# Organocatalysis by poly(amidoamine) dendrimers; Knoevenagel and Mannich reactions catalyzed in water

**G. Rajesh Krishnan, Jinimol Thomas, and Krishnapillai Sreekumar***

*Department of Applied Chemistry, Cochin University of Science and Technology, Cochin-682022, Kerala, India*
*E-mail: ksk@cusat.ac.in*

**Abstract**
Knoevenagel condensation between carbonyl compounds and active methylene compounds as well as three component Mannich reaction between aldehydes, ketones and amines proceeded smoothly in water with good to excellent yield and high selectivity in the presence of zero and first generation poly(amidoamine) (PAMAM) dendrimers. The products and the catalyst were separated by simple biphasic extraction. The catalyst was found to be reusable.

**Keywords:** Dendrimer, organocatalyst, water, Knoevenagel condensation, Mannich reaction

## Introduction

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom.[1] Organocatalysis is an important area of research in recent times because it provides a means for catalyzing reactions in the absence of precious transition metals and a way to mimic nature in the enzyme catalysis which is a basic process of life. Many organocatalysts are simple molecules that show excellent selectivity and give good yield. Organocatalysts have several advantages. They are usually robust, inexpensive, readily available and non-toxic. Many organocatalysts are inert towards moisture and oxygen, Because of this, demanding reaction conditions, for example inert atmosphere, low temperature, absolute solvents etc. are in many instances, not required. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g. pharmaceuticals.[2,3] Moreover some organocatalysts have the extraordinary capacity to mediate efficiently a variety of mechanistically distinct reactions and such privileged catalyst classes showing general superiority for many reaction types is undoubtedly one of the most intriguing aspects and may have a considerable impact on the development of new catalytic systems.[1]

 ©ARKAT USA, Inc.

Dendrimers are molecules, which build the gap between simple organic molecules and complex synthetic and biopolymers like enzymes.[4-6] Metal complexes of core and surface functionalised dendrimers play an important role in synthetic chemistry because of the curiosity in their symmetrical structures and the catalytic properties they offer.[7,8] Dendrimer encapsulated nanoparticles comprise another emerging area which utilizes dendrimers in catalysis.[9] Organocatalysis by dendrimers is an emerging area of research due to the environmental friendliness and efficiency of these catalysts.[10] In this manuscript we describe applications of zero and first generation poly(amidoamine) (PAMAM) dendrimers as organocatalysts. PAMAM dendrimers offer a number of advantages as organocatalysts. They are commercially available or easy to be prepared compared to other dendrimers. They are highly basic (pKa=9.23 for surface amino groups) [9] and so it is expected that these dendrimers can act as base catalysts. PAMAM dendrimers are water soluble that make them a green catalyst with ease of separation from products. The number of surface groups in dendrimers increases exponentially with increase of generation. The presence of a large number of functional groups in a very small volume makes these groups more catalytically active due to the co-operative effect. These effects increase the product selectivity and yield.

As a classical reaction in organic chemistry Knoevenagel condensation plays an important role in the synthesis of biologically important molecules and molecules for novel materials.[11] A large number of catalysts are reported for Knoevenagel condensation ranging from simple organic molecules to aminated carbon nanotubes.[12] Polycarbosilane dendrimer with rhodium core is also used as catalyst for this condensation.[13] But most of these methods have used metal containing catalysts and in many cases the yield was low and the product isolation step included column chromatography. An interesting example of organocatalyzed Knoevenagel reaction using polymer supported dendrimers was reported by this group recently.[14]

Because of the simplicity and the availability of a large number of substrates that can undergo the reaction, Mannich reaction is a versatile reaction and used widely in the synthesis of biologically important molecules and natural products.[15] Now- a- days a special interest is aroused in three component Mannich reaction because of the environmental friendly and simple nature of the synthetic strategy. Various catalysts are used for this type of reaction ranging from strong inorganic acids or bases to transition metal complexes.[16] But reports on the use of dendrimer based catalysts for Mannich reaction was less or absent.

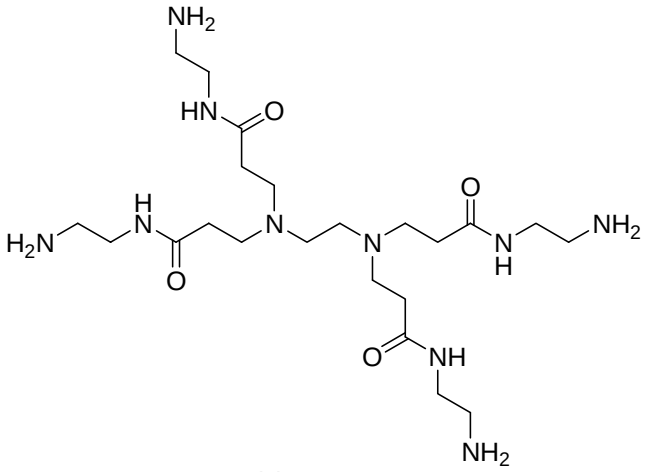
In this manuscript we report for the first time the applications of PAMAM dendrimers as organocatalysts for Knoevenagel condensation as well as for one-pot three component Mannich reaction in water. The reactions proceeded efficiently under mild conditions and the products were isolated with ease compared to many previously reported catalysts. Two important aspects of the present catalytic process are waste reduction and reduction in the use of organic solvents. The catalytic process described in this manuscript contributes equally to two important areas of 'green chemistry' i.e. organic reactions in aqueous media and organocatalysis.

 ©ARKAT USA, Inc.

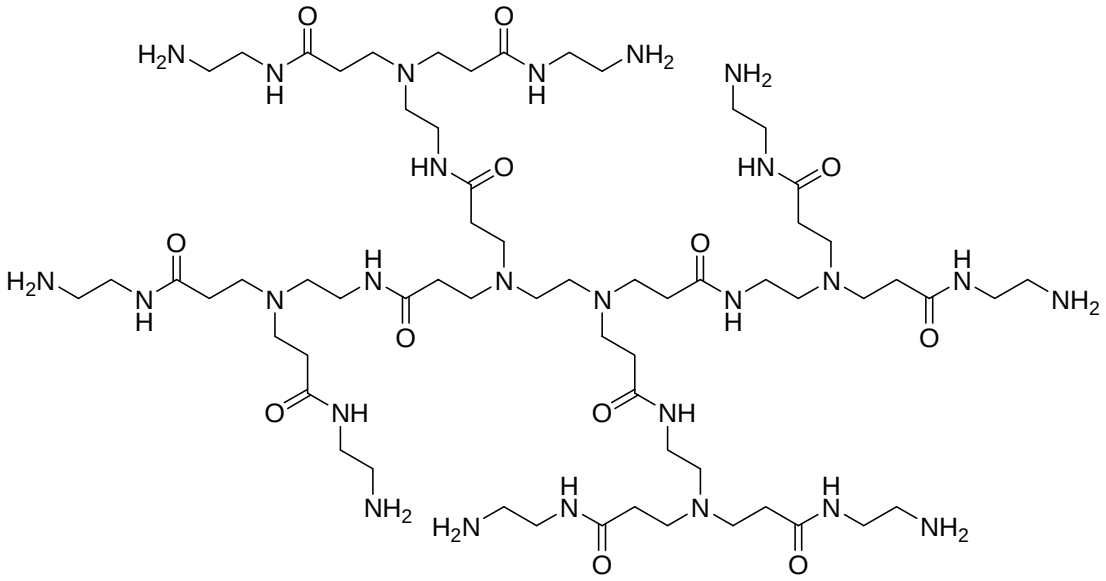
## Results and Discussion

### Catalyst preparation

Zero and first generation poly(amidoamine) dendrimers were prepared according to the standard procedure.[17] The structures of the catalysts are shown in Figure 1.



(a)



(b)

**Figure 1.** Structure of the catalyst (a) zero generation and (b) first generation dendrimers.

Separate solutions of each generation dendrimers were prepared by dissolving a suitable amount of the dendrimer in water. The concentration of the dendrimer was selected in such a

way that each mL of the catalyst solution contained 0.05 mmol of $–NH_2$ groups. A suitable volume of this stock solution was used for each set of reaction so that the final reaction mixture contained the necessary amount of dendrimer for catalysis.

At first the effect of generation of dendrimer on catalytic efficiency was studied. The catalytic efficiency increased from zero to first generation. The results are given in Table 1.

**Table1.** Effect of generation of dendrimer on their catalytic activity

| Entry | Generation of dendrimer | % yield [a] | % yield [b] |
|---|---|---|---|
| 1 | 0 | 92 | 79 |
| 2 | 1 | 100 | 90 |

[a] Isolated yield of Knoevenagel condensation product of benzaldehyde and malononitrile
[b] Isolated yield of Mannich product of benzaldehyde, aniline and cyclohexanone

There is an exponential increase in the number of primary amino groups on going from zero to first generation dendrimer. These primary amino groups are assumed to be the real catalytic sites. This increase in the number of catalytic sites with generation results in the better activity of the first generation dendrimer. Moreover it is expected that a co-operative effect come into play in the case of higher generation dendrimers as the surface groups are packed in a denser manner in higher generation dendrimers. First generation dendrimer was found to be a sufficiently active catalyst in the reactions studied in this work and so use of higher generation dendrimers were not considered.

**Knoevenagel condensation**

Knoevenagel condensation between different carbonyl compounds and various active hydrogen compounds was studied. The scheme of the reaction is given in Figure 2. Initially the condensation between benzaldehyde and malononitrile was studied as a model reaction in the presence of various amounts of first generation dendrimer. The reaction proceeded swiftly in water in the presence of 1 mol % of the catalyst to give 100% yield of the product.

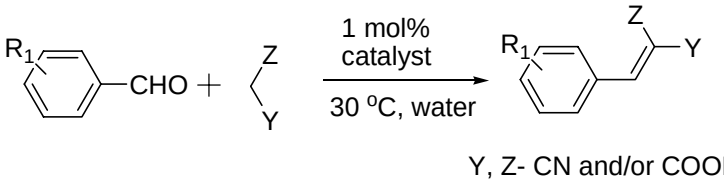



**Figure 2.** General scheme of Knoevenagel condensation catalyzed by PAMAM dendrimer in water.

In a similar manner condensation between other substrates also proceeded in a short period of time with excellent yield and selectivity (Table 2). The products were isolated by simple filtration or solvent extraction. Generally, the products obtained were of high purity and no more purification was required. In contrast to conventional catalysts, no side product by Michael addition or bis adduct formation was observed and the reaction gave 100% selectivity with excellent yield. The electronic environment of substrates had no considerable effect on the reaction. Both electron rich and electron deficient aldehydes gave excellent yield of the condensation product in a short period of time. Heterocyclic aldehydes also gave good results. On the other hand the reactivity of the active hydrogen compound shows slight influence on the reaction. Less reactive compounds like diethyl malonate took slightly longer reaction time. The shorter reaction time required for the completion of reaction may be due to the co-operative effect of a number of amino groups on the surface of the dendrimers. When ethyl cyanoacetate was used as the active hydrogen compound for condensation only *E* isomer was formed. The formation of the *E* isomer is evident from the NMR data.

**Table 2.** Knoevenagel condensation catalyzed by PAMAM dendriemr in water

| Entry | $R_1$ | Y | Z | Time (minutes) | % Yield [a, b] |
|---|---|---|---|---|---|
| 1 | H | CN | CN | 2 | 100 |
| 2 | 4-$OCH_3$ | CN | CN | 3 | 100 |
| 3 | 2-OH | CN | CN | 2 | 97 |
| 4 | 4-Cl | CN | CN | 3 | 100 |
| 5 | 4-$NO_2$ | CN | CN | 4 | 97 |
| 6 | furfural | CN | CN | 3 | 98 |
| 7 | H | COOEt | COOEt | 10 | 90 |
| 8 | 4-$OCH_3$ | COOEt | COOEt | 15 | 95 |
| 9 | H | CN | COOEt | 5 | 95 |
| 10 | 4-$OCH_3$ | CN | COOEt | 5 | 95 |
| 11 | 2-OH | CN | COOEt | 10 | 95 |
| 12 | furfural | CN | COOEt | 5 | 97 |

[a] Reaction conditions: 5 mmol carbonyl compound, 5 mmol active hydrogen compound, 1 mL water, 0.0062 mmol G1 PAMAM.
[b] Isolated yield.

A possible mechanism of the reaction is shown in Figure 3. This mechanism involves the formation of an anion by deprotonation of the active hydrogen compound by the dendrimer molecules. Its addition to the carbonyl compound creates a metastable adduct that rapidly transform into the final condensation product with the release of a hydroxyl anion.[18] But to prove this and to obtain a clear picture of the mechanism of the reaction, more mechanistic and computational studies are required.

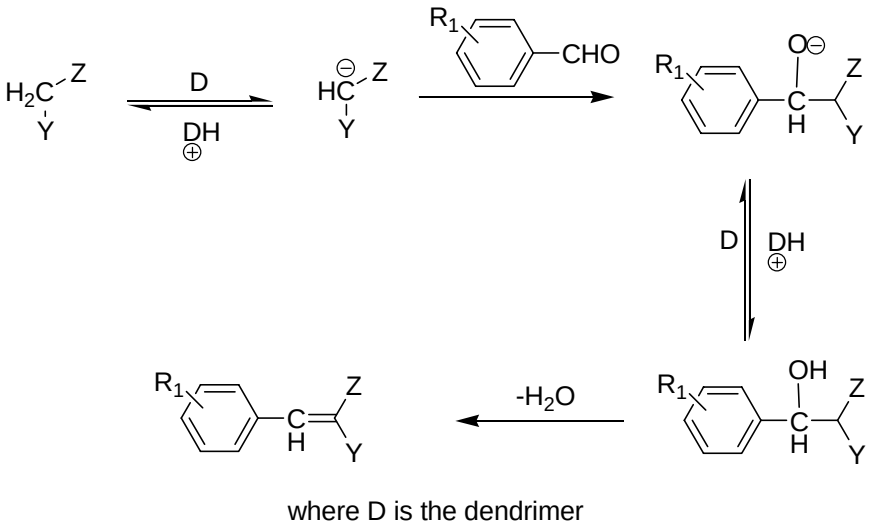



**Figure 3.** Possible mechanism of PAMAM dendrimer catalyzed Knoevenagel condensation.

**Three component Mannich reaction**

Three component one-pot Mannich reactions between various aromatic aldehydes, anilines and ketones proceeded smoothly in the presence of PAMAM dendrimer as catalyst in water. The general scheme of the reaction is given in Figure 4. Initially, the reaction between benzaldehyde, aniline and cyclohexanone was studied as a model reaction in water in the presence of various amounts of first generation dendrimer. It was found that only 2 mol% of the catalyst was required to drive the reaction smoothly to completion.

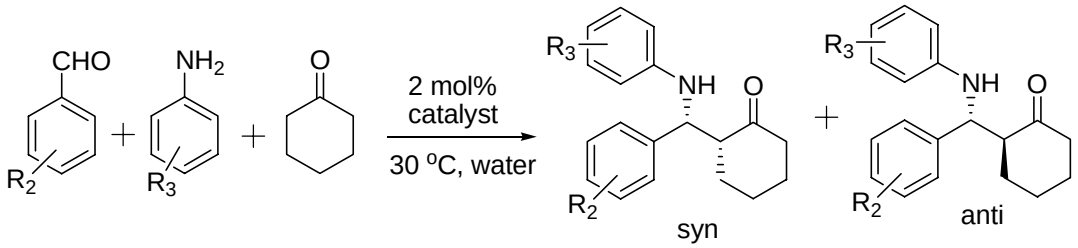



**Figure 4.** One pot three-component Mannich reaction catalyzed by PAMAM dendrimer in water.

The scope of the dendrimer catalyzed Mannich reaction was extended to other aldehydes, ketones and anilines. The results are summarized in Table 3. The reaction proceeded smoothly within four to twelve hours to give products in good yield in the presence of 2 mol % of the catalyst. Aldehydes carrying electron withdrawing groups on the para position of the aromatic rings gave good yields with good *syn* selectivity. In the case of anilines, those carrying electron donating groups on the aromatic ring gave better results. Anilines carrying electron withdrawing groups like $NO_2$ did not undergo the reaction. Heterocyclic aldehyde like furfural also gave good yield and selectivity. When acetophenone was used as donor instead of cyclohexanone the yield

of the Mannich product decreased and the reaction required more time for completion. This may be due to the poor reactivity of acetophenone compared to cyclohexanone.

**Table 3**. One-pot three component Mannich reaction catalyzed by PAMAM dendrimer

| Entry | $R_2$ | $R_3$ | Ketone | Time (h) [a] | % Yield [b, c,d] |
|---|---|---|---|---|---|
| 1 | H | H | $C_6H_{10}O$ | 8 | 88 (70:30) |
| 2 | 4-$OCH_3$ | H | $C_6H_{10}O$ | 10 | 75 (68:32) |
| 3 | 4-$NO_2$ | H | $C_6H_{10}O$ | 8 | 87 (73:32) |
| 4 | 4-Cl | H | $C_6H_{10}O$ | 8 | 87 (73:32) |
| 5 | H | 4-$OCH_3$ | $C_6H_{10}O$ | 4 | 92 (80:20) |
| 6 | H | 4-$NO_2$ | $C_6H_{10}O$ | 12 | No reaction |
| 7 | 4-Cl | 4-$CH_3$ | $C_6H_{10}O$ | 10 | 82 (90:10) |
| 8 | furfural | H | $C_6H_{10}O$ | 8 | 82 (67:33) |
| 9 | H | H | $C_6H_5COCH_3$ | 12 | 80 |
| 10 | 4-$OCH_3$ | H | $C_6H_5COCH_3$ | 12 | 83 |
| 11 | 4-Cl | H | $C_6H_5COCH_3$ | 12 | 78 |
| 12 | H | 4-Cl | $C_6H_5COCH_3$ | 12 | 79 |

[a] $C_6H_{10}O$ and $C_6H_5COCH_3$ are cyclohexanone and acetophenone respectively.
[b] Reaction conditions: 5 mmol aldehyde, 5 mmol ketone, 5.2 mmol aniline, 2 mL water, 0.0124 mmol G1 PAMAM dendrimer.
[c] Isolated yield.
[d] in parenthesis *syn/anti* ratio detected from $^1$HNMR.

The possibility of formation of the aldol product under the same reaction conditions was checked. For this, the reaction between cyclohexanone and benzaldehyde was carried out in water in the presence of 2 mol % first generation PAMAM dendrimer. It was observed that there was no aldol condensation product even after a long period of time.

In general the reaction proceeded in a *syn* selective fashion, as observed from NMR spectral data. A possible mechanism of the reaction can be predicted to explain this diastereoselective nature (Figure 5). An enamine is expected to be formed by the reaction of the donor ketone with the catalyst. This enamine reacts with the acceptor-the insitu formed imine from the aldehyde and aniline- to give the product and release the catalyst to the next cycle of reaction.

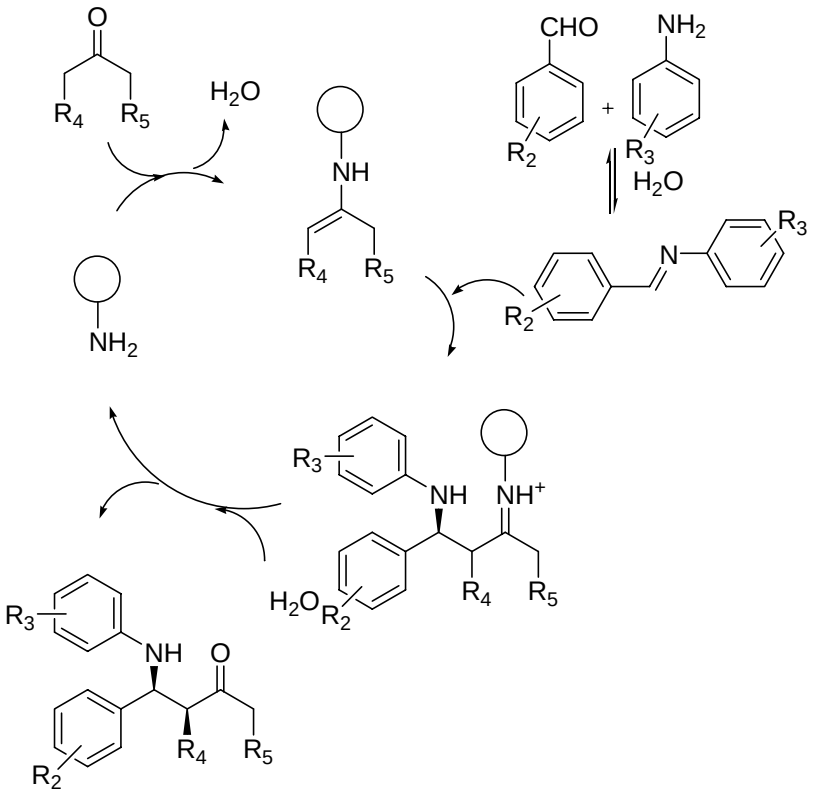



**Figure 5.** Possible mechanism of three component Mannich reaction catalyzed by PAMAM dendrimer in water.

But as stated earlier it required lot of mechanistic and computational studies before assigning a mechanism to this reaction. The primary amino groups of the catalysts did not take part in the reaction and it may be due to the fact that the catalyst remains in a separate phase. Example of molecules containing primary amino groups which effectively catalyzed three component Mannich reactions without taking part in the reaction was previously reported.[19]

**Recycling of the catalyst**

The possibility of recycling of the catalyst was investigated. The aqueous layers obtained after the reactions were reused for the same reaction in the next cycles. The reaction proceeded smoothly for four consecutive cycles in the case of Knoevenagel reaction without any loss of activity or selectivity. The catalyst remained active for four cycles in the case of Mannich reaction also. But the yield gradually decreased in the successive cycles and the yield dropped considerably in the fifth cycle. The results are summarized in Table 4. FTIR spectra of the catalyst showed that the peaks corresponding to the amino groups in the dendrimer remained unaltered for the recycled catalyst. A dark cloudiness was gradually formed in the aqueous layer after each cycle and this may be due to some side reactions like atmospheric oxidation the dendrimers underwent and this may be the reason in the drop in activity. This effect was

predominant in the case of Mannich reactions. The low loading of the catalyst can compensate this loss of activity.

**Table 4.** Recycling of the catalyst

| Entry | No. of Recycling steps | % Yield | |
|---|---|---|---|
| | | Knoevenagel reaction[b] | Mannich condensation[a] |
| 1 | 1 | 100 | 88 |
| 2 | 2 | 100 | 88 |
| 3 | 3 | 100 | 87 |
| 4 | 4 | 100 | 85 |
| 5 | 5 | 98 | 80 |
| 6 | 6 | 96 | 76 |

[a] Isolated yield of Knoevenagel condensation product of benzaldehyde and malononitrile.
[b] Isolated yield of Mannich reaction product of benzaldehyde, aniline and cyclohexanone.

## Conclusions

In short, poly(amidoamine) dendrimers were found to be highly efficient organocatalysts for Knoevenagel condensation and one-pot three component Mannich reaction in water. The reactions proceeded with good to excellent yield of the products in the presence of very small amount of catalyst loading. The catalyst was found to be reusable. This offers a new strategy for the applications of dendrimers with tunable solubility and suitable functional groups in environmentally friendly catalysis. The catalytic process helped in the elimination of toxic organic solvents as well as transition metal based catalysts in two synthetically important reactions.

## Experimental Section

**General Procedure.** Benzaldehyde, anisaldehyde, salicyladehyde and methyl acrylate were purified according to the standard procedures. All other chemicals were used as received. All the solvents were purified according to standard procedures prior to use. FTIR measurements were done on a JASCO-4000 FTIR spectrometer as KBr pellets. $^1$H-NMR spectra were recorded on Bruker 300 MHz or 400 MHz instrument with TMS as internal standard using $CDCl_3$ or $CD_3OD$ as solvents (from NMR research centre IISC, Bangalore). FAB MS was taken on a Jeol JMS 600 model mass spectrometer. MALDI TOF MS was carried out with a Schimadzu Kratos compact analytical MALDI TOF MS with use of an Nd-YAG laser with an operating wavelength of 354

nm (results obtained from RGCB, Thiruvananthapuram, Kerala, India). The matrix used was α-cyano-4-hydroxycinnamic acid. Angiotensin II and insulin were used as internal standards. GC/MS was taken on a Varian 1200 L single quadrapole GC/MS with capillary column (from STIC, CUSAT).

**Preparation of the dendrimer**

Zero (G0 PAMAM) and first generation (G1 PAMAM) dendrimers were prepared according to a standard procedure.[17]

**Preparation of G 0 PAMAM**

A solution of methyl acrylate (17.5 g, 0.203 mol) in methanol (20 mL) was prepared in a two necked round bottom flask fitted with a condenser and a dropping funnel. The flask was kept in an ice bath. A solution of ethylene diamine (2.5 g, 0.041 mol) in methanol (10 mL) was added drop wise with stirring over a period of 1 h. The resulting solution was stirred for further 30 min at the same temperature and allowed to warm to room temperature and stirred for further 48 h. The volatiles were removed under reduced pressure at 40 $^{o}$C using a rotary evaporator to give the desired product and it was dissolved in methanol (10 mL) and evacuated as before. The product was dried under vacuum overnight. Yield= 13.52 g (97%)

Ethylene diamine (37.56 g, 0.625 mol) was dissolved in methanol (50 mL) taken in a two necked round bottom flask fitted with a condenser and a dropping funnel kept in an ice bath. A solution of the above ester (5 g, 0.0125 mol) in methanol (20 mL) was added drop wise to it with constant stirring over a period of 1 h. The resulting solution was allowed to warm to room temperature and stirred for further 96 h at room temperature. The volatiles were removed under reduced pressure using a rotary evaporator maintaing the temperature not higher than 40 $^{o}$C and the excess 1,2 diaminoethane was removed using an azeotropic mixture of toluene and methanol (9:1 v/v) .The remaining toluene was removed by azeotropic distillation using methanol. Finally the remaining methanol was removed under vacuum to provide the amino-terminated product as yellow oil. It was dried under vacuum overnight. Yield=6.32 g, 98%.

FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 1640, 3200, 3400; $^{1}$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ=2.27 (8 H), 2.46 (8 H), 2.56 (4 H), 2.57 (8 H), 2.73 (8 H), 3.33 (8 H), 8.07 (4 H), Mass spectrum (FAB): m/z 517 (M+H), 540 (M+Na)

**Preparation of G 1 PAMAM**

A solution of methyl acrylate (8.26 g, 0.096 mol) in methanol (20 mL) was prepared in a two necked round bottom flask fitted with a condenser and a dropping funnel. The flask was kept in an ice bath. A solution of G0 dendrimer (5 g, 0.0096 mol) in methanol (10 mL) was added drop wise with stirring over a period of 1 h. The resulting solution was stirred for further 30 min at the same temperature and allowed to warm to room temperature and stirred for further 48 h. The volatiles were removed under reduced pressure at 40 $^{o}$C using a rotary evaporator to give the

desired product and it was dissolved in methanol (10 mL) and evacuated as before. The product was dried under vacuum overnight. Yield= 10.13 g (98%)

Ethylene diamine(60 g, 0.625 mol) was dissolved in methanol (100 mL) taken in a two necked round bottom flask fitted with a condenser and a dropping funnel kept in an ice bath. A solution of the above ester (5 g, 0.004 mol) in methanol (20 mL) was added drop wise to it with constant stirring over a period of 1 h. The resulting solution was allowed to warm to room temperature and stirred for further 96 h at room temperature. The volatiles were removed under reduced pressure using a rotary evaporator maintaing the temperature not higher than 40 $^{o}$C and the excess 1,2 diaminoethane was removed using an azeotropic mixture of toluene and methanol (9:1 v/v) .The remaining toluene was removed by azeotropic distillation using methanol. Finally, the remaining methanol was removed under vacuum to provide the amino-terminated product as light brown oil. It was dried under vacuum overnight. Yield=5.60 g, 98% . FTIR (KBr, $\nu_{max}$, cm$^{-1}$) 1640, 3420, $^{1}$HNMR (300 MHz; DMSO; $Me_4Si$) δ=2.26 (16 H), 2.47 (16 H), 2.62-2.52 (52 H), 2.67 (8 H), 3.34-3.13 (24 H), 8.06 (12 H), MALDI MS: m/z 1430 (M+H).

**Preparation of the catalyst solution**

Separate solutions of zero and first generation dendrimers were prepared by dissolving a suitable amount of the dendrimer in water. The concentration of the dendrimer was selected in such a way that each mL of the catalyst solution contains 0.05 mmol of $–NH_2$ groups. For this 64.5 mg of G0 PAMAM and 89.3 mg of G1 PAMAM were dissolved separately in 100 mL each of water. A suitable amount of these stock solutions were used for further studies.

**General procedure for Knoevenagel condensation**

A 10 mL round bottom flask was charged with the water solution of the catalyst (1 mL, 1 mol% of catalyst), 5 mmol carbonyl compound and 5 mmol active methylene compound. The reaction mixture was stirred at room temperature for the required time. The progress of the reaction was followed by TLC on a silica gel plate using hexane-ethyl acetate (10:1 v/v) mixture as eluent. The product was isolated by simple filtration (in the case of solids) or extraction with hexane. The solid products were washed with water and dried. In the case of liquid products, evaporation of the solvent gave the product in pure form. Generally, the products obtained were of high purity and required no further purification. All the products were known compounds and characterized using $^{1}$HNMR and FTIR spectroscopy.[12,14] Characterization data of some representative products are given below.

**2-[(4-Methoxyphenyl)methylene]malononitrile** (**Table 2 Entry 2).** FTIR (KBr, $\nu_{max}$ ,cm$^{-1}$) 2218, 1598; $^{1}$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ=3.9 (s, $OCH_3$, 3H), 7.0 (d, *J*=8.5 Hz, phenyl, 2H), 7.6 (s, CH, 1H), 7.9 (d, *J*=8.5 Hz, phenyl, 2H).

2-[(2-Hydroxyphenyl)methylene]malononitrile (**Table 2 Entry 3).** FTIR (KBr, $\nu_{max}$ ,cm$^{-1}$) 2202, 1598, 3390; $^{1}$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ= 5.0 (s, OH, 1H), 6.8(q, *J*=2.8 Hz, phenyl, 2H), 7.9 (q, *J*=3.1 Hz, phenyl, 2H,), 8.2 (s, CH, 1H).

 ©ARKAT USA, Inc.

**2-(Furylmethylene)malononitrile** (**Table 2 Entry 6**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 2228, 1603; $^1$HNMR (300 MHz; MeOD; $Me_4Si$) δ= 6.7(q, *J*=1.6 Hz, furyl, 1H), 7.3 (d, *J*=3.6 Hz, furyl, 1H), 7.5(s, CH, 1H), 7.8 (d, *J*=1.4 Hz, furyl, 1H).

**Diethyl 2-(4-methoxybenzylidene)malonate** (**Table 2 Entry 8**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 1728, 1283, 1112; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ= 1.3 (t, *J*=7.0 Hz, $CH_3$, 3H), 1.4 (t, *J*=7.0 Hz, $CH_3$, 3H), 3.8 (s, $OCH_3$, 3H), 4.3 (q, *J*=7.0 Hz, $CH_2$, 2H), 4.4 (q, *J*=7.0 Hz, $CH_2$, 2H), 6.8 (d, *J*=8.0 Hz, phenyl, 2H), 7.3 (d, *J*=8.0 Hz, phenyl, 2H), 7.6 (s, CH, 1H).

**Ethyl(E)-2-cyano-3-(4-methoxyphenyl)-2-propenoate** (**Table 2 Entry 10**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 2947, 2844, 2216, 1717, 1588, 1256, 1121; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ=1.3–1.4 (t, *J*=7 Hz, $CH_3$, 3H), 3.9 (s, $OCH_3$, 3H), 4.3–4.4 (q, *J*=7 Hz, $CH_2$, 2H), 7.0 (d, *J*=7 Hz, phenyl, 2H,), 8.0 (d, *J*=7.0 Hz, phenyl, 2H), 8.1 (s, CH, 1H).

**Ethyl(E)-2-cyano-3-furyl-2-propenoate** (**Table 2 Entry 12**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 2221, 1717, 1604, 1209, 1017; $^1$HNMR (300 MHz; MeOD; $Me_4Si$) δ= 1.4 (t, *J*=2.0 Hz, $CH_3$, 3H), 4.3 (q, *J*=1.9 Hz, $CH_2$, 2H), 6.6 (t, *J*=1.8 Hz, furyl, 1H), 7.4 (d, *J*=3.2 Hz, furyl, 1H), 7.7 (s, furyl, 1H), 8.0 (s, CH, 1H).

## General procedure for one pot three component Mannich reaction

A 10 mL round bottom flask was charged with aldehyde (5 mmol), ketone (5 mmol), aniline (5.2 mmol) and 2 mL catalyst solution (2 mol% of catalyst). The final reaction mixture was stirred at room temperature for the required time. The progress of the reaction was followed by TLC on a silica gel plate using hexane-ethyl acetate (20:1 v/v) mixture as eluent. After the completion of the reaction 5 mL hexane-ethyl acetate mixture (25:1 v/v) was added to the reaction mixture and the organic layer was separated. After the removal of the solvent the pure product was isolated by column chromatography on a small column of silica using hexane ethyl acetate mixture (25:1 v/v) as eluent. All the β- keto amines obtained were known compounds and were characterized by FTIR and $^1$HNMR spectroscopies.[16] Characterization data of some typical products are given below. The syn/anti ratio was determined from the relative areas under the absorption peaks for CH proton in the $^1$HNMR spectra of the crude product.

**2-[1'-(*N*-*p*-methoxyphenylamino)-1'-phenyl]methylcyclohexanone** (**Table 3 Entry 2**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 3361, 2930, 1706, 1600, 1510; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ=1.60-1.85 (m, cyclohexyl, 6H), 2.28-2.40 (m, cyclohexyl, 2H), 2.71-2.72 (m, cyclohexyl, 1H), 3.65 (s, $OCH_3$, 3H), 4.51 (br, s, NH, 1H), 4.55 (d, *J*=7.3 Hz, CH, 0.32H), 4.75(d, *J*=4.2 Hz, CH, 0.68 H), 6.45-6.50 (m, phenyl, 2H), 6.62-6.67 (m, phenyl, 2H), 7.19-7.34 (m, phenyl, 5H).

**2-[1'-(*N*-phenylamino)-1'-(4-chlorophenyl)]methylcyclohexanone** (**Table 3 Entry 4**): FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 3377, 2924, 1670, 1507, 1489, 1282, 1003; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ= 1.68-1.55 (m, cyclohexyl, 3H), 1.89-1.85 (m, cyclohexyl, 3H), 2.31-2.30 (m, cyclohexyl, 1H), 2.40-2.37 (m, cyclohexyl, 1H), 2.73-2.70 (m, cyclohexyl, 1H), 4.45 (d, *J*= 8.0, CH, 0.30H), 4.57 (d, *J*=5.4 Hz, CH, 0.70 H), 4.66 (br, s, NH, 1H), 6.50-6.47 (m, phenyl, 2H), 6.63 (m, phenyl, 1H), 7.07-7.03 (m, phenyl, 2H), 7.25-7.23 (m, phenyl, 2H), 7.30-7.26 (m, phenyl, 2H)

**2-[1'-(*N*-*p*-methylphenylamino)-1'-(4-chlorophenyl)]methylcyclohexanone (Table 3 Entry 7).** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 3372, 1697, 1523, 1490, 1285, 813; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ= 1.65–1.81 (m, cyclohexyl, 6H), 2.24 (s, $CH_3$, 3H), 2.31 (s, cyclohexyl, 1H), 2.36–2.51 (m, cyclohexyl, 2H), 4.13 (br, s, NH, 1H), 4.52 (d, *J* = 8.22 Hz, 0.10 H), 4.63 (d, *J* = 5.5 Hz, 0.90 H), 6.79 (d, *J* = 7.6 Hz, phenyl, 2H), 6.93 (d, *J*= 8.17 Hz, phenyl, 2H), 7.10 (d, *J*= 7.9, phenyl, 2H), 7.23 (d, *J* = 8.27 Hz phenyl, 2H)

**2-[1'-(2-furyl)-1'-*N*-phenylamino]methylcyclohexanone** (**Table 3 Entry 8**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 3357, 2940, 1673, 1594, 1503; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ=1.60-2.40 (m, cyclohexyl, 8H), 2.90-2.99 (m, cyclohexyl,1H), 4.54 (br, s, NH, 1H), 4.81 (d, *J* = 5.3 Hz, CH, 0.33H), 4.88 (d, *J* = 4.7 Hz, CH, 0.67H), 6.17-6.27 (m, phenyl, 2H), 6.61-6.71 (m, phenyl, 3H), 7.11-7.29 (m, phenyl, 3H).

**3-[1'-(*N*-phenylamino)-1'-phenyl]1-phenyl-2-propanone** (**Table 3, Entry 9**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 3340, 2934, 1675, 1515, 1492, 1290, 1013; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ= 2.03-2.62 (m, $CH_2$, 2H), 4.15 (br, s, NH, 1H), 4.75-4.90 (m, CH, 1H), 6.34-6.45 (m, phenyl, 2 H), 7.20–7.25 (m, phenyl, 2 H), 7.25–7.37 (m, phenyl, 4 H), 7.39–7.48 (m, phenyl, 3 H), 7.50–7.58 (m, phenyl, 2 H), 7.87–7.96 (m, phenyl, 2 H).

***3*-[1'-(N-p-chlorophenylamino)-1'-phenyl]1-phenyl-2-propanone** (**Table 3, Entry 12**)**.** FTIR (KBr, $\nu_{max}$ ,$cm^{-1}$) 3369, 2927, 1666, 1502, 1486, 1286, 1003, 823, 700; $^1$HNMR (300 MHz; $CDCl_3$; $Me_4Si$) δ= 3.26–3.50 (m, $CH_2$, 2 H), 4.55 (br, s, NH, 1 H), 4.80–4.93 (m, CH, 1 H), 6.34–6.45 (m, phenyl, 2 H), 6.90–6.99 (m, phenyl, 2 H), 7.11–7.29 (m, phenyl, 4 H), 7.30–7.41 (m, phenyl, 3 H), 7.44–7.55 (m, phenyl, 1 H), 7.78–7.88 (m, phenyl, 2 H).

## Acknowledgements

The authors thank the Defence Research and Development Organization, India for the financial support. We are grateful to NMR research centre IISc Bangalore and STIC CUSAT for various analytical facilities.

## References

1. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.
2. (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.
3. (a) *Organocatalysis*; Reetz, M. T.; List, B.; Jaroch, S.; Weinmann, H. Eds.; Springer Verlag: Berlin Heidelberg, 2008. (b). *Enantioselective Organocatalysis*; Dalko, P. I. Eds.; Wiley-VCH: Weinheim, 2007. (c) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005.
4. (a) Tomalia, D. A. *Prog. Polym. Sci.* **2005**, *30*, 294. (b) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. *Angew. Chem. Int. Ed.* **1990**, *29*, 138.

5. (a) Newkome, G. R.; Moorefield, C. N.; Vogtle, F. *Dendrimers and Dendrons*; Wiley-VCH: Verlag GmbH, 2002. (b) *Dendrimers and Other Dendritic Polymers*; Frechet, J. M. J.; Tomalia, D. A., Eds.; John Wiley & Sons: Chichester, 2001.
6. (a) Jang, W. D.; Selim, K. M. K.; Lee, C. H.; Kang, I. K. *Prog. Polym. Sci.* **2009**, *34*, 1. (b). Guillot-Nieckowski, M.; Eisler, S.; Diederich, F. *New J. Chem.* **2007**, *31*, 1111.(c). Kofoed, J.; Reymond, J. L. *Curr. Opin. Chem. Biol.* **2005**, *9*, 656.
7. (a) *Dendrimers in Catalysis; Topics in Organometallic Chemistry*; Gade, L. H., Eds.; Springer-Verlag: Heidelberg 2006; Vol. 20., p 1 (b) Méry, D.; Astruc, D. *Coord. Chem. Rev.* **2006**, *250*, 1965. (c) Helms, B.; Frechet, J. M. J. *Adv. Synth. Catal.* **2006**, *348*, 1125. (d) Astruc, D.; Heuze, K.; Gatard, S.; Méry, D.; Nlate, S.; Plault, L. *Adv. Synth. Catal.* **2005**, *347*, 329. (e) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991. (f) Ooosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1828.
8. (a) Astruc, D.; Ornelas, C.; Ruiz, J. *Acc. Chem. Res.* **2008**, *41*, 841. (b) Hwang, S. H.; Shreiner, C. D.; Moorefield, C. N.; Newkome, G. R. *New. J. Chem.* **2007**, *31*, 1192.
9. Scot, R. W. J.; Wilson, O. M.; Crooks, R. M. *J. Phys. Chem. B.* **2005**, *109*, 692.
10. (a) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (b) Li, Y.; Liu, X. Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2034. (c) Sarkar, A.; Ilankumaran, P.; Kisanga, P.; Verkade, J. G. *Adv. Synth. Catal.* **2004**, *346*, 1093.
11. (a) Tietze, L. F.; Rackelman, N. In *Multicomponent Reactions*; Zhu, J.; Bienayme, H. Eds.; Wiley-VCH: Weinheim, 2005; p 121. (b) Cui, H.; Li, P.; Chai, Z.; Zheng, C.; Zhao, G.; Zhu, S. *J. Org. Chem.* **2009**, *74*, 1400. (c) Hu, M.; Li, J.; Yao, S. Q. *Org. Lett.* **2008**, *10*, 5529. (d) Qin, P.; Zhu, H.; Edvinsson, T.; Boschloo, G.; Hagfeldt, A.; Sun, L. *J. Am. Chem. Soc.* **2008**, *130*, 8570. (e) Zhang, X. R.; Chao, W.; Chuai, Y. T.; Ma, Y.; Hao, R.; Zou, D. C.; Wei, Y. G.; Wang, Y. *Org. Lett.* **2006**, *8*, 2563. (f) Kwak, V.; Fujiki, M. *Macromolecules* **2004**, *37*, 2021. (g) Liao, J.; Wang, Q. *Macromolecules* **2004**, *37*, 7061. (h) Nokami, J.; Kataoka, K.; Shiraishi, K.; Osafune, M.; Hussain, I.; Sumida, S. *J. Org. Chem.* **2001**, *66*, 1228.
12. (a) Jones, G. *Organic Reactions*; John Wiley & Sons: New York, 1967, Vol. 15, p 204. (b) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis* Trost, B. M.; Fleming, I. Eds.; Pergamon Press: New York, 1991; Vol. 2, p 341. (c) Xia, Y.; Mokaya R. *J. Phys. Chem. C* **2008**, *112*, 1455. (d) Berrue, V.; Antoniotti, S.; Thomas, O. P.; Amade, P. *Eur. J. Org. Chem.* **2007**, *11*, 1743. (e) Xin, X.; Gou, X.; Duan, H.; Lin, Y.; Sun, H. *Catal. Commun.* **2007**, *8*, 115. (f) Gupta, M.; Wakhloo, B. P. *ARKIVOC* **2007**, *(i)*, 94. (g) Reddy, K. R.; Rajagopal, K.; Maheswari, C. U.; Kantam, M. L. *New. J. Chem.* **2006**, *30*, 1549. (h) van Dommele, S.; de Jong, K. P.; Bitter, J. H. *Chem. Commun.* **2006**, 4859. (i) Hangarge, R. K.; Jarikote, D. V.; Shingare, M. S. *Green Chem.* **2002**, *4*, 266.
13. Maraval, V.; Caminade, A. M.; Majoral, J. P. *Organometallics* **2000**, *19*, 4025.
14. Krishnan, G. R.; Sreekumar, K. *Eur. J. Org. Chem.* **2008**, 4763.
15. (a) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: New York, 1991; Vol. 2, p 953. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (c) Denmark, S. E.; Nicaise, O. J. C. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999, Vol. 2, p 923. (d)

Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (e) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

16. (a) Wu, H.; Chen, X.; Wan, Y.; Ye, L.; Xin, H.; Xu, H.; Yue, C.; Pang, L.; Ma, R. Shi, D. *Tetrahedron Lett.* **2009**, *50*, 1062. (b) Dziedzic, V.; Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2008**, *49*, 803. (c) Hayashi, Y.; Urushima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett.* **2008**, *10*, 21. (d) Khan, A. T.; Pravin, T.; Choudhary, L. H. *Eur. J. Org. Chem.* **2008**, *2008*, 834. (e) Bigdeli, M. A.; Nemati, F.; Mahdavinia, G. H. *Tetrahedron Lett.* **2007**, *48*, 6801. (f) Guo, Q. X.; Liu, H.; Guo, C.; Luo, S. W.; Gu, Y.; Gong, L. Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. (g) Wang, R.; Li, B. G.; Huang, T. K.; Shi, L.; Lu, X. X. *Tetrahedron Lett.* **2007**, *48*, 2071. (h) Wu, H.; Shen, L. Y.; Fan, Y.; Zhang, P.; Chen, C. F.; Wang, W. X. *Tetrahedron* **2007**, *63*, 2404. (i) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018. (j) Azizi, N.; Torkiyan, L.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 2079. (k) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208
17. (a) Tomalia, D. A. In *Polymer Chemistry A Practical Approach*: Davis, F. J. Eds.; Oxford University Press: UK, 2004; p 188. (b) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117.
18. Zhang, X.; Lai, E. S. M.; Aranda, R. M.; Yeung, K. L. *Appl. Catal. A: Gen.* **2004**, *261*, 109.
19. (a) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Cordova, A. *Chem. Eur. J.* **2005**, *11*, 7024. (b) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, J.; Barbas, C. F. *J. Org. Chem.* **2003**, *68*, 9624.