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Asymmetric Allylation of Unsymmetrical 1,3-Diketones Using a BINAP–Palladium Catalyst

Ryoichi Kuwano,*,† Kei-ichi Uchida,‡ and Yoshihiko Ito*,‡

Department of Chemistry, Graduate School of Sciences, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan, and Department of Synthetic Chemistry & Biological Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

rkuwascc@mbox.nc.kyushu-u.ac.jp

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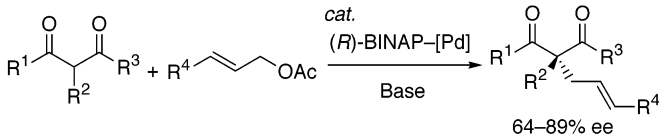
ABSTRACT



The chiral palladium complex generated in situ from [Pd(η^3-allyl)Cl]$_2$ and (*R*)-BINAP is a good catalyst for the catalytic asymmetric allylation of 1,3-diketones. The reaction provided chiral 2,2-dialkyl-1,3-diketones with 64–89% ee in high yields (13 examples). Enantiomeric excesses are strongly affected by the γ-substituent of the allylic substrates. A variety of unsymmetrical 1,3-diketones were alkylated with cinnamyl acetate in good enantioselectivities via use of the BINAP–palladium catalyst (77–89% ee).

Highly enantioselective formation of a quaternary chiral carbon center is an important goal in organic synthetic chemistry.[1] Alkylation of 2-substituted 1,3-diketones is one of the synthetic approaches for the formation of quaternary carbons. However, enantioselective versions of the alkylation have so far been regarded as difficult, probably due to the steric and electronic similarities of the two carbonyl groups of the 1,3-diketones.[2−4]

This paper reports an enantioselective alkylation of unsymmetrical 1,3-diketones using allylic acetates in the presence of a chiral palladium catalyst. Efficient enantioselective allylations for creation of a chiral carbon center on a soft nucleophile have only been achieved with difficulty.[3,5] The prochiral 1,3-diketone enolate is generally believed to be located far from the chiral ligand in the transition state of the nucleophlic attack on the chiral (η^3-allyl)palladium intermediate.

Previously, we reported a highly enantioselective allylation of prochiral nucleophiles, α-acetamido-β-ketoesters.[6] In the asymmetric reaction, a BINAP−palladium complex was the most enantioselective catalyst for the preparation of α-amino acids bearing a quaternary chiral α-carbon with up to 95% ee. To evaluate the BINAP−palladium catalyst for the

† Kyushu University.
‡ Kyoto University.

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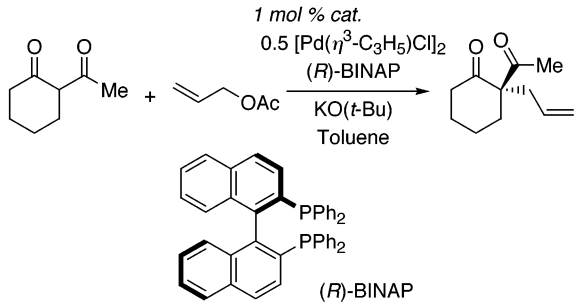
asymmetric allylation of 1,3-diketones, the reaction of 2-acetylcyclohexanone with allyl acetate in the presence of KO(*t*-Bu) and 1 mol % [Pd(η^3-C_3H_5)Cl]-(*R*)-BINAP catalyst in toluene (Scheme 1) was conducted. The reaction at −60

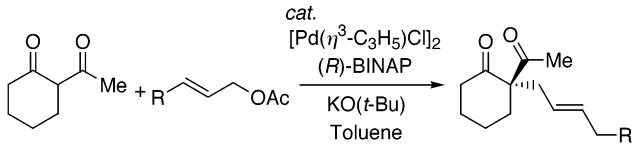
Scheme 1



°C produced (*S*)-2-acetyl-2-allylcyclohexanone with 64% ee in 82% yield.

The BINAP−palladium catalyst promoted alkylations with γ-substituted allylic acetates as well as allyl acetate (Table 1). No formation of a regioisomeric side product was

Table 1. Catalytic Asymmetric Alkylations of 2-Acetylcyclohexanone with Allylic Acetates[a]



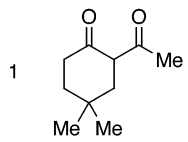
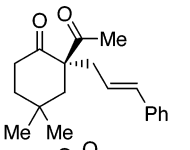
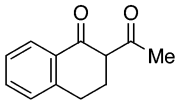
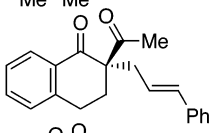
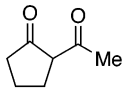
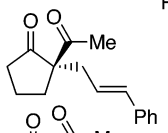
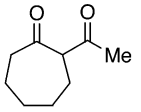
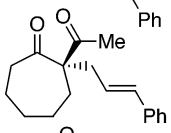
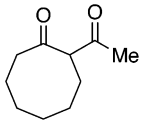
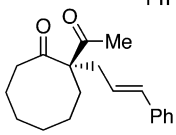
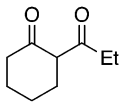
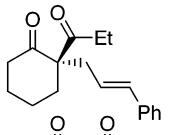
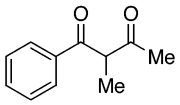
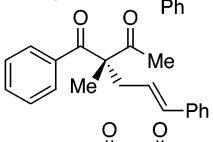
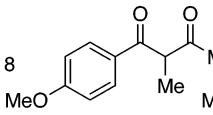
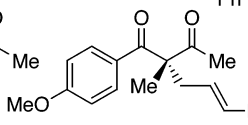
entry	R	temp, °C	yield, %[b]	ee, %[c]
1	C_3H_7	−30	79	64
2	*cyclo*-C_6H_{11}	−30	65	65
3	Ph	−60	99	85
4	*p*-MeO-C_6H_4	−60	87	83
5	*p*-CF_3-C_6H_4	−60	87	84

[a] Reactions were conducted in 2.5 mL of toluene for 24 h. 2-Acetylcyclohexanone/allylic acetate (0.5 mmol)/KO(*t*-Bu)/[Pd(η^3-C_3H_5)Cl]$_2$/BINAP = 120/100/120/0.5/1.05. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis.

observed. Aromatic γ-substituents yielded chiral products with a higher enantiomeric excess than aliphatic ones (entries 3−5 vs 1 and 2). The highest selectivity [85% ee (*S*)] in this series was achieved with cinnamyl acetates (entry 3). No reaction of prenyl, methallyl, and 1,3-diphenyl-2-propenyl acetates occurred under the reaction conditions.

The scope of 1,3-diketones in the BINAP−palladium-catalyzed allylation is extensive, as shown in Table 2. The highest enantioselectivity (89% ee) was observed in the reaction of 2-acetyl-4,4-dimethylcyclohexanone (entry 1). Substrates with a five-, seven-, and eight-membered ring underwent alkylation with cinnamyl acetate at a high level of enantioselectivity (entries 3−5). The reaction of a 2-pro-

Table 2. Catalytic Asymmetric Allylation of 1,3-Diketones with Cinnamyl Acetate[a]

Entry	Diketone	Product	Yield, %[b]	Ee, %[c]
1			92	89
2			87	87
3			92	81
4			95	77
5			90	84
6			91	82
7			90	83
8			96	80

[a] Reactions were conducted at −60 °C in 2.5 mL of toluene for 24 h. 1,3-Diketones/cinnamyl acetate (0.5 mmol)/KO(*t*-Bu)/[Pd(η^3-C_3H_5)Cl]$_2$/(*R*)-BINAP = 120/100/120/0.5/1.05. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

pionyl substrate (entry 6) proceeded with selectivity similar to that of the 2-acetyl substrate (Table 1, entry 3). Acyclic 1,3-diketones were alkylated with cinnamyl acetate in the presence of the BINAP−palladium catalyst and yielded the corresponding chiral 2,2-dialkyl-1,3-diketones with over 80% ee (entries 7 and 8).

The cinnamyl group of the products given in Table 2 can readily convert into a carboxymethyl group (Scheme 2). After selective protection of cyclohexanone with cyclic ketal,[3c] oxidative cleavage of the C−C double bond with $NaIO_4$−RuO_2 catalyst[7] provided the corresponding carboxylic acid. The acid was isolated as a methyl ester after esterification with (trimethylsilyl)diazomethane[8] in a good yield. This result demonstrates that cinnamyl acetate in the present asymmetric allylation can work as a synthon of a carboxy-

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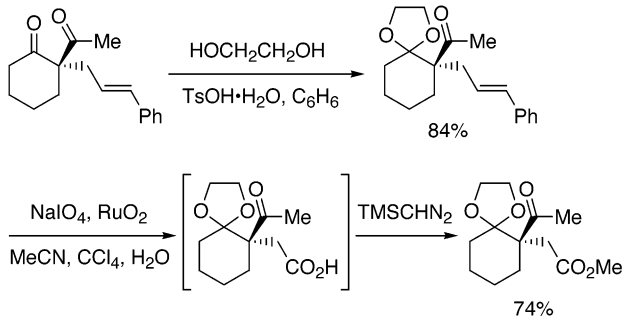
Scheme 2



methyl group, which can be further transformed into various functional groups.

In conclusion, we developed a new protocol of enantioselective allylation of various unsymmetrical 1,3-diketones by a BINAP−palladium catalyst, which is commercially available. This method will allow organic chemists to use the asymmetric allylation of prochiral nucleophiles without synthesizing specialized chiral ligands. Pursuit of the origin of the enantioselectivity in the asymmetric allylation is in progress.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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