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Chiral Phosphinooxazolines as Ligands in Asymmetric Catalysis: Intramolecular Pd-Catalyzed Allylic Alkylation

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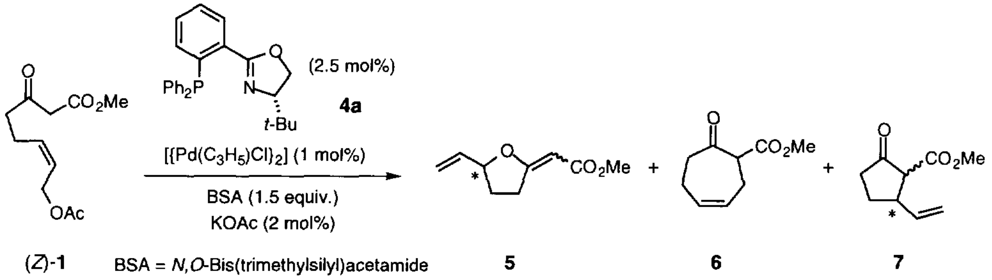
Abstract: *Palladium complexes with chiral phosphinooxazoline ligands were studied as catalysts for the enantioselective intramolecular alkylation of (Z)-methyl 8-acetoxy-3-oxo-6-octenoate (1) and (E)- and (Z)-methyl 2-methoxycarbonyl-8-methoxycarbonyloxy-6-octenoate (2, 3). The best results were obtained with 2 and 3 which cyclized to the corresponding cyclopentane derivative with 60% yield and up to 87% ee under optimized conditions.*

Enantioselective metal-catalyzed allylic substitution is a very active area of current research.[1-3] Recently, we[2b] and others[2c,d] have reported highly enantioselective intermolecular allylic alkylations of (*E*)-1,3-diaryl- and (*E*)-1,3-dialkylpropenyl acetates, catalyzed by palladium complexes with phosphinooxazoline ligands. Although intramolecular Pd-catalyzed allylic alkylations have been frequently used in the synthesis of organic compounds,[4] only a few successful enantioselective variants have been reported, such as the the cyclization of a β-ketoester derivative to 2-methoxycarbonyl-3-vinylcyclohexanone (48% ee; Yamamoto and Tsuji[5]), the synthesis of ergot alkaloids by allylation of a nitroalkyl side chain (69% ee; Genêt *et al.*[6]), and the formation of *cis*-decalin derivatives (83% ee; Shibasaki *et al.*[7]). Here we describe analogous intramolecular reactions of β-dicarbonyl compounds with (phosphinooxazoline)Pd cataysts leading to optically active cyclopentane derivatives.

Scheme 1



The substrates used in this study, (*Z*)-allyl acetate **1** and (*E*)- and (*Z*)-allyl carbonates **2** and **3**, were prepared from the corresponding allylic alcohols synthesized by literature procedures.[8,9] In initial experiments, allylic acetate (*Z*)-**1** was submitted to the standard reaction conditions for *inter*molecular allylic substitutions[2b] (Scheme 1). The catalyst was generated *in situ* from [{Pd(η^3-C$_3$H$_5$)Cl}$_2$] and the corresponding ligand (**4a**:Pd = 1.25). The cyclopentanone derivative **7** was obtained as a *trans/cis* mixture (ca. 15:1) with moderate enantioselectivity whereas the *O*-alkylation product **5** was isolated as a racemate. Variation of the chiral ligand **4a** (replacement of *t*-Bu by *i*-Pr, Ph, Bn) resulted in lower enantioselectivities.

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Ratios of *O*- to *C*-alkylation were solvent dependent (Table 1). In benzene exclusive formation of the *O*-alkylation product was observed, whereas in polar solvents like DMSO and DMF the desired cyclopentane derivative **7** was found as the major product. At longer reaction times the amount of **7** increases at the expense of **5**, indicating that **5** rearranges to **7** *via* a palladium π-allyl-intermediate.

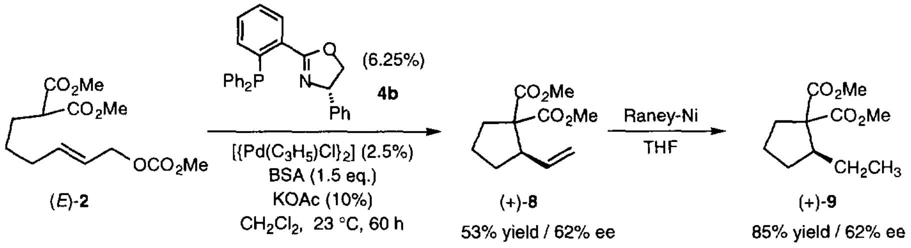
Table 1. Palladium-catalyzed cyclization of allylic acetate (*Z*)-**1**

Entry	Solvent	Temp. [°C]	Time [h]	Relative Ratios of Products **5**	**6**	**7**	Total Yield [%]	ee of **7**[a)] [%]
1	CH_2Cl_2	23	22	55	7	38	21	44
2	benzene	70	25	100	0	0	71	—
3	dioxane	23	50	99	0	1	48	—
4	THF	23	50	100	0	0	72	—
5	DMF	23	50	2	32	66	33	50
6	DMSO	23	50	2	29	69	42	42

a) Determined by GC (γ-CD-TFA) after decarboxylation.[10]

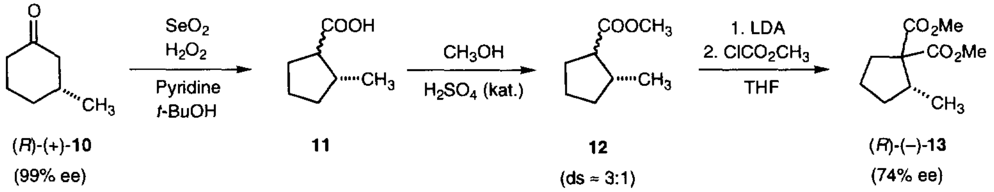
More promising results were obtained with the allyl carbonate (*E*)-**2** (Scheme 2), whereas the corresponding acetate did not react under these conditions. In the cyclization of (*E*)-**2** under standard conditions, conversion was complete within 60 h and the expected cyclopentane derivative **8** was obtained in 53% yield with 62% ee. The yield of **8** was moderate due to formation of a complex mixture of side-products. Notably, none of the cycloheptene isomer could be detected.

Scheme 2



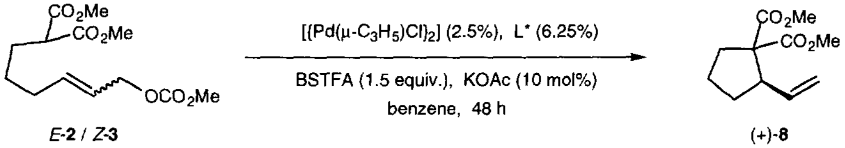
Reduction of the C,C double bond of (+)-**8** with Raney nickel afforded (+)-**9** which was compared by CD spectroscopy with (*R*)-(−)-**13** synthesized from commercially available (*R*)-3-methylcyclohexanone (**10**) as outlined in Scheme 3.[11,12] The two compounds displayed similar but opposite Cotton effects and the absolute configuration of (+)-**9** was thus assigned as (*S*) implying the (*R*) configuration for (+)-**8**.

Scheme 3

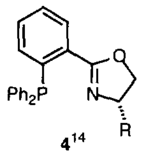


The cyclization reaction was optimized by varying the base, the solvent, the temperature, and the substrate concentration. Among various bases, *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA, 1.5 equiv.) combined with 10 mol% KOAc afforded the highest ee's. Both the enantioselectivity and the yield strongly depend on the solvent. Methylene chloride gave 62% ee and 64% yield, THF and dioxane 70-72% ee but unsatisfactory yields, whereas in polar aprotic solvents both the enantioselectivity and the yield were low. The best results were achieved in benzene (Table 2). In toluene, the highest ee was 72% but yields were below 20%. The two isomers (*E*)-**2** and (*Z*)-**3** gave very similar results (Table 2, Entry 2). Lowering the temperature from 23 to 5 °C increased the yield but not the ee (Entry 3). However, the enantioselectivity could be improved from 81 to 87% ee by lowering the substrate concentration from 0.1 to 0.01 M (Entry 4). Among the various phosphinooxazolines tested, the phenyl- and naphthyl-substituted derivatives **4b** and **4d**[14] proved to be the most effective ligands.

Table 2. Pd-Catalyzed cyclization of allyl carbonates (*E*)- and (*Z*)-**2**[13]

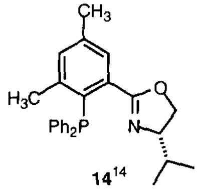


Entry	Substrate	Ligand	Temperature [°C]	Substrate conc. [M]	Yield [%]	% ee
1	(*E*)-**2**	**4b**	23	0.1	48	80
2	(*Z*)-**3**	**4b**	23	0.1	40	82
3	(*E*)-**2**	**4b**	5	0.1	62	81
4	(*E*)-**2**	**4b**	5	0.01	60	87
5	(*E*)-**2**	**4c**	5	0.1	18	54
2	(*E*)-**2**	**4d**	5	0.01	56	87
7	(*E*)-**2**	**14**	5	0.1	23	69
8	(*E*)-**2**	**15**	5	0.1	27	48

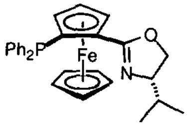


4[14]

a R = *t*-Bu
b R = Ph
c R = *i*-Pr
d R = α-Naphthyl



14[14]



15[15]

Our results show that good enantioselectivities can be achieved in intramolecular Pd-catalyzed allylic alkylations of this type, using phosphinooxazolines as chiral ligands. However, because the ee's and yields strongly depend on the substrate and ligand structures and the reaction conditions, careful optimization of the various reaction parameters is necessary. The observation that the two isomers (*E*)-**2** and (*Z*)-**3** are converted to the same enantiomer (+)-**8** with esssentially the same enantioselectivity is consistent with a reaction path involving rapid equilibration of the (allyl)Pd intermediates. The enantioselectivity of the overall reaction is then determined in the subsequent slow cyclization step.

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12. The enantiomeric excess of dimethyl 2-methyl-cyclopentane-1,1-dicarboxylate (**13**) was determined by GC using a chiral γ-CD-TFA column.
13. Typical procedure: In an ampule equipped with a magnetic stirring bar, $[\{Pd(\mu\text{-}C_3H_5)Cl\}_2]$ (2.48 mg, 2.8 μmol, 2.5 mol%) and **4b** (7.57 mg, 18.2 μmol) were dissolved in dry benzene under nitrogen (0.7 mL). The homogenous slightly yellow solution was degassed at 0.01 torr by three freeze-thaw cycles. The evacuated ampule was sealed with a vacuum-tight teflon stopper and the solution was stirred at 50 °C for 1 h. A solution of (*E*)-**2** (79.3 mg, 0.28 mmol) in benzene was added under nitrogen followed by the addition of BSTFA (59 μL, 0.41 mmol) and KOAc (5 mol%). The reaction mixture was degassed immediately at 0.01 torr by three freeze-thaw cycles. After stirring at 5 °C for 48 h the turbid reaction mixture was diluted with CH_2Cl_2, transferred to a separatory funnel, and washed with ice-cold saturated $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (hexane/EtOAc 5:1).
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