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Efficient *Baylis-Hillman* Reaction *via* a 1,4-Diazabicyclo[2.2.2]octane-based Ionic Catalyst

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Summary. A novel ionic catalyst, 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride based on 1,4-diazabicyclo[2.2.2] octane was synthesized and applied in the *Baylis-Hillman* reaction, which occurred readily at room temperature to afford the corresponding adducts in good yield. The ionic catalyst could be recycled for seven runs without diminution in its catalytic activity.

Keywords. Catalysts; *Baylis-Hillman* reaction; Aldehydes; Acrylates; Homogeneous catalysis.

Introduction

Carbon–carbon bond formation is one of the most fundamental reactions in organic syntheses [1]. The *Baylis-Hillman* reaction, which involves the coupling of activated alkenes with carbon electrophiles in the presence of *Lewis* base catalysts (most commonly tertiary amines, particularly 1,4-diazabicyclo [2.2.2]octane (*DABCO*)), is among the useful C–C bond-forming tools to afford the structural blocks in biological and medicinal chemistry, such as 3-hydroxy-2-methylenepropionate [2–6]. In recent years organic chemists have shown considerable interests in the development of recyclable catalysts from the environmental and economical points of view. For example, the polymer-attached *DMAP* (4-dimethylaminopyridine) [7] and the imidazolium ionic liquid-supported quinuclidine [8] have been reported as recyclable *Baylis-Hillman* catalysts. Nevertheless, these methods did have some limitations. The heterogeneous catalysis of polymer-*DMAP* limited the reaction rate greatly, probably due to resin retardation and mass transfer effect [7]. On the other hand, despite of the successful catalysis of the imidazolium ionic liquid-supported quinuclidine, it suffered from the drawbacks including the tedious preparation, and that the 2-C position of the imidazolium cation could be deprotonated under surprisingly mild conditions [9]. As a result, the undesired side-reaction of aldehydes with imidazolium ionic liquid-supported catalyst occurred. Therefore, we focused our attention on a simple and efficient synthesis of a highly active catalyst with features of recyclability and homogeneity. For this purpose, we now wish to report on a novel and appealing strategy for the synthesis of 1-butyl-4-aza-1-azoniabicyclo [2.2.2]octane chloride (**1**) as catalyst with an ionic nature. Using this catalyst the *Baylis-Hillman* reaction of aldehydes with ethyl acrylate was investigated in terms of reaction conditions, recyclability, and generality to substrates.

Disscussion

The ionic catalyst **1** could easily be prepared *via* quaternization using the readily available reagents *DABCO* · $6H_2O$ and 1-chlorobutane (Scheme 1). The catalyst **1** was characterized by MS (ESI), ^{1}H NMR, and FT-IR.

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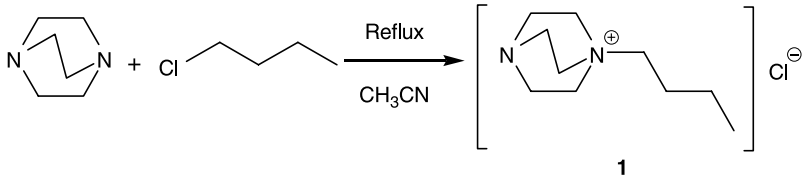
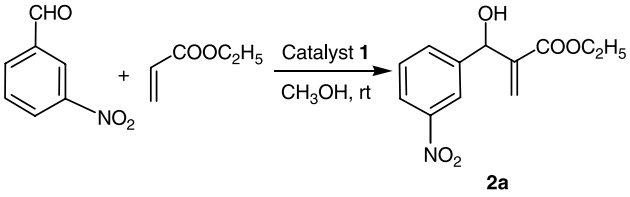


Scheme 1

Table 1. Reactions of 3-nitrobenzaldehyde with ethyl acrylate at room temperature catalyzed by ionic catalyst **1**[a]

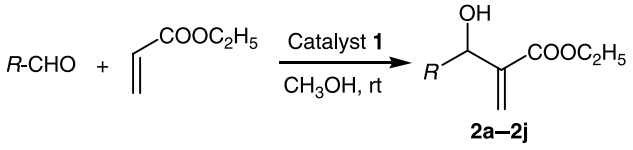


Entry	Methanol/ mmol	Ethyl acrylate/ mmol	Catalyst/ mmol	Time/ h	Conv./ %[b]	Sel./ %[b]
1	15	10	10	24	40	94
2	10	10	10	2	100	91
3	10	6	10	2	100	97
4	10	6	2.5	3	100	95
5	10	6	1.25	5	100	96

[a] 3-Nitrobenzaldehyde (5 mmol)
[b] Determined by GC

The catalytic performance of catalyst **1** was examined in the *Baylis-Hillman* reaction for the coupling of 3-nitrobenzaldehyde with ethyl acrylate at room temperature, in which methanol was chosen as the solvent according to the reported facts that the carbonyl of aldehyde was activated by forming a hydrogen bond with protic solvent of methanol [10–12]. The results in Table 1 also indicated that the amount of methanol influenced the coupling of 5 mmol 3-nitrobenzaldehyde and 10 mmol ethyl acrylate dramatically, probably, since the intermolecular hydrogen bonding between the methanol molecules could deteriorate the interaction between methanol and 3-nitrobenzaldehyde if too much methanol was presented [10]. Only when less methanol (2 equiv.) was applied, the adduct product was obtained with a yield of 91% (Table 1, entry 2). Nevertheless, much excess of ethyl acrylate could be harmful because of the formation of diadduct coming from the coupling

Table 2. *Baylis-Hillman* reactions of aldehydes with ethyl acrylate catalyzed by ionic catalyst **1**[a]



Entry	Aldehydes	Time/h	Product[b]	Conv./%[c]	Sel./%[c]
1	3-Nitrobenzaldehyde	5	**2a** [14]	100	97
2	Benzaldehyde	14	**2b** [3c]	97	92
3	2-Chlorobenzaldehyde	6	**2c** [12a]	99	99
4	4-Dimethylaminobenzaldehyde	10	**2d**	99	95
5	4-Hydroxybenzaldehyde	8	**2e**	100	99
6	Pyridine-2-carboxaldehyde	3	**2f** [15]	100	98
7	Valeraldehyde	16	**2g** [14]	98	92
8	Propionaldehyde	16	**2h** [3c]	98	93
9	Cinnamaldehyde	20	**2i** [15]	90	99
10	Phenyl acetaldehyde	18	**2j**	100	96

[a] Aldehyde (5 mmol), ethyl acrylate (6 mmol), methanol (10 mmol), catalyst **1** (1.25 mmol)
[b] Identified by MS and IR (KBr)
[c] Determined by GC

reaction of the desired adduct with excess ethyl acrylate. Further inspection revealed that the optimal conversion and selectivity to the desired product were achieved when 1.2 equiv. of ethyl acrylate were applied (Table 1, entry 3–5). Additionally, by extending the reaction time from 2 to 5 h, the amount of catalyst **1** could be decreased eight-fold from 10 to 1.25 mmol without loss of activity (Table 1, entry 5). The recycling of catalyst **1** under conditions in entry 5 indicates that the activity and stability was maintained very well (conv.: 100%, sel.: 90–96%) even after seven recycles.

To explore the generality of the *Baylis-Hillman* reaction catalyzed by catalyst **1**, we examined the reactions by selecting a variety of aryl or aliphatic aldehydes to react with ethyl acrylate. All coupling products were easily separated by simple extraction with diethyl ether, leaving behind the solid catalyst **1** simultaneously. As summarized in Table 2, both the electron-rich (deactivated) and electron-poor (activated) aldehydes could be efficiently converted to the desired products with high conversion (90–100%) and selectivity (92–99%). All products were confirmed by MS and IR (KBr) spectra.

The separation step in organic synthesis and catalysis is of practical importance in both of academia and industry. Using a ''phase tag'' for a substrate, reagent, or catalyst could simplify reaction workup, product isolation, and catalyst recovery [13]. In our study, catalyst **1**, tagged with an ammonium salt, could be separated easily from the reaction mixture by precipitation with diethyl ether and could be used in next run without further purification. Compared to the base catalyst *DABCO* for the *Baylis-Hillman* reaction, the most advantageous merits of the developed ionic catalyst **1** system was the facilitation of product/catalyst separation and the simple workup for catalyst recycling uses. Through quaternization of one base-site of *DABCO* by chlorobutane, the ionic feature was endued to solid catalyst **1** with the properties of strong polarity, negligible vapor pressure, and high thermal stability. In such case, catalyst **1** and the substrates (aldehydes and ethyl acrylate) with relatively high polarity were miscible as a homogeneous system, overcoming the mass transfer limitation. Upon completion of the reaction, diethyl ether with poor polarity was applied to extract the non-ionic organic compounds leaving behind solid **1** directly for a next pass. As for the conventional *DABCO* catalyst, which is very soluble in ethers, alcohols, and alkanes, the separation of products/*DABCO* is very tedious, though the catalytic activity was competitive to that of ionic catalyst **1**.

In conclusion, we have developed a simple and efficient method for the *Baylis-Hillman* reaction using the homogeneous ionic catalyst **1**, which was featured with an ammonium salt tag. This catalyst allowed efficient coupling of aldehydes with ethyl acrylate at room temperature affording high conversion and selectivity without activity loss even after seven recycling uses. Furthermore, the workup of product/catalyst separation was facilitated greatly compared to the conventional *DABCO* catalytic system.

Experimental

*Ionic Catalyst **1** Based on DABCO*

A mixture of 2.20 g *DABCO*·$6H_2O$ (10 mmol) and 0.74 g *n*-chlorobutane (8 mmol) in 10 cm^3 acetonitrile was refluxed with stirring for 24 h. Excess *DABCO* was washed off with ethyl acetate, leaving behind the desired product as a white solid (1.62 g, yield 81%). IR (KBr): $\bar{\nu} = 2967$, 2870, 1631, 1464, 1379, 1324, 1099, 1056 cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 0.90$ (t, $J = 7$ Hz, 3H, C*H*$_3$), 1.35 (m, 2H, C*H*$_2$–CH_3), 1.70 (m, 2H, C*H*$_2$–CH_2), 3.15 (t, $J = 7$ Hz, 6H, N–C*H*$_2$), 3.20 (t, $J = 8$ Hz, 2H, N–C*H*$_2$–CH_2), 3.35 (t, $J = 7$ Hz, 6H, N–C*H*$_2$) ppm; MS (ESI): m/z (%) = 169 ([M–Cl]$^+$, 100).

General Procedures for the Baylis-Hillman Reaction of Aldehydes with Ethyl Acrylate

A mixture of 5 mmol aldehyde, 6 mmol ethyl acrylate, and 1.25 mmol catalyst **1** in 10 mmol methanol was stirred at room temperature (monitored by TLC). Upon completion, the obtained residues after stripping of methanol were extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to give the product as yellow oily liquid.

The left residues were dried *in vacuo* to give the recovered catalyst, which could be used without further treatment for the next run.

All the products (except **2d**, **2e**, and **2j**) are known compounds, which were characterized by IR and MS spectra and compared with their literature data reports [3c, 12a, 14, 15].

Ethyl 2-[hydroxy(4-dimetylaminophenyl)methyl]acrylate (**2d**, $C_{14}H_{19}NO_3$)

Yellow oily liquid (conversion: 99%, selectivity: 95%); IR (KBr): $\bar{\nu} = 3471$, 3087, 2986, 1709, 1526, 1351, 1145, 1044, 1091 cm^{-1}; MS: m/z (%) = 250 (M^+, 2), 234 (90), 204 (80), 188 (70), 177 (25), 150 (100), 134 (40), 105 (30), 77 (40), 55 (30), 29 (20); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 1.10$ (t, $J = 8$ Hz, CH_2–C*H*$_3$), 3.60 (s, 6H, N–C*H*$_3$), 4.10 (q, $J = 7$ Hz, 2H, C*H*$_2$–CH_3), 5.60 (d, $J = 4$ Hz, 1H, CH–O*H*), 6.10 (s, 2H, C=C*H*$_2$), 6.30 (d, $J = 6$ Hz, 1H, C*H*–OH), 7.60–7.70 (m, 2H, *Ph*), 8.10–8.20 (m, 2H, *Ph*) ppm.

Ethyl 2-[hydroxy(4-hydroxyphenyl)methyl]acrylate (**2e**, $C_{12}H_{14}O_4$)
Yellow oily liquid (conversion: 100%, selectivity: 99%); IR (KBr): $\bar{\nu} = 3208$, 3169, 3040, 2963, 1719, 1596, 1448, 1282, 1219, 1157 cm^{-1}; MS: m/z (%) = 221 (M^+, 1), 204 (10), 177 (20), 160 (40), 132 (60), 105 (100), 77 (50), 55 (10), 28 (20); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 1.15$ (t, $J = 7$ Hz, 3H, CH_2–C*H*$_3$), 3.65 (s, 1H, CH–O*H*), 4.05 (q, $J = 6$ Hz, 2H, C*H*$_2$–CH_3), 5.55 (s, 1H, Ph–O*H*), 6.15 (s, 2H, C=C*H*$_2$), 6.35 (d, $J = 5$ Hz, 1H, C*H*–OH), 7.65–7.75 (m, 2H, *Ph*), 8.05–8.15 (m, 2H, *Ph*) ppm.

Ethyl 2-[hydroxy(benzyl)methyl]acrylate (**2j**, $C_{13}H_{16}O_3$)
Yellow oily liquid (conversion: 100%, selectivity: 96%); IR (KBr): $\bar{\nu} = 3448$, 3060, 3025, 2974, 2928, 1732, 1596, 1491, 1398, 1177, 1029 cm^{-1}; MS: m/z (%) = 222 (M^+, 10), 204 (2), 178 (2), 165 (2), 149 (1), 131 (2), 103 (5), 77 (2), 28 (100); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 1.20$ (t, $J = 6$ Hz, 3H, CH_2–C*H*$_3$), 2.60 (d, $J = 7$ Hz, 2H, *Ph*–C*H*$_2$), 3.50 (s, 1H, CH–O*H*), 3.90 (q, $J = 6$ Hz, 2H, C*H*$_2$–CH_3), 4.10 (m, 1H, C*H*–OH), 7.05 (s, 2H, C=C*H*$_2$), 7.40–7.50 (m, 5H, *Ph*) ppm.

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