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Water-mediated transition-metal-free Tsuji–Trost-type reaction

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Abstract—The treatment of 1-acetoxy-1,3-diphenylpropene (1) by C-, O-, S- and N-nucleophiles in *basic aqueous media* produced the corresponding substitution products in the absence of a transition-metal catalyst. Mechanistic studies, using (S)-1 and p-MeC₆H₄CH(OAc)CH=CHPh as substrates, led to propose a B_{AL}1 cleavage of the ester function leading to a stabilized allylic carbocation as intermediate.

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Aqueous chemistry has received considerable attention in synthetic organic chemistry for environmental, economical, safety reasons and by showing unique reactivities and selectivities that are not attained in organic solvents.¹ One of the first illustrations of the potentials of this 'green chemistry' was the positive effect of water on rates and selectivities of Diels–Alder reactions observed in the early 1980s by Breslow and Grieco.² The role of water was explained by introducing the concept of hydrophobic effects in organic reactions.³ Water has unique physical and chemical properties such as high dielectric constant and cohesive energy density compared to most organic solvents.^{3,4} By utilizing these properties, it should be possible to observe reactivities that cannot be attained in organic solvents.

For allylic substitution reactions, palladium methods are probably the most widely employed⁵ and, some years ago, Sinou et al. reported the Tsuji–Trost reaction in a two-phase aqueous–organic medium using a sulfonated phosphine ligand, TPPTS, coordinated to palladium.^{6,7}

Recently, we have reported the use of the hydrophilic ligand $[(HOCH_2CH_2NHCOCH_2)_2NCH_2]_2$ (L_H) in copper-catalyzed allylic oxidations in water and the efficient recycling of the catalytic system.⁸ This led us to study allylic substitutions with L_H associated to palladium salts to propose an alternative to the use of

air-sensitive phosphines. Surprisingly, we observed that the reaction may *occur in the absence of any transition metal catalyst* to afford substituted products with N, S, O, or C-nucleophiles when carried out in the presence of water which becomes an essential agent for the success of the process (Eq. (1)).



We first studied the nucleophilic substitution of 1-acetoxy-1,3-diphenylpropene (1) with acetylacetone (2)equiv.) at 50°C in water⁹ in the presence of K_2CO_3 (2 equiv.) and 5% of both $PdCl_2(MeCN)_2$ and L_H (Eq. (1)). The reaction was very sluggish, 36% conversion of 1 in 6 days affording 17% of the expected substituted product 2a. Therefore, the experiment was repeated in using a range of co-solvents:¹⁰ 2a was produced with various yields, the nature of the co-solvent having a dramatic effect on the efficiency and selectivity of the reaction (Fig. 1). For example, only 63% conversion and 36% **2a** were obtained in 6 days in a 1/1 mixture of water and THF while complete conversion of 1 was attained in 1 day with methanol as co-solvent to afford 92% of 2a and traces of the dissymmetric ether 2e (Table 1, entry 1). The reaction mixture in H₂O/MeOH was extracted by methylene chloride and, as expected, we observed that the aqueous phase remained catalytically active, four successive reuses yielding 90-84% 2a.

Keywords: water chemistry; allylic acetate; substitution; palladium; $B_{AL}1$ -SN₁, mechanism.

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Figure 1. Substitution of 1 by acetylacetone in $H_2O/co-sol-$ vent in the presence of $PdCl_2(MeCN)_2-L_H$; experimental conditions as in Table 1 (entry 1) except the reaction time, 144 h, in $H_2O/MeCN$ and H_2O/THF .

When the reaction in H₂O/MeOH was performed in the absence of any Pd and ligand, the quantitative conversion of 1 was obtained in 24 h at 50°C to produce 40% 2a and 55% 2e (Table 1, entry 2). Compared to the previous reaction (entry 1), the selectivity was different, all the conditions, except the palladium- L_H catalyst, being the same. The surprising allylic alkylation of 1 in the absence of a transition-metal^{11,12} led us to examine the influence of other co-solvents on this Pd-uncatalyzed reaction (Fig. 2). The alkylation product was obtained with fair selectivities in the other tested co-solvents but high conversion was only attained in $H_2O/$ DMF (entry 3); this differs from the Pd-catalyzed reaction for which the best solvent was H₂O/MeOH (Fig. 1). It is important to note (i) the unreactivity of 1 when the experiment in DMF was carried out without added water (entry 4) and (ii) the absence of hydrolysis of 1 in basic H_2O/DMF (entry 3). In contrast to DMF,

Table 1. Reactions of 1 (0.8 mmol) at 50°C for 24 h



Figure 2. Substitution of 1 by acetylacetone in $H_2O/co-sol-$ vent; experimental conditions as in Table 1 (entry 2).

a complete conversion of **1** was observed in MeOH (entry 5); however, these conditions did not lead to **2a**, but afforded ether **2e** and alcohol **2f**, this latter, which was not observed using H₂O/MeOH as solvent (entry 2), being here the main product. Since K₂CO₃ is poorly soluble in DMF, an organic base, DBU, was used. Similar results were obtained: no reaction occurred in DMF (entry 6) while **2a** was isolated in 78% yield in H₂O/DMF (entry 7).

Repeating the reaction in H₂O/DMF with new glassware and stirring bar produced again **2a**. Therefore, it appeared that the formation of the C–C bond was really transition-metal-free and that water activated the substrate to the nucleophilic displacement. These results led us to test three other types of nucleophiles, phenol/ K_2CO_3 , sodium *p*-toluenesulfinate and morpholine, in the presence and in the absence of palladium under the above optimum aqueous conditions (entries 8–14). The expected adducts **2b**, **2c**¹³ and **2d** were isolated under

Entry	Cat. ^a (equiv.)	Nucleophile (2 equiv.)	Base (2 equiv.)	H ₂ O (mL)	Solvent (1 mL)	Conv. (%)	Products (%)
1	0.05	Acetylacetone	K ₂ CO ₃	1	MeOH	100	2a, 92+2e, traces
2	0	Acetylacetone	K_2CO_3	1	MeOH	100	2a , 40+ 2e , 55
3	0	Acetylacetone	K ₂ CO ₃	1	DMF	90	2a , 80
4	0	Acetylacetone	K_2CO_3	0	DMF	0	
5	0	Acetylacetone	K_2CO_3	0	MeOH	100	2e , 13+ 2f , 66
6	0	Acetylacetone	DBU	0	DMF	0	
7	0	Acetylacetone	DBU	1	DMF	90	2a , 78
8	0.05	Phenol	K_2CO_3	1	MeOH	32	2b , traces+ 2e , 20
9	0	Phenol	K_2CO_3	1	DMF	53	2b , 44
10 ^b	0	Phenol	K_2CO_3	1	DMF	94	2b , 73
11	0.05	<i>p</i> -MeC ₆ H ₄ SO ₂ Na	0	1	MeOH	100	2c , 74+ 2e , traces
12	0	p-MeC ₆ H ₄ SO ₂ Na	0	1	DMF	82	2c , 79
13	0.05	Morpholine	0	1	MeOH	100	2d , 95
14	0	Morpholine	0	1	DMF	100	2d , 96

^a Cat: equimolecular quantities of PdCl₂(MeCN)₂ and L_H.

^b Reaction time: 84 h.

both conditions and it was of interest to point out that the best yields were obtained without Pd-catalysis. Nevertheless, the substitution by PhOH required a longer reaction time to reach a high conversion (entries 9 and 10).

The transfer of the allyl group from acetate to nucleophilic species formally corresponds to a nucleophilic substitution with the acetate as the leaving group. In order to approach the mechanism of these unusual substitutions in the absence of a transition-metal catalyst, experiments were performed with the dissymmetric allylic acetate 3^{14} and (S)-1.¹⁵ medium may induce the selective cleavage of either the O-allyl or the O-acyl bond of the above allylic acetates.

The reversibility of the O-allyl bond cleavage in H₂O/ DMF, as shown by the isomerization of **3** (Eq. (3)) and the racemization of (S)-**1**, implies a competition between AcO⁻ and the other nucleophiles. This could explain the rather long reaction times required for efficient substitution by the nucleophiles especially with phenol/K₂CO₃.

No reaction of 1 took place in a polar aprotic solvent like DMF. It is known that ionization of neutral sub-

$$p-\text{MeC}_{6}\text{H}_{4} \xrightarrow{\text{OAc}} Ph \xrightarrow{\text{or Nu'Na^{+} or NuH}}_{H_{2}O/\text{DMF}(1/1)} p-\text{MeC}_{6}\text{H}_{4} \xrightarrow{\text{Nu}}_{Ph} \xrightarrow{\text{Nu}}_{p-\text{MeC}_{6}\text{H}_{4}} \xrightarrow{\text{Nu}}_{Ph} \xrightarrow{\text{Nu}}_{p-\text{MeC}_{6}\text{H}_{4}} \xrightarrow{\text{Nu}}_{Ph} \xrightarrow{\text{Nu}}_{p-\text{MeC}_{6}\text{H}_{4}} \xrightarrow{\text{Nu}}_{Ph} \xrightarrow{\text{Nu}}_{p-\text{MeC}_{6}\text{H}_{4}} \xrightarrow{\text{Nu}}_{Ph} \xrightarrow{\text{Nu}}_{p-\text{MeC}_{6}\text{H}_{4}} \xrightarrow{\text{Nu}}_{p-\text{MeC}_{6}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}_{p-\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}} \xrightarrow{\text{Nu}}_{p-\text{Nu}}} \xrightarrow{\text{Nu}}_{p-\text{$$

Subjecting **3** to the previous reagents in H₂O/DMF at 50°C (Eq. (2)) led to a non-regioselective reaction providing, in each case, a 1/1 mixture of **4** and **5** (**4a+5a**: 71%, **4b+5b**: 38%, **4c+5c**: 87%, **4d+5d**: 76%) as indicated by ¹H and ¹³C NMR analysis. In the absence of reagents, **3** was unchanged when heated at 50°C for 24 h in DMF while a 1/1 mixture of **3** and its allylic rearrangement product was recovered in H₂O/DMF (Eq. (3)).

strates is promoted by protic solvents.^{4,16} Therefore, we propose that addition of water to DMF favors the formation of the cation by hydrogen bonding with oxygen doublets of the substrate and then stabilization of the ion pair.

In aprotic solvents, the substitution of allylic acetates is often catalyzed by transition-metal complexes, in particular those of palladium which provide cationic η^3 -

$$p-\text{MeC}_{6}\text{H}_{4} \xrightarrow{\text{Ph}} \frac{\text{H}_{2}\text{O/DMF}(1/1)}{50 \text{ °C}, 24 \text{ h}} \xrightarrow{\text{3}} + p-\text{MeC}_{6}\text{H}_{4} \xrightarrow{\text{Ph}} \text{Ph}$$
(3)

The reaction of (S)-1 (95% e.e.) with acetyl acetone and K_2CO_3 in H_2O/DMF at 50°C for 24 h (conditions of Table 1, entry 3) afforded racemic **2a** (yield: 90%). Using (S)-1 (99% e.e.) and a reaction time reduced to 1 h, the e.e. of the recovered substrate was lowered to 89%. The reaction of (S)-1 (92% e.e.) in MeOH under conditions of Table 1, entry 7, provided alcohol (S)-2f (92% e.e.).

Since (*S*)-**2f** is produced with retention of the e.e., its formation in MeOH is due to a *trans*-esterification involving the classical acyl-oxygen bond cleavage and following the usual B_{AC} mechanism.¹⁶ The addition of water (entry 2) precludes this *trans*-esterification pathway and induces the cleavage of the allyl-O bond. The experiments from (*S*)-**1** (no e.e. of the adduct, racemization of the substrate) and **3** (no selectivity, isomerization of the substrate) in H₂O/DMF indicate that the substitutions occurred on a stabilized allylic carbocation, a $B_{AL}1$ -SN₁['] mechanism being involved.¹⁶ These experiments led to conclude that the modification of the allylpalladium intermediates.⁵ The present study shows that the addition of water may induce the substitution under transition-metal-free conditions, the process involving the formation of stabilized carbocations which react with different types of nucleophiles. Such a reaction pathway may be preferred to the hydrolysis which usually occurs in an aqueous basic medium.

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