*Neo*PHOX—an easily accessible P,N-ligand for iridium-catalyzed asymmetric hydrogenation: preparation, scope and application in the synthesis of demethyl methoxycalamenene†

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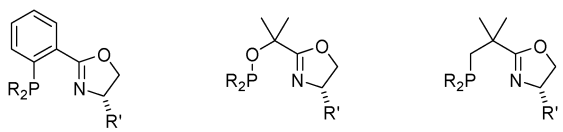
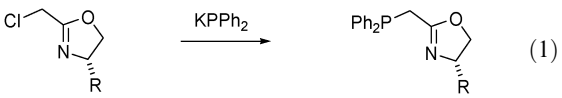
Using a new class of chiral iridium hydrogenation catalysts, the antitumor natural product demethyl calamenene was synthesized in four steps in >20% overall yield and high enantiomeric purity.

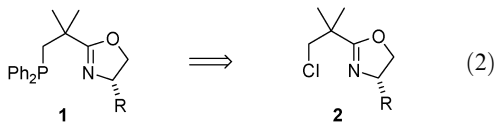
Enantioselective hydrogenation has become the method of choice to convert prochiral olefins to optically active compounds. Since our discovery[1] that complexes of the type [Ir(L*)(COD)][BAr_F] (L*: chiral P,N ligand; COD: cyclooctadiene; BAr_F: tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate) are exceptional catalysts for the enantioselective hydrogenation of unfunctionalized olefins, we[2] and others[3] have invested considerable efforts in finding ligand structures that are easily accessible and also give high catalytic activity and enantioselectivity. Although many efficient P,N- and C,N-ligands for the iridium-catalyzed enantioselective hydrogenation are known today, most ligands do not fulfill the requirements for preparation on manufacturing scale, *i.e.* high overall yield, facile purification, and scalability.[4] We have now found a class of P,N-ligands that fulfills these requirements and employed them in the iridium-catalyzed hydrogenation of unfunctionalized olefins.



Some time ago, we introduced SimplePHOX as an efficient ligand for iridium-catalyzed asymmetric hydrogenation.[5] Although this ligand class is accessible by simple reactions, scale up was hampered by low overall yields and difficult purification steps. We therefore sought a structurally similar ligand motif that is as easy to prepare as SimplePHOX, but, which could be obtained in higher overall yield and without chromatographic purification steps.

Phosphinomethyl-oxazolines can be easily prepared by nucleophilic substitution from 2-chloromethyl-oxazolines (eqn (1)) and give excellent results in the iridium-catalyzed enantioselective hydrogenation of unfunctionalized tetra-substituted olefins.[6] Encouraged by these findings, we hoped that we could also access new phosphino-oxazolines (**1**) by nucleophilic substitution on the corresponding chloro-alkyl-oxazolines (**2**). Obviously, neopentyl systems such as **2** cannot undergo a simple S_N1 or S_N2 reaction, but it is known that neopentyl halides undergo a radical nucleophilic substitution ($S_{NR}1$) with diphenylphosphide anions.[7]





Indeed, the thermally initiated reaction of neopentyl chloride with a commercially available solution of $KPPh_2$ in THF gave considerable amounts of substitution product. Surprisingly, the product was stable enough to be purified by flash chromatography in air. Next we synthesized a series of oxazolines (**2**) starting from commercially available 3-chloropivaloyl chloride. Amides **3** were obtained in good to quantitative yield and could be purified by crystallization or distillation. Cyclization of the amides was achieved using Burgess' reagent,[8] giving the corresponding oxazolines in high yield after a simple Kugelrohr distillation (Scheme 1). The reaction of the oxazolines with $KPPh_2$ proved to be much faster than the analogous reaction with neopentyl chloride. After 6 h at reflux, the starting material ($KPPh_2$) was consumed and only product could be observed in the ^{31}P-NMR-spectrum. We were pleased to see that ligands **1** could be obtained in analytically pure form by simple filtration through silica gel in air. The steric bulk around the phosphorus atom seems to make these ligands remarkably air stable. The formation of ligands **1c** and **1d** with *o*-tolyl (*o*-Tol) and 3,5-dimethylphenyl (Xyl) substituents on the phosphorus atom turned out to be simple as well. These ligands could be prepared by refluxing a mixture of the corresponding secondary phosphines, potassium hydride, the chloro-oxazoline, and THF in one pot. The iridium complexes were either obtained from the crude products (**Ir-1a**, **e**) or alternatively from the purified ligands (**Ir-1b–d**). They are highly stable against air and moisture: a sample, which was

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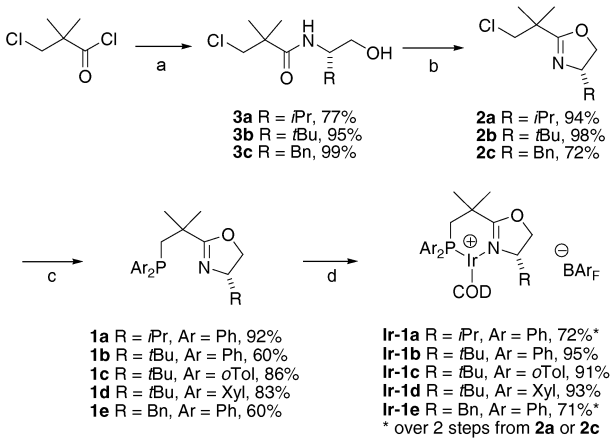
† Electronic supplementary information (ESI) available: Experimental details for compounds **1–3**, **Ir-1**, **13–16** and spectroscopic data. See DOI: 10.1039/b912680e

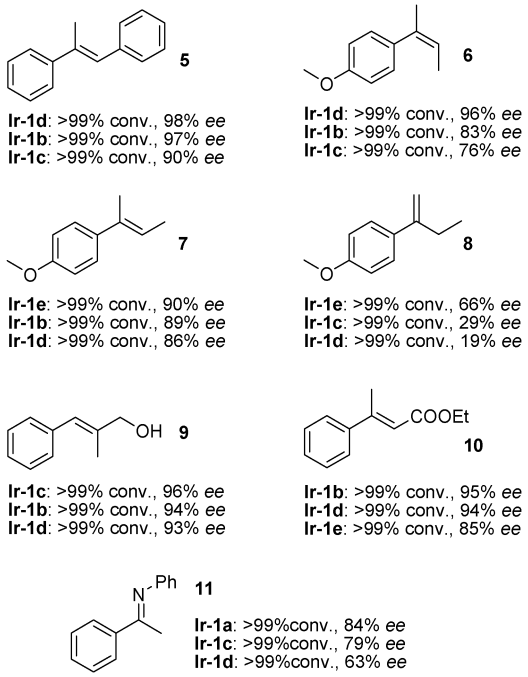


(a) aminoalcohol, NEt_3, CH_2Cl_2 or Et_2O, 0 °C to r.t., 75 min; (b) Burgess' reagent (1.3 eq), THF, 66 °C; (c) $KPPh_2$ in THF or $HPAr_2$, KH, THF, 66 °C, 6 h; (d) $[Ir(COD)Cl]_2$ (0.55 eq), 40 °C, 30 min, $NaBAr_F$, r.t., 30 min.

Scheme 1 Synthesis of *Neo*PHOX-ligands and iridium complexes.

kept in an open vial on the bench showed no traces of decomposition after 8 months.

We evaluated these new iridium complexes in the enantioselective hydrogenation of unfunctionalized olefins (see ESI† for conditions). First, we tested (*E*)-1,2-diphenyl-1-propene (**5**), for which excellent results had been obtained using iridium-P,N catalysts.[2] By employing 1 mol% of catalyst, full conversion and up to 98% ee was routinely obtained without the use of a glove box. Catalyst **Ir-1b** gave similar results to the corresponding SimplePHOX complex **Ir-4a**, while with **Ir-1c** a significantly lower ee-value was obtained relative to the SimplePHOX analogue **Ir-4b**.



Other substrates also gave excellent results, except for terminal olefin **8**. For (*Z*)-2-(4-methoxyphenyl)-2-butene (**6**) an enantiomeric excess of up to 96% could be obtained using complex **Ir-1d**, while for the corresponding (*E*)-isomer **7**, which gives the opposite enantiomer, lower but still good enantioselectivities were obtained. Functionalized olefins such as **9** and **10** were also hydrogenated with full conversions, giving up to 96% ee and 95% ee, respectively. Imine **11** could be hydrogenated with 84% ee using complex **Ir-1a**.

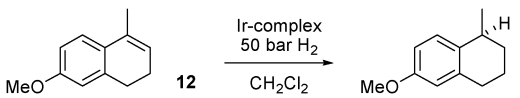
Table 1 Enantioselective hydrogenation of dihydronaphthalene **12**[a]

Entry	Complex (S/C)	Conv. (%)	ee (%)
1	**Ir-1a** (100)	>99	68 (*S*)
2	**Ir-1b** (100)	>99	94 (*S*)
3	**Ir-1c** (100)	>99	96 (*S*)
4	**Ir-1d** (100)	>99	94 (*S*)
5	**Ir-1e** (100)	>99	82 (*S*)
6	SimplePHOX **Ir-4a** (100)	>99	85 (*S*)[5]
7	SimplePHOX **Ir-4b** (100)	>99	95 (*S*)[5]

[a] See ESI† for details; S/C: substrate to catalyst ratio; conversions were determined by GC, enantiomeric excesses were determined by HPLC on a chiral column.

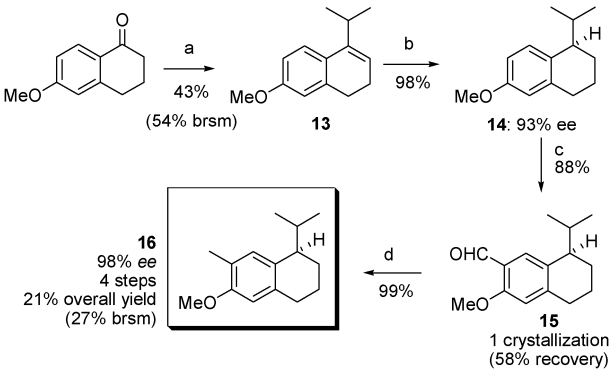
We were particularly interested in the enantioselective hydrogenation of dihydronaphthalene **12** for which our best catalyst so far was Ir-SimplePHOX **Ir-4b** (95% ee, full conv.). The corresponding chiral tetraline motif can be found in numerous natural products and therefore a good hydrogenation catalyst for dihydronaphthalenes would be of considerable synthetic interest. To our delight, complex **Ir-1c** gave a slightly higher enantiomeric excess (96% ee) than the structurally similar Ir-SimplePHOX **Ir-4b** (Table 1).

In view of these results, we envisaged that the antitumor natural product (*R*)-(+)-7-demethyl-2-methoxycalamenene[9] (**16**) would be accessible in 4 steps starting from commercially available 6-methoxytetralone (Scheme 2). The synthesis of **16** has previously been reported by Tietze and Raschke[10] (9 steps, *ca.* 12% overall yield, 92% ee), Nicolaou *et al.*[11] (5 steps, *ca.* 17% overall yield, ~90% ee) and the synthesis of a related compound by Schmalz *et al.*[12] (7 steps, 20% overall yield, 99% ee).



Dihydronaphthalene **13** was obtained in a 43% yield using a $ZnCl_2$-catalyzed addition of *i*PrMgCl[13] to 6-methoxytetralone, followed by an acid-catalyzed dehydration of the corresponding tertiary alcohol. We tested the hydrogenation of this olefin with several iridium complexes which gave good results for the enantioselective hydrogenation of dihydronaphthalene **12**.

Among the complexes tested, **Ir-1c** was found to be the most selective catalyst, giving full conversion and an enantiomeric excess of 93% at 5 bar of hydrogen pressure. The preparative reaction was performed with a catalyst loading of 0.5 mol% on a 1.5 g scale. For the subsequent Vilsmeyer-formylation a combination of *N*-methylformanilide and $POCl_3$ was found to be most efficient,[14] although the reaction was slow. Aldehyde **15** was obtained as a solid in 88% yield and its enantiomeric purity could be increased by recrystallization (58% recovery). Finally, the carbonyl group was reduced in quantitative yield using H_2, Pd/C. In this manner, (*R*)-(+)-7-demethyl-2-methoxycalamenene was prepared in only 4 steps starting from



(a) *i*PrMgCl (1.3 eq), $ZnCl_2$ (0.1 eq), THF, then *p*TsOH (cat.), I_2 (cat.), toluene, 110 °C, 16 h; (b) catalyst **Ir-1c** (0.5 mol%), H_2 (5 bar), CH_2Cl_2, 4 h; (c) *N*-methylformanilide, $POCl_3$, CH_2Cl_2, 40 °C, 48 h; (d) Pd/C (10%), H_2 (100 bar), 24 h; brsm: based on recovered starting material.

Scheme 2 Total synthesis of demethyl methoxycalamenene (**16**).

commercially available 6-methoxytetralone in 21% overall yield with an enantiomeric excess of 98%.[15]

In summary, we have introduced a class of new P,N-ligands that can be easily prepared in high yield using simple purification techniques and, therefore, fulfills the criteria for large scale preparation. In addition these ligands are remarkably air stable. The corresponding [Ir(P,N)(COD)][BAr_F] complexes show excellent activities and enantioselectivities in the hydrogenation of unfunctionalized and functionalized olefins. The utility of our catalysts was demonstrated in the synthesis of (*R*)-(+)-7-demethyl-2-methoxycalamenene (**16**) which is superior to other published routes with regard to the number of steps, overall yield and purification of the intermediates.

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15 Without the recrystallization of **15** the overall yield would be 37% (46% based on recovered starting material), with an enantiomeric excess of 93%.

