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The Synthesis of *N*,*O*-Ferrocenyl Pyrrolidine-Containing Ligands and Their Application in the Diethyl- and Diphenylzinc Addition to Aromatic Aldehydes

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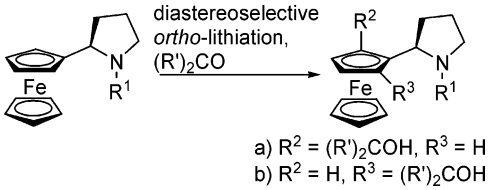

A facile route to a series of planar chiral *N*,*O*-ferrocenyl pyrrolidine-containing ligands with varying substituents at the nitrogen and oxygen donor atoms is described. The oxygen donor atom was introduced via a diastereoselective ortho-metalation of *N*-methylpyrrolidinyl and *N*-allylpyrrolidinyl ferrocene intermediates and was quenched with various ketones. The nitrogen substituent was varied through deallylation and subsequent derivatization of a secondary pyrrolidine. The efficacy of these novel ligands was investigated in the enantioselective addition of diethylzinc and diphenylzinc to aromatic aldehydes. The ligands proved highly effective in the diethylzinc addition to benzaldehyde that resulted in high yields of up to 99% and enantioselectivities (ee's) of up to 95%. The role of planar chirality was explored and the results indicated that the planar chirality, and not the central chirality, of the ferrocenyl ligands was the dominant stereo-controlling element. Employment of a mixed ethyl-phenylzinc reagent in the phenylation of aromatic aldehydes led to a mixture of the two additional products, and the phenylated product was obtained in up to 37% ee.

Introduction

The enantioselective formation of C−C bonds is regarded as one of the most fundamental transformations in asymmetric synthesis.[1] The enantioselective preparation of chiral alcohols is of particular interest, because they represent valuable structural units found in many natural products and they are readily functionalized.[2] The addition of organometallic reagents to carbonyl compounds has emerged as a key method of preparing chiral alcohols. Since the pioneering work of Oguni in 1984,[3] there has been extensive research into the diethylzinc addition to benzaldehyde, and it is now regarded as one of the benchmark reactions for understanding the catalytic potential of new ligands. However, the ligand-specific nature of catalytic reactions ensures that the search for new ligands remains a field of incessant interest. In comparison to the work on dialkylzinc additions, the asymmetric addition of diarylzinc reagents to aldehydes is substantially less developed. Nevertheless, there has been considerable focus on this area in recent years because chiral diarylmethanols are important precursors for pharmacologically and biologically active compounds.[4,5] To date, several *N*,*O*-ferrocenyl ligands, such as the ligands from Schlögl (**1**),[6] Butsugan and Watanabe (**2**),[7] and Bolm (**3**),[8,9] have been successfully applied in the diethyl- and diphenylzinc addition to aromatic aldehydes.

A literature survey of this test reaction prompted us to prepare a series of *N*,*O*-ferrocenyl ligands in which the substituents at

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(1) (a) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed; VCH: Weinheim, Germany, 2000. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1998.

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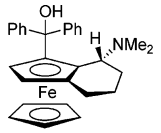

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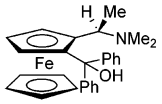

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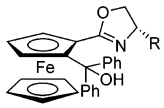

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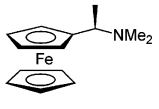
the nitrogen and oxygen donor atoms could be readily manipulated. The introduction of the oxygen donor atom, and consequently planar chirality, employed an ortho-directing lithiation strategy that was developed by Ugi using *N*,*N*-dimethyl-1-ferrocenylethylamine (**4**).[10] Since this pioneering work, a range of ortho-directing auxiliaries, including sulfoxides,[11] acetals,[12] oxazolines,[9,13,14] azepines,[15] sulfoximines,[16] and hydrazones,[17] have been employed. Of greater interest to our research was that ferrocenylpyrrolidine (**5**) developed by Ganter[18] and *trans*-2,5-disubstituted pyrrolidine (**6**) from our research laboratories[19] effected diastereoselective lithiations.



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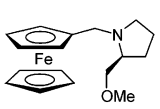

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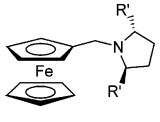

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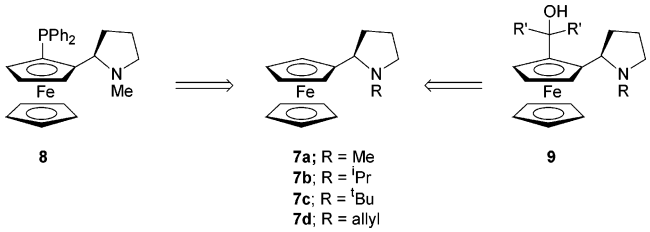
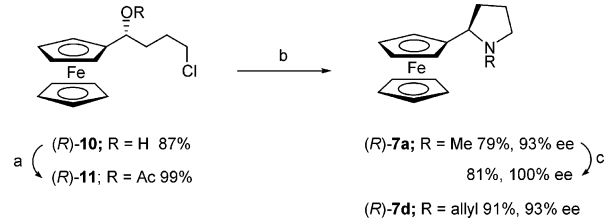
We recently reported the synthesis of *N*-methylpyrrolidinylferrocene (**7a**), which proved to be an efficient ortho-directing group in the synthesis of the *P*,*N*-ferrocenyl ligand (**8**) (Scheme 1).[20] Herein, we describe the synthetic procedures devised for novel *N*,*O*-ferrocenyl ligands of type **9.** An ortho-directed metalation of **7a** and quench with different ketones generated novel *N*,*O*-ferrocenyl ligands with varying degrees of steric bulk at the hydroxyl-bearing carbon atom of ligand **9**. In a previous attempt to vary the substituents at the nitrogen donor atom, the synthesis and lithiation of *N*-pyrrolidinyl analogues **7b** and **7c** was investigated. It immediately was apparent that the drawback to this approach was the erratic nature of the lithiation process. Although the coordination of the lithiating reagent is strongly dependent on the *N*-pyrrolidinyl substituent, each set of lithiation conditions had to be optimized independently. The optimal lithiation of pyrrolidine **7b** proceeded in 15% yield and 40% diastereomeric excess (de), whereas the attempted lithiation of pyrrolidine **7c** did not afford any product.[20] Thus, in an innovative move, the substituents at the nitrogen donor atom were varied by employing a key *N*-allylpyrrolidine intermediate **7d** and an allylation/deallylation approach. The series of *N*,*O*-ferrocenyl ligands was applied in the diethyl- and diphenylzinc addition to aromatic aldehydes to determine the effect of substituents at the donor atoms and the role of planar chirality in inducing asymmetry in these transformations.

SCHEME 1



8 **7a;** R = Me; **7b**; R = ^{i}Pr; **7c**; R = ^{t}Bu; **7d**; R = allyl **9**

SCHEME 2. Synthesis of *N*-Pyrrolidine 7[a]



[a](a) Ac_2O, NEt_3, DMAP, rt, 12 h; (b) $MeNH_2$ (2 M solution MeOH) or $C_3H_5NH_2$ in MeOH, Δ, 3 h; (c) (*i*) hot EtOH, (+)-tartaric Acid, (*ii*) NaOH.

Results and Discussion

Synthesis of Pyrrolidinylferrocene. The strategy for the preparation of ferrocenyl ligands of type **9** involved the synthesis of pyrrolidine **7** followed by a directed ortho-metalation to introduce the tertiary alcohol function. The asymmetric synthesis of pyrrolidine **7**, which utilizes the Corey−Bakshi−Shibata (CBS) reduction protocol,[21] has been reported in a previous communication.[20] The (*R*)-enantiomer was tentatively assigned to alcohol **10** based on the known stereochemical outcome of the CBS reduction of other ferrocenyl ketones and later confirmed by X-ray crystallography of a compound derived from alcohol **10**. The enantiomeric purity of alcohol (*R*)-**10** was determined as 93% enantiomeric excess (ee) from chiral HPLC. Subsequent acetylation of alcohol **10** gave acetate **11**, and treatment with methylamine or allylamine furnished enantioenriched *N*-methylpyrrolidine **7a** or *N*-allylpyrrolidine **7d**, respectively (Scheme 2). It is worth noting that the preparation of enantioenriched pyrrolidines **7a** and **7d** proceeded with the retention of configuration and without the loss of ee, a phenomenon previously observed by Ugi.[22] Enantiopure **7a** was obtained from its enantioenriched mixture in 81% yield through the preparation of diastereomeric salts from tartaric acid in ethanol.[10] Although several resolving agents were screened for the resolution of **7d** (e.g., tartaric acid, ditolyl tartaric acid, dibenzoyl tartaric acid, and mandelic acid, among others) in various solvent systems, its fractional recrystallization was unsuccessful and, thus, enantioenriched **7d** was used for all further synthetic steps. It was noted that previous attempts at

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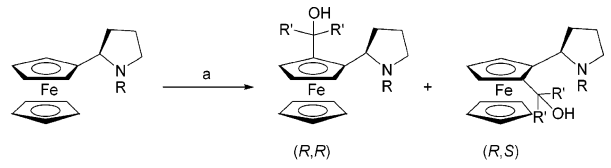
SCHEME 3. Synthesis of *N,O*-Ferrocenyl Ligands 12−15[a]



7a; R = CH_3
7d; R = C_3H_5

12; R = CH_3, R' = CH_3
13; R = CH_3, R' = C_6H_5
14; R = CH_3, R' = 3,5-$(Me)_2C_6H_3$
15; R = C_3H_5, R' = C_6H_5

[a] (a) s-BuLi, Et_2O, −78 °C for 3 h, 0 °C for 1 h, then $(R')_2CO$, 0 °C to rt, 2 h.

TABLE 1. Synthesis of *N,O*-Ferrocenyl Ligands 12−15[a]

entry	ligand	yield (*R,R*) (%)[b]	yield (*R,S*) (%)[b]	de (%)[c]
1	**12**	38	0	>99
2	**13**	73	12	73
3	**14**	55	8	76
4	**15**	45	22	33

[a] Lithiation conditions of − 78 °C for 3 h followed by 0 °C for 1 h then quenched with ketone. [b] Isolated yield of diastereomer after column chromatography. [c] Determined by ^{1}H NMR.

the resolution of enantioenriched pyrrolidines **7b** and **7c** also failed. It was suggested that the steric bulk on the nitrogen atom may inhibit salt formation in the resolution of tertiary amines.[23]

Using a directed ortho-lithiation and quench with the appropriate electrophile, it was possible to generate planar chiral ferrocene derivatives with different degrees of steric bulk in the immediate vicinity of the hydroxyl group. In general, the lithiation procedure can be quite capricious, because its success is highly dependent on the reaction conditions.[24] After a preliminary optimization of the lithiation conditions, **7a** was treated with *s*-BuLi (1.2 equiv) in Et_2O at −78 °C for 3 h followed by 1 h at 0 °C to ensure complete lithiation before the addition of the electrophile. Using this strategy, the lithiated intermediate of **7a** was quenched with three symmetrical ketones, namely, acetone, benzophenone, and bis-(3,5-dimethyl-phenyl)methanone, to furnish **12**, **13**, and **14**, respectively (Scheme 3). Similarly, the lithiated intermediate of **7d** was quenched with benzophenone to generate *N,O*-ferrocenyl ligand **15**.

For the acetone-derived ligand **12**, the lithiation of **7a** was completely diastereoselective (Table 1) with the sole diastereomer being isolated in 38% yield. The lithiation of **7a** and quenching with benzophenone and bis-(3,5-dimethyl-phenyl)-methanone furnished ligands **13** and **14**, respectively. By comparing the *N*-Me signals in the crude ^{1}H NMR spectrum, the diastereomeric ratios were determined as 73 and 76% de, respectively. The mixures of the diastereomers were separated by column chromatography. Crystals grown from *n*-hexane of the major diastereomers of **12** and **13** were suitable for X-ray diffraction, and analysis confirmed the (*R*)-central chirality of the pyrrolidine and demonstrated the (*R*)-planar chirality of the ferrocene backbone (Figure 1). Similarly, the lithiation intermediate of **7d** was quenched with benzophenone to furnish **15** in 33% de as determined from the ^{1}H NMR spectrum. We propose that the lower diastereoselectivity observed for **7d** is a result of inferior differentiation in the lithiation transition states as compared to those for **7a**. In the absence of an X-ray crystal structure of the major diastereomer, (*R*)-planar chirality was inferred from the asymmetric lithiation in addition to trends in optical rotations within this series. Purification by column chromatography and subsequent recrystallization from pentane afforded (*R,R*)-**15** with absolute diastereomeric and enantiomeric purity as determined by chiral HPLC. This was advantageous to our synthetic scheme as it illustrated that in the case of **15** it was possible to obtain optically pure material at this late stage.

Selective Preparation of Minor Diasteromeric Ligands. The selective preparation of the minor diastereomers involved temporarily protecting the preferred ortho-position of **7a** and **7d** with a trimethylsilyl (TMS) group (Scheme 4).[25] The diastereoselectivity of the TMS-derivative **16a** and **16b** were determined from the ^{1}H NMR as 73 and 70% de, respectively. Prior to subsequent transformations, the mixtures of diastereomers were separated by column chromatography on silica gel with the major diastereomers (*R,R*)-**16a** being isolated in 60% yield and (*R,R*)-**16b** being isolated in 55% yield. Subsequent deprotonation at the remaining ortho-position of **16a** and **16b** and quenching with benzophenone or bis(3,5-dimethyl-phenyl)-methanone yielded trisubstituted ferrocenyl ligands **17**, **18**, and **19**. Treatment of the TMS-containing derivatives with tetrabutylammonium fluoride (TBAF) furnished the (*R,S*)-diasteromers **13**, **14**, and **15** in high yields. The predicted (*R*)-central chirality and (*S*)-planar chirality of ligands **13** and **14** were confirmed by X-ray crystallographic analysis (Figure 1). The chirality of (*R,S*)-**15** was similarly inferred. Selected bond lengths, angles, and torsion angles are presented in Table 2.

It was noted that the precursor to the minor diastereomers, namely, trisubstituted ferrocene derivatives **17**, **18**, and **19**, are also potential ligands for asymmetric catalysis. Previous reports suggest that the TMS group can influence the conformation of the other substituents on the ferrocene ring leading to augmented enantiocontrol of the reaction.[20,26] We decided to investigate this potential TMS effect by comparing the catalytic results of (*R,R*)-**14** and (*R,R*)-**17**. To fully ascertain the effect of the TMS group, it was necessary to prepare its diastereomer (*R,S*)-**17** for comparative purposes with (*R,S*)-**14**. One approach taken to prepare (*R,S*)-**17** involved protecting the hydroxyl group of (*R,R*)-**14** and then lithiating at the ortho-position and quenching with trimethylsilyl chloride. Unfortunately, several attempts to temporarily protect the hydroxyl group of (*R,R*)-**14** failed.[27] However, the required ligand (*R,S*)-**17** was prepared in 63% yield through lithiation of (*R,S*)-**16a** (the minor diastereomer in the preparation of TMS-containing derivative **16a**) and quench with benzophenone (Scheme 5).

As outlined above, the variation of the *N*-pyrrolidine substituent prior to the lithiation step was problematic in its resolution and in the individual optimization of the lithiation conditions. We investigated an alternative route in which pyrrolidine (*R,R*)-**15** was employed to access a series of closely related ligands with varying N-substituents (Scheme 6). The deallylation procedure involved the treatment of **15** with palladium(tetrakistriphenylphosphine) and *N,N*-dimethyl barbi-

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(27) (a) *s*-BuLi, Et_2O, TMSCl, −78 °C.; (b) Imidazole, DMF, TMSCl, 50 °C.; (c) HMDS, TMSCl, *n*-hexane, 50 °C.; (d) DDQ, MeOH, 40 °C.

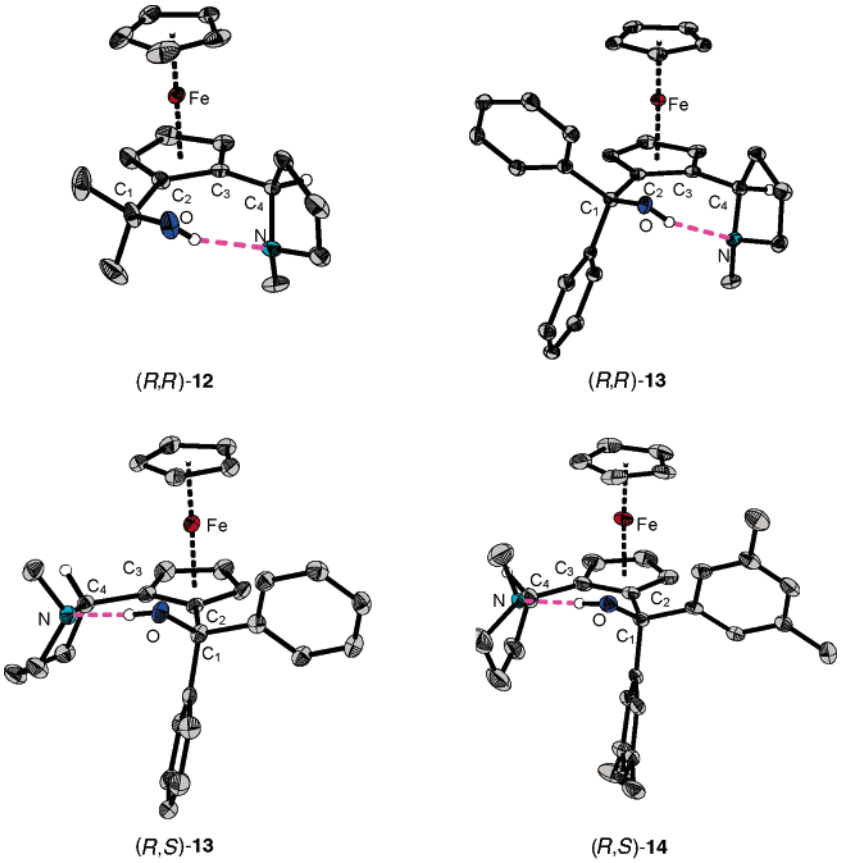
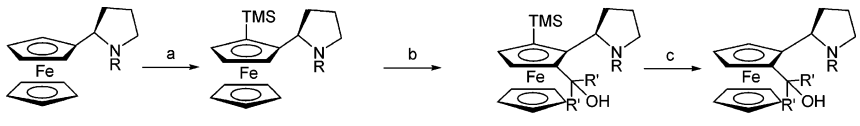


FIGURE 1. X-ray crystal structure of (*R*,*R*)-**12**, (*R*,*R*)-**13**, (*R*,*S*)-**13**, (*R*,*R*)-**14** (H atoms have been omitted for clarity except the C_2-pyrrolidine and hydroxyl proton). Displacement ellipsoids are shown at 50% probability.

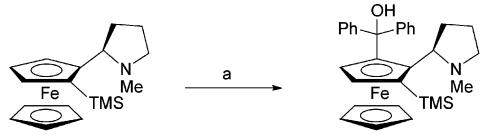
SCHEME 4. Synthesis of Minor Diastereomeric Ligands (*R*,*S*)-13−15[a]



7a; R = CH_3	**16a**; R = CH_3	R = CH_3, R' = C_6H_5	**17**	73%	**13** 89%
7d; R= C_3H_5	**16b**; R= C_3H_5	R = CH_3, R' = 3,5-$(Me)_2C_6H_3$	**18**	52%	**14** 78%
		R = C_3H_5, R' = C_6H_5	**19**	71%	**15** 83%

[a](a) s-BuLi, ether, −78 °C for 3 h then 0 °C for 1.5 h, then TMSCl, 1 h; (b) s-BuLi, ether, −78 °C for 3 h then 0 °C for 1 h, then (R′)$_2$CO, THF, −78 °C to rt, 2 h; (c) TBAF (1 M soln THF), Δ, 2 d.

SCHEME 5. Synthesis of Ferrocene (*R*,*S*)-17[a]



[a](a) s-BuLi, Et_2O, −78 °C for 3 h, 0 °C for 1 h, then Ph_2CO, THF, −78 °C−rt overnight.

turic acid (NDMBA) to furnish pyrrolidine (*R*,*R*)-**20** in 87% yield.[28] The secondary pyrrolidine (*R*,*R*)-**20** was derivatized in the presence of potassium carbonate and benzylbromide to furnish *N*-benzylpyrrolidine (*R*,*R*)-**21** in 76% yield. The minor diastereomer (*R*,*S*)-**21** was prepared in a similar procedure.

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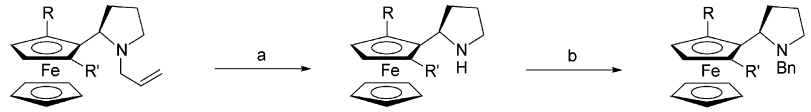
Diethylzinc Addition to Aromatic Aldehydes. A series of experiments were conducted to determine the efficacy of *N*,*O*-ferrocenyl ligands **12**, **13**, **14**, **15**, **17**, **20**, and **21** in the diethylzinc addition to aromatic aldehydes. The reactions were typically carried out in toluene on a 1 mmol scale of aldehyde substrate employing 5 or 10 mol % ligand (Scheme 7). After a general optimization of the reaction conditions, our investigation focused on three main inquiries: first, the role of planar chirality in determining the ee and stereochemical outcome of the alkylation process; second, the influence of steric bulk directly on the hydroxyl-bearing carbon atom on the ee; and third, the steric and electronic influence of varying the *N*-pyrrolidinyl substituent.

The optimal reaction conditions with regard to temperature, catalyst loading, and solvent were determined using ligands (*R*,*R*)-**13** and (*R*,*S*)-**13** and benzaldehyde as the substrate (Table 3). It was immediately apparent that the planar chirality plays

TABLE 2. Selected Bond Lengths, Angles, and Torsion Angles of (*R*,*R*)-12, (*R*,*R*)-13, (*R*,*S*)-13, and (*R*,*R*)-14

	bond length (Å)		bond angle (°C)			torsion angle (°C)	
ligand	O−H	N−H	C_2-C_1-O	C_3-C_4-N	O−H−N	$C_3-C_2-C_1-O$	$C_2-C_3-C_4-N$
(*R*,*R*)-**12**	0.71	2.16	111.80	110.94	155	19.1	51.3
(*R*,*R*)-**13**	0.79	2.00	111.51	102.99	154	23.1	44.6
(*R*,*S*)-**13**	0.86	1.82	111.79	115.83	174	−46.7	19.0
(*R*,*S*)-**14**	0.88	1.82	112.30	115.90	179	−45.1	33.4

SCHEME 6. Synthesis *N*-Benzylpyrrolidine 21[a]



(*R*,*R*)-**15**; R = Ph_2COH, R' = H — (*R*,*R*)-**20** 87% — (*R*,*R*)-**21** 76%

(*R*,*S*)-**15**; R = H, R' = Ph_2COH — (*R*,*S*)-**20** 82% — (*R*,*S*)-**21** 61%

[a] (a) NDMBA, $Pd(PPh_3)_4$, CH_2Cl_2, 30 °C, 5 h; (b) benzylbromide, K_2CO_3, THF, 24 h, rt.

SCHEME 7. Diethylzinc Addition to Benzaldehyde

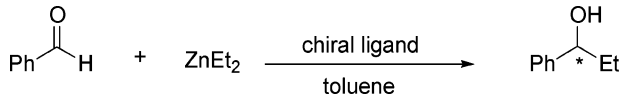


TABLE 3. Diethylzinc Addition to Benzaldehyde Catalyzed by (*R*,*R*)-13 and (*R*,*S*)-13[a]

entry	planar chirality	ligand (mol %)	temp (°C)	yield (%)	ee (%)[b]	config[c]
1	(*R*)	5	−20	87	84	*R*
2	(*R*)	10	−20	96	83	*R*
3	(*R*)	5	0	99	78	*R*
4[d]	(*R*)	5	−20	94	85	*R*
5	(*S*)	5	−20	98	92	*S*
6	(*S*)	10	−20	99	91	*S*
7	(*S*)	5	0	99	90	*S*
8[e]	(*S*)	5	−20	99	92	*S*

[a] The reactions were carried out in toluene unless otherwise stated. [b] Determined by HPLC analysis on Chiracel OD column. [c] Determined by comparison with literature data (optical rotation and HPLC retention times). [d] *n*-Hexane used as solvent. [e] 1:2 ratio of *n*-hexane/toluene used as solvent.

a dominant role in determining the stereochemical outcome of the catalytic reaction, (*R*)-planar chiral (*R*,*R*)-**13** furnished the (*R*)-product, and (*R*,*S*)-**13** furnished the (*S*)-product. For (*R*,*R*)-**13**, an increase in temperature from −20 °C to 0 °C resulted in an increased yield of 1-phenylpropanol product (from 87 to 99%) with a concomitant reduction in the ee (from 84 to 78% ee) (Table 1, entries 1 and 3). In a parallel study, an increase in temperature had a negligible effect when (*R*,*S*)-**13** as the ligand (Table 1, entries 5 and 7) was used. Increasing the ligand loading from 5 to 10 mol % (*R*,*R*)-**13** increased the yield (87 to 96%) without affecting the ee (Table 1, entries 1 and 2). Higher yields (94 versus 87%) and comparable ee's (84 and 85% ee) were obtained in hexane as solvent instead of toluene (Table 1, entries 1 and 4). As per the effect of temperature and solvent, the effect of catalyst loading was less pronounced using (*R*,*S*)-**13** as chiral ligand (Table 3, entries 5, 6, and 7). Ferrocenyl ligand (*R*,*S*)-**13** was only slightly soluble in *n*-hexane and thus a toluene/*n*-hexane mixture was used as its solvent (Table 3, entry 8).

As a result of these studies, the standard reaction conditions of 5 mol % ligand in toluene at −20 °C were chosen to test the efficacy of our other ligands. For amino alcohols, the substituents on the hydroxyl-bearing carbon atom, along with those on the nitrogen atom, significantly influence the outcome of catalysis.[29] To investigate the steric influence at the oxygen donor atom and the role of planar chirality, the series of ferrocenyl ligands was applied in the diethylzinc addition to benzaldehyde under standard conditions (Table 4).

TABLE 4. Diethylzinc Addition to Benzaldehyde Catalyzed by *N*,*O*-Ferrocenyl Ligands 12−14[a]

entry	ligand	time (h)	yield (%)	ee (%)[b]	config[c]
1	(*R*,*R*)-**12**	36	97	67	*R*
2	(*R*,*R*)-**13**	36	87	84	*R*
3	(*R*,*R*)-**14**	48	80	82	*R*
4	(*R*,*R*)-**17**	48	94	95	*R*
5	(*R*,*S*)-**13**	36	98	92	*S*
6	(*R*,*S*)-**14**	48	95	75	*S*
7	(*R*,*S*)-**17**	48	54	67	*R*

[a] The reactions were carried out in toluene in the presence of 5 mol % of ligand at −20 °C. [b] Determined by HPLC analysis using a Chiracel OD column. [c] Determined by comparison with literature data (optical rotation and HPLC retention times).

The appropriate steric bulk of ligands can be difficult to balance because excessively large substituents may adopt conformations in the transition state that lower the efficiency of the reaction. The increase in steric bulk at the hydroxyl-bearing carbon atom from a methyl group in (*R*,*R*)-**12** to a phenyl group in (*R*,*R*)-**13** results in an increase in the ee (67 to 84%) and a decrease in the yield of (*R*)-1-phenylpropanol (97 to 87%) (Table 4, entries 1 and 2). The diarylhydroxymethyl moiety is often referred to as the "magic group" in catalyst design and has been used with increasing frequency in recent years.[30] A further increase in steric bulk in the form of the 3,5-dimethylphenyl analogue (*R*,*R*)-**14** resulted in a slight decrease in the ee (84 to 82%), and a longer reaction time of 48 h was required (Table 4, entries 2 and 3). For the (*S*)-planar chiral ligands, the increase in steric hindrance when changing from a phenyl group (*R*,*S*)-**13** to a 3,5-dimethylphenyl derivative (*R*,*S*)-**14** had a large negative effect on the ee (92 to 75%) (Table 4, entries 4 and 5).

The introduction of a TMS group to (*R*,*R*)-**13** to generate (*R*,*R*)-**17** had a pronounced effect in catalysis as the ee increased from 84 to 95% (Table 4, entries 2 and 4). Alternatively, the introduction of the TMS group to (*R*,*S*)-**13** to generate (*R*,*S*)-**17** had a detrimental effect on the ee. This suggests that the bulky nature of the TMS group in ligand (*R*,*S*)-**17** led to the pyrrolidine ring taking up a conformation which led to poor differentiation

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TABLE 5. Diethylzinc Addition to Benzaldehyde Catalyzed by Diastereomeric Ligands 13, 15, 20, and 21[a]

entry	ligand	R	yield (%)	ee (%)[b]	config.[c]
1	(*R*,*R*)-**13**	Me	87	84	*R*
2	(*R*,*R*)-**15**	allyl	61	37	*R*
3	(*R*,*R*)-**21**	Bn	33	57	*R*
4	(*R*,*R*)-**20**	H	94	66	*S*
5	(*R*,*S*)-**13**	Me	99	92	*S*
6	(*R*,*S*)-**15**	allyl	99	74	*S*
7	(*R*,*S*)-**21**	Bn	28	48	*S*
8	(*R*,*S*)-**20**	H	56	21	*R*

[a] The reactions were carried out in toluene for 48 h at −20 °C using 5 mol % ligand. [b] Determined by HPLC analysis using a Chiracel OD column. [c] Determined by comparison with literature data (optical rotation and HPLC retention times).

of the enantiotopic faces of benzaldehyde. Of the oxygen donor atoms investigated, the diphenylmethanol moiety provided the optimal yields and ee's in the diethylzinc addition to benzaldehyde. It has been documented that the presence of alkyl groups on the nitrogen donor atom favors stable catalytic complexes and promote very rapid reactions, whereas bulky alkyl and aryl substituents may provide higher ee's because of better differentiation of the enantiotopic faces of the aldehyde substrate.[31] Soai demonstrated that substituents on the nitrogen atom of the chiral catalyst affect the formation and stability of the transition state.[32] We had a range of N-substituted ligands in which to study the importance of N-variation employing the chosen conditions of 5 mol % ligand **13**, **15**, **20**, and **21** in toluene at −20 °C for 48 h (Table 5). In general, it was noted that the replacement of the *N*-methyl substituent on the pyrrolidine ring with an allyl or a benzyl moiety led to a reduction in the ee (Table 5, entries 1, 2, and 3). This trend also was observed when replacing the *N*-methyl group in (*R*,*S*)-**8** with an *N*-allyl or *N*-benzyl moiety (Table 5, entries 5, 6, and 7).

More importantly, it was observed that the planar chirality continued to play a dominant role in determining the configuration of the 1-phenylpropanol product. In general, N-substituted ferrocenyl ligands favored induction of the (*R*)-enantiomer. In contrast, secondary pyrrolidine (*R*,*R*)-**20** afforded the opposite chiral induction under the same reaction conditions (Table 5, entries 4 and 8). The change in the stereochemical outcome of the diethylzinc addition product using N-substituted and N−H amino alcohols was previously observed by Soai, Wang, and others.[32,33] The diminished catalytic potential of amino alcohols bearing an N−H group was in agreement with the results previously reported.[34,35]

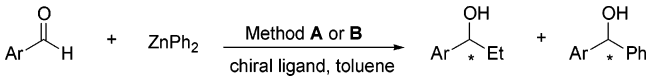
With the conditions optimized for benzaldehyde, we explored the scope of ligands (*R*,*R*)-**13** and (*R*,*S*)-**13** in the asymmetric addition of diethylzinc to several substituted aromatic aldehydes (Table 6). High chemical yields and moderate to good ee's were observed. However, it was noted that any substitution on the aromatic ring lowers the ee relative to the parent benzaldehyde. More interesting to our investigation is that (*R*,*R*)-**13** furnished the secondary alcohol products with the (*R*)-configuration and

TABLE 6. Diethylzinc Addition to Various Aldehydes Catalyzed by (*R*,*R*)-13 and (*R*,*S*)-13[a]

entry	planar chirality	aldehyde	yield (%)	ee (%)[b]	config[c]
1	*R*	benzaldehyde	99	78	*R*
2	*R*	4-chlorobenzaldehyde	78	69	*R*
3	*R*	4-methoxybenzaldehyde	96	71	*R*
4	*R*	*trans*-cinnamaldehyde	99	65	*R*
5	*R*	1-naphthaldehyde	37	55	*R*
6	*R*	2-naphthaldehyde	16	39	*R*
7	*S*	benzaldehyde	99	90	*S*
8	*S*	4-chlorobenzaldehyde	92	49	*S*
9	*S*	4-methoxybenzaldehyde[d]	99	69	*S*
10	*S*	*trans*-cinnamaldehyde	99	56	*S*
11	*S*	1-naphthaldehyde	5	41	*S*
12	*S*	2-naphthaldehyde	18	35	*S*

[a] The reactions were carried out in toluene for 48 h at 0 °C in the presence of 5 mol % ligand. [b] Determined by HPLC analysis using a Chiracel OD column. [c] Determined by comparison with literature data (optical rotation and HPLC retention times). [d] *n*-Hexane used as solvent.

SCHEME 8. Diphenylzinc Addition to Aromatic Aldehydes



(*R*,*S*)-**13** gave the products with (*S*)-configuration. This substantiates our hypothesis that the planar chirality plays a dominant role in determining the configuration of the addition product. Selected aliphatic aldehydes (heptanal and cyclohexanal) also were tested as substrates but proved unreactive under the testing conditions using (*R*,*R*)-**13** and (*R*,*S*)-**13**.

Diphenylzinc Addition to Aromatic Aldehydes. The successful application of our *N*,*O*-ferrocenyl ligands in the diethylzinc addition to aromatic aldehydes encouraged us to apply them in the more challenging diaryl transfer to aldehydes.[8,36,37,38] We were interested in determining if these *N*,*O*-ferrocenyl ligands were as compatible with the diaryltransfer to aldehydes using either diphenylzinc or a modified phenylzinc reagent as the phenyl source. A series of experiments was conducted to determine the efficacy of *N*,*O*-ferrocenyl ligands (*R*,*R*)-**13** and (*R*,*S*)-**13** in the diaryltransfer to aromatic aldehydes. Two protocols for the enantioselective phenyl transfer to aldehydes were employed. Method A consisted of the addition of diphenylzinc to aromatic aldehydes in the presence of 10 mol % ferrocenyl ligand at −20 °C for 48 h in toluene. Method B involved the in situ preparation of an ethyl-phenylzinc reagent by stirring a 2:1 ratio of the diethylzinc/diphenylzinc solution in toluene for 30 min. The ferrocenyl ligand and aldehyde were added and the reaction was stirred at 10 °C for 48 h in toluene (Scheme 8).

Ferrocenyl ligands (*R*,*R*)-**13** and (*R*,*S*)-**13** were employed in the two methods described above (Table 7). Initially, ferrocenyl ligand (*R*,*R*)-**13** was investigated in the diphenylzinc addition to anisaldehyde and 4-chlorobenzaldehyde using method A. Unfortunately, the yields (27−48%) and ee's (3−7%) were poor even after 48 h (Table 7, entries 1 and 2). The low ee's were due in part to the rapid uncatalyzed background reaction, which became more prominent over long reaction times. Similar to the diethylzinc addition to aldehydes, the ferrocenyl ligand with (*R*)-planar chirality furnished the (*R*)-addition product, and (*S*)-planar chirality furnished the (*S*)-product.

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TABLE 7. Phenyl Transfer to Aldehydes Catalyzed by (*R*,*R*)-13 and (*R*,*S*)-13[a]

entry	planar chirality	method	aldehyde	yield (%)[b]	ee (%)[c]	config[d]
1	*R*	**A**	anisaldehyde	27	3	*R*
2	*R*	**A**	4-chlorobenzaldehyde	48	7	*R*
3	*R*	**B**	anisaldehyde	49(3)	30(53)	*R*
4[e]	*R*	**B**	anisaldehyde	37(9)	18(39)	*R*
5	*S*	**B**	anisaldehyde	79(12)	33(61)	*S*
6[e]	*S*	**B**	anisaldehyde	36(3)	37(48)	*S*

[a] The reactions were carried out in toluene in the presence of 10 mol % chiral ligand. Method A: $ZnPh_2$, −20 °C for 48 h. Method B: 2:1 ratio of $ZnEt_2/ZnPh_2$, − 20 °C for 48 h. [b] Isolated yield of phenyl addition product, yields in parentheses are for the ethyl-addition product. [c] ee's for phenyl product as determined by HPLC using a Chiracel OD and AD column, ee's in parentheses are for the ethyl-addition product. [d] Determined by comparison with literature data (HPLC retention times). [e] Reaction carried out at 10 °C.

Subsequently, we focused on the asymmetric phenyl transfer using a modified phenylzinc reagent that was prepared in situ from a 2:1 mixture of diethyl- and diphenylzinc. It has been documented that the use of this mixed zinc reagent improves the ee of the catalytic process.[8] We also observed this trend using anisaldehyde and ferrocenyl ligand (*R*,*R*)-**13**; 3% ee was obtained using method A and 18−30% ee using method B (compare entries 1 with 3 and 4 in Table 7). It has been recorded that the yields for this mixed zinc reagent are lower than when diphenylzinc alone is used.[8] Surprisingly, in this instance, the yields were higher than those achieved using Method A, although a mixture of products was recovered. Ligand (*R*,*S*)-**13** furnished the highest yield with 79% phenyl addition product and 33% ee (Table 7, entry 5). Reducing the temperature to −20 °C was detrimental to the yield (79−36%), although the ee increased marginally (33−37%) (Table 7, entries 5 and 6).

Several research groups have employed the mixed ethylphenylzinc reagent with complete selectivity for the phenyl transfer.[8] To the best of our knowledge, this is the first example of the use of a mixed phenyl-ethylzinc reagent that results in a mixture of the two addition products. However, Norrby postulated that while selective phenyl transfer over ethyl transfer is the prevailing reaction mechanism for the majority of ligands, sterically congested ligands may favor the less demanding ethyl-transfer route.[39] This could possibly account for the small quantities of the ethyl-addition product observed for our sterically demanding ferrocenyl ligands. To rationalize these results, the currently available computational methods need to be extended to incorporate parameters for both phenyl transfer and bulky ligands, such as those containing ferrocene moieties.[39,40]

Conclusion

We have reported a convenient synthesis of novel *N*,*O*-ferrocenyl ligands that allows for a facile modification of the substituents at the oxygen and nitrogen donor atoms. The oxygen donor group was introduced via a distereoselective lithiation to generate two diastereomers in up to 99% de. The selective preparation of the minor diastereomer employed a trimethylsilyl protecting group strategy. The *N*-pyrrolidinyl substituent was varied accordingly using an allylation/deallylation strategy. We have shown that these ferrocene compounds act as efficient ligands in the diethylzinc addition to aromatic aldehydes. Several ligand structure−activity relationships were investigated, predominantly, the role of planar chirality in determining the stereochemical outcome of the catalytic reaction. It was found that the planar chirality governed the stereochemical outcome in catalysis. In general, (*R*)-planar chirality furnished the (*R*)-product, and (*S*)-planar chirality furnished the (*S*)-product with the exception of the secondary pyrrolidine, which gave the product of opposite configuration. Further investigations on the application of these ferrocenyl compounds as chiral ligands in other catalytic reactions will be reported in due course from these laboratories.

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Supporting Information Available: X-ray crystallographic files for **12**, **13**, and **14**, full spectral characterization (^1H and ^{13}C NMR spectra) for all new compounds, HPLC characterization for ferrocenes **7d** and **15**, and experimental details concerning the diethyl- and diphenylzinc additions to aromatic aldehydes. This material is free of charge via the Internet at http://pubs.acs.org.

JO060894R

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