Organic & Biomolecular Chemistry

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Organic & Biomolecular Chemistry

PAPER

Desymmetrizing reductive aldol cyclizations of enethioate derivatives of 1,3-diones catalyzed by a chiral copper hydride†‡

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A range of enethioate derivatives of 1,3-diones underwent reductive aldol cyclizations catalyzed by a chiral copper hydride generated *in situ* from 5 mol% TaniaPhos (SL-T001-1), 5 mol% Cu(OAc)$_2$·H$_2$O, 5 mol% bipyridine and 2.0 equiv. of PhSiH$_3$, to furnish polycyclic β-hydroxythioester products bearing three newly established contiguous stereocenters, with >98 : 2 dr and in up to 94% yield and 98% ee. The use of an amine such as bipyridine or 2,6-lutidine as additive results in an increase of the overall reaction rate. The major bicyclic aldol product has all substituents *cis* and can be rationalized by a reductively generated (*Z*)-enolate reacting with the dione *via* a cyclic transition state.

Introduction

Asymmetric domino reactions are a challenging and highly useful class of reactions to investigate and design.[1] Their potential to provide multiple transformations and bond formations in one step increases the complexity of the products without the concomitant increase in length, steps, reagents or solvents required in multi-step reactions and purifications. In all kinds of syntheses, including the total syntheses of natural products, the application of these reactions makes the overall sequence more efficient, economical and environmentally sound.[2,3]

Copper has emerged as an attractive metal for the mediation or catalysis of a variety of domino reactions.[4] Because of the abundance, comparatively low toxicity and costs of copper, copper-catalyzed reactions are highly practical and desirable, especially in the industrial setting.

Our interest in copper-mediated organic synthesis initiated our work on stoichiometric and catalytic reductions, particularly domino transformations, mediated by copper hydride species.[5] Based on this mild and non-basic method to generate enolates from Michael acceptors, we have developed reductive aldol cyclizations of enediones, keto-enoates, nitroalkenones and alkynediones.[6,7]

Research by Krische, Lam, Riant, Lipshutz, Shibasaki and Kanai, as well as other researchers, has developed asymmetric versions of the reductive intramolecular and intermolecular aldol reactions catalysed by copper, usefully generating aldol products with multiple functional groups and stereogenic centers with enantioselectivity.[8–10]
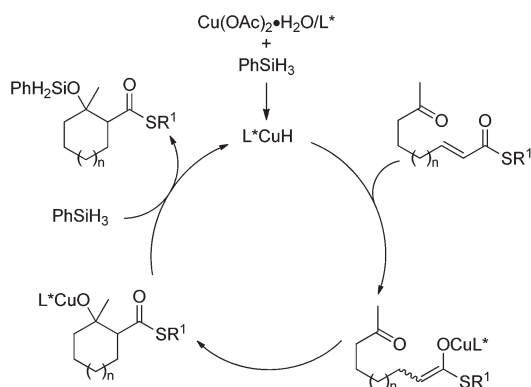
Recently, our research interest has turned to thioesters, versatile substrates which offer unique synthetic opportunities as precursors of nucleophiles as well as electrophiles.[11,12] We have reported on the use of copper ligated with BDP or dppf to effectively catalyse the conjugate reduction of unsaturated thioesters by silanes, which could proceed to completion without suffering detrimental catalyst poisoning. Furthermore, keto–enethioates continue on to an aldol cyclization after reduction in a domino process under these conditions.[13] We have also subsequently reported on the first asymmetric reductive aldol cyclization of symmetrical enethioate derivatives of 1,3-cyclopentandiones catalyzed by a chiral copper complex generated *in situ* from Tania-Phos, Cu(OAc)$_2$·H$_2$O and PhSiH$_3$.[14] Under optimal conditions, β-hydroxythioesters with a bicyclo[4.3.0]nonane carbon framework could be obtained with up to 96% ee. However, presumably due to the competitive interaction between copper and sulphur, this reductive aldol cyclization requires higher reaction temperatures and longer completion times than their oxoester counterpart substrates.[9]

The mechanism of this reductive aldol cyclization is proposed to be through the intermediacy of a chiral copper hydride complex, as shown in Scheme 1. The chiral copper hydride is generated *in situ* and induces conjugate reduction of the unsaturated thioester to offer a chiral copper thioester enolate. The enolate undergoes intramolecular aldol cyclization to generate copper aldolate. Metathesis with silane at this stage completes the catalytic cycle and regenerates chiral copper hydride.

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Scheme 1 Catalytic reductive aldol catalysed by Cu(I).

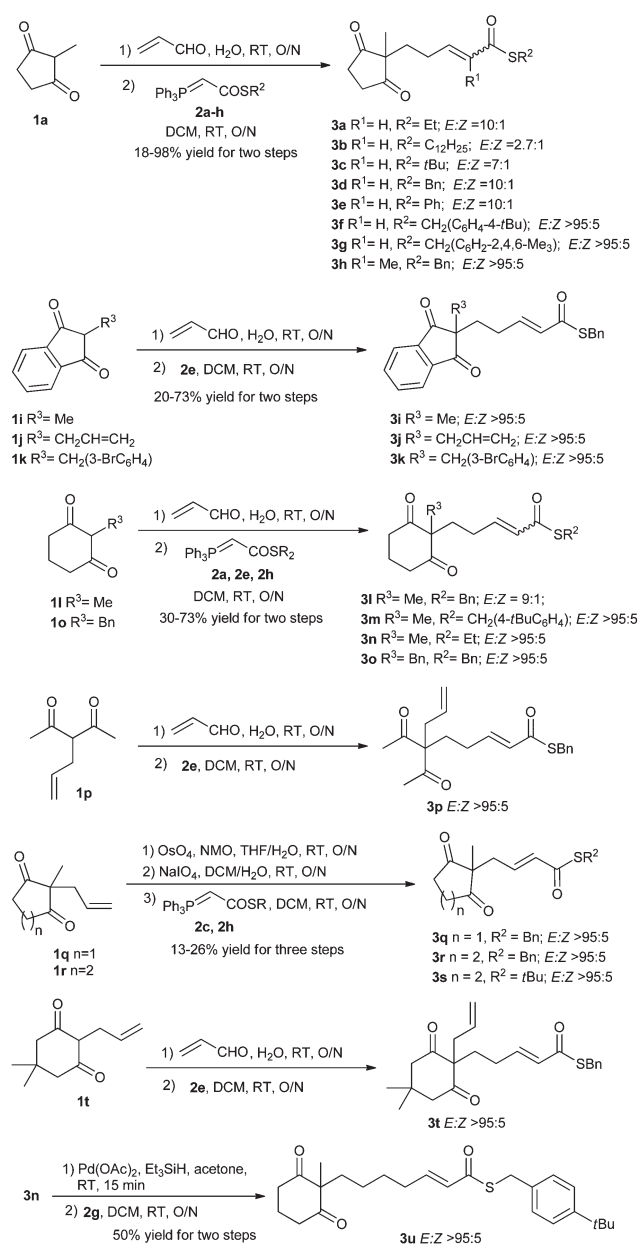**Scheme 2** Synthesis of enethioate derivatives of 1,3-dione.

Herein we report on the results of our continued investigations to explore the optimizations and scope of this reaction.

Results and discussion

We continued our studies to expand the scope of the enethioates examined in this reductive reaction. A range of prochiral enethioate derivatives **3** of 1,3-diones **1** were synthesized by a Wittig reaction with stabilized thioester phosphoranes in a two or three step sequence (Scheme 2). Generally 1,3-diones **1** were converted to their homologated aldehyde intermediates, which were then subjected to the Wittig reaction with phosphoranes **2a–h**,[15] to furnish the corresponding enethioate derivatives **3a–u**. All thioesters **3** were obtained predominantly or exclusively as the (*E*)-olefins, with only one case of low selectivity for **3b**. Although DMAP has been reported to induce the efficient equilibration of unsaturated thioesters to give the more stable geometric isomer,[16] the treatment of an isomeric mixture of **3a** with DMAP returned only a 34% yield of pure (*E*)-**3a** along with side products. Because *E* and *Z* isomers of **3a–h** are inseparable by chromatography, the isomeric mixtures are used as obtained from synthesis. However, this turned out not to be a critical issue, because the geometric isomerism of the substrates has not been observed to have a significant effect on the reaction rate, yields, diastereo- or enantioselectivity of this reductive aldol reaction (*vide infra*).

Our previous study has screened ligands **L1–8** (Fig. 1) in the copper-catalyzed reductive aldol cyclization reactions of **3a** in the presence of polymethylhydrosiloxane (PMHS), and found that hydroxythioester **4a** bearing three contiguous stereocenters was obtained as the major product.[14] Of these, TaniaPhos **L8** (SL-T001-1) afforded the highest yield and enantioselectivity (Scheme 3). We have further screened another member of the TaniaPhos family **L9** (SL-T002-1, Fig. 1) in this reaction, and have found, surprisingly, that the reaction did not produce any **4a**. It may be that, due to both the increase in electron donating ability and steric hindrance conferred by the cyclohexyl groups, **L9** promoted 1,2-reduction instead to give alcohol **5a** as a mixture of diastereomers in 38% yield, along with 37% recovered **3a**.

The variation of the mercaptan R[2] resulted in further improvements in enantioselectivity (Scheme 4). All substrates bearing R[2] larger than Et were reductively cyclized with 10–20% lower

yields. Those that have primary R[2] (**4a**, R[2] = Et; **4b**, R[2] = C$_{12}$H$_{25}$; **4d**, R[2] = Bn) were reduced with higher enantioselectivities than the hindered R[2] (**4c**, R[2] = *t*Bu; **4d**, R[2] = Ph), among which **4d** with R[2] = Bn reacted with the highest ee.

Silanes have been among the most effective stoichiometric reductants used in copper-catalyzed reductions, the metathesis driven by exploiting the strong Si–O bond formation that concomitantly promotes copper hydride regeneration. Our screening of several silanes revealed that phenylsilane is the most reactive and it significantly reduced the time required for complete reaction (Table 1, entry 1). Except for PhMe$_2$SiH which appeared to be unable to undergo effective metathesis (Table 1, entry 5), the dr and the ee remained virtually the same regardless of the identity of the silane; only the reaction time and, to a lesser extent, the yields were affected. This observation, together with the
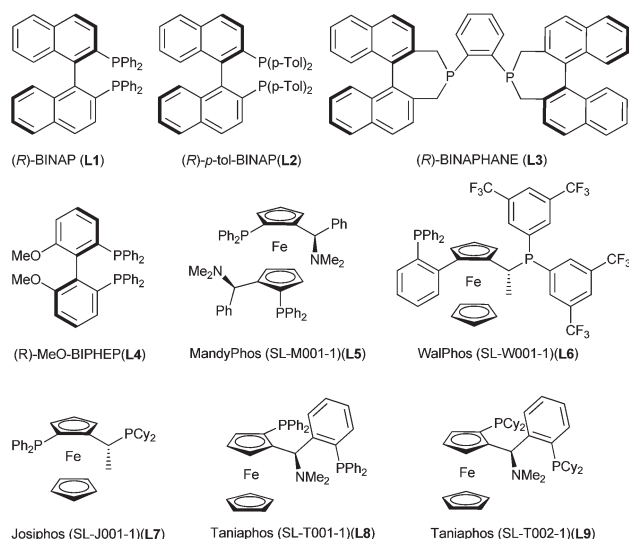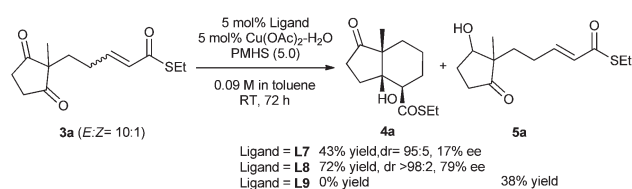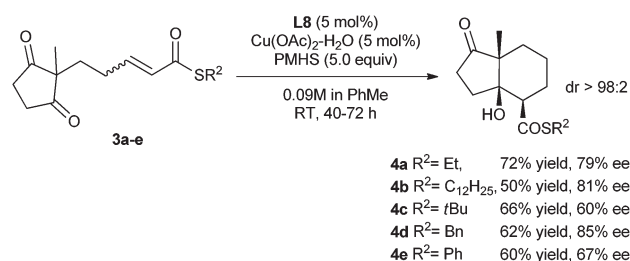
(R)-BINAP (L1)

(R)-p-tol-BINAP(L2)

(R)-BINAPHANE (L3)

(R)-MeO-BIPHEP(L4)

MandyPhos (SL-M001-1)(L5)

WalPhos (SL-W001-1)(L6)

Josiphos (SL-J001-1)(L7)

Taniaphos (SL-T001-1)(L8)

Taniaphos (SL-T002-1)(L9)

Fig. 1 Chiral bisphosphine ligands.

5 mol% Ligand
5 mol% Cu(OAc)$_2$-H$_2$O
PMHS (5.0)

0.09 M in toluene
RT, 72 h

3a (E:Z= 10:1)

4a + **5a**

Ligand = L7 43% yield,dr= 95:5, 17% ee
Ligand = L8 72% yield, dr >98:2, 79% ee
Ligand = L9 0% yield

5a 38% yield

Scheme 3 Copper-catalyzed reductions of **3a**.

L8 (5 mol%)
Cu(OAc)$_2$-H$_2$O (5 mol%)
PMHS (5.0 equiv)

0.09M in PhMe
RT, 40-72 h

3a-e

dr > 98:2

4a R^2= Et,   72% yield, 79% ee
4b R^2= C$_{12}$H$_{25}$, 50% yield, 81% ee
4c R^2= tBu,   66% yield, 60% ee
4d R^2= Bn,   62% yield, 85% ee
4e R^2= Ph,   60% yield, 67% ee

Scheme 4 The effect of R^1 on enantioselectivity.

Table 1 Screening of reductants

TaniaPhos **L8** (5 mol%)
Cu(OAc)$_2$-H$_2$O (5 mol%)
Reductant (2.0 eq)

0.9M in PhMe
RT, t

3d (E:Z= 10:1)

4d

Entry	Reductant	t (h)	Yield[a]	dr	ee[b] (%)
1	PhSiH$_3$	4	83%	>98 : 2	84
2	Ph$_2$SiH$_2$	16	82%	>98 : 2	83
3	(EtO)$_2$MeSiH	48	71%	>98 : 2	84
4	PMHS	62	62%	>98 : 2	85
5	PhMe$_2$SiH	48	NR	—	—
6	PinBH	16	74%	>98 : 2	75

[a] Isolated yields. [b] Determined by HPLC on a CHIRACEL AY-3 column.

Table 2 Screening of amine additives

TaniaPhos **L8** (5 mol%)
Cu(OAc)$_2$•H$_2$O (5 mol%)
PhSiH$_3$ (2.0 eq.)
additive (X mol%)

0.09M in PhMe
-20 °C, t

3d (E:Z= 10:1)

4d

Entry	Additive	X	t (h)	Yield[a]	dr	ee[b] (%)
1	None	—	40	81	>98 : 2	91
2	Pyridine	10	11	85	>98 : 2	90
3	2,6-Lutidine	5	12	75	>98 : 2	90
4	2,6-Lutidine	10	11	87	>98 : 2	90
5	Bipy	5	18	84	>98 : 2	90
6[b]	Phenanthroline	5	5	62	>98 : 2	90

[a] Isolated yields. [b] Determined by HPLC on a CHIRACEL AY-3 column.

TaniaPhos **L8** (5 mol%)
CuOAc (5 mol%)
PhSiH$_3$ (2.0 eq.), bipy (5 mol%)

0.09M in PhMe, -10 °C, 12 h
80% yield, >98:2 dr
90%ee

(E)-**3d**

4d

Scheme 5 Reduction of pure (E)-**3d**.

significant enantioselectivity in the reaction that has been induced as a result of the ligand on copper, supports the mechanism (Scheme 1) that the aldol reaction occurred via the copper enolate intermediates, not through the silyl enol ethers, and that the role of the silane is post-cyclization and affects the rate of the ensuing copper hydride regeneration from the aldolate.[17] This also suggests that copper hydride regeneration, and not conjugate reduction or aldol cyclization, is the rate limiting step in the reduction of substrates such as **3d**. We also examined pinacolborane (PinBH) as a reductant (Table 1, entry 6) in this reaction. While the reductive aldol reaction proceeded effectively, both the yield and the ee of **4d** obtained were inferior to those obtained using phenylsilane.

There have been a number of reports of catalytic asymmetric reactions whose enantioselectivities are increased by the addition of achiral ligands that operate by modifying the coordination sphere and magnifying the asymmetric environment.[18] However, when we screened several amine additives in this reaction (Table 2), we found that the diastereo- and enantioselectivity of
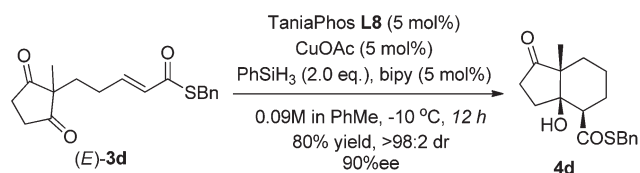
the reaction remained unchanged, but the reaction rates were increased, thereby reducing the time required for complete reaction. For example, the reaction of **3d** requires about 40 h at −20 °C (Table 2, entry 1), but in the presence of 5 mol% 2,6-lutidine or bipyridine (bipy) (Table 2, entries 3 and 5), the reaction could be complete in 12 and 18 h respectively, reducing the reaction time by two-thirds to half.

Similarly, pure (E)-**3d** was reduced in approximately 12 h in the presence of bipy to give an 80% yield of **4d** with the same 90% ee (Scheme 5), demonstrating that the E/Z ratio of the substrate does not have a significant effect on the outcome of the reaction.[19]
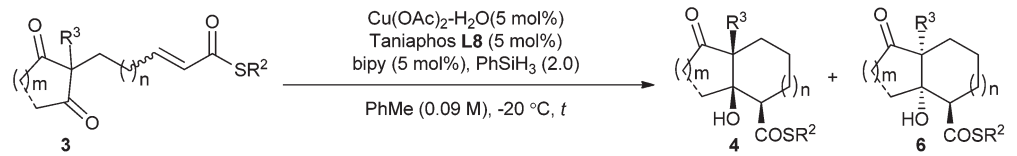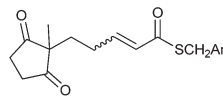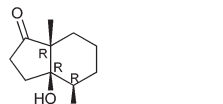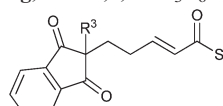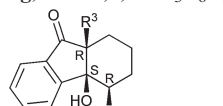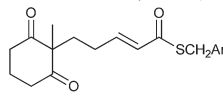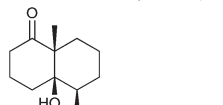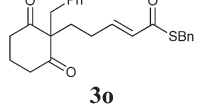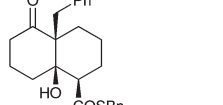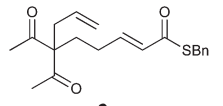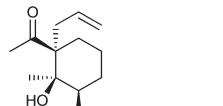
At this time, we surmise that the role of the amine does not appear to be a ligand to the copper enolate, as there has been no

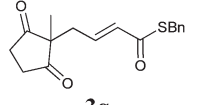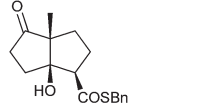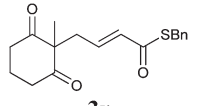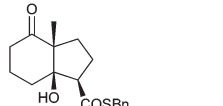difference observed in the ee of the cyclizations, and it may be related to post-reduction and post-cyclization events, for example, facilitating metathesis in some way to exert its rate-accelerating effect.

Nevertheless, the discovery of the rate enhancement of the reductive aldol reaction of enethioates in the presence of amines facilitates the optimization of enantioselectivity by allowing us to carry out the reactions at lower temperatures, and completing them in a more practical time scale. We therefore expanded and explored the scope of enethioates that can undergo this chiral copper-catalyzed desymmetrizing reductive aldol reaction, at −20 °C in the presence of bipy as an additive. Table 3 shows the

Table 3 Reductive aldol cyclizations of **3** with bipyridine as additive

Entry	Enethioates 3	t^a (h)	Major products	Yield^{a,b}	dr (**4** : **6**)^a	ee^{a,c} (%)
1	**3d**, Ar = Ph	18 (40)	**4d**,^{d} Ar = Ph	84% (84%)	>98 : 2 (>98 : 2)	90 (90)
2	**3f**, Ar = 4-tBuC$_6$H$_4$	15 (24)	**4f**, Ar = 4-tBuC$_6$H$_4$	94% (75%)	>98 : 2 (>98 : 2)	90 (91)
3	**3g**, Ar = 2,4,6-Me$_3$C$_6$H$_2$	15 (40)	**4g**, Ar = 2,4,6-Me$_3$C$_6$H$_2$	93% (64%)	>98 : 2 (>98 : 2)	93 (89)
4[20]	**3i**, R^3 = Me	(120)	**4i**,^{d} R^3 = Me	(71^e)	(>98 : 2)	(96)
5	**3j**, R^3 = CH$_2$CH=CH$_2$	48 (120)	**4j**, R^3 = CH$_2$CH=CH$_2$	60 (54^f)	87 : 13 (>98 : 2)	95/73 (95)
6	**3k**, R^3 = CH$_2$(3-BrC$_6$H$_4$)	30 (96)	**4k**, R^3 = CH$_2$(3-BrC$_6$H$_4$)	65 (63)	78 : 22 (81 : 19)	98/91 (97/92)
7	**3l**, Ar = Ph	15 (18)	**4l**, Ar = Ph	72 (73)	>98 : 2 (88 : 12)	93 (85/68)
8	**3m**, Ar = 4-tBuC$_6$H$_4$	20	**4m**, Ar = 4-tBuC$_6$H$_4$	86	90 : 10	88/74
9	**3o**	20	**4o**	65	>98 : 2	93
10	**3p**	(18)	**4p**	(35^g)	(>98 : 2)	(68)
11	**3q**	18 (21)	**4q**	56 (57)	>98 : 2 (>98 : 2)	27 (30)
12	**3r**	7 (21)	**4r**	44 (35)	>98 : 2 (>98 : 2)	59 (59)

^{a} Results with no bipy/−10 °C, in parentheses. ^{b} Isolated yields. ^{c} ee determined by HPLC. ^{d} Absolute stereochemistry determined for **4d**, **4i**. ^{e} 13% recovered **3i**. ^{f} 18% recovered **3j**. ^{g} 17% simple conjugate reduction product.

scope of the reductive cyclizations of a spectrum of enethioates **3**. Also shown in parentheses are the results of the reduction of the same substrates at a slightly higher temperature of −10 °C in the absence of bipy for comparison.

It can be seen that in all cases of substrates **3**, the presence of bipy resulted in an overall decrease of 15–60% in the time required for complete reaction. The same all-*cis* diastereomer **4** was obtained as the major or exclusive bicyclic aldol product in all cases. The diastereoselectivity was very high, and in many reactions, no other diastereomer was observed in the ^{1}H NMR spectra of the crude reaction mixtures. In the few cases where a minor aldol diastereomer was observable (Table 3, entries 5–8), it was determined to have the structure **6**, having a *cis–trans* stereochemistry as shown.

The yields of the reactions, without or with the additive, were similar, but in some cases they were improved in the presence of bipy, as in the reductions of enethioates **3g** and **3h** (Table 3, entries 2 and 3). The dr and the ee were also approximately the same. Only in the reductions of **3g** and **3l** was there a slight increase of 4–8% in the ee in the presence of bipyridine (Table 3, entries 3 and 7), which may be a result of conducting the reaction at a slightly lower temperature.

Examining the scope of the substrates reveals that the copper-catalyzed reductive aldol cyclization with **L8** was most effective for generating six-membered ring aldols. Substrates **3a–3k** underwent desymmetrizing reduction typically in the range of 90–98% ee (Table 3, entries 1–9), with the derivatives of indane-1,3-dione giving the highest ee's (Table 3, entries 4–6). The only exception is the acyclic substrate **3p**, which produced **4p** as product diastereoselectively, but with only 68% ee, along with product from a simple conjugate reduction that failed to cyclize, which was also isolated in 17% yield. Several R^3 substituents are tolerated, although groups bulkier than methyl tend to be reductively cyclized with lower yields (Table 3, entries 5, 6 and 9). We explored the effects of substituents on the *S*-benzyl group by variation of the substitution on the aromatic ring; but the enantioselectivity of the reductive cyclization did not improve significantly as a result of modifications on the ring (Table 3, entries 2–3). Overall, the copper-catalyzed reductive aldol cyclization of enethioate substrates with **L8** as ligand proceeded to give six-membered ring aldols with up to 94% yields, excellent to exclusive diastereoselectivity and up to 98% ee.

On the other hand, reductions that continue on to five-membered ring aldol formation are not efficient (Table 3, entries 11–12). Both the yields and enantioselectivities were greatly inferior to the previous reductive cyclizations. It may be that for this substrate type, TaniaPhos **L8** is not the optimum phosphine, and another ligand with alternative stereochemical features could engender improved enantioselectivities.

For the analysis of ee, the corresponding racemic products were generated by copper-catalyzed reductive cyclizations using either bis(diphenylphosphino)benzene (BDP) or 1,1′-bis(diphenylphosphino)ferrocene (dppf) as ligands. It was noted that such reductions proceeded in much lower yields (trace to 39%), and in some cases also with grossly reduced diastereoselectivity. Therefore it is apparent that the chiral ligands not only conferred enantioselectivity, but their steric bulk in the copper complex also prevented competing reactions and stabilized the transition state leading to the all-*cis* aldol diastereomer **4**.
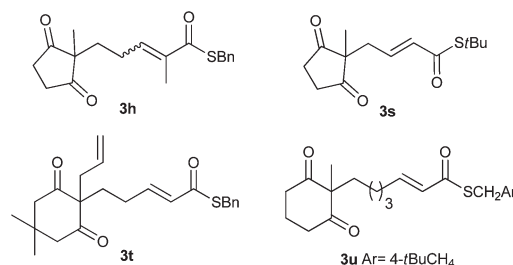

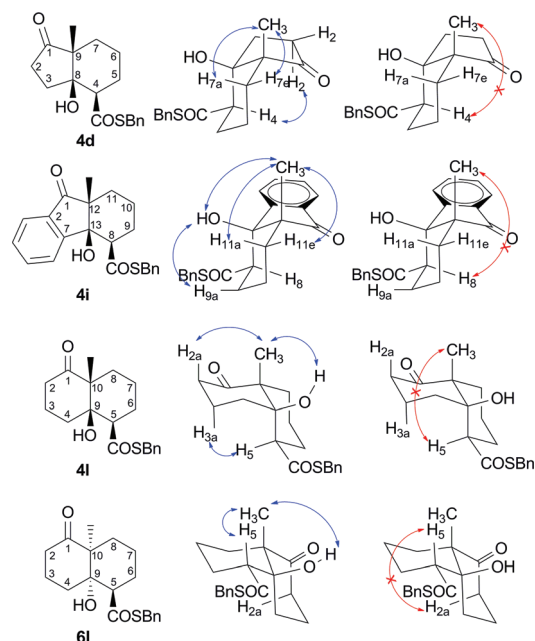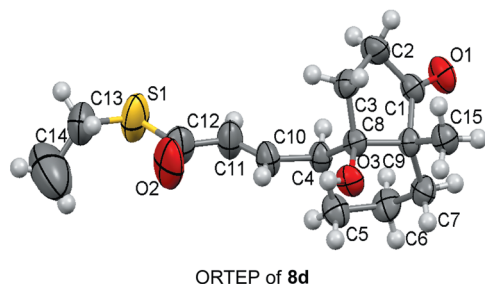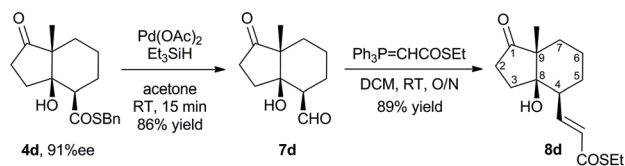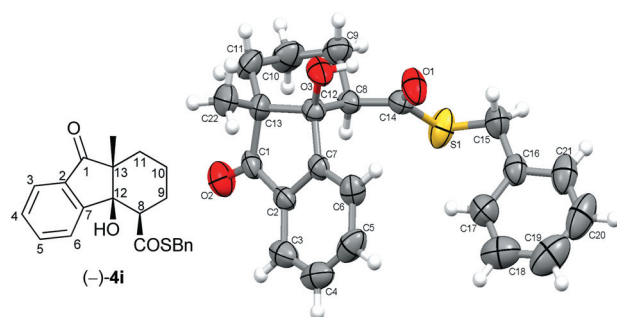**Fig. 2** Substrates that failed in reductive aldol cyclization.

Fig. 3 Summary of nOe correlations for **4d**, **4i**, **4l**, **6l**.

Several hindered substrates failed to undergo any reductive cyclization under these conditions (Fig. 2). Steric hindrance in the form of α-substituents (**3h**), in the mercaptan (**3s**) and in the cyclic scaffold (**3t**) retarded the reaction greatly. These experiments returned unreacted enethioates in 82–84% yields; not even the conjugate reduction was observed. For these hindered substrates, the initial conjugate reduction has become the rate limiting step. For substrate **3u**, only simple conjugate reduction in 76% yield occurred without cyclization, due to the inefficiency of formation of large rings.

The relative stereochemistries of the major and minor aldol products **4** and **6** can be deduced on the basis of 2D-NMR (H–H NOESY, COSY) spectral analysis. Four representative examples and their informing NOE correlations are shown in Fig. 3. The relative stereochemistry has been confirmed by an X-ray crystal structure of (±)-**4c**.[14]

The absolute configuration of **4d** has additionally been determined by conversion to aldehyde **7d** by a Fukuyama reduction in 86% yield,[20] then by a Wittig reaction to afford the crystalline **8d** in 89% yield (Scheme 6). X-ray crystallographic analysis of **8d** indicates that the absolute configurations at the stereocenters are 4*S*,8*R*,9*R*.[21] This infers that its precursor is (4*R*,8*R*,9*R*)-**4d**.
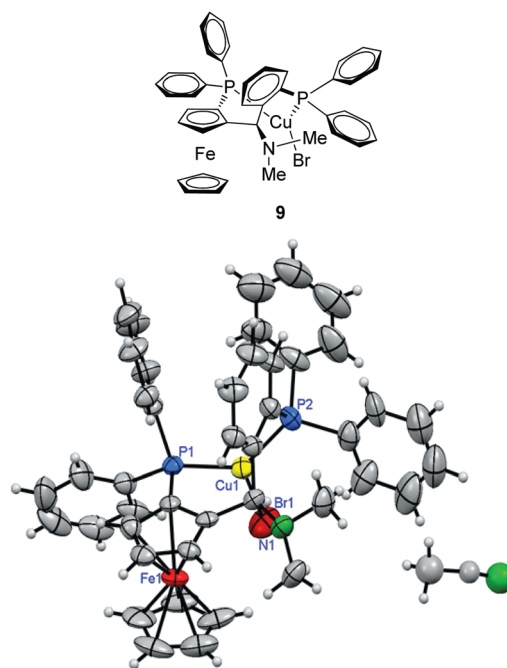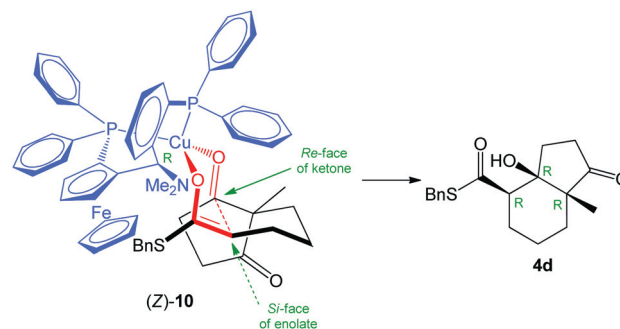
Scheme 6 Determination of absolute configuration of **4d** and **8d**.

Fig. 5 ORTEP plot of **L8**–CuBr, **9**.

Fig. 4 ORTEP of **4i**.

Because product **4i** is a crystalline compound, it was directly subjected to X-ray analysis and determined to be (8R,12S,13R)-**4i** (Fig. 4).[22]

Based on the consistent absolute stereochemical outcome of **4d** and **4i**, the other aldol products are assumed to have the same absolute stereochemistry by analogy, as represented by the structures in Table 3 as shown.

To better understand the nature of the copper hydride and copper enolate ligated to TaniaPhos (**L8**), we sought to investigate the coordination at the metal center. In the literature, a Josi-Phos–copper(I) bromide complex has been previously prepared and its crystal structure has been elucidated.[23] This monomeric copper complex is trigonal planar, as expected for copper(I) having three ligands occupying sp²-hybridized orbitals. There are many differences in the steric and electronic properties between JosiPhos (**L7**) and TaniaPhos (**L8**), so it was not clear how **L8** conferred superior enantioselectivity on the **L8**–copper(I) hydride mediated reaction, compared with the JosiPhos-ligated copper hydride which afforded a much lower ee (Scheme 3).[24] In particular, it was not clear whether the dimethyl-amino unit in **L8** was functioning as an additional ligand in any way, in either the **L8**-ligated copper hydride or the copper enolate.

To clarify this issue, we prepared, crystallized and characterized the TaniaPhos **L8**–copper(I) bromide complex **9**.[25] From the X-ray crystallographic analysis (Fig. 5), **9** co-crystallized with a

molecule of MeCN. It can be seen clearly that in **9** the dimethylamino group does not coordinate with copper, so its function is steric in nature. Together with the *ortho*-disubstituted phenyl group, the dimethylamino group effectively blocks the β-face of the copper complex, leaving the α-face open for coordination and approach. It could be inferred that the monomeric **L8**–copper(I) hydride complex would have similar structural features to **9**, but the state of aggregation of the copper hydride complex in solution and in various solvents could differ greatly.

Nevertheless, based on the absolute configuration of (4R,8R,9R)-**4d**, the aldol cyclization could be rationalized as a chiral copper (Z)-enolate **10** whose β-face is blocked by the dimethylamino unit of (R_P)-1-[(R)-α-(dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene (TaniaPhos **L8**) (Scheme 7), undergoing aldol attack from the α-face. The **L8** stereochemistry therefore directs the attack by the enolate from its *Si*-face to the *Re*-face of the ketone.

Scheme 7 Putative transition state in the formation of **4d**.

Conclusions

In summary, twenty enethioate derivatives of various symmetrical prochiral 1,3-diones have been examined in the asymmetric reductive aldol cyclization catalyzed by copper. Using chiral copper hydride generated from 5 mol% of each of TaniaPhos **L8**, Cu(OAc)$_2$·H$_2$O and bipyridine, with PhSiH$_3$ as the stoichiometric reductant, a range of enethioates undergo desymmetrizing reductive cyclization to afford bicyclic or polycyclic β-hydroxythioester products bearing three newly generated contiguous stereocenters diastereoselectively (>98 : 2) in up to 94% yield and up to 98% ee. The incorporation of a catalytic amount of bipyridine or other amines as additive accelerates the reaction rate to allow the reaction to proceed at a lower temperature and in less reaction time. This catalytic system generally induces the reductive formation of six-membered ring aldol products with good to excellent ee, but the enantioselectivity in five-membered ring aldol formation is markedly inferior. The stereochemistry of the major bicyclic β-hydroxythioester product is the all-*cis* diastereomer, and the absolute configurations of the products have been ascertained through X-ray crystallography. The crystal structure of the monomeric **L8**–CuBr complex has been obtained, which helps to postulate a transition state that rationalizes the observed stereochemical outcome. The thioester functional group has a rich chemistry, and further reactions of this class of thioester aldol product have also been demonstrated to offer stereodefined scalemic intermediates such as **7d** and **8d** for synthesis.

Experimental section

General procedure for the preparation of keto–enethioates 3

The thioester-derived phosphoranes were prepared as previously described.[14,15]

To a solution of 1,3-dione (1.0 equiv.) in H$_2$O–THF (30 mL, 1 : 1) was added acrolein (2.0 equiv.). The reaction mixture was stirred for 24–48 h. The solvent was removed *in vacuo* to give the crude aldehyde, which was used in the next reaction without further purification.

To a solution of aldehyde (1.0 equiv.) in CH$_2$Cl$_2$ was added the phosphorane (1.2 equiv.). The reaction mixture was stirred at room temperature for 12 h. The solvent was removed *in vacuo*, and the residue was subjected to flash chromatography on silica gel to give the corresponding enethioates **3** as a mixture of (*E*)- and (*Z*)-isomers.

General procedure for asymmetric reductive aldol cyclizations

Cu(OAc)$_2$·H$_2$O (0.015 mmol), **L8** (TaniaPhos SL-T001-1, 0.015 mmol) and bipy (0.015 mmol) were transferred into an oven-dried 5 mL round-bottomed flask, to which anhydrous PhMe (1.0 mL) and phenylsilane (0.75 mmol) were added under argon. The reaction mixture was stirred at room temperature until a characteristic greenish-yellow color was observed. The reaction mixture was cooled to the desired reaction temperature. Substrate **3** (0.15 mmol) in PhMe (1.0 mL) was added to the reaction mixture *via* a cannula. The progress of the reaction was monitored by TLC. The reaction was quenched by the addition of

1 M HCl (1.0 mL). The organic layer was separated, and the aqueous layer was back-extracted with EtOAc (3 × 5 mL). The combined organics were dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. Flash chromatography of the residue on silica gel using 5%–20% EtOAc in hexane afforded the aldol products.

Acknowledgements

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22 Crystal data for **4i**: $C_{22}H_{22}O_3S$, M_w = 366.46, triclinic, space group $P1$ (#1), a = 8.6495(6) Å, b = 8.6869(6) Å, c = 13.4401(9) Å, α = 72.062 (4)°, β = 89.472(4)°, γ = 85.803(5)°, V = 958.09(11) Å³, Z = 2, μ(Mo Kα) = 0.19 mm⁻¹, $F(000)$ = 388, T = 296 K; crystal dimensions: 0.76 mm × 0.34 mm × 0.16 mm. Of the 13 175 reflections that were collected, 5970 reflections were unique. (R_{int} = 0.0479); equivalent reflections were merged. R_1 = 0.071, wR_2 = 0.236. Crystallographic data for **4i** have been deposited at the Cambridge Crystallographic Data Center, CCDC 851778.

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