Ag(I)-Catalyzed Michael Additions of β-Ketoesters to Nitroalkenes in Water: Remarkable Effect of Water as a Reaction Medium on Reaction Rates

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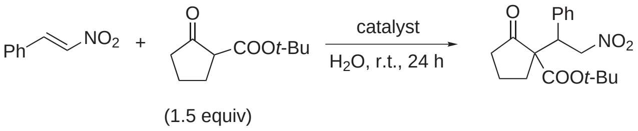
Abstract: AgOTf–PPh_3 complex-catalyzed Michael additions of β-ketoesters to nitroalkenes in water were performed. The system promotes the reaction efficiently only in water, and interestingly the reaction does not proceed well in organic solvents. In addition, this reaction system could be applied to catalytic asymmetric synthesis in water.

Key words: water, silver, Michael additions, solvent effects, asymmetric synthesis

The use of water as a reaction medium has received considerable attention in organic synthesis due to its advantages in terms of economy and from environmental and safety standpoints.[1] In addition, reactions in water may offer different reactivity and selectivity compared with those in common organic solvents due to the unique physical and chemical properties of the solvent.[2] In the course of our investigations into developing efficient organic reactions in aqueous media, we have exploited several carbon–carbon bond-forming reactions catalyzed by water-compatible metal catalysts, and some of them have been applied to catalytic asymmetric reactions.[3] However, examples of catalytic asymmetric reactions in pure water are still limited.[4] Herein we report AgOTf–PPh_3 complex-catalyzed Michael additions of β-ketoesters to nitroalkenes[5] that proceed in pure water without the need for any additives. A remarkable point is that the catalyst system promotes the reaction efficiently only in water, but does not work well in organic solvents. Moreover, this system can be conveniently applied to catalytic asymmetric synthesis by the use of chiral phosphine ligands.

Initially, we examined the AgOTf-catalyzed Michael addition[6,7] of cyclopentanone-2-carboxylic acid *tert*-butyl ester to nitrostyrene in water (Table 1). Interestingly, AgOTf that was soluble in water did not catalyze the reaction and only starting materials were recovered (entry 1). However, when PPh_3 was added to the system, the reaction proceeded smoothly to give the desired product in excellent yield (entry 3). It is noted that PPh_3 itself promoted the reaction sluggishly (entry 2). This result clearly indicated that the AgOTf–PPh_3 complex was the real catalyst (entry 3). Furthermore, the water-soluble AgOTf–$P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ complex was tested as a catalyst, and it was found that no reaction took place (entry 4). These results suggest that the catalyst should be hydrophobic for efficient reaction to take place, probably because hydrophobic catalysts come into contact most easily with hydrophobic substrates in water.

Table 1 Effect of Catalysts

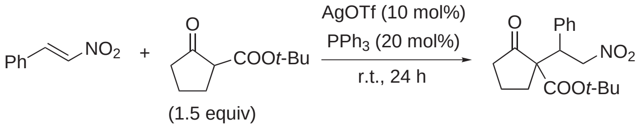


Entry	Catalyst	dr[a]	Yield (%)[b]
1	AgOTf (10 mol%)	–	0
2	PPh_3 (20 mol%)	79: 21	13
3	AgOTf (10 mol%) + PPh_3 (20 mol%)	80: 20	90
4	AgOTf (10 mol%) + $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ (20 mol%)	–	0

[a] Determined by ^1H NMR analysis.
[b] Isolated yield.

Next, we examined the effect of solvents in the reaction system (Table 2). Intriguingly, the reaction in CH_2Cl_2 and THF proceeded very slowly and gave the product only in

Table 2 Effect of Solvents



Entry	Solvent	dr[a]	Yield (%)[b]
1	CH_2Cl_2	82:18	9
2	THF	76:24	3
3	THF–H_2O (1:1)	83:17	10
4	No solvent	78:22	5
5	H_2O	80:20	90

[a] Determined by ^1H NMR analysis.
[b] Isolated yield.

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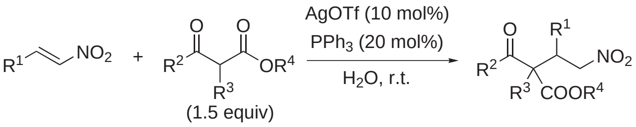
9% and 3% yields, respectively (entries 1, 2). The reactions in THF–H_2O and no-solvent conditions gave poor results (entries 3, 4). It is noteworthy that this reaction was promoted effectively only in pure water (entry 5).

With these interesting observations in hand, we then investigated the substrate generality of the reaction system. As shown in Table 3, the reactions of nitroalkenes having aromatic, heteroaromatic, and alkyl groups gave the corresponding products in good yields. Additionally, it was found that a range of β-ketoesters could be employed as nucleophiles in the reaction, leading to the formation of the desired products in good yields.[8]

Significantly, the present reaction system was transformed into an asymmetric version[9] by switching the phosphine ligand to (*R*)-Tol-BINAP.[10] As shown in Scheme 1, the Michael addition products were obtained with good enantioselectivities.[11]

The assumed catalytic cycle of the present reaction system is shown in Scheme 2. Although the remarkable effect of water on reaction rates is not clear at this stage, a plausible mechanism may be put forward. In the formation of metal enolate **B**, TfOH is generated and in the case of a normal organic solvent system, the reaction mixture is homogeneous and the reverse reaction from **B** to **A** may be fast. However, in a water system, the reaction mixture is heterogeneous and metal enolate **B** and TfOH occupy separate phases due to the difference in their hydrophobicity. As a result, metal enolate **B** does not come into contact with TfOH, and the reverse reaction from **B** to **A** is suppressed. Metal enolate **B** and nitrostyrene would thus combine in high concentration and the Michael addition step (**B** to **C** in Scheme 2) may proceed smoothly.

Table 3 Michael Additions of β-Ketoesters to Nitroalkenes in Water



Entry	R^1	β-Keto-ester	Time (h)	dr[a]	Yield (%)[b]
1	Ph	**1**	24	80:20[c]	90
2	2-Furyl	**1**	24	81:19[c]	86
3	2-Thienyl	**1**	24	81:19[c]	90
4	Ph	**2**	24	84:16[c]	80
5	4-$MeOC_6H_4$	**2**	48	83:17[c]	76
6	4-$NO_2C_6H_4$	**2**	48	88:12[c]	90
7	Ph	**3**	3	59:41	99
8	Cyclohexyl	**3**	8	62:38	89
9	Ph	**4**	96	89:11[c]	66
10	Ph	**5**	48	66:34	71
11	Ph	**6**	24	67:33	86

[a] Determined by ^1H NMR analysis.

[b] Isolated yield.

[c] Relative configuration of the major isomer was shown in below (Figure 1).[9b,c]

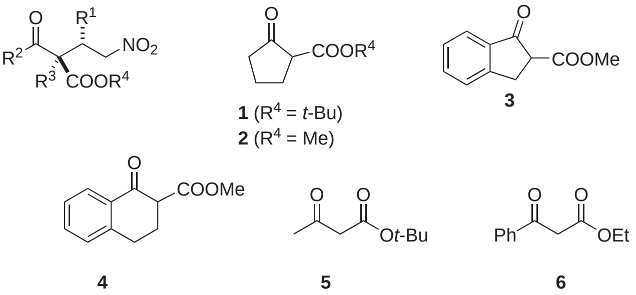
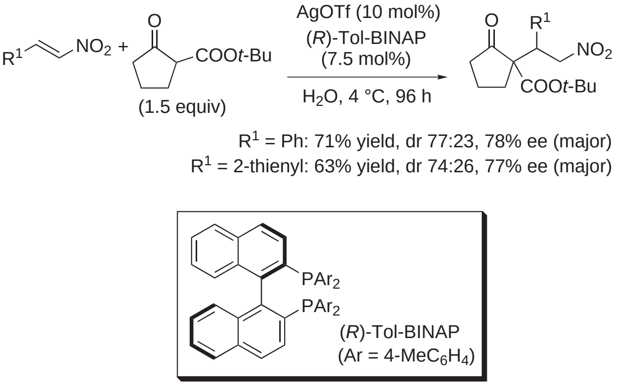
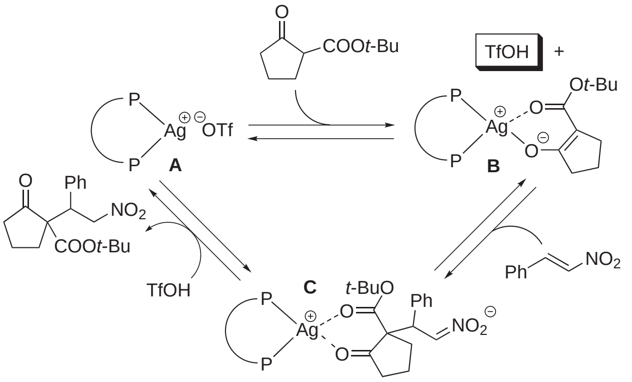


Figure 1



R^1 = Ph: 71% yield, dr 77:23, 78% ee (major)
R^1 = 2-thienyl: 63% yield, dr 74:26, 77% ee (major)

Scheme 1



Scheme 2

In summary, we have developed AgOTf–PPh_3-catalyzed Michael additions of β-ketoesters to nitroalkenes in water. The present system promotes the reaction efficiently only in water. Moreover, this reaction system could be applied to catalytic asymmetric synthesis in water. Further investigations fully to elucidate the mechanism as well as the application of the methodology to other reactions of this system are in progress.

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Typical Experimental Procedures

Entry 1 of Table 3: AgOTf (0.020 mmol) and PPh_3 (0.040 mmol) were added to H_2O (2.0 mL) and the mixture was stirred for 15 min at r.t. Cyclopentanone-2-carboxylic acid *tert*-butyl ester (0.30 mmol) and nitrostyrene (0.20 mmol) were added to the reaction solution. The reaction mixture was stirred for 24 h at r.t., and then CH_2Cl_2 (5.0 mL) and H_2O (5.0 mL) were added. The mixture was extracted with CH_2Cl_2 (2×5.0 mL)[12] and the organic phase was concentrated. Purification of the crude product by flash chromatography (neutral silica gel, hexane–EtOAc = 15:1) provided the desired product.

Scheme 1 (R^1 = Ph): AgOTf (0.020 mmol) and (*R*)-Tol-BINAP (0.015 mmol) were dissolved in THF (1.0 mL) and the mixture was stirred for 15 min at r.t. The solvent was evaporated and the residue was dried in vacuo for 30 min. To the resulting white solid was added H_2O (2.0 mL) and the mixture was cooled to 4 °C. Cyclopentanone-2-carboxylic acid *tert*-butyl ester (0.30 mmol) and nitrostyrene (0.20 mmol) were added to the reaction solution and the mixture was stirred for 96 h at 4 °C. Isolation of the product was performed in a manner similar to that described above. IR (neat): 2977, 2930, 1746, 1722, 1554, 1454, 1373, 1250, 1146, 844, 704 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.17–7.32 (m, 5 H), 5.33 (dd, *J* = 13.1, 11.3 Hz, 0.23 H), 5.16 (dd, *J* = 13.0, 3.5 Hz, 0.77 H), 4.98 (dd, *J* = 13.0, 11.3 Hz, 0.77 H), 4.84 (dd, *J* = 13.1, 3.4 Hz, 0.23 H), 4.13 (dd, *J* = 11.3, 3.4 Hz, 0.23 H), 4.04 (dd, *J* = 11.3, 3.5 Hz, 0.77 H), 2.24–2.42 (m, 2 H), 1.77–1.99 (m, 4 H), 1.46 (s, 2.07 H), 1.45 (s, 6.93 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 215.9, 212.7, 170.3, 168.4, 135.7, 135.6, 129.4, 129.2, 128.9, 128.7, 128.3, 128.1, 83.5, 83.3, 77.2, 76.6, 63.0, 62.8, 47.3, 46.3, 39.5, 37.8, 33.6, 31.5, 27.78, 27.76, 19.6, 19.4 ppm. HRMS (FAB^+): *m*/*z* calcd for $C_{18}H_{24}NO_5$: 334.1649 $[M + H]^+$; found: 334.1660 $[M + H]^+$. HPLC Chiralcel OD-H columun (hexane–*i*-PrOH = 150:1, 1.0 mL/min, 254 nm) t_R (major diastereomer, 78% ee) = 24.9 min (major enantiomer), 29.5 min (minor enantiomer); t_R (minor diastereomer, 61% ee) = 17.7 min (major enantiomer), 20.1 min (minor enantiomer).

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(11) Various Ag/(*R*)-Tol-BINAP ratios were tested, and the ratio in Scheme 1 gave better results.

(12) Extraction solvents other than CH_2Cl_2 (ex. EtOAc) can also be used.

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