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Highly efficient kinetic resolution of 2-cyclohexenyl acetate in Pd-catalyzed allylic alkylation

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Abstract

A new phosphine ligand has been synthesized and employed in the Pd-catalyzed alkylation of 2-cyclohexenyl esters. A very efficient resolution of 2-cyclohexenyl acetate was observed during alkylation. In addition, the reactivity and enantioselectivity showed a strong dependence on the acetate salt with the BSA/MOAc (M = alkali metal) base system during alkyation of cyclohexenyl carbonate. © 2000 Published by Elsevier Science Ltd.

The design and synthesis of new chiral ligands remains an important area of research with respect to developing highly enantioselective transition metal-catalyzed reactions. A successful ligand should therefore be readily accessible, stable, and highly tunable since modification of the steric and electronic properties are often necessary for achieving high asymmetric induction.

We have begun to develop ligand families derived from effective chiral synthons with the aim of meeting the above-mentioned requirements. One such synthon, **3**, as shown in Scheme 1, is derived from the well-known chiral phosphinoferrocenyloxazoline (**1**).[1] Hydrolysis of the oxazoline ring in **1** using triflic acid followed by acylation gives the amide-ester **2**.[2] Compound **2** is then converted in high yield to the desired acid **3** upon treatment with *t*-BuOK.[3] The benefits of **3** are that it is readily available in large quantities and is air-stable. Ligand modifications can then be easily realized by appending various units to the carboxylate functionality. Furthermore, the planar chirality of ferrocene, usually in conjunction with additional sources of chirality, has proven to be quite an effective framework for providing high asymmetric induction.[4] Herein we wish to report our findings for the Pd-catalyzed allylic alkylation reaction employing ligands **4** and **5**. These ligands are easily obtained by coupling acid **3** with (1*S*,2*S*) and (1*R*,2*R*)-diaminocyclohexane as outlined in Scheme 1.[5]

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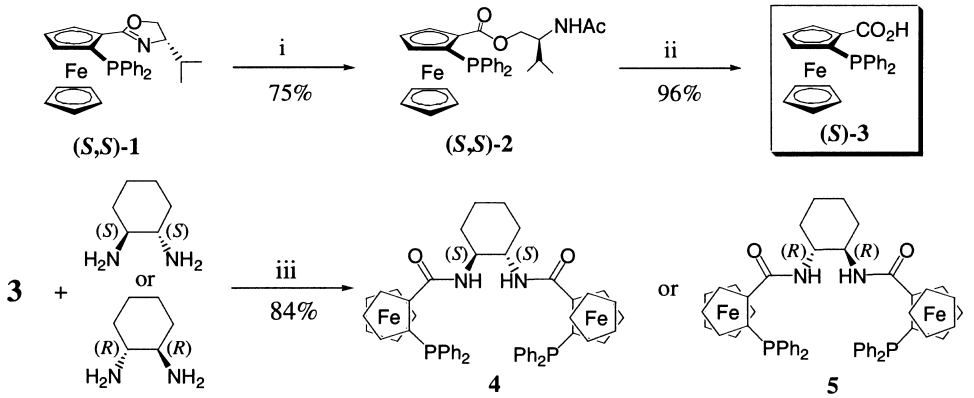
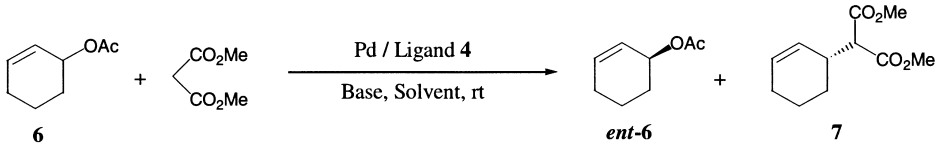


Scheme 1. Reagents: (i) (a) trifluoroacetic acid, Na_2SO_4, H_2O/THF, 0°C to rt, 24 h; (b) acetic anhydride, pyridine, CH_2Cl_2, 0°C to rt, 24 h; (ii) *t*-BuOK, Et_2O, H_2O, 0°C to rt, 24 h; (iii) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide-HCl, 4-(dimethylamino)pyridine, CH_2Cl_2, 24 h, rt

The Pd-catalyzed allylic alkylation reaction has become the standard test reaction for gauging the effectiveness of new ligands. Specifically, (*E*)-1,3-diphenylprop-2-enyl acetate has been the substrate most often used and numerous ligands have been successfully applied to the enantioselective alkylation of this compound.[6] As for the more challenging cycloalkenyl ester substrates, far fewer successful ligands have been reported.[7] Employing ligands **4** and **5** we sought to find conditions to alkylate cyclohexenyl acetate **6** with high enantioselectivity.



Using dimethyl malonate as nucleophile and ligand **4**, the reaction conditions were optimized as outlined in Table 1. The highest enantioselectivity was obtained using THF as solvent and BSA/KOAc as base. Under these conditions, there was very little difference between $[(\eta^3\text{-allyl})PdCl]_2$ and $Pd_2(dba)_3CHCl_3$ (entry 10 versus 11, Table 1). Furthermore, under the conditions in entries 10 and 11, ligand **5** gave much lower enantioselectivity (37% and 30% ee, respectively, of (*R*)-**7**). It is clear from the results that the (*S*)-planar chirality and the (*S*) configuration of the diamine backbone work in a cooperative sense. However, despite the conditions employed, the reaction conversion remained only moderate. Conveniently, GC could be used to monitor the progress of the reaction. Using a chiral capillary column, conditions were found which allowed determination of both the product and unreacted starting material enantioselectivity. As Table 2 shows, a very efficient kinetic resolution of **6** is occurring.[8] After 54% conversion unreacted **6** has an ee of 99% and the alkylation product **7** an ee of 92%. This equates to an S-factor of 61 illustrating the remarkable efficiency of this resolution.[9] Furthermore, the results in Table 2 also illustrate how the reaction slows considerably after 54% conversion is reached. An additional 20 hours of reaction time results only in a further 20% reaction conversion. Based on the optical rotations of isolated **7** and unreacted **6**, it is (*R*)-**6**, which proceeds rapidly to product.[10] On the other hand, (*S*)-**6** proceeds slowly to product and may inhibit, in some way, catalyst turnover since the reaction never reaches 100% conversion. These results indicate that the stereochemistry of the allylic

Table 1
Optimization for alkylation of **6**[a]

Entry	Pd	Base	Solvent	%Conv.[e]	%ee **7**[f]
1	$[(\eta^3\text{-allyl})PdCl]_2$	NaH	CH_2Cl_2	61	20(*R*)
2	"	NaH/Bu_4NBr	"	35	31
3	"	TMG[b]	"	28	38
4	"	DBU[c]	"	60	33
5	"	Cs_2CO_3	"	39	54
6	"	BSA/KOAc[d]	"	65	69
7	$Pd_2(dba)_3CHCl_3$	"	"	80	67
8	"	"	Toluene	66	75
9	"	"	CH_3CN	71	49
10	"	"	THF	66	83
11	$[(\eta^3\text{-allyl})PdCl]_2$	"	"	68	81

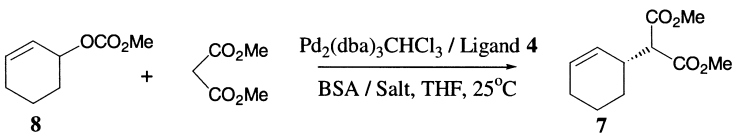
a) all reactions were carried out at rt in 3ml of solvent with the following stoichiometry: **6** (0.4 mmol), dimethyl malonate (1.2 mmol), base (1.2 mmol), Pd (3 mol%), **4** (4.5 mol%). b) TMG = 1,1,3,3-tetramethylguanidine. c) DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. d) BSA = *N*, *O*-bis(trimethylsilyl)acetamide; 5 mol % of KOAc was used. e) conversion was determined by GC. f) %ee was determined by GC using a β-DEX 120 chiral capillary column.

Table 2
Kinetic resolution of **6**[a]

Entry[b]	Time(h)	%Conv.	%ee *ent*-**6**	%ee **7**
1	1	24	31(*S*)	97(*R*)
2	2	38	59	95
3	4	54	99	92
4	6	63	>99	82
5	24	74	>99	71
6[c]	24	-	96(44)[d]	91(51)[d]

a) conversion and ee were determined by GC using a β-DEX 120 chiral capillary column; absolute configuration for **6** and **7** was determined by optical rotation (see ref. 10). b) Pd (3 mol%), **4** (4.5 mol%), **6** (0.4 mmol), dimethyl malonate (1.2 mmol), BSA (1.2 mmol), CsOAc (5 mol%), THF (3ml) at rt. c) Pd (1 mol%), **4** (1.5 mol%), **6** (1.5 mmol). d) isolated yield by silica gel chromatography

substrate **6** has an influence over the intermediate π-allyl/Pd complex formed prior to nucleophilic attack. This so-called *memory effect* has been the topic of recent reports in the area of Pd-catalyzed allylic alkylation.[11]



Interestingly, by changing the leaving group in **6** from acetate to the methyl carbonate **8**, complete reaction conversion could be achieved. The reaction reached complete conversion without slowing significantly or ceasing as with acetate **6**. What is most interesting is the effect of the acetate salt.[12] As Table 3 illustrates, both the reactivity and enantioselectivity increase as the size of the alkali metal increases, reaching a maximum with Cs.[13] Such a trend was not observed with substrate **6**.

Table 3
Effect of acetate salt on alkylation of **8**

Entry[a]	Salt	%Conv.	%ee[c]	Time
1	none	55	75	48
2	LiOAc	64	52	48
3	NaOAc	90	77	48
4	KOAc	100	79	24
5	RbOAc	100	85	20
6	CsOAc	100	89	20
7[b]	CsOAc	100(91)[d]	92	24

a) Pd (3 mol%), **4** (4.5 mol%), **8** (0.4 mmol), dimethyl malonate (1.2 mmol), BSA (1.2 mmol), acetate salt (5 mol%), THF (3 ml). b) reaction was run at 0°C. c) conversion and %ee were determined by GC using a β-dex 120 chiral capillary column. d) isolated yield by silica gel chromatography

In conclusion, we have developed a very selective ligand that can that can differentiate quite effectively between the *R* and *S* enantiomers of acetate **6**. This selectivity results in a very efficient kinetic resolution of acetate **6** during alkylation. Currently, we are investigating a variety of transition metal-catalyzed reactions as well as synthesizing additional ligands derived from synthon **3**. The results of this work will be reported in due course.

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