

Reports

Polystyrene-Supported Phosphine-Catalyzed aza-Baylis–Hillman Reactions and the Relationship between Resin Loading Level and Catalyst Efficiency

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Received April 25, 2004

The Baylis–Hillman reaction has become an important tool in organic synthesis, since it allows for the formation of carbon–carbon bonds under mild reaction conditions.¹ While early versions of this reaction were marked by some irreproducible results and long reaction times, recent years have seen much advancement in the understanding of its mechanism² and improvements in its efficiency and reliability. Aggarwal and co-workers have been among the many researchers at the forefront of elucidating the mechanistic nuances of this reaction and have recently reported a definitive study describing the relationship between the pK_a of an amine and its effectiveness as a catalyst in Baylis–Hillman reactions.³ In their work, it was found that quinuclidine, with its relatively high pK_a , is a much better catalyst than the more commonly used 1,4-diazabicyclo[2.2.2]octane, with its relatively low pK_a . In fact, it is reported that quinuclidine is the most effective amine catalyst yet examined for Baylis–Hillman reactions and that it allows for previously unreactive substrates to participate in such reactions.

We too have had a long standing interest in the development of this reaction⁴ and have reported on the use of not only nucleophilic amine Lewis base catalysts but phosphines as well in aza-Baylis–Hillman reactions in which the electrophile is a sulfonated imine rather than an aldehyde.^{5,6} We have examined the scope of this reaction in terms of nucleophiles, electrophiles, and catalysts and have developed

convenient methods for the synthesis of a large variety of β -amino carbonyl compounds.

Another area of interest for us has been the development of polymer-supported reagents for use in solution-phase organic synthesis. We have recently reported both soluble and insoluble amine,⁷ phosphine,⁸ sulfide,⁹ and sulfoxide¹⁰ reagents that are useful in a range of synthetic transformations. In a bridging of our areas of interest, we have examined the use of a soluble poly(ethylene glycol)-supported alkyl-diphenylphosphine and an insoluble polystyrene-supported 4-dimethylaminopyridine (DMAP) analogue as catalysts in aza-Baylis–Hillman reactions and observed results similar to those obtained using the analogous small molecule catalysts.^{11–13} Herein we wish to disclose the use of an insoluble polystyrene-supported triphenylphosphine catalyst in aza-Baylis–Hillman reactions and discuss how the loading level of the polymers relate to catalyst efficiency.

As polymer-supported reagents and catalysts¹⁴ have become frequently used in organic synthesis, a common concern is the loading level of the polymer. A more densely functionalized polymeric reagent with its resulting higher loading level is generally preferred, because this will minimize the necessary quantities of both the reagent and the solvent used, and a number of strategies have been developed to prepare such highly loaded polymers. These include the use of low-molecular-weight monomers,¹⁵ the homopolymerization of functional monomers,¹⁶ and the grafting of densely functionalized polymeric chains onto a resin core¹⁷ to minimize the amount of inert polymer carrier for the functional reagent moieties. While this strategy of using densely functionalized polymers may be effective in scavenging applications, it may not be optimal in situations in which the polymer-supported reagent is to be delivered selectively to dissolved reactants because of the influence that the reagent groups have on the microenvironment of the polymer.¹⁸

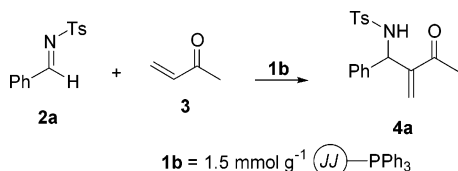
Fréchet et al. and others have observed that some polymer-supported DMAP analogues are most effective when the polymer backbone is less than 50% functionalized.¹⁹ Additionally, Alexandratos et al. reported similar studies in which the loading levels of polymer-supported benzyldiphenyl phosphine and sulfonic acid reagents were varied and studied the use of these variously loaded reagents in Mitsunobu^{20a} and Prins^{20b} reactions, respectively. For these reactions, it was also found that resins with less than maximum loading levels afforded the best results in terms of product yield and reaction time. We, therefore, chose to examine if our previously reported JandaJel-PPh₃ polymers,^{9,21,22} which have loading levels of 0.5, 1.5, and 3.2 mmol PPh₃ gm⁻¹ (**1a–c**, respectively), were effective

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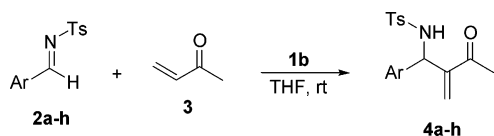
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Table 1. Reactions Using Catalyst **1b** in a Variety of Solvents

entry	solvent	yield (%) ^a
1	DCM	73
2	DMF	69
3	THF	91
4	ACN	68
5	toluene	66
6	ethyl ether	37

^a Isolated yield of **4a** from reaction between **2a** (1.0 equiv) and **3** (1.5 equiv) with **1b** (0.1 equiv) as catalyst at room temperature after 10 h.

Table 2. Reactions of **2a–h** with **3** Using **1b** as Catalyst

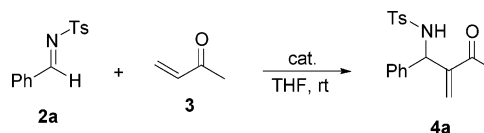
entry	electrophile	time (h) ^a	yield (%) ^b
1	2a , Ar = C ₆ H ₅ –	10	91
2	2b , Ar = <i>p</i> -MeO–C ₆ H ₄ –	30	82
3	2c , Ar = <i>p</i> -Me–C ₆ H ₄ –	24	90
4	2d , Ar = <i>p</i> -Me ₂ N–C ₆ H ₄ –	48	trace
5	2e , Ar = <i>m</i> -NO ₂ –C ₆ H ₄ –	24	63
6	2f , Ar = <i>p</i> -F–C ₆ H ₄ –	12	77
7	2g , Ar = <i>p</i> -Cl–C ₆ H ₄ –	10	92
8	2h , Ar = <i>p</i> -Br–C ₆ H ₄ –	24	99

^a The reaction was stopped when TLC analysis showed the complete disappearance of **2**. ^b Isolated yield of **4** from reaction between **2** (1.0 equiv) and **3** (1.5 equiv) with **1b** (0.1 equiv) as catalyst at room temperature in THF.

catalysts and if they exhibit such loading-dependent catalytic efficiency in aza-Baylis–Hillman reactions.²³

As a starting point, we set out to determine if **1a–c** can, indeed, efficiently catalyze the reaction between *N*-benzylidene-4-methylbenzenesulfonamide (**2a**) and methyl vinyl ketone (MVK, **3**) by using **1b** as the catalyst in a variety of solvents (Table 1). These reactions were carried out at room temperature for 10 h to determine the best solvent for future studies. The highest yield of **4a** was observed with THF (Table 1, entry 3), and thus, this was chosen as the solvent for all further experiments.

Next, we examined the generality of this process by reacting a range of sulfonated imines with **3** in the presence of **1b**. These reactions were not limited in time, but were allowed to continue until TLC analysis indicated the complete disappearance of **2a–h** (except for **2d**). As can be seen in Table 2, sulfonated imines substituted with both electron-donating (Table 2, entries 2 and 3) and electron-withdrawing (Table 2, entries 5–8) substituents afforded good to excellent yields of the desired adducts **4b–c** and **4e–h**, respectively, in reasonable reaction times. Only *p*-dimethylamino substituted substrate **2d** did not give a

Table 3. Reactions Using New and Recycled **1a–c** as Catalyst

entry	catalyst	time (h)	yield (%) ^a
1	1a	10	73
2	1a ^b	28 ^c	80
3	1a ^b	30 ^c	78
4	1a ^b	48 ^c	86
5	1b	10	91
6	1b ^b	29 ^c	90
7	1b ^b	48 ^c	89
8	1b ^b	60 ^c	91
9	1c	10	70
10	1c ^b	28 ^c	76
11	1c ^b	36 ^c	88
12	1c ^b	36 ^c	93

^a Isolated yield of **4a** from reaction between **2a** (1.0 equiv) and **3** (1.5 equiv) with **1a–c** (0.1 equiv) as catalyst at room temperature.

^b The catalyst used was recovered from the previous reaction entry.

^c The reaction was stopped when TLC analysis showed the complete disappearance of **2**.

significant quantity of the expected product (**4d**), even after an extended reaction time (Table 2, entry 4).

Once it was established that **1b** is an effective catalyst in these aza-Baylis–Hillman reactions, we examined the relationship between resin loading and catalytic efficiency and recyclability. For these experiments, we returned to the use of **2a** as the sulfonated imine substrate, and the results are summarized in Table 3. As can be seen, both **1a** and **1c** (0.5 and 3.2 mmol PPh₃ g⁻¹, respectively) were slightly less efficient catalysts and afforded somewhat lower yields than **1b** did in reactions that were performed under identical conditions (Table 3, entries 1, 5, and 9).

At the end of these reactions, catalysts **1a–c** were recovered and reused multiple times in the same reaction to examine their recyclability (Table 3, entries 2–4, 6–8, and 10–12). It was found that successive reaction cycles required progressively longer reaction times to go to completion, especially for **1a** and **1b**. We speculate that a portion of the phosphine groups of the polymers became irreversibly derivatized at some point during the recycling process, and thus, the actual amount of active phosphine catalyst groups was reduced in the later cycles. Unfortunately, IR analysis of the recovered resins did not definitively indicate the nature of the derivitization, but signals suggesting the possibility of some phosphine oxide formation were observed. However, despite the reduced catalyst efficiency, the isolated yields remained high.

Finally, in an attempt to explain our observed results regarding the correlation between resin loading and catalytic efficiency, we measured the swelling of **1a–c** in the same set of solvents used in Table 1. The results of these swelling measurements are summarized in Table 4, and it is clear that in the solvents examined, resin swelling dramatically decreases with increasing resin loading/phosphine group concentration. It is also interesting to note that one of the best solvents for swelling **1b** is THF, which was also the solvent

Table 4. Swelling of Phosphine Resins **1a–c**^a

solvent	1a	1b	1c
DCM	9.2	6.6	5.4
DMF	6.2	4.4	3.2
THF	8.2	6.2	5.0
ACN	1.8	1.6	1.4
toluene	8.2	5.4	5.4
ethyl ether	3.0	2.0	1.8
dry volume	1.8	1.6	1.4

^a Data are given in mL gm⁻¹ resin.

that afforded the highest yield of **4a** (Table 1, entry 4)²⁴ and that the poor swelling solvents acetonitrile and ethyl ether afforded the lowest yields of **4a** (Table 1, entries 4 and 6). Thus, at first glance, it seems that resin swelling for a particular catalyst is a determining factor for catalytic efficiency in these reactions and that it should be maximized when possible. The relationship between resin swelling and loading may be explained by the ratio of triphenylphosphine equivalents to styrene used to prepare the resins. For the preparation of catalysts **1a**, **1b**, and **1c**, ratios of 1:16, 1:3, and 1:0 were used, respectively (see Supporting Information). In other words, for every triphenylphosphine equivalent in **1a**, there are 16 ethylbenzene units, whereas **1c** is composed completely of tightly packed phosphine groups separated only by ethyl units. Thus, it is not difficult to imagine that **1a** is a much more flexible and dynamic polymer than is **1c** and that its interior should be more accessible to solvent and reagent molecules. Although it has been previously reported that resin swelling is dependent upon cross-linking level,²⁵ our observations clearly indicate that functional group loading is also an important factor in this process and that lightly cross-linked but highly functionalized resins can have reduced solvent absorption and swelling and, thus, reduced reactant diffusion through their interiors.

In summary, we have for the first time demonstrated that insoluble polystyrene-supported triphenylphosphine is an effective catalyst in aza-Baylis–Hillman reactions between a variety of *N*-sulfonated arylimines and methyl vinyl ketone. Additionally, we have examined the relationship between resin loading level and catalytic efficiency and have observed that in these reactions, there is a clear trend in which the swelling of a specific catalyst resin by a solvent is directly proportional to its catalytic efficiency in that solvent.²⁶ However, this trend is not maintained when comparing resins with different loadings. If it did, resin **1a** would have been the best catalyst, which it clearly was not (Table 3, entry 1 vs entry 5). The reasons why resin swelling is not the only determinant of catalyst efficiency and why an intermediate concentration of phosphine groups attached to the resin backbone affords the most effective catalyst are not clear at this time; however, this phenomenon has been observed previously in other applications of polymer-supported reagents and catalysts.^{19,20} Both our present and the previous observations could be due to the fact that the polarities of such intermediately loaded polymers best stabilize the polar transition states of the reactions studied and, thus, make these polymers the best catalysts. Regardless of the origin of the observed effects, it is clear from the present study that high resin loading does not automatically result in the best results

in terms of product yield and reaction time. Therefore, it is clear that a polymer's microenvironment¹⁸ does play an important role in determining the utility of the polymer as a reagent carrier in polymer-assisted organic synthesis, and factors that affect it should be considered during the planning stages of any such project.

Acknowledgment. This research was supported financially by the University of Hong Kong; the Research Grants Council of the Hong Kong Special Administrative Region, P. R. of China (Project No. HKU 7112/02P); the State Key Project of Basic Research (Project 973, No. G2000048007), the Shanghai Municipal Committee of Science and Technology; and the National Natural Science Foundation of China (Nos. 20025206, 203900502, and 20272069).

Supporting Information Available. Detailed experimental procedures, including characterization information, for the synthesis of catalysts **1a–c** and the aza-Baylis–Hillman reactions and product **4a–h** ¹H NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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