Self-Assembled Ligands

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Exploiting Self-Assembly for Ligand-Scaffold Optimization: Substrate-Tailored Ligands for Efficient Catalytic Asymmetric Hydroboration**

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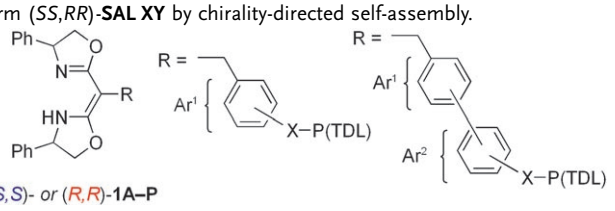
Rhodium-catalyzed hydroboration has attracted much interest, in part owing to the complementary regio- and diastereoselectivity obtained with certain substrates compared to the uncatalyzed process.[1,2] The novel regiocontrol is exemplified in the rhodium-catalyzed hydroborations of vinyl arenes, which, in contrast to the uncatalyzed reaction, introduce boron at the benzylic position. For example, styrene affords 1-phenylethanol after hydroboration and oxidation. Several catalyst systems exhibit both high regio- and enantioselectivity for the catalytic asymmetric hydroboration of styrene and some of its substituted derivatives.[3] However, the reaction is sensitive to both steric and electronic factors, and for the reactions of *ortho*-substituted styrene derivatives, an important subclass of these substrates, high levels of enantioselection have proved elusive.[4] Herein, we report the use of self-assembled ligands (SALs) for the catalytic asymmetric hydroboration of a family of *ortho*-substituted styrene derivatives varying in steric and electronic character.

Several strategies for preparing novel ligands by self-assembly have emerged as promising approaches to unsolved problems in catalysis.[5,6] We reported a novel method for the in situ preparation of chiral ligand libraries by chirality-directed self-assembly, a strategy by which the topography at the catalytic site is varied over a wide range by subtle changes in the ligand scaffold.[7]

Bifunctional subunits (*S*,*S*)- and (*R*,*R*)-**1A–P** exploit a chiral bisoxazoline to direct the self-assembly, substituted with a series of phenylmethyl or biphenylmethyl tethers terminating in a phosphite ligating group derived from TADDOL[8] ((4*R*,5*R*)-α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol, TDL). The subunits differ with respect to the tether substitution pattern (Table 1).

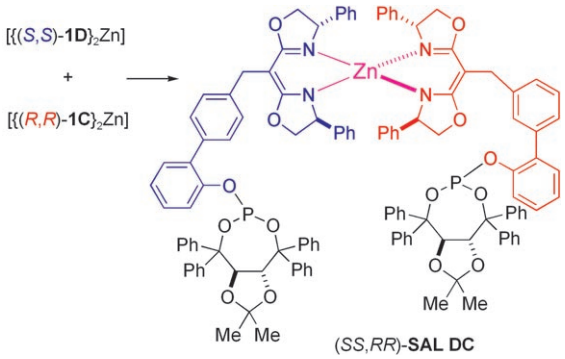
Table 1: TADDOL-derived subunits (*S*,*S*)- and (*R*,*R*)-**1A–P** are used to form (*SS*,*RR*)-**SAL XY** by chirality-directed self-assembly.



(*S*,*S*)- *or* (*R*,*R*)-**1A–P**

	X = O			X = CH_2O	
Ar^2	1,3-Ar^1	1,4-Ar^1	Ar^2	1,3-Ar^1	1,4-Ar^1
–	**A**	**B**	–	**I**	**J**
1,2-	**C**	**D**	1,2-	**K**	**L**
1,3-	**E**	**F**	1.3-	**M**	**N**
1,4-	**G**	**H**	1,4-	**O**	**P**

A mixture of (*S*,*S*)- and (*R*,*R*)-**1A–P** readily undergoes chirality-directed self-assembly upon addition of zinc(II) to yield the heterodimeric (*SS*,*RR*)-SALs.[9] In the present study, we found it convenient to first prepare the (*S*,*S*)- and (*R*,*R*)-homodimers from **1A–P**, which upon mixing rapidly equilibrate to the (*SS*,*RR*)-heterodimer. For example, mixing [{(*S*,*S*)-**1D**}$_2$Zn] with [{(*R*,*R*)-**1C**}$_2$Zn] affords (*SS*,*RR*)-**SAL DC** (Scheme 1). The latter can be isolated; however,



Scheme 1. Heterodimer (*SS*,*RR*)-**SAL DC** is readily prepared by ligand exchange of the appropriate homodimers.

the SALs and their derived catalyst systems are typically generated in situ and used without isolation.[10] Combining various pairs of (*S*,*S*)- and (*R*,*R*)-**1A–P** quickly affords a library of unique (*SS*,*RR*)-**SAL XY** differing only in scaffold structure.

The hydroboration of 2-methoxystyrene (**2a**) with pinacolborane (PBH) was screened using [{Rh(nbd)Cl}$_2$] (nbd = 2,5-norbornadiene) in combination with 162 in situ prepared **SAL XY** [Eq. (1), DME = dimethoxyethane].[11] Remarka-

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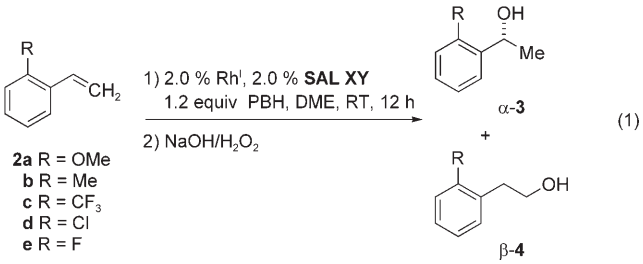


(1)

bly, this readily accessible, focused ligand library affords *R*:*S* enantiomeric ratios ranging from 98:2 to 35:65 (Figure 1).[12] Analysis of these data reveals that with few exceptions the most efficient catalysts combine SALs containing only phenyl phosphite subunits **1A–H** (65 to 96% *ee* (*R*)). The SALs containing only benzyl phosphite subunits (**1I–P**) afford lower levels of enantioselectivity (30% *ee* (*S*) to 40% *ee* (*R*)). Mixed phenyl/benzyl combinations tend to fall in between.

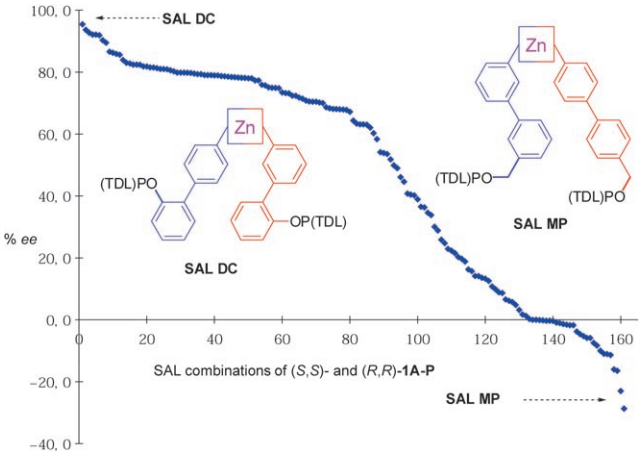


Figure 1. Wide variation in enantioselectivity is observed for the SAL/[{Rh(nbd)Cl}$_2$]-catalyzed asymmetric hydroboration of 2-methoxystyrene (**2a**) as a function of ligand scaffold.

Varying the catalyst precursor reveals other remarkable features of the role of scaffold structure in catalyst optimization. The nature of the Rh^I catalyst precursor can be an important factor in catalytic asymmetric hydroboration.[13] Having obtained data using [{Rh(nbd)Cl}$_2$], the reaction of 2-methoxystyrene (**2a**) was carried out using [Rh(nbd)$_2$BF$_4$] in combination with each of the 64 possible SALs from derived from subunits **1A–H**. As summarized in Table 2, different optimal ligand scaffolds were found for each catalyst precursor. **SAL DC** (96% *ee*) was best for [{Rh(nbd)Cl}$_2$] while **SAL HC** (95% *ee*) proved best for [Rh(nbd)$_2$BF$_4$]. It is interesting to note that while subunit (*R*,*R*)-**1C** is present in both optimal SALs, the SAL combination containing only **1C** (i.e., the pseudo-C_2-symmetric **SAL CC**) is less effective with either catalyst precursor. In addition, **SAL DC** is more selective than its closely related diastereomer **SAL CD**, and **SAL HC** is more selective than its corresponding diastereomer **SAL CH**.

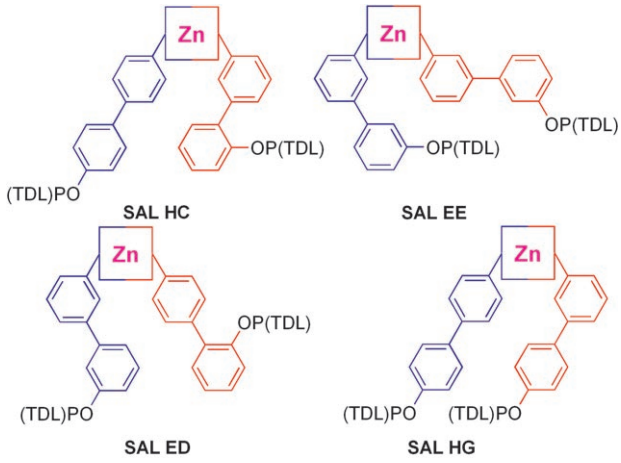
Prior studies have shown that the efficiency of rhodium-catalyzed asymmetric hydroboration is quite sensitive to steric and electronic factors in the substrate.[14] The availability of a range of different SAL scaffolds proves useful for the rapid optimization of different catalysts for individual substrates. High regio- and enantioselectivity can be obtained for each substrate within the series of *ortho*-substituted styrene derivatives **2a–e** using in situ generated [(**SAL XY**)Rh(nbd)BF$_4$] catalysts derived from the subunits **1A–H**.[15] The best results for each substrate are highlighted in Table 3 (entries in boldface); these results are for preparative reactions run on a 1-mmol or greater scale. The regio- and enantioselectivities found in preparative reactions are similar to those obtained under the screening conditions (±1–2%); the yields of isolated product range from 82–98%. For comparison, Table 3 also gives the results achieved using two equivalents of (TDL)POPh (53–81% *ee*), the monodentate

Table 2: {Rh^{I}Cl} and {Rh^{I}BF$_4$} catalyst precursors require different ligand scaffolds for the hydroboration of 2-methoxystyrene (**2a**).[a]

Ligand	[{Rh(nbd)Cl}$_2$]	[Rh(nbd)$_2$BF$_4$]
SAL DC	96 (98)	78 (96)
SAL HC	86 (94)	95 (98)
SAL CC	75 (88)	84 (97)
SAL CD	92 (94)	–
SAL CH	–	86 (97)
SAL DD	79 (90)	–
SAL HH	–	93 (94)

[a] Conditions: see Equation (1). The results listed indicate % *ee* (% α-isomer).

Table 3: Different ligand scaffolds are used to achieve optimal results for substrates **2a–e** with [(**SAL XY**)Rh(nbd)BF$_4$] catalysts.[a]



Ligand	**3a** (R = OMe)	**3b** (R = Me)	**3c** (R = CF$_3$)	**3d** (R = Cl)	**3e** (R = F)
SAL HC	**94 (99)**[b]	87 (86)	66 (66)	78 (96)	76 (88)
SAL EE	66 (93)	**91 (95)**[b]	76 (49)	73 (87)	**91 (92)**[b]
SAL ED	75 (96)	85 (93)	**91 (95)**[b]	68 (67)	68 (78)
SAL HG	91 (95)	87 (81)	53 (72)	**93 (92)**[b]	77 (73)
(TDL)POPh	81 (91)	73 (78)	69 (73)	77 (83)	53 (76)
literature[c]	82 (99)	92 (93)	83 (97)	69 (93)	72 (92)

[a] Conditions: see Equation (1). The results indicate % *ee* (% α-isomer). [b] Reaction run on a 1-mmol scale. [c] The best results previously reported for each substrate; see reference [7] for details.

chiral phosphite moiety present in each SAL, as well as the best results previously reported for each substrate. For substrates **2a** (R = OMe) and **2c–e** (R = CF_3, Cl, F), the SAL identified is the most selective catalyst reported to date. For **2b** (R = Me), the best SAL and literature results are nearly equivalent.

The importance of the heterodimeric zinc complex as a structural element for the SALs is further illustrated by comparing three diastereomeric ligands derived from (*S*,*S*)- and (*R*,*R*)-**1E**. Even though the ligating groups and tethers are identical in all three zinc complexes, the results obtained in the hydroboration of 2-methylstyrene (**2b**) vary significantly. In contrast to the (*SS*,*RR*)-heterodimer, **SAL EE** (91% *ee*, 95% α-**3b**), the diastereomeric (*SS*,*SS*)- and (*RR*,*RR*)-homodimers, that is, [{(*S*,*S*)-**1E**}$_2$Zn] and [{(*R*,*R*)-**1E**}$_2$Zn], exhibit low reactivity and lower selectivity: 87% *ee* (84% α-**3b**) and 79% *ee* (82% α-**3b**), respectively.

In summary, a series of TADDOL phosphite-bearing SALs, readily prepared in combinatorial arrays by chirality-directed self-assembly, provides a focused ligand library for Rh^I-catalyzed hydroboration. These SALs exhibit the unique feature of achieving high enantioselectivity through the subtle manipulation of the chiral catalytic pocket by small systematic changes in the ligand scaffold, an approach not available with classic ligand designs. The ligands differ only in scaffold structure, yet the enantioselectivity obtained in catalytic asymmetric hydroboration of 2-methoxystyrene varies from 96% *ee* favoring the *R*-configuration to 30% *ee* favoring *S*. {Rh^ICl} and {Rh^IBF_4} catalyst precursors and different substrates require different ligand scaffolds to achieve success. Nevertheless, {(**SAL XY**)Rh^I} catalysts afford high regioselectivity (92–99% α**3**) and enantioselectivity (91–96% *ee*) across a series of *ortho*-substituted styrenes varying in electronic character and steric demand. Thus, a facile method of self-assembly is exploited to fine tune catalysts by ligand scaffold optimization, improving substrate generality in a reaction that has thus far exhibited rather limited substrate scope. Studies directed toward understanding the structural basis for the wide variation in selectivity as a function of ligand scaffold (i.e. the structure–activity relationship of these ligands) are in progress.

Experimental Section

[(**SAL HC**)Rh(nbd)BF_4]-catalyzed asymmetric hydroboration of 2-methoxystyrene: A solution of [{(*S*,*S*)-**1H**}$_2$Zn] (10.0 mg, 1.4×10^{-2} mmol) and [{(*R*,*R*)-**1C**}$_2$Zn] (10.0 mg, 1.4×10^{-2} mmol) in CH_2Cl_2 (10 mL) was stirred at ambient temperature (10 min), and then a solution of [Rh(nbd)$_2$$BF_4$] (9.7 mg, 2.6×10^{-2} mmol) in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred at ambient temperature (0.5 h), after which the volatile solvent was removed under vacuum. The residue was dissolved in DME (10 mL), stirred (0.5 h), and then a solution of 2-methoxystyrene (**2a**, 174.0 mg, 1.30 mmol) in DME (2.0 mL) and powdered 4-Å molecular sieves (ca. 0.5 g) were added. The resulting mixture was cooled (0 °C) and a solution of pinacolborane (199.0 mg, 1.56 mmol) in DME (4.0 mL) added dropwise. The reaction mixture was gradually warmed to room temperature and stirred (12 h). Afterwards, the mixture was again cooled (0 °C) and quenched by the addition of MeOH (10 mL), NaOH(aq) (3.0 M, 15 mL), and H_2O_2(aq) (1 mL of a 30% solution). The ice bath was removed, and the resulting mixture stirred (3 h, RT) and then filtered. The filtrate was extracted with diethyl ether (3 × 15 mL) and the combined organics were dried (anhydrous Na_2SO_4), filtered, and concentrated. Chromatography on silica (10% 1:9 EtOAc/Hex) gives 1-(2-methoxyphenyl)ethanol (**3a**, 194 mg, 98%) as a clear oil: capillary GC analysis (J&W Scientific 30 m × 0.25 mm ID Cyclosil *β*, 120 °C (1 min hold) to 130° at 1° min^{-1} then to 165° at 2° min^{-1}) found peaks at 21.19 (97.2%, (*R*)-**3a**) and 23.55 (2.8%, (*S*)-**3a**); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (1H, dd, $J = 7.5$, 1.4 Hz), 7.37–7.26 (1H, dt, $J = 8.2$, 1.6 Hz), 7.00 (1H, t, $J = 7.5$ Hz), 6.90 (1H, d, $J = 8.2$ Hz), 5.15–5.11 (1H, q, $J = 13.0$, 6.5 Hz), 3.88 (3H, s) 1.53 ppm (3H, d, $J = 6.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.5$, 133.6, 128.2, 126.1, 120.8, 110.4, 66.4, 55.3, 23.0 ppm; $[\alpha]_D^{25} = +25.8°$ ($c = 1.4$ g (100 mL)$^{-1}$, $CHCl_3$).

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[10] (*SS*,*RR*)-**SAL DC** was combined with [{Rh(nbd)Cl}$_2$] to generate the heterobimetallic complex [(**SAL DC**)Rh(nbd)Cl]. Its ^{31}P NMR spectrum, obtained after addition of a stoichiometric amount of 1,10-phenanthroline (see reference [2i]), shows a doublet at $\delta = 112.8$ ppm ($J_{P,Rh} = 250$ Hz).

[11] In contrast to the results found using pinacol borane, the use of catechol borane gave low levels of asymmetric induction.

[12] The regioselectivity also varies as a function of SAL scaffold structure, but to a lesser extent (70–99 % α-**3**), with {Rh^{I}BF$_4$} catalysts generally affording higher regioselectivity. We find no strong correlation between regio- and enantioselectivity, however, there seems to be a loose correlation between enantioselectivity and conversion/yield under the conditions examined.

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[15] While [Rh(nbd)$_2$BF$_4$] is an effective catalyst precursor, other complexes can give comparable or superior results for some substrates in Table 3. For example, slightly higher enantioselectivity can be obtained for 2-methoxystryene (96 % *ee*, 98 % α-**3a**) using [{Rh(nbd)Cl}$_2$] and SAL (*SS*,*RR*)-**SAL DC** and for 2-(trifluoromethyl)styrene (94 % *ee*, 92 % α-**3c**) using [Rh(cod)$_2$OTf] using (*SS*,*RR*)-**SAL CH**.

