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New modular P-chiral ligands for Rh-catalyzed asymmetric hydrogenation

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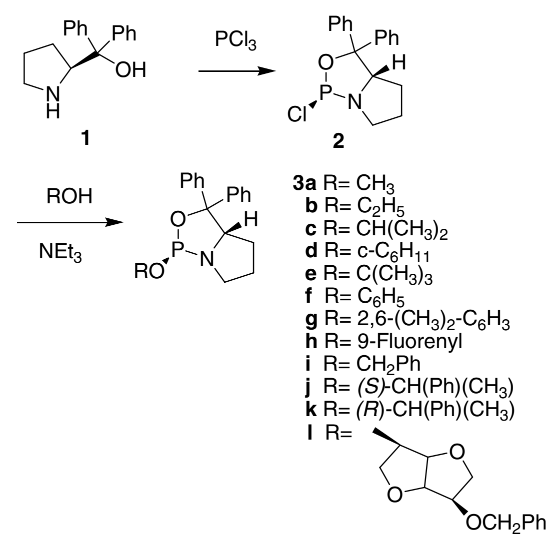
Abstract—New modular P-chiral ligands have been prepared from commercially available (*S*)-α,α-diphenylprolinol. With these new types of ligands, up to 95% ee was achieved in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins.

We recently reported the synthesis and catalytic application to asymmetric hydrogenation of P,P-bidentate ligands derived from commercially available (*S*)-α,α-diphenylprolinol.[1] Recent catalytic results showing that traditional chelating ligands are not necessary to achieve a high enantioselectivity[2] prompted us to develop further analogous P-monodentate ligands.

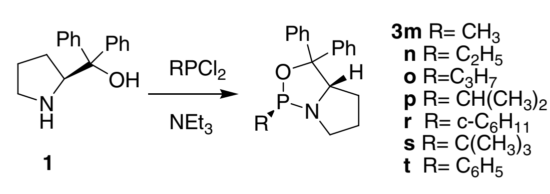
In contrast to the extensive use of BINOL-based monodentate chiral phosphites, phosphonites, and phosphoramidites,[3] little is known concerning similar ligands based on other building blocks.[4] The concept of replacing the BINOL chiral scaffold with amino alcohols leads to the design of new chiral ligands. The variable environment of the phosphorus atom in such compounds provides an excellent opportunity for facile modular construction of structurally tunable ligands, which can be considered as one of the advantages of this class of ligands.

In this letter, we describe the synthesis of (*S*)-α,α-diphenylprolinol derived P-chiral monodentate ligands and some preliminary results of their application in Rh-catalyzed asymmetric hydrogenation.

Synthesis of ligands involves diastereoselective phosphorylation of **1** by PCl_3 with an exclusive formation of (S,R_P)-**2**[5] followed by the standard phosphorylation of alcohols (Scheme 1).[6] An alternative procedure used for the preparation of phosphonite ligands **3m–t** is the treatment of **1** with chlorophosphines $RPCl_2$ as phosphorylating agent (Scheme 2).[2d,7] Monodentate



Scheme 1.



Scheme 2.

Keywords: Asymmetric reactions; Phosphorus ligands; Rhodium; Hydrogenation.

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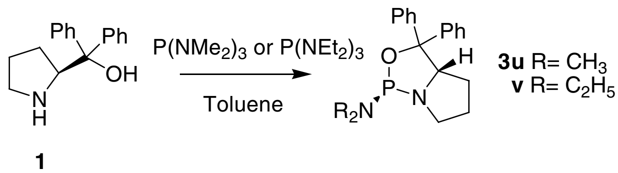
phosphoramidite derivatives **3u–v** were prepared by reacting **1** with hexamethyl- and ethylphosphorustriamide in refluxing toluene (Scheme 3).[2e,8]



Scheme 3.

An X-ray analysis of **3g**[9] was performed in order to confirm its structure and determine absolute configuration at the phosphorus atom (Fig. 1). According to the X-ray diffraction data, the ligand has an expected pseudo-equatorial orientation of the exocyclic substituent at the phosphorus atom (i.e., *S* configuration at the P-stereocenter).

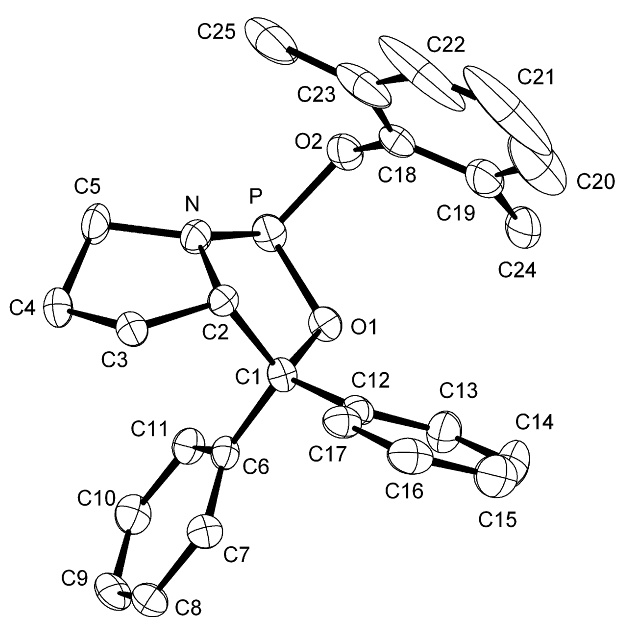
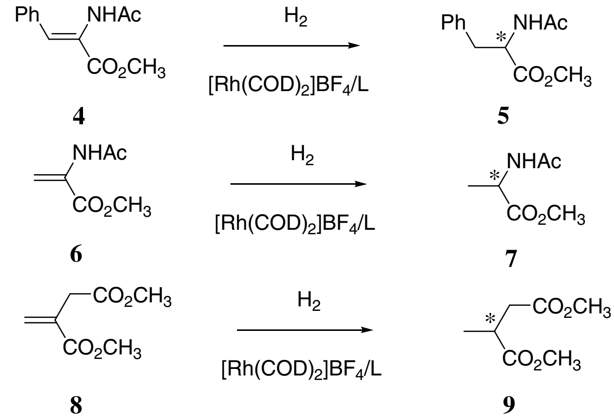


Figure 1. X-ray crystal structure of **3g**.

The new ligands were efficiently applied in the Rh-catalyzed hydrogenation of common benchmark substrates, namely, methyl α-acetylaminocinnamate **4**, methyl α-acetamidoacrylate **6**, and dimethyl itaconate **8** (Scheme 4). In all cases the cationic rhodium catalyst was prepared in situ by treating $[Rh(cod)_2]BF_4$ with 2 equiv of the corresponding monodentate ligand in CH_2Cl_2.

The results summarized in Table 1 show that the degree of enantioselectivity strongly depends on the nature of the R-group in the ligands. Increasing of the substituent R steric demands by changing methyl and ethyl groups to bulkier ones led to a sharp decrease of enantioselectivity (entry 1 and 2 vs 3–5; entry 13 and 14 vs 15–18; entry 20 vs 21).



Scheme 4.

Table 1. Rh-catalyzed olefin-hydrogenation[a]

Entry	Ligand	ee of **5**	ee of **7**	ee of **9**
1	**3a**	78 (*S*)	84.6 (*S*)	90.2 (*R*)
2	**3b**	87.2 (*S*)	91 (*S*)	87 (*R*)
3	**3c**	63.2 (*S*)	69.4 (*S*)	84.3 (*R*)
4	**3d**	67.8 (*S*)	74.6 (*S*)	62.4 (*R*)
5	**3e**	54.4 (*S*)	71 (*S*)	53.3 (*R*)
6	**3f**	76.2 (*S*)	77.2 (*S*)	62 (*R*)
7	**3g**	25.4 (*S*)	21.8 (*S*)	18.8 (*R*)
8	**3h**	60.6 (*S*)	43.4 (*S*)	32.8 (*R*)
9	**3i**	87.4 (*S*)	88.3 (*S*)	84 (*R*)
10	**3j**	21.8 (*S*)	25 (*S*)	32.8 (*R*)
11	**3k**	76.2 (*S*)	73.2 (*S*)	87.3 (*R*)
12	**3l**	91.8 (*S*)	91.3 (*S*)	94.5 (*R*)
13	**3m**	95.2 (*S*)	88 (*S*)	60.4 (*R*)
14	**3n**	91.7 (*S*)	83.7 (*S*)	65.5 (*R*)
15	**3o**	87.6 (*S*)	76.8 (*S*)	60.6 (*R*)
16	**3p**	43[b] (*S*)	71.6[c] (*S*)	24.2[d] (*R*)
17	**3r**	35.8[e] (*S*)	69.2[f] (*S*)	16.2[g] (*R*)
18	**3s**	35[h] (*S*)	—[i]	—[j]
19	**3t**	80.7 (*S*)	71.8 (*S*)	62 (*R*)
20	**3u**	88.4 (*S*)	91.1 (*S*)	61 (*R*)
21	**3v**	47.6[k] (*S*)	59[l] (*S*)	44.4[m] (*R*)

[a] Rh/substrate ratio 1:1000, CH_2Cl_2, 1.3 bar H_2, 20 °C, 20 h, conversion: 100%.
[b] Conversion: 85%.
[c] Conversion: 72%.
[d] Conversion: 64%.
[e] Conversion: 58%.
[f] Conversion: 68%.
[g] Conversion: 38%.
[h] Conversion: 10%.
[i] Conversion: 3%.
[j] Conversion: 2%.
[k] Conversion: 78%.
[l] Conversion: 79%.
[m] Conversion: 49%.

The configuration at R-substituent plays a very important role. (R,S,S_P)-**3k** represents a matched (entry 11) case versus mismatched case (S,S,S_P)-**3j** (entry 10). The best results were shown by ligand **3l** (entry 12, 91–95% ee) prepared from 1,4:3,6-dianhydro-D-mannitol. From entries 1, 13, 20 it becomes evident that the nature of phosphorus atom (phosphites, phosphonites, and phosphoramidites) has a pronounced influence on the enantioselectivity in hydrogenation. The results obtained in the asymmetric hydrogenation of dimethyl itaconate followed the same trend as those for methyl α-acetamidoacrylate and methyl α-acetylaminocinnamate, but the enantioselectivity for phosphonites **3m–t** and phosphoramidites **3u–v** were somewhat lower.

In summary, new modular P-chiral ligands derived from (*S*)-α,α-diphenylprolinol have been synthesized for the first time. The new ligands have demonstrated a high enantioselectivity in the Rh-catalyzed hydrogenation of methyl α-acetamidoacrylate (up to 91% ee), methyl α-acetylaminocinnamate (up to 95% ee), and dimethyl itaconate (up to 95% ee). Also, we have taken the advantage of these highly modular ligands to show that catalyst optimization can be done easily by variation of the substituent attached to the phosphorus atom.

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6. *General procedure for the preparation of ligands* **3a–l**: The appropriate alcohol (5.4 mmol) was added at −78 °C to stirred solution of reagent **2** (1.7 g, 5.4 mmol) and Et_3N (0.73 mL, 5.4 mmol) in ether (30 mL). The reaction mixture was warmed to rt and stirred for 10 h. Then the solution was filtered and the solvent evaporated in vacuum. The residue was dried in vacuum to give the desired product. Yield: 86–92%. Spectral data of **3a**: ^{31}P NMR (121.5 MHz, CD_2Cl_2): δ 141.1; ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.42 (m, 2H), 7.25–7.28 (m, 2H), 7.06–7.20 (m, 6H), 4.33 (dd, *J* = 7.7, 3.6 Hz, 1H), 3.31 (m, 1H), 3.01 (d, *J* = 9.0 Hz, 3H), 2.91 (m, 1H), 1.73 (m, 1H), 1.40 (m, 2H), 0.77 (m, 1H); ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ 144.2, 142.0, 127.3, 126.9, 126.5, 126.3, 126.2, 125.9, 94.1 (d, *J* = 12.4 Hz), 69.8 (d, *J* = 2.5 Hz), 48.2, 45.3 (d, *J* = 32.2 Hz), 28.4, 24.9 (d, *J* = 3.3 Hz). MS (EI), *m/z* (*I*, %): 313 (41) $[M]^+$. Anal. Calcd for $C_{18}H_{20}NO_2P$: C, 69.00; H, 6.43; N, 4.47. Found: C, 69.22; H, 6.68; N, 4.24.
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8. (a) Delapierre, G.; Brunel, J. M.; Constantieux, T.; Buono, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1345–1352; (b) *General procedure for the preparation of ligands* **3u–v**: A solution of **1** (0.759 g, 3 mmol) with $P(NMe_2)_3$ or $P(NEt_2)_3$ (3 mmol) in toluene (10 mL) was heated to reflux for 12 h. After cooling to rt, the solvent was evaporated in vacuum, and the residue was dried in a high vacuum. Yields: 96–98%. The spectral data of **3u**: ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 145.1; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 144.9, 142.8, 127.0, 126.5, 126.1, 125.9, 125.8, 125.5, 91.6 (d, *J* = 12.3 Hz), 69.0, 46.7 (d, *J* = 35.3 Hz), 34.8 (d, *J* = 17.5 Hz), 28.5, 24.3 (d, *J* = 3.4 Hz). HRMS (ESI): Calcd *m/z* 327.161916 ($C_{19}H_{23}N_2OP$+H). Found *m/z* 327.162076.
9. *Crystal data*: (*S*,S_P)-**3g**: $C_{25}H_{26}NO_2P$, $M = 403.44$, monoclinic, space group $P2_1$ (No. 4), $a = 8.5828(12)$, $b = 10.3342(15)$, $c = 13.3894(9)$ Å, $U = 1054.1(2)$ Å^3, $Z = 2$, $\mu = 1.314$ mm^{-1}, $T = 100$ K, 3122 unique data, $R_1 = 0.0420$. CCDC 620477.