Asymmetric Catalysis

DOI: 10.1002/ange.200601501

Synthesis of Triphosphorous Bidentate Phosphine–Phosphoramidite Ligands: Application in the Highly Enantioselective Hydrogenation of *ortho*-Substituted Aryl Enamides**

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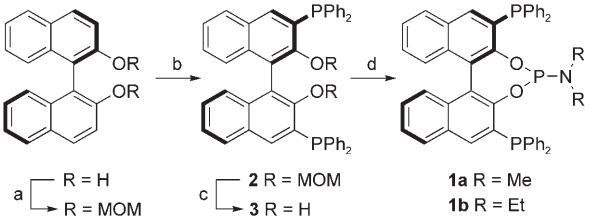
The development of new effective chiral ligands is fundamental to asymmetric hydrogenation. Over recent decades, many excellent bisphosphine ligands have been reported for highly enantioselective hydrogenation reactions.[1] However, the modification of a desired structural motif of most bidentate ligands is impeded by multistep synthesis. Recently, this situation has been partially remedied by the emerging monodentate ligands,[2] including phosphoramidites,[3] phosphonites,[4] and phosphites,[5] which have modular structures and can be prepared in one step from chiral binaphthol (BINOL) or its analogues. As part of our continuous interest in exploring new ligands for hydrogenation, we wonder whether the design of new bidentate ligands can benefit from the advantages of modular monodentate ligands for further structural optimization. From a practical viewpoint, ligands should be prepared in a few steps from readily available starting materials. Although various modified BINOL ligands have been utilized for asymmetric catalysis,[6] few efforts have been made to attach the phosphorous group directly at the 3,3′-positions.[7] Inspired by the success of many hybrid C_1-symmetric chelating ligands,[8] we herein report the synthesis and application of a new phosphine–phosphoramidite ligand **1**. To our knowledge, this pseudo-C_2-symmetric triphosphorous bidentate ligand is the first of its class and represents a conceptually new approach to ligand design. Importantly, unprecedented enantioselectivities have been achieved with this new ligand for the hydrogenation of *ortho*-substituted aryl enamides and a 1-naphthylenamide, thereby solving a long-standing problem in the hydrogenation of enamides.

Ligand **1** was synthesized in four steps from (*R*)-BINOL (Scheme 1). Protection of the hydroxy groups of BINOL was



Scheme 1. Ligand synthesis. Reagents and conditions: a) 1. NaH (5 equiv), THF, 0°C; 2. CH_3OCH_2Cl (2.4 equiv), 0°C (98%); b) 1. *n*BuLi, Et_2O/THF, RT; 2. $ClPPh_2$, 0°C (70%); c) HCl (cat.), MeOH, 60°C (79%); d) HMPT or HEPT, toluene, 110°C (88% for **1a**, 80% for **1b**).

followed by double lithiation and subsequent attachment of two identical phosphorous groups at the 3,3′-positions.[9] After removal of the methoxy methyl (MOM) groups of **2** in HCl/MeOH, the desired product **1** was prepared by heating **3** with hexamethylphosphorous triamide (HMPT) or hexaethylphosphorous triamide (HEPT) in toluene at 110°C. As the whole synthesis features a sequential assembly of two types of phosphorous donors onto the chiral BINOL backbone, structural tuning can be achieved by varying the starting R_2PCl reagent and the substitution mode at the central phosphorous donor, thus allowing for the efficient expansion of ligand derivatives. We investigated the effectiveness of the representative member **1** in hydrogenation reactions to demonstrate the potential of this new class of ligand. Thus a [Rh/**1a**] complex was prepared by treating **1a** with $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene) in 1:1 molar ratio. As evidenced by NMR spectroscopic analysis, among the three phosphorous donors of **1**, only two form an effective chelation with the Rh center and generate a well-defined complex, thus leaving an uncoordinated free phosphine group.[10] The coordination environment of the [Rh/**1a**] complex based on MM2 calculations is illustrated in Figure 1. Similar to C_2-symmetric bisphosphines, two nonadjacent quadrants (black and gray in Figure 1) are blocked by the equatorial phenyl and the dimethylamino groups, thus creating an effective chiral environment around the transition-metal center.

The catalytic performance of **1** was first tested in the Rh-catalyzed hydrogenation of several standard α-aryl enamides. Initial studies on the [Rh/**1a**] system using the benchmark substrate **4a** showed a strong solvent effect reminiscent of the monodentate ligand systems[3a,c] (Table 1): non-protic solvents, such as CH_2Cl_2 and toluene, give excellent results

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[**] This work was supported by the National Institutes of Health (NIH-GM58832).

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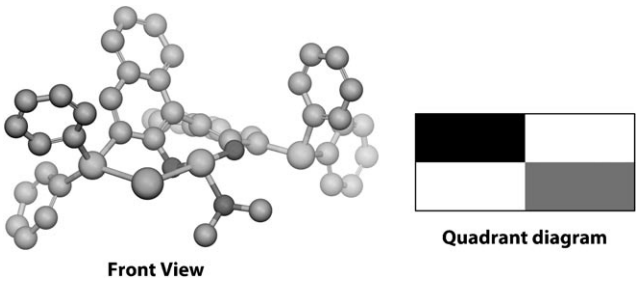
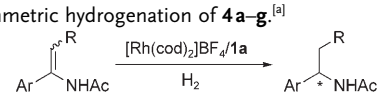


Figure 1. MM2 calculations of the [Rh/**1a**] complex from the CAChe program.

Table 1: Asymmetric hydrogenation of **4a**–**g**.[a]



Entry	Substrate	Ar	R	P_{H_2} [bar]	Solvent	*ee* [%][b] (config.)
1	**4a**	Ph	H	1	CH_2Cl_2	99 (*R*)
2	**4a**	Ph	H	1	toluene	99 (*R*)
3	**4a**	Ph	H	1	THF	97 (*R*)
4	**4a**	Ph	H	1	EtOAc	98 (*R*)
5	**4a**	Ph	H	1	acetone	94 (*R*)
6	**4a**	Ph	H	1	MeOH	91 (*R*)
7	**4a**	Ph	H	5	CH_2Cl_2	98 (*R*)
8	**4a**	Ph	H	10	CH_2Cl_2	97 (*R*)
9[c]	**4a**	Ph	H	1	CH_2Cl_2	98 (*R*)
10	**4b**	3-Me-C_6H_4	H	1	CH_2Cl_2	99 (*R*)
11	**4c**	4-CF_3-C_6H_4	H	1	CH_2Cl_2	99 (*R*)
12	**4d**	4-CF_3-C_6H_4	Me	5	CH_2Cl_2	99 (*R*)
13	**4e**	4-MeO-C_6H_4	Me	5	CH_2Cl_2	96 (*R*)
14	**4f**	2-naphthyl	H	1	CH_2Cl_2	98 (*R*)
15	**4g**	2-naphthyl	Me	5	CH_2Cl_2	97.0 (*R*)

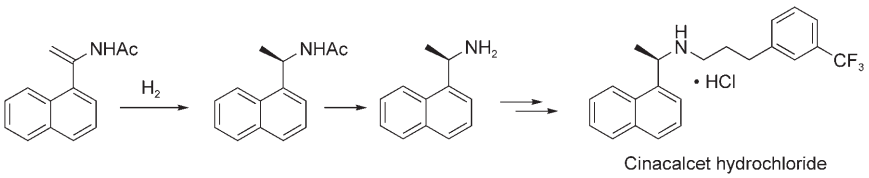
[a] Unless mentioned otherwise, all reactions were carried out with a substrate/catalyst (S/C) ratio of 100:1 at RT for 24 h. In all cases, 100% conversion was achieved. [b] Determined by chiral GC or HPLC. The absolute configuration was assigned by comparison of the observed optical rotation with reported data. [c] S/C = 1000.

(entries 1–2); those with increased polarity tend to lower enantioselectivities (entries 3–5); whereas a further decrease in the enantiomeric excess occurs in the protic solvent MeOH (entry 6). Increasing hydrogen pressure led to a minor deterioration in enantiomeric excess (entries 1, 7, and 8). Compared with monophos, the diphenylphosphine group in **1a** plays an important role in achieving high enantioselectivities as well as high reactivities (entry 9; turnover number (TON) = 1000). Under the established reaction conditions (room temperature, CH_2Cl_2, 1 or 5 bar of H_2), several other enamides were reduced smoothly with high *ee* values were obtained (entries 10–15).

Encouraged by our initial success, we then focused on the hydrogenation of challenging *ortho*-substituted aryl enamides and a 1-naphthylenamide, which are useful synthetic intermediates for pharmaceutical products. For example, the asymmetric hydrogenation of 1-naphthylenamide **4n** leads to (*R*)-1-(1-naphthyl)ethylamine, a key precursor to Cinacalcet hydrochloride for the treatment of hyperparathyroidism and hypercalcemia (Scheme 2).[11] Compared with the hydrogenation of most unhindered aryl enamides, limited progress has been made for those substrates with *ortho* functionalities.[12] Mechanistic studies by Imamoto and co-workers suggested a simultaneous execution of two competitive hydrid insertion pathways, which would account for the low *ee* values observed in the hydrogenation of 2-methoxy- and 2-chloro-substituted phenylenamides with 1,2-bis(alkylmethylphosphino)ethanes (BisP*) and 1,2-bis(alkylmethylphosphino)methanes (miniphos).[12b] To address this challenging problem, we screened commercially available (1*S*,1*S*′,2*R*,2*R*′)-tangphos (L1), (*R*,*R*)-Et-duphos (L2), and the new ligand **1** under the same reaction conditions. As revealed in the screening process, L1 and L2 failed to show high selectivities for most *ortho*-substituted aryl enamides and a 1-naphthylenamide (Table 2). In two extreme cases, a reversal of enantioselectivity was observed with the use of L1 (entries 1 and 7). To our delight, the new ligand **1a**,**b** gave excellent *ee* values. Moreover, further improvement in the hydrogenation of **4h** and **4n** can be achieved by lowering the temperature (0 °C), varying the structure (namely, the use of **1b** instead), or choosing a different solvent (entry 7).

To put our results in another context, we have listed the highest *ee* values reported by other groups using several ligands under a variety of reaction conditions (Table 2). In each case, our results are comparable with or superior to the best results reported so far.[12] These comparative results confirm that the new ligand **1**, which bears a novel combination of phosphine and phosphoramidite groups, is unique in the asymmetric hydrogenation of hindered enamides. Further exploration of the substrate scope is currently ongoing.

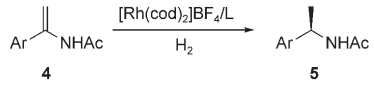
To evaluate the potential application of this system in industry, we also studied the hydrogenation of **4n** with [Rh(cod)**1a**]BF_4 at a decreased catalyst loading (TON = 1000) in TFE. It was found that 93% of **4n** was converted into **5n** with 88% *ee* under 80 bar of H_2 within 24 h; furthermore, **5n** was isolated by flash chromatography in 90% yield.[13]



Scheme 2. Asymmetric hydrogenation route to Cinacalcet hydrochloride.

In conclusion, new triphosphorous bidentate phosphine–phosphoramidite ligands have been developed and applied to the highly enantioselective hydrogenation of α-aryl enamides, including *ortho*-substituted aryl enamides and a 1-naphthylenamide. The modular structure and straightforward synthesis of the ligands allows for further systematic modification of the

Table 2: Ligand screening for the asymmetric hydrogenation of *ortho*-substituted aryl enamides and 1-naphthylenamides **4h–n**.[a]



Entry	Substrate	Ar	*ee* [%] (config.)[b] L1[c]	L2[c]	**1a**[c]	**1b**[c]	The best reported *ee* [%]
1	**4h**	2-Me-C_6H_4	51.8 (*S*)	52.6 (*R*)	84.0 (*R*) 91.0 (*R*)[e]	87.2 (*R*)	74.8[12a]
2	**4i**	2-MeO-C_6H_4	54.4 (*R*)	51.4 (*R*)	99.4 (*R*)	99.0 (*R*)	83.1[12d]
3	**4j**	2-F-C_6H_4	95.8 (*R*)	80.8 (*R*)	99.0 (*R*)	97.0 (*R*)	95.7[12a]
4	**4k**	2-Cl-C_6H_4	9.4 (*R*)	55.6 (*R*)	99.6 (*R*)	98.2 (*R*)	85[12j]
5[d]	**4l**	2-NO_2-C_6H_4	88.0 (−)	85.8 (−)	98.2 (−)	98.2 (−)	–
6[d]	**4m**	2-CF_3-C_6H_4	68.8 (+)	88.4 (+)	93.8 (+)	94.2 (+)	–
7	**4n**	1-naphthyl	74.8 (*S*)	51.8 (*R*)	91.0 (*R*) 92.4 (*R*)[f]	92.8 (*R*) 93.8 (*R*)[g]	91.2[12f]

[a] Unless mentioned otherwise, all reactions were carried out with an S/C ratio of 100:1 in CH_2Cl_2 under 5 bar hydrogen pressure at RT for 24 h. In all cases, 100% conversion was achieved. [b] Determined by chiral GC. The absolute configuration was assigned by comparison of observed optical rotation with literature data. [c] [Rh(nbd)L1]SbF_6 (nbd = 2,5-norbornadiene) , [Rh(cod)L2]BF_4, Rh[(cod)**1a**]BF_4, and Rh[(cod)**1b**]BF_4 were used. [d] Absolution configurations were not determined. [e] $T = 0\,^\circ C$, $P_{H_2} = 25$ bar. [f] $T = 0\,^\circ C$, $P_{H_2} = 50$ bar. [g] 2,2,2-Trifluoroethanol (TFE) was used as solvent.

chiral biaryl backbone and the two types of phosphorous donors. Synthesis and application of analogous triphosphorous bidentate ligands will be reported in due course.

Experimental Section

General procedure for the hydrogenation: A stock solution of [Rh/**1a**] or [Rh/**1b**] complex (2×10^{-3} mol L^{-1}) was prepared by stirring $[Rh(cod)_2]BF_4$ and **1a** or **1b** at a 1:1.1 molar ratio in CH_2Cl_2 at room temperature for 1 h in a nitrogen-filled glovebox. The required amount of catalyst solution (0.5 mL, 0.001 mmol) was transferred by syringe into the vial charged with substrate (0.1 mmol), and the solvent (2.5 mL) was added. All the vials were placed together in a steel autoclave into which hydrogen gas was charged at the desired pressure. After stirring at room temperature for 24 h, the hydrogen was released carefully and the solution was concentrated and subjected to a short column of silica gel to remove the metal complex. The purified solution was analyzed by chiral GC or HPLC to determine the *ee* value.

Received: April 15, 2006
Published online: August 7, 2006

Keywords: asymmetric catalysis · enamides · enantioselectivity · hydrogenation · rhodium

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[9] If only one phosphine group is attached to the *ortho* position of the BINOL unit, two diastereomeric phosphine–phosphoramidite ligands will be obtained as a result of the creation of a *P*-stereogenic center; this principle was applied to the preparation of a series of single *ortho*-substituted monodentate ligands, see: M. T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem.* **2005**, *117*, 416; *Angew. Chem. Int. Ed.* **2005**, *44*, 412.

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[13] A small amount of **4n** (7% calculated from ^{1}H NMR spectroscopic analysis) was decomposed into 1-acetonaphthone during hydrogenation.

