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Ionic Liquid-Immobilized Quinuclidine-Catalyzed Morita−Baylis−Hillman Reactions

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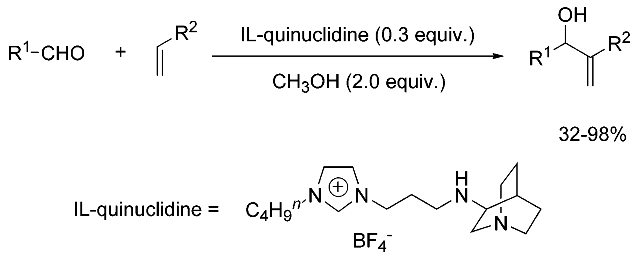
Received September 13, 2004



The ionic liquid-bound quinuclidine catalyzed Baylis−Hillman reactions were investigated. The IL-supported catalyst showed equally good catalytic activity as compared with its nonimmobilized counterpart. The corresponding Baylis−Hillman adducts were obtained in moderate to high yields in all the cases tested. The IL-supported quinuclidine can be readily recovered and reused six times without significant loss of catalytic activity.

The Morita−Baylis−Hillman reaction is one of the most versatile carbon−carbon bond-forming reactions in modern organic synthesis and has drawn considerable attention in the past decades due to its many advantages in regard to atomic economy, nonmetal catalysis, mild conditions, compatibility of multiple functional groups, and so on.[1] This reaction is usually carried out under homogeneous conditions in the presence of Lewis base catalysts such as DABCO,[2] DMAP,[3] DBU,[4] PPh_3,[5] PBu_3,[6] PPh_2Me,[7] and imidazoles.[8] In most cases, stoichiometric or excess amount of Lewis bases is required to facilitate faster reactions. It is therefore of interest to develop recyclable and reusable Baylis−Hillman catalysts, which will make the reaction more atom-economic and efficient. Shi[9] and Corma[10] independently investigated the use of commercially available poly-DMAP as the recyclable Baylis−Hillman catalyst. Those heterogeneous catalyses were quite slow (generally required several days to achieve acceptable yields), probably due to resin retardation effect. In fact, it has been demonstrated that Baylis−Hillman reaction under homogeneous conditions had faster rate and higher yields compared to the reaction under heterogeneous conditions.[11] Further, Shi[9] and co-workers reported the PEG-bound alkyl diphenylphosphines as recyclable Baylis−Hillman catalysts and indeed observed faster reaction. However, an additional activating step was required in order for the immobilized catalyst to be reused.

As a continuation of our work in Baylis-Hillman reactions[8a−c] and applications of ionic liquids (ILs),[12] we have designed and synthesized a series of ionic liquid-linked catalysts on the basis of the biphasic strategy, i.e., homogeneous reaction and heterogeneous separation. Herein we wish to report the first example of this type of Baylis−Hillman catalyst, the ionic liquid-supported quinuclidine, and its efficient applications in the Baylis−Hillman reactions.

The so-called room temperature ionic liquids, especially those derived from 1-*n*-alkyl-3-methylimidazolium cations, have demonstrated to have versatile applications in organic synthesis as reaction media.[13,14] Earlier work has shown that ionic liquid as reaction media can accelerate Baylis−Hillman coupling in the presence of DABCO.[15] Later, Aggarwal[16] and co-workers pointed out that the imidazolium-containing ionic liquid was not inert under the reaction conditions. In our examination of the stability of the synthesized IL-bound catalysts, we found,

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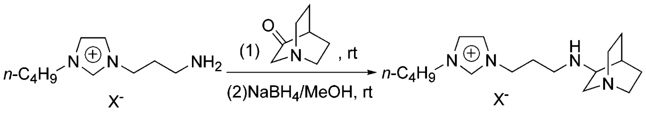
10.1021/jo048391d CCC: $30.25

SCHEME 1



1a: X=Br
1b: X=BF_4
1c: X=PF_6

SCHEME 2

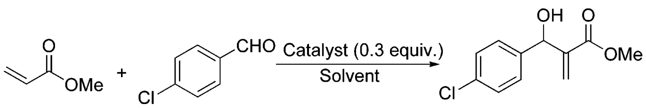


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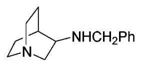
TABLE 1. Reactions of *p*-Chlorobenzaldehyde with Methyl Acrylate in Various Media at Room Temperature[a]

entry	catalyst	solvent	yield[b] (%)
1	**1a**	CH_3CN	18
2	**1a**	CH_2Cl_2	5
3	**1a**	$CHCl_3$	9
4	**1a**	THF	8
5	**1a**	EtOH	36
6	**1a**	MeOH	37
7	**1a**	MeOH[c]	46
8	**1a**	MeOH[d]	52
9	**1b**	MeOH[d]	84
10	**1c**	MeOH[d]	71
11	**1b**	[BMIM]BF_4[e]	13
12	**1b**	[BMIM]BF_4[f]	26
13	**1b**	[BMIM]PF_6[f,g]	13
14	**1b**	[bupy]BF_4[h]	21
15	**1b**	[BMMIM]BF_4[i]	15

[a] Carried out on a 0.5 mmol scale in 0.5 mL of solvent (except those specified) for 8 h in the presence of 0.3 equiv of the catalyst at room temperature. Molar ratio of *p*-chloro-benzaldehyde/methyl acrylate = 1:1.5. [b] Isolated yields of pure product. [c] Aldehyde/methanol = 1:10. [d] Aldehyde/methanol = 1:2.0. [e] [BMIM]BF_4/1-butyl-3-methylimidazolium tetrafluoroborate. [f] Aldehyde/ionic liquid = 1:2.0. [g] [BMIM]PF_6/1-butyl-3-methylimidazolium hexafluorophosphate. [h] [bupy]BF_4: 1-butylpyridinium tetrafluoroborate. [bupy]BF_4: decomposition occurred during the reaction. [i] [BMMIM]BF_4: 1-butyl-2,3-dimethylimidazolium tetrafluoroborate.

TABLE 2. Reactions of *p*-Chlorobenzaldehyde (1.0 equiv) and Methyl Acrylate (1.5 equiv) in the Presence of 0.3 equiv of Different Catalysts in 2.0 equiv of Methanol at Room Temperature[a]

entry	Catalyst	Time (h)	Yield (%) [b]
1	DABCO	8	79
2	DABCO	8	12[c]
3	DABCO [d]	8	59
4	3-quinuclidinone	8	10
5		8	92
6[e]	**1b** (1st run)	8	84
7[e]	**1b** (2nd run)	8	92
8[e]	**1b** (3rd run)	8	75
9[e]	**1b** (4th run)	24	76
10[e]	**1b** (5th run)	24	72
11[e]	**1b** (6th run)	36	74

[a] The reactions were carried out on a 0.5 mmol scale. [b] Isolated yields of the pure products. [c] 1 mL of methanol was used. [d] The aldehyde used is benzaldehyde. [e] Reuse of catalyst from 1 to 6 runs.

however, that the ionic liquid tags were actually quite stable under the Baylis–Hillman reaction conditions when methanol was used as the reaction medium (see the Supporting Information).[17] This encouraged us to pursue the use of ionic liquid as a new support for Baylis–Hillman catalyst, aiming to develop an effective catalyst system that can be readily recycled and reused.

Synthesis. The synthesis of IL-supported quinuclidine was straightforward as depicted in Scheme 1. The reductive amination of 3-quinuclidinone with amino ionic liquid afforded the desired IL-bound quinuclidine **1** as a pale yellow viscous liquid. This new type ionic liquid was characterized by ^{1}H NMR and ^{13}C NMR, IR, and MS.

Catalytic Conditions. The Baylis–Hillman reaction of *p*-chlorobenzaldehyde and methyl acrylate was selected as the model for subsequent screening. The reaction was conducted in the presence of 0.3 equiv of catalyst **1** at room temperature (Scheme 2). As shown in Table 1, the ionic liquid-supported quinuclidine worked well for the desired Baylis–Hillman reaction and was more efficient in protic solvents than in aprotic solvents (entries 1–6). Of the solvents examined, methanol was found to be the best medium (entry 6). These results are consistent with previous observations that the Baylis–Hillman reactions generally proceed faster in protic solvents such as methanol and water than in aprotic solvents.[8,11] Further inspection revealed that the amount of methanol also affected the reaction quite notably. Optimal yield was achieved in the presence of 2.0 equiv. of methanol in the reaction mixture (Table 1, entries 6–8).

When ionic liquids were used as solvent for the model reaction instead of methanol, the product yields were found to be substantially lower than those in methanol (Table 1, entries 11–15). This indicates that the ionic liquid itself does not have a large rate-enhancing effect on Baylis–Hillman reaction and that the protic solvent plays a dominant role in accelerating the reaction, probably via hydrogen bonding.[11,18] On the other hand, catalyst **1b** was found to give the best result in terms of product yield (Table 1, entry 9), so it was selected for the subsequent catalytic experiments.

The reactions catalyzed by some conventional catalysts were also examined for the purpose of comparison. The results are listed in Table 2. As shown, the IL-supported catalyst **1b** of this work not only exhibited a much better activity than its parent catalyst 3-quinuclidinone, but also was shown to be better than DABCO under the same conditions (Table 2, entries 1–4). The reaction catalyzed by 3-benzylaminoquinuclidine, a nonbounded analogue of **1b,** gave a slightly higher yield (Table 2, entry 5). These results are comparable with those obtained from the reaction catalyzed by quinuclidine, the "optimum" catalyst claimed by Aggarwal (50 mol % of catalyst, 3 h, 88%).[19] Our present observations indicate that the ionic liquid-supported quinuclidine is an excellent homogen-

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(17) Decomposition does occur after extensive use probably due to the reactivity of the ionic liquid, but reasonable catalytic activity is still maintained.

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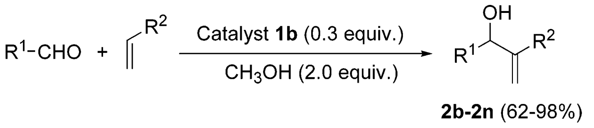
TABLE 3. Baylis−Hillman Reactions of Aldehydes (1.0 equiv) and Acrylates (1.5 equiv) Catalyzed by Ionic Liquid-Supported Quinuclidine 1b (0.3 equiv) in 2.0 equiv of Methanol at Room Temperature



entry	R^1	R^2	time (h)	product	yield[a] (%)
1	*n*-C_3H_7	$COOCH_3$	12	**2b**	62
2	*i*-C_4H_9	$COOCH_3$	12	**2c**	83
3	*n*-C_6H_{13}	$COOCH_3$	12	**2d**	84
4	Ph	$COOCH_3$	8	**2e**	82
5	*p*-ClPh	$COOC_2H_5$	8	**2f**	92
6	*p*-ClPh	$COOC_4H_9$	8	**2g**	84
7	*p*-CH_3Ph	$COOCH_3$	10	**2h**	75
8	*p*-*i*PrPh	$COOCH_3$	12	**2i**	74
9	*p*-NO_2Ph	$COOCH_3$	1	**2j**	97
10	*o*-NO_2Ph	$COOCH_3$	0.5	**2k**	88
11	*m*-NO_2Ph	$COOCH_3$	1	**2l**	90
12	2-pyridyl	$COOCH_3$	0.5	**2m**	96
13	3-pyridyl	$COOCH_3$	1	**2n**	90
14	4-pyridyl	$COOCH_3$	0.5	**2o**	98
15	2-furyl	$COOCH_3$	1	**2p**	90

TABLE 4. Baylis−Hillman Reactions of Aldehydes (1.0 equiv) and Acrylonitrile (1.5 equiv) in the Presence of 1b (0.3 equiv) in 2.0 equiv of Methanol at Room Temperature

entry	R^1	time (h)	product	yield[a] (%)
1	Ph	8	**3a**	91
2	*p*-ClPh	9	**3b**	89
3	*p*-CH_3Ph	10	**3c**	83
4	*p*-CH_3OPh	24	**3d**	69
5	*p*-NO_2Ph	0.5	**3e**	92
6	2-pyridyl	0.5	**3f**	97

[a] Isolated yields.

SCHEME 3

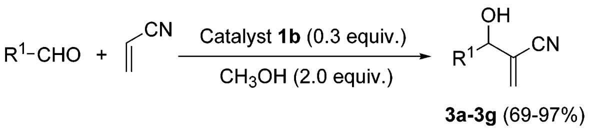
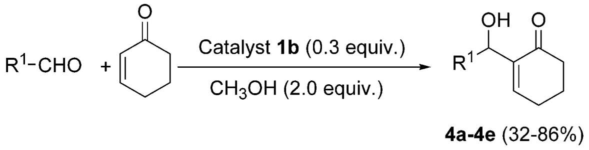


TABLE 5. Baylis−Hillman Reactions of Aldehydes (1.0 equiv) and Cyclohexenones (1.5 equiv) in the Presence of 1b (0.3 equiv) in Methanol (2.0 equiv) at Room Temperature

entry	R^1	time (h)	product	yield[a] (%)
1	Ph	12	**4a**	73 (5)
2	*p*-ClPh	12	**4b**	86 (8)
3	*p*-CH_3Ph	24	**4c**	41
4	*p*-NO_2Ph	6	**4d**	69 (27)
5	piperonal	48	**4e**	32

[a] Isolated yields. The numbers in parentheses are yields of aldol products.

SCHEME 4



eous catalyst for Baylis-Hillman reactions. And more importantly, the use of the ionic liquid-linked catalyst can facilitate easy product separation and reuse of the catalyst. After each run, the product was readily separated by extraction with diethyl ether, and the ionic liquid residue, i.e., the catalyst, can then be used directly for next run without further treatment. It was found that the ionic liquid-supported catalyst could be recycled for at least six times without too much loss of its activity (Table 2, entries 6−11).

Applicability. Under the optimum conditions established above, the **1b**-catalyzed Baylis−Hillman reactions of acrylates with a variety of aldehydes were examined at room temperature (Table 3). As demonstrated in Table 3, both aliphatic and aromatic aldehydes can undergo very efficient Baylis−Hillman reactions with acrylates in the presence of 0.3 equiv of **1b**, giving the corresponding Baylis−Hillman adducts **2b**−**n** in good to excellent yields (62−98%).[11,19] No apparent side reaction of aldehydes such as aldol condensation was observed under the conditions of the present study.

The analogous reactions of acrylonitrile were also investigated. Again, high yields were achieved in shorter reaction time. As shown in Table 4, the ionic liquid-supported catalyst was highly effective for all the substrates tested. It was found that the reaction of *p*-methoxybenzaldehyde, which is usually quite an inert substrate, could provide a fairly good yield (69%, entry 4) of isolated Baylis−Hillman adduct under the present conditions, demonstrating the good activity of the ionic liquid-bound catalyst synthesized in this work (Scheme 3).

Cyclic enones are poor Michael acceptors, and consequently the Baylis−Hillman reactions involving cyclic enones were usually observed to be sluggish under normal conditions. A variety of catalysts have therefore been employed for this kind of reaction in order to improve its efficiency.[8,20] In our study, we found that the reactions of 2-cyclohexenone proceeded quite effectively using **1b** as catalyst under the conditions mentioned above, providing the Baylis−Hillman adducts in fair to high yields (Table 5). Minor amount of aldol products was also isolated in some cases probably due to the relatively strong basicity of the catalyst (Scheme 4).

In summary, we in the present work have investigated a range of Baylis−Hillman reactions using the ionic liquid-supported **1b** as a new catalyst. Generally, the reactions demonstrated higher efficiency and gave high yields in comparison with the cases where other common homogeneous or heterogeneous catalysts were used. The ionic liquid-bound catalyst can be readily recovered from the reaction mixture and be reused several times without much loss of its activity, thus providing a highly efficient

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alternative for the Baylis−Hillman-type synthesis to be carried out under environmentally more friendly conditions. The design and synthesis of ionic liquid-bound asymmetric Baylis−Hillman catalyst are currently underway in our laboratory.

Experimental Section

General Procedure. To the solution of **1b** (57 mg, 0.15 mmol) in CH_3OH (41 μL, 2.0 equiv) were added aldehyde (0.5 mmol) and activated alkene (0.75 mmol). The resulting solution was stirred at ambient temperature and monitored by TLC. After the indicated reaction time, the solution was concentrated and the residue was extracted with diethyl ether. The ether extracts were rotary-evaporated, and the crude product was purified by flash chromatography on silica gel to afford the desired product. The remaining layer was further vacuumed to dryness and the resulting catalyst was reused directly for the next run. The reactions using the recycled catalyst were conducted in a similar manner.

Acknowledgment. We are very grateful to the Natural Science Foundation of China (NSFC Nos. 20452001, 20332020) and the Ministry of Science and Technology (MoST) of China for financial support.

Supporting Information Available: The syntheses of **1a**−**c**, the NMR spectra of **1a**−**c**, the stability study of **1b**, and ^{1}H NMR spectra of all the Baylis−Hillman products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048391D