Henry Reaction Catalyzed by Aminopropylated Nanosilica

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The Henry reaction was catalyzed by 0.01 equiv of aminopropylated nanosilica particles (nano-NAP) in refluxing nitroalkanes to provide nitrostyrenes in good yields. The catalyst could be recycled up to three times in 76% average yield.

Immobilization of an organocatalytic residue on a solid support imparts stability and recyclability to the original homogeneous organocatalyst. Silica gel with grafted organic residues on the surface has played an important role as a heterogeneous organocatalyst in synthetic organic chemistry.[1] We have successfully utilized amorphous aminopropylated silica of micrometer particle size (NAP) as sustainable catalysts for 1,4-conjugate additions of naked aldehydes,[2] aldol condensation,[3] transesterifications,[4] Michael reactions,[5] hydropyran synthesis by three component condensations,[6] Knoevenagel reactions,[7] and subsequent Mislow–Evans rearrangements[8] in environmentally benign reaction media such as water or ionic liquids.

Currently, catalysts of nanometer particle size attract considerable attention because they have the advantages of both homogeneous and heterogeneous catalysts. Their fine size and miscibility in solvent are expected to enhance catalytic activity. However, due to the strong interactions between nanoparticles, they usually are present in micromolar concentrations in solvent, while at higher concentrations they aggregate to form a gel. In order to prevent aggregation and to increase the concentration of the nanoparticles in solution, modification of the surface is required. Thus, we have newly developed an efficient solvent-free protocol for grafting aminopropyl residues on nanosilica particles having an average size of 12 nm (Figure 1). In this process, a solution of 3-aminopropyltriethoxysilane in ethanol is sprayed directly onto silica nanoparticles.[9] This protocol is environmentally benign and favorable for large-scale preparation. One of the characteristic features of such aminopropylated nanosilica particles (nano-NAP) compared to amorphous silica is the higher graft density of the organic residue due to its large surface area.

As part of our efforts to develop heterogeneously immobilized organocatalysts, we investigated the catalytic activity of nano-NAP as an immobilized organocatalyst for the Henry reaction.[10,11] This reaction is one of the most powerful procedures for the production of α,β-unsaturated nitro compounds, which are important substrates as dienophiles of Diels–Alder reaction or Michael acceptor and building blocks in the synthesis of pharmaceutical products.[12]

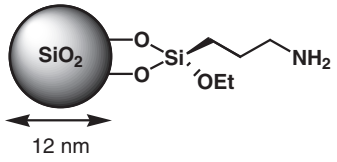
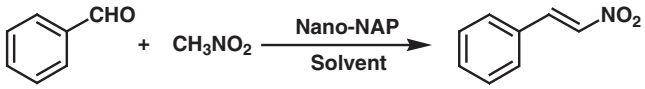


Figure 1. Nano-NAP: aminopropylated nano-silica.



Scheme 1. Henry reaction of benzaldehyde catalyzed by nano-NAP.

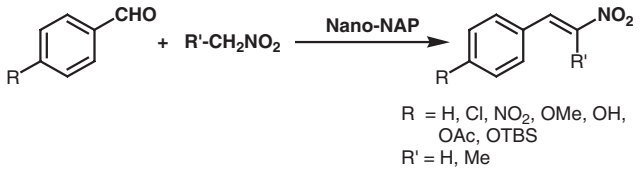
Table 1. Optimization of reaction conditions

Run	Catalyst	Solvent	Time/h	Yield/%
1[a]	None	CH_3NO_2	20	3
2[a]	NAP	CH_3NO_2	5	31
3[a]	Nano-NAP	CH_3NO_2	2	0
4[a]	Nano-NAP	CH_3NO_2	12	95
5[a]	Nano-silica	CH_3NO_2	20	4
6[a]	*n*-Octylamine	CH_3NO_2	12	81
7[a]	*n*-Octylamine + Nano-silica	CH_3NO_2	12	60
8[b]	Nano-NAP	[bmim]PF_6	2	0

[a]Reaction was carried out under reflux of nitromethane with 0.01 equiv of catalyst. Product was isolated by medium pressure LC after decantation followed by evaporation of nitromethane. [b]Reaction was carried out with 0.05 equiv of nano-NAP and 1.2 equiv of nitromethane at 85 °C under microwave heating.

Nano-NAP disperses homogeneously into nitromethane without forming a gel even at concentrations of 1.4 M. Optimized reaction conditions for the Henry reaction were investigated by examining the reaction of benzaldehyde and nitromethane (Scheme 1), and the results are shown in Table 1. The reaction was dependent on reaction temperature and time, probably due to initial formation of iminium cation. At the refluxing temperature of nitromethane, the reaction went to completion after 12 h (Table 1, Runs 3 and 4). A catalyst loading of 0.01 equiv of nano-NAP was sufficient to produce a 95% yield of nitrostyrene (Table 1, Run 4). The ionic liquid [bmim]PF_6 was not suitable as a recyclable and activating reaction medium even under microwave irradiation at 85 °C, even though nano-NAP was miscible under the reaction conditions (Table 1, Run 8).

The optimized reaction conditions (Table 1, Run 4) were general to a variety of arylaldehydes as shown in Scheme 2 and Table 2. Aldehydes bearing not only electron-withdrawing (Table 2, Runs 2 and 3) but also electron-donating substituents (Table 2, Runs 4 and 5) provided nitrostyrenes in good yields. The reaction conditions are so mild that base- or acid-sensitive protecting groups such as OAc or OTBDMS groups remained intact (Table 2, Runs 6 and 7), which is favorable for use with multifunctional substrates such as in natural product synthesis. Moreover, nitroethane provided nitrostyrene when 0.1 equiv of



Scheme 2. Henry reaction of arylaldehyde catalyzed by nano-NAP.

Table 2. Nano-NAP-catalyzed Henry reaction with a variety of aldehydes[a]

Run	R	R′	Time/h	Yield/%
1	H	H	12	95
2	Cl	H	12	86
3	NO_2	H	10	81
4	OMe	H	13	91
5	OH	H	11	89
6	OAc	H	12	95
7[b,c]	OTBS	H	24	44
8[b]	H	Me	24	89

[a]Reaction was carried out with 0.01 equiv of nano-NAP under reflux of nitromethane. [b]0.1 equiv of nano-NAP was used. [c]Starting aldehyde was recovered in 56% yield.

nano-NAP was used (Table 2, Run 8). The reaction of 4-*tert*-(butyldimethylsiloxy)benzaldehyde also required 0.1 equiv of nano-NAP due to the low reactivity of the aldehyde (Table 2, Run 7). The reactions of aliphatic aldehydes such as citronellal, decanal, or hydrocinnamaldehyde resulted in recovery of the starting materials, which exemplifies the chemoselective nature of the present protocol.

The initial content of silanol groups in the nanosilica was 1.37 mmol g^{-1} as determined by volumetric measurements[8] employing trimethylaluminium. The loading of amino residues on nano-NAP was 0.28 mmol g^{-1} as determined by elemental analysis, which indicates that more than 40% of the silanol groups on the nanosilica were functionalized with aminopropyl residues. The original nanosilica could not catalyze the reaction, resulting in the recovery of the starting aldehyde (Table 1, Run 5). These results show that the aminopropyl residues on the nano-NAP are active as the catalytic site. Although *n*-octylamine also catalyzed the reaction in a similar manner (Table 1, Run 6), the yield was slightly lower. According to TLC analysis, this is probably due to the formation of aldimine. Although by-products were obtained when a mixture of *n*-octylamine and nanosilica was employed as the catalyst (Table 1, Run 7), the spatial proximity of the basic amine and acidic silanol on the nanosilica surface might be effective for realizing acid and base bicatalytic synergy, which attracts and activates both the aldehyde and nitromethane.[1a,11c] The turnover number of the nano-NAP catalyst was 110 in the reaction of benzaldehyde and nitromethane.

NAP (0.01 equiv) could be reused up to three times in 76% average yield for the reaction of benzaldehyde in refluxing nitromethane (Table 3). The catalyst was isolated after the reaction by precipitation with *n*-hexane followed by weak and brief centrifugation followed by evacuation. Loss of reactivity in the third cycle might be due to loss of nano-NAP particles during isolation. Performing the reaction on a larger scale or using a more powerful centrifuge may prevent loss of the catalyst during work.

Table 3. Recyclability of nano-NAP in the reaction with benzaldehyde

Cycle	Time/h	Yield/%
1	12	95
2[a]	12	81
3[a]	16	52

[a]Reaction was carried out with recovered nano-NAP under reflux of nitromethane.

In summary, we found that aminopropylated nanosilica particles—nano-NAP—catalyze the Henry reaction for various combinations of arylaldehydes and nitroalkanes to afford a variety of substituted nitrostyrenes. The reaction conditions are mild enough to ensure that acid- or base-sensitive substituents of the substrates remain intact. Nano-NAP could be recycled up to three times in 76% average yield. Miscibility of nano-NAP in solution due to its hyperfine structure might be useful as a pseudo-heterogeneous catalyst.

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