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Highly Effective and Recyclable Dendritic Ligands for the Enantioselective Aryl Transfer Reactions to Aldehydes

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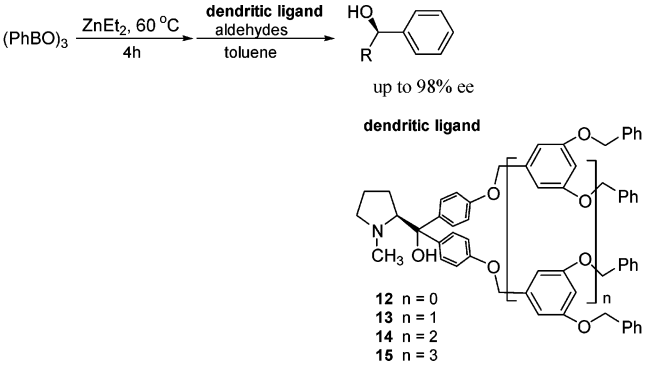

A series of chiral pyrrolidinylmethanol-based dendritic ligands were synthesized for application in enantioselective aryl transfer reactions to aldehydes with the $(ArBO)_3/ZnEt_2$ system in up to 98% ee.

Optically active diarylmethanols are versatile and important chiral building blocks for therapeutically important medicines such as (*R*)-neobenodine, (*R*)-orphenadrine, or (*S*)-carbinoxamine.[1] Two general approaches aimed at the enantioselective synthesis of these compounds have been reported: the enantioselective reduction of prochiral ketones[2,3] and asymmetric aryl transfers onto aromatic aldehydes.[4,5] However, some of these cases suffer from inherent drawbacks: For example, the reduction method requires the presence of electronically and/or stereochemically differentiated aryls for optimum results. The method of aryl transfer reaction seems more suitable for chiral induction because of the large steric and electronic differences between an aryl group and a hydrogen atom on an aldehyde substrate, and great progress has been achieved in this field.[4−6]

Fu et al. first reported, in 1997, the addition of salt-free Ph_2Zn to *p*-chlorobenzaldehyde using a planar-chiral azoferrocene ligand with moderate enantioselectivity.[4a] Pu and co-workers reported that performing the addition reaction at a low concentration of substrate improved the enantioselectivity dramatically, using chiral 3,3′-diaryl binaphthol as a ligand.[4b] Recently, Bolm et al. and, later, Chan et al. have reported an excellent protocol wherein the aryl transfer reagent was generated by mixing arylboronic acids, a substantially more stable and less expensive reagent than diphenylzinc, with diethylzinc.[6,4g] With the intention to facilitate the workup as well as the recovery and reuse of the catalyst in asymmetric synthesis, we have now focused on the immobilization of a chiral ligand by anchoring it onto a polymeric support.[7] Recently, several catalytically active dendrimers have been reported that perform with very high enantioselectivities in the catalytic enantioselective addition of diethylzinc to both aromatic and aliphatic aldehydes.[8,9] However, in the field of asymmetric phenyl transfer from organozinc reagents to aldehydes, to the best of our knowledge, a dendritic system has not been widely investigated except for a few examples.[4b,5f] Since previous

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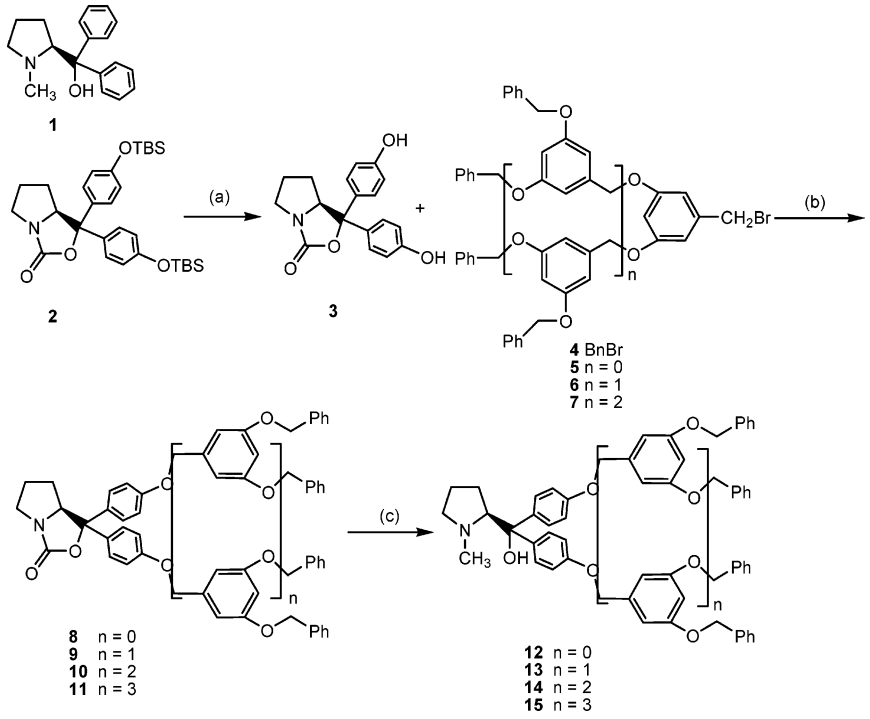
SCHEME 1. Synthesis of Pyrrolidinylmethanol Ligands with Polyether Dendritic Wedges.[a]



[a] Reagents and Conditions: (a) TBAF, THF, rt, 5 h. (b) K_2CO_3, 18-crown-6, acetone. (c) $LiAlH_4$, THF.

studies on the aryl transfer from diphenylzinc-derived arylation reagents had shown that the presence of polyethers could lead to a significant increase in enantioselectivity,[4g,5,6] we decided to choose a polyether as a supporting matrix as well. Herein, we wish to report the synthesis of new polyether dendritic chiral pyrrolidinylmethanol derivatives and their application in catalytic, highly enatioselective aryl transfer to aldehydes.

Pyrrolidinylmethanol derivative **1** was chosen as a model ligand for this study because it is the most effective chiral ligand among all the chiral nitrogen ligands that have been studied for asymmetric catalysis in our group and because it can also be easily prepared.[4d,10] Considering that pyrrolidinylmethanol **1** itself cannot be easily attached to a dendrimer, **2** was synthesized according to the literature.[9e] Cleavage of the two protecting groups with Bu_4NF gave the compound **3** in good yield. Polyether dendritic wedges **5**−**7** with bromo groups located at the focal point were synthesized by the convergent growth method introduced by Hawker and Fréchet.[11] The chiral dendritic pyrrolidinylmethanol ligands **8**−**11** were synthesized in >79% yields by the coupling of the wedges **4**−**7** with **3** in the presence of K_2CO_3 and 18-crown-6 in *N*,*N*-dimethylformamide (DMF) or acetone at between room temperature and ∼40 °C. Reduction of the ester moieties with $LiAlH_4$ afforded the corresponding alcohols **12**−**15** in high yields (Scheme 1). These ligands were purified by flash column chromatography and characterized by ^1H and ^{13}C NMR spectroscopy, MALDI mass spectrometry, and elemental analysis. All results were in full agreement for the proposed structures.

A preliminary study was performed to test the catalytic property of the known ligand **1** in the phenyl transfer reaction to *p*-chlorobenzaldehyde. Indeed, the reaction of the nucleophile, preformed from phenylboronic acid and diethyl zinc in toluene according to Bolm's protocol, with *p*-chlorobenzaldehyde in the presence of **1** in various catalyst loadings and temperatures afforded (*S*)-*p*-chlorobenzhydrol in 49−93% ee and in good yields (Table 1, entries 1−6). The optimum yield and ee were obtained when the reaction was performed at −15 °C, and the optimum amount of catalyst loading was 20 mol % for 6 h (entry 3). To investigate the influence of the dendritic branches on the catalytic activity and the stereoselectivity of the pyrrolidinylmethanol, we tested dendrimers **12**−**15** in the enantioselective phenyl transfer reaction in the optimum reaction conditions. In general, an excellent conversion of *p*-chlorobenzaldehyde was achieved, and the corresponding optically active alcohols were obtained in excellent yields (>90%). The enantioselectivities were high (88−93%), and the (*S*)-configured products were formed predominantly (Table 1, entries 7−10). Among all the dendritic chiral catalysts evaluated in this reaction, the second-generation ligand of **14** was the best one in terms of yield and ee (Table 1, entry 9).

With these promising results, attention was then turned to modify the above protocol in anticipation of obtaining better results. Inspired by Hayashi and coworkers' report that the rhodium-catalyzed asymmetric 1,4-addition to 1-alkenylphosphonates was greatly improved by carrying out the reaction with triphenylcyclotriboroxane [phenylboroxine, $(PhBO)_3$][12] in place of phen-

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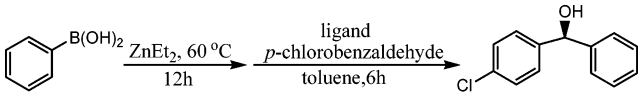
TABLE 1. Catalyzed Phenyl Transfer from Boronic Acid to *p*-Chlorobenzaldehyde[a]

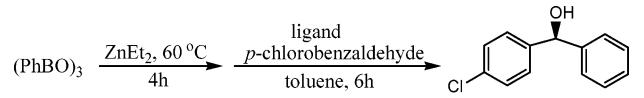


16a

entry	ligand	catalyst loading (mol %)	*T* (°C)	yield (%)[b]	ee (%)[c,d]
1	**1**	10	10	83	49
2	**1**	15	0	92	77
3	**1**	20	0	93	86
4	**1**	20	−15	96	93
5	**1**	20	−30	87	88
6	**1**	15	−30	95	78
7	**12**	20	−15	90	88
8	**13**	20	−15	92	89
9	**14**	20	−15	98	93
10	**15**	20	−15	98	91

[a] In toluene, 7.2 equiv of $ZnEt_2$ and 2.4 equiv of $PhB(OH)_2$ with respect to 4-Cl-C_6H_4CHO. [b] After column chromatography. [c] Determined by HPLC using a chiral stationary phase. [d] Comparison of the HPLC peak elution order of **16a** with known data revealed that the (*S*)-enantiomer was formed in excess.

TABLE 2. Catalyzed Asymmetric Aryl Transfer Reactions to *p*-Chlorobenzaldehyde with Phenylboroxine as a Phenyl Source and Recycling of Dendritic Catalyst[a]



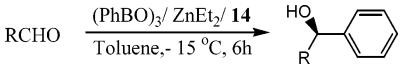
16a

entry	ligand	*T* (h)	yield (%)[b]	ee (%)[c]
1	**1**	6	94	94
2	**12**	6	98	94
3	**13**	6	92	97
4	**14** (run 1)	6	98	98
5	**15**	6	97	96
6	**14** (run 2)	6	92	95
7	**14** (run 3)	6	98	96
8	**14** (run 4)	6	97	97
9	**14** (run 5)	6	91	96

[a] In toluene, 4.5 equiv of $ZnEt_2$ and 0.5 equiv. of $(PhBO)_3$ with respect to 4-Cl−C_6H_4CHO (catalyst loading is 20 mol %). [b] After column chromatography. [c] Determined by HPLC using a chiral stationary phase.

yl boronic acid as the phenyl source, we found that after optimizing the reaction conditions, using phenylboroxine $(PhBO)_3$ as the phenyl source, a slightly higher enantioselectivity could be achieved with a shorter reaction time (from 12 to 4 h) and a reduced amount of diethyl zinc (from 7.2 to 4.5 equiv) under the same conditions when **1** was used as the ligand (Table 2, entry 1). Then, *p*-chlorobenzaldehyde was again used in the modified protocol to investigate the catalytic activity and enantioselectivity of the dendritic ligands. The results are summarized in Table 2, and in the best case, with 20 mol % **14**, the (*S*)-configured product **16a** was obtained with 98% ee and 98% yield (Table 2, entry 4). These ligands (**12**−**15**) showed higher ee values than **1**, although the highest-generation ligand **15** gave a slightly lower enantioselectivity (Table 2, entry 5). Furthermore, the large molecular size and different solubility of the dendritic

TABLE 3. Catalyzed Asymmetric Phenyl Transfer to Various Aldehydes[a]



entry	R in RCHO	*T* (h)	yield (%)[b]	ee of **16** (%)[c]	absolute configuration
1	4-Cl−C_6H_4	6	**16a**, 98	98	*S*
2	4-Br−C_6H_4	6	**16b**, 92	98	*S*
3	2-Br−C_6H_4	6	**16c**, 92	97	*S*
4	4-F−C_6H_4	6	**16d**, 98	96	*S*
5	4-CH_3O−C_6H_4	10	**16e**, 98	98	*S*
6	4-CH_3−C_6H_4	10	**16f**, 98	93	*S*
7	4-CF_3−C_6H_4	6	**16g**, 88	95	*S*
8	2-$C_{10}H_9$	6	**16h**, 90	97	*S*
9	(*E*)-C_6H_5CH=CH	6	**16i**, 96	88	*R*
10	$CH(CH_3)_2$	6	**16k**, 77	65	*R*

[a] In toluene, 20 mol % **14**, 4.5 equiv of $ZnEt_2$, and 0.5 equiv of $(PhBO)_3$ with respect to RCHO. [b] After column chromatography. [c] Determined by HPLC analysis.

pyrrolidinylmethanol ligands in various solvents provided a convenient and reliable method for the separation and reuse of the ligands. For example, upon completion of the reaction, methanol was added to the reaction mixture, and the ligand **14** was quantitatively precipitated and recovered via filtration. The recovered ligand was reused at least five times with little or no loss of activity and enantioselectivity (Table 2, entries 6−9).

With the purpose of determining the scope and utility of the present system [$(PhBO)_3/Et_2Zn$ and **14**] for the asymmetric arylation of aldehydes, a series of substrates with different steric and electronic properties were investigated (Table 3). It should be emphasized that the level of enantiocontrol for all aromatic substrates was outstanding. The corresponding diarylcarbinols were obtained in optical purities in the range of 93 to 98% enantiomeric excess. Furthermore, even substrate 2-bromobenzaldehyde bearing an ortho substituent, which previously proved to be difficult, afforded the corresponding product in good yield and with high ee (97% ee) (Table 3, entry 3). *trans*-Cinnamaldehyde also reacted highly selectively and gave the corresponding alcohol with 88% ee (Table 3, entry 9). Unfortunately, aliphatic aldehyde provided poorer selectivity. Addition to *iso*-butyraldehyde yielded the product alcohol in only 65% ee (Table 3, entry 10).

Next, we investigated the possibility of varying the structure of the aryl source and studied the asymmetric aryl transfer from various substituted phenylboroxines (**17b**−**f**) to benzaldehyde (Table 4). To our delight, we found that substituted aryls were transferred very well, affording the corresponding products in good yields and with excellent ee. In all cases, no ethyl transfer product was formed that was consistent with others' results[4g,6] and related theoretical study.[5g,5h] As for the mechanism of this reaction, it appears that the phenylzinc species was produced in situ by boron-to-zinc exchange, and the reactive catalyst was formed from the dendritic ligand and zinc species.

In summary, a series of new dendritic chiral pyrrolidinylmethanol derivatives were synthesized and proved to be highly effective ligands for the asymmetric catalytic aryl transfer to aldehydes with the $PhB(OH)_2/ZnEt_2$ or $(ArBO)_3/ZnEt_2$ systems. This study opens up a new

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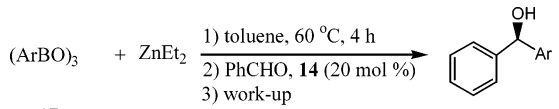
TABLE 4. Catalyzed Aryl Transfer from 17 to Benzaldehyde[a]



17 18

entry	$(ArBO)_3$	product	T (h)	yield (%)[b]	ee of **18** (%)[c,d]
1	Ar = 4-chlorophenyl (**17b**)	**18b**	6	92	98 (*R*)
2	Ar = 4-bromophenyl (**17c**)	**18c**	6	95	95
3	Ar = 4-fluorophenyl (**17d**)	**18d**	6	92	92
4	Ar = 4-methylphenyl (**17e**)	**18e**	8	86	91
5	Ar = 4-methoxyphenyl (**17f**)	**18f**	8	80	89

[a] In toluene, 7.2 equiv of $ZnEt_2$ and 2.4 equiv of $PhB(OH)_2$ with respect to 4-Cl-C_6H_4CHO. [b] After column chromatography. [c] Determined by HPLC using a chiral stationary phase. [d] Comparison of the HPLC peak elution order of **18b** with known data revealed that the (*R*)-enantiomer was formed in excess. Assuming an analogous mechanism for the aryl transfer and on the basis of the HPLC elution order, we assume that the other products have the (*R*)-configuration as well.

frontier for the development of highly effective and easily separable chiral ligand. Current work is focused on gaining detailed insight into the nature of the dendrictic effect and the exploration of these catalysts in other reactions.

Experimental Section

Preparation of 8. Benzyl bromide (0.428 g, 2.5 mmol) was added to a solution of **3** (0.389 g, 1.25 mmol) in DMF (5 mL). To this solution was added dried and finely powdered K_2CO_3 (0.345 g, 2.5 mmol), and the resulting suspension was stirred for 3 h at room temperature. H_2O (10 mL) and CH_2Cl_2 (20 mL) were added; the two layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with H_2O and then dried over Na_2SO_4, and the solvent was evaporated to yield the crude product as a yellow oil. Flash chromatography (EtOAc/petroleum ether 1:3) yielded **8** (0.588 g, 96%) as a white solid: mp 136−138 °C; $[\alpha]_D^{20}$ −180.3 (*c* 1.10, $CHCl_3$); IR (film, cm^{-1}) υ 1750, 1609, 1513, 1259; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09−1.13 (m, 1H), 1.64−1.71 (m, 1H), 1.77−1.96 (m, 2H), 3.21−3.29 (m, 1H), 3.69−3.78 (m, 1H), 4.15−4.52 (m, 1H), 5.04 (s, 4H), 6.96 (d, J = 9.0 Hz, 4H), 7.26−7.43 (m, 14H); MS (EI) *m/e* 491 (M^+, 8.31), 378 (M^+ − 113, 15.75), 91 (M^+ − 400, 100). Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.19; H, 5.95; N, 2.85. Found: C, 78.32; H, 5.99; N, 2.75.

Preparation of 12. To a cooled (0 °C) suspension of $LiAlH_4$ (75 mg, 2 equiv) in freshly distilled THF (2 mL) was added dropwise a THF (2 mL) solution of **8** (488 mg, 1 equiv). Upon complete addition of **8**, the ice−water bath was removed, and the suspension was stirred until the reaction was complete, as indicated by TLC (3 h). The reaction was quenched with Baechströms reagent ($Na_2SO_4 \cdot 10H_2O$), stirred for 15 min, filtered, and concentrated in vacuo to afford a yellow oil. Flash chromatography (CH_2Cl_2/acetone 1:1) yielded **12** (0.394 g, 83%) as a white solid: mp 128−130 °C; $[\alpha]_D^{20}$ 15.6 (*c* 1.30, $CHCl_3$); IR (film, cm^{-1}) υ 3292, 1604, 1506, 1379, 1236; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−1.72 (m, 4H), 1.83 (s, 3H), 2.16−2.44 (m, 1H), 3.08−3.11 (m, 1H), 3.49−3.54 (m, 1H,), 4.98 (s, 4H), 6.84−6.94 (m, 4H), 7.24−7.50 (m, 14H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 24.2, 30.0, 43.3, 59.3, 70.1, 72.1, 77.1, 114.4, 126.6, 127.6, 128.0, 128.6, 137.2, 139.8, 141.2, 157.2; ESI, MS *m/e* 480 ($[M + H]^+$); HRMS (ESI) *m/e* calcd for $[C_{32}H_3NO_3 + H]^+$ 480.2533, found 480.2533.

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Supporting Information Available: Experimental procedure and characterization data, including ^1H NMR spectral data and HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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