Dendritic HMPA as a Promoter for the Mukaiyama Aldol and Allylation Reaction

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Abstract: We synthesized a hexamethylphosphoramide (HMPA) analogue that was immobilized on hyperbranched polyglycerol (hPG) via a covalent approach. This polymeric analogue (hPG-HMPA) can potentially replace carcinogenic HMPA as a Lewis base additive in many reactions involving trichlorosilyl substrates. We investigated immobilized HMPA in the Mukaiyama aldol and allylation reactions. In most cases, yields and selectivities of supported and nonsupported HMPA were similar. Moreover, in the allylation reaction a positive dendritic effect could be observed, and the loading of HMPA could be lowered with hPG-HMPA to catalytic quantities (0.5 mol%). These results demonstrate that the use of HMPA can be avoided by hPG-HMPA without loss in terms of yield or selectivity.

Key words: aldol reaction, homogeneous catalysis, supported catalysts, organocatalysis, HMPA, polymeric support

Hexamethylphosphoramide (HMPA) is an extremely effective polar aprotic solvent (E_T = 40.9)[1] with a remarkable Lewis basicity. HMPA has been extensively used as a cosolvent and additive for organolithium-based chemistry as well as in reactions promoted by samarium diiodide.[1] Just recently it has been applied in organocatalysis,[2,3] where chiral phosphoramides have been used for several interesting stereoselective transformations, such as in aldol and allylation reactions. It has been demonstrated that stoichiometric quantities of phosphoramides are usually needed for high stereoinduction.[2,3]

Unfortunately, HMPA is known as a carcinogenic and mutagenic compound, which limits its broad use in organic synthesis. In many laboratories it has been forbidden and it has to be handled with caution, especially as it easily penetrates the skin.[1] In animal experiments it has been shown that HMPA is metabolized by demethylation, and the methyl groups of HMPA are responsible for the harmful effects. In conclusion an HMPA analogue which cannot be inhaled or which does not easily penetrate the skin may serve as a potential HMPA substitute.

Due to the superior solvent effects of HMPA, many attempts have been made to find a substitute for HMPA. Several potential substitutes have been investigated in the past such as *N*,*N*′-dimethylpropyleneurea (DMPU) and tripyrrolidinophosphoric acid triamide (TPPA) which were found to be good replacements for some reactions but the scope of these substitutes is mostly limited.[4] Little has been done to replace HMPA by an immobilized analogue on an insoluble support.[5]

We have recently reported several catalysts that were supported on a soluble polymeric support and generally showed high catalytic activity.[6,7] The superior solvent and coordination properties of HMPA in combination with its practical limitations make the development of a supported HMPA analogue most desirable.[5,8] It seemed likely that the polymeric support might show new and potentially useful catalytic properties. We and others have shown that dendronized catalysts often benefit from better reaction kinetic in solution and that catalyst loadings can often be decreased using dendritic architectures.[6,7,9] The multivalent presentation of HMPA also generates a high local concentration, which is required in many reactions, where it is currently being employed.[2,3] Immobilization onto a polymeric support also decreases the threat of HMPA inhalation, and potential contamination by skin penetration can at last be reduced by the polymeric support,[10] whereas the nonsupported HMPA easily penetrates the skin due to its high swelling property.[11]

In 1999 we introduced hyperbranched polyglycerol (hPG, **1**)[12] as a soluble, multifunctional, dendritic support with applications in the field of organic synthesis[13,14] and catalysis.[6,7,15] This polyether (Figure 1) can be easily synthesized on a kilogram scale by a one-step polymerization reaction. Due to the dendritic structure, hPG contains a large number of primary and secondary hydroxy groups (13.5 mmol g^{-1}), which can be easily converted into other functional groups by simple standard organic methods.[13] Its superior properties, such as high loading capacity, good solubility in a wide range of organic solvents (depending on the surface functionalization), chemical stability (inert ether bonds), and noncoordinating properties, make this aliphatic polyether a promising candidate for support of catalysts.

Herein, we present the synthesis of an HMPA analogue which is supported on a soluble dendritic polyglycerol [hPG-HMPA (**4**)] and we show typical results of **4** in the aldol and allylation reaction. Recycling experiments by ultrafiltration are included to show the extra benefits of hPG-HMPA.

For the immobilization of HMPA, hPG-methylamine (**2**) was prepared starting from hPG-OH (**1**) with M_n = 10.000 g mol^{-1}, where the OH groups of **1** were transformed into methylamino groups. This replacement was achieved by

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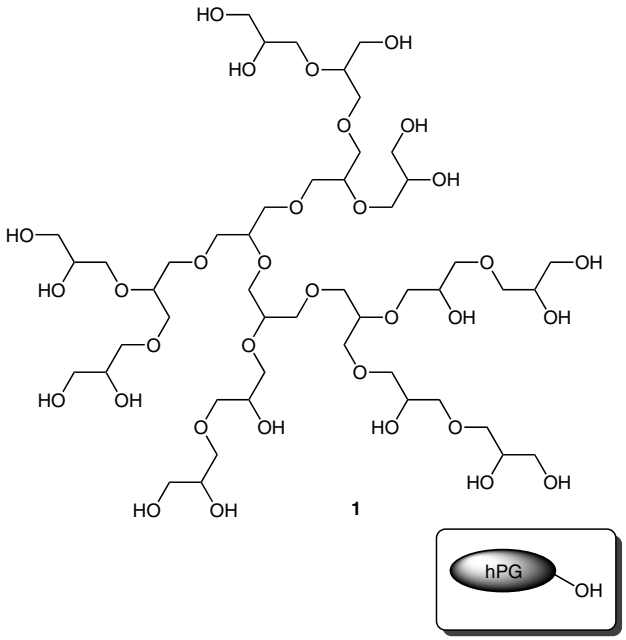
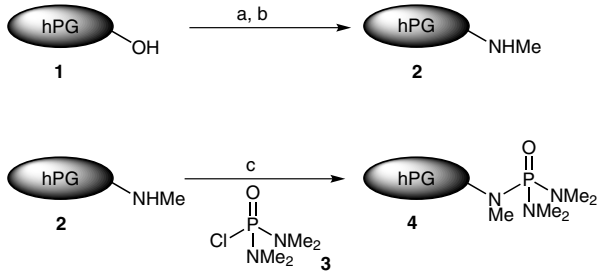


Figure 1 Hyperbranched polyglycerol (hPG, **1**): The structure shown represents a small idealized fragment of hPG (M_n = 10 000 g mol^{-1}). The structure is abbreviated hereafter as shown in the inset.

first converting the alcohol **1** into the mesylate[13] and subsequently displacing the mesylate with methylamine in an autoclave. For the modified hPG **2** we could prove with ^{1}H NMR spectroscopy and elemental analysis that all mesylate groups were replaced by amine. The commercial bis(dimethylamido)phosphoric chloride (**3**) was then directly coupled to the hPG **2** using *n*-BuLi as a base to yield hPG-supported HMPA (**4**, Scheme 1).



Scheme 1 Synthesis of hPG-supported HMPA (**4**): a) MsCl, pyridine, 0 °C, 16 h; b) $MeNH_2$, DMF, 60 °C, 24 h, autoclave; c) *n*-BuLi, –78 °C, 12 h.

The final polymeric compound **4** was purified by ultrafiltration, and the degree of HMPA functionalization was determined by ^{31}P NMR spectroscopy using triphenylphosphine oxide as an internal standard and was found to be up to 2 mmol g^{-1}. Two different loadings were synthesized, whereby 1 mmol HMPA per gram refers to catalyst **4** and 2 mmol HMPA loading refers to catalyst **5**.

As its broad usability is strongly dependent on its solubility in most common organic solvents, its solubility was tested (Table 1). The supported organocatalyst **4** was soluble in a variety of organic solvents (Table 1), as well as in water, but it was insoluble in alkyl ethers.

Table 1 Solubility of hPG-HMPA Catalyst **4**

Entry	Solvent	Solubility[a]
1	$CHCl_3$	+
2	DMF	+
3	MeOH	+
4	MeCN	+
5	H_2O	+
6	CH_2Cl_2	+
7	Et_2O	–
8	THF	–

[a] Conditions: 5 mg hPG-HMPA in 1 mL of solvent.

We compared the efficacy of the two systems, which were supported HMPA **4** and monomeric HMPA **6** (Figure 2) in the Mukaiyama aldol[5] (Scheme 2 and Table 2) and allylation reaction of trichlorosilyl compounds to benzaldehyde.

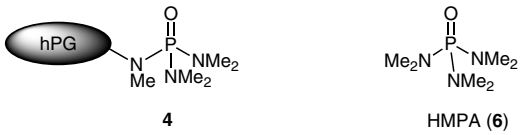
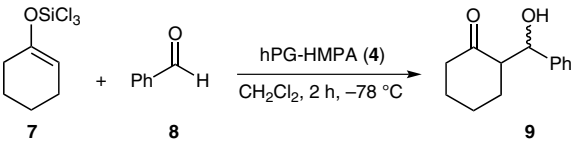


Figure 2 Structures of polymer-supported HMPA analogue **4** and commercial hexamethylphosphoramide **6**



Scheme 2 Mukaiyama aldol reaction of enol ether **7** with aldehyde **8** to β-hydroxy ketone **9**

The aldol reaction of trichlorosiloxycyclohexene (**7**) to benzaldehyde (**8**) showed that the yields for the supported HMPA **4** were even slightly better than for the HMPA-(**6**)-promoted reaction (Table 2, entries 2 and 3). As a control, the reaction gave very low yields (Table 2, entry 1) in the absence of a catalyst. As result, immobilization on HMPA led to a highly active catalyst, which was further investigated in terms of selectivity. Polymeric catalyst **4** as well as HMPA (**6**) led to a *syn*/*anti* ratio of the aldol product of 1:1 (Table 2). Whereas a ratio of >20:1 was observed without a catalyst. In light of the fact that both catalysts **4** and **6** gave the same stereoselective outcome, this finding is rather surprising, especially because we have observed in the past that selectivities usually change upon immobilization of the catalyst.[7]

Table 2 Initial Results for the Aldol Reaction Catalyzed by **4** and **6**[a]

Entry	Catalyst	Loading (mol%)	*syn*/*anti*[b]	Yield (%)[c]
1	none	0	>20:1	<5
2	hPG-HMPA (**4**)	10	1:1	63
3	HMPA (**6**)	10	1:1	60

[a] Reaction conditions: catalyst (0.1 equiv), silane (1.1 equiv), and fast addition of aldehyde **8**.
[b] Determined by ^{1}H NMR analysis.
[c] Isolated yield after column chromatography.

Secondly, when HMPA was used in solvent-like quantities a *syn*/*anti* ratio of 1:5 was observed in the product. To increase the amount of *anti* product with catalyst **4**, we first optimized the reaction parameters under catalytic conditions in accordance to literature examples (Table 3).[2] The aldehyde was slowly added and diluted, diisopropylethylamine was introduced as an additive, and the aldol reaction was performed at higher concentration. As result, HMPA (**6**) led to nearly quantitative yield, and a *syn*/*anti* ratio of 1:5 and the performance of catalyst **4** could be remarkably improved to a yield of 93% and a ratio of 1:4. These findings clearly show hPG-HMPA is a possible HMPA substitute, which is as effective as the monomer but without the negative toxic effects of **6** like inhalation.

Table 3 Aldol Reaction under Optimized Conditions with Slow Addition of Aldehyde **8**[a]

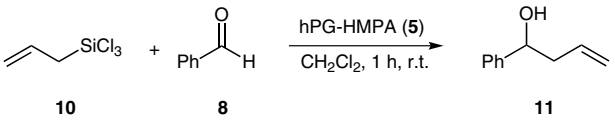
Entry	Catalyst	Loading (mol%)	*syn*/*anti*[b]	Yield (%)[b]
1	HMPA (**6**)	10	1:5.3	98
2	hPG-HMPA (**4**)	10	1:4.2	93

[a] Reaction conditions: see experimental details.[16]
[b] Determined by ^{1}H NMR analysis.

Inspired by the catalytic performance of dendritic HMPA **4**, we focused on the investigation of **4** in the allylation reaction. This reaction type gives access to homoallylic alcohols, which are applied in natural product synthesis. In contrast to the aldol reaction, a potential dendritic effect can be investigated without the problems of a background reaction.

As we could not observe a dendritic effect in the aldol reaction we hoped that double the local concentration of HMPA group on the polymer to 2 mmol would reinforce a potential dendritic effect. With catalyst **5** in hand we investigated the allylation reaction of benzaldehyde with allyl trichlorosilane (Scheme 3).[3]

As a result, dendritic catalyst **5** gave the allylated product in almost quantitative yield, whereas with catalyst **6** just 40% yield was observed. As a control, the reaction without a catalyst gave no conversion after one hour (by ^{1}H NMR analysis), while the catalyzed reactions were almost finished after less than ten minutes (observed by TLC).



10 **8** **11**

Scheme 3 Allylation of aldehyde **8** with silane **10** to allylic alcohol **11**

The next goal was to reduce the catalyst loading. To our surprise, we obtained nearly quantitative yield with just 0.5 mol% of dendritic catalyst **5**, while the reaction catalyzed by HMPA (**6**) was very slow and just showed less than 2% yield after one hour (Table 4). With this experiment we could nicely demonstrate how the high local concentration of HMPA on the polymer made reactions feasible that usually needed higher HMPA concentrations. With polymeric catalyst **5** we could present a HMPA substitute that showed a positive dendritic effect.

Table 4 Application of hPG-HMPA (**5**) in the Allylation of Aldehyde **8**[a]

Entry	Catalyst	Loading (mol%)	Yield (%)[b]
1	none	0	0
2	HMPA (**6**)	10	40
3	HMPA (**6**)	0.5	<2
4	hPG-HMPA (**5**)	10	97
5	hPG-HMPA (**5**)	0.5	99

[a] Reaction conditions: see experimental details.[16]
[b] Determined by ^{1}H NMR analysis.

A potential benefit of supported catalysts is their reusability and recyclability. To test the recyclability of hPG-HMPA (**5**), allylation of benzaldehyde with allyl trichlorosilane was performed in consecutive cycles and full conversion was achieved for three runs (Table 5). After each run the dendritic catalyst was successfully separated from the product by ultrafiltration using a Millipore membrane of regenerated cellulose with a molecular weight cut-off of 5000 g mol^{-1} and methanol as solvent. It was possible to use the same ultrafiltration membrane throughout the whole experiment.

The catalyst leaching was determined by ^{31}P NMR analysis. For the three runs, no leaching of the catalyst from the polymeric support could be observed (Table 5).

We have been able to show with the first successful synthesis of a homogeneous HMPA-supported polymeric catalyst that dendritic polyglycerol is a suitable support for HMPA. The high local concentration of HMPA groups at the surface of the polymer was used to mimic a high total concentration of HMPA in the reaction. The examples presented in this communication show that supported HMPA is a very good substitute for HMPA in

Table 5 Recycling of hPG-HMPA (**5**) in the Allylation of Benzaldehyde[a]

Run	Conversion (%)[b]	Catalyst leaching[c]
1st	quant.	not detectable
2nd	quant.	not detectable
3rd	quant.	not detectable

[a] Reaction conditions: see experimental details,[16] 2 h, r.t.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{31}P NMR spectroscopy.

trichlorosilyl-based transformations. In the aldol reaction we could show that highly active catalyst **4** dramatically enhanced the reaction rate and the selectivities.

In the allylation reaction, we could lower the catalyst ratio to 0.5 mol% (for **5**), yielding almost quantitative yield, while HMPA (**6**) did not show significant conversion (<2%) at this level of catalyst concentration. By lowering the catalyst ratio and comparing with the monomeric HMPA (**6**) we could show a positive dendritic effect in the allylation reaction.

Recycling of the catalyst **5** was successfully achieved three times by membrane filtration without loss of its activity. More synthetic work to develop chiral phosphoramides on hPG for a catalytic asymmetric version of this reaction is currently in progress.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) All experiments were carried out under an argon atmosphere using dried glassware. Chemicals were purchased from commercial suppliers and used as received unless otherwise noted. Benzaldehyde was freshly distilled prior to use. Dry CH_2Cl_2 was purchased from Sigma-Aldrich and dried via a Solvent Purification System MB-SPS 800 from MBraun. Column chromatography was performed on Merck Silica Gel 60 (230–400 mesh). Ultrafiltration was performed with a 300 mL solvent-resistant stirred cell with regenerated cellulose membranes (molecular weight cut-off 5000 g mol^{-1}), both from Millipore. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at room temperature using a Jeol ECX 400 and Bruker AV 700. 2D spectra were recorded on a Jeol Eclipse 500. Chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane and coupling constants (*J*) in hertz (Hz). The spectra were referenced against the internal solvent ($CDCl_3$, δ ^{1}H = 7.26 ppm, ^{13}C = 77.0 ppm). *O*-Mesylpolyglycerol was synthesized according to the literature procedure.[13]
Polyglycerylmethylamine (2): *O*-Mesylpolyglycerol (4.4 g, 28.6 mmol mesyl groups) was dissolved in p.a. DMF (20 mL) in a 48 mL ACE pressure tube using ultrasonication. In the next step, $MeNH_2$ gas (15 mL) was condensed into the tube and sealed afterwards. The mixture was stirred and heated up to 60 °C for 24 h. For workup the mixture was diluted with MeOH and filtered using a glass frit. The dissolved crude product was further purified by ultrafiltration with MeOH as solvent and Et_3N (2 mL) as an additive in the first run. After the third run the filtrate became colorless. The solvent was evaporated and a brown honey-like product was obtained. Yield: 95%, 8 mmol methylamine groups per gram polymer; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87–3.16 (br m, PG-backbone), 2.77–2.62 (m, functionalized PG groups), 2.42–2.17 (br m, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 78.6–68.7 (PG), 62.0–46.0 (functionalized PG groups); 43.0–34.0 (NHMe).
PG-Hexamethylphosphoramide (4):
Polyglycerylmethylamine (**2**) (1 g, 8 mmol) was dissolved in anhyd THF (20 mL) in a 50 mL Schlenk tube. The clear yellow solution was cooled to –78 °C and after 30 min, *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidic chloride (8 mmol, 1.2 mL) was added dropwise via syringe. The reaction was warmed to r.t. overnight and then quenched by addition of MeOH. The crude product was purified by ultrafiltration

(membrane: 5 kDa, solvent: MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85–3.28 (br m, PG-backbone), 2.65–2.16 (br m, NCH_3); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 26.0, 27.4 ppm. Loading: 1 mmol HMPA per gram polymer; determined by addition of triphenylphosphine oxide as internal standard, followed by integration in the ^{31}P spectra.

General procedure for the catalyzed aldol reaction with slow addition of aldehyde:[2] The catalyst PG-HMPA (50 mg, 0.05 mmol, 0.1 equiv) was dissolved in CH_2Cl_2 (0.5 mL), and the solution was cooled to –78 °C. 1-Cyclohexenyloxytrichlorosilane (100 µL, 0.55 mmol, 1.1 equiv) was added dropwise. A solution of benzaldehyde (50 µL, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) was then added dropwise to the first solution with the help of a syringe pump (speed: 0.3 mL/h). During the addition the temperature remained constant at –78 °C. The reaction mixture was stirred at –78 °C for an additional 60 min and then quickly poured into cold (2 °C) sat. aq $NaHCO_3$ (2 mL). The mixture was allowed to warm to r.t. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The *syn*/*anti* ratio was determined by ^{1}H NMR (400 MHz). The crude product was purified by column chromatography (SiO_2, $CHCl_3$) and was obtained as amixture of *syn* and *anti* products as a colorless solid. Analytical data for *syn*/*anti* ratio 1:1: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 10 H, 2 Ph), 5.38 (d, *J* = 2.5 Hz, 1 H, *syn*-PhC*H*OH), 4.78 (d, *J* = 8.8 Hz, 1 H, *anti*-PhC*H*OH), 3.97 (s, 1 H, *anti*-OH), 3.06 (s, 1 H, *syn*-OH), 2.64–1.25 (m, 18 H, CH_{ax} + CH_{eq}).

General procedure for the allylation reaction of benzaldehyde with allyl trichlorosilane: To a solution of PG-HMPA (2 mmol HMPA/g) (50 mg, 0.1 mmol, 10 mol%) in 0.2 mL of CH_2Cl_2 under N_2 at r.t. was added (*i*-Pr)$_2$NEt (0.5 mL), benzaldehyde (102 µL, 1.0 mmol, 1.0 equiv), and allyl trichlorosilane (290 µL, 2.0 mmol, 2.0 equiv). The resulting mixture was stirred for 1 h, before it was quenched with 2.0 mL NH_4Cl solution and 2.0 mL CH_2C1_2 were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10mL). The combined organic layers were washed with brine and dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was analyzed by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H, HC_{aryl}), 5.86–5.76 (m, 1 H, HC-3), 5.18–5.13 (m, 2 H, H_2C-4), 4.78 (dd, *J* = 7.3, 5.5, 1 H, HC-1), 2.57–2.45 (m, 1 H, HC-2), 2.05 (br s, 1 H, OH)..

