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Enantioselective addition of organozinc reagents to carbonyl compounds catalyzed by a camphor derived chiral γ-amino thiol ligand

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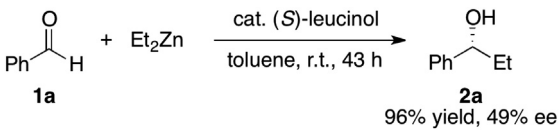
ABSTRACT

In this article, the design and synthesis of the chiral camphor derived γ-amino thiol ligand **17** and its application in catalytic enantioselective carbon-carbon forming reactions through the addition of organozinc reagents to carbonyl compounds is described. The catalytic activity and enantioselectivity of ligand **17** is demonstrated in the enantioselective addition of various organozinc reagents to aldehydes and ketoesters, offering the corresponding alcohols in high yields and enantioselectivities. The role of the mercapto group in the highly enantioselective 1,2-addition reaction of organozincs to aldehyde is also discussed.

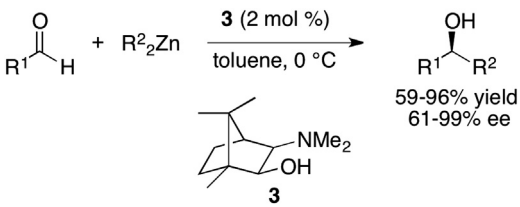
1. Introduction

Chiral alcohols are not only pivotal synthetic building blocks but they are also common components in natural products as well as in biologically active compounds. Given their importance, tremendous effort has been focused on the efficient synthesis of chiral alcohols. As compared with the enantioselective reduction of carbonyl compounds,[1] enantioselective addition of organometallic reagents to carbonyl compounds is a more practical route to the synthesis of optically active alcohols.[2] In the pioneering work of Oguni and Omi, the enantioselective addition reaction of Et_2Zn to benzaldehyde (**1a**) in the presence of (*S*)-leucinol offered (*R*)-1-phenylpropanol (**2a**) in moderate ee (Eq. 1).[3]



(1)

Noyori and co-workers subsequently reported the first highly enantioselective addition of dialkylzincs to aryl aldehydes catalyzed by a chiral β-amino alcohol (Eq. 2).[4] (−)-3-*exo*-(Dimethylamino)isoborneol (DAIB, **3**), a camphor derived β−amino alcohol with a tertiary amino group, exhibited high enantioinduction in the addition reaction of dialkylzincs to aromatic aldehydes. Following these preliminary examples, and given that the reactions employing organozinc reagents were conducted under mild reaction conditions with high degree of functional group compatibility and low metal toxicity of zinc, it has attracted tremendous interest in the design and synthesis of chiral ligands, primarily based on naturally occurring chiral scaffolds, for the enantioselective addition of organozincs to aldehydes.[5]



(2)

2. The development of camphor derived ligands for catalytic C–C bond formation reactions

2.1. Camphor derived γ-amino alcohol as ligands

In our efforts on the development of camphor derived ligands for asymmetric catalysis,[6a–e] bis-sulfonamide ligand **4** was

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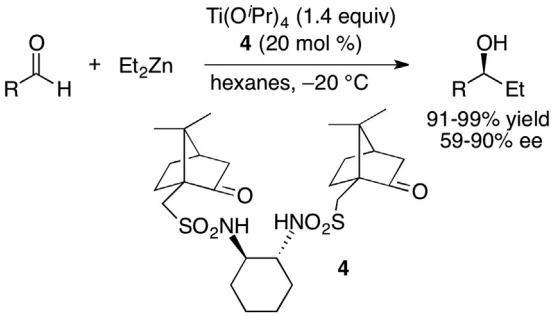
0040-4020/

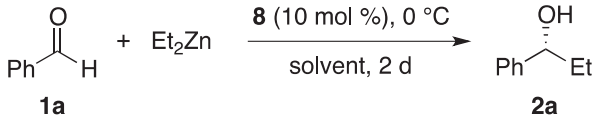
prepared and applied to the Ti(IV)-catalyzed enantioselective addition of Et_2Zn to aldehydes (Eq. 3).[6a] The corresponding adducts were isolated in high yields (91–99%), however, with only moderate to good enantioselectivities (59–90% ee). Although it was reported later by Walsh[6f] that bis-sulfonamide **4** was able to induce higher enantioselectivities in a similar catalytic system, the use of stoichiometric amount of $Ti(O^iPr)_4$ may not be ideal for the scale up purpose.



(3)

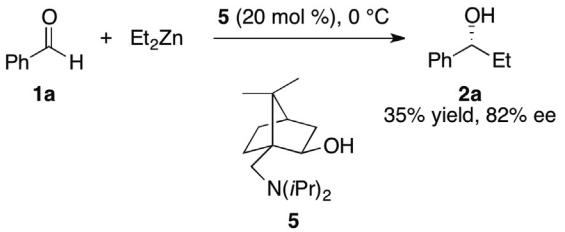
The development of a catalytic system that is not merely required of high catalytic activity and enantioselectivity but also could be prepared concisely. It had been shown that the use of chiral γ-amino alcohol **5**, bearing an isonorborneol scaffold derived from ketopinic acid, in the catalytic enantioselective addition of Et_2Zn to benzaldehyde (**1a**) could give the addition product **2a** in 35% yield and in 82% ee (Eq. 4).[7a] We anticipated that optimization of the substituents on the nitrogen atom based on ligand **5** might provide enhanced selectivity. Hence, a series of γ-amino alcohols **8** were prepared from (1*S*)-ketopinic acid **6**[8] via amidation with various amines followed with a one-pot selective ketone reduction at −40 °C and subsequent amide reduction under refluxing temperature with LAH in THF (Scheme 1). Each of **8a**–**f** was obtained as a single diastereomer. Reaction of benzaldehyde (**1a**) with Et_2Zn in toluene at 0 °C was conducted in the presence of ligand **8** to understand the effect of amino substituent on stereocontrol (Table 1). Among the six ligands, the less bulky substituted γ-amino alcohol **8b** turned out to be the best ligand that gave 71% ee and 94% yield in the catalytic addition reaction when the reaction was conducted in toluene (entry 2). The enantioselectivity could be improved to 80% ee when the reaction was conducted in hexanes (entry 7). This observation contradicted both Oppozler's result and our anticipation that bulkier *N*-substituents would give higher asymmetric induction.[7b]

Table 1
Enantioselective addition reaction of benzaldehyde (**1a**) with Et_2Zn catalyzed by γ-amino alcohols **8**



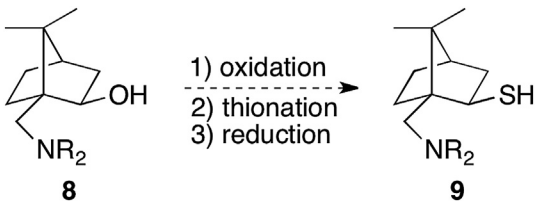
Entry	Ligand	Solvent	Yield[a] (%)	ee[b] (%)
1	**8a**	Toluene	95	57
2	**8b**	Toluene	94	71
3	**8c**	Toluene	95	30
4	**8d**	Toluene	93	31
5	**8e**	Toluene	95	61
6	**8f**	Toluene	90	30
7	**8b**	Hexanes	93	80

[a] Isolated yield.
[b] Determined by chiral HPLC.

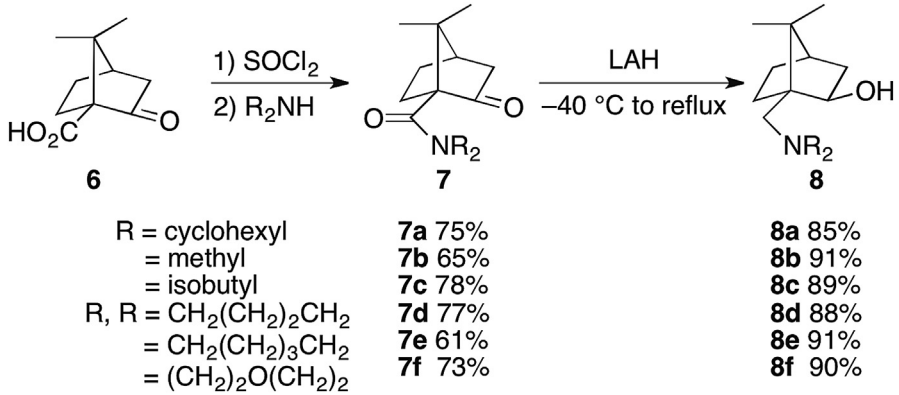


(4)

While amino alcohol ligands are prevalent in the realm of catalytic enantioselective organozinc addition to carbonyl compounds, amino thiol ligands[5d,9] have also received considerable attention owing to: 1) higher polarizability of a sulfur atom than an oxygen atom; 2) better binding affinity of thiols and thiolates with metals, zinc in particular; and 3) lower Lewis acidity of metal alcoholates than metal thiolates.[9f] Having achieved moderately good enantioselectivity using γ-amino alcohol **8b** in the enantioselective addition reaction of Et_2Zn and benzaldehyde (**1a**), we envisaged that new γ-amino thiol **9** might exhibit improved selectivity (Scheme 2). In



Scheme 2. A proposed synthesis of γ-amino thiol **9** from γ-amino alcohol **8**.



Scheme 1. Synthesis of γ-amino alcohols **8** bearing an isonorborneol backbone.

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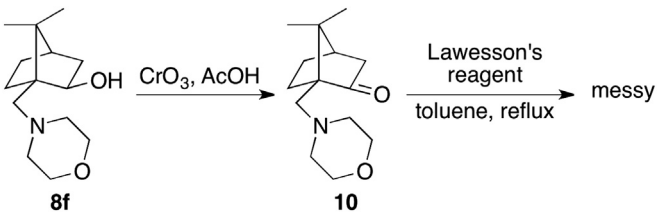
principle, amino thiol **9** could be prepared from γ-amino alcohol **8** by converting the hydroxyl group into the corresponding thiol group.

2.2. Camphor derived γ-amino thiol ligands

In an attempt to synthesize γ-amino thiol **9**, oxidation of compound **8f** was carried out with CrO_3 under acidic conditions to provide amino ketone **10** in 92% yield; however, thionation of **10** with Lawesson's reagent[10] failed to give the corresponding thione compound (Scheme 3).



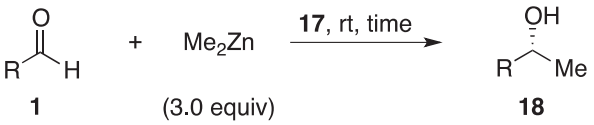
Scheme 3. An attempt to synthesize γ-amino thiol **9** from γ-amino alcohol **8f**.

Since the preparation of γ-amino thiol ligands from γ-amino alcohols **8** seemed infeasible, the installment of thiol group at an early stage of ligand synthesis was sought. According Oae's protocol,[11] ketothiol **12** was synthesized from the reduction of camphorsulfonyl chloride **11** with PPh_3 in 87% yield (Scheme 4). After benzylation of primary thiol, compound **13** was efficiently transformed into oxime **14** by the condensation with hydroxylamine. Oxime **14** was reduced with tBuNH$_2$·BH$_3$ in conjunction with $TiCl_3$ to offer primary amine **15** as the sole diastereomer. Subsequent N,N-dialkylation of amine **15** with 2-bromoethyl ether under basic condition furnished compound **16** in 77% yield. (−)-2-*Exo*-morpholino-isobornane-10-thiol (MITH) (**17**) was obtained in 64% yield after removing the benzyl group of compound **16** by reduction reaction with sodium in liquid ammonia at −78 °C.[12]

3. Catalytic enantioselective Et_2Zn and Me_2Zn addition to aldehydes

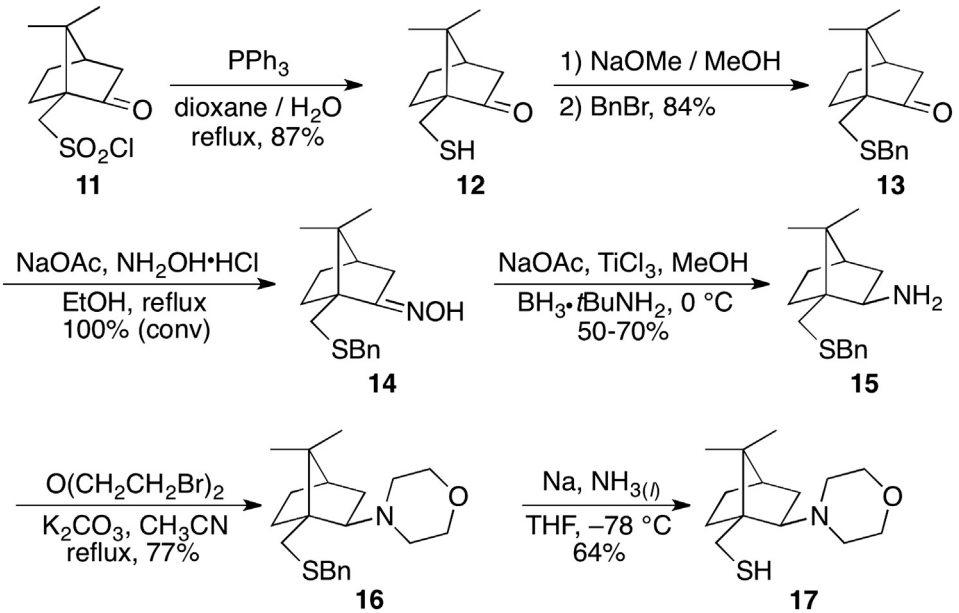
Although the position of amino and thiol functional groups are reversed in the new ligand, compared to the original plan, γ-amino thiol **17** catalyzed the addition reactions of Me_2Zn or Et_2Zn with aldehydes to give the corresponding secondary alcohols with high enantioselectivities.[14] While the enantioselective addition reaction of Me_2Zn to benzaldehyde (**1a**) in the presence of 0.1 mol % of **17** offer alcohol **18a** in 68% yield and 92% ee after 96 h (Table 2, entry 1), the reaction was accelerated and completed in 48 h to provide 89% yield of compound **18a** with 94% ee when using 0.5 mol % of **17** (entry 2). An extended reaction time was necessary at these low ligand loadings, but good yield and enantioselectivity were generally obtained when the reaction was carried out in the presence of 0.5 mol % of chiral ligand **17**. Moderate levels of enantio-induction

Table 2
Enantioselective addition reaction of aldehyde **1** with Me_2Zn catalyzed by γ-amino thiol **17**[a]



Entry	R	**17** (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	C_6H_5 (**1a**)	0.1	96	68 (**18a**)	92
2	C_6H_5 (**1a**)	0.5	48	89 (**18a**)	94
3	2-Me-C_6H_4 (**1b**)	0.5	48	82 (**18b**)	90
4	3-Me-C_6H_4 (**1c**)	0.5	48	80 (**18c**)	90
5	4-Me-C_6H_4 (**1d**)	2.0	48	89 (**18d**)	96
6	4-MeO-C_6H_4 (**1e**)	0.5	72	82 (**18e**)	85
7	4-CF_3-C_6H_4 (**1f**)	2.0	48	91 (**18f**)	78
8	2-Cl-C_6H_4 (**1g**)	0.5	48	83 (**18g**)	84
9	3-Cl-C_6H_4 (**1h**)	0.5	48	86 (**18h**)	90
10	4-Cl-C_6H_4 (**1i**)	0.5	48	77 (**18i**)	93
11	4-Br-C_6H_4 (**1j**)	0.5	48	70 (**18j**)	89
12	2-Thienyl (**1k**)	0.5	48	82 (**18k**)	92
13	2-Furyl (**1l**)	0.5	48	77 (**18l**)	78
14	3-Furyl (**1m**)	0.5	48	82 (**18m**)	83
15	1-Naphthyl (**1n**)	2.0	48	90 (**18n**)	93
16	2-Naphthyl (**1o**)	0.5	48	86 (**18o**)	92
17	Cinnamyl (**1p**)	0.5	48	95 (**18p**)	64
18	2-Me-Cinnamyl (**1q**)	0.5	72	65 (**18q**)	83
19	Hydrocinnamyl (**1r**)	0.5	48	83 (**18r**)	42
20	Cyclohexyl (**1s**)	0.5	48	70 (**18s**)	86

[a] A 0.73 M solution of Me_2Zn in hexanes was used.[13]
[b] Isolated yield.
[c] Determined by chiral HPLC.



Scheme 4. Synthesis of γ-amino thiol **17**.

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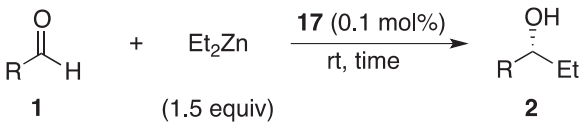
were observed for 4-trifluoromethylbenzaldehyde (**1f**) (entry 7), 2-furaldehyde (**1l**) and 3-furaldehyde (**1m**) (entries 13–14), and cinnamaldehydes **1p**–**1r** (entries 17–19) when 0.5 mol % of ligand **17** was used. In addition, the reaction of 4-methylbenzaldehyde (**1d**) (entry 5) and 1-naphthaldehyde (**1n**) (entry 15) provided good yields and enantioselectivities when conducted in the presence of 2 mol % of ligand **17**.

The catalytic enantioselective addition of Et_2Zn to aldehydes **1** conducted in the presence of 0.1 mol % of chiral ligand **17** at 0 °C afforded the corresponding secondary alcohols **2** in excellent enantioselectivities (92–99% ee) regardless of the aromatic substituent pattern of the aryl aldehydes (Table 3, entries 1–11) except for 4-chlorobenzaldehyde (**1i**) (86% ee, entry 9). Under similar reaction conditions, cinnamaldehydes (**1p**, **1q**, and **1r**) and cyclohexanecarboxaldehyde (**1s**) were good electrophiles provided the corresponding addition adducts in moderate to good yields (56–95% yield) and enantioselectivities (64–90% ee) (entries 12–15).

Table 3
Enantioselective addition reaction of aldehyde **1** with Et_2Zn catalyzed by γ-amino thiol **17**[a]



1 **2**

Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	C_6H_5 (**1a**)	24	95 (**2a**)	96
2	2-Me-C_6H_4 (**1b**)	24	95 (**2b**)	94
3	3-Me-C_6H_4 (**1c**)	24	94 (**2c**)	94
4	4-Me-C_6H_4 (**1d**)	24	95 (**2d**)	97
5	4-MeO-C_6H_4 (**1e**)	48	94 (**2e**)	93
6	4-CF_3-C_6H_4 (**1f**)	24	96 (**2f**)	97
7	2-Cl-C_6H_4 (**1g**)	24	88 (**2g**)	99
8	3-Cl-C_6H_4 (**1h**)	24	92 (**2h**)	96
9	4-Cl-C_6H_4 (**1i**)	48	80 (**2i**)	86
10	4-Br-C_6H_4 (**1j**)	24	85 (**2j**)	96
11	2-Naphthyl (**1o**)	24	94 (**2o**)	95
12	Cinnamyl (**1p**)	24	95 (**2p**)	71
13	2-Me-Cinnamyl (**1q**)	48	77 (**2q**)	90
14	Hydrocinnamyl (**1r**)	24	83 (**2r**)	64
15	Cyclohexyl (**1s**)	24	56 (**2s**)	82

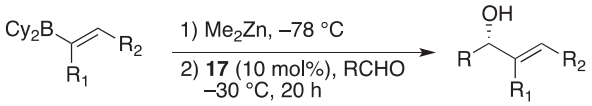
[a] A 1.0 M solution of Et_2Zn in hexanes was used.
[b] Isolated yield.
[c] Determined by chiral HPLC.

4. Catalytic enantioselective alkenylzinc addition to aldehydes

In 1992, Oppolzer and co-workers reported an efficient preparation of chiral (*E*)-allylic alcohols, which are versatile and invaluable synthetic intermediates, via a catalytic enantioselective addition of alkenylzinc reagents to aldehydes.[15a] This method involved the in situ generation of nucleophilic alkenylzincs by transmetalation of Et_2Zn and the (*E*)-alkenylboron species, which could be directly synthesized from hydroboration of dicyclohexylborane and alkynes. The efficiency of this method has prompted considerable focus to investigate the catalytic activities and enantioselectivities of various ligands including β-amino alcohols,[15,16] ketimines of chiral [2,2]paracyclophane,[17] β-amino thiols,[18] γ-amino naphthols,[19] and dipeptides.[20]

Taking advantage of Oppolzer's protocol, the catalytic activity of chiral γ-amino thiol **17** was tested in the enantioselective addition reaction of 1-octenylzinc and benzaldehyde (**1a**). The optimal result was obtained when the reaction was carried out in the presence of 10 mol % of ligand **17** at −30 °C, giving the corresponding product (*R*)-**21a** in 85% yield with 96% ee (Table 4, entry 1).[21] Aryl aldehydes, either with electron-withdrawing or electron-donating groups

Table 4
Enantioselective addition reaction of aldehyde **1** with alkenylzinc reagents catalyzed by γ-amino thiol **17**



19: R_1 = H, R_2 = C_6H_{13}
20: R_1 = H, R_2 = C_4H_9
21: R_1 = C_2H_5, R_2 = C_2H_5
22: R_1 = H, R_2 = *t*Bu
23: R_1 = H, R_2 = $C_6H_5(CH_2)_3$

Entry	R	R_1	R_2	Yield[a] (%)	ee[b] (%)
1	C_6H_5 (**1a**)	H	C_6H_{13}	85 (**19a**)	96
2	2-Me-C_6H_4 (**1b**)	H	C_6H_{13}	83 (**19b**)	96
3	4-Me-C_6H_4 (**1d**)	H	C_6H_{13}	83 (**19d**)	95
4	4-CF_3-C_6H_4 (**1f**)	H	C_6H_{13}	90 (**19f**)	>99.5
5	3-CF_3-C_6H_4 (**1t**)	H	C_6H_{13}	87 (**19t**)	98
6	2-Cl-C_6H_4 (**1g**)	H	C_6H_{13}	85 (**19g**)	95
7	3-Cl-C_6H_4 (**1h**)	H	C_6H_{13}	88 (**19h**)	97
8	4-Cl-C_6H_4 (**1i**)	H	C_6H_{13}	90 (**19i**)	96
9	3-F-C_6H_4 (**1u**)	H	C_6H_{13}	88 (**19u**)	96
10	3-MeO-C_6H_4 (**1v**)	H	C_6H_{13}	81 (**19v**)	95
11	C_6H_5 (**1a**)	H	C_4H_9	83 (**20a**)	97
12	3-CF_3-C_6H_4 (**1t**)	H	C_4H_9	82 (**20t**)	98
13	C_6H_5 (**1a**)	C_2H_5	C_2H_5	89 (**21a**)	96
14	C_6H_5 (**1a**)	H	*t*Bu	91 (**22a**)	96
15	Cyclohexyl (**1s**)	H	$C_6H_5(CH_2)_3$	80 (**23s**)	97

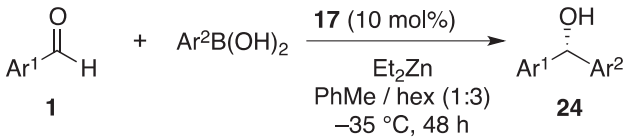
[a] Isolated yield.
[b] Determined by chiral HPLC.

were suitable, offered chiral allylic alcohols **19** in 81–90% yield and 95–>99.5% ee under similar reaction conditions (entries 2–10). The addition of 1-hexenylzinc reagent (R_1=H, R_2=C_4H_9) to benzaldehyde (**1a**) and 3-trifluoromethylbenzaldehyde (**1t**) gave alcohols **20a** and **20t** in 83% and 82% yields with 97% and 98% ee's, respectively (entries 11 and 12). Notably, alkenylzinc reagents with a bulky substituent (R_1=H, R_2=*t*Bu) or two ethyl substituents (R_1=C_2H_5, R_2=C_2H_5) were good nucleophiles producing vinylic alcohols **21a** and **22a** both in excellent yields and ee's (entries 13 and 14). A wide substrate scope in the enantioselective alkenylzincs addition catalyzed by chiral amino thiol **17** was tolerated including aromatic and α-branched aliphatic aldehydes and internal or terminal alkenylzinc reagents.

5. Catalytic enantioselective arylzinc addition to aryl aldehydes

Optically active diarylmethanols are vital building blocks for the synthesis of natural products and molecules of biological interest.[22] In 1997, Fu and co-workers reported a catalytic enantioselective addition of diphenylzinc to 4-chlorobenzaldehyde (**1i**), offering the corresponding chiral diarylmethanol in 57% ee.[23] Despite subsequent work showing the enantioselective addition could proceed in a highly enantioselective manner, the fact that only one of the two phenyl groups was transferred during the course of the addition reaction rendered the use of diphenylzinc uneconomic.[5f,24] A flexible solution came when Bolm and co-workers reported that arylboronic acids could be transmetalated with Et_2Zn, giving nucleophilic arylzinc reagents useful for catalytic enantioselective synthesis of diarylmethanols with not only high efficiency but also improved reactivity.[25] When chiral amino thiol **17** (10 mol %) was employed in this catalytic enantioselective transformation, addition of the phenylethylzinc reagent, derived from the reaction of phenylboronic acid and Et_2Zn to 2-methylbenzaldehyde (**1b**) provided the corresponding (*R*)-alcohol **24b** in 95% yield and >99.5% ee (Table 5, entry 1).[26] In contrast to Bolm's findings that a catalytic amount of additive (DiMPEG, 10 mol %) is required to

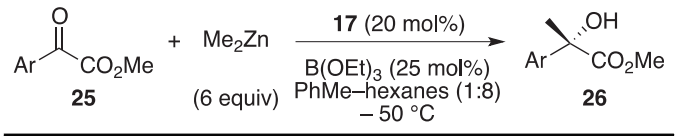
Table 5
Enantioselective addition reaction of aldehyde **1** with arylzinc reagents catalyzed by γ-amino thiol **17**[a]



Entry	Ar^1	Ar^2	Yield[b] (%)	ee[c,d] (%)
1	2-Me-C_6H_4 (**1b**)	C_6H_5	95 (**24b**)	>99.5
2	3-Me-C_6H_4 (**1c**)	C_6H_5	90 (**24c**)	97
3	4-Me-C_6H_4 (**1d**)	C_6H_5	84 (**24d**)	97
4	4-MeO-C_6H_4 (**1e**)	C_6H_5	73 (**24e**)	97
5	4-CF_3-C_6H_4 (**1f**)	C_6H_5	83 (**24f**)	97
6	2-Cl-C_6H_4 (**1g**)	C_6H_5	90 (**24g**)	98
7	3-Cl-C_6H_4 (**1h**)	C_6H_5	96 (**24h**)	95
8	4-Cl-C_6H_4 (**1i**)	C_6H_5	96 (**24i**)	96
9[e]	2-Naphthyl (**1o**)	C_6H_5	73 (**24o**)	95
10	4-CO_2Me-C_6H_4 (**1t**)	C_6H_5	84 (**24t**)	96
11	C_6H_5 (**1a**)	4-Me-C_6H_4	86 (**24d**)	97
12	C_6H_5 (**1a**)	4-Cl-C_6H_4	98 (**24i**)	96

[a] Conditions: $PhB(OH)_2$ (2 equiv) and Et_2Zn (6 equiv) were used with respect to ArCHO.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] In entries 1–10, (*R*)-products were obtained, and in entries 11 and 12, (*S*)-products were obtained.
[e] 27% of the ethylation product was isolated.

Table 6
Enantioselective Me_2Zn addition reaction of α-ketoesters **25** catalyzed by γ-amino thiol **17**



Entry	Ar	Time (h)	Yield[a] (%)	ee[b] (%)
1	C_6H_5 (**25a**)	22	85 (**26a**)	79
2	2-Me-C_6H_4 (**25b**)	72	46[c] (**26b**)	76
3	3-Me-C_6H_4 (**25c**)	27	76 (**26c**)	84
4	4-Me-C_6H_4 (**25d**)	24	84 (**26d**)	85
5	4-MeO-C_6H_4 (**25e**)	96	54[d] (**26e**)	89
6	4-CF_3-C_6H_4 (**25f**)	12	71 (**26f**)	16
7	4-Cl-C_6H_4 (**25i**)	41	79 (**26i**)	59
8	4-Br-C_6H_4 (**25j**)	22	52[e] (**26j**)	55
9	2-Thienyl (**25k**)	18	87 (**26k**)	85
10	2-Furyl (**25l**)	96	82 (**26l**)	75
11	2-Naphthyl (**25o**)	23	70 (**26o**)	82
12	Hydrocinnamyl (**25r**)	24	83 (**26r**)	19

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] **25b** was recovered in 25% yield.
[d] **25e** was recovered in 32% yield.
[e] **25j** was recovered in 18% yield.

achieve high enantio excess, high enantioselectivity was achieved without any additive in our study. Further investigation of reaction scope showed that phenylation occurred smoothly with alkyl-substituted, electron-donating and electron-withdrawing aryl aldehydes, furnishing diarylmethanols **24** with high enantioinduction (95–>99.5% ee, entries 1–10). Catalytic addition of 4-methylphenylzinc and 4-chlorophenylzinc species to benzaldehyde (**1a**) gave (*S*)-**24d** (entry 11) and (*S*)-**24i** (entry 12) with similar levels of selectivity, demonstrating the advantage of this method for the synthesis of both (*R*)- and (*S*)-alcohols using chiral ligand **17** by aptly assigning the two aromatic groups to either the nucleophilic or electrophilic reaction components.

6. Catalytic enantioselective Me_2Zn addition to α-ketoesters

Chiral quaternary substituted α-hydroxy esters are key precursors for the preparation of natural products and pharmacologically active molecules. Although diastereoselective addition of organometallics to α-ketoesters with chiral auxiliaries offers optically active α-hydroxy esters,[27] the employment of stoichiometric amount of the chiral modifier renders the corresponding catalytic enantioselective addition of nucleophiles to α-ketoesters a more attractive route. On the contrary to the addition chemistry of organozincs to aldehydes and ketones, coordination of organozincs to α-ketoesters promotes a non-selective addition process, giving rise to a few applicable catalytic systems.[28] In 2003, Shibasaki and co-workers reported a highly enantioselective preparation of α-hydroxy esters through a Me_2Zn addition to α-ketoesters catalyzed by an α-amino alcohol.[28c] Given the competence of our chiral γ-amino thiol **17**, the catalytic addition of Me_2Zn to α-ketoesters was investigated. When α-ketoesters with various ester groups were tested, the corresponding α-hydroxy esters **26** were isolated with diminishing selectivity as the size of ester group increased; methyl α-ketoesters **25** were identified as optimal substrates in our study (Table 6).[29] Enantioselective addition of Me_2Zn to methyl benzoyl formate (**25a**), in the presence of ligand **17** (20 mol%), gave the corresponding product **26a** in 85% yield with 79% ee at −50 °C (entry 1). Notably, the addition of a catalytic amount of $B(OEt)_3$ (25 mol%) enhanced the catalytic activity and enantioselectivity of chiral ligand **17**.[30] Enantioselective reaction of compound **25b** (entry 2) having an *ortho*-tolyl group was less selective than *meta*- and *para*-tolyl substituted substrates (**25c** and **25d**, entries 3 and 4). High levels of enantioselectivity were observed when α-ketoesters bearing aromatic rings substituted with electron-donating groups (entries 1–5), whereas analogues with electron-withdrawing groups provided the corresponding products with moderate ee's (entries 6–8). While α-ketoesters substituted with 2-thienyl (**25k**, entry 9), 2-furyl (**25l**, entry 10) and 2-naphthyl (**25o**, entry 11) groups were good electrophiles in this enantioselective transformation furnishing the corresponding alcohols in good yields and ee's, the reaction with an aliphatic α-ketoester (**25r**, entry 12) offered the corresponding α-hydroxyester **26r** with a less than satisfactory enantioselectivity.

7. Catalytic enantioselective alkynylzincs addition to aldehydes

The enantioselective synthesis of propargylic alcohols, which see wide application in the synthesis of enantioenriched pharmaceutical components as well as natural products, with high optically purity is a particularly important enantioselective transformation.[31] Preparation of chiral propargylic alcohols from the addition of nucleophilic Zn-acetylides, generated in situ from the deprotonation of alkynes with Et_2Zn or Me_2Zn, to carbonyl compounds is straightforward and operates under mild reaction conditions, but usually requires high ligand loading to achieve high ee.[5e] In the presence of 2.5 mol% of ligand **17**, enantioselective alkynylation of the zinc acetylide, prepared from 1-phenylethyne (**27a**) and Me_2Zn, with benzaldehyde (**1a**) at −20 °C gave (*S*)-**28aa** in 68% yield with 86% ee (Table 7, entry 1).[32] Various substituted aromatic aldehydes were tolerated by this catalytic system, providing the corresponding propargylic alcohols with 80–87% ee (entries 2–9). While the enantioselective reaction of cinnamaldehyde (**1p**) was less selective (61% ee, entry 10) than those of aryl aldehydes, the corresponding α-methyl substituted congener **1q** underwent a much more selective addition (entry 11). Moderate to good enantioselectivities (66–84% ee) were obtained for zinc acetylides with varied substituents, while unsatisfactory chemical yields (15–55%) were observed (entries 13–16).

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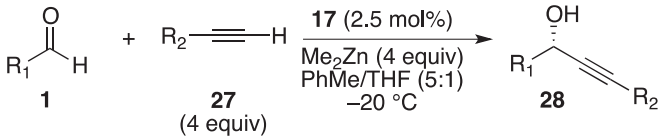
Table 7
Enantioselective alkynylzincs addition reaction of aldehydes **1** catalyzed by γ-amino thiol **17**



Entry	R_1	R_2	Time (h)	Yield[a] (%)	ee[b] (%)
1	C_6H_5 (**1a**)	C_6H_5 (**27a**)	48	68 (**28aa**)	86
2	2-Me-C_6H_4 (**1b**)	C_6H_5 (**27a**)	72	79 (**28ba**)	86
3	3-Me-C_6H_4 (**1c**)	C_6H_5 (**27a**)	72	88 (**28ca**)	85
4	4-Me-C_6H_4 (**1d**)	C_6H_5 (**27a**)	72	70 (**28da**)	86
5	4-MeO-C_6H_4 (**1e**)	C_6H_5 (**27a**)	72	27[c] (**28ea**)	80
6	4-CF_3-C_6H_4 (**1f**)	C_6H_5 (**27a**)	48	84 (**28fa**)	87
7	2-Cl-C_6H_4 (**1g**)	C_6H_5 (**27a**)	48	79 (**28ga**)	83
8	3-Cl-C_6H_4 (**1h**)	C_6H_5 (**27a**)	48	82 (**28ha**)	86
9	4-Cl-C_6H_4 (**1i**)	C_6H_5 (**27a**)	48	80 (**28ia**)	86
10	Cinnamyl (**1p**)	C_6H_5 (**27a**)	48	41 (**28pa**)	61
11	2-Me-Cinnamyl (**1q**)	C_6H_5 (**27a**)	48	21[d] (**28qa**)	71
12	Hydrocinnamyl (**1r**)	C_6H_5 (**27a**)	48	69 (**28ra**)	49
13	C_6H_5 (**1a**)	4-CF_3-C_6H_4 (**27b**)	48	46 (**28ab**)	84
14	C_6H_5 (**1a**)	4-MeO-C_6H_4 (**27c**)	48	55 (**28ac**)	76
15	C_6H_5 (**1a**)	4-Cl-C_6H_4 (**27d**)	48	15 (**28ad**)	66
16	C_6H_5 (**1a**)	*n*-Bu (**27e**)	48	15 (**28ae**)	75

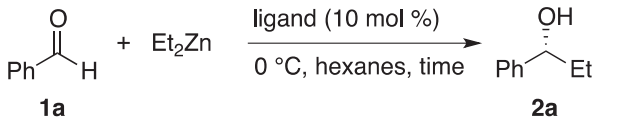
[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] **1e** was recovered in 68% yield.
[d] **1q** was recovered in 59% yield.

8. γ-Amino thiol versus γ-amino alcohol: catalytic activity and enantioselectivity

The unsuccessful synthesis of γ-amino thiol **9** from γ-amino alcohol **8** instead resulted in the originally unintended design and synthesis of ligand **17** from camphorsulfonyl chloride **11**. The catalytic activity and enantioselectivity of ligand **17** has been demonstrated in this manuscript to be useful in the preparation of a structurally diverse series of alcohols with high optical purity. Although ligand **17** shares same bicyclo[2.2.1] framework as ligand **8**, the corresponding amino group is situated at C2 instead of C10 and possesses a thiol group at C10 instead of a hydroxyl group at C2. We questioned whether the presence of the thiol group attributed to the high performance of ligand **17** in catalytic organozinc addition reactions, or whether instead the installment of an amino group at 2-position of the [2.2.1]bornane scaffold was responsible. To elucidate this, synthesis of γ-amino alcohol **29**, a hydroxy analogue of γ-amino thiol **17** was conducted and its catalytic activity and enantioselectivity was investigated. Based on Dallacker's protocol, substitution of 10-iodocamphor (**31**),[11] synthesized from camphor sulfonic acid (**30**), with KOAc under acidic conditions, ensued by a basic saponification efficiently furnished 10-hydroxylcamphor (**32**) (Scheme 5).[33] Treatment of alcohol **32** with hydroxylamine gave oxime **33** in 93% yield, which was reduced by $NiCl_2/NaBH_4$ to provide amine **34** in 84% as a single diastereomer.[34] Amine **34** underwent N,N-dialkylation reaction with 2-bromoethyl ether under basic conditions to provide compound **29** in 68% yield.

Shown in Table 8 are the results obtained from the catalytic addition of Et_2Zn to benzaldehyde (**1a**) carried out in the presence of 10 mol % of ligands (**17** and **29**) at 0 °C in hexanes. While compound **2a** was isolated in 95% yield with 97% ee (entry 1) when ligand **17** was utilized, using ligand **29** produced alcohol **2a** in a 66% yield with 30% ee (entry 2). These results clearly demonstrated the decisive influence of the thiol group for gaining high catalytic activity and enantioselectivity.

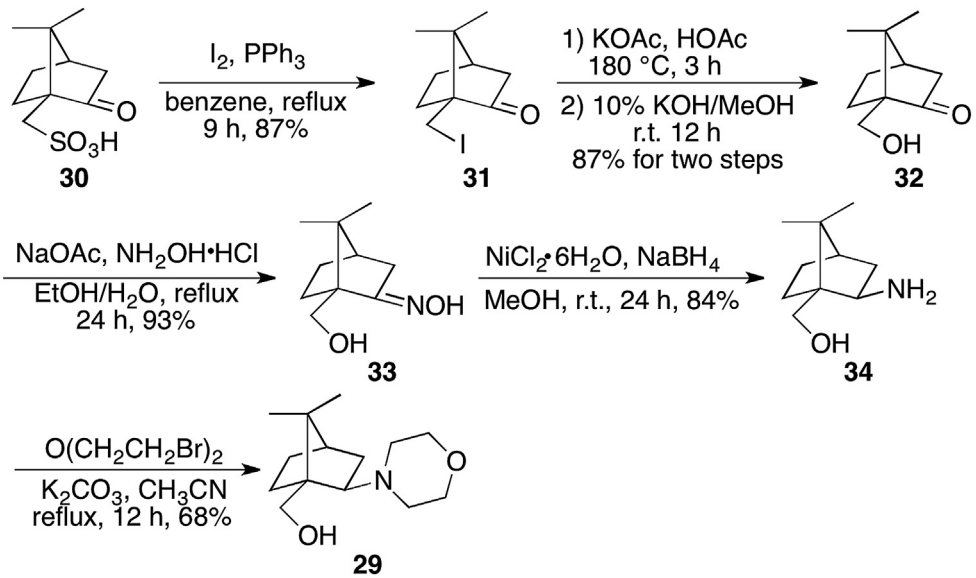
Table 8
Enantioselective Et_2Zn addition reaction of benzaldehyde catalyzed by γ-amino thiol and γ-amino alcohols



Entry	Ligand	Time (h)	Yield[a] (%)	ee[b] (%)
1	**17**	24	95	97
2	**29**	48	66	30

[a] Isolated yield.
[b] Determined by chiral HPLC.

In conclusion, a series of camphor derived chiral γ-amino alcohols and γ-amino thiols were synthesized. The catalytic efficiency and selectivity of these structurally similar ligands was tested in the enantioselective addition of Et_2Zn to benzaldehyde.



Scheme 5. Synthesis of γ-amino alcohol **29**.

Among them chiral γ-amino thiol **17** was found to be an efficient chiral modifier. Subsequent studies using ligand **17** in the catalytic organozincs addition reactions were conducted giving chiral secondary alcohols, chiral allylic alcohols, chiral diarylmethanols, chiral α-hydroxy esters with quaternary stereogenic centers, and chiral propargylic alcohols with high levels of optical purity. Given its wide application, several concise synthetic routes have been devised,[12] aside from the original synthesis, to access ligand **17** on larger scales. While chiral ligand **17** has been proved to show high stereocontrol based on a bicyclo[2.2.1]heptane skeleton, lowering catalytic loading of catalyst and reducing reaction time remain challenging. We are currently developing novel amino thiol ligands with higher efficiency and applicability for the catalytic addition reactions of organozinc reagents to carbonyl compounds.

9. Experimental section

General information. All commercial chemicals and solvents were reagent grade and were used without further treatment unless otherwise noted. All reactions were carried out under an atmosphere of argon gas. Reactions were monitored by TLC using Merck 60 F 254 silica gel plates; zones were detected visually under ultraviolet irradiation (254 nm) or by spraying with 2,4-dinitrophenylhydrazine solution (Aldrich) followed by heating. Flash column chromatography was done using silica gel. ^{1}H NMR spectra were obtained on 400 MHz and 500 MHz spectrometers. ^{13}C NMR spectra were obtained on 100 MHz and 125 MHz spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) and were reported relative to the solvent peak. High-resolution mass spectra were obtained using EI method. Optical purities of the final compounds were determined using chiral HPLC. Optical rotations were measured on a polarimeter.

9.1. General procedures for the preparation of chiral ligands

*9.1.1. Synthesis of ketoamide compound **7**.* In a 50 mL round-bottom flask was added ketopinic acid (**6**) (5.0 g, 27.4 mmol), $SOCl_2$ (41.1 mmol), the whole was heated to reflux for 2 h. After removal of the remaining $SOCl_2$, the thus-obtained acylchloride was dissolved in CH_2Cl_2 (50 mL) and was slowly added to a mixture of NEt_3 (5.8 mL, 41.6 mmol) and amine (41.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C. It was warmed up to room temperature 10 min later, and H_2O (20 mL) was added after being stirred at ambient temperature for 10 h. The aqueous layer was separated, extracted with CH_2Cl_2 (20 mL×3) and the combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and evaporated at reduced pressure to give a brown crude solid compound, which was purified column chromatography to give a white solid.

*9.1.1.1. N,N-dicyclohexyl-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-car-boxamide (**7a**).* Yield: 7.1 g, 75%, white solid [Eluting with (EtOAc: Hexanes=1:10)]. Mp 208.3–209.0 °C. $[\alpha]_D^{25}$ −13.9 (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (tt, *J*=11.6, 3.4 Hz, 1H), 2.82 (tt, *J*=11.8, 3.4 Hz, 1H), 2.56–2.38 (m, 4H), 2.24–2.16 (m, 1H), 2.12–1.97 (m, 2H), 1.95–1.83 (m, 3H), 1.82–1.66 (m, 6H), 1.63–1.49 (m, 5H), 1.47–1.28 (m, 6H), 1.18 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.0 (C═O), 168.3 (C═O), 68.8 (C), 57.4 (CH), 57.0 (CH), 50.8 (C), 43.7 (CH_2), 43.2 (CH_2), 31.9 (CH), 31.4 (CH_2), 30.1 (CH_2), 29.5 (CH_2), 27.6 (CH_2), 27.0 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 21.6 (CH_3), 21.1 (CH_3). FTIR (neat): 2968, 2929, 2849, 1733, 1635, 1521, 1507 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{22}H_{35}NO_2]^+$ 345.2668, found 345.2675.

*9.1.1.2. N,N,7,7-tetramethyl-2-oxobicyclo[2.2.1]heptane-1-carboxamide (**7b**).* Yield: 65%, white solid [Eluting with (EtOAc: Hexanes=2:3)]. Mp 81.4–82.2 °C. $[\alpha]_D^{22}$ −67.4 (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (s, 6H), 2.45 (ddd, *J*=18.0, 5.1 2.7 Hz, 1H), 2.26–2.14 (m, 1H), 2.10–1.96 (m, 2H), 1.96–1.80 (m, 2H), 1.86 (d, *J*=18.0 Hz, 1H), 1.39 (ddd, *J*=12.7, 9.1, 3.6 Hz, 1H), 1.16 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.3 (C═O), 168.9 (C═O), 67.4 (C), 50.4 (C), 43.6 (CH_2), 43.1 (CH), 38.0 (CH_3), 36.5 (CH_3), 27.1 (CH_2), 26.9 (CH_2), 21.3 (CH_3), 20.7 (CH_3). FTIR (neat): 2952, 2899, 1736, 1622, 1489, 1466 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{12}H_{19}NO_2]^+$ 209.1416, found 209.1416.

*9.1.1.3. N,N-diisobutyl-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carbox-amide (**7c**).* Yield: 78%, white solid [Eluting with (EtOAc: Hexanes=1:10)]. Mp 93.4–93.9 °C. $[\alpha]_D^{22}$ +8.5 (*c* 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.60 (dd, *J*=13.3, 7.5 Hz, 1H), 3.16–2.98 (m, 2H), 2.85 (dd, *J*=13.3, 7.5 Hz, 1H), 2.45 (ddd, *J*=18.3, 5.0, 2.7, 1H), 2.28–2.16 (m, 1H), 2.12–1.82 (m, 6H), 1.48–1.38 (m, 1H), 1.20 (s, 3H), 1.17 (s, 3H), 0.98–0.76 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1 (C═O), 169.6 (C═O), 67.8 (C), 54.1 (CH_2), 50.9 (CH_2), 43.7 (CH_2), 42.8 (CH), 28.6 (CH_2), 27.3 (CH_2), 26.4 (CH), 25.6 (CH), 21.4 (CH_3), 21.1 (CH_3), 20.2 (CH_3), 19.9 (CH_3), 19.6(CH_3). FTIR (neat): 2961, 2928, 2872, 1737, 1624, 1456, 1418 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{18}H_{31}NO_2]^+$ 293.2355, found 293.2357.

*9.1.1.4. 7,7-Dimethyl-1-(pyrrolidine-1-carbonyl)-bicyclo[2.2.1]heptane-2-one (**7d**).* Yield: 77%, white solid [Eluting with (EtOAc: Hexanes=1:6)]. Mp 116.4–117.4 °C. $[\alpha]_D^{25}$ −42.3 (*c* 2.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (dt, *J*=11.6, 5.8 Hz, 1H), 3.58–3.42 (m, 2H), 3.24–3.12 (m, 1H), 2.48 (ddd, *J*=18.4, 5.0, 2.4 Hz, 1H), 2.28–2.14 (m, 1H), 2.12–1.98 (m, 2H), 1.98–1.82 (m, 5H), 1.80–1.64 (m, 1H), 1.48–1.36 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.3 (C═O), 167.9 (C═O), 67.7 (C), 50.0 (C), 46.9 (CH_2), 46.7 (CH_2), 43.9 (CH_2), 43.4 (CH), 28.9 (CH_2), 26.7 (CH_2), 23.4 (CH_2), 21.6 (CH_3), 20.4 (CH_3). FTIR (neat): 2978, 2942, 2878, 1742, 1615, 1451, 1416 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{14}H_{21}NO_2]^+$ 235.1572, found 235.1581.

*9.1.1.5. 7,7-Dimethyl-1-(piperidine-1-carbonyl)-bicyclo[2.2.1]heptane-2-one (**7e**).* Yield: 61%, white solid [Eluting with (EtOAc: Hexanes=1:6)]. Mp 89.2–90.0 °C. $[\alpha]_D^{25}$ −21.5 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60–3.24 (m, 4H), 2.47 (ddd, *J*=18.3, 4.8, 2.8 Hz, 1H), 2.34–2.20 (m, 1H), 2.14–1.94 (m, 3H), 1.88 (d, *J*=18.4 Hz, 1H), 1.74–1.46 (m, 6H), 1.46–1.34 (m, 1H), 1.20 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.3 (C═O), 167.2 (C═O), 67.3 (C), 50.4 (C), 47.3 (CH_2), 43.5 (CH_2), 43.0 (CH), 27.3 (CH_2), 26.9 (CH_2), 26.0 (CH_2), 24.4 (CH_2), 21.2 (CH_3), 20.9 (CH_3). FTIR (neat): 2932, 2854, 1739, 1618, 1452, 1435 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{15}H_{23}NO_2]^+$ 249.1729, found 249.1745.

*9.1.1.6. 7,7-Dimethyl-1-(morpholine-1-carbonyl)-bicyclo[2.2.1]heptane-2-one (**7f**).* Yield: 73%, white solid [Eluting with (EtOAc: Hexanes=1:15)]. Mp 107.5–108.4 °C. $[\alpha]_D^{25}$ −27.4 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (ddd, *J*=11.5, 6.0, 3.6 Hz, 2H), 3.63 (ddd, *J*=11.5, 6.0, 3.6 Hz, 2H), 3.54–3.24 (m, 4H), 2.48 (ddd, *J*=18.0, 4.8, 3.2 Hz, 1H), 2.30–2.16 (m, 1H), 2.12–1.92 (m, 3H), 1.87 (d, *J*=18.8 Hz, 1H), 1.42 (ddd, *J*=12.4, 8.8, 3.2 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H). ^{1}H NMR (100 MHz, $CDCl_3$): δ 212.5 (C═O), 167.7 (C═O), 67.3 (C), 67.1 (CH_2), 50.6 (C), 43.7 (CH_2), 43.1 (CH), 27.2 (CH_2), 27.0 (CH_2), 21.3 (CH_3), 20.9 (CH_3). FTIR (neat): 2967, 2917, 2895, 1740, 1615, 1432, cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{14}H_{21}NO_3]^+$ 251.1521, found 251.1521.

9.2. Synthesis of aminoalocohol 8

To a 50 mL round-bottom flask was charged with compound **7a** (0.5 g, 1.45 mmol) and THF (5 mL). At −78 °C, a solution of $LiAlH_4$ (1.0 M, 4.0 mL, 4 mmol) was slowly added to the above-mentioned solution. It was warmed to −40 °C 2 h later, and was gradually

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warmed to ambient temperature after 2 h, and the whole mixture was heated to reflux. After refluxing for another 12 h, the mixture was cooled to 0 °C and 3 *N* $NaOH_{(aq)}$ was slowly added to stop the reaction. The solid material was filtered off on a pad of Celite and the organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to give a yellow crude product, which was purified by column chromatography.

*9.2.1. 1-((Dicyclohexylamino)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (**8a**).* Yield: 73%, white solid [Eluting with (EtOAc: Hexanes=1:2)]. Mp 129.8–130.5 °C. $[\alpha]_D^{25}$ −67.0 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.05 (br, 1H), 3.88 (dd, *J*=8.0, 4.4 Hz, 1H), 2.80 (d, *J*=12.8 Hz, 1H), 2.71 (d, *J*=12.8 Hz, 1H), 2.62 (tt, *J*=11.0, 3.3 Hz, 2H), 1.88–1.70 (m, 8H), 1.70–1.55 (m, 7H), 1.52–1.20 (m, 6H), 1.16 (s, 3H), 1.14–0.97 (m, 6H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.1 (CH), 58.1 (CH), 50.3 (C), 48.6 (C), 45.0 (CH_2), 44.5 (CH), 39.2 (CH_2), 35.1 (CH_2), 33.0 (CH_2), 28.9 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 20.6 (CH_3), 20.4 (CH_3). FTIR (neat): 3269, 2947, 2926, 2851, 1338, cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{22}H_{39}NO]^+$ 333.3032, found 333.3035.

*9.2.2. 1-((Dimethylamino)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (**8b**).* Yield: 91%, colorless oil [Eluting with (MeOH: $CHCl_3$=1:20)]. $[\alpha]_D^{25}$ −62.3 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.96 (dd, *J*=8.0, 4.4 Hz, 1H), 2.78 (d, *J*=13.2 Hz, 1H), 2.26 (s, 6H), 2.09 (d, *J*=13.2 Hz, 1H), 1.84–1.72 (m, 1H), 1.72–1.58 (m, 4H), 1.52–1.42 (m, 1H), 1.38–1.26 (m, 1H), 1.10 (s, 3H), 1.08–0.96 (m, 1H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.1 (CH), 60.0 (CH_2), 51.0 (C), 47.9 (C), 47.3 (CH_3), 44.7 (CH), 39.0 (CH_2), 33.5 (CH_2), 27.6 (CH_2), 20.4 (CH_3), 20.3 (CH_3). FTIR (neat): 3411, 2949, 2878, 2820, 1461, 1338, cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{12}H_{23}NO]^+$ 197.1780, found 197.1785.

*9.2.3. 1-((Diisobutylamino)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (**8c**).* Yield: 89%, colorless oil [Eluting with (MeOH: $CHCl_3$=1:20)]. $[\alpha]_D^{25}$ −151.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 5.35 (br, 1H), 3.92 (dd, *J*=8.0, 3.6 Hz, 1H), 2.86 (d, *J*=13.2 Hz, 1H), 2.28 (dd, *J*=12.8, 10.8 Hz, 2H), 2.06 (d, *J*=12.8 Hz, 1H), 1.91 (dd, *J*=12.8, 3.4 Hz, 2H), 1.82–1.70 (m, 3H), 1.70–1.58 (m, 3H), 1.56–1.42 (m, 1H), 1.40–1.28 (m, 1H), 1.12 (s, 3H), 1.08–0.96 (m, 1H), 0.95 (d, *J*=6.4 Hz, 6H), 0.84 (d, *J*=6.4 Hz, 6H), 0.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 77.7 (CH), 65.4 (CH_2), 56.9 (CH_2), 50.7 (C), 48.4 (C), 44.5 (CH), 38.9 (CH_2), 34.7 (CH_2), 27.8 (CH_2), 26.2 (CH), 21.6 (CH_3), 20.9 (CH_3), 20.5 (CH_3), 20.4 (CH_3). FTIR (neat): 3300, 2949, 2870, 2806, 1461, 1393, cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{18}H_{35}NO]^+$ 281.2719, found 281.2704.

*9.2.4. 7,7-Dimethyl-1-pyrrolidin-1-ylmethylbicyclo[2.2.1]heptane-2-ol (**8d**).* Yield: 88%, colorless oil [Eluting with (MeOH: $CHCl_3$=1:20)]. $[\alpha]_D^{24}$ −67.7 (*c* 1.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 3.91 (dd, *J*=7.8, 3.8 Hz, 1H), 3.08 (d, *J*=12.5 Hz, 1H), 2.70–2.56 (m, 2H), 2.52–2.40 (m, 2H), 2.10 (d, *J*=12.5 Hz, 1H), 1.82–1.70 (m, 6H), 1.70–1.60 (m, 3H), 1.42–1.32 (m, 1H), 1.34–1.24 (m, 1H), 1.10 (s, 3H), 1.00 (ddd, *J*=12.5, 9.0, 4.3 Hz, 1H), 0.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.5 (CH), 55.9 (CH_2), 55.8 (CH_2), 51.2 (C), 47.5 (C), 44.9 (CH), 38.9 (CH_2), 33.3 (CH_2), 27.5 (CH_2), 23.9 (CH_2), 20.5 (CH_3), 20.4 (CH_3). FTIR (neat): 3441, 2952, 2875, 2800, 1473, 1455, cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{14}H_{25}NO]^+$ 223.1936, found 223.1929.

*9.2.5. 7,7-Dimethyl-1-pyrrolidin-1-ylmethylbicyclo[2.2.1]heptane-2-ol (**8e**).* Yield: 91%, colorless oil [Eluting with (MeOH: $CHCl_3$=1:20)]. $[\alpha]_D^{24}$ −68.2 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 3.92 (dd, *J*=8.5, 3.5 Hz, 1H), 2.66 (d, *J*=13.5 Hz, 1H), 2.62–2.42 (m, 2H), 2.40–2.24 (m, 2H), 2.21 (d, *J*=13.5 Hz, 1H), 1.77 (ddd, *J*=12.9, 7.6, 4.0 Hz, 1H), 1.69–1.60 (m, 4H), 1.57–1.49 (m, 6H), 1.49–1.41 (m, 1H), 1.35 (br, 1H), 1.32–1.20 (m, 1H), 1.10 (s, 3H), 1.02–0.94 (m, 1H), 0.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.3 (CH), 59.5 (CH_2), 56.1 (CH_2), 50.6 (C), 47.8 (C), 44.7 (CH), 39.1 (CH_2), 34.2 (CH_2), 27.6 (CH_2), 26.1 (CH), 23.9 (CH_3), 20.4 (CH_3). FTIR (neat): 3393, 2933, 2876, 2806, 1386, 1369, 1350 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{15}H_{27}NO]^+$ 237.2093, found 237.2102.

*9.2.6. 7,7-Dimethyl-1-morpholin-4-ylmethylbicyclo[2.2.1]heptane-2-ol (**8f**).* Yield: 89%, colorless oil [Eluting with (EtOAc: Hexanes=1:6)]. $[\alpha]_D^{25}$ −64.8 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 3.91 (dd, *J*=8.0, 4.0 Hz, 1H), 3.67 (t, *J*=4.5 Hz, 4H), 2.72 (d, *J*=13.0 Hz, 1H), 2.68–2.54 (m, 2H), 2.46–2.32 (m, 2H), 2.25 (d, *J*=13.0 Hz, 1H), 1.82–1.74 (m, 1H), 1.72–1.60 (m, 4H), 1.55–1.46 (m, 1H), 1.30–1.18 (m, 1H), 1.10 (s, 3H), 1.04–0.94 (m, 1H), 0.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.1 (CH), 66.9 (CH_2), 59.2 (CH_2), 55.1 (CH_2), 50.8 (C), 47.9 (C), 44.6 (CH), 38.9 (CH_2), 34.0 (CH_2), 27.6 (CH_2), 20.4 (CH_3), 20.3 (CH_3). FTIR (neat): 3478, 2805, 2731, 1476, 1112 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{14}H_{25}NO_2]^+$ 239.1885, found 239.1895.

9.3. 1-Hydroxymethyl-7,7-dimethyl-bicyclo[2,2,1]heptan-2-one (32)

A flask, equipped with a condenser, containing 10-iodocamphor (**31**) (2.06 g, 7.4 mmol), glacial acetic acid (3.3 mL, 58 mmol) and potassium acetate (5.09 g, 52 mmol) was heated at 180 °C for 3 h. After the flask was cooled to room temperature, the mixture was added H_2O (10 mL), and was extracted with EtOAc (20 mL×3). The combined organic solution was concentrated and then evaporated in vacuo. The residue was added 10% KOH/MeOH solution (35 mL). The solution was stirred at room temperature for 12 h, and then neutralized with aqueous 3 *N* NaOH solution. The solution was added ethyl acetate (40 mL) and water (40 mL), and the layers were separated. The organic layer was extracted with EtOAc (40 mL×2). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the crude product. The crude product was purified by column chromatography (EtOAc:*n*-hexanes=1:4) to yield 10-hydroxycamphor (**32**) as a white powder (1.08 g, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (d, *J*=12.0 Hz, 1H), 3.63 (d, *J*=12.0 Hz, 1H), 2.40 (d, *J*=18.4 Hz, 1H), 2.06 (t, *J*=4.6 Hz, 1H), 2.03–1.94 (m, 1H), 1.85 (d, *J*=18.4 Hz, 1H), 1.82 (td, *J*=12.6, 4.0 Hz, 1H), 1.62–1.55 (m, 1H), 1.41–1.35 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H).

9.4. 1-Hydroxymethyl-7,7-dimethyl-bicyclo[2.2.1]heptan-2-one oxime (33)

A mixture of 10-hydroxycamphor (**32**) (0.29 g, 1.7 mmol), $NH_2OH{\cdot}HCl$ (0.24 g, 3.4 mmol), NaOAc (0.28 g, 3.4 mmol), EtOH (6.0 mL), and H_2O (2.5 mL) in a 25 mL flask was heated to reflux for 24 h. After cooling to room temperature, the mixture was extracted with EtOAc (20 mL×3). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield the crude product. The crude product was purified by column chromatography (EtOAc:*n*-hexanes=1:3 as an eluent) to afford oxime **33** as colorless crystals (0.294 g, 93%). Mp 140–145 °C. $[\alpha]_D^{27}$ −57.4 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.90 (d, *J*=11.6 Hz, 1H), 3.63 (d, *J*=11.6 Hz, 1H), 2.56 (dt, *J*=18.0, 3.6 Hz, 1H), 2.04 (d, *J*=18.0 Hz, 1H), 1.90–1.76 (m, 3H), 1.68–1.62 (m, 1H), 1.30–1.24 (m, 1H), 0.94 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (C), 61.5 (CH_2), 56.2 (C), 48.1 (C), 44.5 (CH), 33.0 (CH_2), 28.8 (CH_2), 26.9 (CH_2), 20.3 (CH_3), 18.8 (CH_3). FTIR (neat): 3390, 2948, 2878, 2249, 1680, 1451, 1424 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{10}H_{17}NO_2]^+$ 183.1259, found 183.1274.

9.5. (2*R*)-(2-Amino-7,7-dimethyl-bicyclo[2,2,1]hept-1-yl)-methanol (34)

Oxime **33** (0.579 g, 3.2 mmol) and $NiCl_2{\cdot}6H_2O$ (4.5 g, 19 mmol) were dissolved in MeOH (15 mL), and the mixture was cooled

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to−30 °C. After 30 min, $NaBH_4$ (3.6 g, 95 mmol) was added in portions in 30 min. After stirring for another 30 min, the mixture was slowly warmed to room temperature in 2 h. The mixture was stirred at room temperature for 12 h and was diluted with Et_2O (15 mL). The mixture was slowly added concentrated ammonia water (10 mL, 28%). The suspended mixture was filtrated through a pad of Celite. The filtrate was diluted with aqueous 3 *N* NaOH (20 mL), and the mixture was extracted with EtOAc (20 mL×3). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield the crude product. The crude product was purified by column chromatography (eluent: chloroform then methanol) to afford amine **34** as colorless crystals (0.449 g, 84%). Mp>200 °C. $[\alpha]_D^{27}$ +35.3 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 3.82 (d, *J*=11.5 Hz, 1H), 3.77 (d, *J*=11.5 Hz, 1H), 3.03 (dd, *J*=8.5, 5.0 Hz, 1H), 2.63 (br, 3H), 1.82 (dd, *J*=13.3, 8.8 Hz, 1H), 1.70–1.62 (m, 2H), 1.56–1.51 (m, 1H), 1.41–1.35 (m, 1H), 1.14 (s, 3H), 1.02 (td, *J*=7.0, 3.0 Hz, 2H), 0.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 63.9 (CH_2), 59.4 (CH), 51.5 (C), 46.7 (C), 46.1 (CH), 42.6 (CH_2), 32.5 (CH_2), 26.7 (CH_2), 21.7 (CH_3), 20.7 (CH_3). FTIR (neat): 3381, 3306, 2987, 2951, 2878, 1588, 1479, 1458 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{10}H_{19}NO]^+$ 169.1467, found 169.1471.

9.6. (2*R*)-(7,7-Dimethyl-2-morpholin-4-yl-bicylco[2,2,1]hept-1-yl)-methanol (29)

Amine **34** (0.155 g, 0.92 mmol) and K_2CO_3 (0.25 g, 1.8 mmol) were dissolved in CH_3CN (4.6 mL). The mixture was added dibromoethyl ether (0.17 mL, 1.4 mmol) and heated to reflux for 12 h. After cooling to room temperature, the mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield the crude product. The crude product was purified by column chromatography (EtOAc:hexanes=1:2 as an eluent) to afford amino alcohol **29** as a colorless oil (0.149 g, 68%). $[\alpha]_D^{26}$ −88.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 5.29 (br, 1H), 3.97 (d, *J*=12.0 Hz, 1H), 3.77 (d, *J*=12.0 Hz, 1H), 3.73–3.70 (m, 2H), 3.66–3.60 (m, 2H), 2.65–2.56 (m, 4H), 2.07–2.01 (m, 1H), 1.75–1.66 (m, 2H), 1.62 (t, *J*=4.4 Hz, 1H), 1.39 (dd, *J*=12.8, 9.6 Hz, 1H), 1.28 (td, *J*=12.2, 4.8 Hz, 1H), 1.10 (s, 3H), 1.08–1.03 (m, 1H), 0.96–0.88 (m, 1H), 0.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 74.2 (CH), 67.6 (CH_2), 67.6 (CH_2), 64.4 (CH_2), 51.9 (C), 47.0 (C), 45.8 (CH), 33.0 (CH_2), 31.5 (CH_2), 26.7 (CH_2), 22.1 (CH_3), 20.2 (CH_3). FTIR (neat): 3445, 2954, 2879, 2852, 1454, 1260, 1115 cm^{-1}. HRMS (EI): *m*/*z* calcd for $[C_{14}H_{25}NO_2]^+$ calculated 239.1885, found 239.1884.

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Supplementary data

Supplementary data (Copies of ^1H and ^{13}C NMR spectra for all products) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.07.038. These data include MOL files and InChiKeys of the most important compounds described in this article.

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