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Enantioselective reduction of acetophenone with PMHS and tin(II) complexes of chiral pyridine ligands

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Abstract

A number of tin(II) complexes, prepared in situ from tin(II) triflate and pyridine derivatives (2,2′:6′,2″-terpyridine, 1,10-phenanthroline, 2,2′-bipyridine, dipyridylmethane, 2-(thiophen-2-yl)pyridine and 2-(2-diphenylphosphinophenyl)-5,6,7,8-tetrahydroquinoline), have been used as chiral catalysts for the reduction of acetophenone in the presence of polymethylhydrosiloxane (PMHS). Yields up to 82% and enantioselectivities up to 19% have been obtained.

Keywords: Polymethylhydrosiloxane (PMHS); Tin; Reduction; Catalysis; Enantioselectivity

1. Introduction

In the last years, chiral ligands with nitrogen donors and in particular those in which the N atom is included in a pyridine ring (such as 2,2′-bipyridines, phenanthrolines, 2,2′:6′,2″-terpyridines, etc.) are received a great deal of attention because of their utility in asymmetric catalysis [1–4]. Despite this, the value of these ligands in various catalytic processes is yet to be explored.

Lawrence et al. have recently reported that a mixture of polymethylhydrosiloxane (PMHS) and pyridine/tin(II) triflate in methanol effects the efficient reduction of acetophenone. The same authors have also found that 2,6-bis(4,5-dihydrooxazol-2-yl)pyridine (pybox) is an excellent catalyst in combination with tin(II) triflate and PMHS for the reduction of ketones and that the use of enantiomerically pure pybox ligands leads to moderate enantioselectivities (up 58% ee) [5]. The importance of PMHS as an attractive reducing reagent in organic synthesis has been recently highlighted [6].

Continuing our work on the synthesis and application of chiral pyridine derivatives as ligands for metal complexes in enantioselective catalysis [7], we decided to investigate chiral pyridine derivatives and tin(II) triflate as catalysts in the asymmetric reduction of ketones in the presence of PMHS. We now report the results obtained in the catalytic asymmetric reduction of acetophenone by 12 chiral pyridine derivatives.

2. Results and discussion

The 12 ligands were prepared according to the reported procedures and their configurations are illustrated in Scheme 1. They are three 2,2′:6′,2″-terpyridines (**1**–**3**), five phenanthrolines (**4**–**8**), one 2,2′-bipyridine (**9**), dipyridylmethane (**10**), 2-(thiophen-2-yl)pyridine (**11**) and 2-(2-diphenylphosphinophenyl)-5,6,7,8-tetrahydroquinoline (**12**). Each type of ligands bears as common substituent the dimethylnorpinanyl group, derived from (−)-β-pinene, fused in the 2,3-positions of the pyridine framework.

The reaction conditions selected to carry out the catalytic reduction were those used by Lawrence for pyridine and pybox [5]. Tin(II) catalysts where prepared in situ from tin(II) triflate and the ligands, using a 1/1 molar ratio of tin to lig-

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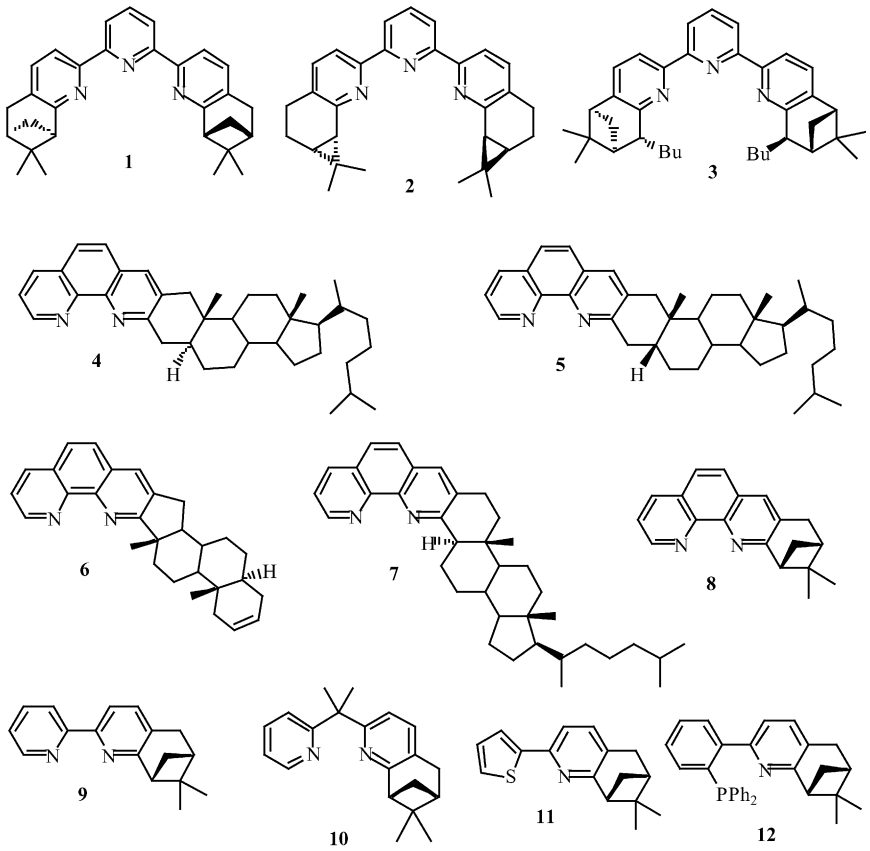


Scheme 1.

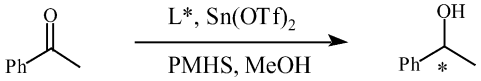
and. These catalysts (5 mol%) were then treated with PMHS (200 mol%) and acetophenone which was used as the model for the evaluation of the efficiency of the examined ligands. To compare the results among the ligands the reactions were carried out for 24 h at room temperature (Scheme 2).

At the outset, we addressed our attention to 2,2′:6′,2″-terpyridines since their framework is strictly related to that of pybox. Disappointing results were obtained with the C_2-symmetric terpyridines (**1**–**3**), concerning both conversions (36–60%) and yields (32–59%). Just like to pybox ligands, conversions and yields decrease as the substituent on the C8 of the tetrahydroquinoline of **1**–**3** become bulkier (Table 1, entries 1–3).

1,10-Phenanthrolines (**4**–**6**, **8**) showed a fairly good catalytic activity (71–79% conversions, 50–79% yields) being the sole exception in this class of ligands, the phenanthroline (**7**) which afforded low conversion (42%) and yield (27%) (entry 7).

Similar levels of conversions (72–75%) and yields (69–71%) were obtained with 2,2′-bipyridine (**9**) and dipyridylmethane (**10**) which differ from the presence of an isopropylidene backbone between two pyridine rings, indicating that in this case the variation of the ligand bite-angle [8] is not an important factor to optimize the catalytic process.

The 2-(thiophen-2-yl)pyridine (**11**) was the worse ligand (entry 11), whereas the 2-(2-diphenylphosphinophenyl)-



Scheme 2.

Table 1
Asymmetric reduction of acetophenone catalyzed by Sn(II)/L* complexes with PMHS[a] (Scheme 2)

Entry	Ligand	Conversion[b]	Yield (%)[c]	ee (%)[d]	Configuration
1	**1**	60	59	8	*R*
2	**2**	41	41	19	*S*
3	**3**	36	32	6	*R*
4	**4**	77	54	6	*R*
5	**5**	71	50	3	*R*
6	**6**	78	59	2	*R*
7	**7**	42	27	3	*R*
8	**8**	79	79	4	*R*
9	**9**	72	71	7	*R*
10	**10**	75	69	6	*R*
11	**11**	32	29	2	*R*
12	**12**	75	82	2	*R*

[a] The reaction was carried out by generating the catalyst in situ by reaction of the ligand (5 mol%) and $Sn(OTf)_2$ (5 mol%) for 1 h. Then acetophenone (1.0 mmol) and PMHS (200 mol%) were added and the mixture was stirred at room temperature for 24 h.
[b] Based on recovered starting material.
[c] Isolated yields.
[d] Determined by GC on a chiral column.

5,6,7,8-tetrahydroquinoline (**12**) was the better one (entry 12) among the examined pyridine derivatives.

All ligands afforded low enantioselectivities (2–19% ee) with the best result being obtained with ligand **2** (19% ee, entry 2).

In conclusion, we have explored 12 chiral ligands with pyridine sp^2-nitrogen donators in the tin(II)-mediated reduction of acetophenone in the presence of PMHS. The obtained results point out that terpyridines are poorly suitable ligands, whereas bipyridines, dipyridines and phenanthrolines, showing moderate catalytic activity, seem to deserve attention for their possible application in this type of reduction. Interestingly, the phosphino-pyridine (**12**) has provided a good yield of 1-phenylethanol indicating that the use of this class of P,N-ligands merits a more deeper investigation. We are currently investigating further applications of these ligands to asymmetric synthesis.

3. Experimental

3.1. General methods

Gas chromatographic analyses were performed with a HP 5900 chromatograph using He (60 kPa) as the carrier gas. Tin(II) triflate and polymethylhydrosiloxane (PMHS) were purchased from Aldrich. Methanol was purified by distillation and stored under 4A molecular sieves.

The pyridine ligands (**1**–**12**) were prepared according to reported procedures: (6*S*,8*S*)-2,6-bis(7,7-dimethyl-5,6,7,8-tetrahydro-6,8-methanoquinolin-2-yl)pyridine (**1**) [9], (7*R*,8*S*)-2,6-bis(9,9-dimethyl-5,6,7,8-tetrahydro-7,8-methanoquinolin-2-yl)pyridine (**2**) [9], (5*S*,7*S*,8*R*)-2,6-bis(6,6-dimethyl-8-butyl-5,6,7,8-tetrahydro-5,7-methanoquinolin-2-yl)pyridine (**3**) [10], 5α-cholest-2-eno[3,2-*b*]-1,10-phenanthroline (**4**) [11], 5β-cholest-2-eno[2,3-*b*]-1,10-phenanthroline (**5**) [11], 5α-androsta-2,16-dieno[17,16-*b*]-1,10-phenanthroline (**6**) [11], 5α-cholest-3-eno[4,3-*b*]-1,10-phenanthroline (**7**) [12], (1*R*,3*R*)-(+)-1,3-methano-2,2-dimethyl-1,2,3,4-tetrahydrobenzo[*b*]-1,10-phenanthroline (**8**) [13], (6*R*,8*R*)-6,8-methano-7,7-dimethyl-2-(2-pyridinyl)-5,6,7,8-tetrahydroquinoline (**9**) [14], (6*R*,8*R*)-(−)-6,8-methano-7,7-dimethyl-2-[1-methyl-1-(pyridin-2-yl)ethyl]-5,6,7,8-tetrahydroquinoline (**10**) [15], (6*R*,8*R*)-7,7-dimethyl-2-(thiophen-2-yl)-5,6,7,8-tetrahydro-6,8-methanoquinoline (**11**) [15,16], (6*R*,8*R*)-(+)-5,6,7,8-tetrahydro-7,7-dimethyl-2-(2-diphenylphosphinophenyl)-6,8-methanoquinoline (**12**) [17].

3.2. Reduction of acetophenone: general procedure

The ligand (0.05 mmol) in dry methanol (0.5 ml) was added to a slurry of $Sn(OTf)_2$ (21 mg, 0.05 mmol) in dry methanol (0.5 ml) under an atmosphere of argon at room temperature. The resulting solution was stirred at room temperature for 1 h before sequential addition of acetophenone (120.15 mg, 1.0 mmol) in dry methanol (0.5 ml) and PMHS (120 mg, 2.0 mmol). The resulting mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 7/3) to afford 1-phenylethanol and the starting material. The enantiomeric excess (ee) was determined by GC analysis on a diethyl-*t*-butylsilyl β-cyclodextrin column operated at 60 °C for 5 min, then programmed at 3 °C/min to 150 °C. Retention times: 23.75 min [(*R*)-1-phenylethanol] and 24.20 min [(*S*)-1-phenylethanol].

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