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Synthesis of novel norephedrine-based chiral ligands with multiple stereogenic centers and their application in enantioselective addition of diethylzinc to aldehyde and chalcone

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Abstract—Novel norephedrine-based chiral ligands with multiple stereogenic centers were conveniently prepared from norephedrine and N-substituted pyrrole. These novel chiral ligands were used to catalyze the enantioselective addition of diethylzinc to aldehydes and to chalcone in high yields and with good to high enantioselectivities. The absolute configuration of products was found to be affected by the stereogenic centers on the norephedrine part of the novel chiral ligands.

1. Introduction

Catalytic asymmetric C–C bond formation is an important field of synthetic chemistry. Considerable attention has been devoted to the development of new chiral ligands to be used in asymmetric catalysis over the past decade.[1] The success of catalytic asymmetric synthesis is critically dependent on the structural features of chiral ligands as well as their availability. Among the whole variety of chiral ligands used in asymmetric synthesis, β-amino alcohol-based ligands have been extremely promising compounds.[2] Most of the amino alcohols used in asymmetric reactions as chiral ligands are amino acid derivatives,[3] ephedrine derivatives,[4] borneol derivatives,[5] and pyrrolidine derivatives.[6] They have become the most-often used ligands because of their easy availability, simple preparation, and efficient asymmetric induction.

N-Alkylated derivatives of norephedrine have been reported by Soai et al.[7] to catalyze diethylzinc addition to aliphatic and aromatic aldehydes with high asymmetric induction. To the author's knowledge, little work on asymmetric diethylzinc addition to enones with norephedrine derivatives has been published in the literature.[8] As reported in previous studies, the substituent on the nitrogen atom of norephedrine plays an important role in the enantioselectivity of the addition.[1a,2,7d]

Herein, we report the effect of the presence of an *N*-substituted chiral pyrrole as a substituent on norephedrine, during enantioselective addition reactions. We designed novel chiral ligands conveniently and efficiently from norephedrine and *N*-substituted pyrrole carbaldehyde. We tested the efficiency of these novel ligands in asymmetric induction with diethylzinc addition reaction to benzaldeydes and to chalcone.

2. Results and discussion

2.1. Synthesis of chiral ligands

Optically active *N*-substituted pyrroles (*S*)-**1** and (*R*)-**1** were prepared from both enantiomers of the commercially available amine and 5-chloropent-3-ene-2-one as described previously.[9] The formylation of (*S*)-**1** and (*R*)-**1** using DMF and $POCl_3$ was performed in pentane/diethyl ether. We obtained C-3 [(*S*)-**2** in 70% yield, (*R*)-**2** in 68% yield] and C-2 [(*S*)-**3** in 24% yield, (*R*)-**3** in 21% yield] formulated products under conditions (i) (pyrrole/DMF/$POCl_3$, 1:1:1 at 0 °C to rt) as shown in Scheme 1. Under a different Vilsmeier–Haack reaction conditions (ii) where the molar ratios of pyrrole,

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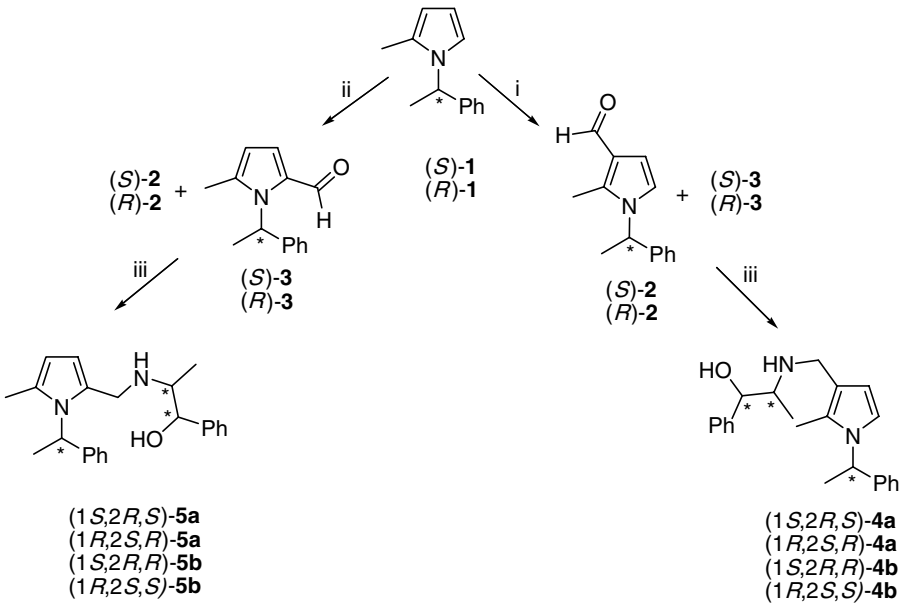
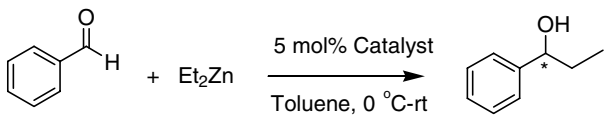


Scheme 1. Reagents and conditions: (i) DMF, $POCl_3$, 0 °C to rt (pyrrole/DMF/$POCl_3$, 1:1:1); (ii) DMF, $POCl_3$, 0 °C (pyrrole/DMF/$POCl_3$, 1:10:10); (iii) norephedrine, benzene, reflux and then $LiAlH_4$, ether, reflux.

DMF, and $POCl_3$ were 1:10:10 at 0 °C, C-2 [(*S*)-**3**, (*R*)-**3**] and C-3 [(*S*)-**2**, (*R*)-**2**] formulated products were formed in 52%, 53%, 43%, and 40% yield, respectively. The products were characterized using one- and two-dimensional NMR techniques. Reductive amination of aldehydes with norephedrine furnished chiral ligands **4a** and **b** and **5a** and **b** by using $LiAlH_4$ without isolating the corresponding imines. All possible stereoisomers (1*S*,2*R*,*S*)-**4a** (69%), (1*R*,2*S*,*R*)-**4a** (71%), (1*S*,2*R*,*R*)-**4b** (73%), (1*R*,2*S*,*S*)-**4b** (70%), (1*S*,2*R*,*S*)-**5a** (72%), (1*R*,2S,*R*)-**5a** (70%), (1*S*,2*R*,*R*)-**5b** (68%), (1*R*,2*S*,*S*)-**5b** (73%) are isolated after purification of the crude products by column chromatography.

2.2. Enantioselective diethylzinc addition to aldehydes

The addition of diethylzinc to benzaldehyde was investigated first in order to examine the catalytic behavior of ligands **4a** and **b** and **5a** and **b** (Scheme 2). The reactions were screened in toluene at 0 °C to rt in the presence of **4a** and **b** and **5a** and **b** at different molar ratios (2.5–20%). The best results were obtained by using (1*S*,2*R*,*S*)-**4a** (75% ee, 70% yield) and (1*S*,2*R*,*S*)-**5a** (68% ee, 65% yield) as catalysts in a 5 mol % ratio.



Scheme 2.

Table 1 shows the absolute configurations of 1-phenylpropan-1-ol obtained by using the ligands **4a** and **b** and **5a** and **b**. These results indicate that the stereochemistry of norephedrine plays a crucial role with regards to the absolute configuration of the product.

Table 1. The effect of stereogenic centers of chiral ligands **4a**,**b** and **5a**,**b** on the absolute configuration of 1-phenylpropan-1-ol in diethylzinc addition to benzaldehyde[a]

Entry	Ligand	ee[b] (%)	Absolute configuration of product
1	(1*S*,2*R*,*S*)-**4a**	75	*S*
2	(1*R*,2*S*,*R*)-**4a**	69	*R*
3	(1*S*,2*R*,*R*)-**4b**	51	*S*
4	(1*R*,2*S*,*S*)-**4b**	46	*R*
5	(1*S*,2*R*,*S*)-**5a**	68	*S*
6	(1*R*,2*S*,*R*)-**5a**	57	*R*
7	(1*S*,2*R*,*R*)-**5b**	51	*S*
8	(1*R*,2*S*,*S*)-**5b**	43	*R*

[a] 5 mol % ligand in toluene at 0 °C to rt.
[b] The ee values were determined by HPLC with a Chiralcel-OD column; 2% 2-propanol in hexane, flow rate: 1 mL/min, UV detection (254 nm) t_R: 17 min for (*R*), 19 min for (*S*).

Ligand (1*S*,2*R*,*S*)-**4a** was used to investigate the effect of temperature on the diethylzinc addition to benzaldehyde. As shown in Table 2, similar enantioselectivities were obtained at 0 °C to rt and at 0 °C. When the reaction was carried out at −20 °C, the ee of the product decreased to 10%. No product formation was observed at −78 °C. We also carried out the reaction in different solvents and solvent mixtures (Table 2, entries 5–8). Comparable enantiomeric excesses of the products were noted in CH_2Cl_2 and toluene/hexane. The highest ee (75%) was obtained by using toluene as the solvent (Table 2, entry 1).

The reactions were performed in different solvents and solvent mixtures for the ligand (1*S*,2*R*,*S*)-**5a** at 0 °C to rt (Table 2, entries 9–13). In this case, the highest enantiomeric excess (68%) was obtained in toluene (Table 2, entry 9).

Table 2. Diethylzinc addition to benzaldehyde with (1*S*,2*R*,*S*)-**4a** and (1*S*,2*R*,*S*)-**5a**

Entry	Ligand	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	ee[b] (%)	Conf.
1	(1*S*,2*R*,*S*)-**4a**	Toluene	0 to rt	16	70	75	*S*
2	(1*S*,2*R*,*S*)-**4a**	Toluene	0	16	68	74	*S*
3	(1*S*,2*R*,*S*)-**4a**	Toluene	−20	16	77	10	*S*
4	(1*S*,2*R*,*S*)-**4a**	Toluene	−78	16	—	—	—
5	(1*S*,2*R*,*S*)-**4a**	CH_2Cl_2	0 to rt	16	71	72	*S*
6	(1*S*,2*R*,*S*)-**4a**	Tolene/CH_2Cl_2 (5:1)	0 to rt	24	41	69	*S*
7	(1*S*,2*R*,*S*)-**4a**	Toluene/hexane (5:1)	0 to rt	20	82	72	*S*
8	(1*S*,2*R*,*S*)-**4a**	Toluene/THF (5:1)	0 to rt	24	5	31	*S*
9	(1*S*,2*R*,*S*)-**5a**	Toluene	0 to rt	16	65	68	*S*
10	(1*S*,2*R*,*S*)-**5a**	CH_2Cl_2	0 to rt	16	62	58	*S*
11	(1*S*,2*R*,*S*)-**5a**	Tolene/CH_2Cl_2 (5:1)	0 to rt	16	57	62	*S*
12	(1*S*,2*R*,*S*)-**5a**	Toluene/hexane (5:1)	0 to rt	16	72	62	*S*
13	(1*S*,2*R*,*S*)-**5a**	Toluene/THF (5:1)	0 to rt	16	5	4	*S*

[a] Isolated yield.
[b] The ee values were determined by HPLC with a Chiralcel-OD column; 2% 2-propanol in hexane, flow rate: 1 mL/min, UV detection (254 nm) t_R: 17 min for (*R*), 19 min for (*S*).

Table 3. Effects of Ti(O-*i*-Pr)$_4$/ligand system and various additives on the enantioselective addition of diethylzinc to benzaldehyde

Entry	Ligand[a]	Ti(O-*i*-Pr)$_4$/ligand	Additive	Yield (%)[b]	ee (%)	Conf.
1	(1*S*,2*R*,*S*)-**4a**	5	—	74	62	*S*
2	(1*S*,2*R*,*S*)-**4a**	15	—	75	56	*S*
3	(1*S*,2*R*,*S*)-**4a**	100	—	78	48	*S*
4	(1*S*,2*R*,*S*)-**4a**	—	LiCl (0.92 mmol)	65	70	*S*
5	(1*S*,2*R*,*S*)-**4a**	—	BuLi (0.196 mmol)	98	64	*S*
6	(1*S*,2*R*,*S*)-**4a**	—	[LiCl (0.92 mmol) + BuLi (0.196 mmol)]	96	60	*S*
7	(1*S*,2*R*,*S*)-**5a**	5	—	70	58	*S*
8	(1*S*,2*R*,*S*)-**5a**	15	—	73	52	*S*
9	(1*S*,2*R*,*S*)-**5a**	100	—	76	43	*S*
10	(1*S*,2*R*,*S*)-**5a**	—	LiCl (0.92 mmol)	40	61	*S*
11	(1*S*,2*R*,*S*)-**5a**	—	BuLi (0.196 mmol)	92	57	*S*
12	(1*S*,2*R*,*S*)-**5a**	—	[LiCl (0.92 mmol) + BuLi (0.196 mmol)]	82	51	*S*

[a] 5 mol % ligand.
[b] Isolated yield.

It has been reported that the chiral catalyst in the presence of Ti(O-*i*-Pr)$_4$ has an enhancement effect on the enantioselectivity.[10] We decided to test the diethylzinc addition reaction with ligands (1*S*,2*R*,*S*)-**4a** and (1*S*,2*R*,*S*)-**5a** in the presence of Ti(O-*i*-Pr)$_4$.

The asymmetric addition of diethylzinc with 5 mol % ligand (1*S*,2*R*,*S*)-**4a** in toluene at 0 °C to rt was performed applying the Ti(O-*i*-Pr)$_4$/ligand (entries 1–3 in Table 3). The reaction with a molar ratio of Ti(O-*i*-Pr)$_4$/(1*S*,2*R*,*S*)-**4a** (5:1) gave (*S*)-1-phenylpropanol in 74% yield with 62% ee (entry 1) and (*S*)-1-phenylpropan-1-ol was formed in 75% yield with 56% ee when the Ti(O-*i*-Pr)$_4$/(1*S*,2*R*,*S*)-**4a** ratio was 15 (entry 2). The addition reaction with Ti(O-*i*-Pr)$_4$/(1*S*,2*R*,*S*)-**4a** (100:1) gave (*S*)-1-phenylpropanol in 78% yield with 48% ee. Increasing the Ti(O-*i*-Pr)$_4$/ligand ratios lowered the enantioselectivity from 62% to 48% for these reaction conditions. The same ratios as given above for Ti(O-*i*-Pr)$_4$/ligand were used in the asymmetric addition of diethylzinc to benzaldehyde with (1*S*,2*R*,*S*)-**5a** as ligand. The increasing Ti(O-*i*-Pr)$_4$/ligand ratios decreased the enantioselectivity from 58% ee to 52% ee and 43% ee (Table 3, entries 7–9). When the diethylzinc addition reaction was achieved in the absence of Ti(O-*i*-Pr)$_4$, (*S*)-1-phenylpropan-1-ol was formed in 70% yield with 75% ee by using (1*S*,2*R*,*S*)-**4a** and in 65% yield with 68% ee by using (1*S*,2*R*,*S*)-**5a**.

The addition reaction of diethylzinc to benzaldehyde was carried out with various additives (LiCl, BuLi, LiCl/BuLi). As summarized in Table 3, no increase in the ee values were observed. Only BuLi appeared to have an increasing effect on the chemical yield.

We continued to test the catalytic efficiency of ligand (1*S*,2*R*,*S*)-**4a** and (1*S*,2*R*,*S*)-**5a** on various aldehydes, as shown in Table 4. The diethylzinc additions to *p*-methoxybenzaldehyde gave the lowest yield and enantiomeric excesses. The best ee value (88%) was obtained with *p*-trifluoromethylbenzaldehyde. Accordingly, the electron withdrawing group enhanced the enantioselectivity while electron donating groups such as methoxy lowered enantioselectivity.

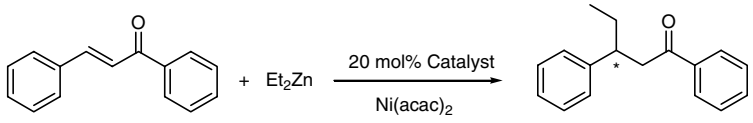
2.3. The enantioselective addition of diethylzinc to chalcone

The enantioselective conjugate addition reaction of organozinc reagents to enones by using chiral catalysts is a particular focus of interest and has been applied in numerous total syntheses. However, whereas most of

Table 4. The diethylzinc addition to various benzaldehyde with chiral ligand (1*S*,2*R*,*S*)-**4a** and (1*S*,2*R*,*S*)-**5a** in toluene

Entry	Ligand	Aldehyde	Time (h)	Yield (%)[a]	ee (%)[b]	Conf.
1	(1*S*,2*R*,*S*)-**4a**	Benzaldehyde	16	70	75	*S*
2	(1*S*,2*R*,*S*)-**4a**	*p*-Methoxybenzaldehyde	20	30	30[c]	*S*
3	(1*S*,2*R*,*S*)-**4a**	*o*-Methoxybenzaldehyde	8	67	48[d]	*S*
4	(1*S*,2*R*,*S*)-**4a**	*p*-Chlorobenzaldehyde	16	98	72[e]	*S*
5	(1*S*,2*R*,*S*)-**4a**	*p*-Trifluoromethylbenzaldehyde	16	72	83[f]	*R*[11]
6	(1*S*,2*R*,*S*)-**5a**	Benzaldehyde	16	65	68	*S*
7	(1*S*,2*R*,*S*)-**5a**	*p*-Methoxybenzaldehyde	16	32	26	*S*
8	(1*S*,2*R*,*S*)-**5a**	*o*-Methoxybenzaldehyde	16	74	50	*S*
9	(1*S*,2*R*,*S*)-**5a**	*p*-Chlorobenzaldehyde	16	76	48	*S*
10	(1*S*,2*R*,*S*)-**5a**	*p*-Trifluoromethylbenzaldehyde	16	75	88	*R*[11]

[a] Isolated yield.
[b] The ee values were determined by HPLC with a Chiralcel-OD column.
[c] 3% 2-propanol in hexane, flow rate: 1 mL/min, UV detection (254 nm) t_R: 35 min for (*R*), 39 min for (*S*).
[d] 2% 2-propanol in hexane, flow rate: 1 mL/min, UV detection (254 nm) t_R: 28 min for (*S*), 39 min for (*R*).
[e] 3% 2-propanol in hexane, flow rate: 0.5 mL/min, UV detection (254 nm) t_R: 23 min for (*R*), 25 min for (*S*).
[f] 5% 2-propanol in hexane, flow rate: 0.8 mL/min, UV detection (254 nm) t_R: 9.11 min for (*R*), 10.92 min for (*S*).



Scheme 3.

the catalysts provide excellent enantioselectivities in the reactions of cyclic enones, the reactions of acyclic enones result in relatively low enantioselectivity, with only some ligands providing very high enantioselectivity.[12] Soai et al.[1b,8b] used the catalyst formed from *N*,*N*-dibutylnorephedrine and Ni(acac)$_2$ in the addition of the diethylzinc to chalcone with a 1:1.2:2.0 molar ratio of Ni:ligand:substrate leading to the product with 45% ee and with 1:1.2:17 (Ni:L:S) molar ratio leading the product with 20% ee.

We examined the enantioselective conjugate addition of diethylzinc to chalcone as a model system with 20 mol % of the chiral ligands **4a** and **b** and 1 mol % of Ni(acac)$_2$ in acetonitrile at −30 °C (Scheme 3). The catalyst was prepared by treatment of 1 mol % of Ni(acac)$_2$ and 20 mol % of ligand in 3 mL of acetonitrile at reflux.

Ligands (1*S*,2*R*,*S*)-**4a**, (1*R*,2*S*,*R*)-**4a**, and (1*R*,2*S*,*S*)-**4b** gave 32–42% ee and 80–93% chemical yields (Table 5).

Table 5. Enantioselective conjugate addition of diethylzinc to chalcone using Ni(acac)$_2$–ligands **4a**,**b** and **5a**,**b** as catalysts[a]

Entry	Ligand	Yield[b] (%)	ee[c] (%)	Conf.
1	(1*S*,2*R*,*S*)-**4a**	80	32	*R*
2	(1*R*,2*S*,*R*)-**4a**	93	36	*S*
3	(1*R*,2*S*,*S*)-**4b**	80	42	*S*
4	(1*S*,2*R*,*R*)-**4b**	70	53	*R*
5	(1*R*,2*S*,*R*)-**5a**	72	48	*S*
6	(1*R*,2*S*,*S*)-**5b**	81	28	*S*

[a] All reactions were carried out with 20 mol % ligand and 1 mol % Ni(acac)$_2$ in acetonitrile at −30 °C for 6 h.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a Chiralcel-OD column. 0.5% 2-propanol in hexane, flow rate: 1 mL/min, UV detector (254 nm) t_R: 14.11 min for (*S*), 15.35 min for (*R*).

The best selectivity was obtained with (1*S*,2*R*,*R*)-**4b** (53% ee and 70% yield). The asymmetric induction of ligand (1*S*,2*R*,*R*)-**4b** formed the product with comparible ees (53%) at 1:20:100 (Ni:L:S) molar ratio under the same reaction conditions.

Table 5 demonstrates the effect of the stereogenic centers of the ligands **4a** and **b** and **5a** and **b** on the absolute configuration of 1,3-diphenylpentan-1-one. It appears that the stereogenic centers on the norephedrine plays a crucial role with regards to the absolute configuration of 1,3-diphenylpentan-1-one.

Ligand (1*S*,2*R*,*R*)-**4b** was used to examine the effect of the temperature and solvent on the addition reaction. The reaction was carried out at different temperatures in acetonitrile and in different solvents at −30 °C, as shown in Table 6. The highest ee (53%) was obtained in acetonitrile at −30 °C. Reducing the temperature from −30 to −45 °C did not obviously affect the enantioselectivity.

We performed a series of reactions to find out the effects of the Ni:L ratios on the diethylzinc addition to chalcone at −30 °C and in CH_3CN. We examined the ratio of Ni:L (Table 7). The enantiomeric excess of the reaction depends on the Ni:L ratio and the highest ee (53%) was obtained by using Ni:L ratios in the range of 1:20 and 1:30. Under these reaction conditions, the best yield (70%) and ee (53%) was obtained by using chalcone:L in a 10:2 ratio.

We tested the catalytic effect of ligands **5a** and **b** using the optimized reaction conditions, which were found by using ligands **4a** and **b**, for the 1,4-addition reaction to chalcone. Ligand (1*R*,2*S*,*S*)-**5b** provided the addition

Table 6. The effect of the solvent and temperature on the diethylzinc addition to chalcone with ligand (1*S*,2*R*,*R*)-**4b**

Entry	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	ee (%)	Conf.
1	CH_3CN	−30	6	70	53	*R*
2	CH_3CN	−45	6	76	52	*R*
3	CH_3CN	0	6	70	11	*R*
4	CH_2Cl_2	−30	6	6	2	*R*
5	Toluene	−30	6	70	17	*R*
6	Toluene/THF (10:1)	−30	6	74	14	*R*
7	*n*-Hexane/THF (10:1)	−30	6	82	6	*R*
8	CH_3CN/THF (10:1)	−30	6	86	27	*R*
9	DMF	−30	6	83	19	*R*

[a] Isolated yield.

Table 7. The effect of the Ni:L molar ratio in the presence of 20 mol % (1*S*,2*R*,*R*)-**4b** on the diethylzinc addition to chalcone

Entry	Ni:L	Yield[a] (%)	ee (%)	Conf.
1	1:1	64	26	*R*
2	1:20	70	53	*R*
3	1:30	60	53	*R*

[a] Isolated yield.

product, (*S*)-1,3-diphenylpentane-1-one in 81% yield with 28% ee (Table 5, entries 5 and 6). By using (1*R*,2*S*,*R*)-**5a**, (*S*)-1,3-diphenylpentane-1-one was obtained with 48% ee and 72% yield.

3. Conclusion

In summary, we have synthesized novel chiral ligands with multiple stereogenic center from norephedrine and N-substituted pyrrole. Moderate enantioselectivities were obtained with (1*S*,2*R*,*S*)-**4a** and (1*S*,2*R*,*S*)-**4a** in the addition of diethylzinc to aldehydes and with (1*S*,2*R*,*R*)-**4b** and (1*S*,2*R*,*R*)-**4b** in the addition of diethylzinc to chalcone. In both reactions, the absolute configuration of the products are mainly controlled by the stereogenic centers of norephedrine on chiral ligands **4a** and **b** and **5a** and **b.**

4. Experimental

4.1. General

All solvents were dried before use according to standard procedures. Melting points were obtained using an electrothermal digital melting point apparatus (Gallenkamp). ^1H and ^{13}C NMR spectra were measured with a Bruker 400 MHz NMR spectrometer using $CDCl_3$ as solvent at room temperature. Chemical shifts (parts per million) were reported relative to Me_4Si. Coupling constant were expressed as *J* values in Hertz unit. Optical rotations were measured with a Autopol IV polarimeter. Infrared spectra were recorded on Mattson 1000 FTIR spectrometer. All reactions were carried out under an Ar atmosphere and monitored by thin-layer chromatography (TLC) on Merck silica gel plates (60 F-254) using UV light or phosphomolybdic acid in methanol. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Diethylzinc was purchased from Aldrich. Enantiomeric excesses were determined by HPLC analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column.

4.2. Formylation of 2-substituted pyrroles

Conditions i: 2-Substituted pyrrole (*S*)-**1** (0.213 g, 1 mmol) and dimethylformamide (0.074 g, 1 mmol) were dissolved in 5 mL of pentane/ether (5:3). This solution was cooled to 0 °C and $POCl_3$ (0.230 g, 1.5 mmol) added with stirring over 1.5 h. Stirring was continued overnight at rt and the iminium salt precipitated as a red oil and the upper layer was decanted. Then 4 M NaOH (15 mL) was added to the red oil with stirring and cooling of the solution. After 1 h, the aqueous mixture was extracted with chloroform (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (EtOAc/hexane, 1:3).

Conditions ii: 2-Substituted pyrrole (*S*)-**1** (0.213 g, 1 mmol) and dimethylformamide (0.740 g, 10 mmol) were dissolved in a 5 mL of pentane/ether (5:3). This solution was cooled to 0 °C and $POCl_3$ (1.530 g, 10 mmol) added with stirring over 1.5 h. Stirring was continued overnight at 0 °C and the iminium salt precipitated as a red oil and the upper layer was decanted. Then 4 M NaOH (15 mL) was added to the red oil with stirring and cooling of the solution. After 1 h, the aqueous mixture was extracted with chloroform (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (EtOAc/hexane, 1:3).

4.2.1. 2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde, (*S*)-2. Light yellow solid (0.149 g, 70%), mp = 107–108 °C. $R_f = 0.71$ (EtOAc/hexane, 1:3). $[\alpha]_D^{25} = -21.9$ (*c* 0.8, $CHCl_3$). IR (KBr): 3144, 2981, 2840, 1653, 1499, 1145, 1228, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.78 (d, 3H, $J = 7.1$, $CHCH_3$), 2.35 (s, 3H, CH_3), 5.33 (q, 1H, $J = 7.0$, $CHCH_3$), 6.57 (d, 1H, $J = 3.2$, C*H*-4), 6.65 (d, 1H, $J = 3.2$, C*H*-5), 6.93 (d, 2H, $J = 7.4$, ArH), 6.90–7.30 (m, 3H, ArH), 9.78 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 10.4, 22.1, 54.9, 109.1, 118.5, 122.9, 125.6, 127.7, 128.9, 136.8, 141.8, 185.2 (CO). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.55; H, 7.31; N, 6.30.

4.2.2. 2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde, (*R*)-2. Light yellow solid (0.145 g, 68%), mp = 107–108 °C. $R_f = 0.71$ (EtOAc/hexane, 1:3). $[\alpha]_D^{25} = +21.1$ (*c* 0.8, $CHCl_3$). IR (KBr): 3144, 2981, 2840, 1653, 1499, 1145, 1228, 1141, 1029 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 1.76 (d, 3H, $J = 7.1$, $CHCH_3$), 2.34 (s, 3H, CH_3), 5.27 (q, 1H, $J = 7.0$, $CHCH_3$), 6.51 (d, 1H, $J = 3.2$, C*H*-4), 6.67 (d, 1H, $J = 3.2$, C*H*-5), 6.86 (d, 2H, $J = 7.4$, ArH), 6.94–7.43 (m, 3H, ArH), 9.76 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 12.2, 18.1, 54.8, 108.6, 118.6, 122.8, 125.3, 127.6, 128.7, 137.1, 141.9, 184.8 (C=O). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.60; H, 7.24; N, 6.45

4.2.3. 5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde, (*S*)-3. Brown oil (0.111 g, 52%). $R_f = 0.87$ (EtOAc/hexane, 1:3). $[\alpha]_D^{25} = -118.9$ (*c* 11, $CHCl_3$). IR (KBr): 3026, 2973, 2807, 2774, 1658, 1481, 1447, 1284, 1185, 1029 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 2.05 (d, 3H, $J = 7.1$, $CHCH_3$), 2.12 (s, 3H, CH_3), 6.15 (d, 1H, $J = 3.8$, C*H*-4), 7.02 (d, 1H, $J = 3.9$, C*H*-3), 7.13 (q, 1H, $J = 7.0$, $CHCH_3$), 7.26 (d, 2H, $J = 7.9$, ArH) 7.36–7.47 (m, 3H, ArH), 9.60 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.2, 18.5, 53.2, 111.6, 125.7, 126.1, 126.9, 128.1, 128.4, 132.2, 140.8, 141.2, 178.3 (C=O). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.72; H, 6.86; N, 6.67.

4.2.4. 5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde, (*R*)-3. Brown oil (0.113 g, 53%). $R_f = 0.87$ (EtOAc/hexane, 1:3). $[\alpha]_D^{25} = +119.7$ (*c* 11, $CHCl_3$). IR (KBr): 3026, 2973, 2807, 2774, 1658, 1481, 1447, 1284, 1185, 1029 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 1.99 (d, 3H, $J = 7.1$, $CHCH_3$), 2.06 (s, 3H, CH_3), 6.09 (d, 1H, $J = 3.9$, C*H*-4), 6.96 (d, 1H, $J = 3.9$, C*H*-3), 7.15 (q, 1H, $J = 6.8$, $CHCH_3$), 7.19 (d, 2H, $J = 7.8$, ArH), 7.26–7.57 (m, 3H, ArH), 9.54 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.2, 18.5, 53.2, 111.6, 125.7, 126.1, 126.9, 128.4, 132.1, 140.8, 141.1, 178.2(C=O).

4.3. General procedure for the synthesis of pyrrole-based derivatives of norephedrine

Formylated pyrrole (2.5 g, 11.74 mmol) was dissolved in 10 mL dry benzene. To this solution was added norephedrine (1.76 g, 11.74 mmol) in 10 mL of dry benzene under argon. The mixture was refluxed under a Dean Stark trapp apparatus for 3 days, and the imine was then concentrated to dryness without purification. Imine (4.28 g, 12.36 mmol) in dry ether (10 mL) was added to the suspension of LAH (0.54 g, 13.60 mmol) in dry ether (50 mL). After the addition was completed, the mixture was heated under argon for 10 h. The reaction was quenched by sequential addition of water (15 mL), 15% NaOH (10 mL), and water (10 mL). The mixture was filtered off and the white precipitate refluxed three times with dry ether. The mixture was filtered off, the organic layers combined, and dried over $MgSO_4$. After evaporation of solvent, the crude product was purified by flash column chromatography (EtOAc/MeOH/hexane, 1:1:6).

4.3.1. (1*S*,2*R*)-2-((2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol (1*S*,2*R*,*S*)-4a. White solid (2.82 g, 69%), mp = 99.5–100.5 °C. $R_f = 0.24$ (EtOAc/MeOH/hexane, 1:1:6). $[\alpha]_D^{25} = +3.7$ (*c* 11, $CHCl_3$). IR (KBr): 3093, 3054, 2977, 2900, 1488, 1450, 1141, 1326, 1121, 1133 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.81 (d, 3H, $J = 6.8$, $CHCH_3$), 1.84 (d, 3H, $J = 7.2$, $NCHCH_3$), 2.08 (s, 3H, CH_3), 3.00–3.06 (m, 1H, $NHCHCH_3$), 3.73 (d, 1H, $J = 12.8$, $NHCH_2$), 3.76 (d, 1H, $J = 12.8$, $NHCH_2$), 4.79 (d, 1H, $J = 3.6$, $CHOH$), 5.28 (q, 1H, $J = 7.2$, $NCHCH_3$), 6.13 (d, 1H, $J = 3.2$, C*H*), 6.77 (d, 1H, $J = 3.2$, C*H*), 6.97 (d, 2H, $J = 7.2$, ArH), 7.13–7.31 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$) δ (ppm): 10.4, 15.7, 22.8, 43.4, 55.5, 58.3, 72.6, 108.2, 116.9, 118.7, 125.1, 125.8, 125.9, 126.7, 127.1, 128.4, 129.0, 141.7, 144.0. Anal. Calcd for $C_{23}H_{15}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.17; H, 7.99; N, 8.04.

4.3.2. (1*R*,2*S*)-2-((2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol (1*R*,2*S*,*R*)-4a. White solid (2.90 g, 71%), mp = 101–102 °C. $R_f = 0.24$ (EtOAc/MeOH/hexane, 1:1:6). $[\alpha]_D^{25} = -3.2$ (*c* 13, $CHCl_3$). IR (KBr): 3060, 3027, 2977, 2900, 2830, 1486, 1444, 1411, 1322, 1241, 1132 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.81 (d, 3H, $J = 6.5$, $CHCH_3$), 1.84 (d, 3H, $J = 7.1$, $NCHCH_3$), 2.09 (s, 3H, CH_3), 2.98–3.04 (m, 1H, $NHCHCH_3$), 3.72 (d, 1H, $J = 12.9$, $NHCH_2$), 3.77 (d, 1H, $J = 12.9$, $NHCH_2$), 4.88 (d, 1H, $J = 4.0$, $CHOH$), 5.28 (q, 1H, $J = 7.2$, $NCHCH_3$), 6.14 (d, 1H, $J = 2.8$, C*H*), 6.78 (d, 1H, $J = 2.8$, C*H*), 6.96 (d, 2H, $J = 7.2$, ArH), 7.23–7.32 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 14.7, 22.9, 43.6, 55.5, 58.1, 72.6, 107.9, 115.5, 118.9, 125.9, 127.1, 127.5, 128.3, 128.5, 129.1, 129.6, 141.9, 144.1.

4.3.3. (1*S*,2*R*)-2-((2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol (1*S*,2*R*,*R*)-4b. Brown oil (2.98 g, 73%), $R_f = 0.24$ (EtOAc/MeOH/hexane, 1:1:6). $[\alpha]_D^{25} = +5.6$ (*c* 7.3, $CHCl_3$); IR (KBr): 3060, 2975, 2928, 1489, 1446, 1320, 1216 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): (400 MHz, $CDCl_3$); 0.79 (d, 3H, $J = 6.4$, $CHCH_3$), 1.96 (d, 3H, $J = 7.2$, $NHCHCH_3$), 1.98 (s, 3H, CH_3), 2.95–3.01 (m, 1H, $NHCHCH_3$), 3.78 (d, 2H, $J = 13.6$, $NHCH_2$), 3.85 (d, 1H, $J = 13.6$, $NHCH_2$), 4.73 (d, 1H, $J = 3.6$, $CHOH$), 5.29 (q, 1H, $J = 7.2$, $NCHCH_3$), 5.82 (d, 1H, $J = 3.3$, C*H*), 6.00 (d, 1H, $J = 3.4$, C*H*), 7.07 (d, 2H, $J = 7.2$, ArH), 7.22–7.34 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$) δ (ppm): 10.3, 14.9, 22.8, 43.7, 55.5, 58.2, 72.9, 107.9, 116.6, 118.2, 125.9, 126.7, 126.7, 127.8, 128.8, 129.1, 129.9, 141.9, 144.1. Anal. Calcd for $C_{23}H_{15}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.10.; H, 8.05; N, 8.01.

4.3.4. (1*R*,2*S*)-2-((2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol (1*R*,2*S*,*S*)-4b. Brown oil (2.86 g, 70%). $R_f = 0.24$ (EtOAc/MeOH/hexane, 1:1:6). $[\alpha]_D^{25} = -4.5$ (*c* 9.2, $CHCl_3$), IR (KBr): 3060, 3027, 2977, 2900–2830, 1492, 1450, 1323,

1219 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.83 (d, 3H, $J = 6.5$, $CHCH_3$), 1.84 (d, 3H, $J = 7.1$, $NCHCH_3$), 2.08 (s, 3H, CH_3), 2.99–3.05 (m, 1H, $NHCHCH_3$), 3.71 (d, 2H, $J = 12.9$, $NHCH_2$), 3.76 (d, 1H, $J = 12.9$, $NHCH_2$), 4.81 (d, 1H, $J = 3.7$, CHOH), 5.28 (q, 1H, $J = 7.2$, $NCHCH_3$), 6.15 (d, 1H, $J = 2.9$, CH), 6.78 (d, 1H, $J = 2.9$, CH), 6.97 (d, 2H $J = 7.2$, ArH), 7.23–7.32 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$) δ (ppm): 10.4, 15.7, 22.8, 43.4, 55.5, 58.3, 72.6, 108.2, 116.9, 118.3 125.9, 126.0, 126.4, 127.1, 127.5, 128.3, 129.1, 141.8, 144.0.

4.3.5. (1*S*,2*R*)-2-((5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol (1*S*,2*R*,*S*)-5a. Brown oil (2.94 g, 72%). $R_f = 0.32$ (EtOAc/hexane, 1:1). $[\alpha]_D^{27} = +28.2$ (*c* 11, $CHCl_3$). IR (KBr): 3059, 3054, 2973, 2927, 1493, 1449, 1407, 1291, 1108 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.79 (d, 3H, $J = 6.5$, $CHCH_3$), 1.95 (d, 3H, $J = 7.2$, $NHCHCH_3$), 2.05 (s, 3H, CH_3), 2.93–2.98 (m, 1H, $NHCHCH_3$), 3.75 (d, 1H, $J = 13.6$, $NHCH_2$), 3.82 (d, 1H, $J = 13.6$, $NHCH_2$), 4.71 (d, 1H, $J = 3.5$, CHOH), 5.73 (q, 1H, $J = 7.1$, $NCHCH_3$), 5.83 (d, 1H, $J = 3.1$, CH), 5.98 (d, 1H, $J = 3.2$, CH), 7.11 (d, 2H, $J = 7.1$, ArH), 7.19–7.38 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.2, 14.6, 19.8, 44.1, 52.6, 57.9, 73.1, 107.2, 107.7, 125.9, 126.1, 126.9, 127.0, 127.9, 128.6, 129.4, 130.3, 141.1, 142.5. Anal. Calcd for $C_{23}H_{15}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.01; H, 7.82; N, 8.09.

4.3.6. (1*R*,2*S*)-2-((5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol (1*R*,2*S*,*R*)-5a. Brown oil (2.86 g, 70%). $R_f = 0.31$ (EtOAc/hexane, 1:1). $[\alpha]_D^{27} = -31.0$ (*c* 10, $CHCl_3$). IR (KBr): 3425, 3060, 2974, 2930–2868, 1495, 1449, 1407, 1291, 1112 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.80 (d, 3H, $J = 6.5$, $CHCH_3$), 1.96 (d, 3H, $J = 7.2$, $NCHCH_3$), 2.03 (s, 3H, CH_3), 2.96–3.00 (m, 1H, $NHCHCH_3$), 3.78 (d, 1H, $J = 13.6$, $NHCH_2$), 3.84 (d, 1H, $J = 13.6$, $NHCH_2$), 4.71 (d, 1H, $J = 3.7$, CHOH), 5.69 (q, 1H, $J = 7.2$, $NCHCH_3$), 5.82 (d, 1H, $J = 3.3$, CH), 5.99 (d, 1H, $J = 3.3$, CH), 7.08 (d, 2H, $J = 7.4$, ArH), 7.19–7.37 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$): δ ppm 14.2, 14.4, 19.6, 44.0, 52.7, 57.8, 73.0, 107.3, 107.8, 125.9, 126.0, 126.9, 126.9, 128.0, 128.6, 129.5, 130.2, 141.2, 142.4.

4.3.7. (1*S*,2*R*)-2-((5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol (1*S*,2*R*,*R*)-5b. Brown oil (2.78 g, 68%). $R_f = 0.32$ (EtOAc/hexane, 1:1). $[\alpha]_D^{27} = +20.6$ (*c* 15.7, $CHCl_3$). IR (KBr): 3425, 3027, 2976, 2930–2864, 1497, 1451, 1405, 1291, 1112 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.82 (d, 3H, $J = 6.5$, $CHCH_3$), 1.97 (d, 3H, $J = 7.2$, $NCHCH_3$), 2.09 (s, 3H, CH_3), 2.95–3.01 (m, 1H, $NHCHCH_3$), 3.78 (d, 1H, $J = 13.6$, $NHCH_2$), 3.85 (d, 1H, $J = 13.6$, $NHCH_2$), 4.71 (d, 1H, $J = 3.7$, CHOH), 5.71 (q, 1H, $J = 7.1$, $NCHCH_3$), 5.86 (d, 1H, $J = 2.5$, CH), 6.00 (d, 1H, $J = 3.3$, CH), 7.10 (d, 2H, $J = 7.6$, Ph) 7.19–7.38 (m, 8H, Ph). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.2, 14.4, 19.6, 44.0, 52.7, 57.8, 73.0, 107.3, 107.8, 125.9, 126.0, 126.9, 127.0, 128.0, 128.6, 129.4, 130.3, 141.3, 142.5. Anal. Calcd for $C_{23}H_{15}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.05; H, 7.94; N, 8.13.

4.3.8. (1*R*,2*S*)-2-((5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol (1*R*,2*S*,*S*)-5b. Brown oil (2.98 g, 73%). $R_f = 0.32$ (EtOAc/hexane, 1:1). $[\alpha]_D^{27} = -22.5$ (*c* 14, $CHCl_3$), IR (KBr): 3428, 3087, 2974, 2930–2868, 1495, 1449, 1406, 1333, 1291, 1110 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.80 (d, 3H, $J = 6.5$, $CHCH_3$), 1.96 (d, 3H, $J = 7.2$, $NCHCH_3$), 2.03 (s, 3H, CH_3), 2.93–2.99 (m, 1H, $CHCH_3$), 3.74 (d, 1H, $J = 13.6$, $NHCH_2$), 3.81 (d, 1H, $J = 13.6$, $NHCH_2$), 4.70 (d, 1H, $J = 3.7$, CHOH), 5.69 (q, 1H, $J = 7.2$, $NCHCH_3$), 5.82 (d, 1H, $J = 3.2$, CH), 5.99 (d, 1H, $J = 3.7$, CH), 7.08 (d, 2H, $J = 7.4$, ArH), 7.21–7.37 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.2, 14.6, 19.8, 44.1, 52.6, 57.8, 73.1, 107.2, 107.7, 125.9, 126.1, 126.9, 127.0, 128.0, 128.6, 129.4, 130.1, 141.1, 142.5.

4.4. General procedure for the addition of diethylzinc to aldehyde

To a solution of chiral ligands (1*S*,2*R*,*S*)-**4a** (0.0174 g, 0.05 mmol) in dry toluene (5 mL) at 0 °C under an argon atmosphere was added a solution of diethylzinc (2 mL, 1.0 M in hexane) via a syringe. After stirring for 6 h at 0 °C, the aldehyde (0.1 mL, 1.00 mmol) was added into the mixture. The reaction mixture was stirred at room temperature and the reaction monitored by TLC. The reaction was quenched by the addition of 10 mL of 1 M HCl solution. The layers were separated and aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: EtOAc/hexane, 1:6). (*S*)-1-Phenylpropan-1-ol was isolated as a colorless oil in 70% yield with 75% ee. The ee values were determined by HPLC with a Chiralcel-OD column; 2% 2-propanol in hexane, flow rate: 1 mL/min, UV detection (254 nm) t_R: 17 min for (*R*), 19 min for (*S*). ^1H NMR ($CDCl_3$) δ (ppm): 0.94 (t, 3H, $J = 7.6$, CH_2CH_3), 1.71–1.86 (m, 2H, CH_2CH_3), 2.12 (s, 1H, OH), 4.58 (t, 1H, $J = 6.8$, CH), 7.24–7.36 (m, 5H, ArH).

4.5. General procedure for the addition of diethylzinc to aldehyde in the presence of Ti(O-*i*-Pr)$_4$

Chiral ligand (0.0174 g, 0.05 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 g, 0.25 mmol) were mixed in dry toluene at room temperature. After 1 h, diethylzinc (2 mL, 1.0 M solution in hexane) was added at 0 °C. The mixture was stirred for 1 h and then benzaldehyde (0.1 mL, 1 mmol) was added at 0 °C. The mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated ammonium chloride solution, extracted with dichloromethane (2×25 mL), and dried over $MgSO_4$. The purification of crude product was accomplished by flash column chromatography (Silica gel, eluent: EtOAc/hexane, 1:6).

4.6. General procedure for the addition of diethylzinc to chalcone

A solution of $Ni(acac)_2$ (0.026 g, 0.01 mmol) and chiral ligand (1*S*,2*R*,*R*)-**4b** (0.069 g, 0.2 mmol) in acetonitrile

was stirred and refluxed for 1 h under an argon atmosphere. The solution was cooled to room temperature and chalcone (0.208 g, 1 mmol) was added. The mixture was cooled to −30 °C and a solution of diethylzinc (1.5 mL, 1 M solution in hexane) was added. The color changed from bright green to a dark brown red. Stirring was continued at −30 °C for 6 h. The mixture was quenched with 1 M HCl (10 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, crude product was purified by flash column chromatography (silica gel, eluent: EtOAc/hexane, 1:20). (*R*)-1,3-Diphenylpentane-1-one was isolated as light yellow solid in 70% yield with 53% ee. The ee values were determined by HPLC with a Chiralcel-OD column. 0.5% 2-propanol in hexane, flow rate: 1 mL/min, UV detector (254 nm) t_R: 14.11 min for (*S*), 15.35 min for (*R*). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85 (t, 3H, $J = 7.4$, CH_2CH_3), 1.67–1.71 (m, 1H, CH_2CH_3), 1.80–1.83 (m, 1H, CH_2CH_3), 3.22–3.30 (m, 3H, $CHCH_2$), 7.18–7.29 (m, 5H, ArH), 7.43–7.45 (m, 2H, ArH), 7.52–7.55 (m, 1H, ArH), 7.90–7.92 (m, 2H, ArH).

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