Recyclable Polymeric π-Acid Catalyst Effective in Aqueous and Solvent-Free Inverse-Electron-Demand Aza-Diels–Alder Reactions

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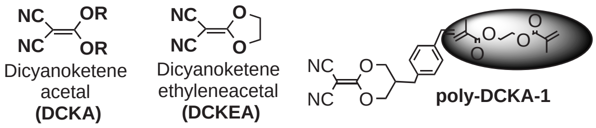
Abstract: A polymer-supported π-acid (poly-DCKA-1) was found to be a highly efficient and recyclable catalyst in two- and three-component inverse-electron-demand aza-Diels–Alder reactions at room temperature not only in water but also under solvent-free conditions.

Key words: polymer, π-acid catalyst, aza-Diels–Alder reaction, aqueous reaction, solvent-free reaction

Organic reactions in water[1] and under solvent-free conditions[2] have recently been recognized as useful and environmentally sustainable tools for synthesis. The development of insoluble and highly efficient reagents[3] has recently attracted much attention from the points of view of convenient manipulation and green chemistry.[4] In this context, polymeric modification of reagents, especially, reaction promoters and catalysts effective in organic reactions in water and in solvent-free reactions has shown much promise.[5]

In our work on the development of dicyanoketene acetals (DCKA) (Figure 1) as novel π-acid catalysts,[6] we reported that polymer-supported DCKA (poly-DCKA-1), prepared by copolymerization of a DCKA bearing a styrene functionality with ethyleneglycol dimethacrylate (EGDMA), catalyzes reactions of acetals, monothioacetalization,[7a,b] cyanation,[7b,c] and the Mukaiyama aldol reaction with silicone nucleophiles,[7b,c] as well as Mannich-type reactions of imines with silicone enolates in acetonitrile.[7d] The polymer was also found to catalyze hydrolysis of acetals and silyl ethers in an aqueous system.[7e,f]



Dicyanoketene acetal **(DCKA)**
Dicyanoketene ethyleneacetal **(DCKEA)**
poly-DCKA-1

Figure 1 Dicyanoketene acetals (DCKA).

Aza-Diels–Alder reactions are a very important method for the synthesis of nitrogen-containing heterocyclic compounds.[8] The inverse-electron-demand (IED) aza-Diels–Alder reaction[9] of *N*-arylimines and nucleophilic olefins in the presence of a variety of acid catalysts is a useful tool for the synthesis of the tetrahydroquinoline skeleton, which is a key structure in the biological activity of various natural products and pharmaceutical agents.[10] Although the IED-aza-Diels–Alder reactions producing tetrahydroquinolines have been carried out in organic solvents, recently the reaction was found to proceed in aqueous conditions using indium(III) chloride as a catalyst.[11]

During our work with poly-DCKA-1, we found it to be a highly efficient and recyclable catalyst promoting aqueous Mannich-type reactions of various imines including unstable imines prepared in situ from aromatic and aliphatic aldehydes.[12] Encouraged by these results we have examined aza-Diels–Alder reactions using poly-DCKA-1. Here we report preliminary results on IED-aza-Diels–Alder reactions catalyzed by poly-DCKA-1, which was found to be a highly efficient catalyst for the two- and three-component IED-Aza-Diels–Alder reaction at room temperature not only in water but also under solvent-free conditions, and the catalyst could be reused repeatedly without appreciable loss of activity after a simple recovery procedure.

Initially, dicyanoketene ethylene acetal (DCKEA),[13] a simple standard DCKA, was observed not to react with 1-methoxy-3-trimethylsiloxy-1,3-diene (Danishefsky's diene),[14] a highly reactive diene, at room temperature, after a reaction time of 24 hours and the diene was recovered quantitatively. It had been reported that tetracyanoethylene (TCNE) reacts vigorously with 1,3-butadiene to give a cycloadduct.[15]

We examined the catalytic activity of DCKEA in the aza-Diels–Alder reactions of *N*-benzylideneaniline (**1**) with representative 1,3-dienes, Danishefsky's diene (**2**), 2,3-dimethyl-1,3-butadiene (**3**), and cyclopentadiene (**4**) (Scheme 1). Although 0.2 equivalents of DCKEA catalyzed the reaction with **2** in acetonitrile at room temperature to give 1,2-diphenyl-2,3-dihydropyridine-4-one (**5**) in quantitative yield after 0.5 hours, DCKEA induced no reaction with **3**, and sluggishly promoted the reaction with **4** giving cyclopenta[*c*]quinoline (**6**) in 7% yield after 24 hours, without any trace of 2-azabicyclo[2.2.1]hepta-4-ene (**7**), the other cycloadduct which could form with **1** as the dienophile. The results, however, suggested that DCKAs have the ability to catalyze IED-aza-Diels–Alder reactions. Thus, the catalytic properties of DCKEA and the polymer-supported DCKA (poly-DCKA-1) were

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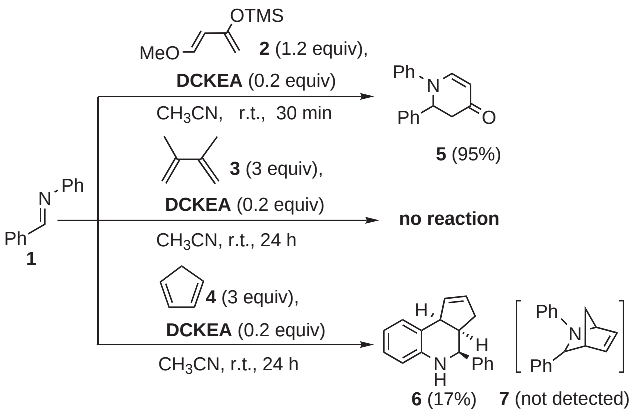
assessed in the reaction of **1** and 2,3-dihydro-4*H*-pyran (**8**) at room temperature in various solvents including water and under solvent-free conditions[17] to provide pyrano[3,2-*c*]quinoline derivatives [**9a** (*syn*) and **9b** (*anti*)].[16] The simple molecular catalyst DCKEA promoted the reaction moderately well in acetonitrile with poor *syn*/*anti* selectivity although the reaction proceeded sluggishly or not at all in water and under solvent-free conditions (Table 1, entries 2–6). On the contrary, higher efficiencies were exhibited by poly-DCKA-1 in water and under solvent-free conditions (Table 1, entries 7–10), and high levels of *syn*/*anti* selectivity were observed for poly-DCKA-1 compared with DCKEA. Organic solvents including acetonitrile gave poor results providing low yields of the cycloadducts (**9a** and **9b**) (Table 1, entries 11–16).

Poly-DCKA-1 as a catalyst worked well in the three-component IED-aza-Diels–Alder reaction of benzaldehyde (one equivalent), aniline (one equivalent), and **8** (six equivalents) in water at room temperature as shown in Table 2. Although a large excess of dienophile **8** (11 equivalents) was necessary, the reaction also proceeded under solvent-free conditions.

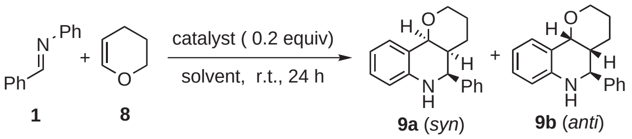


Scheme 1 Reaction of benzylideneaniline with 1,3-dienes catalyzed by DCKEA.

Table 3 demonstrates that poly-DCKA-1 could be used repeatedly without appreciable loss of catalytic activity in the IED-aza-Diels–Alder reaction after the simple operation to recover the catalyst.[18]

Although the mechanism for the excellent polymer effect observed in water is not clear, pores of the polymer catalyst are supposed to offer local hydrophobic micro-

Table 1 IED-Aza-Diels–Alder Reaction of Benzylideneaniline and Dihydropyran Catalyzed by DCKAs



Entry	Catalyst	**8** (equiv)	Solvent	Yield (%)	*syn*/*anti*
1	–	6.0	CH_3CN	–	–
2	DCKEA	1.5	CH_3CN	29	44:56
3	DCKEA	6.0	CH_3CN	43	52:48
4	DCKEA	13	–	Trace	–
5	DCKEA	1.5	H_2O	Trace	–
6	DCKEA	6.0	H_2O	8	–
7	poly-DCKA-1	1.5	CH_3CN	5	–
8	poly-DCKA-1	6.0	CH_3CN	19	75:25
9	poly-DCKA-1	6.0	H_2O	71	84:16
10	poly-DCKA-1	13	–	66	81:19
11	poly-DCKA-1	6.0	Et_2O	10	70:30
12	poly-DCKA-1	6.0	THF	6	–
13	poly-DCKA-1	6.0	Benzene	8	–
14	poly-DCKA-1	6.0	CH_2Cl_2	8	–
15	poly-DCKA-1	6.0	DMF	2	–
16	poly-DCKA-1	6.0	Acetone	Complex mixture	

Table 2 Three-Component IED-Aza-Diels–Alder Reaction Catalyzed by Poly-DCKA-1 in Water and under Solvent-Free Conditions

$$\underset{\text{(1 equiv)}}{\textbf{PhCHO}} + \underset{\text{(1 equiv)}}{\textbf{PhNH}_2} + \textbf{8} \xrightarrow[\text{H}_2\text{O or no solvent, r.t., 24 h}]{\textbf{poly-DCKA-1}\ \text{(0.2 equiv)}} \textbf{9a}\ (syn) + \textbf{9b}\ (anti)$$

Solvent	8 **(equiv)**	Yield (%)	**9a**/**9b**
H_2O	6.0	73	85:15
–	11	61	84:16

Table 3 Application of Recycled Poly-DCKA-1

$$\textbf{1} + \textbf{8}\ \text{(6 equiv)} \xrightarrow[\text{H}_2\text{O, r.t., 24 h}]{\textbf{poly-DCKA-1}\ \text{(0.2 equiv)}} \textbf{9a}\ (syn) + \textbf{9b}\ (anti)$$

Cycle	1st	2nd	3rd
Yield (%)	71	74	73
9a/**9b**	84:16	86:14	85:15

environments of condensed areas for the active part of the catalyst, DCKA portion. The microenvironment might enhance the local concentration of the lipophilic substrate by positive incorporation from the aqueous media through a hydrophobic interaction of the substrate and the catalyst, resulting in rate acceleration and higher *syn*/*anti* stereoselectivity.

In conclusion, a polymer-supported DCKA (poly-DCKA-1) was found to be a proton-free, metal-free, and recyclable catalyst for the IED-aza-Diels–Alder reaction at room temperature in water and under solvent free conditions.

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(17) **Typical Procedure** To a mixture of benzylideneaniline (453 mg, 2.5 mmol) and poly-DCKA-1 (189 mg, 0.5 mmol equiv) in H_2O (5.0 mL), was added 3,4-dihydro-4*H*-pyran (1.26 g, 15 mmol) at r.t., and the mixture was stirred for 24 h. EtOAc was added, the poly-DCKA-1 was removed by filtration, and the filtrate was extracted with EtOAc. The organic layer was washed with H_2O, dried over anhyd $MgSO_4$, and concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel (hexane–EtOAc) to give pure diastereoisomers **9a** (404 mg, 60%) and **9b** (64 mg, 11%).

(18) The catalyst poly-DCKA-1 was recovered by filtration from the reaction mixture followed by washing successively with H_2O and EtOAc, and drying in vacuo at r.t. for 4 h.