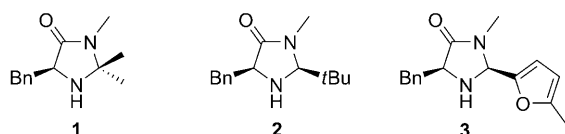


On the Roles of Protic Solvents in Imidazolidinone-Catalyzed Transformations**

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Over the past decade, organocatalysis has caught the imagination of synthetic chemists, advancing the boundaries of chemical synthesis.^[1] Of particular note is the use of secondary amines in iminium ion^[2] and enamine-catalyzed^[3] processes. Within iminium ion catalyzed reactions the imidazolidinone architecture (Scheme 1) has emerged as a priv-



Scheme 1. Principal imidazolidinone catalysts.

ileged catalyst scaffold.^[4] Imidazolidinone **1** has been used in the acceleration of [4 + 2],^[5] [3 + 2],^[6] and [4 + 3]^[7] cycloadditions as well as the conjugate addition of pyrroles^[8] to α,β -unsaturated aldehydes. The pivaldehyde-derived imidazolidinone **2** has been used for the conjugate addition of indoles^[9] and electron-rich aromatics^[10] to form new C–C bonds, the addition of nitrogen^[11] and hydride-based^[12] nucleophiles and for intramolecular [4 + 2] cycloadditions.^[13] Imidazolidinone **3** has been used in iminium ion catalyzed Diels–Alder cycloaddition^[14] and conjugate reduction^[15] reactions of α,β -unsaturated ketones.

In the initial publication on the Diels–Alder cycloaddition using catalyst **1**·HCl it was noted that water had a dual role in the reaction, increasing both yield and *ee* obtained for the products.^[5a] These observations have yet to be explained through experimental findings. In subsequent reports using catalysts **1**–**3**^[5–15] the majority of optimized reaction conditions involve use of a protic solvent in the reaction medium (water, isopropyl alcohol, or ethanol).

From a practical perspective, the ability to perform these transformations without the rigorous exclusion of moisture

makes them operationally simple and has undoubtedly been instrumental in the rapid development of the field. Investigations focussing on the reactivity of the imidazolidinone scaffold and improvements in catalyst activity have been previously reported^[16] and experimental evidence to rationalize selectivities and kinetic profiles in iminium ion catalyzed transformations have also received attention.^[17–19] However, to date the precise role of protic solvents in affecting the outcome of an iminium ion catalyzed process has yet to be rigorously examined experimentally. Here we report on the subtle roles of protic solvents in determining the rate and stereochemical outcome of the Diels–Alder cycloaddition catalyzed by imidazolidinone **1**·HCl.

As a starting point to this investigation we confirmed and further exemplified the effect of water on the stereochemical outcome and yield in the Diels–Alder cycloaddition between cinnamaldehyde (**7**) and cyclopentadiene catalyzed by imidazolidinone **1**·HCl in a series of solvents (Table 1). This data was not explicitly included in the initial report.^[5a]

Table 1: Solvent effect in the Diels–Alder cycloaddition between cyclopentadiene and cinnamaldehyde catalyzed by imidazolidinone **1**·HCl.^[a]

Entry	Solvent	<i>endo</i> / <i>exo</i> ^[b]	<i>endo ee</i> ^[c]	<i>exo ee</i> ^[c]	Yield [%] ^[d]
1	MeOH/H ₂ O	1:1.3	93 %	93 %	93
2	MeOH	1:1.3	93 %	91 %	88
3 ^[e]	MeOH/H ₂ O	1:1.3	93 %	93 %	92 ^[f]
4 ^[e]	MeOH	1:1.3	n.d.	n.d.	64 ^[f]
5	CH ₃ CN/H ₂ O	1:1.2	93 %	90 %	88
6	CH ₃ CN	1:1.2	89 %	87 %	37
7	CH ₃ NO ₂ /H ₂ O	1:1.3	90 %	86 %	88
8	CH ₃ NO ₂	1:1.3	79 %	81 %	22

[a] Reaction of cinnamaldehyde and cyclopentadiene in solvent/H₂O (19:1) or anhydrous solvent, 1 M, 25 °C, 24 h, 5 mol % **1**·HCl; aldehyde products isolated following hydrolysis of the crude reaction mixture (see the Supporting Information for details). [b] *endo*/*exo* ratio determined by ¹H NMR spectroscopy. [c] Determined by conversion to 2,4-dinitrophenyl hydrazine derivative and examination by HPLC using Chiracel OD-R (see Ref. [21]). [d] Yield of isolated product. [e] Reaction carried out for 6 h in the presence of 10 mol % **1**·HCl. [f] Conversions determined by ¹H NMR spectroscopy.

In anhydrous methanol the Diels–Alder reaction between cyclopentadiene and cinnamaldehyde (**7**) provided the *endo* and *exo* adducts in 93 % *ee* and 91 % *ee*, respectively (88 % yield) (Table 1, entry 2). Similar levels of asymmetric induction but higher yield were obtained in a methanol/water system (entry 1; 93 % *ee* *endo*, 93 % *ee* *exo*, 93 % yield). Addition of water therefore increases the yield obtained but does not substantially alter selectivities in an alcoholic

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solvent. The effect on yield is better exemplified by shorter reaction times (entries 3 and 4). In the presence of water (entry 3) a 92% conversion to the products is observed, whereas, running the same reaction in anhydrous methanol leads to a substantially reduced 64% conversion (entry 4). In nonprotic solvents the results are more complex. Changing the reaction medium to CH₃CN or CH₃NO₂ and examining the Diels–Alder cycloaddition under anhydrous conditions (entries 6 and 8) or in the presence of water (5 vol%) (entries 5 and 7) shows two clear trends: Both the rate of product formation and the *ee* of the cycloadducts is higher in the presence of water.

The origins of the effect of water on the stereochemical outcome of reactions conducted in the aprotic solvents CH₃CN and MeNO₂ (Table 1; entries 6 and 8) can be clarified by reaction of **4**·PF₆ with cyclopentadiene under anhydrous conditions (Table 2).

Table 2: Effect of time on the Diels–Alder cycloaddition of imidazolidinone **4**·PF₆ and cyclopentadiene.^[a]

Entry	<i>t</i> [h]	<i>endo ee</i> ^[b]	<i>exo ee</i> ^[b]	
1	1	88%	86%	
2	6	70%	75%	
3	24	42%	53%	
4	2352	< 3%	< 3%	

[a] Reaction of **4**·PF₆ and cyclopentadiene in acetonitrile, 0.2 M, 25 °C.

[b] Determined by conversion to the 2,4-dinitrophenyl hydrazine derivative and examination by HPLC using Chiracel OD-R (see Ref. [21]).

In the absence of water, the *ee* for both the *endo*- and *exo*-adducts erodes over time, showing the Diels–Alder cycloaddition to be a reversible process (Table 2; entries 1–4). Under these conditions, cycloaddition is under thermodynamic control. In the presence of a nucleophilic protic solvent (such as water or methanol) the iminium ions of the Diels–Alder adducts (**9** and **10**) are rapidly hydrolyzed leading to the kinetic Diels–Alder adducts. We therefore believe that the role of water in increasing the *ee* values in the reaction is due to interception of the iminium ion adducts before they undergo retro Diels–Alder reaction.

Stirring the Diels–Alder products **5** (93% *ee*) and **6** (93% *ee*) with **1**·HPF₆ in either acetonitrile or acetonitrile/H₂O (19:1) for 24 h leads to no change in the *ee* of the adducts or in the *endo/exo* ratio. The equilibrium constant for the reaction between imidazolidinone **1**·HCl and Diels–Alder adducts **5** or **6** is low, presumably due to steric reasons, and in a typical catalytic reaction **1**·HCl will form an iminium ion with cinnamaldehyde (**7**) rather than the Diels–Alder adducts **5** or **6**. When the catalytic reaction is carried out in the absence of a protic (nucleophilic) solvent the concentration of

water in the reaction is low (<20 mol%) such that retro Diels–Alder reaction can occur prior to iminium ion hydrolysis, resulting in lower *ee* values for the products (Table 1; entries 6 and 8). By increasing the concentration of water in the catalytic reaction, rapid hydrolysis of the iminium ions **9** and **10** occurs resulting in high levels of asymmetry in the products.

Along with providing the products in higher *ee* water also leads to enhanced reaction rates in CH₃CN and CH₃NO₂. As well as increasing the rate of catalyst turnover (described above) we propose this is due to an increased rate of formation (and hence concentration) of the reactive iminium ion **4**·Cl. Figure 1 shows the reaction of cinnamaldehyde (**7**)

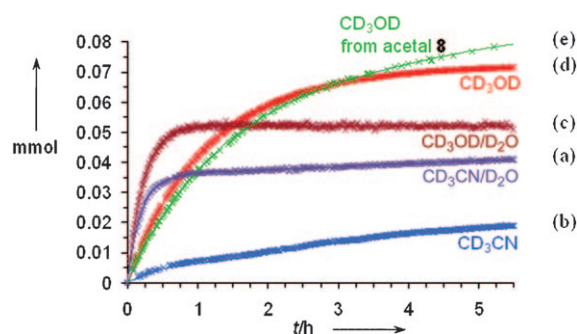


Figure 1. Relative rates of iminium ion formation: a) Cinnamaldehyde (**7**) in CD₃CN/D₂O (19:1) 1 M, 25 °C, 20 mol% **1**·HCl (purple trace); b) cinnamaldehyde (**7**) in CD₃CN 1 M, 25 °C, 20 mol% **1**·HCl (blue trace); c) cinnamaldehyde (**7**) in CD₃OD/D₂O (19:1) 1 M, 25 °C, 20 mol% **1**·HCl (dark red trace); d) cinnamaldehyde (**7**) in CD₃OD 1 M, 25 °C, 20 mol% **1**·HCl (red trace); e) cinnamaldehyde dimethyl acetal (**8**) in CD₃OD 1 M, 25 °C, 20 mol% **1**·HCl (green trace).

and **1**·HCl (20 mol%) in different solvent mixtures. In CD₃CN/D₂O (19:1) ((a), purple trace) iminium ion formation is substantially faster than in anhydrous CD₃CN ((b), blue trace). Therefore, water increases the rate of iminium ion formation, perhaps due to hydrogen bonding activating cinnamaldehyde toward nucleophilic attack.^[20]

A third role of water in aprotic solvents (e.g. CH₃CN) is to dissolve the catalyst. Solubility of **1**·HCl in nonpolar solvents is limited, such that under typical concentrations for a catalytic reaction the mixture is heterogeneous. Addition of water (5 vol%) solubilizes the catalyst at standard concentration promoting reaction.

The origins of rate acceleration by addition of water to methanol are less apparent but were revealed by monitoring the reaction by ¹H NMR spectroscopy. Figure 2 shows two graphs for the reaction of cinnamaldehyde (**7**) (1 equiv) and cyclopentadiene (3 equiv) catalyzed by **1**·HCl (20 mol%) in CD₃OD (Figure 2a) and CD₃OD/D₂O (19:1) (Figure 2b). Under these reaction concentrations, Diels–Alder cycloaddition is faster than iminium ion formation. In each reaction, prior to the addition of cyclopentadiene, equilibrium was established between cinnamaldehyde (**7**), cinnamaldehyde dimethyl acetal (**8**), and iminium ion (**4**·Cl). At equilibrium, the ratio of cinnamaldehyde/dimethyl acetal/iminium ion is

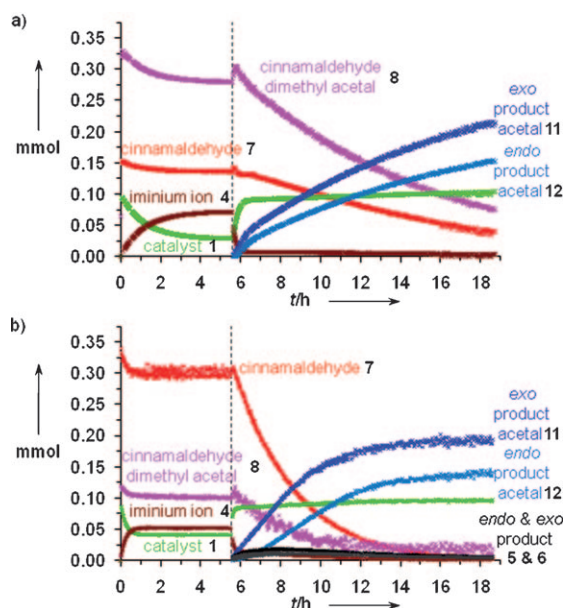


Figure 2. Diels–Alder reaction between cinnamaldehyde and cyclopentadiene catalyzed by **1**·HCl in a) CD_3OD and b) $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ (19:1).

1.9:3.9:1 in CD_3OD and 5.8:1.9:1 in $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ (19:1). Water therefore alters the equilibrium position between cinnamaldehyde (**7**) and cinnamaldehyde dimethyl acetal (**8**).

For the equilibrium (**7/8/4-Cl**) to affect the rate of the catalytic cycle it would be necessary for the conversion of cinnamaldehyde dimethyl acetal (**8**) to iminium ion **4-Cl** to be slower than the conversion of cinnamaldehyde (**7**) to iminium ion **4-Cl**. We therefore monitored the equilibrium between **7**, **8**, and **4-Cl** in CD_3OD and $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ mixtures (Figure 1).

The rate of iminium ion formation from reaction of cinnamaldehyde (**7**) in $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ (19:1) (Figure 1 c, dark red trace) is higher than in anhydrous CD_3OD (Figure 1 d, red trace). Reaction of cinnamaldehyde dimethyl acetal (**8**) and **1**·HCl in anhydrous CD_3OD (Figure 1 e, green trace) is slower still. Reaction of cinnamaldehyde (**7**) with imidazolidinone

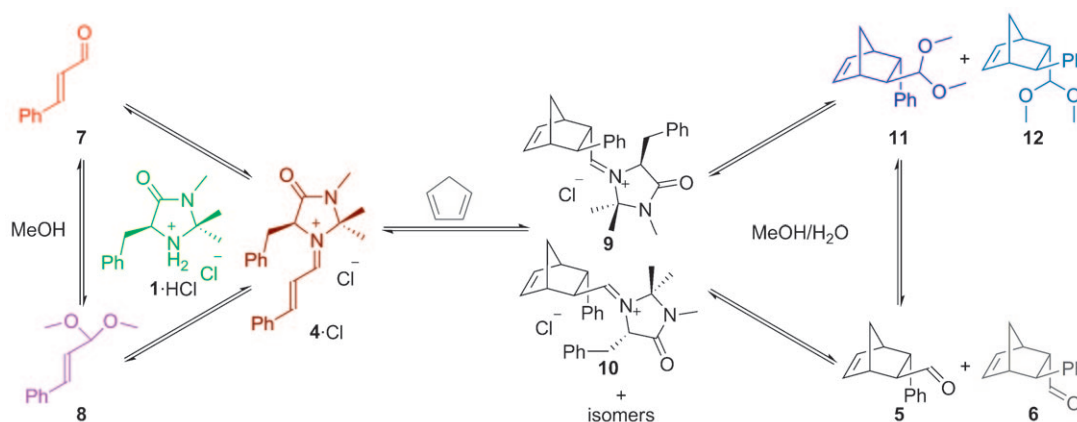
catalyst **1**·HCl is therefore faster than reaction of acetal **8** with the catalyst.

It is appropriate to reconsider the overall catalytic cycle for this transformation to account for the precise reaction pathway (Scheme 2). Within this revised reaction sequence the dimethyl acetal of cinnamaldehyde (**8**) and the Diels–Alder adducts (**11** and **12**) are present within the reaction mixture. The secondary equilibrium which occurs between cinnamaldehyde and methanol is a rapid acid-catalyzed process but the position of this equilibrium alters the rate of the catalytic cycle. Addition of water perturbs the equilibrium position (**7/8**) leading to an increased concentration of cinnamaldehyde (**7**) and therefore a higher overall rate of reaction. As would be expected, there will be a point at which increasing water concentration further would inhibit iminium ion formation. Indeed, conducting the reaction in the presence of 10 vol% H_2O led to a lower overall rate for Diels–Alder cycloaddition (see the Supporting Information).

One of the distinct advantages provided by iminium ion catalyzed processes is the highly practical reaction conditions: reactions proceed without the need for rigorous exclusion of moisture and air. It is clear that water (or an alternative protic/nucleophilic solvent) is an essential component of these transformations, and for Diels–Alder cycloaddition, increases both the rate and *ee* values observed. Under the optimized literature reaction conditions, water alters the position of equilibrium between cinnamaldehyde (**7**) and cinnamaldehyde dimethyl acetal (**8**) increasing the concentration of **7**. In nonprotic solvents, water accelerates iminium ion formation through hydrogen bonding, intercepts iminium ion products preventing retro Diels–Alder reaction and loss of enantioselectivity, and solubilizes the catalyst. An important goal in this area of organocatalysis is improving reaction efficiency. These results show that both catalyst and solvent play critical roles in dictating reaction outcomes and should both be considered in catalyst and protocol development.

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Scheme 2. Revised reaction sequence for the iminium ion catalyzed Diels–Alder reaction.

Keywords: Diels–Alder reaction · imidazolidinone · iminium ion catalysis · organocatalysis

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