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Synthesis of Novel Chiral (Thio)ureas and Their Application as Organocatalysts and Ligands in Asymmetric Synthesis

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The synthesis of novel chiral (thio)ureas **1**–**10** and **14**–**26** is described. These (thio)ureas incorporate chiral auxiliaries derived from (*R*)- or (*S*)-α-phenylethylamine, (*R*)-phenylglycine, or (1*R*,2*S*)-ephedrine. The phenylethyl group in compounds **1**–**10** and **21**–**24** adopts a particular orientation in the molecular structure as a consequence of 1,3-allylic strain with the (thio)carbonyl group. Ureas **1**–**10** were tested as Lewis basic organocatalysts in epoxide ring opening and in aldolic condensation, and it was found that the tetrasubstituted urea (*R*,*R*)-**2** afforded the best results in terms of reaction yields. (Thio)ureas **20**–**26** were examined as ligands in the enantioselective diethylzinc addition to benzaldehyde, observing that C_2-symmetric chiral urea (*R*,*S*,*R*,*S*)-**20** provides the expected carbinol in nearly quantitative yield and in up to 62% enantiomeric excess.

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Introduction

The search for new synthetic methodologies by means of novel reagents or catalysts is a never-ending task in organic chemistry. In the past few years, organocatalysis has become a powerful tool in synthetic chemistry as a consequence of several major advantages; in particular, (1) it employs relatively simple and inexpensive reagents; (2) it proceeds under mild reaction conditions; and (3) it does not require of the use of potentially toxic or sensitive metals.[1] Salient developments in organocatalysis recently reported are based in the (thio)urea moiety, which can act as a Brønsted acid by forming hydrogen bonds to activate the substrate.[2] Here it is worth mentioning relevant applications such as the enantioselective 1,4-additions achieved with bifunctional organocatalysts,[3] enantioselective Mannich reactions in the generation of β-amino acids,[4] asymmetric Strecker reactions in the preparation of natural and unnatural α-amino acids,[5] Baylis–Hillman reactions,[6] and others.[7] These applications demonstrate the usefulness of hydrogen bonding with chiral Brønsted acids in the activation of prochiral substrates for the preparation of enantioenriched derivatives.

The urea functionality is also present in the structure of *N*,*N*′-dimethylpropyleneurea (DMPU), which is a polar aprotic solvent that is used as a non-toxic substitute to the even more polar but known carcinogen hexamethylphosphoric triamide (HMPA).[8] An interesting effect of HMPA and DMPU as solvents or additives in organolithium chemistry is that both of them have a determinant effect on the aggregation state of alkyllithiums and thus on their reactivity.[9] With these precedents, a few years ago we synthesized several chiral analogues of DMPU and explored their potential use in regio- and enantioselective addition of 2-(1,3-dithianyl)lithium to 2-cyclohexenone.[10]

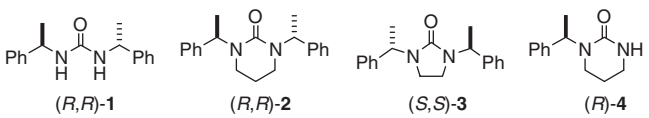
In this context, Denmark's work with chiral phosphoramides (chiral HMPA analogues) provided a novel kind of organocatalytic activity, i.e. by means of Lewis basic activation, in the following reactions: aldol condensation,[11] epoxide ring opening by weak nucleophiles,[12] and allylation.[13] In principle, ureas can also be employed as Lewis bases for this kind of nucleophilic reactions,[14] as well as in organolithium chemistry. In particular, related Lewis bases that have been used as chiral organocatalysts in enantioselective allylation reactions are *N*-oxides,[15] and sulfoxides.[16]

In addition, thioureas have been shown to be efficient and air-stable ligands that enhance reaction rates in a large variety of systems.[17] Furthermore, the capability to act as hydrogen-bond donors enables (thio)ureas to function as anion recognizing and sensing agents.[18] Indeed, when a chiral carboxylate is perceived with a chiral thiourea, enantiodiscrimination becomes feasible.[19]

Results and Discussion

Synthesis of Chiral Ureas ***1*–*9*, *14*–*18*, *and* *20***

The α-phenylethylamine group was selected as chiral adjuvant as it has showed extended applicability in asymmetric synthesis.[20] In a previous article,[21] we showed that ureas **1**–**4** (Scheme 1) incorporating the α-phenylethylamine group exhibit



(*R*,*R*)-**1** (*R*,*R*)-**2** (*S*,*S*)-**3** (*R*)-**4**

Scheme 1.

10.1071/CH08116 0004-9425/08/050364

a substantial preference (6.3–10.9 kJ mol^{-1}) in favour of those conformations with a *syn*-periplanar arrangement of the C–H bond and the N–C(O) segment (Fig. 1). This substantial conformational bias is a consequence of allylic A[1,3] strain[22] and could lead, in principle, to good enantioinduction in reactions catalyzed by them.

Additional ureas incorporating the α-phenylethylamine group ((*R*)-**5**–**7**) were obtained via the deprotonation of (*R*)-**4** with sodium hydride and subsequent alkylation with the corresponding alkyl halide (Scheme 2). Repeated attempts to synthesize bis-ureas with 1,3-diiodopropane as the electrophile were unsuccessful because of a competitive elimination–substitution reaction to give (*R*)-**7** (Scheme 2).

Nevertheless, chiral bis-ureas (*R*,*R*)-**8** and (*R*,*R*)-**9** were successfully prepared when 1,2-di(bromomethyl)benzene and 1,8-di(bromomethyl)naphthalene, which lack labile α-hydrogens, were employed as the electrophiles (Scheme 3).

Interestingly, when (*S*,*S*)-bis-α-phenylethylamine was treated with triphosgene, air-stable chloroformamide (*S*,*S*)-**10** was formed instead of the expected linear urea (Scheme 4). Recrystallization of (*S*,*S*)-**10** gave suitable crystals for X-ray analysis (Fig. 2).

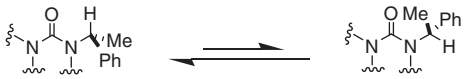
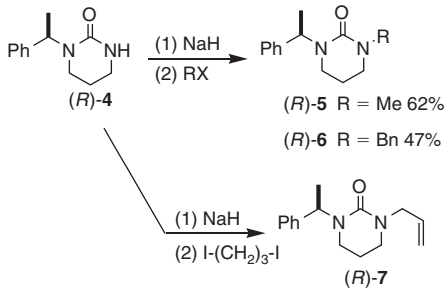
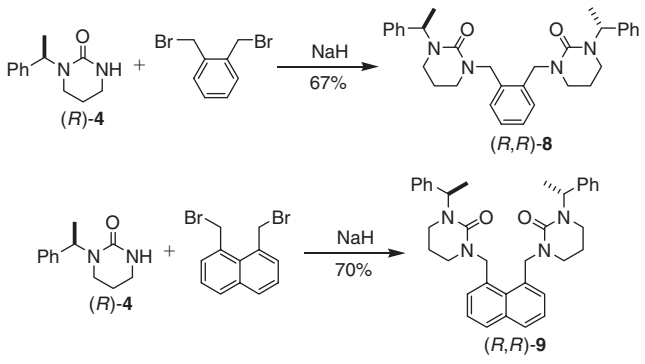


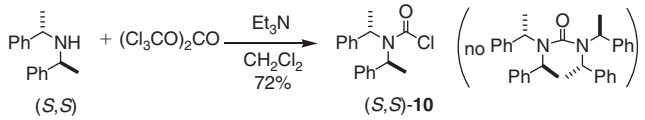
Fig. 1. Conformational preference of the α-phenylethylamine in chiral ureas **1**–**4**.



Scheme 2.



Scheme 3.



Scheme 4.

Scheme 5 shows the synthetic procedure used in the preparation of ureas (*R*)-**14**–**16**. The synthesis started with (*R*)-phenylglycine, which was protected at the amino function with a benzyloxycarbonyl group (Cbz) and converted to the corresponding amides incorporating bulky groups such as diphenylmethyl (Dpm), *tert*-butyl (*t*-Bu), and triphenylmethyl (trityl, Tr), obtaining in this form (*R*)-**11**–**13**. The next step consisted in the removal of the protecting group, and reduction of the amide function afforded the expected diamines, which on reaction with triphosgene afforded the desired ureas (*R*)-**14**–**16** in good yields (Scheme 5). Recrystallization of (*R*)-**14** provided suitable crystals for X-ray crystallographic analysis (Fig. 3).

A third family of compounds incorporating an additional coordination site was synthesized with (1*R*,2*S*)-ephedrine as chiral auxiliary, where the β-hydroxy group was anticipated to act as an additional coordinating site. The straightforward reaction of the aminoalcohol present in ephedrine with the corresponding isocyanate gave the desired ureas, compounds (1*S*,2*R*)-**17** and (1*S*,2*R*)-**18** (Scheme 6). Finally, for the synthesis of the C_2-symmetric urea **20**, protection of the hydroxy group with trimethylsilane (TMS) provided a suitable precursor (Scheme 6). Recrystallization of (1*S*,2*R*)-**17** provided suitable crystals for X-ray crystallographic analysis (Fig. 4).

*Synthesis of Chiral Thioureas **21**–**26***

The C_2-symmetric thiourea (*S*,*S*)-**21** was prepared by reaction of thiophosgene and two equivalents of (*S*)-α-phenylethylamine (Scheme 7). For the preparation of tetrasubstituted thiourea (*R*,*R*)-**22**, a similar procedure was followed with *N*,*N*′-bis-((*S*)-α-phenylethylamine)-propane-1,3-diamine and half an equivalent

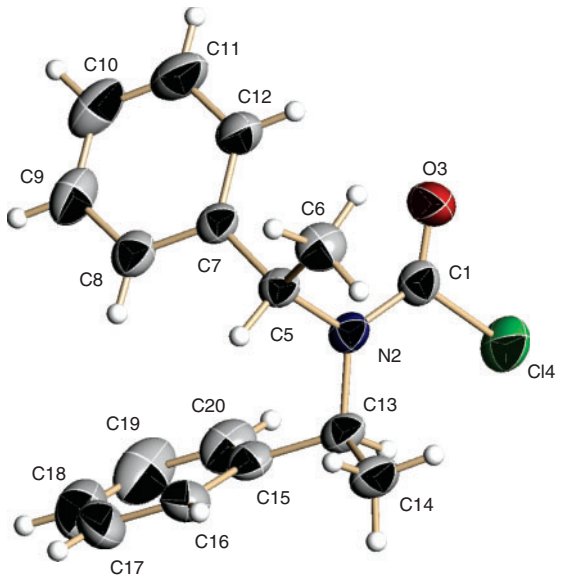
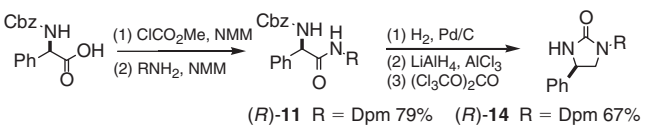
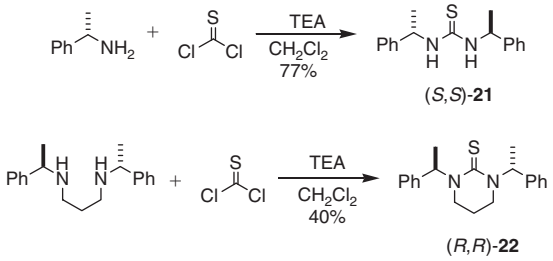


Fig. 2. X-Ray crystallographic structure and solid-state conformation of chloroformamide (*S*,*S*)-**10**.[23]



Scheme 5.

of thiophosgene (Scheme 7). Recrystallization of (*R*,*R*)-**22** gave suitable crystals for X-ray diffraction analysis, showing the *syn*-periplanar orientation of the C–H bond at the phenylethyl group and the thiocarbonyl group, again as a consequence of allylic 1,3-strain (Fig. 5).[22]



Scheme 7.

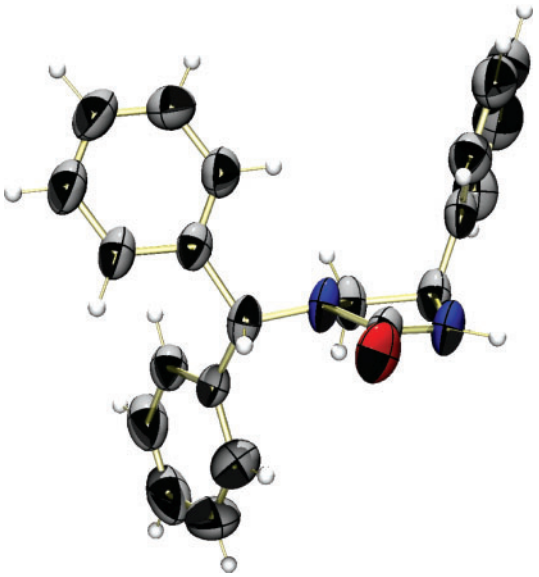


Fig. 3. X-Ray crystallographic structure and solid-state conformation of cyclic urea (*R*)-**14**.[23]

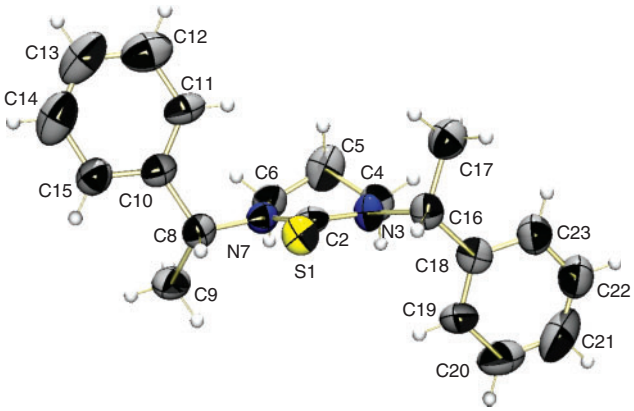
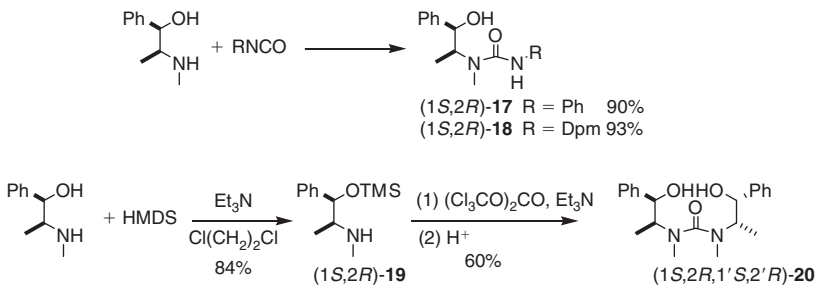


Fig. 5. X-Ray crystallographic structure and solid-state conformation of thiourea (*R*,*R*)-**22**.[23]



Scheme 6.

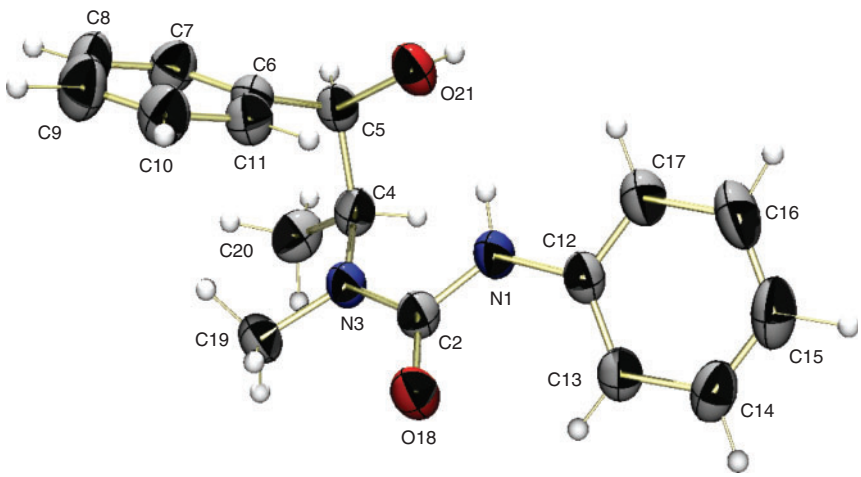
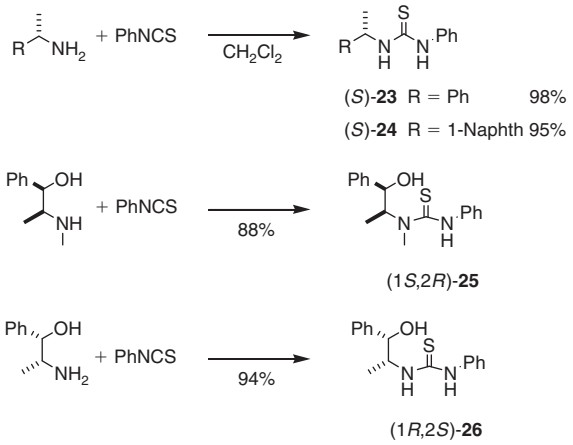


Fig. 4. X-Ray crystallographic structure and solid-state conformation of hydroxylated urea (1*S*,2*R*)-**17**.[23]



Scheme 8.

By the same token, thioureas (*S*)-**23**, (*S*)-**24**, (1*S*,2*R*)-**25**, and (1*R*,2*S*)-**26** were prepared in almost quantitative yield by treatment of the corresponding chiral amine or aminoalcohol with phenylisothiocyanate (Scheme 8).

Analysis of the X-Ray Crystallographic Structures Obtained in the Present Work

Molecular structures for compounds (*S*,*S*)-**10**, (*R*)-**14**, (1*S*,2*R*)-**17**, and (*R*,*R*)-**22** are shown in Figs 2–5. Selected bond lengths and angles are given in Table 1.

Bond distances and angles in the C(X)–NR segment show some differences in the four compounds depending on the substituents at the urea fragment. An analysis of data obtained from the Cambridge Crystallographic database some years ago[24] reports that C–N distances in substituted ureas present average values of 1.347 and 1.363 Å for *N*-monosubstituted and *N*,*N*-disubstituted derivatives respectively. The values observed in compounds (*R*)-**14** and (*R*,*S*)-**17**, which incorporate an NH–C(O) fragment, show C–N distances of 1.352(1) and 1.366(1) Å – larger than the values given above but similar to those described in other cases.[25,26]

A larger value of C–N bond length appears to correlate with the steric demand of the substituent. Thus, the largest C–N distance, 1.382(2) Å, is observed in cyclic urea (*R*)-**14**, where a diphenylmethyl –C(H)Ph_2 group is bonded to the nitrogen atom. The shortest C–N bond length among the four compounds described here is 1.336(3) Å, observed in (*S*,*S*)-**10**; nevertheless, this value is probably influenced by the presence of the electronegative chlorine atom bonded to the carbonyl group. Compound (1*S*,2*R*)-**17** shows slightly different values for the two C–N bonds; in this case, not only are the *N*-substituents different, but the nitrogen atom bound to ephedrine is also involved in an intramolecular hydrogen bridge with the proton on the –OH group. The oxygen–nitrogen distance is 2.854 Å.

Carbonyl C=O distances show a small increase on going from (*R*)-**14**, 1.228(2) Å, to (1*R*,2*S*)-**17**, 1.243(2) Å, but both values are within the range observed for this type of bond. The corresponding bond in (*S*,*S*)-**10** is much shorter, 1.191(3) Å, again probably as a consequence of the electronegative chlorine atom.

The thiocarbonyl C=S bond in (*R*,*R*)-**22** shows a value of 1.703(8) Å, which is significantly shorter than the values reported by Flippen and Karle (1.73 Å)[27] but that determination was not very precise.

The replacement of oxygen by sulfur in the urea fragment does not affect significantly the angles around the carbon atom of the carbonyl (or thiocarbonyl) group, suggesting little change on the hybridization of the carbon atom.

As anticipated, the presence of a ring around the urea fragment has a much larger effect on the N–C–O angles. The effect is more pronounced in (*R*)-**14** where the small size of the ring leads to a smaller N–C–N angle (107.29(18)°) and simultaneously to wider N–C–O angles (1278(16) and 124.92(18)°). The angle about the nitrogen atoms inside the ring show values closer to an ideal of 109° (110.17(16)° and 113.56(16)°), in sharp contrast with the angles around the carbon atoms that complete the ring, which show angles N(3)–C(4)–C(5) and N(1)–C(5)–C(4) of 100.91(17) and 101.90(15)°, respectively.

The chloro–carbonyl–nitrogen fragment in compound (*S*,*S*)-**10** shows a nearly planar conformation with torsion angles for O(3)–C(1)–N(2)–C(5) and O(3)–C(1)–N(2)–C(13) of −5.4(3) and −176(2)°, respectively, whereas the Cl(4)–C(1)–N(2)–C(5) and Cl(4)–C(1)–N(2)–C(13) show values of 174.03(14) and 4.6(3)°, respectively.

Thiourea (*R*,*R*)-**22** also shows nearly planar conformations in the Y–C–N–C fragments, with torsion angle values between 174.1(8) and 178.2(6)°. Larger deviations are observed in compound (*R*)-**14** with absolute values of 163.34(16), 168.3(2), 17.8(3)°, owing to the conformation imposed by the five-membered ring. Interestingly, related five-membered ring urea derivatives[25] do not show substantial differences from 0 or 180° angles; these last compounds have $SiMe_3$ groups substituted on the nitrogen atoms and these bulky groups probably affect the overall conformation or the urea fragment.

Compound (1*R*,2*S*)-**17** presents torsion angles that indicate a substantial deviation from planarity, and this could be due to the presence of the hydrogen bridge already mentioned that affects the conformation adopted by the urea group.

Ureas in Organocatalysts (Lewis Bases)

As demonstrated by Denmark,[12] Lewis bases such as phosphoramide or *N*-oxide derivatives are able to coordinate to weak Lewis acids such as $SiCl_4$, allyltrichlorosilane, and trichlorosilylenolethers and are efficient promoters of epoxide ring opening, allylation, and aldol condensation reactions. In the present paper, we show that ureas are also capable of promoting those reactions.

Indeed, the opening of cyclohexene oxide with silicon tetrachloride does not proceed in the absence of a promoter. However, in the presence of 0.1 equiv. of the urea as Lewis base, the desired reaction took place and afforded good yields of the expected chlorohydrin **27**, especially under activation by tetrasubstituted ureas (*R*,*R*)-**2** and (*S*,*S*)-**3** (entries 3 and 4 in Table 2).

By the same token, several (thio)ureas prepared in the current work were tested as potential activators in the aldol condensation reaction of acetophenone trimethylsilyl ether enolate via in situ transilylation to the corresponding trichlorosilylenol derivative. As shown in Table 3, essentially no reaction takes place in the absence of (thio)urea (entry 1 in Table 3); however, aldol product **28** is obtained in moderate to good yields with urea activation. Two salient observations from Table 3 are: (1) relative to carbonyl, thiocarbonyl results in a dramatic decrease of the reaction rate (entries 2 and 3 in Table 3), which can be explained in terms of the softer nature of the thioureas (weaker coordination to the benzaldehyde carbonyl). (2) Trisubstituted ureas are less effective than tetrasubstitued ureas (cf. entries 4 and 8–12 v. entries 2

Table 1. Some selected bond lengths [Å] and angles [°] of compounds (*S*,*S*)-10, (*R*)-14, (1*S*,2*R*)-17, and (*R*,*R*)-22

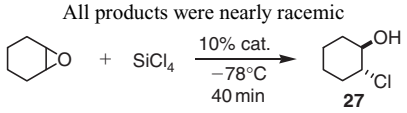
E, heteroatom

Compound bond	(*S*,*S*)-**10**	(*R*)-**14**	(1*S*,2*R*)-**17**	(*R*,*R*)-**22**
C=Y(E=O, S)[A]	1.191(3)	1.228(2)	1.243(2)	1.703(8)
N–C(Y)[A]	1.336(3)	1.352(2) (N3)	1.357(3) (N3)	1.359(8) (N3)
		1.382(2) (N1)	1.366(3) (N1)	1.360(7) (N7)
Cl–C(O)	1.803(2)			
N–C–Y[A]	128.4(2)	127.78(16) (N3)	121.45(18)	121.5(5) (N3)
		124.92(18) (N1)	122.77(19)	120.7(5) (N7)
Cl–C–O	116.20(16)			
N–C–X[B]	115.44(17)	107.29(18)	115.78(17)	117.8(6)
C–N–C(E)	124.31(17)	110.17(17) (C5)	115.78(17)	122.0(5) (C2)
		113.46(16) (C4)		123.1(5) (C7)

[A]Y = O in compounds (*S*,*S*)-**10**, (*R*)-**14**, and (*S*,*R*)-**17**; Y = S in (*R*,*R*)-**22**. [B]X = Cl in compound (*S*,*S*)-**10**, and X = N in compounds (*R*)-**14**, (1*S*,2*R*)-**17**, and (*R*,*R*)-**22**.

Table 2. Opening of cyclohexene oxide with silicon tetrachloride

All products were nearly racemic



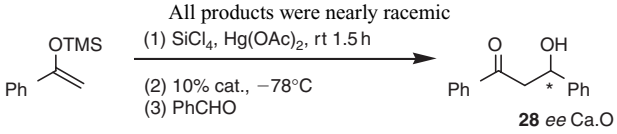
27

Entry	Catalyst	Yield [%]
1	–	<5
2	(*R*,*R*)-**1**	46
3	(*R*,*R*)-**2**	83[A]
4	(*S*,*S*)-**3**	82

[A]95% yield with 1 equiv. catalyst.

Table 3. Aldol condensation reaction between acetophenone trimethylsilyl ether enolate and benzaldehyde

All products were nearly racemic



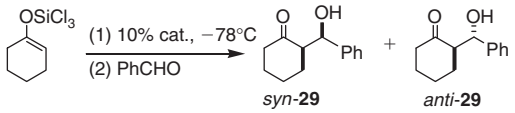
28 *ee* Ca.O

Entry	Catalyst	Yield [%]
1	–	<5
2	(*R*,*R*)-**2**	90
3	(*R*,*R*)-**22**	42
4	(*R*)-**4**	42
5	(*R*)-**5**	79
6	(*R*,*R*)-**8**	77
7	(*R*,*R*)-**9**	79
8	(*R*)-**14**	57
9	(*R*)-**15**	42
10	(*R*)-**16**	46
11	(*R*,*S*)-**17**	20
12	(*R*,*S*,*R*,*S*)-**20**	33

and 5–7 in Table 3). Unexpectedly, all aldol products in Table 3 were nearly racemic.

In this context, the diastereo- and enantioselectivity of the aldol condensation reaction between the corresponding trichlorosilyl enolate of cyclohexanone with benzaldehyde were evaluated. The results are collected in Table 4 and show again moderate to good chemical yields of *syn*-**29** and *anti*-**29**. Tetrasubstituted urea (*R*,*R*)-**2** proved to be the best organocatalyst for this conversion (83% yield, 95% diastereoselectivity, 8% enantiomeric excess (*ee*)).

Table 4. Aldol condensation reaction between the trichlorosilyloxicyclohexene and benzaldehyde



syn-**29** *anti*-**29**

Entry	Catalyst	Yield [%]	*syn*/*anti*
1	(*R*,*R*)-**2**	83	95:5[A]
2	(*R*)-**14**	44	59:41
3	(*R*,*S*,*R*,*S*)-**20**	43[B]	74:26[B]

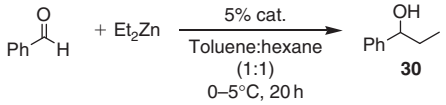
[A]8% *ee* was determined for the *syn* isomer.
[B]10% *ee* was determined for the *syn* isomer.

(Thio)ureas as Ligands in the Addition of Diethylzinc to Benzaldehyde

The enantioselective reaction between organometallic reagents and carbonyl compounds is one of the most useful methods for the synthesis of carbinols. Among organometallic compounds, dialkylzincs have the limitation that no addition reaction takes place without the activation of the metal by a ligand (usually aminoalcohols). It was deemed of interest to verify whether the addition of diethylzinc to benzaldehyde could be promoted by the (thio)ureas prepared in the present work.

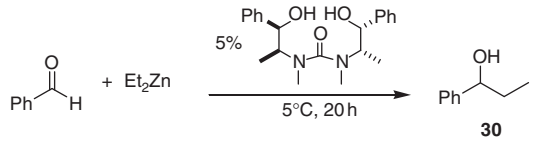
The reaction was carried out with 5 mol-% of the ligand in a mixture of solvents, toluene/hexane (1:1). As it can be observed in Table 5, monodentade ligands were not efficient ligands for this reaction because they led to product formation in only poor yield (entries 1–3). Bis-ureas gave better yields of the addition product **30**, although this product was obtained in racemic form (entries 4 and 5 in Table 5). Most interestingly, among those ureas containing a hydroxy group, the one with two ephedrine segments (entry 8 in Table 5) afforded a 46% *ee* of the (*R*)-enantiomer. Also remarkably, disubstituted thioureas provided carbinol **30** in a quantitative yield (entries 9–11 and 13 in Table 5).

Table 5. Additon of diethylzinc to benzaldehyde in the presence of (thio)ureas



Entry	Ligand	Yield [%]	Enantiomeric ratio (*R*)/(*S*)
1	(*R*,*R*)-**2**	16	49:51
2	(*R*,*R*)-**22**	19	47:53
3	(*R*)-**14**	15	55:45
4	(*R*,*R*)-**8**	63	50:50
5	(*R*,*R*)-**9**	70	51:49
6	(1*R*,2*S*)-**17**	37	49:51
7	(*R*,*S*)-**18**	36	48:52
8	(*R*,*S*,*R*,*S*)-**20**	50	73:27
9	(*S*,*S*)-**21**	99	56:44
10	(*S*)-**23**	99	40:60
11	(*S*)-**24**	94	52:48
12	(*R*,*S*)-**25**	82	63:37
13	(*S*,*R*)-**26**	99	40:60

Table 6. Addition of diethylzinc to benzaldehyde with (*R*,*S*,*R*,*S*)-20 as ligand



Entry	Temp. [°C]	Additive	Yield [%]	Enantiomeric ratio (*R*)/(*S*)
1	−20	–	10	68:32
2	5	–	50	73:27
3	25	–	55	68:32
4	5	–	54[A]	76:24
5	5	5% BuLi	51	81:19
6	5	10% BuLi	35	76:24

[A] 10% of the urea was employed.

Additional experiments were carried out to optimize the results obtained with chiral C_2-symmetric (*R*,*S*,*R*,*S*)-**20** as ligand (Table 6). When the reaction was carried out at different temperatures, highest *ee* was obtained at 5°C (entries 1–3 in Table 6). Most relevantly, when 10% of the ligand was used, a 52% *ee* was obtained (entry 4); furthermore, by adding 5 mol-% of BuLi, carbinol **30** was formed with a higher 62% *ee* (entry 5 in Table 6).

Conclusions

In conclusion, several novel chiral (thio)ureas were prepared, which showed potential as efficient Lewis basic organocatalysts in aldol reactions and epoxide ring-opening reactions, although no significant enantioinduction was observed. The present work also shows that ureas are good catalysts for the addition of diethylzinc to benzaldehyde. In particular, C_2-symmetric urea (*R*,*S*,*R*,*S*)-**20** promoted the high-yield formation of carbinol **30** in up to 62% *ee*.

Experimental

General

THF and toluene were distilled from sodium, CH_2Cl_2 was distilled from P_2O_5, and silicon tetrachloride was heated to reflux for 2 h and distilled before use. High resolution mass spectra were registered on an Agilent Technology Model LS/MSD Ion TOF mass spectrometer coupled to a HPLC Model 1100. TLC was carried out on silica gel F_{254} plates, with detection using UV radiation or 10% aqueous H_2SO_4. Flash column chromatography (FC)[28] was carried out with silica gel (230–400 mesh). Melting points were not corrected. ^{1}H NMR spectra were recorded using JEOL Eclipse-400 (400 MHz), Bruker Avance (300 MHz), and Jeol GSX-270 (270 MHz) spectrometers. ^{13}C NMR spectra were recorded with JEOL Eclipse-400 (100 MHz), Bruker Avance (75 MHz), and Jeol GSX-270 (68 MHz) spectrometers. Chemical shifts (δ) are in ppm downfield from the internal TMS reference; the coupling constants (*J*) are given in Hz. Optical rotations were measured in a Perkin–Elmer 240 polarimeter, using the sodium D-line (589 nm) unless indicated otherwise.

General Procedure for the N-Alkylation of (R)-*4*

A solution of 0.55 g (2.7 mmol) of (*R*)-**4**[21] in 25 mL of anhydrous THF under a N_2 atmosphere was cooled to 0°C and treated with 0.178 g (2.9 mmol) of 40% NaH. The resulting solution was stirred for 30 min before the addition of the alkylating agent (2.97 mmol). The resulting mixture was stirred for 20 h at room temperature and then quenched with the slow addition of 20 mL of water. The product was extracted with EtOAc (2 × 30 mL), the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The purification was accomplished by FC (hexane/EtOAc, 1:1).

N-*Methyl*-N′-*((*R*)-α-phenylethyl)propyleneurea (*R*)-**5**. The general procedure for *N*-alkylation was followed. Yield 62% (0.37 g). Colourless oil, $[\alpha]_D^{25°}$ +86.5° (*c* 0.86, $CHCl_3$). (Found: $[M + 1]^+$ 219.1506. Calc. for $C_{13}H_{18}N_2O$: $[M + 1]^+$ 219.1497). δ_H ($CDCl_3$, 270 MHz) 7.32–7.12 (5H, m), 5.86 (1H, q, *J* 7.1), 3.20–2.98 (3H, m), 2.93 (3H, s), 2.78–2.68 (1H, m), 1.82–1.70 (2H, m), 1.43 (3H, d, *J* 7.1). δ_C ($CDCl_3$, 68 MHz) 156.4, 141.8, 128.3, 127.3, 126.9, 51.0, 47.8, 39.5, 35.9, 22.3, 15.9.

N-*Benzyl*-N′-*((*R*)-α-phenylethyl)propyleneurea (*R*)-**6**. The general procedure for *N*-alkylation was followed. Yield 47% (0.37 g). Colourless oil, $[\alpha]_D^{25°}$ +68.1° (*c* 1.32, $CHCl_3$). (Found: $[M + 1]^+$ 295.1810. Calc. for $C_{19}H_{22}N_2O$: $[M + 1]^+$ 295.1810). δ_H ($CDCl_3$, 270 MHz) 7.41–7.18 (10H, m), 6.00 (1H, q, *J* 7.1), 4.62 (2H, s), 3.31–3.0 (3H, m), 2.83–2.75 (1H, m), 1.77–1.70 (2H, m), 1.51 (3H, d, *J* 7.1). δ_C ($CDCl_3$, 68 MHz) 156.3, 141.8, 138.7, 128.6, 128.3, 127.8, 127.3, 127.1, 127.0, 51.7, 51.2, 45.2, 39.6, 22.4, 15.9.

*1,2-Bis-(3-(*R*)-α-phenylethyl-2-oxotetrahydropyrimidyl)methylbenzene (*R,R*)-**8***. The general procedure for *N*-alkylation was followed with 0.75 g (3.7 mmol) of (*R*)-**4** and 0.44 g (1.66 mmol) of 1,2-di(bromomethyl)benzene. 67% yield (0.57 g). White semisolid, mp 45–47°C. $[\alpha]_D^{25°}$ +89.7° (*c* 0.97, $CHCl_3$). (Found: $[M + 1]^+$ 511.3064. Calc. for $C_{32}H_{39}N_4O_2$: $[M + 1]^+$ 511.3073). δ_H ($CDCl_3$, 400 MHz) 7.42–7.23 (14H, m), 6.01 (2H, q, *J* 7.0), 4.76 (2H, d, *J* 15.76), 4.71 (2H, d, *J* 15.76), 3.17–3.05 (6H, m), 2.87–2.80 (2H, m), 1.80–1.76 (4H, m), 1.54 (6H, d, *J* 7.0). δ_C ($CDCl_3$, 100 MHz) 156.2, 141.8, 136.6, 128.4, 128.3, 127.4, 127.0, 51.3, 48.7, 45.1, 39.7, 22.4, 16.1.

*1,8-Bis(3-(*R*)-α-phenylethyl-2-oxotetrahydropyrimidyl)methylnaphthalene (*R,R*)-**9***. The general procedure for *N*-alkylation

was followed with 0.18 g (0.9 mmol) of (*R*)-**4** and 0.13 g (0.4 mmol) of 1,8-di(bromomethyl)naphthalene. 70% yield (0.16 g). White crystals, mp 178–179°C. $[\alpha]_D^{25^\circ}$ +112.8° (*c* 0.91, $CHCl_3$). (Found: C 76.9, H 7.3, N 10.2. Calc. for $C_{36}H_{40}N_4O_2$: C 77.1, H 7.2, N 10.0%). δ_H ($CDCl_3$, 400 MHz) 7.76 (2H, d, *J* 7.0), 7.45–7.34 (12H, m), 7.28 (2H, dd, *J* 6.6 and 6.2), 6.04 (2H, q, *J* 7.0), 5.35 (2H, d, *J* 16.1), 5.24 (2H, d, *J* 16.1), 3.30–3.23 (6H, m), 2.89 (2H, ddd, *J* 11.4, 5.8 and 5.1), 1.90–1.78 (4H, m), 1.50 (6H, d, *J* 7.0). δ_C ($CDCl_3$, 100 MHz) 156.6, 141.8, 136.0, 134.4, 132.0, 128.9, 128.5, 127.4, 127.6, 125.3, 125.1, 53.0, 51.3, 45.6, 39.7, 22.5, 16.0.

N,N-*Bis((*S*)-α-phenylethyl)chloroformamide (*S,S*)-**10**. (*S*,*S*)-Bis-α-phenylethylamine 4.67 g (20.7 mmol), 5.8 mL (41.4 mmol) of Et_3N, and 40 mL of dry CH_2Cl_2 were placed in a round-bottom flask, and the resulting mixture was cooled to 0°C before the dropwise addition of a solution containing 3.2 g (10.9 mmol) of triphosgene in 15 mL of CH_2Cl_2. Stirring was continued at 0°C for 2 h and for 18 h at room temperature, and then 30 mL of 1 M HCl were added. The aqueous phase was separated and the organic layer washed with 40 mL of brine, dried (Na_2SO_4), and concentrated. The product was purified by FC (hexane/EtOAc, 85:15) yielding 4.65 g (78% yield) of (*S*,*S*)-**10** as white crystals, mp 95–97°C. $[\alpha]_D^{25^\circ}$ −191.5° (*c* 2.14, $CHCl_3$). (Found: C 71.1, H 6.6. Calc. for $C_{17}H_{18}ClNO$: C 71.0, H 6.3%). ν_{max} (KBr)/cm^{-1} 3434, 3066, 3032, 3001, 2977, 2935, 1956, 1888, 1727 (C=O), 1495, 1453, 1414, 1245, 1144, 1097, 1069, 960, 839, 698. δ_H ($CDCl_3$, 400 MHz) 7.50–7.05 (8H, m), 6.74 (2H, br), 5.82 (1H, br), 4.60 (1H, br), 1.80 (6H, d, *J* 7.1). δ_C ($CDCl_3$, 100 MHz) 146.9, 139.1, 138.8, 128.7, 128.4, 128.1, 127.9, 127.7, 127.3, 59.1, 56.1, 18.1, 17.3.

General Procedure for the Synthesis of Amides Derived from Phenylglycine

In a round bottom flask were placed 1.5 g (5.3 mmol) of (*R*)-benzyloxycarbonylaminophenylacetic acid[29] in 60 mL of THF. The solution was cooled to 0°C before the addition of 0.63 mL (5.8 mmol) of *N*-methylmorpholine. The resulting mixture was stirred for 5 min and then 0.5 mL (5.9 mmol) of methyl chloroformate was added slowly. The resulting mixture was stirred for 1 h and then a solution containing 5.8 mmol of the amine and 0.75 mL (6.9 mmol) of *N*-methylmorpholine was added. The reaction mixture was stirred for 2 h at 0°C and for 16 h at room temperature. The reaction was quenched with 50 mL of 0.1 M HCl and extracted with EtOAc (2 × 30 mL). The organic extracts were dried and concentrated, and the product purified by FC using hexane/EtOAc (1:1).

*(*R*)*-N-*Diphenylmethylbenzyloxycarbonylaminophenylacetamide (*R*)-**11***. This was prepared according to the general procedure. 78% yield (1.86 g). White solid, mp 187–188°C. −98.7° (*c* 1.1, $CHCl_3$). (Found: $[M+1]^+$ 451.2028. Calc. for $C_{29}H_{26}N_2O_3$: $[M+1]^+$ 451.2022). δ_H ([D_6]DMSO, 400 MHz) 9.11 (1H, d, *J* 8.0), 8.0 (1H, d, *J* 8.4), 7.47 (2H, d, *J* 7.0), 7.45–7.15 (16H, m), 7.07 (2H, d, *J* 6.6), 6.07 (1H, d, *J* 8.0), 5.46 (1H, d, *J* 8.4), 5.04 (2H, s). δ_C ([D_6]DMSO, 100 MHz) 169.7, 156.2, 142.6, 142.5, 138.9, 137.4, 128.9, 128.8, 128.7, 128.7, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 66.1, 58.6, 56.5.

*(*R*)*-N-*Triphenylmethylbenzyloxycarbonylaminophenylacetamide (*R*)-**12***. The general procedure was followed. 77% yield (2.15 g). White solid, mp 150–151°C. $[\alpha]_D^{25^\circ}$ −4.3° (*c* 1.12, $CHCl_3$). (Found: $[M+Na]^+$ 549.2146. Calc. for $C_{35}H_{30}N_2O_3$: $[M+Na]^+$ 549.2149). δ_H ($CDCl_3$, 400 MHz) 7.38–7.19 (19H, m), 7.10–7.08 (6H, m), 6.84 (1H, br), 6.17 (1H, br), 5.31 (1H, br), 5.08 (1H, d, *J* 12.4), 4.10 (1H, d, *J* 12.4). δ_C ($CDCl_3$, 100 MHz) 168.4, 155.7, 144.1, 138.0, 136.3, 129.2, 128.7, 128.5, 128.48, 128.14, 128.04, 127.37, 127.18, 70.72, 66.96, 59.57.

*(*R*)*-N-tert-*Butylbenzyloxycarbonylaminophenylacetamide (*R*)-**13***. The general procedure was followed. 82% yield (1.48 g). White solid, mp 136–137°C. $[\alpha]_D^{25^\circ}$ −0.5° (*c* 3.4, $CHCl_3$). (Found: $[M+Na]^+$ 363.1681. Calc. for $C_{20}H_{24}N_2O_3$: $[M+Na]^+$ 363.1679). δ_H ($CDCl_3$, 400 MHz) 7.41–7.26 (10H, m), 6.17 (1H, br), 5.47 (1H, br), 5.63 (1H, d, *J* 12), 5.12–5.09 (2H, m), 1.27 (9H, s). δ_C ($CDCl_3$, 100 MHz) 168.8, 155.7, 138.8, 136.4, 129.1, 128.6, 128.4, 128.2, 128.1, 127.3, 67.0, 59.1, 51.9, 28.6.

*General Procedure for the Synthesis of Ureas (*R*)-**14**–**16***

In a flask provided with magnetic stirring was placed 1.7 mmol of the chiral amide ((*R*)-**11**, (*R*)-**12**, or (*R*)-**13**), Pd/C (10% w/w relative to amide), and 15 mL of MeOH. The resulting mixture was exposed to a hydrogen atmosphere (14.6 psi) for 18 h. Filtration and concentration afforded the unprotected desired product in quantitative yield, according to ^1H NMR analysis. This product was redissolved in 40 mL of anhydrous THF and cooled to 0°C before the addition of 343 mg (2.6 mmol) of $AlCl_3$ followed by 325 mg (8.6 mmol) of $LiAlH_4$ (slow addition). The reaction mixture was stirred at 0°C for 2 h, the ice-bath was removed and the reaction continued for 22 h at room temperature. The reaction mixture was cooled again to 0°C before the slow addition of 30 mL of a 1 M aqueous solution of NaOH. Stirring was continued until the suspension turned white (15 min to 1 h), and the resulting diamine was extracted with EtOAc (3 × 40 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to afford the pure diamine, according to ^{13}C NMR spectroscopy. This product was treated with 0.47 mL (3.4 mmol) of Et_3N dissolved in 50 mL of CH_2Cl_2, and the resulting mixture was cooled to 0°C before the dropwise addition of a solution of triphosgene (169 mg (0.57 mmol)) in 10 mL of CH_2Cl_2. Once the addition was complete, the ice bath was removed and the stirring was continued for 24 h at room temperature. Then, 50 mL of HCl (1 M) were added, the aqueous phase was separated and the organic layer was washed with 30 mL of brine, dried (Na_2SO_4), and concentrated. The product was purified by FC (hexane/EtOAc, 1:1) producing a white solid in all cases.

*(*R*)-1-Diphenylmethyl-4-phenylimidazolidin-2-one (*R*)-**14***. The general procedure was followed, affording 0.37 g (67% yield) of a white solid, mp 184–185°C. $[\alpha]_D^{25^\circ}$ +63.4° (*c* 1, $CHCl_3$). (Found: C 80.3, H 6.2, N 8.5. Calc. for $C_{22}H_{20}N_2O$: C 80.5, H 6.1, N 8.5%). δ_H ($CDCl_3$, 400 MHz) 7.40–7.13 (15H, m), 6.49 (1H, s), 5.48 (1H, br), 4.79 (1H, dd, *J* 8.8 and 8.0), 3.62 (1H, dd, *J* 8.8 and 8.4), 3.05 (1H, dd, *J* 8.4 and 8.0). δ_C ($CDCl_3$, 100 MHz) 161.7, 141.5, 139.3, 139.0, 129.0, 128.5, 128.5, 128.4, 128.1, 127.5, 127.4, 126.1, 59.0, 54.0, 50.6.

*(*R*)-1-Trityl-4-phenylimidazolidin-2-one (*R*)-**15***. The general procedure was followed, affording 0.36 g (52% yield) of a white solid, mp 156–158°C. $[\alpha]_D^{25^\circ}$ almost null. (Found: C 83.0, H 6.3, N 7.2. Calc. for $C_{28}H_{24}N_2O$: C 83.1, H 6.0, N 6.9%). δ_H ($CDCl_3$, 400 MHz) 7.50–7.15 (20H, m), 5.03 (1H, br), 4.74 (1H, dd, *J* 8.8 and 8.0), 3.86 (1H, dd, *J* 8.8 and 8.4), 3.26 (1H, dd, *J* 8.4 and 8.0). δ_C ($CDCl_3$, 100 MHz) 161.6, 143.1, 141.4, 129.5, 128.9, 128.3, 127.7, 126.7, 126.3, 73.3, 54.9, 53.8.

*(*R*)-1-*tert*-Butyl-4-phenylimidazolidin-2-one (*R*)-**16***. The general procedure was followed, affording 0.20 g (55% yield) of a white solid, mp 118–120°C. $[\alpha]_D^{25^\circ}$ −0.5° (*c* 2.51, $CHCl_3$). (Found: C 71.5, H 8.5, N 12.8. Calc. for $C_{13}H_{18}N_2O$: C 71.5, H 8.3, N 12.8%). δ_H ($CDCl_3$, 400 MHz) 7.40–7.27 (5H, m), 4.63

(1H, dd, *J* 8.8 and 8.0), 4.58 (1H, br), 3.88 (1H, dd, *J* 8.8 and 8.4), 3.22 (1H, dd, *J* 8.4 and 8.0), 1.37 (9H, s). δ_C ($CDCl_3$, 100 MHz) 162.1, 141.7, 128.9, 128.2, 126.2, 53.6, 53.0, 52.3, 27.6.

General Procedure for the Reaction of Ephedrine with Isocyanates

In a 50-mL round-bottom flask provided with a magnetic stirrer was placed 0.92 g (5.6 mmol) of (−)-ephedrine dissolved in 35 mL of CH_2Cl_2, before the addition of 5.3 mmol of the corresponding isocyanate and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was treated with 25 mL of 1.0 M HCl and the organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated to give the crude product, which was purified by flash chromatography using hexane/EtOAc (8:2 to 1:1).

*1-[(2*R*)-Hydroxy-(1*S*)-methyl-2-phenylethyl]-1-methyl-3-phenylurea (1*S*,2*R*)-**17***. This urea was obtained according to the general procedure, affording 1.43 g (90% yield). White crystals, mp 134–135°C. $[\alpha]_D^{25°}$ −217.0° (*c* 1.03, $CHCl_3$). (Found: C 71.6, H 7.2, N 9.9. Calc. for $C_{17}H_{20}N_2O_2$: C 71.8, H 7.1, N 9.9%). δ_H ($CDCl_3$, 300 MHz) 7.34–7.23 (10H, m), 7.03–6.98 (1H, m), 4.77 (1H, s), 4.34–4.26 (1H, m), 4.18 (1H, br), 2.48 (3H, s), 1.20 (3H, d, *J* 7.1). δ_C ($CDCl_3$, 75 MHz) 157.6, 141.1, 139.5, 129.0, 128.5, 128.1, 126.8, 123.0, 120.0, 77.9, 58.3, 31.6, 14.1. Enantiomeric [(1*R*,2*S*)-**17**] has been reported previously.[29]

*1-[(2*R*)-Hydroxy-(1*S*)-methyl-2-phenylethyl]-1-methyl-3-diphenylmethylurea (1*S*,2*R*)-**18***. This urea was obtained according to the general procedure, affording 1.95 g (93% yield). White crystals, mp 123–125°C. $[\alpha]_D^{25°}$ −121.3° (*c* 0.8, $CHCl_3$). (Found: C 77.4, H 7.4, N 7.4. Calc. for $C_{24}H_{26}N_2O_2$: C 77.0, H 7.0, N 7.5%). δ_H ($CDCl_3$, 270 MHz) 7.37–7.17 (15H, m), 6.12 (1H, d, *J* 7.2), 5.10 (1H, d, *J* 7.2), 4.76 (1H, dd, *J* 3.5 and 3.5), 4.38 (1H, dq, *J* 7.1 and 3.5), 4.10 (1H, br), 2.48 (3H, s), 1.20 (3H, d, *J* 7.1). δ_C ($CDCl_3$, 68 MHz) 158.8, 142.6, 141.6, 128.7, 128.6, 128.2, 127.7, 127.5, 127.4, 127.3, 126.6, 77.9, 58.5, 58.1, 31.3, 13.9.

N-*Methyl-[(1*S*,2*R*)-(2-phenyl-1-methyl-2-trimethylsilyloxy)]ethylamine (1*R*,2*S*)-**19***. Following the reported protection for pseudoephedrine,[30] in a round-bottom flask were placed 1.4 g (8.9 mmol) of (−)-ephedrine, 2.6 mL (18.9 mmol) of triethylamine and 4.0 mL (18.9 mmol) of hexamethyldisilazane in 10 mL of dichloroethane. The resulting mixture was heated to reflux for 5 h and then concentrated. The product was distilled in a Kugelrohr apparatus, bp 110°C/0.05 psi, producing 1.77 g (84% yield) of a colourless oil. $[\alpha]_D^{25°}$ −49.0° (*c* 2.06, $CHCl_3$). (Found: $[M+1]^+$ 238.1629. Calc. for $C_{13}H_{24}NOSi$: $[M+1]^+$ 238.1627). δ_H ($CDCl_3$, 400 MHz) 7.40–7.26 (5H, m), 4.42 (1H, d, *J* 4.8), 4.41 (1H, dq, *J* 6.6 and 4.8), 2.12 (3H, s), 1.05 (1H, br), 0.77 (3H, d, *J* 6.6), 0.21 (9H, s). δ_C ($CDCl_3$, 100 MHz) 142.8, 127.9, 127.0, 126.5, 77.1, 61.2, 33.8, 14.3, 0 ($SiCH_3$). δ_{Si} ($CDCl_3$, 399.8 MHz) 18.02 (s).

*Bis-1,3-[(2*R*)-Hydroxy-(1*S*)-methyl-2-phenylethyl]-1,3-dimethylurea (1*S*,2*R*,1′*S*,2′*R*)-**20***. The starting amine (1*R*,2*S*)-**19** (0.86 g, 3.6 mmol), Et_3N (1.0 mL, 7.8 mmol), and 15 mL of dry CH_2Cl_2 were placed in a round-bottom flask and the resulting mixture was cooled to 0°C before the dropwise addition of a solution of 0.18 g (0.6 mmol) of triphosgene in 10 mL of CH_2Cl_2. Stirring was continued at room temperature for 34 h, and then 30 mL of 1 M HCl were added. The aqueous phase was separated and extracted with two 30-mL portions of CH_2Cl_2, the combined organic phases were washed with brine solution, dried (Na_2SO_4), and concentrated. The product was purified by FC (hexane/EtOAc, 8:2 to 1:1) producing 0.6 g (47% yield) of the desired product as a white solid, mp 170–171°C. $[\alpha]_D^{25°}$ +8.4° (*c* 1.11, $CHCl_3$). (Found: C 70.5, H 7.9, N 7.9. Calc. for $C_{21}H_{28}N_2O_3$: C 70.8, H 7.9, N 7.9%). δ_H ($CDCl_3$, 400 MHz) 7.42–7.23 (10H, m), 5.48 (2H, s), 4.91 (2H, s), 3.56 (2H, dq, *J* 7.0 and 3.7), 2.61 (6H, s), 1.21 (6H, d, *J* 7.0). δ_C ($CDCl_3$, 100 MHz) 165.2, 142.5, 128.3, 127.4, 126.4, 75.4, 62.0, 36.4, 11.9.

N,N′-*Bis((*S*)-α-phenylethyl)thiourea (*S,S*)-**21***. See ref. [19f].

N,N′-*Bis((*S*)-α-phenylethyl)propylenethiourea (*S,S*)-**22***. In a round-bottom flask were placed 1.5 g (5.3 mmol) of *N,N′*-bis-((*S*)-α-phenylethyl)propane-1,3-diamine,[31] 1.5 mL (10.6 mmol) of Et_3N, and 40 mL of dry CH_2Cl_2. The resulting solution was cooled to 0°C and then it was treated slowly with a solution of 0.2 mL (2.65 mmol) of thiophosgene in 10 mL of CH_2Cl_2. The reaction mixture was stirred for 2 h at 0°C and for 18 h at room temperature, before the addition of 50 mL of 1 M HCl. The organic layer was washed with 50 mL of brine, dried (Na_2SO_4), and concentrated. The product was purified by FC (hexane/EtOAc, 7:3) yielding 0.77 g (45% yield) of a white solid, mp 205–206°C. $[\alpha]_D^{25°}$ −144 (*c* 1.04, $CHCl_3$). (Found: C 73.8, H 7.7. Calc. for $C_{20}H_{24}N_2S$: C 74.0, H 7.5%). δ_H ($CDCl_3$, 400 MHz) 7.40–7.24 (12H, m), 3.05 (2H, dt, *J* 12.6 and 5.9), 2.80 (2H, dt, *J* 12.6 and 5.9), 1.66 (2H, quintuplet, *J* 5.9), 1.61 (6H, d, *J* 6.9). δ_C ($CDCl_3$, 100 MHz) 179.8, 140.7, 128.5, 127.3, 58.9, 41.1, 21.4, 15.1.

General Procedure for the Synthesis of Thioureas Using Phenylisothiocyanate

In a 25 mL round-bottom flask provided with a magnetic stirrer was placed 2.94 mmol of the chiral amine dissolved in 10 mL of CH_2Cl_2. To this solution was added 0.6 mL (2.94 mmol) of phenylisothiocyanate and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was treated with 15 mL of 1 M HCl and the organic phase was separated, washed with brine solution, dried (Na_2SO_4), and concentrated to give the crude product, which was purified by flash chromatography using hexane/EtOAc (9:1 to 7:3).

N-*((*S*)-α-Phenylethyl)-*N*′-phenylthiourea (*S*)-**23***. This was obtained according to the general procedure and afforded 0.74 g (98% yield) of a white solid, mp 64–65°C. $[\alpha]_D^{25°}$ +87.7° (*c* 1.06, $CHCl_3$). (Found: $[M+1]^+$ 257.1111. Calc. for $C_{15}H_{17}N_2S$: $[M+1]^+$ 257.1112). δ_H ($CDCl_3$, 400 MHz) 8.27 (1H, br), 7.55–7.12 (10H, m), 6.31 (1H, br), 5.68 (1H, br), 1.53 (3H, d, *J* 7.0). δ_C ($CDCl_3$, 100 MHz) 179.7, 142.3, 136.3, 130.2, 128.9, 127.7, 127.2, 126.3, 125.1, 54.7, 21.7.

N-*((*S*)-1-(α-Naphthyl)ethyl)-*N*′-phenylthiourea (*S*)-**24***. This was obtained according to the general procedure and afforded 0.86 g (95% yield) of a white solid, mp 97–98°C. $[\alpha]_D^{25°}$ +128.8° (*c* 0.81, $CHCl_3$). (Found: C 74.7, H 6.1, N 9.5. Calc. for $C_{19}H_{18}N_2S$: C 74.5, H 5.9, N 9.1%). δ_H ($CDCl_3$, 400 MHz) 8.24 (1H, d, *J* 8.4), 8.17 (1H, br), 7.87 (1H, d, *J* 8.0), 7.80 (1H, dd, *J* 6.9 and 2.9), 7.60 (1H, ddd, *J* 7.6, 7.3 and 1.4), 7.55–7.50 (1H, m), 7.46–7.39 (2H, m), 7.27 (2H, dd, *J* 7.8 and 7.8), 7.21–7.15 (1H, m), 7.05 (2H, d, *J* 7.7), 6.39 (1H, br), 6.25 (1H, br), 1.75 (3H, d, *J* 6.6). δ_C ($CDCl_3$, 100 MHz) 179.4, 137.4, 136.2, 134.0, 131.3, 130.2, 128.9, 128.8, 127.1, 127.0, 126.1, 125.2, 124.9, 123.9, 123.0, 51.1, 20.2.

*1-((2*R*)-Hydroxy-(1*S*)-methyl-2-phenylethyl)-1-methyl-3-phenylthiourea (1*S*,2*R*)-**25***. This was obtained according to the general procedure and afforded 0.77 g (88% yield) of a white solid, mp 105–107°C (lit. 97–98°C[32]). $[\alpha]_D^{25°}$ −281.4° (*c* 0.97,

Table 7. Summary of crystal data for compounds 10, 14, 17, and 22

Parameter	Coumpound **10**	Coumpound **14**	Coumpound **17**	Coumpound **22**
Empirical formula	$C_{17}H_{18}ClNO$	$C_{22}H_{20}N_2O$	$C_{17}H_{20}N_2O_2$	$C_{20}H_{24}N_2O$
Molecular weight	287.77	328.40	284.35	308.41
Crystal size [mm^3]	0.30 × 0.25 × 0.20	0.45 × 0.27 × 0.25	0.27 × 0.27 × 0.1	0.64 × 0.5 × 0.42
Temperature [K]	293(2)	293(2)	293(2)	223(2)
Space group	*P* 21 21 21	*P* 21 21 21	*P* 21 21 21	*P* 43 21 2
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
a [Å]	7.6657(2)	6.28700(10)	10.4910(4)	14.460(5)
b [Å]	12.4219(3)	8.70050(10)	11.3633(5)	14.460(5)
c [Å]	16.2106(4)	32.4210(6)	13.0381(6)	8.385(5)
α [°]	90	90	90	90
β [°]	90	90	90	90
γ [°]	90	90	90	90
U [$Å^3$]	1543.62(7)	1773.43(5)	1554.30(12)	1753.2(14)
$\mu(Mo_{K\alpha})$ [Å]	0.71069	0.71069	0.71069	0.71069
D_{calc} [Mg m^{-3}]	1.238	1.230	1.215	1.168
Z	4	4	4	4
F(000)	608	696	608	664
θ range [°]	3.51–27.48	3.44–27.47	4.08–27.41	2.81–26.95
Reflections collected	3262	3560	3458	4380
Unique reflections	1904	3560	3458	1921
R_{int}	0.0174	0.0000	0.0000	0.6237
R_1, wR_2 [$I > 2\sigma(I)$]	0.0357, 0.0826	0.0426, 0.0808	0.0469, 0.0868	0.0530, 0.1343
R_1, wR_2 (all data)	0.0495, 0.0885	0.0895, 0.0949	0.0845, 0.1002	0.1242, 0.1549
Goodness-of-fit on F^2	1.055	1.012	1.043	1.137

$CHCl_3$). δ_H ($CDCl_3$, 400 MHz) 7.45–7.10 (10H, m), 5.27 (1H, br), 4.95 (1H, br), 3.22 (1H, br), 2.80 (3H, s), 1.70 (1H, s), 1.25 (3H, d, *J* 7.0). δ_C ($CDCl_3$, 100 MHz) 183.9, 140.5, 140.1, 128.8, 128.6, 128.3, 126.6, 125.3, 124.8, 77.5, 61.0, 35.2, 13.5.

*1-((2*S*)-Hydroxy-(1*R*)-methyl-2-phenylethyl)-3-phenylthiourea (1*R*,2*S*)-**26***. This was obtained according to the general procedure and afforded 0.79 g (94% yield) of a white solid, mp 138–139°C. $[\alpha]_D^{25°}$ +49.1° (*c* 0.55, $CHCl_3$). (Found: C 67.2, H 6.4, N 9.9, S 11.6. Calc. for $C_{16}H_{18}N_2OS$: C 67.1, H 6.3, N 9.8, S 11.2%). δ_H ($CDCl_3$, 270 MHz) 7.98 (1H, br), 7.46–7.15 (10H, m), 6.22 (1H, d, *J* 8.4), 5.08 (1H, dd, *J* 3.5 and 3.2), 4.89 (1H, br), 0.85 (1H, d, *J* 3.5), 0.97 (3H, d, *J* 6.9). δ_C ($CDCl_3$, 68 MHz) 179.8, 140.4, 135.9, 130.2, 128.3, 127.7, 127.3, 126.1, 125.1, 75.8, 56.2, 13.9.

trans-*2-Chlorocyclohexanol **27***. In a 50-mL round-bottom flask provided with a magnetic stirrer and under a nitrogen atmosphere was placed the chiral urea (0.1 mmol) dissolved in 10 mL of dry CH_2Cl_2, and this solution was treated with 0.1 mL (1.0 mmol) of cyclohexene oxide. The reaction mixture was cooled to −78°C (dry ice/acetone bath) before the addition of 0.13 mL (1.1 mmol) of silicon tetrachloride. Following 40 min of stirring, the reaction was placed in an ice bath and quenched with 20 mL of an aqueous saturated $NaHCO_3$ solution. Then 20 mL of CH_2Cl_2 were added and the aqueous phase separated and extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined and washed with 30 mL of brine, dried (Na_2SO_4), and concentrated. The product was purified with FC using hexane/EtOAc (95:5), producing a colourless liquid with the yields summarized in Table 2. δ_H ($CDCl_3$, 400 MHz) 3.68 (1H, ddd, *J* 11.5, 9.3 and 4.5), 3.50–3.43 (1H, m), 2.85 (1H, s), 2.22–2.13 (1H, m), 2.08–2.00 (1H, m), 1.73–1.53 (3H, m), 1.34–1.18 (3H, m). δ_C ($CDCl_3$, 100 MHz) 75.2, 67.3, 35.1, 33.1, 25.6, 23.9.

*3-Hydroxy-1,3-diphenylpropan-1-one **28***. In a Schlenk flask was placed 288 mg (1.5 mmol) of the phenyltrimethylsilyloxyethene with 4.7 mg (0.015 mmol) of mercury acetate under a nitrogen atmosphere and dissolved in 3 mL of dry CH_2Cl_2. After the addition of 0.34 mL (3 mmol) of silicon tetrachloride, the mixture was stirred for 1.5 h for complete transilylation. The mixture was concentrated to dryness under vacuum and the resulting oil was redissolved with a solution of 0.1 mmol of the Lewis base in 2.5 mL dry CH_2Cl_2, and cooled to −78°C with a dry ice–acetone bath before 0.1 mL (1 mmol) of benzaldehyde was slowly added and the mixture stirred for 2.5 h. The dry-ice bath was removed and 30 mL of a solution of 1:1 1 M NaF saturated NaH_2PO_4 was added. After 1.5 h of continuous stirring, the product was extracted with CH_2Cl_2 (2 × 40 mL), the organic phases were combined, washed with 40 mL of brine, dried (Na_2SO_4), and concentrated. The aldol product was purified with FC (hexane/EtOAc, 9:1) yielding a semisolid with yield dependent on the Lewis base employed (Table 2), mp 49–51°C. δ_H ($CDCl_3$, 400 MHz) 8.00–7.25 (10H, m), 5.38–5.33 (1H, m), 3.69 (1H, br), 3.40–3.35 (2H, m). δ_C ($CDCl_3$, 100 MHz) 200.2, 143.1, 136.7, 133.7, 128.8, 128.7, 128.3, 127.8, 125.9, 70.1, 47.5.

*1-Cyclohexyl-3-hydroxy-3-phenylpropan-1-one **29***. In a Schlenk flask under a nitrogen atmosphere was placed 278 mg (1.2 mmol) of the trichlorosilyloxycyclohexene.[33] The corresponding urea was added (0.1 mmol) dissolved in 10 mL of dry CH_2Cl_2 and then the solution was cooled to −78°C before the slow addition of 0.1 mL (1.0 mmol) of benzaldehyde. After 2 h with stirring, the dry-ice bath was removed and a 30 mL solution of 1:1 saturated NaF:NaH_2PO_4 was added and the resulting mixture was stirred for 2 h. The product was extracted with CH_2Cl_2 (2 × 40 mL), the organic phases were combined, washed with 40 mL of brine, dried (Na_2SO_4), and concentrated.

The aldol product was purified with FC (hexane/EtOAc, 9:1) producing a semisolid with yields that depended on the Lewis base employed (see Table 4). δ_H ($CDCl_3$, 270 MHz) 7.37–7.19 (5H, m), 5.38 (1H, br), 3.02 (1H, br), 2.66–2.29 (3H, m), 2.14–2.00 (1H, m), 1.90–1.40 (5H, m). δ_C ($CDCl_3$, 68 MHz) 214.9, 141.5, 70.6, 57.3, 42.7, 28.0, 26.1, 24.9. HPLC: Chiracel-OD (Detector wavelength 220 nm), eluent hexane/Pr^{i}OH (90:10), flow 0.5 mL min^{-1}, retention time (t_R) 14.67 and 17.57 min.

1-Phenylpropanol ***30***. In a 50-mL round bottom flask provided with a magnetic stirrer and nitrogen atmosphere was placed the urea ligand (0.1 mmol) dissolved in 5 mL of dry toluene (for some ligands, the use of an ultrasonic bath or heating was required for complete dissolution). The solution was cooled with an ice bath and then 5 mL (5 mmol) of a 1 M solution of diethylzinc in hexane was added slowly. After 45 min stirring, 0.2 mL (2 mmol) of benzaldehyde was added and the reaction mixture was allowed to react for 20 h at a temperature between 0 and 5°C. The remaining diethylzinc was destroyed with the slow addition of 15 mL of 1 M HCl (vigorous evolution of gas). A white suspension was formed and following the dissolution of the solid (15 min to 1 h), the product was extracted with ether (2×15 mL). The organic extracts were dried (Na_2SO_4), concentrated, and the product purified by FC (hexane/EtOAc, 9:1), producing a colourless liquid in the yield and enantiomeric ratios summarized in Table 6. δ_H ($CDCl_3$, 400 MHz) 7.38–7.25 (5H, m), 4.60 (1H, t, J 6.6), 2.05 (1H, br), 1.89–1.70 (2H, m), 0.92 (3H, t, J 7.5). δ_C ($CDCl_3$, 100 MHz) 144.7, 128.5, 127.6, 126.1, 76.1, 32.0, 10.3. HPLC: Chiracel-OD, λ 220 nm, flow 1 mL min^{-1}, hexane/Pr^{i}OH (95:5), t_R (*R*) 7.3 min, t_R (*S*) 9.1 min.

Crystallographic Studies

Datasets were collected in a Nonius Kappa CCD diffractometer using $Mo_{K\alpha}$ radiation. All the structures were solved using *SHELX-97*[23] and were refined by full matrix least-squares methods. All non-hydrogen atoms were refined anisotropically. Most hydrogen atoms were placed in idealized positions and included in the refinement. Crystal data, data collection parameters, and results of the analyses are listed in Table 7. Full crystallographic information can be found in the supplementary data deposited at the Cambridge Crystallographic Data Centre.

Supporting Information Available

The crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033. CCDC nos. 666357–666360.

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