New Chiral β-Phosphinocarboxylic Acids and their Application in Palladium-catalysed Asymmetric Allylic Alkylations

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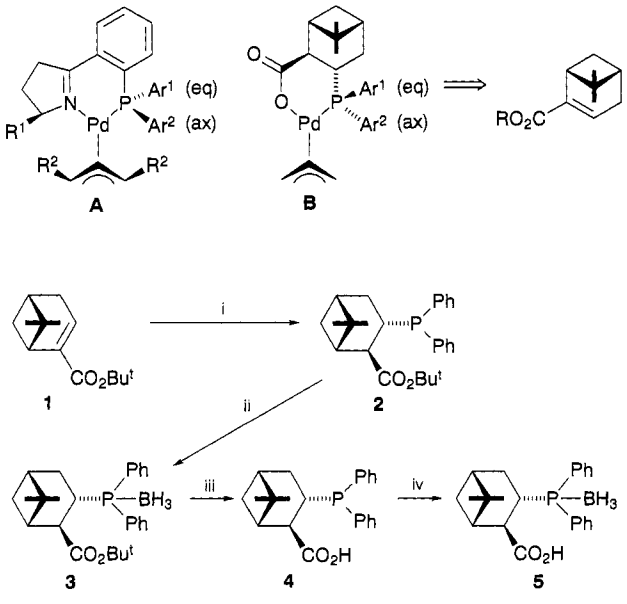
Chiral β-phosphinocarboxylic acids, conveniently available by conjugate addition of lithium diarylphosphides to α,β-unsaturated carboxylic esters from the chiral pool, show excellent potential as ligands in asymmetric catalysis; in Pd-catalysed allylic substitutions extremely high enantiomeric excess (up to >99% e.e.) is achieved with cyclic substrates.

Great progress was recently achieved for asymmetric Pd-catalysed allylic substitutions due to the introduction of new chiral ligands. One class of new ligands are phosphinoaryloxazolines, introduced by us[1] and others.[2] These ligands form chelate complexes **A** with two donor atoms, P and N, of different electronic and, *via* substituents, steric properties. For *acyclic* substrates enantiomeric excesses of up to 99% (1,3-diphenylprop-2-enyl system) were obtained. For the preparatively particularly interesting cycloalkenyl substrates these ligands furnished enantiomeric excess of only 54–85%.[3] Here diphosphines constructed from chiral modules[4] appear particularly well suited. However, an application of such ligands to an acyclic substrate has not been reported. We have now developed new ligands on the basis of the following considerations.

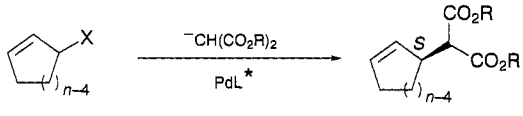
According to X-ray crystal structures, the chelate ring in system **A** adopts an envelope conformation and the aryl groups Ar^1 and Ar^2 occupy pseudoequatorial/face-on and pseudoaxial/edge-on positions, respectively.[1b] The most effective interaction with an acyclic, *syn-syn* allylic moiety, as in formula **A**, is provided by group Ar^1. The interaction with a comparatively slim cyclic, *i.e.*, *anti-anti* allylic system is small. One logical way to increase the relative size of an aryl group at P is to decrease the size of the oxazoline moiety. As the group R^1 was invariably found in a pseudoaxial position of the five-membered ring we replaced the oxazoline by a carboxylate group in order to decrease the steric effect of the hard donor moiety as much as possible. Dismissing the chiral oxazoline group necessitated introduction of a new element of chirality. Of various possibilities, π-allyl complexes of β-phosphinocarboxylic acids[5] **B** with a chiral backbone were first chosen. These chiral phosphines are readily accessible by conjugate addition as described in Scheme 1 for a particular example.[6] Currently, a whole range of such compounds are being developed in our laboratory. However, even the very first gave highly remarkable results that we report here.



Scheme 1 *Reagents and conditions*: i, $LiPh_2$ (1.8 equiv.), THF, −78 °C, 3 h, then $Na_2SO_4 \cdot 10H_2O$; ii, BH_3·THF, −50 °C, 66%; iii, CF_3CO_2H, then NaOH, 90%; iv, NaH, THF, 25 °C, BH_3·THF, −78 °C, 1 mol dm^{-3} HCl, 90%

The ester (−)-(1*R*)-*tert*-butyl myrtenate **1** was prepared[7] in 61% yield from (−)-(1*R*)-myrtenal. Reaction of the ester **1** with $LiPPh_2$, prepared from BuLi and $HPPh_2$ (THF, −78 °C, 3 h, then $Na_2SO_4 \cdot 10H_2O$), proceeded smoothly and diastereoselectively. The crude product **2** was treated with BH_3·THF to give the air-stable adduct **3** which could be conveniently purified by flash chromatography [SiO_2, light petroleum (bp 30–70 °C)–ethyl acetate (95:5), 66% yield]. Treatment of ester **3** with CF_3CO_2H (room temp., 1 h, evaporation of the CF_3CO_2H and neutralisation with aqueous NaOH) resulted in cleavage of the Bu^t group and removal of the protecting BH_3† to give the acid **4**‡ in 90% yield after extraction with diethyl ether. The acid **4** is sensitive to oxygen. In order to facilitate handling, the corresponding borane adduct **5** was prepared by treating the Li or Na salt of **4** with BH_3·THF followed by acidification. The crystalline adduct **5**, mp 172–173 °C, is stable to air and moisture. For catalyst preparation, the

Table 1 Allylic alkylations of cyclic substrates[a]



Entry	*n*	X	R	Counter ion	*T*/°C	*t*/h	Yield[b] (%)	E.e. (%)[c]
1	5	OAc	Me	Na^+	25	1	86	75
2	5	Cl	Me	Na^+	−30	1	93	70
3	5	Cl	Bu^t	Na^+	−30	1	82	81
4	5	OAc	Bu^t	Na^+	0	12	84	81
5	5	OAc	Me	Li^+	25	12	76	83
6	5	OAc	Bu^t	Li^+	25	12	74	85
7	6	OAc	Me	Na^+	25	2	90	91
8[d]	6	OAc	Me	Na^+	25	2	93	90
9	6	OAc	Bu^t	Na^+	25	12	92	96
10	6	OAc	Me	Li^+	25	2	91	98
11	6	OAc	Bu^t	Li^+	25	2	89	98
12[e]	6	OAc	Me	Li^+	25	2	92	98
13	7	OAc	Me	Na^+	25	1	64	87
14	7	OAc	Bu^t	Na^+	0	12	82	>99
15	7	OAc	Me	Li^+	25	2	75	98
16	7	OAc	Bu^t	Li^+	25	2	73	>99

[a] Reactions were carried out with 1 mmol of substrate with the salt prepared from 2 mmol of dialkyl malonate and 1.5 mmol of NaH or BuLi in 3 ml of THF at room temp.; molar ratio of Pd:substrate = 0.03:1; molar ratio of ligand:Pd = 3:1. [b] Yields refer to products after isolation and chromatographic purification. [c] Enantiomeric excess was determined as described in ref. 3, *i.e.*, entries 1–6: HPLC analysis of the corresponding iodolactones on Chiracel DIACEL OJ [hexane–EtOH (90:10), flow: 0.5 ml min^{-1}, detection UV–VIS: 260 nm]; entry 7: by ^1H NMR using the paramagnetic shift reagent Eu(hfbc)$_3$ by integration of the signals of the OMe groups of the malonate moiety; entries 8–16: GC: Chrompack Permethyl β-CD, 50 m × 0.25 mm. [d] As footnote *a*, but solvent DMF. [e] As footnote *a*, but catalyst preparation from borane adduct **5** (*cf.* text).

ligand **4** is liberated in standard manner by treating a toluene solution of **5** with 1.1 equiv. of 1,4-diazabicyclo[2.2.2]octane (100 °C, 1 h).

Allylic substitutions were studied with the cyclic substrates given in Table 1. With the new ligand **4** the level of enantioselectivity was generally higher than that achieved with any of the phosphinooxazolines. As anticipated, preferred products displayed (*S*)-configuration. Of the reaction variables, the size of the nucleophile and the counter ion were investigated. Generally, *tert*-butyl malonate was superior to methyl malonate and lithium salts gave higher degrees of enantioselectivity than sodium salts.§ With the potassium salt (conditions as given by entry 9) 62% e.e. resulted. Furthermore, with the methyl ester of **4** as ligand 4% e.e. (yield 36 %) were obtained under conditions as given in entry 7 of Table 1. All these observations strongly suggest that the acid **4** gives rise to O,P chelate coordination rather than to only coordination of phosphorus.

In conclusion, we have described new chiral ligands that possess broad variability, modularity as well as ease of preparation and handling. In the case of six- and seven-membered rings unprecedented enantioselectivity is achieved. Extension of this work to further ligands and reactions is being actively pursued.

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Footnotes

† Deprotection of phosphine–borane complexes with CF_3CO_2H has not been previously reported to the best of our knowledge. According to ^{31}P NMR, treatment with CF_3CO_2H yields an acyloxyborane complex from which NaOH liberates the free phosphine.

‡ The configuration of **4** as given in Scheme 1 was determined by oxidation of **4** to the corresponding phosphine oxide and a X-ray structure analysis; Dr B. Nuber, unpublished work.

§ A strong effect of the counter ion in allylic substitutions was previously reported by Trost and Bunt[4] who obtained best results with tetrahexylammonium salts. In contrast, best results were here obtained with lithium salts.

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