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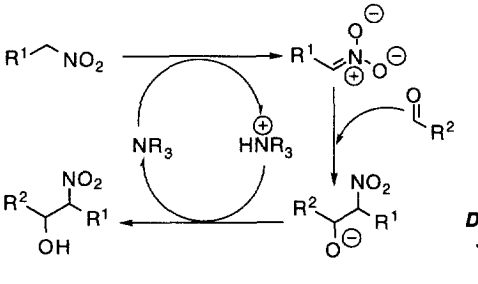
# Dendritic Catalysts for the Nitroaldol (Henry) Reaction

**Iñaki Morao and Fernando P. Cossío***

Kimika Fakultatea, Euskal Herriko Unibertsitatea,
P.K. 1072. 20080 San Sebastián-Donostia, Spain

**Abstract**: Dendritic molecules with a single triethylene amine core surrounded by hyperbranched polyether sectors catalyze the nitroaldol reaction between aromatic aldehydes and nitroalkanes.


The nitroaldol (Henry) reaction is a classical method for the generation of carbon-carbon bonds, which leads to the formation of nitroalcohols. These compounds in turn, are very versatile intermediates in the synthesis of valuable compounds.[1] One of the variants of the nitroaldol reaction consists in the use of amines as catalysts, according to the cycle depicted in Scheme 1. Very recently, we have reported a study on the mechanism of this reaction.[2] On the basis of the structural features of the transition structures associated with the reaction coordinate,[2] we reasoned that a dendrimer with an amine core surrounded by hyperbranched polyether sections could catalyze[3] efficiently the nitroaldol reaction. The most important requirement of these dendrimeric monoamines is that the cavities around the active site must be large enough to accommodate the substrates and the transition structures (Figure 1). Preliminary molecular modeling studies showed that triethanolamine-based dendrimers **3** (Scheme 2) could fulfil the above requirements and therefore were selected for further experimental work.




Scheme 1

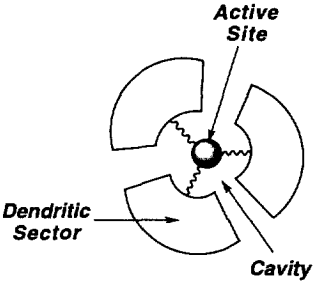
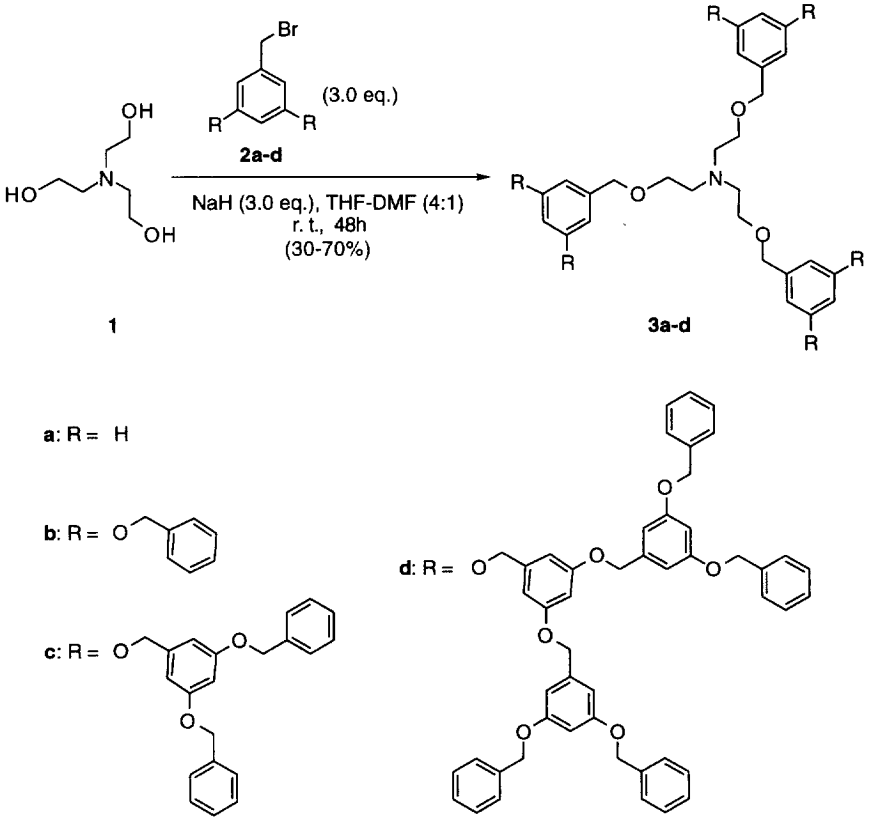



Figure 1

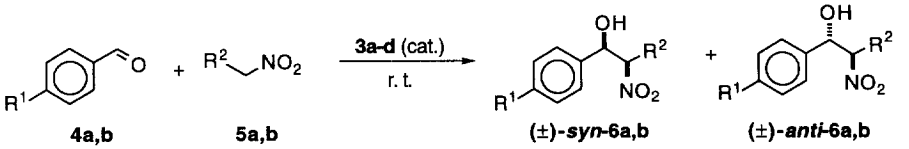
The synthesis of dendrimers **3a-d** was achieved in moderate yields by means of Williamson couplings between triethanolamine **1** and benzyl bromide **2a** or the Fréchet's dendrons[4] **2b-d** (Scheme 2). Under our reaction conditions, no quaternization of the amine was observed, except in the case of **3a**. In order to maximize the formation of this latter compound, only 2.5 eq. of benzyl bromide were used, and the

reaction time was prolonged to three days. The remaining amines **3** were readily obtained and characterized after purification by flash chromatography (silicagel 230-400 mesh, AcOEt/hexane as eluent).[5]




Scheme 2

With amines **3a-d** in hands we tested their ability to catalyze the nitroaldol reaction between aromatic aldehydes **4a,b** and nitroalkanes **5a,b** (Scheme 3). The results of the two reactions studied are summarized in Table 1. All nitroalcohols were purified by flash chromatography and characterized on the basis of their physical and spectroscopic features.[6]




**4a**: $R^1$ = H
**4b**: $R^1$ = $NO_2$

**5a**: $R^2$ = $CH_3$
**5b**: $R^2$ = $CH_2OH$

**6a**: $R^1$ = H, $R^2$ = $CH_2OH$
**6b**: $R^1$ = $NO_2$, $R^2$ = $CH_3$

Scheme 3

Table 1. Formation of nitroalcohols **6a,b** by catalysis of dendrimers **3a-d**.[a]

| | | **4a +5b → 6a** | | | **4b +5a → 6b** | | |
|---|---|---|---|---|---|---|---|
| Catalyst | $M_W$(kDa) | time(h) | $\tau^b$(%) | *syn:anti*[b] | time(h) | $\tau^b$(%) | *syn:anti*[b] |
| none | -- | 48 | n.o.[c] | -- | 48 | n.o.[c] | -- |
| $NEt_3$ | 0.101 | 0.5 | >95 | 2:1 | 0.5 | >95 | 1:1 |
| **3a** | 0.419 | 4 | 90 | 2:1 | 4 | >95 | 1:1 |
| **3b** | 1.055 | 6 | 85 | 2:1 | 6 | 90 | 1:1 |
| **3c** | 2.327 | 48 | 85 | 2:1 | 48 | >95 | 1:1 |
| **3d** | 4.821 | 48 | 75 | 2:1 | 48 | >95 | 1:1 |

[a]All reactions were conducted at room temperature using the nitroalkane as solvent and the catalyst (15%/mol). [b]Conversions τ and diastereomeric ratios were calculated by 300 MHz $^1$H-NMR on the crude reaction mixtures. [c]n.o.: no conversion was observed.

As it can be seen from the results reported in Table 1, the activity of the catalysts **3** decreases when the generation number increases. As expected, the more electrophilic p-nitrobenzaldehyde **4b** is more reactive and requires lower reaction times than benzaldehyde **4a**. In addition, the **4a + 5b → 6a** reaction is more selective than **4b + 5a → 6b** transformation. Unfortunately, no significant changes in stereocontrol were observed on passing from lower to higher generation dendrimers. Our results indicate that there is a pronounced change in reactivity on passing from compounds **3a,b** to **3c,d**. Thus, the latter dendrimers require *ca.* two days to achieve high conversions, whereas the former amines promote efficiently the formation of the corresponding nitroaldols in *ca.* 4-6 hours. Computational model studies[7] show that these high generation dendrimers, in particular **3d**, cannot accommodate planar geometries and therefore the catalytic site is buried under the dendritic arms, thus limiting the accessibility of the nitroalkane to the central nitrogen atom. However, it is remarkable that these highly encumbered catalysts show significant activity.

In summary, we have shown that dendritic equivalents of trialkyl amines catalyze the nitroaldol reaction, thus demonstrating that dendrimers with a sole active site at the central core can exhibit catalytic properties. Work is in progress in our laboratory to design new dendrimers which could improve the stereochemical outcome of this reaction.

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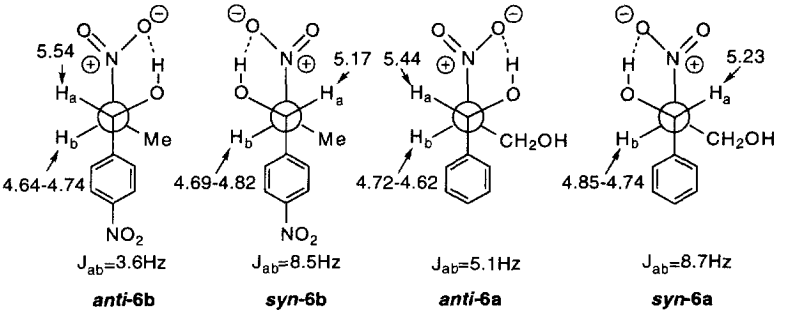
**References and Notes:**


1. Rosini, G. In *Comprehensive Organic Synthesis*, Vol. 2 (Trost, B.M. Ed.); Pergamon: New York, 1991, pp 321-340.
2. Lecea, B.: Arrieta, A.; Morao, I.; Cossío, F.P. *Chem. Eur. J.* **1997**, *3*, 20.
3. For other recent examples of different reactions catalyzed by dendrimers, see: (a) Knapen, J.W.J.; van der Made, A.W.; de Wilde, J.C.; van Leeuwen, P.W.N.M.; Wijkens, P.; Grove, D.M.; van Koten, G. *Nature* **1994**, 372, 659. (b) Brunner, H.J. *J. Organomet. Chem.* **1995**, *500*, 39. (c) Bolm, C.; Derrien, N.; Seger, A. *Synlett* **1996**, 387. (d) Bhyrappa, P.; Young, J.K.; Moore, J.S.; Suslick, K.S. *J. Am. Chem. Soc.* **1996**, *118*, 5708. (e) Mak, C.C.; Chow, H.-F. *Macromolecules* **1997**, *30*, 1228.
4. (a) Hawker, C.J.; Fréchet, J.M.J. *J. Am. Chem. Soc.* **1990**, *112*, 7638. (b) Gitsov, I.; Wooley, K.L.; Fréchet, J.M.J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1200.
5. All compounds were isolated as pale yellow oils. Selected $^1$H-NMR ($CDCl_3$, δ ppm) data : **3a** (Yield 60%): 7.28-7.31 (m, 15H), 4.48 (s, 6H), 3.55 (t, J= 6.0 Hz, 6H), 2.84 (t, J= 6.0 Hz, 6H). **3b** (Yield 70%): 7.29-7.41 (m, 30H), 6.58 (d, J= 2.2 Hz, 6H), 6.50 (t, J= 2.2 Hz, 3H), 4.95 (s, 12H), 4.40 (s, 6H), 3.55 (t, J= 6.5 Hz, 6H), 2.81 (t, J= 6.5 Hz, 6H). **3c** (Yield 50%): 7.20-7.40 (m, 60H), 6.67 (d, J= 2.2 Hz, 12H), 6.59 (d, J= 2.2 Hz, 6H), 6.57 (t, J= 2.2 Hz, 6H), 6.52 (t, J= 2.2 Hz, 3H), 5.05 (s, 24H), 4.90 (s, 12H), 4.37 (s, 6H), 3.50 (t, J= 6.1 Hz, 6H), 2.76 (t, J= 6.1 Hz, 6H). **3d** (Yield 30%): 7.10-7.35 (m, 120H), 6.45-6.55 (m, 63H), 4.37-4.88 (m, 90H), 3.45 (m, 6H), 2.75 (m, 6H).
6. The chief $^1$H-NMR data ($CDCl_3$, δ ppm) for the diastereomeric nitroaldols **6a,b** can be summarized as follows:




For the complete characterization of these compounds see: (a) Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 3601. (b) Ballini, R.; Bosica, G. *J. Org. Chem.* **1997**, *62*, 425.

7. MacroModel V5.0: Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caudifield, C.; Chang, G.; Hendrickson, T.; Still, C. *J. Comput.Chem.* **1990**, *11*, 440.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