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Enantiomerically Pure Cycloalkenylacetic Acid Derivatives *via* Pd-Catalyzed Asymmetric Allylic Alkylation and Subsequent Enantiomeric Enrichment *via* Iodolactones[1]

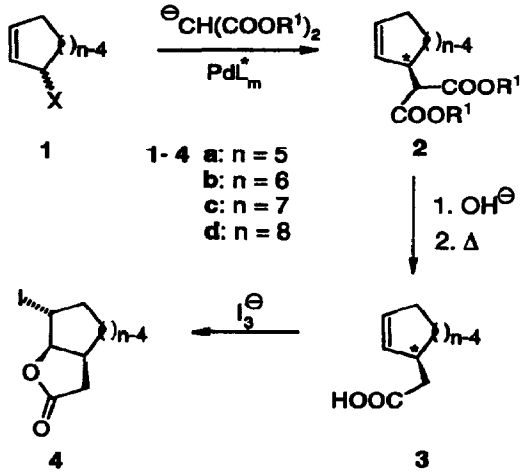
Peter Sennhenn, Bert Gabler and Günter Helmchen*

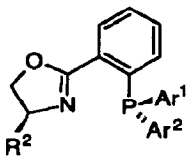
Organisch-Chemisches Institut der Universität, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

Abstract: *Chiral (phosphinoaryl-oxazoline)Pd complexes with stereogenic phosphorus were used as catalysts for alkylation of cycloalkenyl acetates which gave products with up to 85% ee. Excellent reactivity allowed reactions with as little as 0.02 mol% of Pd. Five- and six-membered ring synthons of interest for syntheses of biologically active compounds with > 99% ee were obtained via recrystallization of iodolactones.*

Recently, we[2] and others[3] introduced Pd complexes of chiral phosphinoaryl-oxazolines (**A**) as very effective catalysts for enantioselective allylic alkylation and amination. For acyclic substrates enantiomeric excesses of up to 99 % (1,3-diphenyl-2-propenyl system) were obtained. However, the preparatively particularly interesting allylic substitutions of cycloalkenyl substrates gave initially almost racemic products. Improvement was achieved by employing ligands **B-E** with a stereogenic phosphorus centre and systematic optimization of reaction conditions. Induced by the very considerable attention currently directed at cyclic substrates, by the groups of Brown[4], Kang[5], Minami[6], Togni[7] and Trost[8], we here report our results with focus on preparative aspects[9].

Scheme 1





	R^2	Ar^1	Ar^2
A	i-Pr	Ph	Ph
B	i-Pr	Ph	1-Naphthyl
C	i-Pr	1-Naphthyl	Ph
D	i-Pr	2-Biphenylyl	Ph
E	Ph	2-Biphenylyl	Ph

For work in asymmetric catalysis determination of enantiomeric purity of reaction products is of crucial importance. Previous work had relied on optical rotation and ^1H NMR chiral shift reagents of which the first is often unreliable and the second is often not precise. We were able to achieve the direct separation of **2b**, **2c** and **2d** on a GC cyclodextrin column[10]. As a consequence, precise maximal optical rotations could be determined. The values of maximal optical rotations from this and earlier work are displayed in Table 1. The value found for **2b** is in agreement with recently reported work[6], but at variance with older work for which enantioselectivities probably must be corrected to lower values than stated. From esters **2a-c** iodolactones **4a-c** were formed and were found separable by HPLC on a Daicel column[11]. This allowed us to precisely determine optical rotations for the five-membered ring compounds, in particular **2a**.

Table 1. Absolute values of optical rotations of malonates 2a-d ($R^1 = CH_3$) (extrapolated to 100% ee).

Compound	$[\alpha]_D$		Ref.
2a	73.1	(c = 3.09, CH_2Cl_2)	8
	99.6	(c = 3.21, CH_2Cl_2)	this w.
	98.7	(c = 2.27, $CHCl_3$)	this w.
2b	31.2	(c = 2.60, $CHCl_3$)	7
	36.4	(c = 2.60, $CHCl_3$)	4
	14.0	(c = 1.36, CH_2Cl_2)	5
	44.3	(c = 2.94, CH_2Cl_2)	8
	46.1	(c = 3.11, CH_2Cl_2)	this w.
	46.1	(c = 2.86, $CHCl_3$)	this w.
2c	8.3	(c = 4.52, CH_2Cl_2)	8
	7.1	(c = 2.92, CH_2Cl_2)	this w.
	7.8	(c = 3.04, $CHCl_3$)	this w.
2d	103.1	(c = 2.89, $CHCl_3$)	this w.

In our initial experiments with cyclohexenyl acetate as substrate, several diphenylphosphinophenyl oxazolines, for example **A**, were employed as ligands. These gave nearly racemic products (Table 2, entry 1), in contrast to the high degree of enantioselection typical for acyclic substrates. Molecular models based on X-ray data[2b,9] make it clear that ligands of type **A** are not effective because there are no direct interactions of the axial group R^2 and phenyl groups at phosphorus in the comparatively narrow area of space occupied by a cyclic allylic group. The models suggested that ligands with a stereogenic phosphorus centre should be better suited. Indeed, the epimeric 1-naphthyl derivatives **B** and **C** gave rise to enantiomeric products (entries 2, 3) with some selectivity. Even better results were achieved with the biphenyl derivatives **D** and **E**[12].

Further improvement was achieved by variation of substrate structures and reaction conditions. Of a series of malonates $CH_2(COOR^1)_2$ that with the smallest group R^1 gave the best results. Of a variety of solvents, highest selectivity was provided by dioxane. The molar ratio Pd:ligand showed a marked effect: reactivity and selectivity were significantly improved by an increase from 1:1.1 to 1:3 (cf. entries 4 and 5). Complexation of the cation with crown ether or employing tetraalkylammonium salts, which can have dramatic effects on enantioselectivity according to recent reports[4,8], led to a decrease in yields and enantioselectivities. In contrast, maximal enantioselectivity was obtained with Li^+ as counter ion (entries 6-12). The leaving group in the substrate did not effect the selectivity, but reactivity and yield varied significantly (entries 7-9).

Table 2. Allylic alkylation of 3-(acyloxy)-cycloalkenes

Entry	n	X	Ligand	Method[a]	Solvent	Counter Ion	t	Yield[b] [%]	% ee[c] (Config.)
1	6	OAc	A	A	THF	K^+	3 d	30	0
2	6	OAc	C	A	THF	K^+	1 d	81	22 (*S*)
3	6	OAc	B	A	THF	K^+	18 h	83	32 (*R*)
4	6	OAc	B	B[d]	dioxane	Na^+	20 h	19	35 (*R*)
5	6	OAc	B	B	dioxane	Na^+	1 h	81	45 (*R*)
6	6	OAc	B	B	dioxane	Li^+	1 d	76	47 (*R*)
7	6	OAc	D	B	dioxane	Li^+	10 h	73	51 (*R*)
8	6	OCOPh	D	B	dioxane	Li^+	6 h	98	49 (*R*)
9	6	OCOOMe	D	B	dioxane	Li^+	2 h	99	50 (*R*)
10	6	OAc	ent-E	B	dioxane	Li^+	3 h	93	54 (*R*)
11	5	OAc	ent-E	B	dioxane	Li^+	1 h	81	62[e] (*R*)
12	7	OAc	D	B	dioxane	Li^+	17 h	84	83[e] (*R*)
13	8	OAc	B	B	dioxane	Li^+	2 d	26	36 (*R*)
14	6	Br	ent-E	B	THF	Na^+	1 d	64	85 (S)

a) In all experiments the ratio of Pd : 1 was 0.01. Method A: Reaction of 1 mmol of substrate with 3 mmol of dimethyl malonate, 3 mmol of *N,O*-bis-trimethylsilylacetamide (BSA) and 10 µmol of KOAc in 3 ml of solvent at room temperature; ratio Pd : ligand = 1 : 1.1. Method B: Reaction of 1 mmol of substrate with the salt prepared from 2 mmol of dimethyl malonate and 1.5 mmol of NaH or BuLi in 3 ml of solvent at room temperature; ratio Pd : ligand = 1 : 3. b) Yields refer to products after isolation and chromatographic purification. c) Enantiomeric excess was determined by GC (permethyl ß-CD), cf. ref. 10. d) In this experiment the ratio Pd : B was 1:1.1. e) Enantiomeric excess was determined by HPLC analysis of the corresponding iodolactones on Daicel Chiralcel OJ (*n*-hexane : EtOH 90 : 10, flow: 0.5 ml/min).

Table 3. Allylic alkylation of 3-chloro-cyclopentene (1, X = Cl)[a]

Entry	Ratio of Pd : 1	Ratio of Pd : ent-E	Temp. [°C]	t [h]	Yield [%]	%ee
1	0.002	1:3	-30	12	97	60
2	0.001	1:3	-35	15	98	62
3	0.0005	1:1.5	0	5	71[b]	62
4	0.0002	1:1.5	0	14	89[c]	59

a) For a representative procedure see note 16. b) The reaction was run on a 0.1 mol scale. c) The reaction was run on a 1 mol scale.

With reaction conditions optimized as far as possible with the oxazoline ligands, we needed a method of providing enantiomerically pure material. Eventually, it was found that the readily accessible iodolactones **4a**[13a] and **4b** (Scheme 1) are crystalline (mp of 68-68.5 °C and 94-96 °C for **4a** and **4b**, respectively, and mp of the racemic compounds 35-36 °C[13b] and 68 °C[13c], respectively) and enantiomerically pure **4a** and **4b** (>99.6% ee, HPLC) were easily obtained after recrystallization from ethyl acetate/n-hexane. Both compounds are most valuable starting materials for syntheses of biologically active compounds. The iodolactone **4c** did not crystallize.

For synthetic applications it was desirable to reduce the amount of catalyst to a minimum and to optimize reaction time and cost of the starting materials. Therefore, 3-cyclopentenyl chloride, easily available on a 100 g scale by reaction of HCl with cyclopentadiene[14], was used and showed excellent reactivity and yield (Table 3). In order to suppress the non-catalyzed allylic alkylation which starts at ca. 0 °C under the conditions employed, reactions were run at -35 °C with *freshly distilled* starting material. Even at 0 °C the catalyzed reaction could successfully compete with the noncata-

lyzed. A subsequent reduction of the amount of catalyst from 1 mol% down to a minimum of 0.02 mol% did not show any influence on enantioselectivity while reaction time slightly increased. Yields were nearly quantitative when pure starting material[15] was employed (cf. representative procedure[16]). It is our general experience that with freshly purified starting materials allylic alkylations can be often catalyzed with much smaller amounts of Pd complexes than the currently typically employed 2-5 mol%.

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9. Mechanistic aspects, based on six X-ray structures of π-allyl complexes and extensive NMR studies, will be reported separately.
10. GC: Chrompack Permethyl-β-CD, 50 m x 0.25 mm.
11. HPLC: Chiralcel DAICEL OJ, n-hexane: EtOH (9:1), flow: 0.5 ml/min, Det. UV-VIS: 260 nm.
12. Ligands **D** and **E** were prepared in the same way as previously described for **B** and **C** (ref. 2a). The configuration at phosphorus was determined by NOESY NMR techniques (unpublished work of M. Reggelin, Frankfurt M).
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15. This observation proved to be general for all substrates employed for Pd catalyzed allylic substitutions in our labs.
16. *Procedure for preparation of enantiomerically pure iodolactone* **4a**: Dimethyl malonate (145 g, 1.1 mol) was added dropwise to a stirred, cooled (0 °C) suspension of NaH (26 g, 1.05 mol) in THF (3 L) over a period of 1 h. Then 3-chloro-cyclopentene (113 g, 1.1 mol) and a mixture of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (45 mg, 123 μmol) and ligand ***ent-E*** (180 mg, 372 μmol, 1.5 eq) in THF (2 ml) were added. Stirring at 0 °C overnight and work-up in standard manner gave 185 g of **2a** (89 %). This was transformed into (*S*)-cyclopentenyl acetic acid (**3a**) as previously described[17], which was subjected to standard iodolactonization (THF/H_2O, I_2, KI). The crude product was three times recrystallized from n-hexane/ethyl acetate to yield 52 g of enantiomerically pure iodolactone **4a**, mp 68-68.5 °C, $[\alpha]_D^{20}$ = -40.7 (c = 3.95, CCl_4) as colourless crystals (> 99% ee, HPLC[11], overall yield: 20 %).
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