

단 신

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Palladium-Catalyzed Asymmetric Allylic Alkylation in the Presence of Chiral Cinchonidinium Salts

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Palladium-catalyzed asymmetric allylic substitution is a widely employed process in organic synthesis for the enantioselective formation of carbon-carbon bonds.¹ In general, chiral ligands were found to be efficient chiral sources for asymmetric allylic substitutions. These ligands regulate the enantioselectivity through their steric and ligand effects.¹ While a number of efficient asymmetric palladium-catalyzed asymmetric allylic substitutions using chiral ligands have been developed, a drawback is that the majority of reported reaction conditions are sensitive to moisture. Therefore, the development of asymmetric allylic substitutions under moisture-stable reaction conditions is still in great demand.

Phase-transfer catalysis is an important and useful method in organic synthesis.² Recently, there have been successful applications to catalytic asymmetric synthesis using cinchona alkaloid-derived quaternary ammonium salts.³ The introduction of the bulky subunit at the bridgehead nitrogen of cinchona alkaloids leads to enhancement of the stereoselectivity in catalytic phase-transfer reactions.⁴ As

a part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,⁵ we reported the catalytic enantioselective alkylation of active methylenes and methines promoted by chiral phase-transfer catalysts.⁶ In this paper, we wish to report the Pd-catalyzed enantioselective allylic alkylation of malonates **2** with *rac*-1,3-diphenyl-2-enyl acetate (**1**) in the presence of cinchonidine-derived quaternary ammonium salts **I-VIII** (Fig. 1).

To determine optimum reaction conditions for the Pd-catalyzed enantioselective allylic alkylation of malonates **2** with *rac*-1,3-diphenyl-2-enyl acetate (**1**), we initially investigated the reaction of catalytic enantioselective allylic alkylation of dimethyl malonates (**2a**) with *rac*-1,3-diphenyl-2-enyl acetate (**1**), catalyzed by 2.5 mol% of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)_2\text{Cl}]_2$ in the

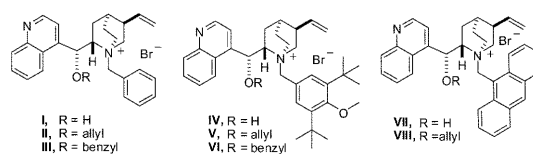
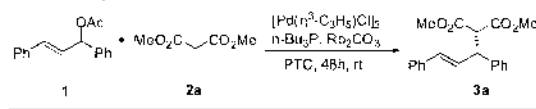


Fig. 1. Structures of chiral ammonium salts.

Table 1. Optimization of the reaction conditions



entry	PTC	solvent	yield ^a (%)	ee ^b (%)
1	I	toluene	67	12
2	II	toluene	61	40
3	III	toluene	71	31
4	IV	toluene	55	13
5	V	toluene	67	45
6	VI	toluene	61	37
7	VII	toluene	68	43
8	VIII	toluene	51	55
9	VIII	toluene	52	31
10	VIII	CH₂Cl₂	72	5
11	VIII	Et₂O	62	59
12	VIII	benzene	54	45
13	VIII	<i>p</i> -xylene	60	63
14	VIII	mesitylene	65	73

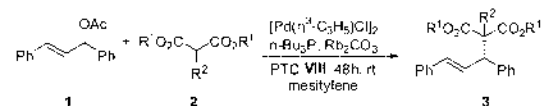
^aYield of isolated product. ^bEnantiopurity of **3a** was determined by HPLC analysis with Chiralpak AD-H column. ^cReaction was carried out using K₂CO₃ instead of Rb₂CO₃ as a base.

presence of cinchonidine-derived quaternary ammonium salts in toluene for 48 h at room temperature. We first examined the impact of the structure of cinchonidine-derived quaternary ammonium salts **I-VIII** on enantioselectivity (Table 1, entries 1-8). Under the standard reaction conditions, The high selectivity was obtained with quaternary ammonium salt **VIII**, which have anthracenylmethyl group. Concerning the solvent (entries 8, 10-14), the use of mesitylene gave the best results in the yield and the enantiomeric excess (entry 14).

To examine the generality of the Pd-catalyzed enantioselective allylic alkylation of malonates **2** with *rac*-1,3-diphenyl-2-enyl acetate (**1**) in the presence of cinchonidine-derived quaternary ammonium salt **VIII**, we studied the allylic alkylation of malonates **2a-2d**. As it can be seen by the results summarized in Table 2, the corresponding α -alkylated malonates **3a-d** were obtained in moderate yields (60-69%) and enantioselectivities (55-73% ee).

In conclusion, we have developed a practical Pd-catalyzed enantioselective allylic alkylation of malonates **2** with *rac*-1,3-diphenyl-2-enyl acetate (**1**) in

Table 2. Pd-catalyzed enantioselective allylic alkylation of malonates **2**



entry	2, R ¹ , R ²	yield ^a (%)	ee ^b (%)
1	2a , Me, H	3a , 65	73
2	2b , Et, H	3b , 69	75
3	2c , Bn, H	3c , 60	55
4	2d , Me, Me	3d , 63	57

^aYield of isolated product. ^bEnantiopurity of **3** was determined by HPLC analysis with Chiralpak AD-H column. ^cAbsolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding malonates with literature value.⁷

the presence of cinchonidine-derived quaternary ammonium salts. The desired α -alkylated malonates were obtained in moderate yields and reasonable enantioselectivities (up to 75% ee) under mild reaction conditions. We believe that Pd-catalyzed enantioselective allylic alkylation with chiral quaternary ammonium salts would be a useful alternative to the chiral Pd-ligand mediated reaction for constructing stereogenic centers. Further details and application of this allylic alkylation will be presented in due course.

EXPERIMENTAL

General procedure for the Pd-catalyzed enantioselective allylic alkylation of malonates **2**

To a solution of [Pd(η^3 -C₃H₅)Cl]₂ (0.9 mg, 0.0025 mmol), *n*-tributyl phosphine (1 mL, 0.005 mmol), and *rac*-1,3-diphenyl-2-enyl acetate (**1**, 25.2 mg, 0.1 mmol) in mesitylene (0.5 mL) were successively added Rb₂CO₃ (184.7 mg, 0.8 mmol), chiral ammonium salt **VIII** (6.1 mg, 0.01 mmol), and malonate (**2**, 0.2 mmol) at room temperature. After being stirred vigorously for 48 h, the reaction mixture was diluted with ethyl acetate (20 mL). The organic phase was washed with water (2 × 10 mL) and brine (10 mL). The extract was dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate : benzene : hexane =

1:1:12) to give alkylated products **3**.

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