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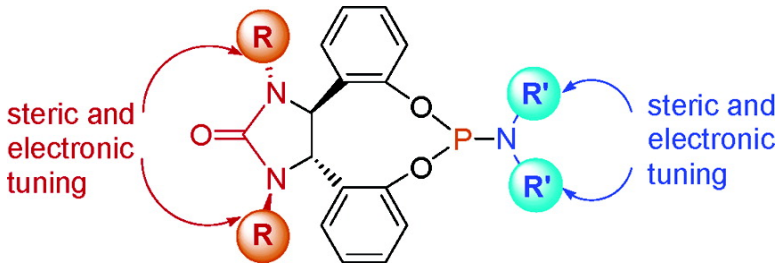
J. Am. Chem. Soc., **2005**, 127 (30), 10488-10489• DOI: 10.1021/ja052749l • Publication Date (Web): 09 July 2005



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Modular Monodentate Phosphoramidite Ligands for Rhodium-Catalyzed Enantioselective Hydrogenation

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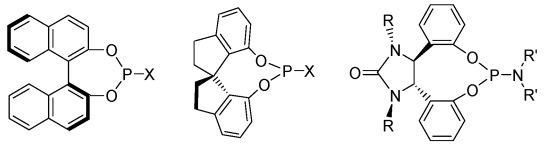
After 30 years neglect, the monodentate phosphorus ligand[1] got its renaissance in asymmetric catalysis at the beginning of this millennium by the pioneering works of Ferringa, de Vries, Reetz, Pringle, and others.[2] Since then, the development of monodentate phosphorus ligands (e.g., **1** and **2**) for asymmetric catalysis has been a research topic of increasing interest due to the facts of their easy preparation, good stability, and excellent performance in the catalysis.[2−5] To achieve the highly efficient and enantioselective catalysis of asymmetric reactions, the tuning of the catalyst to make a perfect match among chiral ligands, metallic ion, as well as substrate and so on, is the key issue, in which the adjustment of the steric and electronic modifications in chiral ligands plays a central role. Therefore, the development of structurally tunable ligands will merit the ligand and catalyst diversity. In the present work, we report our preliminary results on the design, synthesis, and applications of a new class of monodentate phosphoramidite ligands **3** (DpenPhos) on the basis of a modular approach.



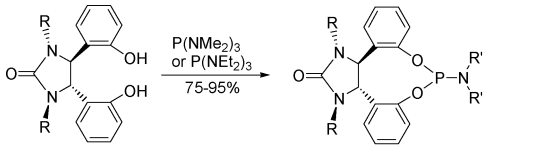
1a X = OR
1b X = alkyl or aryl
1c X = NR_2, MonoPhos

2a X = OR
2b X = NR_2, SpiroPhos

3, DpenPhos

As shown in Scheme 1, the synthesis of ligands **3** was quite simple. The key diphenol intermediates **4a**−**f** were readily prepared from a chiral diamine, (*R*,*R*)-1,2-di(2-dimethoxyphenyl)-1,2-ethylenediamine, via a three-step reaction sequence (see Supporting Information). The monodentate phosphoramidite ligands (*R*,*R*)-**3** were finally obtained by the reaction of (*R*,*R*)-**4a**−**f** with hexamethylphosphorus triamide (HMPT) or hexaethylphosphorus triamide in good yields. These ligands are stable enough in the air to be purified by column chromatography on silica gel without special precaution to water or air.

Scheme 1. Synthesis of Modular Monodentate Ligands **3a**−**h**



4a-f

4a: R = H
4b: R = CH_3
4c: R = Et
4d: R = $PhCH_2$
4e: R = 3,5-$(Me)_2C_6H_3CH_2$
4f: R = 3,5-$(tBu)_2C_6H_3CH_2$

3a-h

3a: R = H, R' = Me
3b: R = Me, R' = Me
3c: R = Et, R' = Me
3d: R = $PhCH_2$, R' = Me
3e: R = 3,5-$(Me)_2C_6H_3CH_2$ R' = Me
3f: R = 3,5-$(tBu)_2C_6H_3CH_2$ R' = Me
3g: R = Bn, R' = Et
3h: R = Et, R' = Et

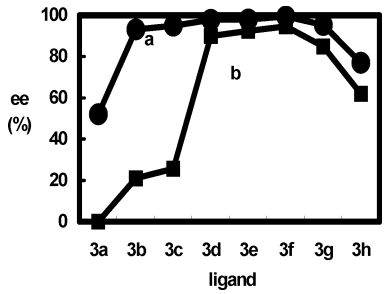


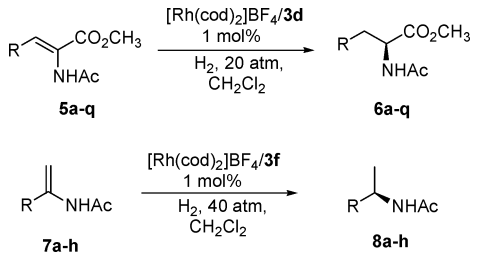
Figure 1. The impacts of R and R′ in monodentate ligands **3a**−**h** on the enantioselectivity of Rh(I)-catalyzed hydrogenations of α-dehydroamino acid derivative **5c** (a) and enamide **7a** (b).

Ligands **3a**−**h** were then tested in the Rh(I)-catalyzed enantioselective hydrogenation of olefin derivatives. The olefin derivatives **5c** and **7a** were taken as the model substrates, respectively. As shown in Figure 1a, the enantioselectivity for the hydrogenation of dehydroamino acid derivative **5c** was dramatically enhanced from 52.0 to 99.4% ee with the change of R from the smallest proton (**3a**) to the 3,5-di-*tert*-butylbenzyl group (**3f**). On the other hand, the increase of the steric hindrance of substituents at the phosphorus atom of the ligands (R′) proved to be unfavorable for the enantioselectivity of the reaction (**3h** vs **3c**). The impact of substituents R in ligands **3** on the enantioselectivity of the hydrogenation of enamide derivative **7a** showed the similar tendency of substituent effect (Figure 1b). All these results clearly indicated that dual steric tuning of both R and R′ groups in the monodentate DpenPhos ligands is critically important for achieving maximum asymmetric induction in Rh(I)-catalyzed hydrogenations. The imidazolidinone backbone in the ligands has provided 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. The further optimization of H_2 pressure (Supporting Information) disclosed that 99.6% ee of **6c** could be achieved with ligand **3d** under 20 atm of H_2. Similarly, the enantioselectivity for the hydrogenation of enamide **7a**, up to 97.6% ee, has been achieved using the Rh(I) complex of ligand **3f**.

Under the optimized reaction conditions, various dehydro-α-amino acid derivatives **5a**−**q** could be hydrogenated with the catalysis of Rh/(*R*,*R*)-**3d** to afford the corresponding α-amino acid derivatives with extremely high enantiomeric excess values (95.9−99.9% ee, Table 1, entries 1−17). Either the alkyl or aryl group situated at the *β*-position of dehydro-α-amino acid derivatives has little impact on the enantioselectivity of the reaction. To demonstrate the efficiency of the catalyst Rh/(*R*,*R*)-**3d**, the hydrogenation of **5a** was also carried out with the reduced catalyst loading (0.1 mol %), affording the corresponding amino acid derivative **6a** in quantitative yield without significant loss of enantioselectivity (entry 18 vs 1). For the hydrogenation of enamide substrates, the catalyst composed of monodentate ligand (*R*,*R*)-**3f** was particularly effective.

10.1021/ja052749l CCC: $30.25

Table 1. Rh(I)-Catalyzed Enantioselective Hydrogenation of Dehydro-α-amino Acid Methyl Esters (**5**) and Acetyl Enamides (**7**)[a]



entry	ligand	R in **5** and **7**	ee (%) (config)[b]
1	**3d**	H (**5a**)	99.3 (*S*)
2	**3d**	CH_3 (**5b**)	98.4 (*S*)
3	**3d**	C_6H_5 (**5c**)	99.6 (*S*)
4	**3d**	4-BrC_6H_4 (**5d**)	99.7 (*S*)
5	**3d**	3-BrC_6H_4 (**5e**)	99.0 (*S*)
6	**3d**	2-BrC_6H_4 (**5f**)	98.2 (*S*)
7	**3d**	4-ClC_6H_4 (**5g**)	99.0 (*S*)
8	**3d**	3-ClC_6H_4 (**5h**)	98.6 (*S*)
9	**3d**	2-ClC_6H_4 (**5i**)	98.2 (*S*)
10	**3d**	4-$CH_3OC_6H_4$ (**5j**)	97.2 (*S*)
11	**3d**	3-$CH_3OC_6H_4$ (**5k**)	98.4 (*S*)
12	**3d**	3-FC_6H_4 (**5l**)	99.7 (*S*)
13	**3d**	4-$O_2NC_6H_4$ (**5m**)	99.1 (*S*)
14	**3d**	2-$O_2NC_6H_4$ (**5n**)	>99.9 (*S*)
15	**3d**	3,4-$(CH_3O)_2C_6H_3$ (**5o**)	99.1 (*S*)
16	**3d**	3-AcO-4-$CH_3OC_6H_3$ (**5p**)	99.1 (*S*)
17	**3d**	2-naphthyl (**5q**)	96.9 (*S*)
18[c]	**3d**	H (**5a**)	98.8 (*S*)
19	**3f**	C_6H_5 (**7a**)	97.6 (*S*)
20	**3f**	4-ClC_6H_4 (**7b**)	99.8 (*S*)
21	**3f**	4-$CH_3OC_6H_4$ (**7c**)	97.4 (*S*)
22	**3f**	4-$CH_3C_6H_4$ (**7d**)	99.3 (*S*)
23	**3f**	4-FC_6H_4 (**7e**)	98.2 (*S*)
24	**3f**	4-BrC_6H_4 (**7f**)	99.7 (*S*)
25	**3f**	3-BrC_6H_4 (**7g**)	96.1 (*S*)
26	**3f**	2-naphthyl (**7h**)	98.4 (*S*)

[a] All of the reactions were carried out at room temperature at a substrate concentration of 0.2 M for 2 h (substrate/catalyst = 100:1); the conversion of substrate was determined by ^{1}H NMR. [b] Determined by chiral HPLC or GC; absolute configurations of the products were assigned by comparison of their optical rotation with literature data. [c] With 0.1 mol % of catalyst loading.

Under the optimized conditions, a variety of α-arylenamides has been hydrogenated to afford the corresponding α-arylamine derivatives quantitatively with excellent enantioselectivity (96.0−99.6% ee, Table 2, entries 19−26). Moreover, both the catalysts Rh/(*R*,*R*)-**3d** and Rh/(*R*,*R*)-**3f** were also effective for the hydrogenation of dimethyl itaconate to give corresponding hydrogenated product with 97.2−99% ee in quantitative yield (Supporting Information).

A question is posed regarding how the backbone substituents affect the enantioselectivities of the reactions. A Rh(I) complex of ligand **3e** has been isolated and characterized by X-ray crystallography to have the formula of [Rh{(*R*,*R*)-**3e**}$_2$(cod)]OH (Figure 2) (see Supporting Information). The complex contains two phosphoramidite ligands **3e** and adopts the coordination pattern similar to those reported by Zhou[5b] and Reetz[3a] recently. The hydrogenation of substrate **5c** using isolated [Rh{(*R*,*R*)-**3e**}$_2$(cod)]-OH complex afforded **6c** in 99.1% ee, which is essentially the same with that attained using the corresponding in situ prepared catalyst. In the structure of **3e**-bonded Rh(I) complex, all four phenyl rings of the ligand locate at four different quadrants, respectively, and point to the opposite direction of protruding carbonyl group at the imidazolidinone backbone. The chirality of nitrogen atoms at the backbone is thus fixed as *S* configuration with complete diastereoselectivity. Although the reason for the formation of such

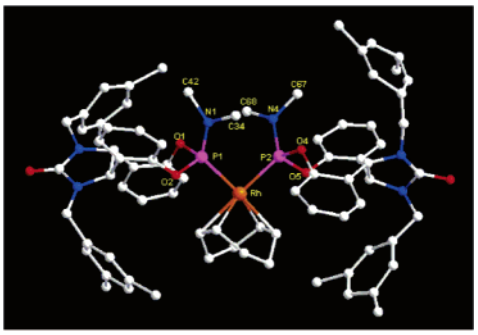


Figure 2. Structure of the cation of [Rh{(*R*,*R*)-**3e**}$_2$(cod)]$^+$[OH]$^-$.

structural feature is not clear, the orientation of benzyl groups in the Rh(I) complex should have some impact on the enantiodiscrimination of the catalytic center. This observation might provide a rationale for the increase in enantioselectivity of hydrogenations, as shown in Figure 1.

In conclusion, a new class of monodentate phosphoramidite ligands (DpenPhos) has been developed based on a modular concept for Rh(I)-catalyzed asymmetric hydrogenations of a variety of olefin derivatives, affording the corresponding optically active compounds in excellent yields and enantioselectivities. The results achieved in this work will stimulate future studies to explore the new applications of these modular ligands in other transition-metal-catalyzed asymmetric reactions,[6,7] including generation of a modular combinatorial chiral catalyst library using mixtures of ligands.[3,8]

Acknowledgment. Financial support from the NNSFC, CAS, and the Major Basic Research Development Program of China (Grant No. G2000077506) and the Commission of Science and Technology, Shanghai Municipality, is gratefully acknowledged.

Supporting Information Available: Synthesis of chiral ligands and chiral HPLC or CG analysis of the products (37 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA052749L