Hyperbranched Polyamines: Tunable Catalysts for the Henry Reaction

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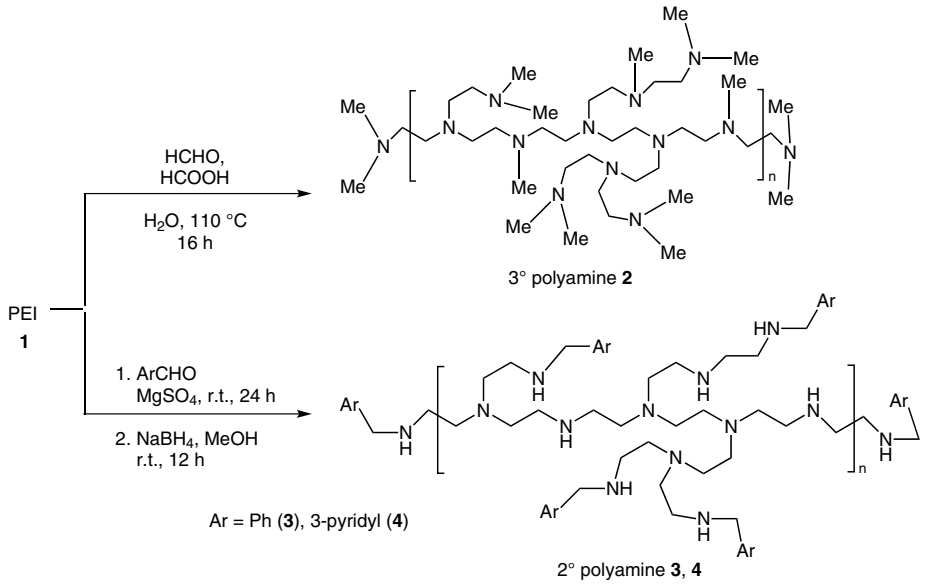
Abstract: Hyperbranched polyethylenimine derivatives were successfully employed as catalyst in the Henry reaction. The nitroalcohol products were obtained in excellent yields within short reaction times. A one-pot synthesis of β-nitrostyrenes was developed by using $ZnCl_2$ along with hyperbranched polyethylenimine derivatives.

Key words: Henry reaction, diastereoselectivity, polyamine, homogeneous catalysis, β-nitrostyrene

The Henry nitroaldol reaction is a key transformation that has been applied to the synthesis of novel bioactive molecules such as epiquinamide,[1] the α1-adrenergic receptor agonist (*R*)-phenylephrine,[2] core fragments of ritonavir and lopinavir; HIV protease inhibitors,[3] and (*R*)-isoproterenol – a potent-β-adrenoreceptor.[4] Henry reaction products are valuable intermediates for the preparation of isoxazole 2-oxides, nitrocyclohexanols, acetophenones, and methylbenzoate derivatives.[5] Several heterogeneous systems such as mesoporous silica,[6] alumina,[7] hydrotalcite,[8] nickel hydroxyapatite,[9] zeolite,[10] and I_2/K_2CO_3[11] have been reported to catalyze the Henry reaction. Recently, Kühbeck et al. reported a gelatin-mediated Henry reaction in DMSO solvent,[12] and Majhi et al. obtained nitroaldol products using TMEDA as catalyst.[13] However, recovery and reusability of such low-molecular-weight molecules are difficult. Hyperbranched polyamines are stable, nontoxic, easily recoverable molecules with high stability towards moisture and air. Unlike dendritic amines, hyperbranched polymamines are easily synthesized by step-growth polymerization.[14] Their applications extend to multicomponent reactions,[15] phase-transfer catalysis,[16] and as fluorescent chemosensors for quantitative detection of Zn^{2+} ions in water.[17] Breslow and coworkers used chiral polyamines as catalyst in the transamination of phenylpyruvic acid and in Michael addition reaction.[18a]

Commercially available unmodified linear hyperbranched polyethylenimine (PEI; number average molecular weight M_n = 1200) **1** was initially examined as a catalyst to carry out Henry reaction between 4-nitrobenzaldehyde and nitromethane. The formation of nitroalcohol product was observed within 15 minutes. Evaporation of nitromethane solvent from the reaction mixture led to the formation of a gummy mass from which recovery of the polyamine catalyst **1** was not successful by simple solvent workup. The product **5** was isolated from the reaction mixture in 90% yield by column chromatography (Scheme 2). Moreover, with linear PEI catalyst **1**, reaction times longer than 15 minutes led to side-product formation. The reaction car-



Scheme 1 Synthesis of secondary and tertiary PEI

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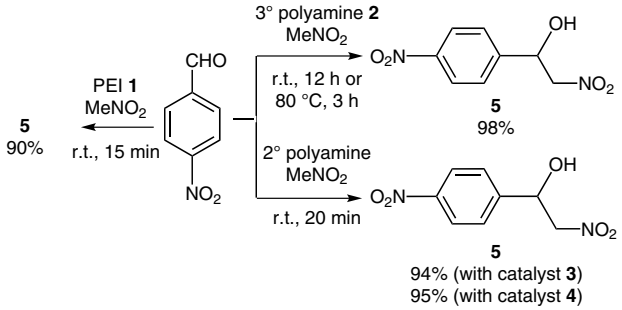
ried out with branched PEI (M_n = 600) also incurred similar problems. We proposed that this may be due to the presence of reactive primary amine groups and hence, the polyamine **1** was subjected to Eschweiler–Clarke reaction (Scheme 1), and the resulting alkylated polyamine catalyst **2** was found to form the nitroaldol product in 98% yield (Scheme 2). At room temperature, the reaction took 12 hours to complete; whereas at 80 °C, the reaction was completed in three hours. It is tentatively proposed that the removal of primary amine functionalities in PEI (**1**) could improve its basicity as well as aiding catalyst recovery.

Hence, hyperbranched PEI (**1**) was treated with both benzaldehyde and pyridine-3-carboxaldehyde separately. The secondary hyperbranched PEI **3** and **4** were then obtained by treating the initial imine products with $NaBH_4$ in MeOH (Scheme 1). Polyamines **3** and **4** derived from both benzaldehyde and pyridine-3-carboxaldehyde gave the nitroaldol product **5** within 20 minutes in 94% and 95% yield, respectively (Scheme 2).



Scheme 2 PEI catalyst screening for Henry reaction

The product was easily isolated from the catalyst by the evaporation of excess nitromethane solvent followed by addition of diethyl ether to the reaction mixture. The catalyst was insoluble in the diethyl ether and hence easily separated from the reaction mixture. The recyclability of the catalyst was investigated by performing the reaction of 3-nitrobenzaldehyde with nitromethane. The catalyst retained its activity up to four cycles, and the product was obtained above 90% yield (Figure 1). From the fifth cycle onwards, the efficiency of the catalyst decreased and hence the reaction took nearly 12 hours to complete, although the yield was not affected (Figure 1). Comparison of ^{1}H NMR spectrum of the recovered catalyst after the first and fifth runs showed an increase in the number of aromatic protons (see Supporting Information). This may be due to the possible side reaction of the aromatic aldehyde with polyamine catalyst **3**. Indeed Wilhelm and coworkers have reported the catalyst-free synthesis of imidazolidines by the reaction of *N*,*N*′-dibenzyl-ethane-1,2-diamine with aromatic aldehydes in water at room temperature for three hours.[18b] Under our conditions, the rate of Henry reaction should be much higher than any side reactions of the catalyst **3** and hence the catalyst retains its activity over four cycles.

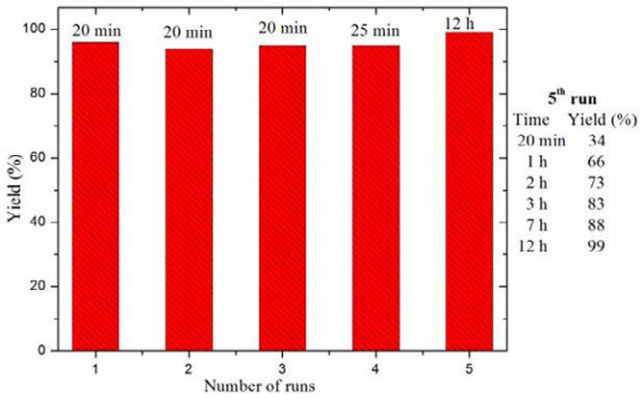
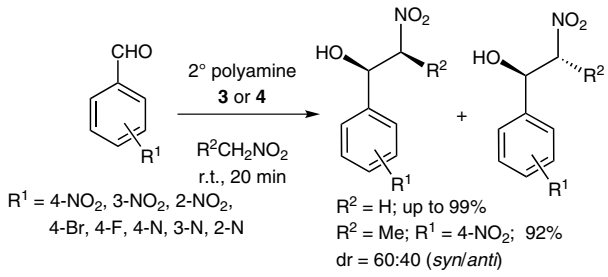


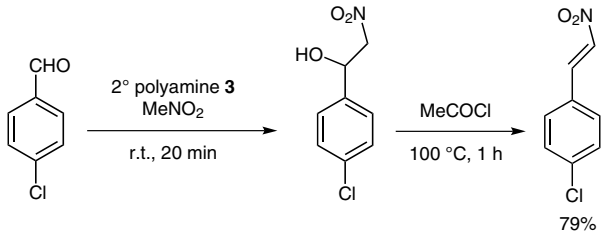
Figure 1 Recyclability of the catalyst **3**

After standardizing the reaction conditions, the procedure was screened with different aldehydes (Scheme 3, Table 1). The reaction carried out with nitroethane gave the nitroaldol product in a 60:40 diastereomeric ratio with the *syn* product as the major isomer.



Scheme 3 2° Polyamine catalyzed Henry reaction

Although 4-chlorobenzaldehyde gave the corresponding nitroaldol product, isolation of the product from the reaction mixture was not successful. Thus, it was attempted to acetylate the alcohol by heating the nitroalcohol with acetyl chloride (Scheme 4). Under these conditions, the corresponding nitrostyrene product was obtained by acetylation followed by in situ elimination.



Scheme 4 β-Nitrostyrene synthesis by in situ acetylation and elimination

We became interested in devising a one-pot methodology to synthesize β-nitrostyrenes. Longer reaction times and higher reaction temperature were examined but formation of elimination product was not observed. The role of additives was also examined. With anhydrous $MgSO_4$ only

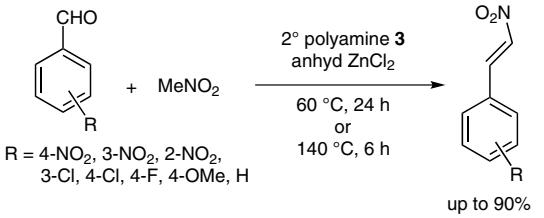
Table 1 Polyamine-Mediated Nitroalcohol Synthesis[a]

Entry	Aldehyde	Product	Catalyst **3** and **4**		Catalyst **2**	
			Time (min), temp (°C)	Yield (%)[b]	Time (h), temp (°C)	Yield (%)[b]
1[c]	4-$O_2NC_6H_4$	**5**	20, r.t.	94 (95)[d]	3, 80	98 (99)[e]
2	4-C_5H_4N	**6**	20, r.t.	99 (80)[d]	3, 80	86 (89)[e]
3	3-C_5H_4N	**7**	20, r.t.	90 (89)[d]	3, 80	82 (84)[e]
4	2-C_5H_4N	**8**	20, r.t.	96 (96)[d]	3, 80	89 (96)[e]
5	3-$O_2NC_6H_4$	**9**	20, r.t.	98 (90)[d]	3, 80	95 (98)[e]
6	2-$O_2NC_6H_4$	**10**	20, r.t.	99 (93)[d]	3, 80	95 (97)[e]
7	4-BrC_6H_4	**11**	180, r.t.	78 (68)[d]	3, 80	trace
8	4-FC_6H_4	**12**	180, r.t.	83 (88)[d]	3, 80	trace

[a] All the reactions were carried out by the addition of 1 mmol of aldehyde to a homogeneous solution of 50 mg of catalyst **3**/**4** (or with 100 mg of catalyst **2**) in 3 mL of nitromethane.
[b] Yields are for the isolated product.
[c] Reaction carried out with nitroethane gave the nitroalcohol product in 60:40 (*syn*/*anti*) dr.
[d] Reaction carried out with catalyst **4**.
[e] Reaction carried out at r.t. for 24 h.

trace amounts of nitrostyrene were formed; whereas with P_2O_5 the product was obtained in 60% yield at 140 °C. Subsequently, anhydrous $ZnCl_2$ was identified as a suitable reagent to carry out the one-pot synthesis of β-nitrostyrenes (Scheme 5). After screening reaction parameters with 4-nitrobenzaldehyde it was found that stirring at 60 °C for 24 hours gave the product in 85% yield (Table 2, entry 1). This optimized protocol was then examined with several other aldehydes.

In conclusion, the catalytic activity of PEI derivatives has been exploited in the synthesis of both nitroalcohol and nitrostyrene derivatives. The stable, nontoxic, recyclable PEI catalyst is a useful addition to the known array of catalysts for Henry reaction and studies on asymmetric induction using chiral PEI are under way in our laboratory.



Scheme 5 β-Nitrostyrene synthesis with 2° polyamine and $ZnCl_2$

Preparation of the catalysts **2**, **3**, **4** and spectroscopic data for the nitroalcohols and β-nitrostyrenes are included in the Supporting Information.

Table 2 Polyamine-Mediated Nitrostyrene Synthesis[a]

Entry	Aldehyde	Product	Time (h)	Temp (°C)	Yield (%)[b]	mp (°C)	Lit. mp (°C)
1	4-$O_2NC_6H_4$	**13**	24	60	85	201–202	202–204[19]
2	3-$O_2NC_6H_4$	**14**	24	60	79	118–120	123–124[20]
3	2-$O_2NC_6H_4$	**15**	24	60	84	104	104[21]
4	4-ClC_6H_4	**16**	24	60	63	110–112	113–114[22]
5	Ph	**17**	24	60	87	57–59	57–58[22]
6	4-$MeOC_6H_4$	**18**	24	60	62	85–87	84–86[19]
7	3-ClC_6H_4	**19**	24	60	87	46–48	42–43[23]
8	4-FC_6H_4	**20**	24	60	90	100–102	102–103[22]

[a] All the reactions were carried out by the addition of 1 mmol of aldehyde to a mixture of 50 mg of catalyst **3** and 0.5 mmol of $ZnCl_2$ in 3 mL of nitromethane.
[b] Yields are for the isolated product.

General Procedure for Henry Reaction with Polyamine Catalyst

To a stirred solution of tertiary polyethylenimine (100 mg) or secondary polyethylenimine (50 mg) in nitromethane (3 mL), 4-nitrobenzaldehyde (151 mg; 1 mmol) was added slowly at r.t. The reaction mixture was stirred at r.t. (12 h) or 80 °C (3 h) for tertiary PEI catalyst **2** or 20 min at r.t. for secondary PEI catalysts **3** or **4**. To remove excess nitromethane, the reaction mixture was concentrated under reduced pressure, and the product was isolated from the catalyst by triturating the residue with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluting with hexane and EtOAc (7:3).

2-Nitro-1-(4-nitrophenyl)ethanol (5)

Yield (catalyst **2**–**4**): 98% (99%), 94%, 95%.

β-Nitrostyrene Synthesis Using Catalyst 3

To a stirred solution of secondary polyethylenimine **3** (50 mg) in nitromethane (3 mL), $ZnCl_2$ (0.5 mmol), and 4-nitrobezaldehyde (151 mg; 1 mmol) were added successively at r.t., and the reaction mixture was stirred at 60 °C (24 h) or 140 °C (6 h). After completion of the reaction excess nitromethane was removed under reduced pressure. The residue was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, eluting with hexane and EtOAc (8:2); yield 85%; mp 201–202 °C (202–204 °C[19]).

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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