Asymmetric Hydrogenation

New P,N Ligands for Asymmetric Ir-Catalyzed Reactions**

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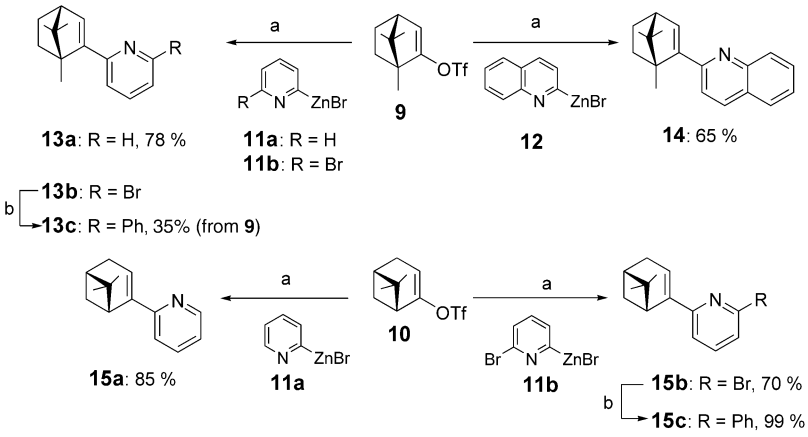
In memory of Alain Louis Rodriguez

The preparation of new ligands for asymmetric metal catalysis has led in recent years to the discovery of several new classes of chiral ligands.[1] Recently, we reported *t*BuOK-catalyzed addition reactions of nucleophiles (carbonyl derivatives and phosphanes) to a variety of functionalized alkenes.[2] Herein, we report the use of this method for the preparation of the new chiral P,N ligands[3] **1**–**6** (see Scheme 2) from readily available chiral building blocks such as D-(+)-camphor (**7**) and (*R*)-(+)-nopinone (**8**). We show that these ligands can be used for highly enantioselective Ir-catalyzed hydrogenations.

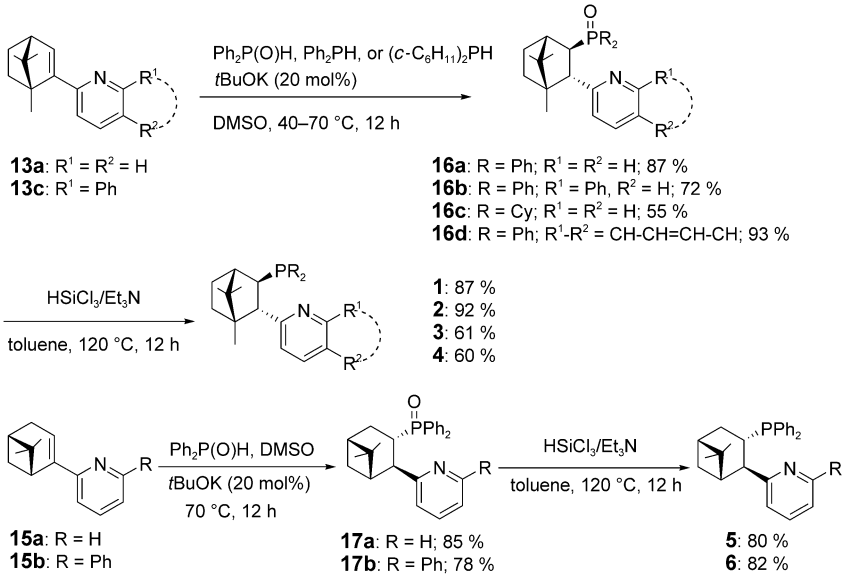
The known alkenyl triflate[4] **9** underwent smooth Negishi cross-coupling reactions[5] to afford the desired 2-alkenyl pyridines **13a**–**c** in 35–78% yield[6] and the 2-alkenyl quinoline **14** in 65% yield. Similarly, the alkenyl triflate **10** was converted into the 2-alkenyl pyridines **15a**–**c** in 69–85% yield (Scheme 1).

The treatment of these unsaturated pyridines with diphenylphosphane (Ph_2PH), dicyclohexylphosphane ($(c\text{-}C_6H_{11})_2PH$), or diphenylphosphane oxide ($Ph_2P(O)H$) in dimethyl sulfoxide (DMSO) or *N*-methylpyrrolidinone (NMP) in the presence of a catalytic amount of *t*BuOK (20 mol%) provided the phosphane oxides **16a**–**d** and **17a**–**b** in 55–93% yield.[2c] The phosphane oxides were reduced with $HSiCl_3/Et_3N$ in toluene[7] to give the desired P,N ligands **1**–**6** in 60–92% yield (Scheme 2). The relative stereochemistry of the P,N ligands was established by NOESY NMR experiments and by X-ray crystal-structure analysis (see Supporting Information).[8]

Although a number of terpene-derived ligands have been prepared and used in asymmetric catalysis,[9] these new modular ligands, in which a broad range of pyridyl and related heterocycles can be incorporated, display particularly high enantioselectivities in asymmetric iridium-catalyzed



Scheme 1. The synthesis of 2-alkenylpyridines **13**–**15**: a) $[Pd(dba)_2]$ (2 mol%), dppf (2 mol%), alkenyl triflate **9** or **10**, THF, LiCl, reflux, overnight; b) $[Pd(PPh_3)_4]$ (5 mol%), $PhB(OH)_2$, Na_2CO_3, toluene, MeOH, H_2O, 85 °C, overnight. dba = dibenzylideneacetone, dppf = 1,1′-bis-(diphenylphosphanyl)ferrocene.



Scheme 2. Preparation of the P,N ligands **1**–**6**.

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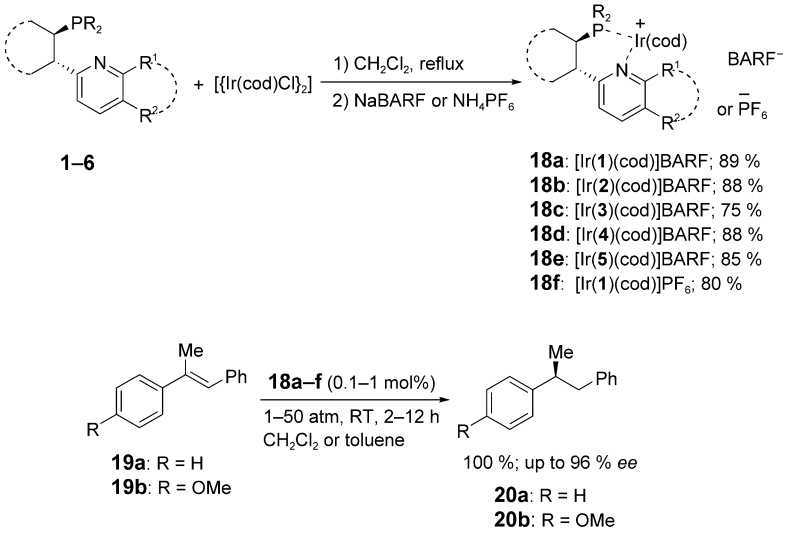
hydrogenations.[10,11] Thus, the P,N ligands **1–6** were heated with $[\{Ir(cod)Cl\}_2]$ in CH_2Cl_2 (40 °C, 1 h), and the reaction was quenched with sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (NaBARF) or with NH_4PF_6 in water to give the corresponding iridium complexes **18a–f** in 75–89% yield, according to the procedure of Pfaltz and co-workers (Scheme 3).[11]



Scheme 3. Preparation of the chiral Ir complexes **18a–f** and their use in the asymmetric hydrogenation of **19a** and **19b**. cod = 1,5-cyclooctadiene.

The Ir-catalyzed hydrogenation of (*E*)-1,2-diphenylpropene (**19a**) and 2-(4-methoxyphenyl)-1-phenyl-1-propene (**19b**) was performed at room temperature in the presence of complexes **18a–e** (0.1–1 mol%; Table 1). A slower reaction was observed in CH_2Cl_2, and excellent conversion was observed in toluene (see Table 1, entries 1 and 2). Remarkably, the use of complex **18d**, which contains a quinolyl group, led to high conversions and high enantioselectivities (Table 1, entries 8–13). As a result of the high activity of this catalyst, the reaction can be carried out at 1 bar of hydrogen (Table 1, entries 10, 11, and 12). Similar results were obtained with **19b** (Table 1, entries 15–18). Catalyst **18d** was the most active of those studied (see Table 1, entries 15 and 16). Other substrates, such as ethyl 3-phenylbut-2-enoate (**21**), 2-methyl-3-phenylallyl alcohol (**22**), and 2-methyl-3-phenylallyl acetate (**23**), were also hydrogenated in the presence of catalyst **18d** (1 mol%; H_2 (50 bar), room temperature, 12 h), and the desired reduced products were obtained with moderate to good enantioselectivities (58–80% *ee*; Scheme 4).

The hydrogenation of unsaturated enamides such as **24** to amino acid derivatives such as **25** is of special interest. This enantioselective hydrogenation has been studied extensively in the presence of Rh catalysts.[1] To our knowledge, no enantioselective Ir-catalyzed hydrogenation of this type has been reported.

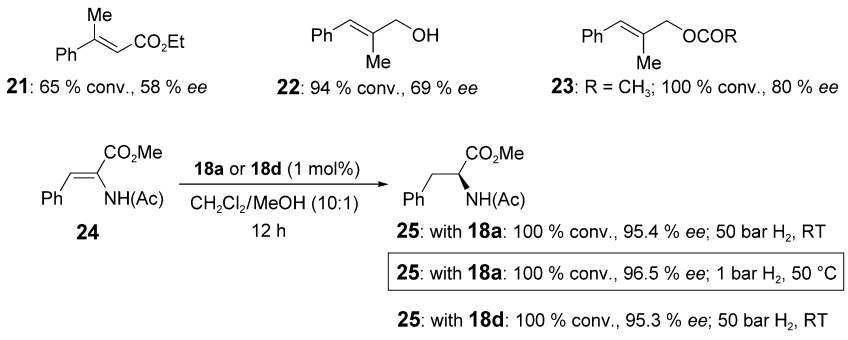
Table 1: Iridium-catalyzed enantioselective hydrogenation of **19a** and **19b** in toluene at 25 °C.

Entry	**18** (mol%)	**19**	*P* [bar][a]	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	**a** (1.0)	**a**	50	12	44	93.5[d]
2	**a** (1.0)	**a**	50	12	100	95.0
3	**a** (0.5)	**a**	50	12	100	95.0
4	**a** (1.0)	**a**	1	5	91	95.0
5	**a** (0.5)	**a**	1	2	90	95.0
6	**b** (1.0)	**a**	50	12	6	–
7	**c** (1.0)	**a**	1	12	80	80.0
8	**d** (1.0)	**a**	50	12	100	95.0
9	**d** (1.0)	**a**	50	2	100	94.0
10	**d** (1.0)	**a**	1	5	100	95.0
11	**d** (0.5)	**a**	1	2	96	96.0
12	**d** (0.1)	**a**	1	12	1	–
13	**d** (0.1)	**a**	50	12	92	95.0
14	**e** (1.0)	**a**	50	2	26	80.0[e]
15	**a** (1.0)	**b**	50	2	87	91.0
16	**d** (1.0)	**b**	50	2	100	94.7
17	**d** (1.0)	**b**	1	2	76	94.0
18	**d** (1.0)	**b**	50	2	75	95.2[d]

[a] Reaction pressure. [b] Conversion. [c] The enantiomeric excess was determined by HPLC on a chiral phase (Daicel Chiracel OJ column). The products have the *S* configuration unless otherwise indicated. [d] This reaction was performed in CH_2Cl_2. [e] *R* configuration.

We found that the hydrogenation of **24** under our standard conditions (H_2 (50 bar), room temperature, 12 h) in CH_2Cl_2/MeOH (10:1) in the presence of the chiral Ir catalysts **18a** and **18d** provided the phenylalanine derivative **25** in 100% conversion and with 95.4% *ee* and 95.3% *ee*, respectively. Moreover, when the reaction was carried out the higher temperature of 50 °C and at just 1 bar of H_2, 100% conversion and an excellent 96.5% *ee* were observed (Scheme 4). These results show the potential of Ir complexes for new applications in the asymmetric synthesis of amino acids.

In summary, we have prepared a new type of P,N ligand, which facilitates the Ir-catalyzed enantioselective hydrogenation of unactivated stilbene derivatives and dehydroamino acid derivatives. Because of the modular synthesis[12] of these ligands, their stereochemical and electronic properties can be tuned to optimize the enantioselectivity of a given asymmetric reaction or for a particular substrate. Further applications in new asymmetric reactions are currently underway in our laboratories.[13]



Scheme 4. Ir-catalyzed hydrogenation of unsaturated substrates with catalysts **18a** and **18d**. conv. = conversion.

Experimental Section

Preparation of (*S*)-**25**: An autoclave was charged with **18a** (4.7 mg, 3.0 μmol, 1 mol%), **24** (65 mg, 0.3 mmol), CH_2Cl_2 (3 mL), and MeOH (0.3 mL). The autoclave was then sealed and pressurized to 1 bar of H_2, and the reaction mixture was stirred at 50 °C for 2 h. The CH_2Cl_2 and MeOH were then removed and the crude product was passed through a short column of silica gel with diethyl ether as eluent. After evaporation of the solvent, (*S*)-**25** was obtained in quantitative yield and with 96.5% *ee*. The *ee* value was determined by GC on a chiral phase (Chiralsil L-Val); 140 °C: $t_r = 10.5$ (*R*), 11.5 min (*S*).

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[8] CCDC 209753–209755 (borane complexes of **1, 16a**, and **17b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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