A General Solid-Phase Synthesis Strategy for the Preparation of 2-Pyrrolidinemethanol Ligands

Guangcheng Liu and Jonathan A. Ellman*

Department of Chemistry, University of California, Berkeley, California 94720

Received September 18, 1995

The development of asymmetric catalysts generally requires the time-consuming screening of a large number of chiral ligands, metals, and reaction conditions.[1] For many asymmetric reactions, optimization of ligand structures for each substrate class must be performed. To expedite these processes, we have worked to apply combinatorial strategies to asymmetric catalyst development and optimization. As progress toward this goal, we report a general approach for the solid-phase synthesis of the 2-pyrrolidinemethanol ligand class (Figure 1) and demonstrate that the ligands can be directly evaluated in dialkylzinc addition reactions without purification. This ligand class, as well as other ligands based on proline, have been used extensively to prepare asymmetric catalysts for a number of reactions including dialkylzinc additions to aldehydes,[2] enantioselective reductions of ketones,[3] and asymmetric Diels–Alder reactions.[4]

We initially chose to focus on dialkylzinc additions to aldehydes for several reasons. First, several groups have reported that support-bound ligands can serve as effective asymmetric catalysts for dialkylzinc additions, although for each of these studies the ligands were synthesized in solution and then attached to the support.[2] Second, Soai has determined that the R^1 and R^2 groups of pyrrolidinemethanol ligands (Figure 1) are important determinants of asymmetric induction.[5] Third, while Soai has developed ligands of this class that provide high enantioselectivities (>95% ee) for dialkylzinc additions to aromatic aldehydes, ligands of this class have not yet been identified that provide comparable enantioselectivities for additions to aliphatic aldehydes.[6] Therefore, ligand optimization for different aliphatic substrate classes is desirable.

We chose to employ a solid-phase synthesis strategy for the construction of the ligands because it provides for facile isolation of products from reaction mixtures, and therefore, reactions can be driven to completion by the use of excess reagents. We also selected commercially available *trans*-4-hydroxy-L-proline as the starting material for the synthesis sequence since the 4-hydroxyl group provides a convenient site for attachment onto the solid support. In addition, we chose to use a tetrahydropyranyl linker[7] for the attachment of the alcohol to the support, since alcohol attachment and cleavage from the support can be accomplished with mild acid catalysis and

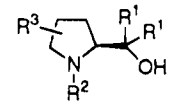


Figure 1. 2-Pyrrolidinemethanol ligand class.

because the linker is stable to the Grignard addition and Red-Al reduction steps that are performed in the synthesis sequence (vide infra).

N-[(Ethyloxy)carbonyl]-4-hydroxyproline methyl ester (**2**)[8] is coupled to the dihydropyran-derivatized resin **1** (commercially available Merrifield resin, 0.70 mmol Cl/g resin, 1% DVB) using PPTS in 1,2-dichloroethane at 80 °C for 48 h (Scheme 1). The coupling efficiency is determined by mass balance after cleavage of the material from the support. Addition of a large excess of Grignard reagents to the support-bound methyl ester **3** provides support-bound alcohol **4**. In our initial studies, the (allyloxy)carbonyl and the [[(trimethylsilyl)ethyl]oxy]-carbonyl groups were employed in place of the (ethyloxy)-carbonyl protecting group, but these more labile protecting groups are not stable to the Grignard reaction conditions.[9] The support-bound *N*-methylated ligand **5** can then be accessed by reduction with Red-Al. Alternatively, deprotection of **4** with KOH in refluxing 1:2 BuOH/1,4-dioxane provides the support-bound free amine **7**. Acylation followed by reduction with Red-Al affords support-bound *N*-alkylated ligand **8**. In initially optimizing the synthesis sequence, we prepared support-bound ligands **5a** (R^1 = Ph) and **8a** (R^1 = Ph, R^2 = Me). After subjection of the support-bound ligands to the cleavage conditions (PPTS in BuOH/1,2-dichloroethane, 60 °C) followed by extractive isolation, ligands **6a** (R^1 = Ph) and **9a** (R^1 = Ph, R^2 = Me) were isolated with no epimerization being observed from the synthesis sequence as determined by NMR and HPLC (<1%).

Initially, the ligands were evaluated while still bound to support. For diethylzinc addition to benzaldehyde, 2 mol % of support-bound ligand **5a** (R^1 = Ph) in toluene at 0 °C for 48 h provided 1-phenylpropanol **10** with 100% conversion and in 89% enantiomeric excess. The same result was obtained when 5 mol % of the ligand was employed, demonstrating that 2 mol % of ligand is sufficient for this ligand-accelerated catalysis. In order to compare the enantioselectivity of the support-bound ligand to that of the corresponding free ligand, ligand **11** was evaluated under the same reaction conditions to provide the chiral alcohol **10** in 94% ee (Table 1). Initially, we attributed the lower enantioselectivity provided by the support-bound ligand relative to that provided by the corresponding free ligand to the tetrahydropyranyl linkage group. However, the same enantioselectivity (94% ee) was obtained by the use of tetrahydropyranyl ether **12** (Table 1). Attempts to improve the enantioselectivity provided by the support-bound ligand, such as using high loading Merrifield resin and macroreticular resin as supports, were not successful.

Since the enantioselectivity provided by the support-bound ligand does not correlate with that provided by

(1) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 1st ed.; VCH Publishers, Inc.: New York, 1993.
(2) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
(3) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(4) Kobayashi, S.; Murakami, M.; Harada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1341.
(5) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
(6) Good enantioselectivities are observed for aliphatic substrates with other ligand classes: (a) Yakahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095. (b) Schmidt, B.; Seebach, D. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99.
(7) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333.
(8) Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.
(9) An amine protecting group is necessary, since many researchers have reported that Grignard additions to proline methyl ester results in extensive racemization when the free amine is employed. (a) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T. ; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751. (b) Ookawa, A.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1987**,1465. (c) Corey, E. J.; Bakshi, R. K.; Shibata. S.; Chen, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

0022-3263/95/1960-7712$09.00/0

Scheme 1

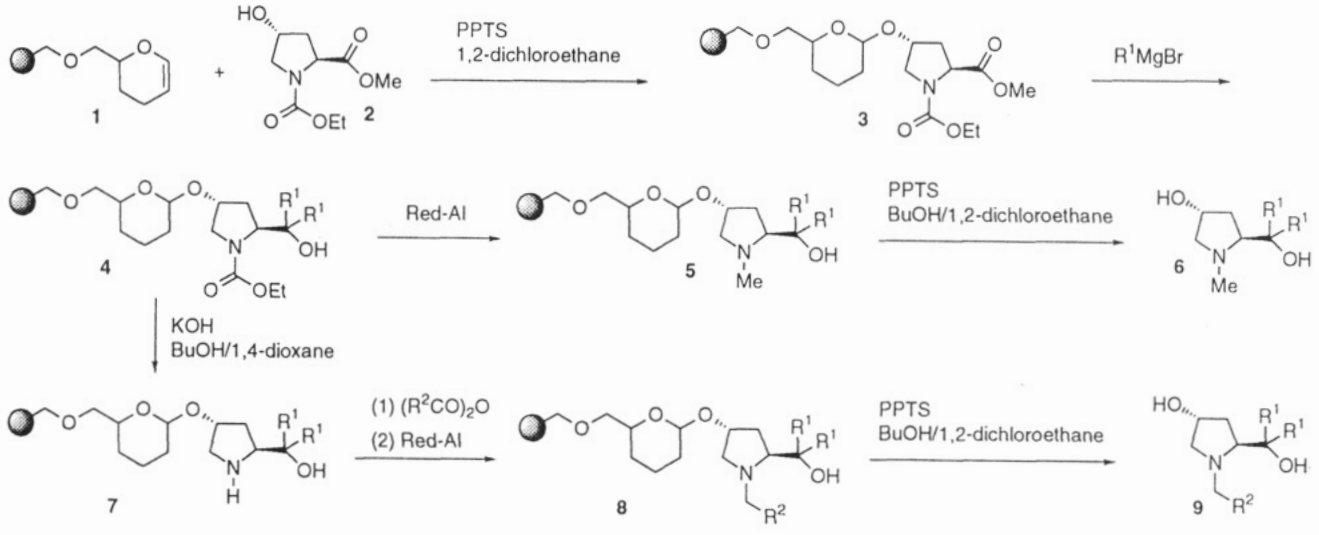
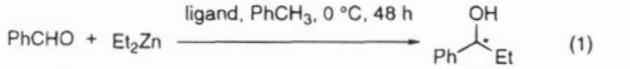


Table 1. Comparison of the Enantioselectivity Provided by the Support-Bound Ligand to That Provided by the Corresponding Free Ligand



10

Ligand	**5a** (R^1 = Ph)	**11**	**12**
ee	89% (S)	94% (S)	94% (S)

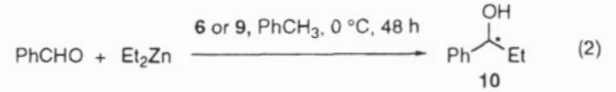
the corresponding free ligand, we investigated the possibility of evaluating the ligands after removal from the solid support. Ligand **6a** (R^1 = Ph) provided the same enantioselectivity as ligand **11** for diethylzinc addition to benzaldehyde, demonstrating that the 4-hydroxyl group on the ligand has no effect on the enantioselectivity. Most likely, ring strain prevents the 4-hydroxyl group from interacting with the zinc that is complexed to the amine and tertiary alcohol of the ligand.

A variety of ligand analogs were then synthesized on the support in order to demonstrate the feasibility of this approach. After cleavage of the ligands off the support, the ligands were isolated by extraction and were used without further purification for diethylzinc addition to benzaldehyde or to 3-methylbutanal. Comparable enantioselectivities to those of the corresponding purified ligands were obtained (Table 2 and 3), even for ligands **6b** (R^1 = 3,5-dimethylphenyl) and **6d** (R^1 = 3,5-dichlorophenyl) that were contaminated with small amounts of side products from the synthesis sequence as observed by NMR. Presumably, the minor side products do not serve as ligands for the diethylzinc addition to aldehydes. These results suggest that ligand accelerated catalysts[10] may be ideally suited for combinatorial strategies where the purification of each ligand will not be possible.

In summary, we have developed a general solid-phase synthesis strategy for the 2-pyrrolidinemethanol ligand class and have demonstrated that the ligands can be directly evaluated for enantioselective additions of diethylzinc reagent to aldehyde substrates. These results suggest that combinatorial strategies may be useful for the development of asymmetric catalysts. We are currently applying combinatorial strategies for the rapid development of asymmetric catalysts to the ligand class described above as well as to other ligand classes.

(10) For a recent review of ligand-accelerated catalysis, see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

Table 2. Enantioselectivities for Diethylzinc Additions to Benzaldehyde

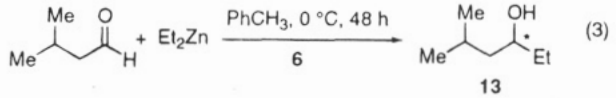


10

entry	R^1	R^2	source 1 (% ee)[a]	source 2 (% ee)[b]
6a	phenyl		93 (*S*)	94 (*S*)
9a	phenyl	methyl	83 (*S*)	84 (*S*)
9b	phenyl	phenyl	89 (*S*)	85 (*S*)
9c	ethyl	methyl	0	0
9d	ethyl	phenyl	30 (*R*)	45 (*R*)

[a] Synthesized on support and isolated by extraction after cleavage. [b] Synthesized in solution and purified by chromatography and recrystallization.

Table 3. Enantioselectivities for Diethylzinc Additions to 3-Methylbutanal[a]



13

entry	R^1	source 1 (% ee)[b]	source 2 (% ee)[c]
6a	phenyl	85 (*S*)	85 (*S*)
6b	3,5-dimethylphenyl	83 (*S*)	81 (*S*)
6c	4-biphenyl	85 (*S*)	84 (*S*)
6d	3,5-dichlorophenyl	81 (*S*)	83 (*S*)
6e	4-(trifluoromethyl)phenyl	85 (*S*)	85 (*S*)
6f	2-naphthyl	82 (*S*)	81 (*S*)

[a] Ligand **11** provides the same enantioselectivity as **6a** (85% ee). [b] Synthesized on support and isolated by extraction after cleavage. [c] Synthesized on support and purified by chromatography.

Acknowledgment. We gratefully acknowledge the ONR and the Alfred P. Sloan Foundation.

Supporting Information Available: Experimental details for the synthesis and evaluation of 2-pyrrolidinemethanol ligands (5 pages).

JO9517050