Catalytic conjugate addition promoted by the copper(I)-monothiobinaphthol system. Part 3.[1] Comparison of three thiolate-based catalytic systems

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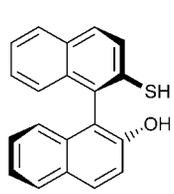
Monothiobinaphthol (MTB, 2-hydroxy-2′-mercapto-1,1′-binaphthyl undergoes *S*-alkylation with BuBr and α,ω-dihalides to afford thioether species. The precursor to MTB, 2-(*N*,*N*-dimethylcarbamoyloxy)-2′-(*N*,*N*-dimethylcarbamoylthio)-1,1′-binaphthyl, undergoes anionic Fries rearrangement of the *O*-aryl carbamate to afford a crystallographically characterised amido species. Hydrolysis of this species affords the 3-C(O)NMe_2 analogue of MTB. These MTB-based ligand systems have been tested in asymmetric conjugate addition reactions of cyclic and acyclic enones and compared with 1,1′-bi(2-thionaphthol). Active catalysts are formed in all cases but only low enantioselectivities are realised (0–55% ee). Full conditions for the separation of the enantiomeric conjugate addition products are reported.

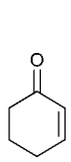
Introduction

Recently we have reported convenient large-scale preparations of both racemic and enantiopure monothiobinaphthol (MTB) **1**.[1,2] The presence of both "hard"[3] naphtholate and "soft"[3] thionaphtholate donors in the deprotonated ligand make this an ideal system for the formation of bimetallic catalysts containing mixed "hard/soft" metals for use in asymmetric catalysis. For example, LiGa(MTB′)$_2$ (MTB′ = dianion of MTB **1**) is a highly selective catalyst for enantioselective ketone hydroboration.[4] Because of their bimetallic nature cuprate species were selected by us as potential targets in which to include enantiopure MTB (and related) ligands and to study these in catalytic asymmetric conjugate addition (ACA) reactions.

An effective ACA system requires the catalyst to deliver the organometallic reagent to one enantioface of the enone and that attack at the carbonyl carbon is prevented.[5,6] General systems that achieve this with all classes of enone have not yet been realised. Cyclohexenone **2** is a popular model compound for cyclic enones and recently a chiral copper–phosphine complex[6,7] has been shown to induce the addition of $ZnEt_2$ to **2** in very high ee. However, few catalytic systems have been introduced that will promote the 1,4-addition of organometallics to linear enones in significant ee.[7,8] Some popular model compounds in this area are benzylidene acetone **3a** and (*E*)-non-3-en-2-one **3b**. This paper reports our continuing study of thiolate ligand synthesis and their application to ACA reactions of enones **2**, **3b**, and **4**.



(R_a)-**1**



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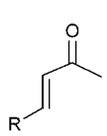
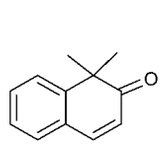


3a R = Ph
3b R = *n*-C_5H_{11}



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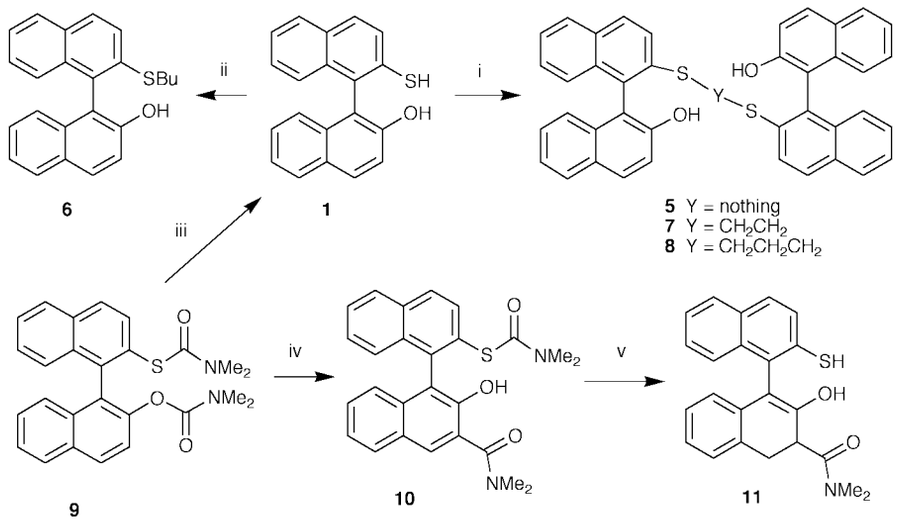
Results and discussion

Ligand modification

The ligand MTB **1** is available through literature transformation of (R_a)- or (S_a)-bi(2-naphthol).[1,2] Typically the enantiopurity of the ligand is assessed through non-selective oxidation to the disulfide **5** followed by assay of the *rac*/*meso* diastereomer ratio by ^{13}C NMR spectroscopy.[1] There is insufficient dispersion in the proton spectrum to accurately measure this ratio on moderate field instruments. We hoped that reaction of two MTB **1** units with an appropriate α,ω-dihalide would fashion related thioethers for which determination of the *rac*/*meso* diastereomer ratio would allow an alternative for ee assay in MTB **1** (Scheme 1). The selectivity in the thiolate alkylation was first checked by deprotonation of MTB **1** with BuLi followed by addition of BuBr. This reaction cleanly furnished **6** with no indication of any *O*-alkylation. Subsequent reaction of racemic (±)-MTB **1** with either 1,2-dibromoethane or 1,3-dibromopropane also cleanly afforded the thioethers **7** and **8** in good yield. For the *rac*/*meso* diastereomer ratio to accurately reflect the enantiopurity of the starting MTB **1** the reactions with $Br(CH_2)_nBr$ (n = 2,3), leading to **7** and **8** must show no innate diastereoselectivity themselves. Regrettably, this is not the case and the *rac* diastereomers predominate. Thus, it appears that oxidation of MTB **1** to the disulfide **5** is still currently the most suitable method for ee determination of samples of **1**.

The ligand MTB **1** is normally prepared by hydrolysis of compound **9**.[1] Because of our experience with lithiation and rearrangement of binaphthyl mono and dicarbamates,[9] we speculated that **9** would undergo directed lithiation at the 3 or 3′ positions in the presence of appropriate bases.[10] Lithiation attempts with various BuLi sources, in the presence or absence of additives led only to complex mixtures. However, low temperature treatment of **9** with LDA led to partial conversion of **9** to a new product, which could be separated from unreacted **9** by simple crystallisation from ethanol. Application of ^1H:^1H DQFCOSY spectrum allowed complete assignment of all



Scheme 1 *Reagents and conditions*: i, for **5**, I_2, NEt_3, 0 °C, 1 h; for **7** and **8**, BuLi, 0 °C, then $Br(CH_2)_nBr$ (n = 2,3), 16 h; ii, BuLi, 0 °C then BuBr, 16 h; iii, KOH, methanol–water reflux, 24 h; iv, LDA, −75 °C, 1 h; v, NaOH, methanol–water, 6 h.

Table 1 Crystallographic and refinement data for (±)-**10**

Molecular formula	$C_{26}H_{24}N_2O_3S$
Molecular weight	444.53
Temperature/K	293(2)
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	
a/Å	14.950(9)
b/Å	8.946(2)
c/Å	17.391(4)
β/°	90.49(3)
Volume/Å^3	2325.8(15)
Z	4
μ/mm^{-1}	0.169
Measured reflections	5212
Independent reflections	2494
R_{int}	0.1204
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0745$, $wR_2 = 0.1862$
S	0.809

proton environments and suggested structure **10**. In particular, the appearance of C(4)–H as a slightly broadened singlet showing a long range (zig-zag, 1,5) coupling to C(8)–H allowed differentiation of the two naphthyl rings. The connectivity in the two separate naphthylene rings could be confirmed in the NOESY spectrum of **10**. The $C(O)NMe_2$ signals for **10** occur as three broad singlets, two of which are overlapping. The signal at δ_H 3.07 is assigned to the *S*-aryl thiocarbamate based on the assumption of greater conformational freedom for the $SC(O)NMe_2$ group and by comparison with the spectra of related compounds. The specific rearrangement of the *O*-aryl carbamate in **9** was confirmed by a crystallographic study on (±)-**10**. The crystallographic and refinement data are given in Table 1. Interestingly the unit cell comprises of a hydrogen bonded dimer in the solid state and this is shown in Fig. 1 together with some selected bond distance and angle data. We have noted before that hydrogen bonding is often an important feature in the structure and reactivity of binaphthyl molecules containing $C(O)NR_2$ functions.[1]

The anionic Fries rearrangement reaction is known to be induced in compounds of this type and, in particular, for those bearing *N*,*N*-dimethyl carbamates such rearrangements are believed to take place from *ortho*-lithiated species. In our case all attempts to intercept any mono- or dilithiated species derived from **9** with either D_2O or MeI were not successful. Additionally, no trace of rearrangement of the *S*-aryl carbamate could be detected for reactions of **9** in the presence of excess LDA (5 or 10 equivalents). The use of one equivalent of LDA only lowered the yield of **10**. Treatment of **10** with sodium

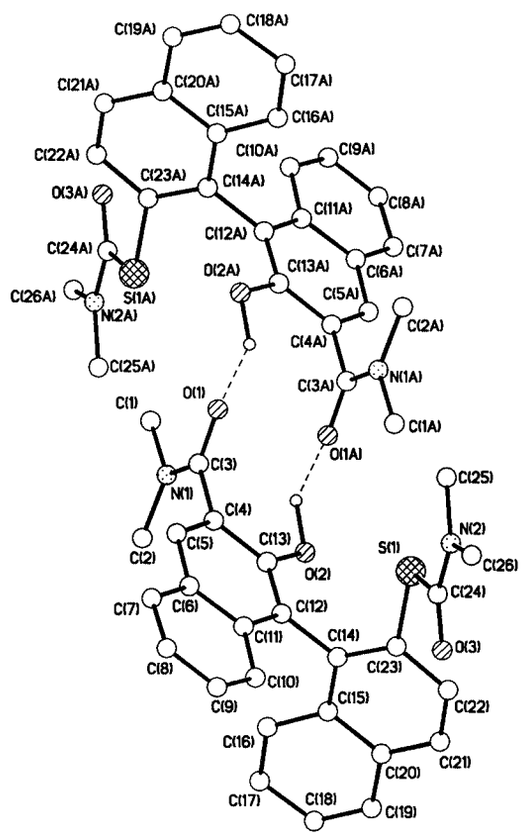


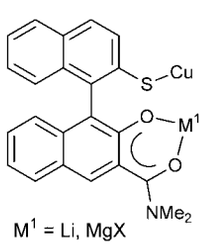
Fig. 1 Hydrogen-bonded dimer found in the crystal structure of (±)-**10**. Selected bond distances (Å) and angles (°): N(1)–C(1) 1.476(10), N(1)–C(2) 1.458(10), N(1)–C(3) 1.322(9), O(1)–C(3) 1.240(9), C(3)–C(4) 1.507(10), C(4)–C(13) 1.414(10), O(2)–C(13) 1.379(8), C(12)–C(13) 1.373(10), C(12)–C(14) 1.501(10), C(14)–C(23) 1.373(9), S(1)–C(23) 1.772(8), S(1)–C(24) 1.763(9), O(3)–C(24) 1.206(10), N(2)–C(25) 1.437(10), N(2)–C(26) 1.421(10), H(2)···O(1) (at $1 - x$, $1 - y$, $1 - z$) 1.571; C(2)–N(1)–C(1) 114.8(8), C(3)–N(1)–C(1) 120.5(7), C(3)–N(1)–C(2) 124.6(8), O(1)–C(3)–N(1) 123.4(8), O(1)–C(3)–C(4) 118.1(8), N(1)–C(3)–C(4) 118.5(8), C(23)–S(1)–C(24) 102.5(5), O(3)–C(24)–N(2) 123.2(9), O(3)–C(24)–S(1) 123.4(8), C(24)–N(2)–C(26) 119.6(8), C(24)–N(2)–C(25) 121.5(8), C(26)–N(2)–C(25) 118.9(8).

hydroxide in refluxing methanol caused selective hydrolysis of the *S*-aryl carbamate and fashioned **11** after purification by column chromatography. The presence of the amido function in **11** offers the opportunity for *ortho* chelation of *O*-ligated cations as in structure **12**. Compound **11** is rather more air

Table 2 Asymmetric conjugate addition reactions of organometallics to enones **2**–**4** in THF

Run	Ligand (mol%)	Copper Source (mol%)	RM	Enone	Method[a]	1,4-Addition yield(%)[b]	ee (%) (hand)
1	**1** (3–12)	K[d] (5)	BuMgCl	**2**	A,B,C (in Et_2O)	60–82	−3–6 (*S*)
2	**1** (12)	K (5)	BuMgCl	**2**	B	71–100	5 (*S*)
3	**1** (6)	K (5)	BuMgCl	**2**	A	88–100	0–6 (*R*) 23[e]
4	**1** (12)	K (5)	BuMgCl	**2**	C	85–99	11 (*R*)
5	**1** (12)	K (5)	BuMgCl	**2**	A + DMI[f]	64	13 (*R*)
6	**1** (12)	K (10)	BuLi	**2**	A	53–66	9–13 (*R*)
7	**1** (24)	K (10)	BuLi	**2**	A	52	23 (*R*)
8	**1** (6–12)	K (5)	BuLi	**2**	B,C	62–78	6–14 (*R*)
9	**1** (24)	D[g] (10)	BuLi	**2**	A	61	16 (*R*)
10	**1** (24)	K (10)	BuLi	**2**	A + DMI[f]	86	10 (*R*)
11	**1** (100)	K (100)	BuLi	**2**	modified A[h]	40	4 (*S*)
12	**1** (200)	K (100)	BuLi	**2**	modified A[h]	32	4 (*S*)
13	**1** (10)	K (10)	MeMgBr	**3b**	A	72	<2
14	**1** (20)	K (10)	MeMgBr	**3b**	A	48	<2
15	**1** (24)	K (10)	MeMgBr	**4**	A	35	<5
16	**11** (10)	K (10)	MeMgBr	**3b**	A	82	<2
17	**13** (24)	K (10)	BuMgCl	**2**	A	30	55 (*R*)
18	**1** (10)	K (10)	$ZnEt_2$	**2**	A,B	66–84	35–36 (*R*)
19	**11** (10)	K (10)	$ZnEt_2$	**2**	A	25	6 (*R*)
20	**1** (10)	K (10)	$AlEt_3$	**2**	A,B,C	2–4	nd[i]
21	**1** (10)	K (10)	$ZnEt_2$	**3b**	A	35	13 (+)[j]
22	**11** (10)	K (10)	$ZnEt_2$	**3b**	A	12	4 (−)[j]
23	**11** (20)	K (10)	$AlMe_3$	**3b**	A	7	14 (+)[j]

[a] Addition modes: A = sequential addition of organometallic then enone, B = addition of organometallic to enone, C = addition of enone to organometallic. See Experimental section for full details. [b] Determined by GC (BP-20 column, reproducibility ±3%), isolated yields were typically ~10% lower. [c] Determined by GC, see Table 3. Sense of asymmetric induction by comparison with authentic samples; all reactions carried out with (R_a) ligands. [d] K = $[Cu(MeCN)_4]BF_4$. [e] Not highly reproducible, normal range 0–6%. [f] DMI = 1,3-dimethylimidazolidin-2-one. [g] D = $CuBr{\cdot}SMe_2$. [h] Stoichiometric reaction (see Experimental section for full details). [i] n/d = not determined. [j] Absolute stereochemistry not known.



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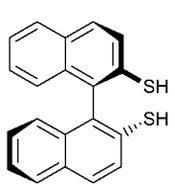

(R_a)-**13**

sensitive than the parent compound **1**. The aerobic reactivity of **11** appears comparable to the dithiobinaphthol compound DTB **13**.

Asymmetric conjugate addition studies

The ligands MTB (R_a)-**1**, (R_a)-**11**, and (R_a)-**13** were compared in copper-catalysed asymmetric conjugate addition (ACA) reactions of various combinations of Grignard reagents, BuLi, $ZnEt_2$, or $AlMe_3$ with enones **2**–**4**. For simplicity all of the catalysts used in this study were prepared *in situ* by treating a mixture of the ligand and copper source with one equivalent of organometallic reagent per acidic proton in the added ligand at −20 °C.

Grignard and organolithium reagents. Initial experiments with BuMgCl and cyclohexenone **2** revealed that the best solvent for the ACA reaction is THF. All subsequent reactions were carried out in THF. The enantioselectivities realised in reactions carried out in Et_2O are negligible regardless of the experimental method or Cu^I:MTB (R_a)-**1** ratio (2:1, 1:1, or 1:2) (Table 2, entry 1). Reactions carried out in THF showed that some slight selectivity is observed if **2** is added to a mixture of excess BuMgCl and catalyst (method C) as opposed to sequential addition of organometallic enone (method A) or slow addition of BuMgCl to a mixture of enone (in excess) and catalyst (method B) (entries 2–5). Additionally, the enantiomer of the product formed is found to depend on the addition mode (entries 2 and 4). The sense of optical induction could also be changed by addition of the polar co-solvent 1,3-dimethylimidazolidin-2-one (entry 5). The enantioselectivity of the catalyst formed from 1:1 mixtures of $[Cu(MeCN)_4]BF_4$ and (R_a)-**1** is batch dependent. Typically the enantioselectivities realised were low but on one occasion a more significant induction was realised (entry 3). Highly reproducible yields and enantioselectivities are realised for conjugate addition reactions using BuLi (runs 6–8). The highest enantioselectivity realised (23%) is attained with a 1:2 Cu^I:MTB **1** ratio. Changing the copper source to $CuBr{\cdot}SMe_2$ (entry 9) or introducing a polar co-solvent (entry 10) lowered this selectivity. Reactions using Cu^{II} triflate or CuX (X = Cl, Br) gave similar results. The stoichiometric cuprates prepared from either 1:1:3:1 or 1:2:4:1 mixtures of $[Cu(MeCN)_4]BF_4$]: (R_a)-**1**:BuLi:**2** gave only very low inductions (entries 11 and 12).

The poor selectivities realised in the ACA reactions of BuMgCl and BuLi with **2** catalysed by (R_a)-**1** could be explained by ligand racemisation during the catalysis. This appears not to be the case. Compound (R_a)-**1** recovered from a number of runs, when oxidised with I_2, led only to enantiomerically pure *rac* **5**. Alternatively, it may be that *in situ* reactions of $[Cu(MeCN)_4]BF_4$ and MTB (R_a)-**1** with organometallics form mixtures of organocuprate species (one or more showing low enantioselectivity) rather than a single selective catalyst. Some credence to the ability of MTB (R_a)-**1** to form mixtures of species with copper(I) sources is given by analysis of the crude inorganic product obtained once the product 3-butylcyclohexanone had been distilled from the reaction mixture. On dissolving in dichloromethane this residue frequently precipitates very reactive, highly solvated, yellow needles whose nature precludes their analysis by most techniques. However, FAB analysis of theses crystals clearly indicates the presence of $Cu_3(MTB')_2$, $Cu_4(MTB')_3$, and $Cu_5(MTB')_3$ species [MTB′ = dianion of MTB (R_a)-**1**]. Finally, it maybe that the catalyst derived from Cu^I/ MTB (R_a)-**1** has an inappropriate structure for enatioselective additions to **2**. To help decide

between these possibilities further experiments were carried out.

In contrast to some organoaluminum catalysts we have described recently,[8a] the MTB (R_a)-**1** system was not effective for 1,4-methyl addition to (*E*)-non-3-en-2-one **3b** (Table 2, entries 13 and 14) using MeMgBr. Even using 100 mol% MTB (R_a)-**1** the product ee remained low (7%). Similarly enone **4** proved unresponsive under a variety of conditions to MeMgX addition of which entry 15 is representative. Equivalent reactions with MeLi led only to 1,2-addition reactions. Use of the *ortho* chelate ligand MTB (R_a)-**11** increased the chemical yield of 1,4-methyl addition to **3b** when using MeMgBr but no significant asymmetric induction could be realised (run 16). Use of the DTB ligand (R_a)-**13** did fashion an enantioselective catalyst for the addition of BuLi to cyclohexenone **2** (run 17). However, in this case the chemical yield of the 1,4-addition product is low.

Organozinc and organoaluminium reagents. The catalytic species formed from the ligands (R_a)-**1** and (R_a)-**11** in the presence of $ZnEt_2$ and AlR_3 (R = Me, Et) were also investigated. Low but significant levels of stereoinduction are realised in reactions of $ZnEt_2$ with **2** catalysed by (R_a)-**1** in the presence of $[Cu(MeCN)_4]BF_4$ (Table 2, entry 18). Interestingly the sense of the optical induction is reversed by use of ligand (R_a)-**11** indicating that although the *ortho* amido function clearly plays an important coordinative role this is not helpful to the enantioselectivity (entry 19). Switching the terminal organometallic to $AlEt_3$ with ligand (R_a)-**1** essentially suppressed the conjugate addition reaction (entry 20). Additionally, only poor reactivity was realised in 1,4-additions to linear enones using (R_a)-**1** (entries 21–23).

Conclusions

Active catalysts showing significant activity and high chemoselectivity towards conjugate addition are formed from (R_a)-**1** and (R_a)-**11** and copper(I) sources. However, the enantioselectivities demonstrated by these catalysts with a range of enones and organometallic sources are low. We note that Seebach has recently reported similar dianionic S/O ligands based on TADDOL cores and that these show improved enantioselectivities (20–84% ee) for addition of Grignard reagents to cycloalkanones.[11] Studies are continuing in our laboratory to identify alternative sulfur-based systems showing improved enatioselectivity.[8a]

Experimental

General

Procedures involving moisture sensitive intermediates were carried out under nitrogen atmospheres using standard Schlenk techniques. Tetrahydrofuran (THF) was distilled from sodium–benzophenone immediately prior to use. Specific rotations were measured using an Optical Activity AA-10 automatic polarimeter at ambient conditions and are given in 10^{-1} deg cm^2 g^{-1}; *c* is in g per 100 cm^3 of solvent. Column chromatography and TLC analyses were performed on silica gel, Rhône Poulenc Sorbsil and Merck Kieselgel 60 $F_{254+366}$, respectively. Infrared spectra were recorded using a Perkin-Elmer 983 G infrared spectrophotometer and a Perkin-Elmer 882 infrared spectrophotometer. Proton and ^{13}C NMR spectra were recorded on either JEOL (JNM-GX270, JNM-LA400) or Bruker (WH 360) spectrometers using tetramethylsilane as standard; *J* values are given in Hz. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were obtained on a Finnigan-MAT 1020 (electron impact ionisation, EI) machine and a VG-ZAB (fast atom bombardment ionisation, FAB) machine (EPSRC Service, Swansea). Elemental analyses were performed using a Fisons Instruments EA 1108 CHN elemental analyser. Compounds **1**, **4**, and **9** were obtained by literature procedures.[1,12] All organometallic reagents were commercial products (Aldrich).

S-Butyl-2-hydroxy-2′-mercapto-1,1′-binaphthyl 6

A solution of BuLi in hexanes (0.7 cm^3, 2.5 M, 1.74 mmol) was added to a solution of MTB **1** (0.50 g, 1.65 mmol) in THF (10 cm^3) at 0 °C under an inert atmosphere. The solution was allowed to stir (30 min) before the addition of neat BuBr (187 μL, 1.74 mmol). The reaction mixture was allowed to warm slowly to room temperature (16 h). After the addition of CH_2Cl_2, the solution was washed with water and dried over Na_2SO_4. Filtration and evaporation under reduced pressure gave the crude product as a colourless oil. Purification by column chromatography on flash silica, using CH_2Cl_2 as the eluent, gave **6** as a colourless oil, 0.50 g (85%); δ_H(270 MHz; $CDCl_3$) 0.83 (3 H, t, *J* 7.1, Me), 1.25–1.40 (2 H, sextet, *J* 7.1, CH_2), 1.48–1.60 (2 H, m , CH_2), 2.80–2.97 (2 H, m, CH_2), 4.80 (1 H, s, OH), 6.96 [1 H, d, $J_{7,8 \text{ or } 7',8'}$ 8.3, C(8 or 8′)-H], 7.13 [1 H, d, $J_{7,8 \text{ or } 7',8'}$ 8.3, C(8 or 8′)-H], 7.35 [1 H, d, $J_{3,4 \text{ or } 3',4'}$ 8.8, C(3 or 3′)-H] overlapped by 7.19–7.45 [4 H, m, C(6,7,6′,7′)-H], 7.64 [1 H, d, $J_{3,4 \text{ or } 3',4'}$ 8.8, C(3 or 3′)-H], 7.84–8.00 [4 H, m, C(4,5,4′,5′)-H]; δ_C(67.8 MHz; $CDCl_3$) 13.6, 22.0, 31.2, 32.0, 116.9, 117.6, 123.5, 124.5 (2C), 125.1, 125.7, 126.7, 127.5, 128.2 (2C), 128.4, 129.2, 129.6, 130.3, 131.7, 133.3, 133.6, 137.9, 150.9; ν_{max}(KBr disc)/cm^{-1} 3530br, 3500br, 3410br, 3050s, 3000m, 2950s, 2920s, 2870m, 1610s, 1590s, 1580s, 1510s, 1500s, 1460s, 1430s, 1380s, 1340s, 1295m, 1270s, 1255s, 1205s, 1215s, 1175s, 1145s, 1135s, 1120s, 970m, 935m, 815s, 750s br; *m*/*z* (EI) 358 (M^+, 100%) [Found (HRMS): M^+, 358.1392. $C_{24}H_{22}OS$ requires *M* 358.1391].

Equivalent reactions using (R_a)-**1** afforded (R_a)-**6** showing $[a]_D$ −10 (*c* 5.0, $CHCl_3$).

1,2-Bis(2′-hydroxy-1,1′-binaphthyl-2-ylthio)ethane 7

A solution of BuLi in hexane (0.14 cm^3, 2.5 M, 0.33 mmol), followed by neat 1,2-dibromoethane (15 μl, 0.17 mmol) (**TOXIC**), was added to a stirred solution of MTB **1** (100 mg, 0.33 mmol) in THF (2 cm^3) at 0 °C under an inert atmosphere. The resultant bright yellow reaction mixture was stirred for 3 hours at 0 °C and allowed to warm to room temperature (16 h). After quenching with saturated $NH_4Cl_{(aq)}$, the solvents were evaporated under reduced pressure and water was added. The crude product was extracted with dichloromethane and this solution was dried over $MgSO_4$. Following filtration, evaporation to dryness gave the crude product as a fluffy white solid (124 mg, 60%, *rac*/*meso* ~ 4 : 1). The product was purified by flash chromatography (2 : 1 mixture of light petroleum and ethyl acetate eluent) to yield mostly the *rac* diastereomer; mp 89–91 °C; δ_H(270 MHz; $CDCl_3$) 2.93 (2 H, apparent s, CH_2), 4.56 (1 H, s, OH), 6.91 [1 H, d, $J_{8,7 \text{ or } 8',7'}$ 8.3, C(8 or 8′)-H], 7.10–7.33 (5 H, m, Ar), 7.46 [2 H, d, $J_{3,4 \text{ or } 3',4'}$ 8.8 C(3 or 3′)-H], 7.54–8.00 [4 H, m, C(4,5,4′,5′)-H], only half of the C_2-symmetric molecule is reported; traces of the *meso* compound were also apparent in the ^1H NMR spectrum; δ_C(67.8 MHz; $CDCl_3$) 25.6 (CH_2), 117.6, 123.6, 124.2, 124.37, 125.0, 125.3, 126.14, 126.8, 126.9, 127.6, 127.7, 128.2, 128.3 (2 C), 128.3, 129.1, 129.8, 130.4, 132.1, 150.8; ν_{max}(KBr disc)/cm^{-1} 3490br, 3400br, 3050m, 2950m, 1610m, 1590m, 1498m, 1390m, 1265m, 1200m, 1140m, 810s, 745s; *m*/*z* (EI) 630 (M^+, 1%), 313 (10), 302 (20), 301 (42), 267 (100) [Found (HRMS): M^+, 630.1685. $C_{42}H_{30}O_2S_2$ requires *M* 630.1687].

1,2-Bis(2′-hydroxy-1,1′-binaphthyl-2-ylthio)propane 8

A solution of BuLi in hexane (0.14 cm^3, 2.5 M, 0.33 mmol), followed by neat 1,3-dibromopropane (17 μL, 0.17 mmol) (**TOXIC**), was added to a stirred solution of MTB **1** (100 mg,

0.33 mmol) in THF (2 cm^3) at 0 °C under an inert atmosphere. The resultant bright yellow reaction mixture was stirred for 3 hours at 0 °C and allowed to warm to room temperature (16 h). After quenching with saturated $NH_4Cl_{(aq)}$, the solvents were evaporated and water was added. The crude product was extracted with dichloromethane and dried ($MgSO_4$). Following filtration, evaporation gave the crude product as a fluffy white solid (168 mg, 80% variable *rac–meso* mixture). The product was purified by column chromatography on flash silica, using a 3:1 mixture of dichloromethane and light petroleum as the eluent to yield mostly *rac*-**8**; mp 118–119 °C (decomp.); δ_H(400 MHz; $CDCl_3$) 1.69–1.74 (1 H, m, central CH_2), 2.68–2.85 (2 H, m, CH_2), 4.78 (1 H, s, OH), 6.78 [1 H, d, $J_{8,7 \text{ or } 8',7'}$ 8.3, C(8 or 8′)-H], 7.18 [1 H, d, $J_{3,4 \text{ or } 3',4'}$ 8.5, C(3 or 3′)-H] overlapped by 6.99–7.28 [4 H, m, C(6,6′,7,7′)-H], 7.30 [1 H, d, $J_{3,4 \text{ or } 3',4'}$ 8.0, C(3 or 3′)-H], 7.59 [1 H, d, $J_{5,6 \text{ or } 5',6'}$ 8.8, C(5 or 5′)-H], 7.65 [1 H, d, $J_{4,3 \text{ or } 4',3'}$ 8.0, C(4 or 4′)-H], 7.72 [1 H, d, $J_{4,3 \text{ or } 4',3'}$ 8.0, C(4 or 4′)-H], 7.77 [1 H, d, $J_{5,6 \text{ or } 5',6'}$ 8.8, C(5 or 5′)-H]; δ_C(100.4 MHz; $CDCl_3$) 28.5, 31.2, 116.8, 117.6, 123.4, 124.3, 125.2, 125.4, 125.9, 126.7, 127.5, 128.1, 128.2, 129.0, 129.3, 130.0, 130.2, 131.8, 133.3, 133.4, 136.5, 150.6; ν_{max}(KBr disc)/cm^{-1} 3500br, 3430br, 3060m, 2930m, 1620m, 1595m, 1505m, 1210m, 1145m, 815s, 750m; *m*/*z* 644 (M^+, 10%), 302 (7), 252 (15), 240 (20), 239 (85), 268 (100) [Found (HRMS) M^+, 644.1840. $C_{43}H_{32}O_2S_2$ requires *M* 644.1843].

2′-(*N*,*N*-Dimethylaminocarbonylthio)-2-hydroxy-3-(*N*,*N*-dimethylaminocarbonyl)-1,1′-binaphthyl 10

To a solution of diisopropylamine (0.90 g, 1.38 cm^3, 9.00 mmol) in THF (10 cm^3) at −40 °C under a nitrogen atmosphere was added dropwise a solution of BuLi (3.6 cm^3, 2.5 M, 9.00 mmol). When addition was complete the solution was cooled to −75 °C and a solution of compound **9** (2.00 g, 4.50 mmol) in tetrahydrofuran (100 cm^3) was added dropwise *via* a cannular over 10 minutes. The resulting dark brown coloured solution was stirred at −75 °C for 1.25 h and then quenched with distilled water (1.5 cm^3) and after warming to room temperature the solvent was removed and the resulting solid taken up in dichloromethane. This solution was washed with water (30 cm^3), dilute hydrochloric acid (2 × 30 cm^3) and water (2 × 30 cm^3). The organic layer was dried (Na_2SO_4) and the solvent removed to yield a cream coloured solid. This was recrystallised from hot ethanol to yield yellow needles of compound **10** (1.3 g, 65%), mp 199–203 °C (Found: C, 70.0; H, 5.5; N, 6.4; S, 7.1%. Calc. For $C_{26}H_{23}N_2O_3S$: C, 70.25; H, 5.4; N, 6.3; S, 7.2); δ_H NMR (360 MHz, $CDCl_3$) 2.86 [3 H, br s, C(O)N-(CH_3)(CH_3)], 2.91 [3 H, br s,C(O)N(CH_3)(CH_3)], 3.07 [6 H, br s, SC(O)N(CH_3)$_2$], 6.88 [1 H, dd, $J_{8,7}$ 8.4, $J_{8,6}$ <0.7, C(8)-H], 7.13 [1 H, d, $J_{8',7'}$ 7.8, C(8′)-H], 7.21 [1 H, td, $J_{7,5}$ 1.3, $J_{7,6}$, $J_{7,8}$ 8.4, C(7)-H], 7.27 [1 H, td, $J_{7',5'}$ 1.3, $J_{7',6'}$, $J_{7',8'}$ 8.4, C(7′)-H), 7.32 [1 H, td, $J_{6,8}$ 1.2, $J_{6,5}$, $J_{6,7}$ 8.1, C(6)-H], coincident peak 7.32 [1 H, s, C(2)-O, OH], 7.51 [1 H, td, $J_{6',8'}$ 1.2, $J_{6',5'}$, $J_{6',7'}$ 8.1, C(6′)-H], 7.75 [1H, d, $J_{3',4'}$ 8.6, C(3′)-H], 7.85 [1 H, d, $J_{5,6}$ 8.0, C(5)-H], 7.93 [1 H, d, $J_{5',6'}$ 8.3, C(5′)-H], 7.96 [1 H, s, C(4)-H], 8.00 [1 H, d, $J_{4',3'}$ 8.6, C(4′)-H]; δ_C NMR (67.8 MHz, $CDCl_3$) 37.1 (overlapped by a second broad NMe_2), 120.3, 124.0, 124.7, 126.6, 126.7, 127.1, 127.4, 128.15, 128.2, 128.4, 128.6, 128.8, 129.6, 133.3, 133.5, 134.2, 134.4, 139.6, 149.5, 168.7, 169.7; ν_{max}(KBr disc)/cm^{-1} 3430br, 3055w, 2922w, 1660s, 1558s, 1099m, 822m, 756m; *m*/*z* (EI) 444 (M^+, 9%).

Reaction of (R_a)-(+)-**9** gave (R_a)-**10** with $[\alpha]_D^{24}$ +313 (*c* 5.0, $CHCl_3$).

3-(*N*,*N*-Dimethylaminocarbonyl)-2-hydroxy-2′-mercapto-1,1′-binaphthyl, 11

Aqueous NaOH solution (10.9 cm^3, 2.5 M, 27.4 mmol) was added to a stirred solution of **10** (1.22 g, 2.74 mmol) in methanol (50 cm^3) under an inert atmosphere. The mixture was heated to reflux for 6 h, the solution was cooled to room temperature and quenched with dilute hydrochloric acid. The mixture was extracted into dichloromethane, washed with brine (30 cm^3), dried (Na_2SO_4) and filtered. This solution was evaporated to dryness to give a yellow oil. Column chromatography (CH_2Cl_2 containing 3% w/w EtOH) gave **11** as a reactive pale yellow solid (0.85 g, 83%); δ_H NMR (400 MHz, $CDCl_3$) 2.26 (6 H, s, -N-(CH_3)$_2$), 3.33 (1 H, s, SH), 7.04 [1 H, d, $J_{8',7'}$ 8.2, C(8′)-H], 7.13 [1 H, d, $J_{8,7}$ 8.0, C(8)-H], 7.27 [1 H, m, C(6 or 6′ or 7 or 7′)-H], 7.32 [1 H, m, C(6 or 6′ or 7 or 7′)-H], 7.38 [1 H, m, C(6 or 6′ or 7 or 7′)-H], 7.40 [1 H, m, C(6 or 6′ or 7 or 7′)-H], 7.57 [1 H, d, $J_{3,4}$ 8.5, C(3)-H], 7.83–7.92 [3 H, m, C(4′)-H, C(5)-H, C(5′)-H], 8.02 [1 H, s, C(4)-H], 8.61 (1 H, s, OH); ν_{max}(KBr disc)/cm^{-1} 3060w br, 2941w, 2579w, 1611s, 1305w, 811w, 755w; *m*/*z* (EI) 373 (M^+, 9%), 355 (100) [Found (HRMS): M^+, 373.1137. $C_{23}H_{19}NO_2S$ requires *M* 373.1137].

Reaction of (R_a)-**10** (2.12 g, 4.77 mmol) gave (R_a)-**11** with $[\alpha]_D^{22}$ *ca.* +102 (*c* 4.3, $CHCl_3$). Accurate polarimetry data on **11** could not be attained due to its reactive nature.

Crystal stucture of (±)-10

Crystals of (±)-**10** were grown by cooling of an absolute ethanol solution. X-Ray intensity data for **10** were collected on a Siemens P4 four-circle diffractometer and experimental details are listed in Table 1. The structure was solved by direct methods;[13] the hydroxy hydrogen was directly located and all other hydrogen atoms were included in idealised positions. Refinement was based on F^2,[13] and all non-hydrogen atoms were assigned anisotropic displacement parameters. CCDC reference number 207/361. See http://www.rsc.org/suppdata/p1/1999/3127 for crystallographic files in .cif format.

Representative catalytic additions

Catalytic solutions were prepared by addition of the appropriate organometallic (0.1, 0.2, or 0.4 mmol) to solutions of $[Cu(MeCN)_4]BF_4$ (0.05 or 0.10 mmol) and (R_a)-**1** or (R_a)-**11** in THF [2 cm^3 for BuMgCl and BuLi; 1 cm^3 for MeMgBr, $ZnEt_2$, and AlR_3 (R = Me, Et)] at −20 °C. The reactions were stirred (1–5 min) to fashion straw coloured solutions of active catalyst which were used immediately. All reactions were carried out in at least duplicate using addition modes A–C. Most reactions were conducted using 1.00 mmol of enone but some were tested at half this scale. Stoichiometric cuprate reactions were performed by deprotonating (R_a)-MTB **1** (1.00 or 2.00 mmol) with BuLi (2.00 mmol) or MeMgBr (2.00 or 4.00 mmol) in the presence of $[Cu(MeCN)_4]BF_4$ (1.00 mmol) in THF at −20 °C followed by sequential addition of either BuLi (1.00 mmol at −78 °C followed by warming for **2**) or MeMgBr (1.50 mmol at −20 °C for **3b**) and enone (**2** or **3b**, 1.00 mmol).

Addition mode A (sequential). Solutions of organometallic [BuMgCl (1.00 mmol, 2.0 M in THF); MeMgBr (1.50 mmol, 3.0 M in Et_2O); BuLi (1.00 mmol, 2.5 M in hexanes); $ZnEt_2$ (1.50 mmol, 1.0 M in hexanes); AlR_3 (R = Me, Et, 1.50 mmol, 1.0 M in hexanes)] and enones **2**, **3b** or **4** (1.00 mmol in THF, 0.5 cm^3) were added dropwise, sequentially (organometallic reagent first) to the stirred reaction mixture at −20 °C over 20 min. The reaction was then stirred at −20 °C for a further 20 min. The reaction mixtures were quenched with $HCl_{(aq.)}$ (2.0 M, 2 drops). Reactions were analysed directly (see below), or alternatively for **2**, the 3-butylcyclohexanone was isolated directly (Kugelrohr distillation 120 °C, 0.1 mmHg).

Addition mode B (organometallic to enone). The catalyst was prepared as described above and neat **2**, **3b**, or **4** (1.00 mmol) added to the solution at −20 °C. Subsequently the organometallic (1.00 to 1.50 mmol as described above) was added to the reaction mixture dropwise over 20 mins. The reaction was

Table 3 Analyses of the enantiomers of the 1,4-addition products

Enone	Addition	Column	Programme	Elution order/ min (hand)
2	Et	LIPODEX-A	75 °C isothermal	10.8 (*R*) 11.0 (*S*)
2	Bu	LIPODEX-A	70 °C ramped to 110 °C at 1 °C min^{-1}	33.3 (*R*) 33.6 (*S*)
3b	Me	(6-Me-2,3-pe-γ-CD)	70 °C isothermal	21.2 (−)[a] 22.8 (+)
3b	Et	(6-Me-2,3-pe-γ-CD)	75 °C isothermal	29.1 (−)[a] 30.2 (+)
4	Me	CYCLODEX-B	125 °C isothermal	61.2[b] 61.5

[a] Absolute stereochemistry not determined. [b] Absolute stereochemistry not determined; asymmetric induction too small for sign of optical rotation to be determined.

stirred for an additional 20 min at −20 °C, quenched, and assayed.

Addition mode C (enone to organometallic). The catalyst was prepared in the presence of an excess of organometallic reagent (1.00 to 1.50 mmol as described above). A solution of enone 2–4 (1.00 mmol in THF, 0.5 cm^3) was added (20 min, −20 °C). Stirring was continued (−20 °C, 20 min), the reaction quenched and assayed.

Analyses. Chemical yield and enantioselectivity data were obtained by GC analysis of the crude reaction mixtures (after filtration through a short pad of silica to remove copper salts). A Varian 3380 machine was used (head pressure = 621 mmHg, injection temperature = 150 °C, detector temperature (FID) = 200 °C, He carrier gas). Chemical yields were obtained using a BP-20 column and a pentadecane internal standard as described previously.[1]

Enantioselectivies were measured using either 30 m LIPODEX A, CYCLODEX-B (J. W. Scientific, equivalent to LIPODEX C), or octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin (6-Me-2,3-pe-γ-CD) columns.[14] Full details of the analyses are given in Table 3. Finally, we note the accidental exchange of compounds **23** (entries 13 and 14) and **24** (entries 15 and 16) in our previous publication (Table 2).[1]

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