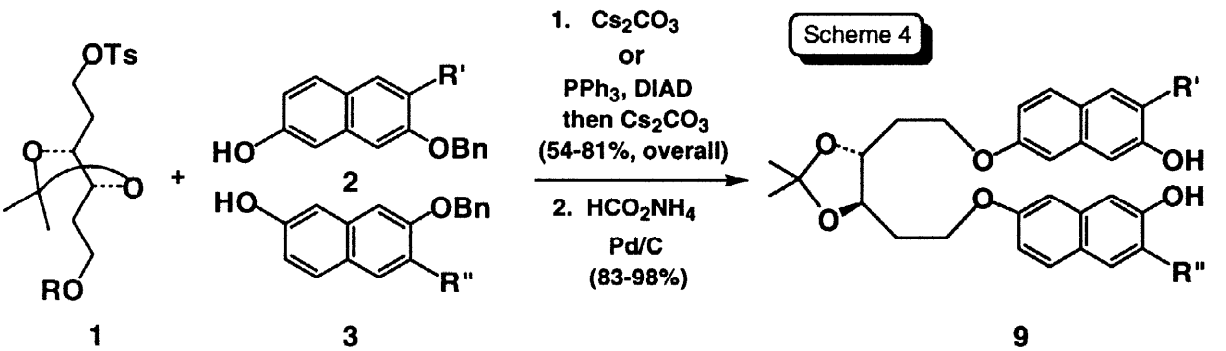
saponification and mono- or bis-sulfonation gives nonracemic mono- or ditosylates **1** (R = H, Ts, respectively).



The naphthylic portions **2** / **3** are prepared from bromide **8**, which is available in quantity following a Diederich procedure[7] starting with diol **7** (Scheme 3). Various organometallic-based couplings with **8** (TBS ether) lead to substituted products **2** / **3** after desilylation (*e.g.*, R = C_6H_5, *via* Suzuki coupling[8a] with $PhB(OH)_2$; $SiEt_3$, *via* lithiation, trapping with Et_3SiOTf; CH_2OMOM, *via* lithiation, trapping with DMF, then $LiAlH_4$, and finally, MOM-Cl; *i*-C_3H_7, *via* Kumada coupling[8b] with cat Ni(0)/*i*-PrMgCl).



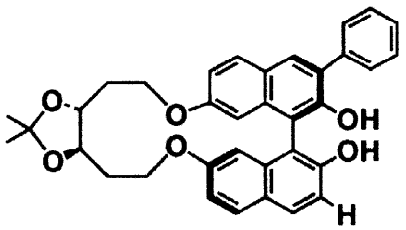
Symmetrical precursors **9** (R′ = R″) can be obtained by simply effecting double displacement of ditosylate **1**, R = Ts with two equivalents of a naphthol in the presence of Cs_2CO_3. Unsymmetrical derivatives **9** require initial exposure of monotosylate **1** (R = H) to a 2-naphthol **2** under Mitsunobu conditions,[9] followed by displacement of the remaining tosylate by a second 2-naphthol **3** (Scheme 4). In either case, transfer hydrogenation removes both benzyl ethers *en route* to **9**, setting the stage for the biaryl oxidation to the corresponding *cyclo*-BINOL system.



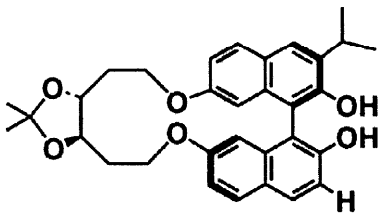
Oxidations of nonracemic *seco* derivatives **9** to the corresponding *cyclo*-BINOLs **4** could be effected with Koga's copper catalyst[10] or, in better yields and with high de's, using a slight excess of Mn(III) in acetonitrile (Equation 1).[11] Several representative examples are illustrated in Figure 1, all of

Figure 1. New *cyclo*-BINOLs prepared *via* oxidative coupling.[a]

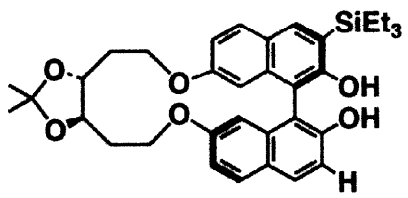
Monosubstituted *cyclo*-BINOLs:



(73%; 95% de)

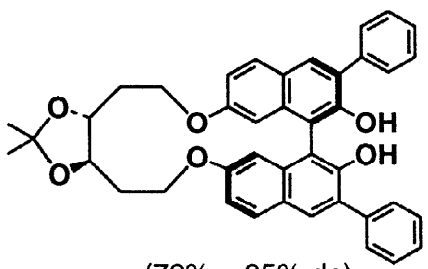


(71%; 93% de)

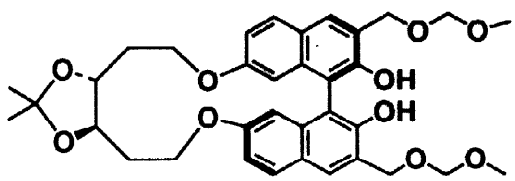


(69%; 91% de)

Symmetrically disubstituted *cyclo*-BINOLs:

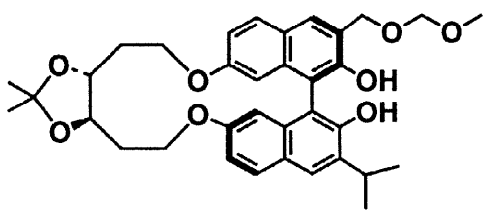


(72%; >95% de)

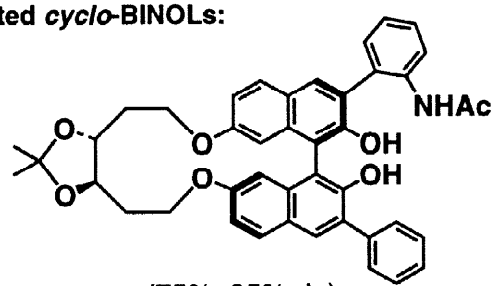


(85%; 84% de)

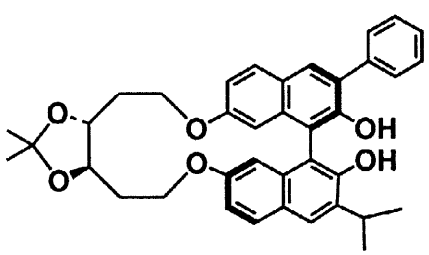
Unsymmetrically disubstituted *cyclo*-BINOLs:



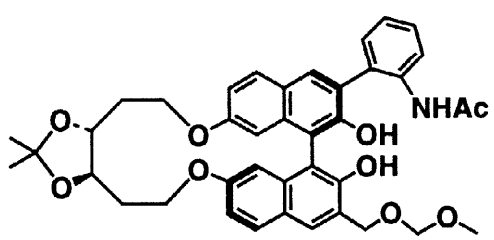
11 (83%; 89% de)



(75%; 95% de)



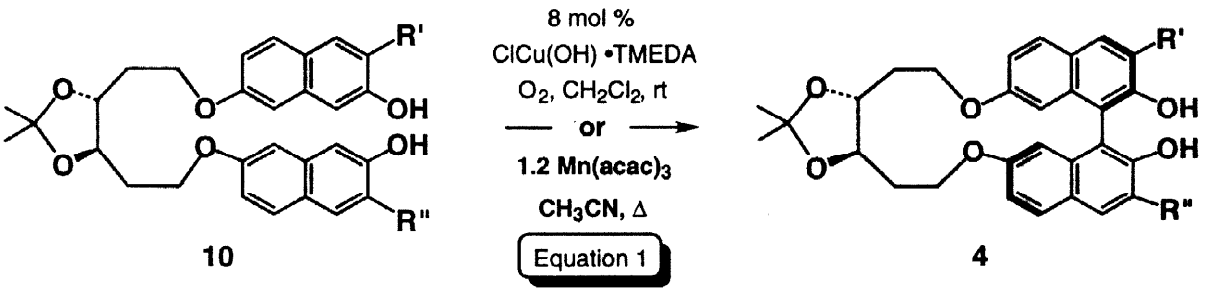
(72%; 97% de)



(89%; 86% de)

[a]All were formed in the biaryl oxidation step using 1.2 eq $Mn(acac)_3$ at 0.01 M in CH_3CN between 50° and reflux. Yields given in % are for isolated, chromatographically purified materials. The de's (± 2%) were measured from 500 MHz proton NMR spectra.

which suggest that placement of substituents in the 3- and 3' sites not only is readily accomplished, but that the binding properties of BINOL to various metals may be manipulated with greater control based on these (or related) residues.[3,12] Noteworthy is the level of chiral induction in the cyclization to the biaryl, with de's usually around 90% or better, judging from relative peak integrations in their 500 MHz proton NMR spectra.



In summary, a new series of nonracemic, substituted *cyclo*-BINOLs has been constructed,[13] the sequence being sufficiently general so as to offer many opportunities for structurally fine tuning this important type of ligand for use in asymmetric catalysis. Further applications of the tethered approach to polymer-bound systems, as well as (substituted) *cyclo*-BINAPs, will be reported in due course.

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References and Notes

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8. (a) See, for example, Sharp, M. J.; Chang, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093, and references therein; (b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, H.; Kodama, S-I.; Nakajima, I.; Minato, A.; Kumada, M. *Bull Chem. Soc. Jpn.* **1976**, *49*, 1958.
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12. For a representative example, see Ishihara, K.; Kurihara, H. Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049.
13. A representative procedure (for the preparation of *cyclo*-BINOL **11**; *cf.* **Figure 1**) is as follows. To a solution of the precursor (200 mg, 0.334 mmol) in anhydrous acetonitrile (34 mL) in a round bottom flask was added $Mn(acac)_3$ (Aldrich, 174 mg, 0.401 mmol) at room temperature. The stirred reaction mixture was heated to 70 °C for 3 h after which it was cooled to rt and the solvent evaporated *in vacuo*. A 2% aqueous EDTA solution (20 mL) was added along with ethyl acetate (20 mL) and the mixture stirred vigorously for 2 h. The ethyl acetate layer was separated, washed with water (2 x 20 mL), and dried over anhydrous $MgSO_4$. Filtration and solvent removal *in vacuo* afforded crude material which was purified by column chromatography (silica gel; 4:1 EtOAc: pet ether) to give a colorless solid (163 mg, 83%).