

Heterogeneous asymmetric nitro-Mannich reaction using a bis(oxazoline) ligand grafted on mesoporous silica

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Abstract—A chiral bis(oxazoline) ligand was immobilized on mesoporous silica (SBA-15) and examined in an asymmetric heterogeneous nitro-Mannich reaction. Depending upon the size of the alkyl chain in the nitroalkane substrates, enantioselectivities comparable to and higher diastereoselectivities (*syn/anti* ratio) than those obtained from homogeneous reactions were observed. In the case of the long chain substituted nitroalkane substrate (nitrohexane), the best selectivities (diastereoselectivity: *syn/anti* = 98/2, and enantioselectivity: 93% and 82% ee's for *syn*- and *anti*-isomers, respectively), were observed. Recycling of the catalyst in subsequent reactions was carried out and gradually diminishing levels of both diastereo and enantioselectivities were observed after each recycle. © 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The asymmetric addition of carbon nucleophiles to imines in the presence of a chiral catalyst is one of the most efficient methods for the generation of chiral amines.¹ The asymmetric nitro-Mannich reaction is one such reaction producing chiral 2-nitroamines from the reaction of nitroalkanes with aldehydes.^{2,3} Recently a novel approach to the catalytic diastereo and enantioselective nitro-Mannich reaction of *N*-protected α -imino esters with nitro compounds using catalysts based upon the bis(oxazoline) (BOX) ligand has been reported.⁴ This new catalytic asymmetric nitro-Mannich reaction leads to a simple procedure for the formation of optically active *N*-protected β -nitro- α -amino esters, which can be converted to 2,3-diamino acid derivatives. One significant drawback of this reaction is that it usually requires a large amount of catalyst (up to 20 mol%). Due to the high cost of the chiral BOX ligand, recycling of the catalyst through immobilization on a solid support can be extremely useful. However, reports are scarce for the heterogeneous asymmetric nitro-Mannich reaction.

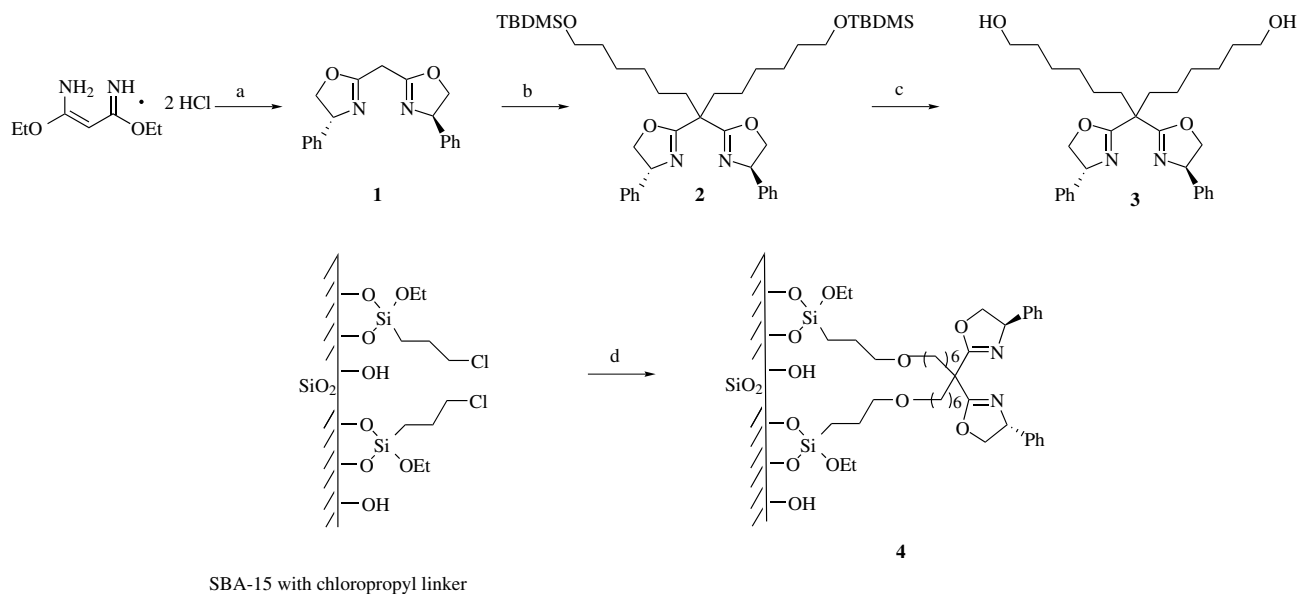
The immobilization of homogeneous catalysts onto a heterogeneous support material offers several advantages

such as catalyst recovery and simplified product purification.⁵ Recently mesoporous silicas with varying pore sizes have been fabricated from the sol-gel polymerization of a silica precursor in the presence of templates including self assemblies of surfactants and block copolymers.⁶ These mesoporous materials have been successfully applied as supports for a variety of catalytic asymmetric reactions.^{7–9} Mesoporous silicas have advantages over amorphous silicas due to high surface area and large pore sizes for favorable reaction kinetics.^{7d} Herein we report on the heterogeneous nitro-Mannich reaction using immobilized chiral BOX ligand onto mesoporous SBA-15 silica support.

2. Results and discussion

The preparation of the chiral catalyst for the asymmetric nitro-Mannich reaction and its immobilization onto SBA-15 are shown in [Scheme 1](#). Treatment of 2,2'-methylenebis[(4*R*)-phenyl-2-oxazoline] with 2.5 equiv of *n*-butyl lithium followed by 3 equiv of *tert*-butyl-(6-iodohexyloxy)dimethylsilane in dry THF provided dialkylated BOX **2** in 70% yield.¹⁰ After deprotection of the *tert*-butyldimethylsilyl group, anchoring of the modified ligand onto the mesoporous silica to **4** was accomplished by heating a mixture of **3**¹¹ and chloropropyl-grafted SBA-15 in dry xylene for 24 h followed by extensive washing with acetone and methylene chloride.¹²

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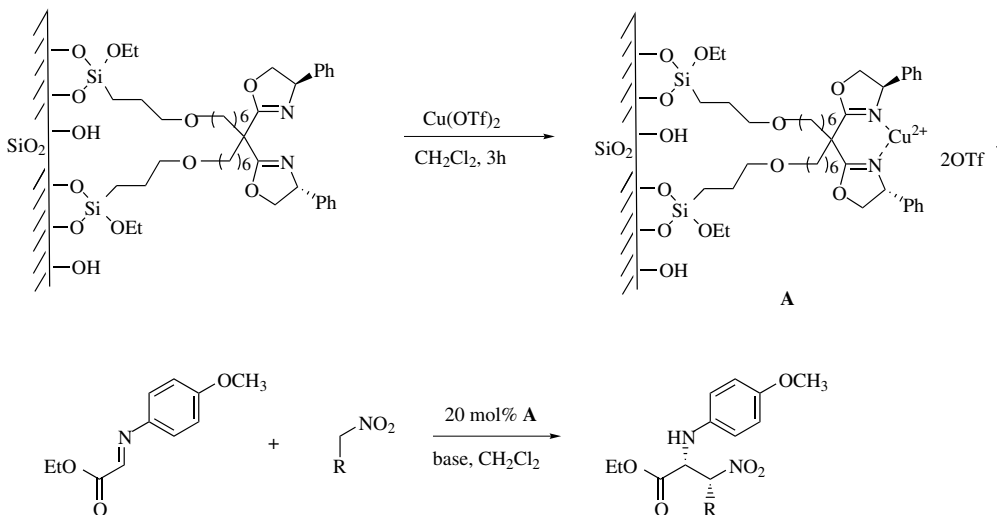
Scheme 1. Reagents and conditions: (a) (*R*)-Phenylglycinol, CH_2Cl_2 , rt, 36h, 86%; (b) *n*-BuLi, *tert*-butyl-(6-iodohexyloxy)dimethylsilane, THF, -78°C to rt, 3h, 70%; (c) tetrabutylammonium fluoride, THF, rt, 3h, 96%; (d) **3**, xylene, reflux, 24h.

The reaction conditions employed in our heterogeneous nitro-Mannich reaction are based upon those of the known asymmetric nitro-Mannich reactions using homogeneous catalyst system.^{4a} Generation of a Cu-BOX catalyst and a representative nitro-Mannich reaction is shown in Scheme 2. Heterogeneous catalyst system **A** was generated from the reaction of **4** with $\text{Cu}(\text{OTf})_2$ in dichloromethane for 3h. A typical protocol for this asymmetric reaction employed catalyst **A** (0.2equiv), triethylamine (0.2equiv), *N*-protected α -imino ester (1.0equiv), and a nitro compound (1.5equiv) in methylene chloride.

We carried out the nitro-Mannich reaction with representative nitro compounds with diverse results being observed depending on the substitution of nitro compounds.¹³ For comparison, homogeneous reactions were

carried out for each substrate using a catalyst generated from compound **1**. These results are summarized in Table 1.

Reaction with nitromethane in the presence of the heterogeneous BOX-Cu(OTf)₂ catalyst **A** gave the desired product of 51% ee in 31% yield, which is quite similar to the result obtained in homogeneous conditions where products of 51% ee were obtained in 39% yield (Table 1, entry 1). Apparently, dialkyl substitution at the methylene bridge of the BOX ligand during heterogenization did not influence the reaction enantioselectivity to a considerable degree. In the case of the reaction with nitroethane, 62% yield was obtained with the diastereomeric ratio (*syn/anti* = 60/40) being the same as the homogeneous case, along with enantiomeric excesses of the *syn* and *anti* products (90% and 64% ee, respec-



Scheme 2. Asymmetric nitro-Mannich reaction catalyzed by silica-BOX **A**.

Table 1. Catalytic enantioselective nitro-Mannich reaction at room temperature

| Entry | R | Homogeneous reaction ^a | | | Heterogeneous reaction ^b | | |
|-------|--------|-----------------------------------|------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|
| | | Yield (%) ^c | <i>syn/anti</i> ratio ^d | Ee (%) <i>syn/anti</i> ^d | Yield (%) ^c | <i>syn/anti</i> ratio ^d | Ee (%) <i>syn/anti</i> ^d |
| 1 | H | 39 | — | 51 | 31 | — | 51 |
| 2 | Me | 62 | 60/40 | 91/65 | 50 | 60/40 | 90/64 |
| 3 | Et | 80 | 90/10 | 94/66 | 52 | 98/2 | 94/66 |
| 4 | Pentyl | 53 | 92/8 | 94/82 | 54 | 98/2 | 93/82 |

^a The reaction was run at rt for one day with ligand **2**.^b The reaction was run at rt for 3 days.^c Yields of isolated products.^d Determined by HPLC with Chiralcel OD[®], see Ref. 4a.**Table 2.** Results of recycling experiments in catalytic enantioselective nitro-Mannich reactions

| Entry | R | Results of recycling experiments ^a , (% yield, ^b <i>syn/anti</i> ratio, ^c % ee <i>syn/anti</i> ^c) | | | | |
|-------|--------|--|------------------|------------------|---------------------|------------------|
| | | First | Second | Third | Fourth ^d | Fifth |
| 1 | H | 31, —, 51 | 33, —, 17 | 30, —, 6 | 32, —, nd | 30, —, nd |
| 2 | Me | 50, 60/40, 90/64 | 45, 70/30, 50/35 | 47, 72/28, 21/24 | 52, 70/30, 22/20 | 50, 68/32, 10/6 |
| 3 | Et | 52, 98/2, 94/66 | 50, 68/32, 70/66 | 51, 65/35, 30/37 | 48, 89/11, 38/6 | 46, 56/44, 13/3 |
| 4 | Pentyl | 54, 98/2, 93/82 | 50, 79/21, 52/31 | 52, 59/41, 41/40 | 56, 92/8, 44/20 | 52, 72/28, 10/10 |
| 5 | Et | Trace, —/—, —/— ^e | — | — | — | — |

^a The reaction was run at rt for 3 days.^b Yields of isolated products.^c Determined by HPLC with Chiralcel OD[®], See Ref. 4a.^d At every fourth experiment, 1 equiv of Cu(OTf)₂ was added.^e Reaction was carried out in presence of SBA-15 without the ligand under otherwise the same conditions.

tively), being almost the same as those obtained for the homogeneous case (91% ee for *syn* and 65% ee for *anti*, entry 2). In reactions involving longer-chain containing nitroalkanes, noticeable improvement in the *syn/anti* ratios were observed under heterogeneous reaction conditions when compared to their homogeneous counterparts (98/2 and 98/2 vs 90/10 and 92/8 for reactions of nitropropane and nitrohexane, respectively, entries 3 and 4). This enhanced diastereoselectivity with longer chain substrates may be due to the mesoporous environment of the catalyst. Almost similar enantioselectivities were obtained for reactions employing both nitroalkanes.

With the heterogeneous catalyst system in hand, we then turned our attention to the recycling of the catalyst for the reactions examined in Table 1 with the results shown in Table 2. When the heterogeneous catalyst was recycled five times for the reaction employing nitromethane, a comparable level of yield was maintained. However, enantioselectivity dropped significantly upon each recycle with only 6% ee being observed in the third recycling experiment (entry 1). In the case of nitroethane, slightly enhanced diastereoselectivities were observed upon recycling of the catalyst. However, the enantioselectivity of the reaction for both *syn* and *anti* diastereomers decreased upon each recycle (entry 2). In the case of nitropropane and nitrohexane, rapid decreases in both diastereo and enantioselectivities were observed after each recycling experiment (entries 3 and 4). Since we envisioned that the reduced stereoselectivities of the recycling experiments might be due to leaching out of the copper metal from the ligand–metal complex, a fresh dose of Cu(OTf)₂ was added after the third recycling

experiment in each reaction. The reaction diastereoselectivities in the fourth recycle rebounded noticeably in both cases (entries 3 and 4). However, the enantioselectivities exhibited a marginal increase in all cases. Only a trace amount of the product was obtained after 3 days when Cu(OTf)₂ and base were used without the box ligand in the presence or absence of mesoporous silica.^{7c}

3. Conclusion

In summary, a modified BOX ligand has been immobilized on SBA-15 while asymmetric nitro-Mannich reactions employing this heterogeneous catalyst system were examined. Comparable enantioselectivities and even higher diastereoselectivities than those from the homogeneous reaction were observed. The catalyst was easily recovered and reused five times without significant loss of reactivity. However, gradually reduced levels of diastereo and enantioselectivities upon each recycling experiment were observed.

Acknowledgements

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10. Compound **2**: $[\alpha]_{\text{D}}^{23} = +63.5$ (c 1.0, C₂H₅OH), ¹H NMR (300 MHz, CDCl₃): δ 0.00 (s, 12H), 0.85 (s, 18H), 1.21–1.24 (m, 16H), 1.46 (m, 4H), 2.06 (m, 4H), 3.55 (t, *J* = 6.6 Hz, 2H), 4.07 (q, *J* = 3.9 Hz, 2H), 4.07 (dd, *J* = 7.17 and 4.28 Hz), 4.61 (dd, *J* = 8.02 and 1.98 Hz, 2H), 5.20 (dd, *J* = 8.02 and 1.98 Hz, 2H), 7.24 (m, 10H). ¹³C NMR (75 MHz, CDCl₃): δ -4.86 (4C), 14.52, 18.79, 23.05, 23.05, 24.43, 24.43, 26.11, 26.11, 26.39 (6C), 30.03, 31.98, 32.96, 33.21, 63.67, 63.67, 69.99, 69.99, 74.42, 74.42, 126.27, 126.27, 127.14, 127.14, 127.14, 127.14, 127.93, 127.93, 129.06, 129.06, 142.77, 142.77, 169.50, 169.50.
11. Compound **3**: $[\alpha]_{\text{D}}^{23} = +87.5$ (c 1.0, C₂H₅OH), ¹H NMR (300 MHz, CDCl₃): δ 1.36 (m, 8H), 1.53 (m, 4H), 1.72 (m, 2H), 2.08 (m, 6H), 3.42 (s, 2H), 3.57 (t, *J* = 6.50 Hz, 4H), 4.13 (t, *J* = 8.18 Hz, 2H), 4.66 (dd, *J* = 8.45 and 1.66 Hz, 2H), 5.25 (dd, *J* = 7.96 and 2.1 Hz, 2H), 7.32 (m, 10H). ¹³C NMR (75 MHz, CDCl₃) 20.59, 20.59, 24.17, 24.17, 25.66, 25.82, 29.81, 29.81, 32.76, 32.98, 46.52, 63.08, 63.08, 69.88, 69.88, 75.47, 75.47, 127.14 (4C), 128.00 (2C), 129.09 (4C), 142.63 (2C), 169.54 (2C).
12. The ligand loading in compound **4** was determined to be 0.51 mmol/g by elemental analysis (average values C: 19.981%, H: 2.501%, N: 1.437%).
13. A representative procedure for the nitro-Mannich reaction and repetition experiments: In a flame-dried Schlenk tube, Cu(OTf)₂ (18.7 mg, 0.052 mmol) and BOX ligand-grafted silica **4** (92 mg, 0.047 mmol) were dried under reduced pressure for 30 min. To the mixture was added dry CH₂Cl₂ (4 mL) and the solution stirred at rt for 3 h to form the ligand–metal complex. The mixture was filtered and washed with CH₂Cl₂ (4 mL × 2) to remove any free Cu(OTf)₂. To the mixture was added CH₂Cl₂ (4 mL), ethyl (4-methoxyphenylimino)acetate (48.6 mg, 0.235 mmol), nitropropane (32 μL, 0.35 mmol), and triethylamine (6.5 μL, 0.047 mmol) via syringe. The resultant solution was stirred at rt for 3 days. The solution was then filtered and washed with CH₂Cl₂ (4 mL × 2). Solvent from the filtrate was removed under reduced pressure and the residue purified on silica gel using CH₂Cl₂/*n*-pentane (1:1) as eluent to give the desired product. Recovered catalyst was washed with dry CH₂Cl₂ (4 mL × 2) and used for recycling experiments after drying under reduced pressure. After the third experiment of recycling, additional Cu(OTf)₂ (18.7 mg, 0.052 mmol) was added and the washing repeated. The diastereo and enantioselectivities were determined through HPLC analysis using Chiralcel OD[®] (hexane/*i*-PrOH = 97:3, 0.5 mL).