

NHC-catalyzed reactions of enals with water as a solvent†

Wendy Wen Yi Leong, Xingkuan Chen and Yonggui Robin Chi*

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Water is demonstrated as a suitable solvent for NHC-catalyzed reactions of enals. The use of D₂O as a solvent allows for the effective incorporation of deuterium isotopes into organic molecules.

A major consideration for active pharmaceutical ingredient (API) synthesis is solvent selection because solvents make up more than 80% of the material usage, consume about 60% of the overall energy used, and account for 50% of the post treatment green-house gas emissions.¹ Although limitations exist, water holds the potential to be an ideal solvent due to economic and environmental reasons. Consequently, considerable attention has been drawn to the development of catalytic reactions that can operate with water as the medium. A large number of metal-catalyzed reactions can now be carried out in aqueous environments,^{2,3} sometimes with the assistance of surfactants.⁴ In recent years, organocatalytic reactions have emerged as an alternative synthetic approach that can eventually reach large-scale applications for the synthesis of pharmaceuticals.⁵ Since organocatalysts are typically stable in the presence of water, the development of organocatalytic reactions in water is particularly promising. For example, multiple amine-catalyzed enamine reactions have been found to work well in aqueous environments.^{6,7} In the same vein, phosphoric acid-catalyzed reduction of imines in water has been achieved by Rueping.⁸

Compared to enamine catalysis, the employment of water as the solvent in *N*-heterocyclic carbene (NHC)-catalyzed polarity inversion reactions is limited.⁹ In 2004, Bode disclosed the use of an organic–water co-solvent (THF–H₂O, 10 : 1) in NHC-catalyzed addition of enals to aldehydes.¹⁰ The same group later used a stoichiometric amount of water as a reagent or co-solvent for the NHC-catalyzed activation of formylcyclopanes and α -chloroaldehyde bisulfite salts.¹¹ In

2010, Rovis and co-workers reported the NHC-catalyzed reaction of α -chloro aldehydes using a toluene–water biphasic solvent containing approximately 1.0 equivalent of water.¹²

In another study, Hoveyda and co-workers demonstrated the NHC-catalyzed enantioselective conjugate addition of a dimethylphenylsilyl group to α,β -unsaturated carbonyls in an aqueous medium.¹³ These studies have shown that water is compatible with NHC catalysis. Indeed, traces of water are commonly assumed to be present even when anhydrous organic solvents are used in NHC-catalyzed reactions. Additionally, experimental and theoretical studies from the groups of Amyes, Diver, Gudat, and Nyulászai have shown that NHCs are reasonably stable under an aqueous environment.¹⁴

However, to the best of our knowledge, the use of water as the sole solvent for NHC-catalyzed reactions of aldehydes remains undisclosed. This is somewhat surprising considering that thiamine, an *N*-heterocyclic carbene precursor, is essential for many biological processes that occur predominantly in an aqueous environment.¹⁵ Following nature's lead, water should be a suitable solvent for *N*-heterocyclic carbene catalyzed reactions. Herein, we report the use of water as the only solvent for NHC-catalyzed addition of enals to several electrophiles (Fig. 1). This aqueous approach also allows for the efficient incorporation of deuterium isotopes into organic molecules when D₂O is used as the solvent.

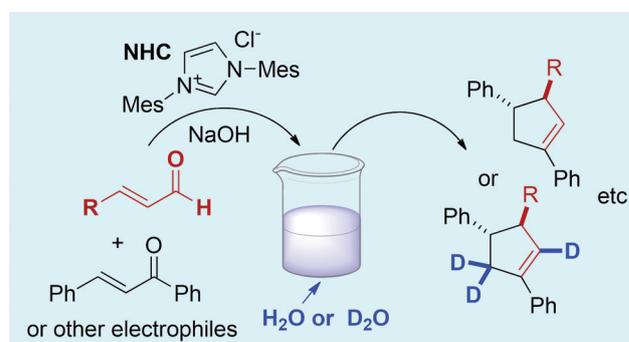


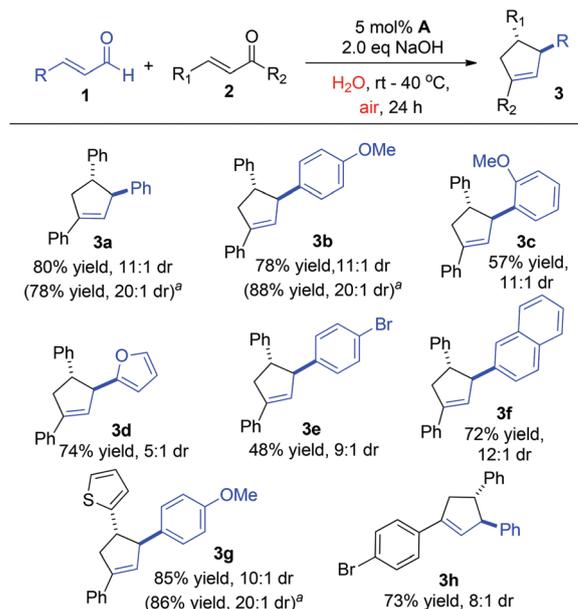
Fig. 1 NHC-catalyzed reactions in aqueous media.

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mail: robinchi@ntu.edu.sg; Fax: (+65) 67911961; Tel: (+65) 65927769
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Results and discussion

We started by investigating the NHC-catalyzed reaction between enals and enones using water as the only solvent. The corresponding reactions of enals and enones in organic solvents have previously been reported by Nair, Bode, Scheidt, and our laboratory.¹⁶ We initially carried out the reaction between enal **1a** and enone **2a**, with a catalytic amount of NHC pre-catalyst **A**, in the presence of a designer surfactant (TPGS-750-M)¹⁷ that was developed by Lipshutz and co-workers for enabling transition metal-catalyzed processes in water (Table 1, entry 1). Screening of the base revealed that inorganic bases (*e.g.*, NaOH) performed better than organic bases (such as DBU) typically used for NHC-catalyzed reactions in organic solvents. The amount of base also made a difference. By using 2.0 equivalents of NaOH (1.0 M) the cyclopentene product **3a** could be obtained in 83% yield with 10 : 1 dr (Table 1, entry 2). As the deprotonation of the azolium NHC pre-catalyst is a reversible process, and water can serve as a proton source, an excess amount of base is required to maintain a basic aqueous environment. We later found that the use of the surfactant was not necessary, as the reaction in the absence of surfactant afforded **3a** with similar yield and diastereoselectivity (74% yield, 10 : 1 dr, entry 3). Raising the reaction temperature to 40 °C improved the reaction yield to 94%, without loss of diastereoselectivity (entry 4). Additional studies (entries 5 and 6) revealed that the use of 5 mol% NHC was sufficient to obtain **3a** with good yield and diastereoselectivity (80% isolated yield, 11 : 1 dr, entry 6). Interestingly, this reaction could be efficiently carried out in air (Table 1, entries 1–6), given that most NHC-catalyzed reactions are conducted in an inert atmosphere. Oxidation of the enals to their corresponding acids was minimal under our aqueous conditions.¹⁸

Examples of the enal and chalcone substrates used in this reaction are shown in Scheme 1. Under the standard



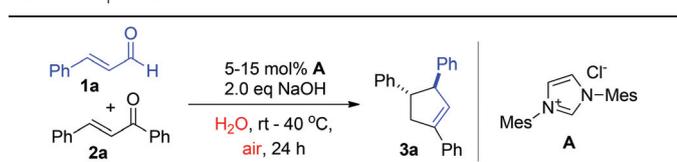
Scheme 1 Examples of enals and chalcones. Reaction conditions: Enal **1** (0.37 mmol), chalcone **2** (0.25 mmol), catalyst **A** (5 mol%), NaOH (0.50 mmol), and water (0.5 mL, 0.5 M). Yields are the isolated yields after SiO₂ column chromatography; dr values were determined via ¹H NMR analysis of the unpurified reaction mixture. ^aThe literature values for reactions in organic solvents.^{16a,d}

conditions (Table 1, entry 6), a variety of enals bearing electron-donating, electron-withdrawing and heteroaromatic groups were all well tolerated. The desired products were afforded in good to excellent yields and diastereoselectivities. In addition, chalcones with different substituents (**3g**, **3h**) worked well. The yields and diastereoselectivities obtained under our aqueous environment are comparable to those reported in the literature using organic solvents.^{16a,d}

The versatility of this methodology in an aqueous environment was demonstrated through selective incorporation of deuterium isotopes into organic molecules. Such a method is valuable because isotope-labeled compounds find wide applications in analytics, pharmacology, material sciences, and the life sciences.^{11a,12,19} As illustrated in Scheme 2a, when the reaction between enal **1a** and chalcone **2a** was carried out in D₂O, deuterated cyclopentene (**D-3a**) was obtained. The deuterium isotopes were incorporated into the former α-carbons of the enal and enone. The key steps of a proposed pathway accounting for the deuterium incorporation are summarised in Scheme 2b. The incorporation of the deuterium into the former α-carbon of enone **1a** involved a deuteration of intermediate **II**, which bears an acidic proton adjacent to the ketone group. The incorporation of deuterium into the former α-carbon of the enal may occur at a few different stages. One possibility, which is shown in Scheme 2b (**III** and **IV**), involves a deuteration of the NHC-bound enolate intermediate **III** via a reversible process.

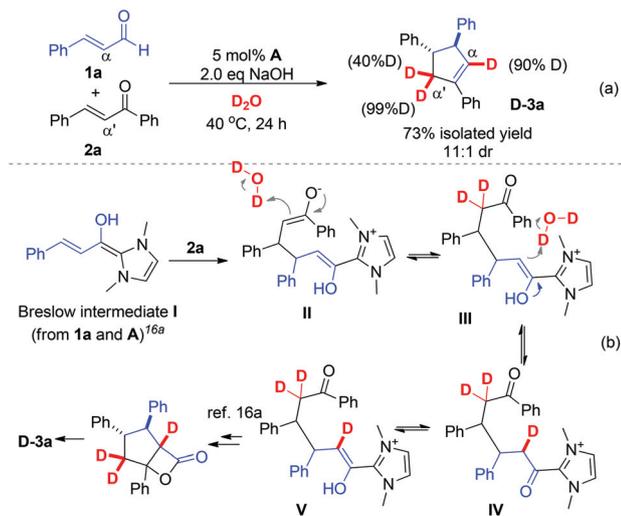
The generality of this aqueous approach was further demonstrated in the reaction between enals and aldehydes to

Table 1 Optimization of reaction conditions^a



| Entry | Conditions | Solvent | Yield ^b (%) | dr ^b |
|-------|--|---------------------------------|------------------------|-----------------|
| 1 | 15 mol% A , 0.45 eq. NaOH, rt | Surfactant/ H ₂ O | 18 | N.D. |
| 2 | 15 mol% A , 2.0 eq. NaOH, rt | Surfactant/ H ₂ O | 83 | 10 : 1 |
| 3 | 15 mol% A , 2.0 eq. NaOH, rt | H ₂ O | 74 | 10 : 1 |
| 4 | 15 mol% A , 2.0 eq. NaOH, 40 °C | H ₂ O | 94 | 9 : 1 |
| 5 | 10 mol% A , 2.0 eq. NaOH, 40 °C | H ₂ O | 89 | 9 : 1 |
| 6 | 5 mol% A , 2.0 eq. NaOH, 40 °C | H ₂ O | 94(80) ^c | 11 : 1 |

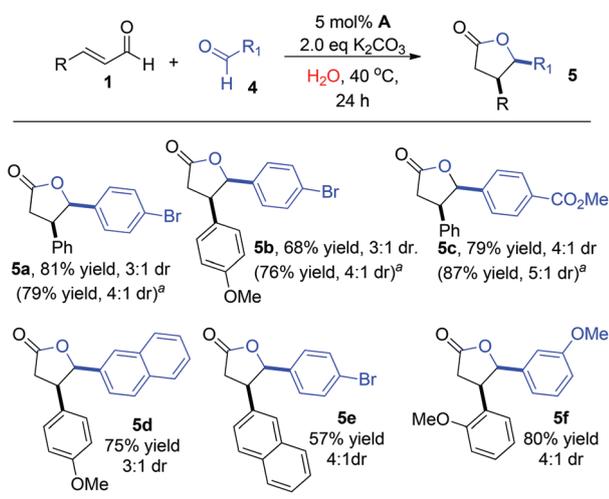
^a Reaction conditions: **1** (0.37 mmol), **2** (0.25 mmol), catalyst, base, 0.5 mL solvent (0.5 M). ^b Estimated via ¹H NMR analysis of the unpurified reaction mixture. ^c Isolated yield after SiO₂ column chromatography. N.D. = not determined.



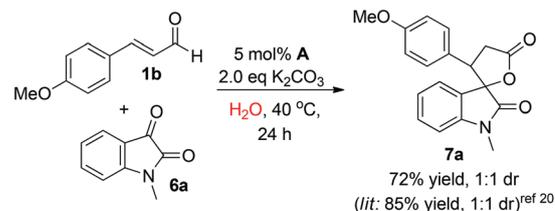
Scheme 2 Isotope incorporation (a) and the postulated pathway (b).

form γ -lactones.¹⁰ In this case, with water as the only solvent, K_2CO_3 was found to be the most suitable base (see the ESI[†]). The lactone product **5a** could be obtained in 81% yield and 3:1 dr (Scheme 3). Examples of several enals and aldehydes used in this reaction are shown in Scheme 3. Essentially, the substrate scope and results (yields, diastereoselectivities) are comparable to the corresponding reactions carried out in organic solvents.¹⁰

One last example to be documented here is the reaction of enals with isatins as the electrophiles (Scheme 4). Once again, results comparable to reactions in organic solvents were obtained when this reaction was run in water under air.²⁰



Scheme 3 Examples of enals and aldehydes. Reaction conditions: Enal **1** (0.1 mmol), aldehyde **4** (0.2 mmol), catalyst **A** (5 mol%), K_2CO_3 (0.2 mmol) and water (0.5 mL, 0.2 M). Yields are isolated yields after SiO_2 column chromatography; dr values were determined via 1H NMR analysis of the unpurified reaction mixture. ^aLiterature values for reactions in organic solvents.¹⁰



Scheme 4 Reaction between enal and isatin.

Conclusion

In summary, we have demonstrated that NHC-catalyzed reactions can be effectively performed with water as the only solvent. Inexpensive inorganic bases (such as NaOH) were found to be optimal under the aqueous reaction environment. Our approach also allows for the simple incorporation of deuterium isotopes into organic molecules.

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