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Polymer-Supported Ferrocenyl Oxazolines for the Catalyzed Highly Enantioselective Phenyl Transfer to Aldehydes

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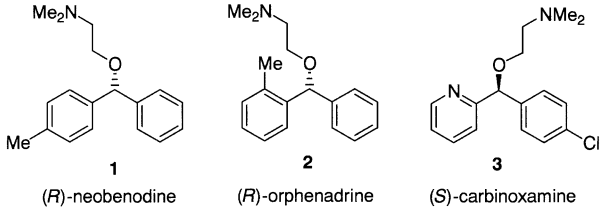
Abstract—A new chiral MeO-PEG-supported ferrocenyl oxazoline was synthesized and successfully employed in the enantioselective phenyl transfer to aldehydes. The products were obtained in high yields and with excellent enantioselectivities (up to 97% ee). Furthermore, the recovery of the ferrocene was facile, and catalyst efficiency was maintained in subsequent reactions.

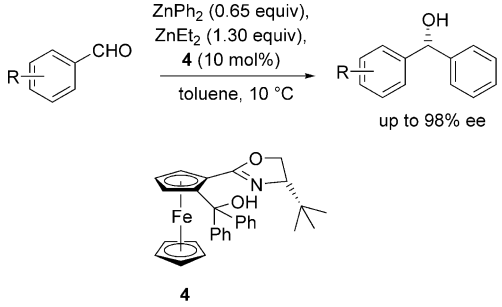
The diarylmethane moiety is essential for the physiological activity of many organic compounds.[1] Hence, chiral diarylmethanols are useful intermediates in the synthesis of biologically active substrates, which have been used as drugs possessing antihistaminic, anticholinergic, local-anesthetic and laxative properties (Scheme 1).

Diarylmethanols may be prepared in an enantioselective manner via the asymmetric addition of a suitable organometallic phenyl transfer reagent to aromatic aldehydes. Recently, we developed various highly enantioselective catalytic systems for this transformation, which, as a common feature, all involve the use of organozinc reagents.[2,3] One of them utilizes ferrocenyl oxazoline **4** and a zinc species formed in situ from $ZnPh_2$ and $ZnEt_2$. Excellent enantioselectivities of up to 98% ee have been obtained for a large variety of aldehydes (Scheme 2).

Generally, a purification by column chromatography must be employed for the isolation of product and for the recovery of ferrocenyl oxazoline **4**. With the intention to facilitate the workup as well as the recovery and reuse of the ferrocene in subsequent catalyses, we have now focused on an immobilization of the ferrocene by anchoring it onto polymeric support.[4] Since the use of insoluble polymers often results in low catalytic activity and enantioselectivity due to the restrictions of the polymer matrix and the difficulty to compete with a rapid and undesired background reaction, respectively, the application of fully soluble enlarged ligands appears particularly attractive. In those systems the immobilized ligands mimic the properties of the corresponding low-molecular weight counterparts, since this methodology provides homogeneous reaction conditions.



Scheme 1. Biologically active diarylmethanol derivatives.



Scheme 2. Enantioselective phenyl transfer from an in situ generated organozinc reagent to aldehydes using a catalyst derived from ferrocenyl oxazoline **4**.

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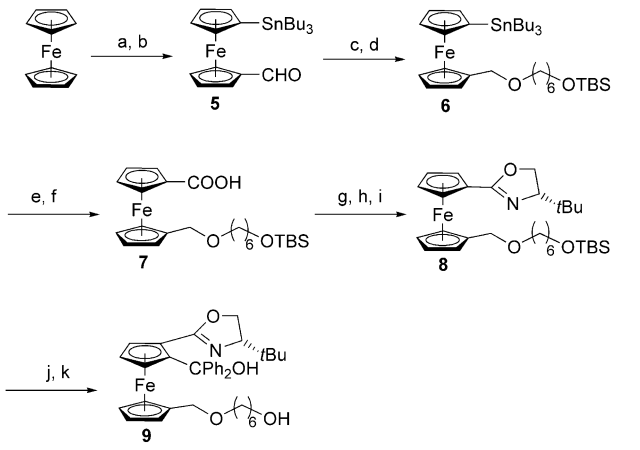
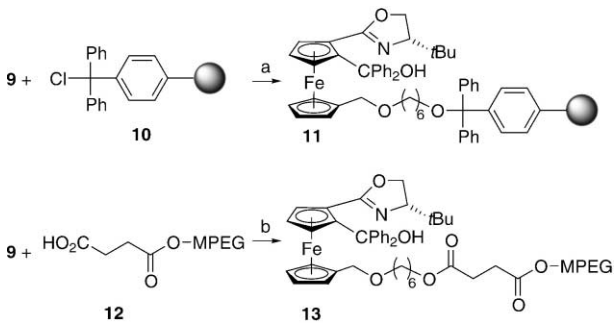


Scheme 3. Synthesis of ferrocenyl oxazoline **9**. Reagents and conditions: (a) *n*BuLi, TMEDA, Et_2O, then Bu_3SnCl, 82%; (b) *n*BuLi, THF, then DMF, 80%; (c) $LiAlH_4$, Et_2O, 98%; (d) NaH, $Br(CH_2)_6OTBS$, THF, 82%; (e) *n*BuLi, THF, then $(MeO)_2CO$, 72%; (f) NaOH, $NaBH_4$, *t*BuOH, H_2O, 98%; (g) C_6F_5OH, DCC, DCM; (h) (*S*)-*tert*-leucinol, NEt_3, DMF, 94%; (i) TsCl, NEt_3, DMAP, DCM, 94%; (j) *s*BuLi, THF, then Ph_2CO, 80%; (k) HF·Py, NEt_3, MeCN, 98%.[9]

Several catalytically active polymers have been reported that perform with very high enantioselectivities in the catalytic enantioselective addition of diethylzinc to both aromatic and aliphatic aldehydes.[5,6] However, in the field of asymmetric phenyl transfer from organozinc reagents to aldehydes, to the best of our knowledge, only Pu et al.[3b] reported a polymeric system. Even though those polybinaphthyl ligands gave rise to diarylcarbinols with high enantiomeric excesses, the reaction conditions were far from being optimal since high catalyst loadings, low temperatures and slow addition of the reacting components via a syringe pump were required.

Herein, we describe the preparation of new polymer-supported ligands based on ferrocenyl oxazoline **4** and their catalytic properties in the enantioselective phenyl transfer to aldehydes. For including both soluble, as well as insoluble supports we chose the application of commercially available polyethylene glycol monomethyl ether [MeO-PEG-OH (MPEG); MW = 5000] and a trityl chloride resin, respectively.

Ferrocenyl oxazoline **9**, which bears a linker at the 1′-carbon, was chosen as key-intermediate for the immobilization.[7] The different substitution pattern of the two cyclopentadienyl rings was accomplished by sequential transmetalation/substitution reactions of 1,1′-bis(tributylstannyl)ferrocene[8] (Scheme 3). Thus, aldehyde **5** was obtained in 80% yield after monolithiation, trapping with DMF, and subsequent hydrolysis. After reduction of **5** to the corresponding alcohol, the TBS-protected linker chain was attached by ether formation, giving rise to ferrocene **6** in 80% overall yield. Transmetalation of the remaining tributyltin moiety of **6** with *n*-butyllithium, followed by reaction of the resulting anion with dimethyl carbonate and subsequent hydrolysis of the intermediate methylester afforded acid **7**. The oxazolinyl substituent was introduced by carboxy group activation via the pentafluorophenyl ester, formation of the amide, and ring closure of the tosylated alcohol. Finally, directed *ortho*-metallation with *s*-butyllithium and subsequent quenching of the resulting anion with benzophenone followed by standard deprotection of the hydroxyl group gave ferrocene **9** in 78% overall yield.



Scheme 4. Synthesis of polymer-supported ferrocenes **11** and **13**. Reagents and conditions: (a) Py, DMAP, 50%; (b) DCC, DMAP, DCM, 95%.

First, ferrocene **9** was bound to insoluble trityl chloride resin **10**[10] to give **11** by selective ether formation. Unfortunately, this coupling proceeded in only 50% yield, as determined by gravimetrical analysis. In contrast, the attachment of **9** onto MeO-PEG **12** gave **13** in 95% yield (determined by gravimetrical and elemental analysis) (Scheme 4).[11]

The polymer supported ferrocenes **11** and **13** were then employed as chiral ligands in enantioselective phenyl and ethyl addition reactions to aldehydes. As test substrates *p*-chloro-benzaldehyde and benzaldehyde were used. The results are summarized in Table 1.

The insoluble resin-bound ferrocene **11** proved to be unsuitable for the catalysis of the asymmetric phenyl transfer reaction, and only racemic product was obtained in the addition of the phenylzinc reagent to *p*-chlorobenzaldehyde (Table 1, entry 1). Obviously, the catalytic reaction is too slow, and most of the product derives from the fast uncatalyzed background reaction which affords a racemate. In contrast, the addition of diethylzinc to benzaldehyde in the presence of ferrocene **11** gave rise to the addition product with 87% ee. In this case it is known that the uncatalyzed background reaction is slow, and therefore it is not able to compete with

Table 1. Enantioselective ethyl/phenyl transfer to benzaldehyde/*p*-chlorobenzaldehyde[a]

Entry	Substrate	Zinc reagent	Ferrocene	ee[b] [%]
1	4-Cl–C_6H_4–CHO	$ZnPh_2/ZnEt_2$	**11**	0 (97)
2	C_6H_5-CHO	$ZnEt_2$	**11**	87 (93)[c]
3	4-Cl–C_6H_4–CHO	$ZnPh_2/ZnEt_2$	**13**	97 (97)
4	C_6H_5–CHO	$ZnEt_2$	**13**	86 (93)[c]

[a]Reactions were carried out with 10 mol% of ferrocene in toluene at 10 °C. The products were obtained in good to quantitative yields.
[b]Determined by HPLC using a chiral stationary phase. Values in parentheses refer to results from catalyses with ferrocenyl oxazoline **4**.
[c]Result in parentheses refers to a catalysis with 5 mol% of ferrocenyl oxazoline **4** at 0 °C.

Table 2. Enantioselective phenyl transfer using recycled ferrocene **13**[a]

Entry	Substrate	Cycle	Yield (%)	ee[b] (%)
1	4-Cl–C_6H_4–CHO	1	80	97
2	4-Cl–C_6H_4–CHO	2	75	96
3	4-Cl–C_6H_4–CHO	3	81	95
4	4-Cl–C_6H_4–CHO	4	97	95
5	4-Cl–C_6H_4–CHO	5	80	95

[a]Reactions were carried out with 10 mol% of catalyst in toluene at 10 °C.
[b]Determined by HPLC using a chiral stationary phase.

the catalytic system. However, compared to the result obtained in a catalysis with low-molecular ferrocenyl oxazoline **4**, the enantioselectivity in the run with **11** was significantly lower (Table 1, entry 2).[12]

When the MeO-PEG-supported ferrocene **13** was employed in the title reaction an excellent enantioselectivity was observed. The addition product of the phenylzinc reagent onto *p*-chloro-benzaldehyde was obtained in quantitative yields and with 97% ee (Table 1, entry 3). It is noteworthy, that this result is identical to the one obtained with low-molecular ferrocenyl oxazoline **4**. Furthermore, for this remarkably high enantioselectivity neither an increase of catalyst loading nor a slow substrate addition was required.

Unfortunately, in the case of the diethylzinc addition to benzaldehyde, a catalysis with the immobilized ligand **13** did not reach the enantioselectivity achieved with ferrocenyl oxazoline **4**. Here, the addition product was only obtained with 86% ee.

In order to gain insight into the recyclability of the MeO-PEG-bound ferrocene **13**, studies on the recovery and reuse were performed (Table 2). To our delight, we found that the excellent enantioselectivity was retained throughout successive addition reactions. Even after consecutive use of **13** in five catalytic cycles, the product from the phenyl transfer to *p*-chlorobenzaldehyde was obtained with an excellent ee of 95%. Furthermore it should be noted that both the reaction protocol as well as the separation and recycling of the catalyst were simple and efficient.[13]

In conclusion, we have reported the syntheses of new polymer-supported ferrocenes and their use in asymmetric C–C-bond formation by phenyl-to-aldehyde addition reactions. The results from the enantioselective catalysis demonstrate that the soluble MeO-PEG-bound ferrocene **13** exhibits excellent catalytic activity and enantioselectivity. Furthermore, **13** can easily be recovered and reused in successive catalytic additions, maintaining excellent enantioselectivity even after five cycles. To the best of our knowledge, this is the first example of a MeO-PEG-supported ligand in the asymmetric addition of organozinc reagents to aldehydes. We have thus devised a suitable way to generate chiral arylphenylmethanols in an asymmetric catalytic fashion.

Acknowledgements

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9. Selected analytical data. **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89–0.96 (m, 9H), 0.99–1.08 (m, 6H), 1.28–1.42 (m, 6H), 1.48–1.60 (m, 6H), 4.09 (s, 2H), 4.46 (s, 2H), 4.51 (s, 2H), 4.72 (s, 2H), 9.95 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.22, 13.70, 27.34, 29.13, 69.45, 71.35, 72.10, 73.12, 75.92, 79.20, 193.24. **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.99–1.05 (m, 6H), 1.26–1.42 (m, 10H), 1.44–1.62 (m, 10H), 3.39 (t, J = 6.7 Hz, 2H), 3.58 (t, J = 6.6 Hz, 2H), 3.96 (t, J = 1.7 Hz, 2H), 4.06 (t, J = 1.7 Hz, 2H), 4.17 (t, J = 1.7 Hz, 2H), 4.25 (s, 2H), 4.28 (t, J = 1.7 Hz,

2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.26, 10.26, 13.72, 18.36, 25.68, 25.98, 27.43, 29.21, 29.73, 32.83, 63.20, 68.43, 69.10, 69.19, 69.38, 70.00, 70.89, 74.80, 83.42. **7**: mp 46–47 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.25–1.40 (m, 4H), 1.45–1.60 (m, 4H), 3.42 (t, J = 6.6 Hz, 2H), 3.58 (t, J = 6.6 Hz, 2H), 4.24 (t, J = 1.9 Hz, 2H), 4.24 (s, 2H), 4.29 (t, J = 1.9 Hz, 2H), 4.43 (t, J = 1.9 Hz, 2H), 4.81 (t, J = 1.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.24, 18.38, 25.64, 26.00, 29.64, 32.80, 63.25, 67.99, 70.51, 71.06, 71.13, 72.42, 85.38, 177.09. IR (KBr) $\tilde{\nu}$ = 2931, 2858, 1653, 1475, 1288, 1104, 834 cm^{-1}. MS (70eV) m/z (%): 474 (M, 3), 55 (100). Anal. calcd for $C_{24}H_{38}FeO_4Si$: C, 60.75; H, 8.07. Found C, 60.82; H, 8.01. **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.26–1.37 (m, 4H), 1.45–1.59 (m, 4H), 3.38 (t, J = 6.6 Hz, 2H), 3.58 (t, J = 6.6 Hz, 2H), 3.90 (dd, J = 7.8, 10.0 Hz, 1H), 4.14–4.18 (m, 3H), 4.22–4.25 (m, 5H), 4.27–4.30 (m, 2H), 4.70–4.73 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.26, 18.33, 25.64, 25.98, 26.00, 29.69, 32.80, 33.57, 63.16, 68.36, 69.49, 69.87, 69.95, 70.09, 70.59, 70.62, 70.74, 70.89, 70.97, 75.99, 84.89, 165.53. IR (kap) $\tilde{\nu}$ = 2952, 2933, 2858, 1660, 1114, 1096 cm^{-1}. MS (70eV) m/z (%): 555 (M, 68), 556 (M + 1, 29), 340 (100). Anal. calcd for $C_{30}H_{49}FeNO_3Si$: C, 64.85; H, 8.89; N, 2.52. Found C, 64.45; H, 9.05; N, 2.82. **9**: $[\alpha]_D^{20} = -286.5°$ (c 1.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 9H), 1.30–1.38 (m, 4H), 1.48–1.70 (m, 4H), 3.34 (br s, 2H), 3.48–3.56 (m, 1H), 3.58–3.66 (m, 2H), 3.73 (s, 1H), 3.95–4.17 (m, 4H), 4.22 (s, 1H), 4.67 (s, 1H), 7.12 (s, 5H), 7.22–7.26 (m, 1H), 7.28–7.35 (m, 2H), 7.50–7.58 (m, 2H), 9.11 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.56, 25.94, 26.26, 29.60, 32.67, 32.91, 62.82, 66.43, 68.26, 68.56, 69.95, 71.19, 71.64,71.90, 75.07, 75.26, 84.86, 100.62, 126.08, 126.43, 126.99, 127.62, 145.84, 148.93, 167.45; IR ($CHCl_3$) $\tilde{\nu}$ = 3408, 3086, 3059, 2935, 2863, 1651, 1448, 756 cm^{-1}. MS (70eV) m/z (%): 623 (M, 56), 624 (M + 1, 24), 411 (100). Anal. calcd for $C_{37}H_{45}FeNO_4$: C, 71.26; H, 7.27; N, 2.25. Found C, 71.16; H, 7.33; N, 2.70.

10. Trityl chloride resin, polymer matrix: copoly(styrene-1% DVB), 200–400 mesh, Novabiochem.
11. Elemental analysis indicated a slightly lower yield as was determined by gravimetrical analysis.
12. Use of 5 mol% of ferrocenyl oxazoline **4** in the diethylzinc addition to benzaldehyde gave the product with 93% ee.
13. **Experimental**: Typical procedure for the addition of the phenylzinc reagent (obtained from $ZnPh_2$ and $ZnEt_2$) to aldehydes using MeO-PEG-supported ferrocene **13**: In a glovebox, a well-dried Schlenk flask was charged with diphenylzinc (39 mg, 0.176 mmol). The flask was sealed and removed from the glovebox. Freshly distilled toluene (3 mL) was added followed by diethylzinc (58 μL, 0.58 mmol). After stirring the mixture for 30 min at room temperature, MeO-PEG-supported ferrocene **13** (137 mg, 0.025 mmol) was added, and the resulting solution was then cooled to 10 °C. Stirring was continued for additional 10 min at this temperature, and the aldehyde (0.25 mmol) was then added directly in one portion. The Schlenk flask was sealed, and the reaction mixture was stirred at 10 °C overnight. Ferrocene **13** was precipitated by addition of 50 mL diethyl ether and then recovered by filtration. The ether filtrate was washed with water. Drying with $MgSO_4$ and evaporation of the solvent under reduced pressure gave the product in good to quantitative yields. The enantiomeric excess of the product was determined by HPLC analysis after filtration over a small pad of silica. The recovered catalyst was used for subsequent reactions without further purification.