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Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition Metal Complexes. 10[1] Gold(I)-Catalyzed Asymmetric Aldol Reaction of Isocyanoacetate

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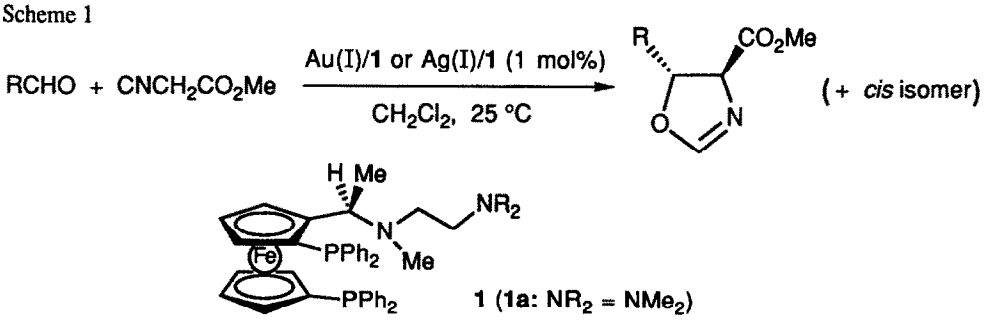
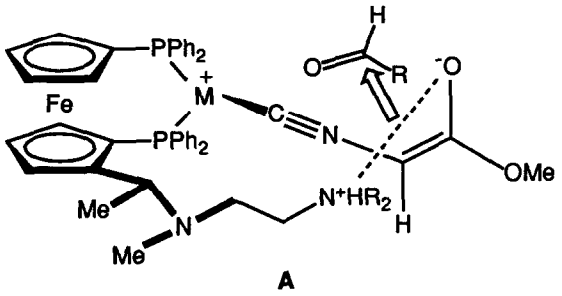
Abstract: *Optically active ferrocenylbisphosphine ligands containing 2-(dialkylamino)ethylamino group on the ferrocenylmethyl position have been prepared and used for the gold(I)-catalyzed asymmetric aldol reaction of isocyanoacetate with aldehydes. Six-membered ring amines, such as morpholino or piperidino group, at the terminal of the side chain were most stereoselective to give optically active trans-4-methoxycarbonyl-5-alkyl-2-oxazolines (up to 97% ee) with high enantio- and diastereoselectivity in a quantitative yield.*

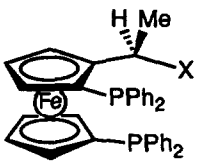
In a series of our studies on catalytic asymmetric synthesis with chiral ferrocenylphosphine-transition metal complexes,[2-4] we have reported that the asymmetric aldol reaction of α-isocyanocarboxylates with aldehydes is efficiently catalyzed by gold(I)[5] or silver(I)[6] complexes coordinated with ferrocenylbisphosphine ligands **1** bearing a 2-(dialkylamino)ethylamino side chain, to give optically active *trans*-5-alkyl-2-oxazoline-4-carboxylates with high enantio- and diastereoselectivity[7] (Scheme 1). The presence of the 2-(dialkylamino)-ethylamino group on the ferrocenylmethyl position is essential for the high selectivity. The terminal amino group in **1** has been proposed to participate in the formation of ammonium enolate, abstracting one of the active methylene hydrogens of isocyanoacetate coordinated with a catalyst (intermediate A). The intramolecular formation of the ammonium enolate will bring about high stereoselectivity by the enhanced steric interactions.

Scheme 1





A



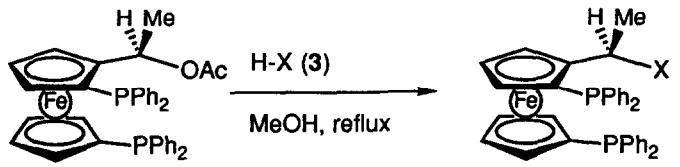
2a: X = $NMe(CH_2)_3NMe_2$
2b: X = NMe_2
2c: X = OMe

On the basis of the proposed mechanism, appropriate modification of the terminal amino group, which plays a key role in the formation of the ammonium enolate, is expected to increase the selectivity by steric and/or electronic effects. Here we report our efforts towards achieving higher selectivity by the modification of the terminal amino group.

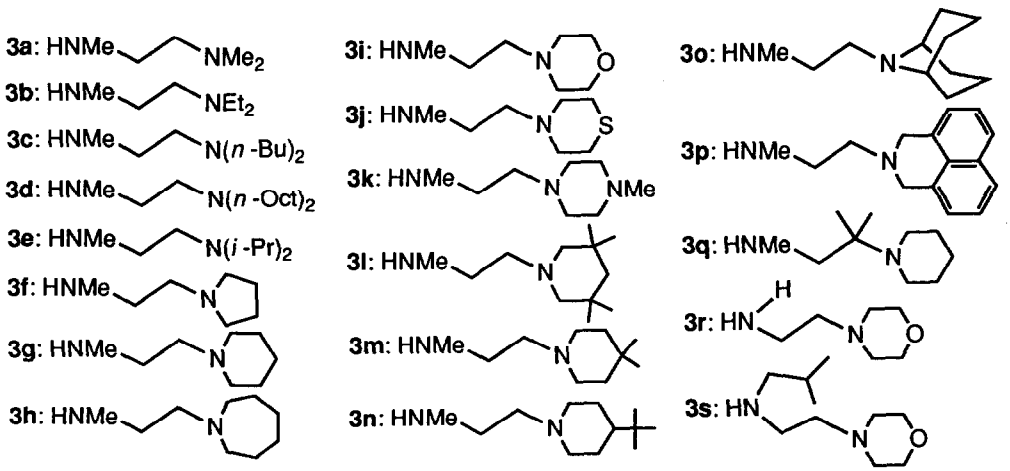
RESULTS AND DISCUSSION

It has been shown by NMR studies that the terminal amino group on the ferrocenylbisphosphines **1a**[4] is located close to the methylene hydrogens of the isocyanoacetate coordinated to the metal catalyst[5a] and therefore is in a good position to participate in the formation of the ammonium enolate (intermediate A).[7g] It has been also demonstrated that the nitrogen atom of the terminal amino group should be located four atoms away from the ferrocenylmethyl position for high stereoselectivity.[5i] Thus, phosphine ligand **2a**, which is analogous to **1a** but contains 3-(dimethylamino)propyl side chain, was much less stereoselective, and ferrocenylphosphines **2b** and **2c**, both of which lack the amino functionality at the proper position[5i] and other types of chiral phosphine ligands such as (S,S)-chiraphos,[8] (–)-DIOP,[9] and p-(+)-TolBINAP[10] gave racemic products.

Scheme 2

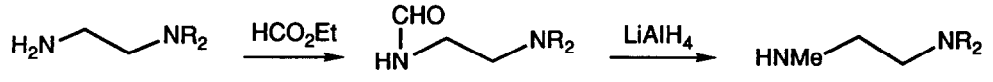


1a-s



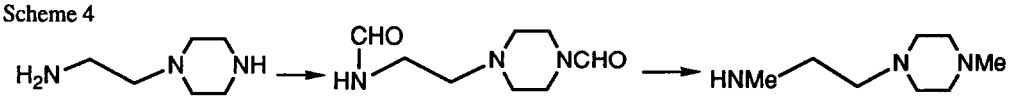
A series of chiral ferrocenylbisphosphines (*R*)-(*S*)-**1a-s**, all of which contain 2-(dialkylamino)-ethylamino groups on the ferrocenylmethyl position, were prepared in high yields by nucleophilic substitution reaction of (*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate[4] with 5-15 equiv of 2-(dialkylamino)ethylamines **3a-s** in refluxing methanol (Scheme 2). Diamines **3b,c,e,f,g,i,q** were prepared by *N*-methylation of the commercially available [2-(dialkylamino)ethyl]amines **4b,c,e,f,g,3r,4q** by *N*-formylation with ethyl formate followed by reduction of the resulting formamides with lithium aluminium hydride (Scheme 3). Dimethylation of *N*-(2-aminoethyl)piperazine (**4k**) by the similar *N*-formylation-reduction procedure gave triamine **3k** (Scheme 4). Diamines **3d,h,j,l-p** were prepared by acylation of the corresponding secondary amines **5d,h,j,l-p** with *N*-protected-glycines followed by reduction with lithium aluminium hydride (Schemes 5 and 6). Introduction of an isobutyl group on the nitrogen of **3r** was effected by platinum-catalyzed reductive alkylation with isobutyraldehyde to give *N*-(2-morpholinoethyl)isobutylamine (**3s**) (Scheme 7).

Scheme 3



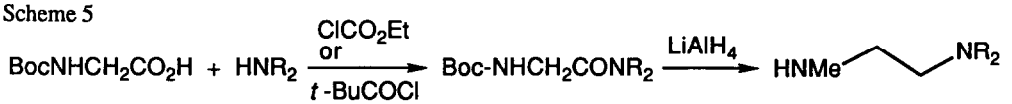
4b,c,e,f,g,3r,4q **3b,c,e,f,g,i,q**

Scheme 4



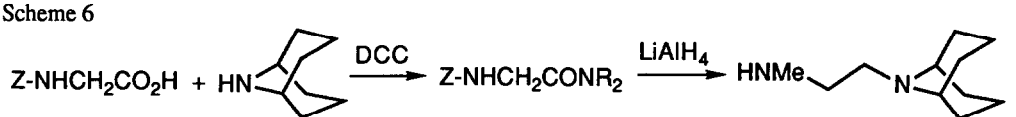
4k **3k**

Scheme 5



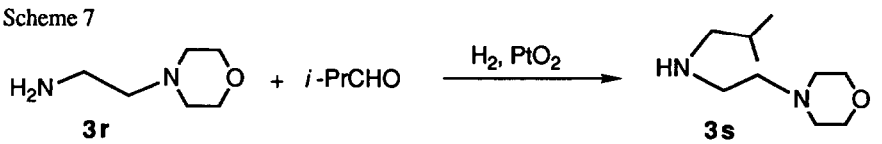
5d,h,j,l-n,p **3d,h,j,l-n,p**

Scheme 6



5o **3o**

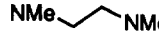
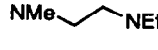
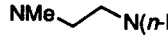
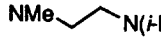
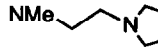
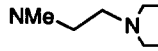
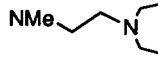
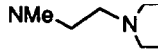
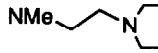
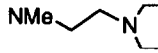
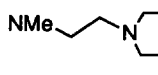
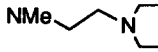
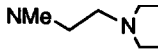
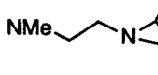
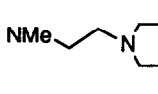
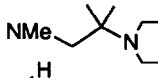
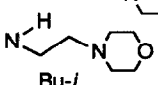
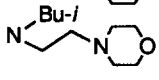
Scheme 7



3r **3s**

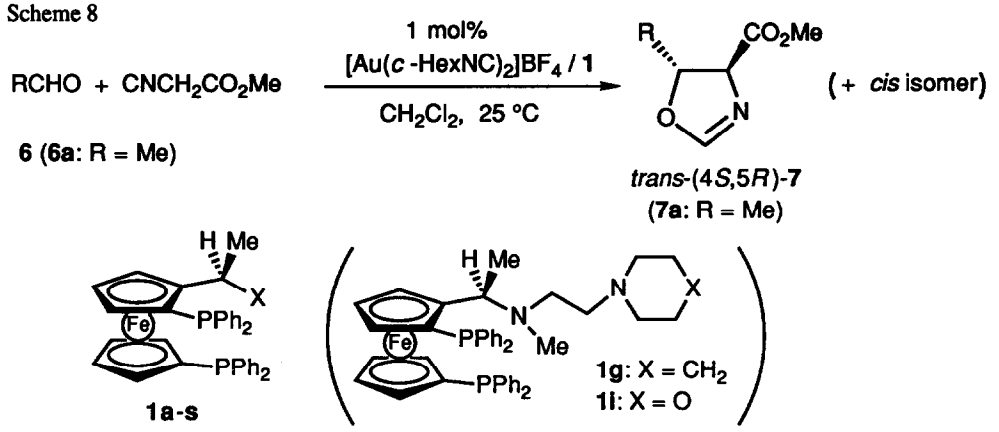
The ferrocenylphosphines **1a-s** were examined for stereoselectivity in the gold(I)-catalyzed aldol reaction of methyl isocyanoacetate with acetaldehyde (**6a**) (Scheme 8). The reaction proceeded in dichloromethane at 25 °C in the presence of 1 mol % of the gold catalyst, generated in situ by mixing bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate with ferrocenylphosphine ligand **1**, to give 4-methoxycarbonyl-5-methyl-2-oxazoline (**7a**)[11] in a quantitative yield. The *trans/cis* ratio of oxazoline **7a**, isolated by bulb-to-bulb distillation, was determined by ^{1}H NMR analysis, and enantiomeric purities of *trans*- and *cis*-**7a** were determined by ^{1}H NMR spectra using a chiral shift reagent Eu(dcm)$_3$. The absolute configuration of *trans*-**7a** obtained with ligands (*R*)-(*S*)-**1** was always (+)-(4*S*,5*R*).[11] The results obtained are summarized in Table 1.

Table 1. Asymmetric Aldol Rection of Methyl Isocyanoacetate with Acetaldehyde (**6a**)[a]

	ligand **1** side chain	yield[b] % of **7a**	ratio[c] of *trans/cis*	% ee[d] *trans*-(4*S*,5*R*)-**7a**	% ee[d] (config) *cis*-**7a**
1a		94	78/22	37	0
1b		100	84/16	72[e]	44 (4*R*,5*R*)
1c		100	78/22	71	40 (4*R*,5*R*)
1d		96	74/26	45	27 (4*R*,5*R*)
1e		99	70/30	55	68 (4*R*,5*R*)
1f		83	87/13	74	18 (4*R*,5*R*)
1g		100	85/15	85	56 (4*R*,5*R*)
1h		100	83/17	78	32 (4*R*,5*R*)
1i[f]		99	89/11	89	10 (4*S*,5*S*)
1j		100	88/12	85	18 (4*R*,5*R*)
1k		85	89/11	83	50 (4*R*,5*R*)
1l		100	79/21	86	70 (4*R*,5*R*)
1m		100	85/15	82	43 (4*R*,5*R*)
1n		100	86/14	84	47 (4*R*,5*R*)
1o		100	84/16	86	61 (4*R*,5*R*)
1p		94	76/24	58	7 (4*S*,5*S*)
1q		100	77/23	42	2 (4*S*,5*S*)
1r		67	77/23	28	6 (4*R*,5*R*)
1s		98	84/16	79	12 (4*R*,5*R*)

[a] The reaction was carried out in dichloromethane at 25 °C for 10-20 h. Isocyanoacetate/**6a**/Au/**1** = 1/2/0.010/0.011 unless otherwise noted. [b] Isolated yield by bulb-to-bulb distillation. [c] Determined by ^{1}H NMR analysis. [d] Determined by ^{1}H NMR spectra using chiral shift reagent Eu(dcm)$_3$. [e] $[\alpha]_D^{20}$ +173° (THF). [f] Reaction with 0.2 mol % of the catalyst.

Scheme 8



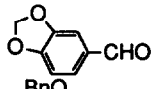
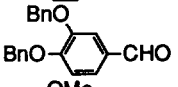
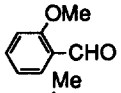
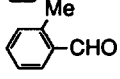
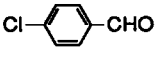
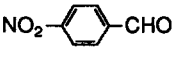
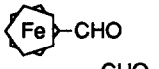
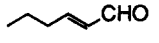
The enantiomeric purities of **7a** and the *trans/cis* ratio were dependent strongly on the structure of the terminal amino group, indicating that the amino group is playing a key role in the stereoselection. Of the acyclic dialkylamino groups at the terminus of the side chain (**1a-e**), highest enantioselectivity (ca. 70% ee) was observed in the reaction with the ligand containing diethylamino group (**1b**) or di-*n*-butylamino group (**1c**). Lower selectivity was observed with other amino groups, **1a** (dimethylamino), **1d** (dioctylamino), and **1e** (diisopropylamino). It seems that the terminal amino group with a reasonable steric size gives high selectivity.

Cyclic amino groups such as pyrrolidino- (**1f**), piperidino- (**1g**) and seven-membered ring amine (**1h**) were found to be more effective than acyclic ones, and the six-membered ring (**1g**) was most effective (85% *trans*-selectivity and 85% ee for the *trans* isomer) among the cyclic systems. Therefore, the six-membered ring system was brought to further modification: Phosphines **1i-k** contain heteroatoms in the six-membered ring and **1l-o** contain alkyl substituents on the piperidino group. Except for **1p** which cannot adopt a chair-like conformation, all of the ligands (**1g,i-o**) containing six-membered ring amines at the terminus gave high enantioselectivity (over 80% ee). The highest is the reaction with ferrocenylphosphine **1i** containing the morpholino group, which gave *trans*-**7a** in 89% ee with 89% *trans* selectivity. It should be noted that *N*-methylpiperazine in **1k** showed a fairly high selectivity in spite of the presence of a second amino group at the undesired position. It is concluded that the six-membered ring system is most efficient as a terminal amino group and the efficiency is not greatly affected by a slight modification of the six-membered ring amine.

Other parts of the side chain were also modified. Introduction of two methyl groups on the carbon which is three atoms away from ferrocenylmethyl position (**1q**) decreased the stereoselectivity remarkably compared with the original ligand **1g**. The lower selectivity observed with **1r** and **1s** indicates that methyl group is suitable as a substituent on the nitrogen which is adjacent to the ferrocenylmethyl position. It is likely that the substituents close to the ferrocenylmethyl carbon function as a handle in controlling the direction of the pendant side chain. The low selectivity with **1e,p,q,s** indicates that too much steric bulk around the side chain is unfavorable for the attractive interactions between the terminal amino base and isocyanoacetate.

The high efficiency of the ferrocenylbisphosphine ligands **1g** and **1i**, which have piperidino and morpholino group, respectively, was also demonstrated in the aldol reaction of several other aldehydes (Table 2). Reaction of benzaldehyde (**6b**) with methyl isocyanoacetate in the presence of the gold catalyst complexed with the ligands **1g** and **1i** gave *trans*-oxazoline **7b** in 95% ee, while the reaction with **1a** and **1b** gave *trans*-**7b** in 91% ee and 93% ee, respectively. The *trans*-selectivity was also improved to over 94%. Substituted aromatic aldehydes, 3,4-methylenedioxy- (**6c**), 3,4-dibenzyloxy- (**6d**), 2-methyl- (**6f**), and 4-chlorobenzaldehyde (**6g**), were converted into the corresponding *trans*-oxazolines **7** of 94-96% ee in 94-96% *trans*-selectivity. A little lower selectivity was observed with 2-methoxybenzaldehyde (**6e**) and 4-nitrobenzaldehyde (**6h**). The enantiomeric purities of the *trans*-oxazolines obtained in the reaction of 2-hexenal (**6j**) and isobutyraldehyde (**6l**) were over 92% ee, higher than those obtained with the ligand **1a** or **1b**. Here again the *trans*-selectivity was also improved by the use of **1g** or **1i**. The exclusive formation of the *trans*-oxazoline was observed in the

Table 2. Asymmetric Aldol Reaction of Methyl Isocyanoacetate with Aldehydes **6b-m**[a]

aldehyde **6**	ligand **1**, terminal amino group	yield[b] % of **7**	ratio[c] of *trans*/*cis*	*trans*-(4*S*,5*R*)-**7** % ee,[d] $[\alpha]_D^{20}$ (THF)	*cis*-**7** % ee[d] (config)
6b PhCHO	**1a** NMe_2	91 (**7b**)	90/10	91	4 (4*S*,5*S*)
	1b NEt_2	98 (**7b**)	89/11	93, +297° (*c* 1.0)	49 (4*R*,5*R*)
	1g 	94 (**7b**)	94/6	95	49 (4*R*,5*R*)
	1i 	93 (**7b**)	95/5	95	12 (4*S*,5*S*)
6c 	**1i** 	86 (**7c**)	95/5	96, +284° (*c* 0.9)	0
6d 	**1i** 	88 (**7d**)[e]	94/6	95, +193° (*c* 1.1)	32 (4*S*,5*S*)
6e 	**1i** 	98 (**7e**)	92/8	92, +179° (*c* 1.1)	73 (4*S*,5*S*)
6f 	**1i** 	98 (**7f**)	96/4	95, +256° (*c* 1.5)	20 (4*S*,5*S*)
6g 	**1i** 	97 (**7g**)	94/6	94, +273° (*c* 1.5)	17 (4*S*,5*S*)
6h 	**1i** 	80 (**7h**)[e]	83/17	86, +211° (*c* 1.9)	75 (4*S*,5*S*)
6i 	**1i** 	80 (**7i**)[e,f]	100/0	89, +102° (*c* 1.0)	—
6j 	**1a** NMe_2	97 (**7j**)	80/20	81	0
	1i 	85 (**7j**)	87/13	92	47 (4*R*,5*R*)
6k *i*-BuCHO	**1i** 	99 (**7k**)	96/4[g]	87, +235° (*c* 1.1)	0
6l *i*-PrCHO	**1b** NEt_2	99 (**7l**)	98/2[g]	90	—
	1g 	99 (**7l**)	99/1[g]	94	—
	1i 	100 (**7l**)	99/1[g]	92	—
6m *t*-BuCHO	**1i** 	94 (**7m**)	100/0	97	—

[a] The reaction was carried out in dichloromethane at 25 °C for 20-40 h unless otherwise noted. Isocyanoacetate/**6**/Au/**1** = 1/1.1/0.010/0.011. [b] Isolated yield by bulb-to-bulb distillation unless otherwise noted. [c] Determined by ^{1}H NMR analysis. [d] Determined by ^{1}H NMR spectra using chiral shift reagent Eu(dcm)$_3$. [e] Isolated yield of *trans*-**7** by MPLC. [f] Reaction time was 85 h. [g] Signals for OCH_3 of the *cis* isomer were separated from those of the *trans* isomer by ^{1}H NMR analysis using the chiral shift reagent.

reaction of ferrocenecarboxaldehyde (**6i**) and pivalaldehyde (**6m**); the enantiomeric purities of oxazolines **7i** and **7m** being 89% ee and 97% ee, respectively.

In summary, chiral ferrocenylbisphosphines **1g** and **1i** have been used successfully for the gold(I)-catalyzed asymmetric aldol reaction of α-isocyanocarboxylates, which provided an efficient approach to optically active β-hydroxy-α-amino acids and their derivatives.[5,12] The stereoselectivity attained here in the catalytic aldol reaction is among the highest for asymmetric carbon-carbon bond forming reactions,[13,14] especially for catalytic asymmetric reactions.[15]

EXPERIMENTAL

General. Optical rotations were recorded on a Perkin-Elmer 243 polarimeter. ^{1}H NMR spectra were measured with a JEOL JNM-MH-100 (100 MHz) or Varian VXR-200 (200 MHz) spectrometer. Chemical shifts are reported in δ ppm. Preparative medium-pressure liquid chromatography (MPLC) was performed with a silica gel 60 prepacked Lobar (Merck) column.

Materials. All aldehydes **6**, diamines **3r**,**4b**,**c**,**e**,**f**,**g**,**k**,**q** and secondary amines **5d**,**h**,**j** are commercially available. Diamine **4q** was prepared according to the procedure for the preparation of *N*-(2-amino-1,1-dimethyl)hexamethyleneimine described in the literature.[16] *N*-(tert-Butoxycarbonyl)glycine was prepared from tert-butyl 4,6-dimethylpyrimidyl-2-thiol carbonate and glycine by the procedure described in the literature.[17] *N*-(Benzyloxycarbonyl)glycine was prepared from benzyloxycarbonyl chloride and glycine by the conventional method.

Ferrocenylphosphines 1. The procedure for the preparation of ferrocenylphosphines **1a**[4] and **1g**[3a] has been reported. Ferrocenylphosphines **1b-f**,**h-s** were prepared by the reaction of (*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate[4] with 5-15 equiv of 2-(dialkylamino)ethyl-*N*-methylamines **3** (Scheme 2) according to the reported procedure.[3a,4]

1b: 78% yield; $[\alpha]_D^{25}$ -368° (*c* 0.3, chloroform); ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.88 (t, *J* = 7 Hz, 6 H), 1.15 (d, *J* = 7 Hz, 3 H), 1.6-2.0 (m, 2 H), 1.66 (s, 3 H), 2.0-2.4 (m, 2 H), 2.38 (q, *J* = 7 Hz, 4 H), 3.54 (m, 1 H), 3.67 (m, 1 H), 3.99 (m, 1 H), 4.0-4.15 (m, 3 H), 4.36 (m, 2 H), 7.0-7.7 (m, 20 H); Anal. Calcd for $C_{43}H_{48}N_2P_2Fe$: C, 72.68; H, 6.81; N, 3.94. Found: C, 72.58; H, 6.88; N, 3.69.

1c: 83% yield; $[\alpha]_D^{25}$ -297° (*c* 0.3, chloroform); ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.8-1.0 (m, 6 H), 1.1-1.5 (m, 11 H), 1.6-2.0 (m, 2 H), 1.68 (s, 3 H), 2.0-2.6 (m, 6 H), 3.55 (m, 1 H), 3.68 (m, 1 H), 4.00 (m, 1 H), 4.10 (m, 2 H), 4.1-4.3 (m, 1 H), 4.39 (m, 2 H), 7.0-7.7 (m, 20 H); Anal. Calcd for $C_{47}H_{56}N_2P_2Fe$: C, 73.62; H, 7.36; N, 3.65. Found: C, 73.79; H, 7.65; N, 3.91.

1d: Isolated by PTLC (silica gel, hexane/ethyl acetate = 1/1) in 67% yield; $[\alpha]_D^{25}$ -207° (*c* 0.4, chloroform); ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.98 (m, 16 H), 1.17 (broad s, 24 H), 1.67 (s, 3 H), 1.6-2.0 (m, 2 H), 2.0-2.6 (m, 6 H), 3.52 (m, 1 H), 3.64 (m, 1 H), 3.96 (m, 1 H), 4.06 (m, 2 H), 4.0-4.3 (m, 1 H), 4.35 (m, 2 H), 7.0-7.6 (m, 20 H); Anal. Calcd for $C_{55}H_{72}N_2P_2Fe$: C, 73.62; H, 7.36; N, 3.65. Found: C, 73.79; H, 7.65; N, 3.91.

1e: 77% yield; $[\alpha]_D^{25}$ -295° (*c* 0.3, chloroform); ^{1}H NMR ($CDCl_3$/TMS, 200 MHz) 0.85 and 0.87 (a pair of d, *J* = 6.4 Hz, 12 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.55-1.85 (m, 2 H), 1.67 (s, 3 H), 2.15 (dt, *J* = 6.0 and 11 Hz, 1 H), 2.35 (dt, *J* = 6.0 and 11 Hz, 1 H), 2.79 (sept, *J* = 6.4 Hz, 2 H), 3.50 (m, 1 H), 3.61 (m,1 H), 3.98 (m, 1 H), 4.05 (m, 2 H), 4.12 (dq, *J* = 2.8 and 6.6 Hz, 1 H), 4.35 (m, 2 H), 7.0-7.4 (m, 18 H), 7.4-7.55 (m, 2 H); Anal. Calcd for $C_{45}H_{52}N_2P_2Fe$: C, 73.17; H, 7.09; N, 3.79. Found: C, 73.39; H, 7.33; N, 3.90.

1f: 69% yield; $[\alpha]_D^{25}$ -325° (*c* 0.3, chloroform); ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.09 (d, *J* = 7 Hz, 3 H), 1.4-2.0 (m, 6 H), 1.63 (s, 3 H), 2.0-2.6 (m, 6 H), 3.46 (m, 1 H), 3.60 (m, 1 H), 3.91 (m, 1 H), 4.00 (m, 2 H), 4.12 (dq, *J* = 3 and 7 Hz, 1 H), 4.28 (m, 2 H), 6.9-7.6 (m, 20 H); Anal. Calcd for $C_{43}H_{46}N_2P_2Fe$: C, 72.88; H, 6.54; N, 3.95. Found: C, 73.11; H, 6.45; N, 3.86.

1h: 81% yield; $[\alpha]_D^{25}$ -298° (*c* 0.3, chloroform); ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.15 (d, *J* = 7 Hz, 3 H), 1.3-1.6 (m, 8 H), 1.65 (s, 3 H), 1.7-2.0 (m, 2 H), 2.1-2.6 (m, 6 H), 3.50 (m, 1 H), 3.62 (m, 1 H),

3.95 (m, 1 H), 4.04 (m, 2 H), 4.05-4.2 (m, 1 H), 4.32 (m, 2 H), 6.9-7.6 (m, 20 H); Anal. Calcd for $C_{45}H_{50}N_2P_2Fe$: C, 73.37; H, 6.84; N, 3.80. Found: C, 73.39; H, 6.89; N, 3.82.

1i: 84% yield; $[\alpha]_D^{25}$ -326° (*c* 0.2, chloroform); ^1H NMR ($CDCl_3$/TMS, 200 MHz) 1.15 (d, *J* = 7.0 Hz, 3 H), 1.55-1.85 (m, 2 H), 1.70 (s, 3 H), 2.08-2.36 (m, 7 H), 2.45 (dt, *J* = 6.0 and 11 Hz, 1 H), 3.50 (m, 1 H), 3.55-3.65 (m, 5 H), 3.94 (m, 1 H), 4.06 (m, 2 H), 4.16 (dq, *J* = 2.8 and 7.0 Hz, 1 H), 4.35 (m, 2 H), 7.0-7.4 (m, 18 H), 7.4-7.55 (m, 2 H); Anal. Calcd for $C_{43}H_{46}N_2OP_2Fe$: C, 71.27; H, 6.40; N, 3.87. Found: C, 71.35; H, 6.31; N, 3.64.

1j: Isolated by PTLC (silica gel, ethyl acetate) in 81% yield; $[\alpha]_D^{25}$ -297° (*c* 0.6, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 1.15 (d, *J* = 7 Hz, 3 H), 1.6-1.9 (m, 2 H), 1.68 (s, 3 H), 2.1-2.8 (m, 10 H), 3.50 (m, 1 H), 3.64 (m, 1 H), 3.94 (m, 1 H), 4.0-4.3 (m, 3 H), 4.34 (m, 2 H), 6.9-7.7 (m, 20 H); Anal. Calcd for $C_{43}H_{46}N_2P_2SFe$: C, 69.73; H, 6.26; N, 3.78. Found: C, 69.55; H, 6.43; N, 3.69.

1k: 73% yield; $[\alpha]_D^{25}$ -305° (*c* 0.3, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 1.17 (d, *J* = 7 Hz, 3 H), 1.6-1.95 (m, 2 H), 1.70 (s, 3 H), 2.1-2.7 (m, 10 H), 2.24 (s, 3 H), 3.55 (m, 1 H), 3.68 (m, 1 H), 3.99 (m, 1 H), 4.10 (m, 2 H), 4.22 (dq, *J* = 3 and 7 Hz, 1 H), 4.38 (m, 2 H), 7.0-7.7 (m, 20 H); Anal. Calcd for $C_{44}H_{49}N_3P_2Fe$: C, 71.64; H, 6.69; N, 5.70. Found: C, 71.54; H, 6.61; N, 5.48.

1l: Isolated by PTLC (silica gel, chloroform/ethyl acetate = 5/1) in 57% yield; $[\alpha]_D^{25}$ -286° (*c* 0.4, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 0.89 (s, 12 H), 0.99 (s, 2 H), 1.15 (d, *J* = 7 Hz 3 H), 1.5-1.9 (m, 6 H), 1.65 (s, 3 H), 2.0-2.6 (m, 2 H), 3.48 (m, 1 H), 3.59 (m, 1 H), 3.95 (m, 1 H), 4.03 (m, 2 H), 4.17 (dq, *J* = 3 and 7 Hz, 1 H), 4.32 (m, 2 H), 6.9-7.6 (m, 20 H); Anal. Calcd for $C_{48}H_{56}N_2P_2Fe$: C, 74.03; H, 7.25; N, 3.60. Found: C, 73.74; H, 7.26; N, 3.57.

1m: 67% yield; $[\alpha]_D^{25}$ -290° (*c* 0.6, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 0.85 (s, 6 H), 1.17 (d, *J* = 7 Hz, 3 H), 1.2-1.6 (m, 4 H), 1.6-2.0 (m, 2 H), 1.70 (s, 3 H), 2.0-2.8 (m, 6 H), 3.55 (m, 1 H), 3.69 (m, 1 H), 4.01 (m, 1 H), 4.12 (m, 2 H), 4.23 (dq, *J* = 3 and 7 Hz, 1 H), 4.40 (m, 2 H), 7.0-7.8 (m, 20 H); Anal. Calcd for $C_{46}H_{52}N_2P_2Fe$: C, 73.60; H, 6.98; N, 3.73. Found: C, 73.31; H, 7.02; N, 3.76.

1n: 67% yield; $[\alpha]_D^{25}$ -289° (*c* 0.4, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 0.80 (s, 9 H), 1.1-2.0 (m, 9 H), 1.17 (d, *J* = 7 Hz, 3 H), 1.69 (s, 3 H), 2.0-3.0 (m, 4 H), 3.53 (m, 1 H), 3.67 (m, 1 H), 3.99 (m, 1 H), 4.08 (m, 2 H), 4.21 (dq, *J* = 3 and 7 Hz, 1 H), 4.37 (m, 2 H), 7.0-7.7 (m, 20 H).

1o: Isolated by PTLC (silica gel, ether/diethylamine = 50/1) in 75% yield; $[\alpha]_D^{25}$ -279° (*c* 0.3, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 1.1-2.5 (m, 16 H), 1.15 (d, *J* = 7 Hz,3 H), 1.69 (s, 3 H), 2.5-2.7 (m, 2 H), 3.52 (m, 1 H), 3.64 (m, 1 H), 3.99 (m, 1 H), 4.07 (m, 2 H), 4.19 (dq, *J* = 3 and 7 Hz, 1 H), 4.36 (m, 2 H), 7.0-7.7 (m, 20 H).

1p: 76% yield; $[\alpha]_D^{25}$ -269° (*c* 0.4, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 1.19 (d, *J* = 7 Hz, 3 H), 1.75 (s, 3 H), 1.85-2.3 (m, 2 H), 2.3-2.9 (m, 2 H), 3.56 (m,1 H), 3.70 (m, 1 H), 3.77 (s, 4 H), 4.01 (m, 1 H), 4.10 (m, 2 H), 4.28 (dq, *J* = 3 and 7 Hz, 1 H), 4.40 (m, 2 H), 7.0-7.8 (m, 26 H); Anal. Calcd for $C_{51}H_{48}N_2P_2Fe$: C, 75.93; H, 6.00; N, 3.47. Found: C, 75.98; H, 6.01; N, 3.46.

1q: 71% yield; $[\alpha]_D^{25}$ -307° (*c* 0.5, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 0.40 (s, 3 H), 0.91 (s, 3 H), 1.1-1.7 (m, 6 H), 1.28 (d, *J* = 7 Hz, 3 H), 1.88 (s, 3 H), 2.1-2.6 (m, 6 H), 3.42 (m, 1 H), 3.74 (m, 1 H), 3.85 (m, 1 H), 3.95-4.25 (m, 3 H), 4.38 (m, 2 H), 6.9-7.7 (m, 20 H); Anal. Calcd for $C_{46}H_{52}N_2P_2Fe$: C, 73.60; H, 6.98; N, 3.73. Found: C, 73.42; H, 7.02; N, 3.73.

1r: 51% yield; $[\alpha]_D^{25}$ -281° (*c* 0.4, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 1.17 (d, *J* = 7 Hz, 3 H), 1.7-2.6 (m, 9 H), 3.3-3.6 (m, 4 H), 3.54 (m, 1 H), 3.67 (m, 1 H), 3.8-4.2 (m, 4 H), 4.3-4.5 (m, 2 H), 7.0-7.6 (m, 20 H); Anal. Calcd for $C_{42}H_{44}N_2OP_2Fe$: C, 70.99; H, 6.24; N, 3.94. Found: C, 70.91; H, 6.15; N, 3.79.

1s: 39% yield; $[\alpha]_D^{25}$ -331° (*c* 0.3, chloroform); ^1H NMR ($CDCl_3$/TMS, 100 MHz) 0.52 and 0.66 (a pair of d, *J* = 7 Hz, 3 H), 0.88 (d, *J* = 7 Hz, 3 H), 1.3-2.7 (m, 9 H), 1.31 (d, *J* = 7 Hz, 3 H), 3.40 (m, 1 H), 3.5-3.9 (m, 4 H), 3.88 (m, 1 H), 4.0-4.6 (m, 6 H), 7.0-7.8 (m, 20 H); Anal. Calcd for $C_{46}H_{52}N_2P_2OFe$: C, 72.06; H, 6.84; N, 3.65. Found: C, 72.17; H, 6.99; N, 3.80.

Preparation of 2-(Dialkylamino)ethyl-*N*-methylamines 3c,e-g,i,q (Scheme 3). Procedure for the preparation of **3i** is typical. A solution of 4.00 g (30.7 mmol) of (2-aminoethyl)morpholine (**4i** = **3r**) in 20

mL of ethyl formate was refluxed for 1 h, and concentrated under reduced pressure. The residual oil was dissolved in 10 mL of tetrahydrofuran, and was added dropwise to a suspension of 1.05 g (27.7 mmol) of lithium aluminium hydride in 50 mL of tetrahydrofuran. After the addition was complete, the mixture was refluxed for 4 h, and cooled by a water-ice bath. Aluminium complexes were decomposed by successive addition of 1 mL of water, 1 mL of 15% aqueous sodium hydroxide, and 2 mL of water. Resulting salts were removed by suction and washed with tetrahydrofuran. The filtrate and washings were concentrated under reduced pressure to give crude **3i** as an oil, from which water was separated by the addition of potassium hydroxide and ether. A supernatant solution was dried over magnesium sulfate. Bulb-to-bulb distillation (ca. 85 °C/16 mmHg) gave 3.54 g (80%) of **3i**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.9 (s, 1 H (NH)), 2.3-2.6 (m, 6 H), 2.44 (s, 3 H), 2.6-2.8 (m, 2 H), 3.6-3.9 (m, 4 H).

3c: 71% yield; bp ca. 100 °C/17 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.90 (broad t, J = 7 Hz, 6 H), 1.1-1.7 (m, 8 H), 1.8 (s, 1 H (NH)), 2.2-2.8 (m, 8 H), 2.44 (s, 3 H).

3e: 80% yield; bp ca. 100 °C/17 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.99 (d, J = 7 Hz, 12 H), 1.65 (s, 1 H (NH)), 2.44 (s, 3 H), 2.58 (s, 4 H), 3.02 (sept, J = 7 Hz, 2 H).

3f: 86% yield; bp ca. 100 °C/19 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.6-1.9 (m, 4 H), 1.94 (s, 1 H (NH)), 2.3-2.9 (m, 8 H), 2.44 (s, 3 H).

3g: 77% yield; bp ca. 100 °C/19 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.2-1.9 (m, 10 H), 2.1-2.6 (m, 6 H), 2.44 (s, 3 H), 2.6-2.8 (m, 2 H).

3q: 79% yield; bp 92 °C/16 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.03 (s, 6 H), 1.2-1.8 (m, 7 H), 2.42 (s, 3 H), 2.47 (broad s, 6 H).

Preparation of 2-(4-Methylpiperazino)ethyl-*N*-methylamine (3k) (Scheme 4). The experimental procedure described for the preparation of **3i** was followed except that double the amount of lithium aluminium hydride was used. Thus, from (2-aminoethyl)piperazine (**4k**) (4.00 g, 31.0 mmol), ethyl formate (20 mL) and lithium aluminium hydride (1.76 g, 46.4 mmol) was obtained 3.01 g (62%) of **3k**: bp ca. 105 °C/17 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.90 (s, 1H (NH)), 2.27 (s, 3 H), 2.3-2.6 (m, 10 H), 2.44 (s, 3 H), 2.6-2.8 (m, 2 H).

Preparation of 2-(Dioctylamino)ethyl-*N*-methylamine (3d) (Scheme 5). To a solution of 1.75 g (10.0 mmol) of *N*-(*tert*-butoxycarbonyl)glycine (Boc-Gly)[17] and 1.4 mL (10 mmol) of triethylamine in 20 mL of tetrahydrofuran was added 1.08 g (10.0 mmol) of ethyl chloroformate at -15 °C. After stirring of the mixture at this temperature was added a solution of 2.41 g (10.0 mmol) of dioctylamine (**5d**) in 5 mL of tetrahydrofuran. The reaction mixture was stirred at -10 °C for 1 h, and then stirred overnight at room temperature. Solvent was evaporated and ethyl acetate and water was added. The organic layer was washed with aqueous sodium bicarbonate, water, 10% citric acid, and then water before drying over magnesium sulfate. Evaporation of solvent gave crude Boc-Gly-N(Oct)$_2$, which was reduced with lithium aluminium hydride according to the procedure for the preparation of **3i** to give 2.01 g (67%) of **3d**: bp ca. 110 °C/1 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.88 (broad t, J = 7 Hz, 6 H), 1.0-1.7 (m, 25 H), 2.2-2.7 (m, 8 H), 2.44 (s, 3 H).

Preparation of 2-(Hexamethyleneimino)ethyl-*N*-methylamine (3h) (Scheme 5). To a solution of 5.14 g (29.3 mmol) of Boc-Gly[17] and 9.0 mL (65 mmol) of triethylamine in 30 mL of chloroform was added a solution of 3.54 g (29.4 mmol) of pivaloyl chloride in 8 mL of chloroform at -10 °C. The reaction mixture was stirred at -10 °C for 10 min. And then, to the mixture was added a solution of 3.20 g (32.3 mmol) of hexamethyleneimine (**5h**) in 8 mL of chloroform at -10 °C. The resulting solution was stirred at room temperature for 1 h, and concentrated under reduced pressure. To the residue was added ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with saturated aqueous sodium bicarbonate, 5% hydrochloric acid and brine, before drying over magnesium sulfate. Evaporation of solvent gave crude Boc-Gly-NR$_2$, which was reduced with lithium aluminium hydride according to the procedure for the preparation of **3i** to give 2.48 g (54%) of **3h**: bp ca. 100 °C/19 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.58 (broad s, 9 H), 2.42 (s, 3 H), 2.58 (broad s, 8 H).

3j,l,m,n,p were prepared according to the procedure for the preparation of **3d** or **3h**. **3j**; from Boc-Gly (0.876 g, 5.00 mmol), triethylamine (0.56 g, 5.53 mmol), ethyl chloroformate (0.546 g, 5.03 mmol) and thiomorpholine (5j) (0.514 g, 4.98 mmol) was obtained 0.48 g (60%) of **3j**: bp ca. 120 °C/40 mmHg; ^{1}H NMR

($CDCl_3$/TMS, 100 MHz) 1.65 (s, 1 H (NH)), 2.4-2.8 (m, 12 H), 2.44 (s, 3 H). **3l**; from Boc-Gly (0.41 g, 2.34 mmol), triethylamine (0.71 mL, 5.1 mmol), pivaloyl chloride (0.280 g, 2.32 mmol) and 3,3,5,5-tetramethylpiperidine (**5l**) (0.30 g, 2.12 mmol) was obtained 0.30 g (71%) of **3l**: bp ca. 80 °C/12 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.96 (s, 12 H), 1.12 (s, 2 H), 1.86 (s, 1 H (NH)), 2.03 (s, 4 H), 2.3-2.6 (m, 2 H), 2.48 (s, 3 H), 2.6-2.8 (m, 2 H). **3m**; from Boc-Gly (2.86 g, 16.3 mmol), triethylamine (5.0 mL, 36 mmol), pivaloyl chloride (1.97 g, 16.3 mmol) and 4,4-dimethylpiperidine (**5m**) (1.85 g, 16.3 mmol) was obtained 2.23 g (80%) of **3m**: bp ca. 100 °C/17 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.92 (s, 6 H), 1.42 (t, J = 6 Hz, 4 H), 1.82 (s, 1 H (NH)), 2.35-2.65 (m, 6 H), 2.48 (s, 3 H), 2.65-2.85 (m, 2 H). **3n**; from Boc-Gly (1.23 g, 7.04 mmol), triethylamine (2.2 mL, 16 mmol), pivaloyl chloride (0.85 g, 7.05 mmol) and 4-tert-butylpiperidine (**5n**) (1.00 g, 7.08 mmol) was obtained 1.06 g (76%) of **3n**: bp ca. 120 °C/15 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.84 (s, 9 H), 1.0-2.1 (m, 8 H), 2.35-2.55 (m, 2 H), 2.45 (s, 3 H), 2.6-2.8 (m, 2 H),2.98 (broad d, J = 12 Hz, 2 H). **3p**; from Boc-Gly (0.456, 2.60 mmol), triethylamine (0.80 mL, 5.7 mmol), pivaloyl chloride (0.314 g, 2.60 mmol), **5p** (0.44 g, 2.6 mmol) was obtained 0.45 g (77%) of **3p**: bp ca. 130 °C/0.3 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.84 (s, 1 H (NH)), 2.46 (s, 3 H), 2.82 (s, 4 H), 4.02 (s, 4 H), 7.25 (d, J = 8 Hz, 2 H), 7.44 (t, J = 8 Hz, 2 H), 7.75 (d, J = 8 Hz, 2 H).

Preparation of 9-[2-(*N*-Methylamino)ethyl]-9-azabicyclo[3,3,1]nonane (3o) (Scheme 6). To a solution of 1.05 g (5.02 mmol) of *N*-(benzyloxycarbonyl)glycine (Z-Gly) and 1.03 g (4.99 mmol) of 1,3-dicyclohexylcarbodiimide in 15 mL of chloroform was added 0.63 g (5.03 mmol) of 9-azabicyclo[3,3,1]nonane (**5o**) at 2 °C. The reaction mixture was stirred at 2 °C for 30 min, and then at room temperature for 1.5 h. Solvent was evaporated, 20 mL of ethyl acetate was added and the mixture was allowed to stand at -20 °C for 30 min. After a precipitate was filtered off by suction, PTLC (silica gel, hexane/ethyl acetate = 1/2) gave 1.04 g (66%) of Z-Gly-NR_2 (HNR_2 = **5o**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.4-2.4 (m, 12 H), 3.83 (m, 1 H), 3.98 (d, J = 5 Hz, 2 H), 4.75 (m, 1 H), 5.12 (s, 2 H), 5.94 (broad s, 1 H (O=C-NH)), 7.34 (broad s, 5 H).

Z-Gly-NR_2 (1.04 g, 3.29 mmol) was reduced with lithium aluminium hydride according to the procedure for the preparation of **3i**. Bulb-to-bulb distillation (ca. 100 °C/15 mmHg) gave 0.71 g of residue which contained 0.45 g (75% yield based on Z-Gly-NR_2) of **3o** and 0.26 g of benzyl alcohol. This material was used for the preparation of ferrocenylphosphine **1o** without further purification. ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) spectra for **3o** are as follows: 1.2-2.2 (m, 12 H), 2.35 (s, 3 H), 2.4-2.6 (m, 2 H), 2.6-2.9 (m, 3 H), 3.38 (broad s, 2 H).

Preparation of (2-Morpholinoethyl)-*N*-isobutylamine (3s) (Scheme 7). In an autoclave containing 1 mL of ethanol, 10 mg (0.044 mmol) of platinum(IV) oxide was hydrogenated to platinum(0) by stirring at room temperature and 120 atm for 5 min. To a solution of 2.62 mL (20 mmol) of (2-aminoethyl)morpholine (**4i**) in 2 mL of ethanol was added 2.1 mL (23 mmol) of isobutyraldehyde at 0 °C. This solution was transferred with 2 mL of ethanol into the autoclave containing the platinum catalyst. The mixture was hydrogenated at room temperature and 120 atm for 12 h. The catalyst was filtered off and washed with ethanol. Bulb-to-bulb distillation (ca. 110 °C/15 mmHg) gave 3.46 g (93%) of **3s**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.90 (d, J = 7 Hz, 6 H), 1.45-2.0 (m, 1 H), 1.77 (s, 1 H (NH)), 2.2-2.6 (m, 8 H), 2.6-2.85 (m, 2 H), 3.6-3.8 (m, 4 H).

(2-Amino-1,1-dimethylethyl)piperidine (4q) was prepared according to the procedure for the preparation of *N*-(2-amino-1,1-dimethyl)hexamethyleneimine described in the literature:[16] bp 53-65 °C/1.8 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.97 (s, 6 H), 1.2-1.7 (m, 6 H), 1.43 (s, 2 H (NH_2)), 2.3-2.6 (m, 4 H), 2.55 (s, 2 H).

3,3,5,5-Tetramethylpiperidine (5l). To a refluxing solution of 15.4 g (96.3 mmol) of 2,2-dimethylglutaric acid and 0.36 g (1.9 mmol) of *p*-toluenesulfonic acid monohydrate in 250 mL of xylenes was added dropwise a solution of 10.2 g (95.2 mmol) of benzylamine in 10 mL of xylenes over 50 min under azeotropic removal of water. After the addition was complete, azeotropic distillation was continued for 10 h. The mixture was concentrated under reduced pressure. Column chromatography (silica gel, hexane/ethyl acetate = 3/1) gave 18.39 g (83%) of 1-benzyl-3,3-dimethylglutarimide: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.28 (s, 6 H), 1.81 (t, J = 7 Hz, 2 H), 2.75 (t, J = 7 Hz, 2 H), 4.98 (s, 2 H), 7.34 (s, 5 H).

To a suspension of 0.18 mol of sodium hydroxide in 100 mL of dimethoxyethane was added a solution of 16.0 g (69.2 mmol) of 1-benzyl-3,3-dimethylglutarimide in 20 mL of dimethoxyethane, and then 17.2 mL (0.276 mol) of methyl iodide. The mixture was warmed carefully, refluxed for 5 h, and cooled by a ice-water bath. Water was added and extracted three times with ether. Combined ether extracts were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give 16.9 g (94%) of 1-benzyl-3,3,5,5-tetramethylglutarimide: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.29 (s, 12 H), 1.75 (s, 2 H), 4.96 (s, 2 H), 7.32 (broad s, 5 H).

To a suspension of 0.70 g (18.4 mmol) of lithium aluminium hydride in 30 mL of ether was added a solution of 4.00 g (15.4 mmol) of 1-benzyl-3,3,5,5-tetramethylglutarimide in 10 mL of ether. The mixture was refluxed for 9 h, and cooled by a ice-water bath. Aluminium complexes were decomposed by successive addition of 0.7 mL of water, 0.7 mL of 15% sodium hydroxide, and then 1.4 mL of water. Resulting salts were filtered off by suction, and washed with ether. The filtrate and washings were concentrated. MPLC purification (silica gel, hexane/ethyl acetate = 10/1) gave 1.50 g (42%) of 1-benzyl-3,3,5,5-tetramethylpiperidine: ^{1}H NMR ($CDCl_3$/TMS) 0.98 (s, 12 H), 1.13 (s, 2 H), 2.02 (s, 4 H), 3.46 (s, 2 H), 7.1-7.5 (m, 5 H).

A solution of 1.48 g (6.40 mmol) of 1-benzyl-3,3,5,5-tetramethylpiperidine in 7.5 mL of ethanol was hydrogenated at 100 °C and 130 atm for 14 h in the presence of 0.45 g of 10% palladium on carbon and 30 mg of di-μ-chloro-bis(π-allyl)dipalladium. Removal of the catalysts and concentration of the filtrate and washings gave 0.30 g (33%) of **5l**, which was subjected to the reaction with Boc-Gly without further purification: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.95 (s, 12 H), 1.20 (s, 2 H), 1.77 (s, 1 H (NH)), 2.48 (s, 4 H).

4,4-Dimethylpiperidine (5m). To a solution of 2.42 g (63.8 mmol) of lithium aluminium hydride in 100 mL of tetrahydrofuran was added 6.00 g (42.5 mmol) of 4,4-dimethylglutarimide. The mixture was refluxed for 5 h, and cooled by a ice-water bath. Aluminium complexes were decomposed with 2.4 mL of water, 2.4 mL of 15% sodium hydroxide, and then 4.8 mL of water. Resulting salts were filtered off by suction, and washed with tetrahydrofuran. The filtrate and washings were concentrated and distilled (84 °C/114 mmHg) to give 1.86 g (39%) of **5m**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.92 (s, 6 H), 1.2-1.5 (m, 4 H), 1.55 (s, 1 H), 1.7-3.0 (m, 4 H).

4-*tert*-Butylpiperidine (5n). A mixture of 4.27 g (31.6 mmol) of 4-*tert*-butylpyridine and 2.0 mL of acetic acid in 20 mL of ethanol was hydrogenated at 50 °C and 100 atm for 24 h in the presence of 1.0 g of 5% rhodium on alumina and 40 mg of $[RhCl(COD)]_2$. The catalysts were filtered off, and the filtrate and washings were concentrated. To the residue was added 30% sodium hydroxide and the aqueous solution was extracted with ether. The ether extracts were dried over magnesium sulfate and concentrated. Bulb-to-bulb distillation (ca. 100 °C/28 mmHg) gave 3.85 g (86%) of **5n**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.84 (s, 9 H), 0.9-1.45 (m, 3 H), 1.45-1.8 (m, 2 H), 1.75 (s, 1 H (NH)), 2.56 (broad t, J = 12 Hz, 2 H), 3.14 (broad d, J = 12 Hz, 2 H).

9-Azabicyclo[3.3.1]nonane (5o). 9-Benzyl-3-oxo-9-azabicyclo[3.3.1]nonane was prepared according to the procedure for the preparation of pseudopelletierine described in the literature:[18] Isolated by column chromatography (silica gel, ethyl acetate) followed by recrystallization from hexane in 61% yield; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.2-1.7 (m, 4 H), 1.7-2.2 (m, 2 H), 1.26 (d, J = 17 Hz, 2 H), 2.76 (dd, J = 17 and 7 Hz, 2 H), 3.2-3.5 (m, 2 H), 3.92 (s, 2 H), 7.2-7.6 (m, 5 H).

9-Benzyl-9-azabicyclo[3.3.1]nonane was prepared according to the procedure for the preparation of 9-methyl-9-azabicyclo[3.3.1]nonane by Wolff-Kishner reduction of pseudopelletierine described in the literature.[19] Thus, from 85% potassium hydroxide (9.05 g, 0.137 mol), diethylene glycol (115 mL), 80% hydrazine hydrate (7.7 mL, 0.126 mol) and 9-benzyl-3-oxo-9-azabicyclo[3.3.1]nonane (8.14 g, 35.4 mmol) was obtained 6.13 g (80%) of 9-benzyl-9-azabicyclo[3.3.1]nonane: 110 °C/0.5 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.2-2.4 (m, 12 H), 2.65-3.0 (m, 2 H), 3.90 (s, 2 H), 7.2-7.6 (m, 5 H).

A solution of 6.04 g (28.1 mmol) of 9-benzyl-9-azabicyclo[3.3.1]nonane in 13 mL of ethanol was hydrogenated at 95 °C and 125 atm for 40 h in the presence of 1.8 g of 10% palladium on carbon and 60 mg of di-μ-chlorobis(π-allyl)dipalladium. After removal of the catalysts and evaporation of the solvent, the residue was diluted with water, and extracted twice with ether. Combined ether layers were extracted twice with 10% hydrochloric acid. The aqueous layer extracted with ether and acidic extracts were combined. After cooling and

basification with ca. 50% sodium hydroxide solution, the amine was extracted twice with ether. Combined extracts were dried over magnesium sulfate and concentrated to give 2.35 g (67%) of crude **5o**, which was used for the preparation of diamine **3o** without further purification.

1H-2,3-Dihydro-2-azaphenalene (5p) was prepared according to the procedure for the preparation of **5m**. Thus, from lithium aluminium hydride (0.87 g, 23 mmol) in tetrahydrofuran (40 mL) and 1,8-naphthalimide (3.00 g, 15.2 mmol) was obtained 0.44 g (17%) of **5p**: bp ca. 120 °C/0.5 mmHg; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 1.44 (s, 1 H (NH)), 4.20 (s, 4 H), 7.15 (broad d, J = 7 Hz, 2 H), 7.40 (broad t, J = 8 Hz, 2 H), 7.72 (broad d, J = 8 Hz, 2 H).

Asymmetric Aldol Reaction of Methyl Isocyanoacetate with Aldehydes 6. General Procedure. To a solution of bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (0.050 mmol), chiral ligand (0.050-0.055 mmol), and aldehyde **6** (5.0-5.5 mmol) in 5 mL of dichloromethane was added methyl isocyanoacetate (5.0 mmol), and the mixture was stirred under nitrogen at 25 °C until methyl isocyanoacetate was not detected by silica gel TLC (hexane/ethyl acetate = 2/1) or IR. Evaporation of the solvent followed by bulb-to-bulb distillation gave oxazoline **7**. The ratio of *trans/cis* was determined by ^{1}H NMR spectra, and the enantiomeric purities of *trans*-**7** and *cis*-**7**, readily separated by MPLC (hexane/ethyl acetate), were determined by ^{1}H NMR studies using Eu(dcm)$_3$.[12] The OCH_3 singlet of the major enantiomer of *trans*-**7** always appeared at a higher field than that of the minor one. Results are summarized in Tables 1 and 2. ^{1}H NMR spectra and analytical data for oxazolines **7** are shown below.

(4*S*,5*R*)-*trans*-4-(Methoxycarbonyl)-5-phenyl-2-oxazoline ((4*S*,5*R*)-**7b**): ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) 3.83 (s, 3 H), 4.63 (dd, J = 2.2 and 7.9 Hz, 1 H), 5.70 (d, J = 7.9 Hz, 1 H), 7.11 (d, J = 2.2 Hz, 1 H), 7.30-7.42 (m, 5 H); Anal. Calcd for $C_{11}H_{11}N_2O_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.13; H, 5.43; N, 7.08. *cis*-**7b**: $[\alpha]_D^{20}$ -80° (*c* 1.2, THF) for the (4*R*,5*R*)-**7b** of 49% ee; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) 3.20 (s, 3 H), 5.09 (dd, J = 2.2 and 11.2 Hz, 1 H), 5.74 (d, J = 11.2 Hz, 1 H), 7.25 (d, J = 2.2 Hz, 1 H), 7.30-7.42 (m, 5 H).

Methyl (4*S*,5*R*)-*trans*-5-(3,4-Methylenedioxyphenyl)-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7c**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 3.74 (s, 3 H), 4.51 (dd, J = 8 and 2 Hz, 1 H), 5.49 (d, J = 8 Hz, 1 H), 5.84 (s, 2 H), 6.66 (s, 3 H), 6.93 (d, J = 2 Hz, 1 H); Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.84; H, 4.45; N, 5.62. Found: C, 58.13; H, 4.46; N, 5.41. *cis*-**7c**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz, measured as a mixture of trans and cis isomers) 3.29 (s, 3 H), 4.95 (dd, J = 11 and 2 Hz, 1 H), 5.57 (d, J = 11 Hz, 1 H), 5.91 (s, 2 H), 6.64 (s, 3 H), 7.08 (d, J = 2 Hz, 1 H).

Methyl (4*S*,5*R*)-*trans*-5-(3,4-Dibenzyloxyphenyl)-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7d**): ^{1}H NMR ($CDCl_3$/TMS, 200 MHz) 3.81 (s, 3 H), 4.56 (dd, J = 7.6 and 2.2 Hz, 1 H), 5.15 (s, 2 H), 5.16 (s, 2 H), 5.57 (d, J = 7.6 Hz, 1 H), 6.8-7.0 (m, 3 H), 7.05 (d, J = 2.2 Hz, 1 H); Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.89; H, 5.53; N, 3.38. (4*S*,5*S*)-*cis*-**7d**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz, measured as a mixture of trans and cis isomers) 3.16 (s, 3 H (OCH_3)).

Methyl (4*S*,5*R*)-*trans*-5-(2-Methoxyphenyl)-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7e**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 3.82 (s, 3 H), 3.85 (s, 3 H), 4.55 (dd, J = 8 and 2 Hz, 1 H), 5.93 (d, J = 8 Hz, 1 H), 6.8-7.5 (m, 5 H); Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.11; H, 5.58; N, 5.93. (4*S*,5*S*)-*cis*-**7e**: $[\alpha]_D^{20}$ +258° (*c* 0.8, THF) for the oxazoline of 73% ee; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 3.20 (s, 3 H), 3.85 (s, 3 H), 5.08 (dd, J = 11 and 2 Hz, 1 H), 6.00 (d, J = 11 Hz, 1 H), 6.75-7.4 (m, 5 H).

Methyl (4*S*,5*R*)-*trans*-5-(2-Methylphenyl)-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7f**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 2.36 (s, 3 H), 3.83 (s, 3 H), 4.56 (dd, J = 8 and 2 Hz, 1 H), 5.93 (d, J = 8 Hz, 1 H), 7.09 (d, J = 2 Hz, 1 H), 7.20 (s, 4 H); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.64; H, 5.98; N, 6.21. (4*S*,5*S*)-*cis*-**7f**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz, measured as a mixture of *trans* and *cis* isomers) 2.61 (s, 3 H (Ar-CH_3)), 3.12 (s, 3 H (OCH_3)).

Methyl (4*S*,5*R*)-*trans*-5-(4-Chlorophenyl)-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7g**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 3.84 (s, 3 H), 4.54 (dd, J = 8 and 2 Hz, 1 H), 5.64 (d, J = 8 Hz, 1 H), 7.05 (d, J = 2 Hz, 1 H), 7.0-7.5 (m, 4 H); Anal. Calcd for $C_{11}H_{10}NO_3Cl$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.16; H,

4.07; N, 5.83. (4*S*,5*S*)-*cis*-**7g**: $[\alpha]_D^{20}$ +17.3° (*c* 0.8, THF) for the oxazoline of 17% ee; ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 3.24 (s, 3 H), 5.05 (dd, *J* = 11 and 2 Hz, 1 H), 5.68 (d, *J* = 11 Hz, 1 H), 7.0-7.5 (m, 5 H).

Methyl (4*S*,5*R*)-*trans*-5-(4-Nitrophenyl)-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7h**): ^{1}H NMR ($CDCl_3$/TMS, 200 MHz) 3.89 (s, 3 H), 4.60 (dd, *J* = 8.0 and 2.2 Hz, 1 H), 5.81 (d, *J* = 8.0 Hz, 1 H), 7.14 (d, J = 2.2 Hz, 1 H), 7.54 (d, J = 8.6 Hz, 2 H), 8.27 (d, J = 8.6 Hz, 2 H); Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 53.00; H, 3.99; N, 11.22. (4*S*,5*S*)-*cis*-**7h**: ^{1}H NMR ($CDCl_3$/TMS, 200 MHz) 3.26 (s, 3 H), 5.18 (dd, *J* = 11.0 and 2.0 Hz, 1 H), 5.84 (d, *J* = 11.0 Hz, 1 H), 7.28 (d, *J* = 2.0 Hz, 1 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 8.22 (d, *J* = 9.0 Hz, 2 H).

Methyl (4*S*,5*R*)-trans-5-Ferrocenyl-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7i**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 3.86 (s, 3 H), 4.1-4.4 (m, 4 H), 4.21 (s, 5 H), 4.41 (dd, *J* = 7 and 2 Hz, 1 H), 5.53 (d, *J* = 7 Hz, 1 H), 6.95 (d, *J* = 2 Hz, 1 H); Anal. Calcd for $C_{15}H_{15}NO_3Fe$: C, 57.53; H, 4.83; N, 4.47. Found: C, 57.47; H, 4.75; N, 4.56.

(4*S*,5*R*)-*trans*-4-(Methoxycarbonyl)-5-[(1*E*)-1-pentenyl]-2-oxazoline ((4*S*,5*R*)-**7j**): 1H NMR ($CDCl_3$/TMS, 100 MHz) 0.93 (t, *J* = 7 Hz, 3 H), 1.47 (sextet, *J* = 7 Hz, 2 H), 2.10 (q, *J* = 7 Hz, 2 H), 3.84 (s, 3 H), 4.44 (dd, *J* = 2 and 7.5 Hz, 1 H), 5.15 (t, *J* = 7 Hz, 1 H), 5.54 (dd, *J* = 7 and 16 Hz, 1 H), 5.96 (dt, *J* = 16 and 7 Hz, 1 H), 7.00 (d, *J* = 2 Hz, 1 H); Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.01; H, 7.92; N, 7.08. *cis*-**7j**: ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.90 (t, *J* = 7 Hz, 3 H), 1.42 (sextet, *J* = 7 Hz, 2 H), 2.05 (q, *J* = 7 Hz, 2 H), 3.75 (s, 3 H), 4.85 (dd, *J* = 2 and 11 Hz, 1 H), 5.16 (dd, *J* = 11 and 8 Hz, 1 H), 5.44 (dd, *J* = 15 and 8 Hz, 1 H), 5.92 (dt, *J* = 15 and 7 Hz, 1 H), 7.10 (d, *J* = 2 Hz, 1 H).

Methyl (4*S*,5*R*)-*trans*-5-Isobutyl-2-oxazoline-4-carboxylate ((4*S*,5*R*)-*trans*-**7k**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.96 (d, *J* = 7 Hz, 6 H), 1.2-2.1 (m, 3 H), 3.78 (s, 3 H), 4.24 (dd, *J* = 8 and 2 Hz, 1 H), 4.71 (dt, *J* = 6 and 8 Hz, 1 H), 6.87 (d, *J* = 2 Hz, 1 H); Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.65; H, 8.40; N, 7.35.

(4*S*,5*R*)-*trans*-4-(Methoxycarbonyl)-5-isopropyl-2-oxazoline ((4*S*,5*R*)-**7l**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.96, 0.98 (a pair of d, *J* = 7 Hz, 6 H), 1.92 (octet, *J* = 7 Hz, 1 H), 3.80 (s, 3 H), 4.41 (dd, *J* = 8 and 2 Hz, 1 H), 4.40-4.65 (m, 1 H), 6.99 (d, *J* = 2 Hz, 1 H); Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.26; H, 8.10; N, 6.72.

(4*S*,5*R*)-*trans*-4-(Methoxycarbonyl)-5-*tert*-butyl-2-oxazoline ((4*S*,5*R*)-**7m**): ^{1}H NMR ($CDCl_3$/TMS, 100 MHz) 0.92 (s, 9 H), 3.78 (s, 3 H), 4.40 (s, 2 H), 6.95 (s, 1 H); Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.13; H, 8.26; N, 7.84.

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