 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. 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. 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. Recently, there have been successful applications to catalytic asymmetric synthesis using cinchona alkaloid-derived quaternary ammonium salts. The introduction of the bulky subunit at the bridgehead nitrogen of cinchona alkaloids leads to enhancement of the stereoselectivity in catalytic phase-transfer reactions. As a part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers, we reported the catalytic enantioselective alkylation of active methylenes and methines promoted by chiral phase-transfer catalysts. 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 [Pd(L-C,H),Cl], in the...
In 1910, we 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 (I) 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 (I) in the presence of cinchonidine-derived quaternary ammonium salts. The desired α-alkylated malonates were obtained in moderate yields and reasonable enantioselectivities (up to 73% 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(n^3-C_3H_5)Cl]_2 \( (0.9 \text{ mg}, 0.0025 \text{ mmol}) \), n-tributyl phosphine \( (1 \text{ mL}, 0.005 \text{ mmol}) \), and rac-1,3-diphenyl-2-enyl acetate \( (1, 25.2 \text{ mg}, 0.1 \text{ mmol}) \) in mesitylene \( (0.5 \text{ mL}) \) were successively added Rh_2CO \( (184.7 \text{ mg}, 0.8 \text{ mmmol}) \), chiral ammonium salt VIII \( (6.1 \text{ mg}, 0.01 \text{ mmol}) \), and malonate \( (2, 0.2 \text{ mmol}) \) at room temperature. After being stirred vigorously for 48 h, the reaction mixture was dilutted with ethyl acetate \( (20 \text{ mL}) \). The organic phase was washed with water \( (2 \times 10 \text{ mL}) \) and brine \( (10 \text{ mL}) \). The extract was dried over MgSO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate : benzene = 2:1:1).
1:1:12) to give alkylated products 3.

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REFERENCES


