



Catalytic asymmetric alkylation in aqueous micelles

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Abstract

Palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate occurred in water in the presence of surfactants, using K_2CO_3 as the base. Enantioselectivities of up to 92% were obtained using chiral atropisomeric diphosphines. © 2000 Elsevier Science Ltd. All rights reserved.

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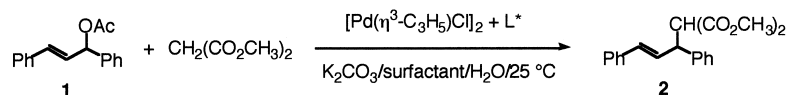
Organometallic homogeneous catalysis is now a well-used methodology in organic synthesis. Generally these systems have the advantages of high activity as well as selectivity, and also good reproducibility under very mild conditions. More recently the idea of biphasic (aqueous/organic) catalysis has attracted great attention.¹ The substitution of organic solvents by water is also advantageous for environmental and economic reasons. One way is the use of water-soluble ligands in order to solubilize the organometallic catalyst in water; however, in this case substrates have to show some significant water solubility. The other way is the use of non-water soluble ligands in the presence of surfactants. This second approach has been successfully applied in asymmetric hydrogenation² as well as the Suzuki coupling reaction.^{2i,3} In the former reaction, higher enantioselectivities than those obtained in organic solvents have been obtained in the reduction of amino-acid precursors using rhodium complexes associated with chiral non-water soluble ligands in the presence of surfactants.

Carbon–carbon bond formation is a general aim in transition metal-catalyzed organic synthetic chemistry. One of the very successful methods for carbon–carbon coupling is the palladium-catalyzed reaction of allylic acetates with carbon nucleophiles, the so-called Tsuji–Trost reaction.⁴ Very high enantioselectivities have been obtained using diphosphines, aminophosphines or bisoxazolines as the chiral ligands.⁵ Recently, Uozumi et al. showed that amphiphilic resin supported palladium complex was active in this coupling reaction, the catalyst being recycled without loss of activity.^{6a} One example of asymmetric allylic alkylation was also

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described using chiral amphiphilic resin supported palladium complex, with enantioselectivity of up to 84%.^{6b} Herein we present some preliminary results about the asymmetric allylic alkylation reaction in a micellar system.

We first investigated the alkylation of 1,3-diphenyl-2-propenyl acetate **1** with dimethyl malonate in the presence of K_2CO_3 as the base, and the palladium complex prepared in situ from $[Pd(\eta^3-C_3H_5)Cl]_2$ and (*R*)-Binap (Scheme 1, Table 1).



Scheme 1.

Table 1
Asymmetric allylic alkylation of **1** with dimethyl malonate using palladium-(*R*)-Binap complex^a

| Entry | Surfactant | Time (h) | Conversion (%) ^b | e.e. (%) (<i>S</i>) ^c |
|-------|---|----------|-----------------------------|------------------------------------|
| 1 | No | 0.5 | 0 | – |
| 2 | <i>n</i> -C ₁₆ H ₃₃ N ⁺ Me ₃ HSO ₄ [–] | 0.5 | 47 | 89 |
| 3 | No | 1 | 45 | 85 |
| 4 | <i>n</i> -C ₁₆ H ₃₃ N ⁺ Me ₃ HSO ₄ [–] | 1 | 100 | 91 |
| 5 | No | 4 | 62 | 89 |
| 6 | <i>n</i> -C ₁₆ H ₃₃ N ⁺ Me ₃ HSO ₄ [–] | 4 | 99 | 90 |
| 7 | <i>n</i> -C ₁₆ H ₃₃ N ⁺ Me ₃ Br [–] | 1 | 47 | 29 |
| 8 | <i>n</i> -C ₁₂ H ₂₅ OSO ₃ Na | 1 | 0 | – |
| 9 | <i>n</i> -C ₁₂ H ₂₅ SO ₃ Na | 1 | 3 | 0 |
| 10 | Brij 35 | 1 | 98 | 81 |
| 11 | Tween 40 | 1 | 100 | 67 |
| 12 | <i>n</i> -C ₁₀ H ₂₁ N ⁺ Me ₂ (CH ₂) ₃ SO ₃ [–] | 1 | 89 | 74 |
| 13 | <i>n</i> -C ₁₂ H ₂₅ N ⁺ Me ₂ (CH ₂) ₃ SO ₃ [–] | 1 | 78 | 82 |
| 14 | <i>n</i> -C ₁₆ H ₃₃ N ⁺ Me ₂ (CH ₂) ₃ SO ₃ [–] | 1 | 76 | 81 |

^a The reaction was carried out in water in the presence of 5 mol% palladium at 25°C, generated in situ by mixing $[Pd(\eta^3-C_3H_5)Cl]_2$ with (*R*)-Binap, with agitation. The ratio of **1** (mol)/dimethyl malonate (mol)/ K_2CO_3 (mol)/surfactant (mol)/H₂O (L)/Pd (mol)/Binap (mol)=0.3/3/3/0.2/4/0.015/0.03.

^b Determined by GC using C₆H₅-O-C₆H₅ as the internal standard.

^c Determined by HPLC analysis with chiral stationary phase column Chiralpak AD.

Reaction in the presence of cetyltrimethylammonium hydrogen sulfate as the surfactant quantitatively gave the alkylated product **2** after 1 h at 25°C with 91% enantioselectivity (Table 1, entry 4). It should be noticed that alkylation also occurred in water without surfactant to give compound **2** with 89% enantioselectivity, but with only 62% conversion after 4 h (Table 1, entry 5). Cetyltrimethylammonium bromide, another cationic surfactant, gave lower conversion (47%) and enantioselectivity (29%) (Table 1, entry 7).

Anionic surfactants, such as sodium dodecylsulfonate or sodium dodecylsulfate, gave no reaction under the above conditions (Table 1, entries 8–9). Although non-ionic surfactants such as Brij 35 or Tween 40 gave a quantitative conversion after 1 h, the observed enantioselectivities were lower (Table 1, entries 10–11). The zwitterionic surfactants, *N*-decyl-, *N*-dodecyl-, and *N*-hexadecyl-*N,N*-dimethyl-3-ammonio-1-propanesulfonate gave quite similar results (Table 1, entries 12–14); however, the conversions and enantioselectivities are lower than in the case of cetyltrimethylammonium hydrogen sulfate.

We then studied the influence of the chiral ligand on both the activity and the enantioselectivity of this alkylation reaction in the presence of cetyltrimethylammonium hydrogen sulfate (Table 2). (*S*)-Biphemp and (*R*)-MeOBiphemp ligands gave a quantitative conversion after 4 h, with enantioselectivities of up to 88 and 92%, respectively (Table 2, entries 4 and 6); again quite closed enantioselectivities were obtained in water alone, but with lower conversions (Table 2, entries 3 and 5). (*R*)-Quinap and Trost ligand gave lower conversions and enantioselectivities (Table 2, entries 7 and 9), although Chiraphos gave no reaction at all (Table 2, entry 8).

These preliminary results show that palladium-catalyzed alkylation reaction of allylic substrates occurred in water in the presence of suitable surfactants with very high activities and enantioselectivities. Work is presently in progress in order to extend this asymmetric reaction in aqueous micelles to other substrates as well as nucleophiles and to supported surfactants.

Table 2
Asymmetric allylic alkylation of **1** with dimethyl malonate using chiral palladium complex in the presence of $n\text{-C}_{16}\text{H}_{33}\text{N}^+\text{Me}_3\text{HSO}_4^-$ ^a

| Entry | Surfactant | Ligand | Time (h) | Conversion (%) ^b | e.e. (%) (config.) ^c |
|-------|------------|--------------------------------------|----------|-----------------------------|---------------------------------|
| 1 | No | (<i>R</i>)-Binap | 4 | 62 | 89 (<i>S</i>) |
| 2 | Yes | (<i>R</i>)-Binap | 1 | 100 | 91 (<i>S</i>) |
| 3 | No | (<i>S</i>)-Biphemp ^d | 4 | 62 | 88 (<i>R</i>) |
| 4 | Yes | (<i>S</i>)-Biphemp ^d | 4 | 100 | 88 (<i>R</i>) |
| 5 | No | (<i>R</i>)-MeOBiphemp ^d | 4 | 56 | 90 (<i>R</i>) |
| 6 | Yes | (<i>R</i>)-MeOBiphemp ^d | 4 | 100 | 92 (<i>R</i>) |
| 7 | Yes | (<i>R</i>)-Quinap | 4 | 50 | 65 (<i>R</i>) |
| 8 | Yes | (<i>S,S</i>)-Chiraphos | 4 | 0 | |
| 9 | Yes | (<i>R,R</i>)-Trost ligand | 4 | 56 | 52 (<i>R</i>) |

^a The reaction was carried out in water in the presence of 5 mol% palladium at 25°C, generated in situ by mixing $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$ with the chiral ligand, with agitation. The ratio of **1** (mol)/dimethyl malonate (mol)/ K_2CO_3 (mol)/surfactant (mol)/ H_2O (L)/Pd (mol)/ligand (mol)=0.3/0.9/0.9/0.2/4/0.015/0.03.

^b Determined by GC using $\text{C}_6\text{H}_5\text{-O-C}_6\text{H}_5$ as the internal standard.

^c Determined by HPLC analysis with chiral stationary phase column Chiralpak AD.

^d Ref. 7.

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