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Enantioselective allylic substitutions using ketene silyl acetals catalyzed by a palladium–chiral amidine complex [†]

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Abstract

Enantioselective allylic substitutions using ketene silyl acetals **3** as a nucleophile have been explored. In the asymmetric reactions of 1,3-diphenylprop-2-enyl pivalate **2** catalyzed by the Pd(0)–chiral amidine **1** complex, excellent levels of stereocontrol are achieved along with good conversions, demonstrating that ketene silyl acetals are able to expand the scope of asymmetric allylic alkylations. The present asymmetric reactions should proceed via nucleophilic attack at the allyl terminus trans to the diphenylphosphinyl group of the amidine on the side opposite to palladium. © 1998 Elsevier Science Ltd. All rights reserved.

Transition metal catalyzed allylic reactions using allyl compounds, alkenes and conjugated dienes have been actively investigated as an important synthetic tool for C–C and C–X (X=H, heteroatoms) bond formation and for mechanistic studies.[1] Palladium(0)-assisted reactions are especially fruitful in the field of organic synthesis because the reaction proceeds catalytically.[1a] For enantioselective allylic reactions using palladium–chiral ligand complexes,[2] a wide variety of ligands have been developed in which high levels of asymmetric induction and mechanistic understanding have been successfully demonstrated. As a nucleophile in the asymmetric allylic alkylations, stabilized 'soft' nucleophiles with electron-withdrawing groups such as anionic species derived from malonates have generally been required. In the aspect of synthetic strategy, we have been exploring the use of ketene silyl acetals in order to extend the scope of asymmetric alkylations. Since ketene silyl acetals[3] can be readily prepared from esters having α-hydrogen atoms, the current approach will expand the utilization of asymmetric alkylations in organic synthesis and play an important role in place of less stabilized 'harder' nucleophiles such as anionic species of monoesters. Herein we wish to describe enantioselective allylic substitutions using ketene silyl acetals as a nucleophile catalyzed by the Pd(0)–amidine complex[4] and their mechanistic interpretation along with the result using (*S*)-BINAP as a more general chiral ligand.

Ketene silyl acetals **3a–d** were prepared according to the literature.[5] The new P–N bidentate ligand, phosphorus-containing chiral amidine **1**,[4] which demonstrated excellent enantiometric excess in the

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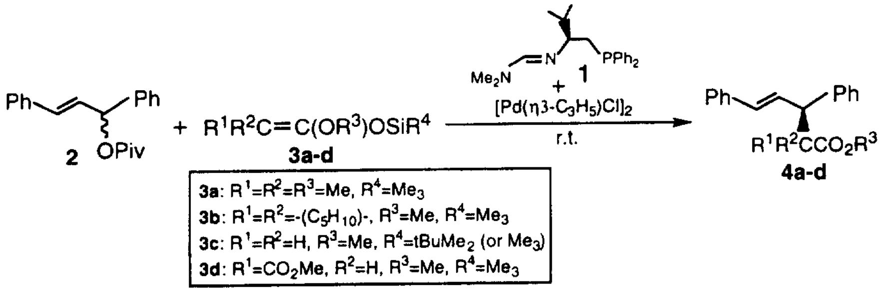
allylic alkylations using Trost's procedure,[6] was firstly applied to the present approach (Scheme 1). As a typical procedure, allylpalladium chloride dimer and the amidine **1** were mixed in a solvent at room temperature under argon, followed by adding (*E*)-1,3-diphenylprop-2-enyl pivalate **2** dissolved in the solvent. Ketene silyl acetal was then added to the π-allyl palladium complex solution. The substituted product thus obtained was isolated by preparative TLC.



3a: $R^1=R^2=R^3=Me$, $R^4=Me_3$
3b: $R^1=R^2=\text{-}(C_5H_{10})\text{-}$, $R^3=Me$, $R^4=Me_3$
3c: $R^1=R^2=H$, $R^3=Me$, $R^4=tBuMe_2$ (or Me_3)
3d: $R^1=CO_2Me$, $R^2=H$, $R^3=Me$, $R^4=Me_3$

Scheme 1.

As summarized in Table 1, the asymmetric alkylations with various ketene silyl acetals[7] proceeded under conditions catalyzed by the Pd–amidine complex in which excellent levels of enantiometric excess were achieved.[8] A reduction of the amount of catalyst did not affect the enantiometric excess significantly (runs 1–3). The use of THF as a solvent resulted in the decrease of chemical yield and enantioselectivity (runs 4, 6, and 10). It appeared that the steric hindrance of ketene silyl acetals at R^1 and R^2 affected the chemical yields (run 5). The reaction using **3c** did not proceed even if the catalyst amount and the reaction time were increased. This result could be derived from the lower nucleophilicity of **3c** compared with alkyl-substituted **3a** and **3b**.

In the well-known procedure[6] to generate a soft anionic nucleophile by reacting dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), and lithium acetate, the anion species would be produced

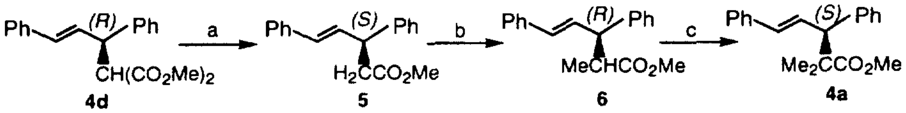
Table 1
Asymmetric allylic substitutions with ketene silyl acetals **3a–d** catalyzed by palladium complex of phosphorus-containing amidine **1**[a]

Run	Ketene silyl acetal $R^1R^2C=C(OR^3)OSiR^4$				Molequiv. of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Solvent	Time (h)	Yield[b] (%)	E.e.[c] (%)
	R^1	R^2	R^3	R^4					
1	Me	Me	Me	Me_3	0.05	CH_2Cl_2	24	81	90(*S*)[d]
2	Me	Me	Me	Me_3	0.025	CH_2Cl_2	24	78	90(*S*)
3	Me	Me	Me	Me_3	0.01	CH_2Cl_2	48	43	87(*S*)
4	Me	Me	Me	Me_3	0.025	THF	24	13	74(*S*)
5	$\text{-}(C_5H_{10})\text{-}$		Me	Me_3	0.025	CH_2Cl_2	24	42	90[e,f]
6	$\text{-}(C_5H_{10})\text{-}$		Me	Me_3	0.025	THF	24	17	77[f]
7	H	H	Me	$tBuMe_2$	0.025, 0.05	CH_2Cl_2	24, 85	-	-
8	CO_2Me	H	Me	Me_3	0.025	CH_2Cl_2	24	93	93(*R*)
9	CO_2Me	H	Me	Me_3	0.025	$ClCH_2CH_2Cl$	24	95	93(*R*)[g]
10	CO_2Me	H	Me	Me_3	0.025	THF	24	25	78(*R*)

a. Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/1,3-diphenyl-2-propenyl pivalate/ketene silyl acetal=1-5/4-20/100/300.
b. Isolated yield by preparative TLC on silica gel.
c. The enantiometric excess was determined by using HPLC with a chiral column, Daicel Chiralpak AD.
d. $[\alpha]_D^{26}=-43.1$ (*c* 0.7, EtOH). e. $[\alpha]_D^{25}=-27.4$ (*c* 0.3, EtOH).
f. The absolute configuration of **4b** is suggested to be *S* according to that of **4a**.
g. $[\alpha]_D^{25}=+19.4$ (*c* 0.7, EtOH).

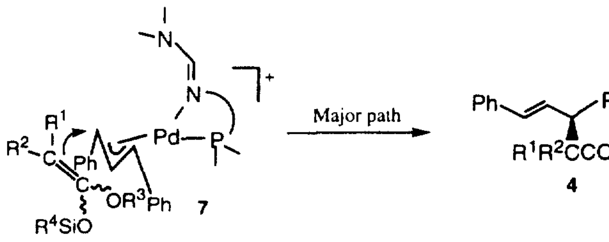
directly from dimethyl malonate. In the reaction using the BSA, the formation of carbomethoxy ketene methyltrimethylsilyl acetal **3d** could not be detected by ^{1}H NMR.[9] This observation suggests that the BSA does not work as a silylating agent to form **3d** but reacts as a base.[6]

The current reaction could proceed by a nucleophilic attack of the ketene silyl acetal on the π-allyl complex through an interaction of π-orbitals between the π-allyl and the carbon–carbon double bond of the ketene silyl acetal. Another possible path is a nucleophilic attack of pivalate anion to the silyl group. The reactions using **3d** might be induced by the latter case because a good conversion was achieved in spite of the lower nucleophilicity due to the attached electron-withdrawing group. The absolute configuration of methyl 2,2-dimethyl-3,5-diphenylpent-4-enoate **4a** was determined by comparing HPLC peaks of **4a** with those of the reference *S* sample[10] derived from (3*R*)-methyl 2-carbomethoxy-3,5-diphenylpent-4-enoate **4d** as depicted in Scheme 2. The absolute configuration of 3-(1-carbomethoxycyclohexyl)-1,3-diphenyl-1-propene **4b** was suggested to have the same *S* configuration as that of **4a** by similarity of elution order in the HPLC analysis. The present asymmetric allylations using ketene silyl acetals could proceed through the complex **7** as a major path in which the nucleophilic attack proceeded from the side opposite the palladium[11] and was induced predominantly at the allyl terminus trans to the diphenylphosphinyl group (Scheme 3).[4]



Reagents: (a) DMSO/H$_2$O, NaCl, 170°C, 13 h, 80% (b) LDA, MeI, -78°C ~ -20°C, 2 h, 89 %
(c) LDA, MeI, -78°C ~ -20°C, 2 h, 63 %

Scheme 2.



Scheme 3.

In order to extend the present approach, the asymmetric allylic alkylation of **2** catalyzed by a Pd(0)–(*S*)-BINAP complex was conducted using **3a** under the same conditions as that of run 2 in Table 1. The reaction using dichloromethane as a solvent afforded the alkylated product **4a** having the *S* configuration in 89% yield (65% e.e.). It was demonstrated that the asymmetric reaction proceeded on a level with that using the amidine ligand in terms of conversion. The enantioselectivity was moderate although the reactivity of ketene silyl acetal was confirmed.

In summary, we have developed a useful route to excellent levels of enantioselective alkylations along with good conversion using ketene silyl acetals as nucleophiles and the new type of chiral ligand, phosphorus-containing amidine. The process could be applied to the Pd(0) catalyst coordinated with another type of chiral ligand. Further efforts are currently in progress with respect to other asymmetric reactions using the amidine ligand, the modification of amidine ligand, and the extension of the present process using ketene silyl acetals to practical applications such as total syntheses of natural products.

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9. Dimethyl malonate (1.644 mmol), BSA (1.644 mmol), and lithium acetate (0.0273 mmol) in 2 ml of dichloromethane were stirred at room temperature under argon for 1.5 h. The volatiles were removed in vacuo immediately. The ^{1}H NMR spectrum of the residue was measured, followed by comparison of the spectrum with that of carbomethoxy ketene methyltrimethylsilyl acetal **3d**.
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