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New Neutral Reaction System with Crown Ether-KCl Complexes in **Aqueous Solution**

Seiji Shirakawa, Lijia Wang, Atsuyuki Kasai, and Keiji Maruoka*^[a]

Alkali metal chlorides, such as NaCl and KCl, are one of the most abundant natural resources on the earth, and are essential for life-supporting systems. The human body requires an aqueous solution of NaCl and KCl, and many biocatalyzed reactions proceed under such aqueous neutral conditions. Accordingly, development of organic reactions in aqueous NaCl and KCl solutions, which are promoted by utilizing the ionic nature of these salts, seems to be very attractive for the development of green sustainable chemistry.^[1] However, alkali metal chlorides are generally known as less reactive neutral molecules for organic reactions, due to the low solubility in organic solvents and the deactivation of the ions through hydration in aqueous solution. To activate the neutral chloride salts for organic synthesis, we are interested in the use of water and crown ethers as ligands for alkali metal chlorides. Crown ethers have long been recognized as one of the most representative and important host molecules in supramolecular chemistry.^[2] The special feature of crown ethers is their strong ability to bind alkali metal cations, such as K⁺ and Na⁺, and the binding property is recognized as an artificial model of ionophores in biological systems. Another feature of crown ethers is the extraction ability of neutral alkali metal salts into organic solvents by complexation with these salts. Furthermore, the anion of the crown ether-neutral salt complex might exist as an activated "naked anion" in organic solvents. Although the activated chloride anion of crown ether-alkali metal chloride complexes has been used as nucleophilic reagent,^[3] the catalytic ability of these complexes is still unexplored in organic synthesis. In this context, we are interested in the development of a new reaction system with crown etheralkali metal chloride complexes as neutral catalysts for the activation of carbon nucleophiles.

Our strategy for the activation of carbon nucleophiles by KCl is that the reaction is performed in H₂O/toluene biphasic conditions with the crown ether (Figure 1). It is expected

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Figure 1. Activation of a carbon nucleophile by a crown ether-KCl complex.

that when the reaction is carried out under homogeneous conditions in toluene, the reverse reaction becomes very fast due to the facile protonation with in situ generated HCl, thereby suppressing the formation of potassium enolate. On the other hand, when the reaction is performed in H₂O/toluene biphasic conditions, hydrophilic HCl would move to the aqueous phase smoothly, thereby enhancing the lifetime of enolate with crown ether-potassium complex to some extent. Herein, we report the synthetic utility of such a new neutral reaction system with [18]crown-6 derivatives and aqueous KCl solution for conjugate-addition reactions (Scheme 1), in which interesting effects of water and lipophilic crown ether are observed in the present reaction system. The roles of water and lipophilic crown ether are also discussed in the present report.

We first investigated the effect of crown ethers-neutral alkali metal chloride complexes on the conjugate addition of β -keto ester to β -nitrostyrene as shown in Table 1. The reaction of β -keto ester 5 and β -nitrostyrene in saturated aqueous KCl/toluene (10:1) biphasic solution with dibenzo[18]crown-6 (1b) at room temperature (25°C) for 2 h afforded a conjugate adduct 6 in 52% yield (Table 1, entry 1). In contrast, almost no reaction was observed in the absence of crown ether or KCl (entries 2 and 3), and hence both crown ether and KCl are essential to promote the reaction. The effects of alkali metal chlorides and ring sizes of dibenzocrown ethers were also examined (entries 4-7). The use of aqueous NaCl and LiCl solutions with catalyst 1b gave product 6 only in 10 and 5% yields, respectively (entries 4 and 5). Furthermore, the change of the ring size of crown

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[[]a] Dr. S. Shirakawa, Dr. L. Wang, A. Kasai, Prof. Dr. K. Maruoka Laboratory of Synthetic Organic Chemistry and Special Laboratory of Organocatalytic Chemistry Department of Chemistry Graduate School of Science, Kyoto University Sakyo, Kyoto 606-8502 (Japan) Fax: (+81)75-753-4041 E-mail: maruoka@kuchem.kyoto-u.ac.jp



Scheme 1. Neutral reaction system with crown ether and aqueous KCl solution for conjugate additions; EWG = electron-withdrawing group.

Table 1. Effects of crown ethers and alkali metal chlorides on the conjugate addition of ${\bf 5}.^{[a]}$



[a] Reaction conditions: β -ketoester **5** (0.10 mmol) and β -nitrostyrene (0.12 mmol) in the presence of crown ether (10 mol%) in saturated aqueous MCl solution (2.0 mL)/toluene (0.20 mL) at RT for 2 h. [b] Determined by ¹H NMR analysis. [c] Determined by ¹H NMR analysis based on hexamethylbenzene as an internal standard. [d] In the absence of crown ether. [e] In H₂O (2.0 mL)/toluene (0.20 mL). [f] Reaction was performed for 5 h. [g] Isolated yield. [h] Use of solid KCl (10 equiv) instead of aqueous KCl solution.

ethers **1a–c** caused a decrease in yields (entries 6 and 7 vs. entry 1). These results clearly indicate that the binding stability of the crown ether complex with the alkali metal chloride is crucial to promote the reaction efficiently.^[4]

Other [18]crown-6 derivatives were also examined for the reaction by using aqueous KCl solution (Table 1, entries 8–10). Although dicyclohexano[18]crown-6 (2) promoted the reaction to give adduct 6 in moderate yield (entry 8), the use of simple [18]crown-6 (3) was found to be less effective (entry 9). These results suggest that the lipophilicity of the

crown ether is also important to promote the reaction under the neutral conditions. Based on this observation, we next employed lipophilic di-*tert*-butyldibenzo[18]crown-6 (4). Pleasingly, lipophilic catalyst 4 efficiently promoted the reaction, and conjugate adduct 6 was obtained in high yield (entry 10). The yield of 6 was further enhanced with prolonged reaction time (entry 11). Notably, the reaction using solid KCl instead of aqueous KCl solution does not proceed at all (entry 12), and hence the presence of water is also essential to promote the reaction under neutral conditions.

With these interesting observations in hand, the applicability of the present neutral reaction system using crown ether 4 with aqueous KCl solution was investigated, and selected examples are listed in Scheme 2. Various types of active methine compounds and conjugate acceptors were employed for the neutral reaction system, and the desired conjugate adducts 6-10 were obtained in high yields. Furthermore, the reaction with azodicarboxylate gives the desired amination product 11 in excellent yield.



Scheme 2. Conjugate-addition reactions of activated carbonyl substrates under neutral conditions. Cbz = carboxybenzyl; Boc = tert-butoxycarbon-yl; Bn = benzyl.

This neutral reaction system was successfully applied to asymmetric conjugate addition^[5,6] with chiral oxazolidinone. Thus, α -substituted nitroacetamide 12 with a chiral oxazolidinone moiety^[7] was treated with 1,1-bis(benzenesulfonyl)ethylene in saturated aqueous KCl/toluene solution (2:1) in the presence of catalytic crown ether 4 (10 mol %) to give the conjugate adduct 13 with excellent stereoselectivity (Scheme 3). The reaction with only 1 mol% of crown ether 4 still worked well with prolonged reaction time. Notably, the reaction in the absence of crown ether or KCl does not proceed at all. Furthermore, the present reaction does not work well under basic conditions using aqueous alkali metal bases, such as KOH and K₂CO₃, which primarily caused the decomposition of starting materials. Hence, the present highly stereoselective reaction was only achieved under neutral conditions using crown ether-KCl complexes.



reaction in H₂O/toluene (without KCl): \approx 0% (no reaction) reaction in 10% KOH (aq.)/toluene: \approx 0% (decomp. of starting materials) reaction in 10% K₂CO₃ (aq.)/toluene: \approx 0% (decomp. of starting materials)

Scheme 3. Asymmetric conjugate addition of chiral oxazolidinone 12.

The absolute configuration of the conjugate adduct 13 was confirmed by X-ray diffraction analysis as shown in Figure 2.^[8]



Figure 2. X-ray crystal structure of the conjugate adduct 13.

In summary, we have successfully developed a new neutral reaction system using lipophilic [18]crown-6 derivatives with aqueous KCl solution. The ring size and lipophilicity of the crown ether as well as the presence of water are crucial to promote the reaction efficiently. The advantage of the present neutral reaction system was clearly demonstrated through the highly stereoselective conjugate addition of chiral acyloxazolidinone. Further investigations on the neutral reaction system including mechanistic studies are currently underway in our group and these studies will be reported in due course.

Experimental Section

General procedure for conjugate-addition reactions under neutral conditions: To a mixture of nucleophile (0.10 mmol), electrophile (0.12 mmol),

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and di-*tert*-butyldibenzo[18]crown-6 (**4**, 0.010 mmol, 10 mol %) in toluene (0.20 mL) was added saturated aqueous KCl solution (2.0 mL), and the mixture was vigorously stirred at RT for 5 h. The resulting mixture was diluted with H_2O (3.0 mL) and extracted with AcOEt (3×5.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (neutral) with hexane/AcOEt as eluent gave the product.

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Keywords: alkali metals • asymmetric synthesis conjugation • crown compounds • synthetic methods

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Crown Compounds -

S. Shirakawa, L. Wang, A. Kasai, K. Maruoka*.....

New Neutral Reaction System with Crown Ether-KCl Complexes in Aqueous Solution



Chiral auxiliaries: A new neutral reaction system with lipophilic [18]crown-6 derivatives and with aqueous KCl solution has been successfully utilized for several conjugate-addition reactions (see scheme). The ring size, lipophilicity of the crown ether, and the presence of water are crucial to promote the reaction efficiently. The reaction system can also be applied to asymmetric conjugate addition of the chiral acyloxazolidinone with excellent diastereoselectivity.