A Polymer-Supported Phosphoramide as a Lewis-Base Catalyst for the Catalytic Aldol Reaction

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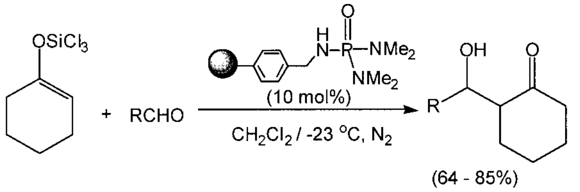
The aldol reactions between trichlorosilyl enol ethers and aldehydes were catalyzed by an environmentally benign polymer-supported phosphoramide organocatalyst. Eight examples are reported with moderate to good chemical yields and stereoselectivity. Significant rate enhancements were observed.

Introduction

Hexamethylphosphoric triamide (HMPA) has been extensively used as a reagent in organic chemistry because of its superior solvation and coordination properties.[1,2] In fact, HMPA is among the most useful organic reagents for a variety of reactions such as aldol reactions,[3] vinyl anionic additions,[4] allylations,[5] enolate alkylations,[6] oxidations,[7] 1,4-conjugate additions,[8] ylide-based C=C bond formations,[9] and various transition-metal-catalyzed reactions.[10] Unfortunately, HMPA is also toxic and has been identified as a potential carcinogenic reagent. This limits its broad utility in organic synthesis.

Results and Discussion

To address the toxicity problems of HMPA, while maintaining its excellent synthetic utility, we attempted to make a polymer-supported HMPA-type derivative (PS-phosphoramide)[11,12] and to examine its use as a catalyst. In this communication, we report the first application of an HMPA-type moiety-derived polymer as the catalyst in an aldol reaction of the trichlorosilyl enol ether of cyclohexanone with a variety of aldehydes (see Scheme 1).



Scheme 1

The use of phosphoramides as catalysts in the addition of trichlorosilyl enol ethers to aldehydes provides a useful method for the synthesis of β-hydroxy ketones.[2] We reasoned that if the present protocol was successful, it could be extended to polymer-bound phosphoramides as catalysts for asymmetric reactions.

Initial studies were carried out on the reaction of the trichlorosilyl enol ether of cyclohexanone and benzaldehyde at −78 °C in the presence of 10 mol % of PS-phosphoramide. The reaction was complete within three hours and afforded a chemical yield of 80 % and a diastereoselectivity of 1:1. The PS-phosphoramide catalyst clearly plays an important role in the reaction, as nearly no product was formed at this temperature in the absence of a catalyst.[13] When the reaction temperature was increased to −23 °C, the reaction-completion time was shortened to two hours, and the diastereoselectivity was improved to 9:1 (*syn*/*anti*). Furthermore, increasing the amount of catalyst resulted in meaningful improvement on reaction efficiencies. As a result of this initial investigation, the aldol reaction of other aromatic aldehydes were examined and the results are summarized in Table 1.

It is interesting to note that the current PS-phosphoramide-catalyzed aldol reaction results in aldol products with an opposite configuration to that of the products obtained by reactions with homogeneous, chiral phosphoramide catalysts.[2a] These products were, in fact, found to be the same as for the uncatalyzed aldol reaction at the higher temperature where *syn* isomers dominated over the *anti* isomers.[13] This observation suggests that the present aldol reaction could proceed through two possible pathways. The first possible pathway potentially involves the formation of

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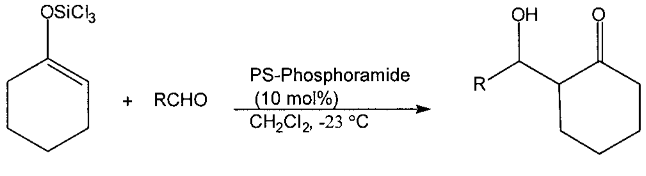
Table 1. Results of the PS-phosphoramide-catalyzed aldol reaction



Entry	R	Product[14]	Time, h	*syn*/*anti*[a]	Yield, %[b]
1	Ph	**1**	2	9:1	83
2	*p*-OMeC$_6$H$_4$	**2**	2	5:1.1	64
3	*p*-F−C$_6$H$_4$	**3**	2	4:1	82
4	*p*-ClC$_6$H$_4$	**4**	2	3:1	79
5	*p*-BrC$_6$H$_4$	**5**	2	4:1	85
6	*p*-NO$_2$C$_6$H$_4$	**6**	6	10:1	66
7	1-Naphthyl	**7**	6	0.9:1	65
8	3,4-(CH$_3$)$_2$C$_6$H$_4$	**8**	2	6.3:1	71

[a] Estimated by crude ^{1}H NMR determination. [b] Isolated yield of pure product after purification by flash chromatography; typical procedure was provided in ESI.

a pre-aldol complex which is responsible for an open-chain mechanism. The second possible mechanism could potentially involve a closed, boat-like transition state. We propose that the first hypothesis is more likely, due to the bulky environment on the polymer. This hypothesis can be indirectly supported by the fact that Denmark's bulky, chiral phosphoramide catalyst resulted in the prevalent *syn* selectivity.[13]

It should be pointed out that at −23 °C, the reaction can occur in the absence of PS-phosphoramide catalyst to give the aldol product in 67 % yield with a diastereoselectivity of 50:1 (*syn*/*anti*). Interestingly, the *syn*/*anti* stereoselectivity changes during the reaction process from 20:1 to 50:1 over 1 hour. After the first hour, this ratio remained unchanged as monitored by ^{1}H NMR analysis. The reaction was obviously accelerated by the presence of the PS-phosphoramide catalyst. Meanwhile, the yield also increased, albeit the *syn*/*anti* stereoselectivity was decreased by a factor of 5 (see Table 2).

Table 2. Effects of the PS-phosphoramide catalyst on the rate and selectivity of the aldol reaction

	Yield[a] (selectivity[b])		
Catalyst loading	0.5 h	1 h	2 h
0 %	17 (20:1)	35 (50:1)	67 (50:1)
10 %	30 (4:1)	55 (8:1)	83 (9:1)

[a] The reaction was incomplete except for the cases of a 2 h period; isolated yield after flash chromatography. [b] Estimated selectivities by crude ^{1}H NMR determination.

It is very interesting to find that the trichlorosilyl enol ether is resistant to reaction with the H−N moiety on the polymer bead under the current conditions. We also found that the aldol reaction proceeded smoothly in the presence of the unprotected aminomethyl resin SS. In order to study the effectiveness of PS-phosphoramide as a reusable organocatalyst, a portion of the catalyst was recovered and reused in several consecutive trials. It was found that the polymer could be reused, however, its effectiveness was somewhat diminished (about 15 % lower then the original reaction). The diminished catalytic activity is presumably due to slow destruction of the polymer when subjected to the vigorous stirring of a magnetic stir bar. One might expect better results if the reaction were agitated with a shaker as opposed to a magnetic stirrer.

In conclusion, the first polymer-supported, phosphoramide-catalyzed aldol reaction of a trichlorosilyl enol ether with aldehydes was successfully developed with significant rate enhancements at low temperature. Moderate to good yields and diastereoselectivities were obtained for eight examples. Compared to homogeneous phosphoramides, this new heterogeneous biphasic approach is potentially safer and shows promise for use as a recyclable catalyst. Efforts to develop chiral, polymer-supported phosphoramides for a catalytic asymmetric version of this reaction are currently in progress.

Experimental Section

1. Procedure for the Synthesis of PS-Phosphoramide: A resin (aminomethyl resin SS purchased from Advanced ChemTech, 244 mg, 0.171 mmol) and fresh CDCl$_3$ (3 mL) were added into a dry vial. The mixture was stirred slowly at room temperature, and then K$_2$CO$_3$ (310 mg), DMAP (15 mg), Et$_3$N (0.6 mL), and dodecane (0.375 mmol, 64 mg, as internal standard material for NMR measurement) were added. Finally, tetramethylphosphorodiamidic chloride (1.85 mmol, 316 mg, 10−11 equiv.) was added to the above mixture. The reaction proceeded for five days, when tetramethylphosphorodiamidic chloride remained constant, as revealed by direct NMR determination. The polymer resin was finally filtered, washed five times with CHCl$_3$ and dried under vacuum.

2. Typical Procedure for Aldol Reaction: Polymer-supported phosphoramide (150 mg) and silyl enol ether (232 mg, 1.0 mmol) were loaded onto an oven-dried vial. The vial was flushed with nitrogen and cooled to −23 °C. Freshly distilled dichloromethane (5 mL) was added and the resulting heterogeneous mixture was allowed to stir for 5 minutes before adding aldehyde (2 mmol) dropwise with a syringe over a period of one minute. The reaction was allowed to stir undisturbed for 2 hours, at which time it was quenched with saturated aqueous sodium hydrogencarbonate solution. The resulting biphasic system was extracted with dichloromethane (3 × 10 mL), washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/hexane, 1:5) afforded the pure products.

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[14] For analytic data for the products in Table 1, see Supporting Information (see also footnote on the first page of this article).

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