ORGANIC LETTERS
2010
Vol. 12, No. 5
948−951

# Improving Catalytic Activity by Synergic Effect between Base and Acid Pairs in Hierarchically Porous Chitosan@Titania Nanoreactors

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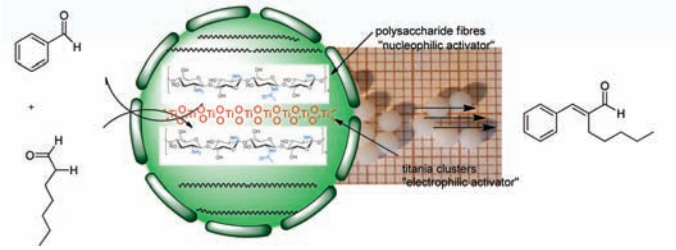
**Received December 21, 2009**

## ABSTRACT



**The beneficial effect of the bifunctional character of the chitosan@titania hybrid in heterogeneous catalysis was elucidated: considering a prototypical Henry condensation, Michael addition, and Jasminaldehyde synthesis, the cohabitation of a basic site ($NH_2$) and an acidic site (Ti) in the same reactor provided clear activity and selectivity enhancements, with respect to the monofunctional acidic titania and basic chitosan counterparts.**

The involvement of heterogeneous catalysis in the synthesis of fine chemicals becomes an exciting area offering environmentally more acceptable processes.[1] The advantages of heterogeneous processes, easier way for product recovery and catalyst recycling, prompted researchers to immobilize a homogeneous catalytic site on various supports. In addition, solid catalysts are very suitable for the regulatory issues of metal contamination in the context of pharmaceutical synthesis.[2] Unfortunately, with very few exceptions, the immobilization of an active catalytic site caused a significant decrease in the catalytic activity when compared to its homogeneous counterparts.[3]

Interestingly, biocatalysis offers some basic lessons for preparing more efficient synthetic catalysts. Indeed, enzymes are able to accelerate chemical reactions through cooperative interactions between precisely positioned reactive groups in the active site. This inspired researchers to design a large library of homogeneous bifunctional catalysts. Surprisingly, few examples describing the synergetic and cooperative effects in heterogeneous systems were reported, and the subject still represents a real challenge.[4−8]

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(1) (a) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686–694. (b) Clark, J. H. *Green Chem.* **1999**, *1*, 1–8.

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(3) Corma, A.; Garcia, H. *Top. Catal.* **2008**, *48*, 8–31.

10.1021/ol9029319

Recently, we have investigated the development of new porous and structured materials from renewable resources, particularly from chitin.[9] This area of research has great importance for the development of cleaner and more efficient processes.[10] In this respect, we report herein an interesting cooperative effect in catalysis using hybrid chitosan@titania porous materials. The preparation of these nanoreactors consists first in the gelation of chitosan biopolymer in basic conditions, which allows shaping chitosan as a hydrocolloid microsphere (Figure 1).[11] This swelled polymer was protracted in titanium alkoxide solution [Ti(Acac)$_2$(O*i*Pr)$_2$, Ti(O*i*Pr)$_4$, or Ti(OBu)$_4$], and then the respectively obtained **M1H**, **M2H**, and **M3H** chitosan@titania hybrid alcogels were dried under CO$_2$ supercritical conditions. Nitrogen adsorption isotherms demonstrated the macroporous character of the materials, with a specific surface area ranging from 370 to 480 m$^2$ g$^{-1}$.[11] SEM analysis showed a fibrillar network of the secondary structure of the biopolymer (Figure 2). TEM analysis revealed the existence of highly dispersed titanium nanoparticles.[11] Both the fibrillar network of the biopolymer and the presence of amine functions play a pivotal role to direct the growth and mineralization of titanium precursors leading to the replication of polysaccharide fibers by highly dispersed titanium dioxide nanoparticles. Excitingly, these hybrid materials are imparted with three main advantages: (i) the higher surface areas and the macroporous network of these scaffolds which are important for the diffusion of bulk molecules to (and from) the active site, (ii) the high dispersion of titanium nanoparticles, which play a crucial role in catalysis, and (iii) the robustness of these microspheres assessed under hydrothermal, acidic, and basic conditions.[11] The stability of these hybrids is very relevant as the faint stability of organic polymers generally limits their use as support.

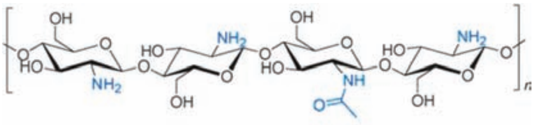

**Figure 1.** Chemical structure of chitosan.

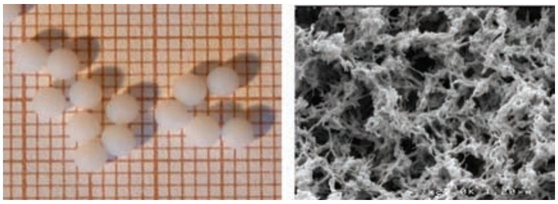

**Figure 2.** Photo and SEM of **M1H**.

Intrigued by this acid−base cohabitation,[12] we decided to examine how these hybrid materials could catalyze cooperatively different condensation reactions involving carbonyl activation. It was expected that *the presence of both NH$_2$ and titanium clusters in close proximity could cooperatively activate the electrophile and nucleophile reactants and consequently enhance the reaction rates of the desired organic transformations.* Herein we investigate this approach for specific model reactions (Henry condensation, Michael addition, jasminal synthesis) and report the proof of concept of the synergetic effect between the two catalytic site partners.

First, Henry condensation of nitromethane with 4-methoxybenzaldehyde as a prototype was investigated because it illustrates the paradoxical statement that initiated the present work (Table 1).[13] The catalytic performances using the various porous chitosan@titania among different catalysts are shown in Table 1. Actually, chitosan@titania microspheres were found to be the more active catalysts (entries 4−6). With chitosan alone, featuring a similar texture, the reaction proceeded smoothly, and a quantitative yield was

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(11) See Supporting Information for details.

(12) An interesting topic is recently introduced by Stephan by designing homogenous noncoordinated Lewis pairs (known as F. L. P.: Frustrated Lewis Pairs). These bifunctional pairs exhibit an unusual reactivity. See for review: Stephan, D. W *Org. Biomol. Chem.* **2008**, *6*, 1535–1539.

(13) (a) Ma, K.; You, J. *Chem.—Eur. J.* **2007**, *13*, 1863–1871. (b) Palomo, C.; Oiarbide, M; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881–3884. (c) Risgaard, T.; Gothelf, K. V.; Jorgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153–156. (d) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055.

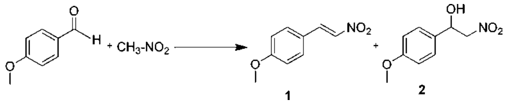
achieved only after 24 h of reaction (entries 2 and 3). Lower yield was obtained with inorganic titanium dioxide (entry 7). This reveals the higher activity of the base catalysts versus acid solids and the crucial role played by the amino groups in these bifunctional chitosan@titania materials. The predominance of nitrostyrene **1** versus nitroalcohol **2** (entries 2−6) suggests that the condensation occurs by an imine formation mechanism as primary amines supported silica that produced preferentially nitrostyrene,[6b] by contrast of supported tertiary amine that switched the selectivity to nitroalcohol. In the latter case, the reaction proceeds via an ion pair mechanism.[6b] Katz et al. showed a dramatic effect of outer sphere acidity on the selectivity in the Henry reaction.[6e] In a hydrophilic primary amine-tethered silica, considered as bifunctional acid−base material, the surface silanols (Si-*OH*) are shown to accelerate the formation of imine and iminium, both of which are intermediate in nitrostyrene formation.[6e] In our case, the higher reactivity of the hybrid chitosan@titania (compared to the monofunctional chitosan) can be explained by an assistance of titanium Lewis acid during the imine formation.

The results obtained with homogeneous bases correlate with the strength of the base and with the proposed mechanism (entries 8−10). When Ti(OiPr)$_4$ was used as catalyst, the yield did not exceed 16% (entry 11). Additionally, the efficiency of either triethylamine or ethylamine was inhibited in the presence of a stoichiometric amount of titanium tetraisopropoxide, and neither nitrostyrene nor nitroalcohol were found in the solution (entries 12 and 13). This trend probably results from a neutralization effect between the Lewis base and Lewis acid in homogeneous media. When heterogeneous chitosan and homogeneous Ti(OiPr)$_4$ were used, no reaction was observed suggesting thus the poisoning of amine functions by homogeneous titanium Lewis acid. On the other hand, no significant improvement was observed by the simultaneous introduction of the two heterogeneous catalysts (chitosan and titanium dioxide).[14]

To rule out the possible role played by chitosan@titania as a reservoir for homogeneous catalyst based on highly active titania nanoparticles, leaching experiments were carried out. The reaction of the three materials (**M1H**, **M2H**, **M3H**) was performed until half conversion was observed (1 h, ∼ 49% of conversion). The material beads were removed from the solution while the reaction mixture was still hot. No further conversion was observed upon heating for 4 h (see Supporting Information). Furthermore, no metal was detected in the solution by ICPMS analysis. This supports the heterogeneous nature of the reaction.

These interesting results prompted us to assess the catalytic behavior of chitosan@titania hybrid materials in other reactions involving electrophilic and nucleophilic activations.

**Table 1.** Henry Reaction of Nitromethane with 4-Methoxybenzaldehyde[a]



| entry | cat. | *t* (h) | % convn[b] | **1** (%) | **2** (%) |
|---|---|---|---|---|---|
| 1 | ---- | 24 | 0 | --- | --- |
| 2 | **M0** | 3 | 15 | 95 | 5 |
| 3 | **M0** | 24 | 68 | 95 | 5 |
| 4 | **M1H** | 3 | 98 | 97 | 3 |
| 5 | **M2H** | 3 | 90 | 93 | 7 |
| 6 | **M3H** | 3 | 95 | 95 | 5 |
| 7 | TiO$_2$[c] | 24 | 7 | 100 | 0 |
| 8 | NEt$_3$ | 5 | 55 | 29 | 71 |
| 9 | Et-NH$_2$ | 5 | 90 | 92 | 8 |
| 10 | Ph-NH$_2$ | 24 | 13 | 81 | 19 |
| 11 | Ti(OiPr)$_4$ | 24 | 16 | 94 | 6 |
| 12 | Et$_3$N/Ti(OiPr)$_4$ | 24 | 0 | --- | --- |
| 13 | Et-NH$_2$/Ti(OiPr)$_4$ | 24 | 0 | --- | --- |

[a] Conditions are as follows: $T$ = 80 °C. 4-Methoxybenzaldehyde (1 mmol), catalyst (0.05 mmol), nitromethane (8 mL). [b] Determined by GC (dodecane as external standard). [c] TiO$_2$ was obtained by calcination of the hybrid **M1H** (see Supporting Information).

The Michael addition of ethyl cyanoacetate with 2 equiv of methyl vinyl ketone demonstrates clearly the higher activity (and selectivity) of our hybrid microspheres (Table 2).

Quantitative yields were obtained after only 30 min at room temperature (entries 2−4). With native chitosan **M0**, a moderate 41% yield was reached after an extended time of 1 h. The poor yield obtained with the nonporous xerogel **M1Hxero** (entry 5) highlights the role of the macroporosity that facilitates the diffusion of the reactant to the active sites and the scavenging of the products (and water byproduct) from the reactor, enhancing thus the kinetics of the reaction. In terms of selectivity, the three hybrid microspheres **M1H**, **M2H**, and **M3H** gave a good selectivity for 5-carboethoxy-5-cyano-2,8-nonanedione **4**. By contrast, in the case of chitosan, longer reaction time improved neither the yield nor the selectivity. After 5 h, the conversion did not exceed 50%, and the selectivity for the product **4** remained 58%. This demonstrates the beneficial effect of the electrophilic activation of the carbonyl group by titanium nanoparticles. Similarly, a significant enhancement of catalytic activity gained by supporting organic amines in silica−alumina (Si−O−Al) was recently reported.[7d,e] This unusual activity was also rationalized by the dual acid−base character of the designed materials which makes them more reactive than the classical amine supported silica catalysts.[7d,e]

An important challenge in organic synthesis is how to force a reaction to result in enrichment with one targeted product. For instance, jasminaldehyde (-2-pentyl-3-phenyl-2-propenal, **5**), an important perfumery chemical, is industrially prepared through the condensation of 1-heptanal and benzaldehyde in the presence of alkali as catalyst (sodium or potassium hydroxide). However, one of the drawbacks of this route is

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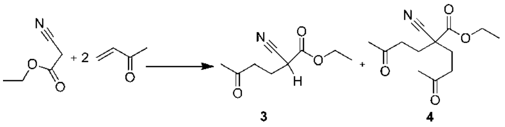
[14] For sequential one-pot reactions using two separated acidic and basic catalysts, known as site isolation concept, see for instance: (a) Voit, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4238–4240. (b) Helms, B.; Guillaudeu, S. J.; Xie, Y.; McMurdo, M.; Hawker, C. J.; Frechet, J. M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6384–6387. (c) Motokura, K.; Nishimura, D.; Mori, K.; Mizugaki, K.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 5662. (d) Gelman, F.; Blum, J.; Avnir, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3647–3649.

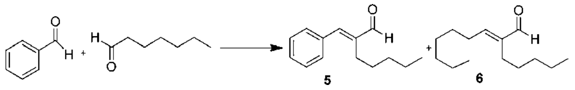
**Table 2.** Michael Addition of Ethyl Cyanoacetate with 2 Equiv of Methyl Vinyl Ketone[a]



| entry | cat. | *t* (h) | % convn[b] | **3** (%) | **4** (%) |
|---|---|---|---|---|---|
| 1 | **M0** | 1 | 41 | 43 | 57 |
| 2 | **M1H** | 0.5 | 78 | 3 | 97 |
| 3 | **M2H** | 0.5 | 70 | 21 | 79 |
| 4 | **M3H** | 0.5 | 70 | 13 | 87 |
| 5 | **M1Hxero**[c] | 1 | 17 | 71 | 29 |
| 6 | $TiO_2$[c] | 3 | 35 | 64 | 36 |

[a] Conditions are as follows: ethyl cyanoacetate (1 mmol), methyl vinyl ketone (2.2 mmol), catalyst (0.05 mmol), toluene (5 mL). [b] Determined by GC (dodecane as external standard). [c] See Supporting Information.

**Table 3.** (*E*/*Z*)-2-Pentyl-3-phenyl-2-propenal Synthesis[a]



| entry | cat. | *t* (h) | temp (°C) | convn heptanal[b] (%) | **5** (%)[c] | **6** (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **M0** | 6 | 80 | 92 | 48 | 50 |
| 2 | **M1H** | 4 | 80 | 98 | 86 | 11 |
| 3 | **M2H** | 4 | 80 | 85 | 81 | 9 |
| 4 | **M3H** | 4 | 80 | 89 | 79 | 12 |
| 5 | $TiO_2$[d] | 24 | 120 | 87 | 53 | 19 |

[a] Conditions are as follows: heptanal (1 mmol), benzaldehyde (5 mmol), catalyst (0.05 mmol), toluene (10 mL). [b] Determined by GC (dodecane as external reference). [c] Mixture of both *E* and *Z* isomers. [d] Obtained by calcination of **M1H** hybrid (see Supporting Information).

the formation of an undesired 2-pentyl-2-nonenal **6** from the self-condensation of heptanal. Efforts were then directed to enhance the selectivity to jasminaldehyde by using various catalysts: HY and $\beta$-zeolites,[5a] aluminosilicates,[15] magnesium organosilicates,[16] and amorphous aluminophosphates,[5a,c] among others. Corma et al. demonstrated the utility of acid−base bifunctional solid catalysts for jasminaldehyde synthesis.[5a−c] The weak acidic site induces an electrophilic activation of the carbonyl group of benzaldehyde, which favors the attack of the enolate heptanal intermediate formed by interaction with the basic sites.[17]

Having these materials in hands, we explored the catalytic condensation of heptanal and benzaldehyde by the hybrid chitosan@titania microspheres (**M1H**, **M2H**, and **M3H**), native chitosan **M0**, and nanotitania (Table 3). Chitosan@titania hybrids (**M1H**, **M2H**, and **M3H**) perform a quantitative conversion of heptanal in relatively short reaction time (entries 2−4). By contrast, native chitosan (entry 1) and nanotitania (entry 5) required a longer reaction time to reach nearly the same conversion level. The bifunctional chitosan@titania catalysts provided in addition the highest selectivity in jasminaldehyde. The undesirable 2-pentyl-2-nonenal **6** did not exceed 12% using these hybrid materials (entries 2−4) witnessing thus on their bifunctional character.

The most crucial issue that should be considered for practical application of heterogeneous systems is the catalyst stability and reusability. With this aim, successive condensations of methylvinylketone with ethyl cyanoacetate (Table 1) using **M1H** catalyst were performed. The recovered nanoreactor **M1H** was successively used for five successive runs, and the obtained results showed consistent activity with an average yield of 72% even though extended reaction time was required (see Supporting Information).

In conclusion, a new class of cooperative acid−base bifunctional hybrid materials was reported. The templating effect of chitosan allowed the control of mineral growth of nanotitania inside the macrochannels of the swelling biopolymer. The supercritical drying improves the textural properties of these materials, thus leading to high surface area nanoreactors. The macrochannels, the naturally spaced amino functions borne by chitosan and the nanosized titanium dioxide, provide a synergetic means of an efficient approach of the reactants to the active sites. The remarkable set of reactions affected by bifunctional catalyst including the higher activity in Henry and Michael addition and the selectivity in jasminaldehyde synthesis attest the cooperative acid−base attainable in chitosan@titania hybrid materials. Other hybrid materials based on chitosan@inorganic oxides and their applications in fine chemical synthesis are under investigation.

**Acknowledgment.** A. E. K. thanks Carnot foundation and INANOTECH for financial support.

**Supporting Information Available:** Experimental procedures and textural and structural characterization of catalysts **M1H**, **M2H**, and **M3H**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9029319

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(16) Sharma, S. K.; Patel, H. A.; Jasra, R. *J. Mol. Catal. A: Chem.* **2008**, *280*, 61.

(17) In homogenous base-catalyzed condensation of alkanals with benzaldehyde, the selectivity to α-alkylcinnamaldehydes can be increased by adding a small amount of an acid. Kuiterman, A.; Castelijns, A. M. C. F.; Dielemans, H. J. A.; Green, R. *European Patent 0771780 A1*, 1997.