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Silica-Supported Boric Acid with Ionic Liquid: A Novel Recyclable Catalytic System for One-Pot Three-Component Mannich Reaction

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A rapid and efficient silica-supported boric acid/ionic liquid ([bmim][PF_6]), catalyzed, one-pot three-component Mannich reaction has been carried out to synthesize *β*-amino carbonyl compounds at room temperature. The reaction afforded desired products in excellent yields with moderate to good diastereoselectivity. The method provides a novel modification of three-component Mannich reaction in terms of mild reaction conditions, clean reaction profiles, low amount of catalyst, recyclability of catalyst and a simple workup procedure. The present report first time describes the preparation of H_3BO_3–SiO_2 catalyst and its use with [bmim][PF_6], to synthesize Mannich products. The catalyst can be reused at least seven times.

Key words *β*-amino carbonyl compound; boric acid; ionic liquid; Mannich reaction; solid-supported catalyst

Developing new synthetic methods for the construction of nitrogenous molecules[1] has defined the frontiers of organic synthesis since its very beginning. The Mannich reaction is a very useful platform for the development of nitrogen containing molecules.[2]

Originally, this reaction produces *β*-amino carbonyl compounds from three-components, amine, aldehyde and ketone. These *β*-amino carbonyl compounds are used for the synthesis of amino alcohols, peptides, lactams and as precursors to synthesize amino acids. The vital importance of the Mannich products as useful precursors of pharmaceutical and natural products[3] always boosted researchers to find out better process for their synthesis. The limitations[4] associated with the classical Mannich type reactions such as drastic reaction conditions, long reaction time with low yields and formation of undesired side products, have induced numerous modern versions[5] of the reaction. These improved methodologies are mainly based on two-component reactions where the imine as electrophile was pre-formed and reacted with stable nucleophiles such as enolates, enol ethers and enamines.[6—13] However, the preferable route is the use of a one-pot three-component setup rather than a two step that allows a wide range of structure variations.[14] Numbers of catalysts have been employed for classical Mannich reaction of aldehydes, ketones and amines mainly involving acids like proline,[15—17] *p*-dodecyl benzenesulphonic acid (DBSA)[18] and some Lewis acids.[19—21] Other catalysts for the reaction include $Yb(OiPr)_3$,[22] $InCl_3$,[23,24] lanthanide triflate[25] in solvents like dichloromethane and acetonitrile, siloxy serine organocatalysts,[26] phosphorodiamidic acid,[27] bromodimethylsulfonium bromide[28] and boric acid/glycerol,[29] 4-hydroxypyrrolidine,[30] Trypsin,[31] Yb/K heterobimetallic catalyst.[32] Some solid-supported catalysts have also been used such as $AlCl_3$–SiO_2,[33] $HClO_4$–SiO_2[34] and H_2SO_4–SiO_2.[35] However, they often suffer from the drawbacks of long reaction times, harsh reaction conditions, toxicity and difficulty in product separation, which limits their use in the synthesis of complex molecules. Some of the methods mentioned above are not capable of giving Mannich products from substrates having strong electron-withdrawing group *e.g.* –NO_2 on aldehyde or amine. Also, the synthesis of Mannich products from the reaction of 4-methoxybenzaldehyde, 4-nitroaniline and cyclohexanone is very difficult. Hence, the development of a simple, efficient, cost effective and nature friendly synthetic protocol applicable to a variety of substrates always remains a challenging task for the synthetic chemists.

Recently, ionic liquids (ILs), which combine the advantages of both traditional molecular solvents and melt salts, have been considered as promising new reaction media and have found wide use in catalytic and non-catalytic reactions. Among the different Mannich type reactions reported ruthenium complexes and ytterbium(III) triflate have been used as catalysts in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]).[36,37] Mannich reaction using Bronsted acid ionic liquids as catalysts and solvent have also been reported.[38,39] However, low yield, use of toxic metal complexes and applicability to limited variety of substrates, limit the scope of these methods.

In this context, a new rapid and environment friendly method has been developed for diastereoselective synthesis of Mannich products using recyclable heterogeneous catalytic system, which is applicable to a large variety of substrates and overcomes the limitations of already reported protocols. Silica-supported boric acid (H_3BO_3–SiO_2) has been synthesized for the first time and its use with ionic liquid, [bmim][PF_6] in catalytic amount for Mannich reaction has been studied. The catalytic system, H_3BO_3–SiO_2+[bmim][PF_6] (Silica-BA-IL) can be recycled for at least seven times without any considerable effect on the yield. The catalytic combination showed moderate to good diastereoselectivity.

Experimental

General Methods Boric acid was purchased from Ranbaxy Chemicals Ltd., India, Silica gel (60—120 mesh) used for catalyst preparation and silica gel (230—400 mesh) for column chromatography was purchased from Sisco Research Laboratories Pvt. Ltd., India, TLC was performed on silica gel 60 F_{254} plates and all other chemicals were purchased from Spectrochem, Merck, Germany, and Sigma-Aldrich, U.S.A. and were used without further purification. The IR spectrum of silica-supported boric acid was recorded on Shimadzu FTIR 8400 S spectrometer. NMR spectra were recorded on a Bruker Avance-300 spectrometer. Mass spectra were recorded on QTOF-Micro of Waters Micromass. Melting points were determined on a Barnstead Electrothermal 9100. X-Ray diffraction (XRD) studies were carried out

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using Panalytical, D/Max-2500 X-Ray Diffractometer equipped with Cu$K\alpha$ radiation (λ=1.5418) employing a scanning rate of 0.02° s^{-1}. Si was used as standard to determine the instrumental broadening and the (111) reflection was analysed.

Preparation of Silica-Supported Boric Acid Boric acid (3.0 g) with 60 ml water was taken in a 250 ml round bottom flask and heated to 60—80 °C. To this, silica gel (60—120 mesh, 27.0 g) was added gradually with constant stirring and refluxed for 5 h. Water was evaporated under vacuum and the residue was stirred at 100 °C for 6—7 h under vacuum to give free flowing white powder. IR (KBr) cm^{-1}: 3400, 3221, 2260, 1345, 1200, 1100, 960, 875, 800 and 720.

Typical Procedure for the Synthesis of *β*-Amino Carbonyl Compounds A mixture of aromatic aldehyde (1.0 mmol), aromatic amine (1.0 mmol), cyclohexanone (3.0 mmol) and H_3BO_3–SiO_2 (7.8 mg, 0.0125 mmol) was stirred in [bmim][PF_6] (0.2 ml) at room temperature until the completion of the reaction (as monitored by TLC). To the crude product, ethyl acetate (5 ml) was added and washed repeatedly with water (3×5 ml). The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated under vacuum. The oily products were subjected to column chromatography over silica gel (230—400) with ethyl acetate : hexane (1 : 9) as eluent. The solid products were crystallized directly from ethanol. The aqueous layers were combined and dried under vacuum to afford catalyst H_3BO_3–SiO_2 (Silica-BA-IL) which was reused without any further purification. The catalyst can be used at least seven times without any considerable effect on yield.

Recyclability of the Catalyst H_3BO_3–SiO_2 catalyst together with ionic liquid was recovered by addition of ethyl acetate (5 ml) to products and washing with four equal volumes of water (5 ml each). The evaporation of water under vacuum afforded H_3BO_3–SiO_2 with ionic liquid which was reused without any further purification. The catalyst can be used at least seven times without any considerable effect on yield.

Spectral Data of Products. 2-[(Phenyl)(phenylamino)methyl]cyclohexanone (4a) Eluent: ethyl acetate : hexane (1 : 9). Yield 95%. White solid, mp 141—142 °C. *Syn* : *anti* (9 : 91); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.72—1.81 (m, 2H), 1.89—1.95 (m, 4H), 2.33—2.50 (m, 2H), 2.78—2.80 (m, 1H), 4.68 (d, 0.91H, J=6.9 Hz), 4.86 (d, 0.09H, J=3.7 Hz), 6.58 (d, 2H, J=7.7 Hz), 6.67 (t, 1H, J=7.1 Hz), 7.11 (t, 2H, J=7.2 Hz), 7.23—7.27 (m, 1H), 7.34 (t, 2H, J=7.1 Hz), 7.41—7.43 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 24.0, 28.2, 31.6, 42.1, 57.7, 58.4, 114.0, 117.9, 127.5, 127.9, 128.7, 129.4, 142.1, 147.6, 213.1. HR-MS (ESI) Calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.3841, Found 280.3822.

2-[(4-Methoxyphenyl)(phenylamino)methyl]cyclohexanone (4b) Eluent: ethyl acetate : hexane (1 : 9). Yield 94%. White solid, mp 134—136 °C. 100% *anti*; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.68—1.91 (m, 6H), 2.35—2.44 (m, 2H), 2.72—2.74 (m, 1H), 3.78 (s, 3H), 4.63 (d, 1H, J=7.1 Hz), 6.56 (d, 2H, J=7.6 Hz), 6.65—6.67 (m, 1H), 6.85—6.88 (m, 2H), 7.05—7.11 (m, 2H), 7.29—7.33 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 27.4, 28.2, 31.5, 42.3, 56.0, 57.8, 58.0, 114.1, 114.3, 117.8, 128.7, 129.4, 134.0, 147.9, 159.1, 213.3. HR-MS (ESI) Calcd for $C_{20}H_{24}NO_2$ $[M+H]^+$ 310.4101, Found 310.4102.

2-[(3-Bromophenylamino)(4-methoxyphenyl)methyl]cyclohexanone (4c) Eluent: ethyl acetate : hexane (1 : 9). Yield 96%. Yellow oil. *Syn* : *anti* (37 : 63); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.57—1.68 (m, 2H), 1.79—1.92 (m, 4H), 2.32—2.39 (m, 2H), 2.73 (m, 1H), 3.76 (s, 3H), 4.56 (d, 0.63H, J=6.8 Hz), 4.71 (d, 0.37H, J=3.9 Hz), 4.86 (br s, 1H), 6.46 (d, 1H, J=8.0 Hz), 6.72—6.75 (m, 2H), 6.84—6.87 (m, 2H), 6.90—6.92 (m, 1H), 7.25—7.29 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 24.1, 28.3, 31.8, 42.2, 55.5, 56.7, 57.7, 112.6, 114.3, 116.7, 120.5, 123.4, 128.6, 130.7, 133.4, 149.3, 159.0, 213.1. HR-MS (ESI) Calcd for $C_{20}H_{23}BrNO_2$ $[M+H]^+$ 389.3062, Found 389.3068.

2-[(4-Chlorophenyl)(phenylamino)methyl]cyclohexanone (4d) Eluent: ethyl acetate : hexane (1 : 9). Yield 98%. Yellow solid, mp 133—135 °C. *Syn* : *anti* (26 : 74); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.71—1.81 (m, 3H), 1.92—1.97 (m, 3H), 2.34—2.41 (m, 2H), 2.77—2.82 (m, 1H), 4.63 (d, 0.74H, J=6.2 Hz), 4.77 (d, 0.26H, J=4.1 Hz), 6.53 (m, 2H), 6.64—6.69 (m, 1H), 7.09 (t, 2H, J=7.1 Hz), 7.27—7.36 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 24.2, 27.4, 31.8, 42.4, 57.7, 57.8, 114.0, 118.3, 129.0, 129.4, 131.9, 140.7, 147.4, 212.7. HR-MS (ESI) Calcd for $C_{19}H_{21}NOCl$ $[M+H]^+$ 314.8289, Found 314.8299.

2-[(4-Methylphenylamino)(phenyl)methyl]cyclohexanone (4e) Eluent: ethyl acetate : hexane (1 : 9). Yield 97%. Brownish solid, mp 116—117 °C. *Syn* : *anti* (32 : 68); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.50—1.79 (m, 6H), 2.05 (s, 3H), 2.21—2.27 (m, 2H), 2.72—2.74 (m, 1H), 4.32 (br s, 1H), 4.50 (d, 0.68H, J=7.1 Hz), 4.68 (d, 0.32H, J=2.25 Hz), 6.34—6.38 (m, 2H), 6.75 (d, 2H, J=6.3 Hz), 7.07—7.10 (m, 1H), 7.14—7.19 (m, 2H), 7.23—7.28 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 20.3, 23.3, 27.8, 31.1, 41.7, 57.5, 58.2, 113.8, 127.1, 127.3, 127.5, 128.4, 129.5, 141.9, 145.0, 212.7. HR-MS (ESI) Calcd for $C_{20}H_{24}NO$ $[M+H]^+$ 294.4107, Found 294.4069.

2-[(4-Nitrophenyl)(phenylamino)methyl]cyclohexanone (4f) Eluent: ethyl acetate : hexane (1 : 9). Yield 98%. Yellow oil. *Syn* : *anti* (59 : 41); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.52—1.97 (m, 6H), 2.24—2.39 (m, 2H), 2.76—2.79 (m, 1H), 4.53 (br s, 1H), 4.63 (d, 0.41H, J=5.1 Hz), 4.77 (d, 0.59H, J=4.0 Hz), 6.42 (d, 2H, J=7.9 Hz), 6.59—6.63 (m, 1H), 6.98—7.03 (m, 2H), 7.46—7.51 (m, 2H), 8.06—8.08 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *syn* isomer, δ: 25.1, 27.2, 29.3, 42.6, 56.4, 57.4, 114.2, 118.6, 123.8, 128.8, 129.4, 146.8, 147.3, 149.7, 210.7. HR-MS (ESI) Calcd for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.3817, Found 325.3820.

2-[(4-Bromophenyl)(phenylamino)methyl]cyclohexanone (4g) Eluent: ethyl acetate : hexane (1 : 9). Yield 96%. Yellow oil. *Syn* : *anti* (39 : 61); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.51—1.85 (m, 6H), 2.24—2.31 (m, 2H), 2.66—2.71 (m, 1H), 4.50 (d, 0.61H, J=6.2 Hz), 4.64 (d, 0.39H, J=3.7 Hz), 6.41—6.44 (m, 2H), 6.54—6.59 (m, 1H), 6.99 (t, 2H, J=6.8 Hz), 7.18—7.19 (m, 2H), 7.32—7.35 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 24.6, 28.4, 32.1, 42.6, 57.8, 58.1, 114.2, 118.4, 121.4, 129.6, 129.7, 132.1, 141.5, 147.7, 212.9. HR-MS (ESI) Calcd for $C_{19}H_{21}BrNO$ $[M+H]^+$ 359.2802, Found 359.2873.

2-[(4-Methoxyphenyl)(4-nitrophenylamino)methyl]cyclohexanone (4h) Eluent: ethyl acetate : hexane (1 : 9). Yield 95%. Yellow solid, mp 63—65 °C. *Syn* : *anti* (59 : 41); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.57—1.67 (m, 4H), 1.99—2.07 (m, 2H), 2.24—2.37 (m, 2H), 2.84 (s, 1H), 3.74 (s, 3H), 4.66 (d, 0.41H, J=5.6 Hz), 4.82 (s, 0.59H), 5.80 (br s, 1H), 6.50 (d, 2H, J=8.5 Hz), 6.82 (d, 2H, J=7.5 Hz), 7.24 (d, 2H, J=7.4 Hz), 7.95 (d, 2H, J=8.4 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), *syn* isomer, δ: 25.0, 27.0, 29.2, 42.6, 55.5, 56.1, 56.8, 112.5, 114.5, 126.5, 128.9, 132.1, 138.2, 153.3, 159.3, 211.7. HR-MS (ESI) Calcd for $C_{20}H_{23}N_2O_4$ $[M+H]^+$ 355.4077, Found 355.4054.

2-[(4-Methylphenylamino)(4-nitrophenyl)methyl]cyclohexanone (4i) Eluent: ethyl acetate : hexane (1 : 9). Yield 98%. Yellow solid, mp 120—122 °C. *Syn* : *anti* (34 : 66); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.63—1.82 (m, 3H), 1.95—2.06 (m, 3H), 2.19 (s, 3H), 2.34—2.41 (m, 2H), 2.86 (s, 1H), 4.74 (d, 0.66H, J=5.0 Hz), 4.87 (d, 0.34H, J=3.1 Hz), 6.46 (d, 2H, J=7.0 Hz), 6.91 (d, 2H, J=7.5 Hz), 7.56—7.61 (m, 2H), 8.14 (d, 2H, J=8.4 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 20.7, 24.8, 28.1, 32.2, 42.7, 57.4, 58.3, 114.1, 124.0, 127.9, 128.7, 130.0, 144.8, 147.4, 150.5, 212.1. HR-MS (ESI) Calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.4083, Found 339.4082.

2-[(3-Chlorophenylamino)(4-methylphenyl)methyl]cyclohexanone (4j) Eluent: ethyl acetate : hexane (1 : 9). Yield 97%. White solid, mp 120—122 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.62—1.80 (m, 3H), 1.90—2.07 (m, 3H), 2.36 (s, 3H), 2.44—2.48 (m, 2H), 2.80—2.82 (m, 1H), 4.61 (d, 1H, J=6.7 Hz), 4.80 (br s, 1H, overlapped with proton signal of *syn* isomer), 6.48 (d, 1H, J=8.0 Hz), 6.59—6.68 (m, 2H), 6.98—7.04 (m, 1H), 7.15—7.17 (m, 2H), 7.26—7.31 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), major isomer, δ: 21.5, 25.1, 27.3, 29.1, 42.7, 56.8, 57.3, 112.5, 114.1, 117.7, 127.8, 129.6, 130.4, 135.1, 137.1, 138.3, 149.2, 211.7. HR-MS (ESI) Calcd for $C_{20}H_{23}ClNO$ $[M+H]^+$ 328.8555, Found 328.8430.

5-[(4-Bromophenyl)(phenylamino)]pantan-3-one (6a) Eluent: ethyl acetate : hexane (1 : 9). Yield 88%. Yellow oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.99—1.04 (m, 3H), 2.36—2.40 (m, 2H), 2.90 (d, 2H, J=6.2 Hz), 4.42 (br s, 1H), 4.83 (t, 1H, J=6.2 Hz), 6.49—6.56 (m, 2H), 6.68—6.73 (m, 1H), 7.08—7.15 (m, 2H), 7.21—7.28 (m, 2H), 7.45—7.47 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 7.9, 37.4, 50.2, 54.5, 114.3, 118.6, 121.5, 128.6, 129.2, 131.9, 142.3, 147.1, 209.9. HR-MS (ESI) Calcd for $C_{17}H_{19}BrNO$ $[M+H]^+$ 333.2429, Found 333.2339.

3-Methyl-4-[(4-bromophenyl)(phenylamino)]butan-2-one (7a) Eluent: ethyl acetate : hexane (1 : 9). Yield 88%. Yellow oil. *Syn* : *anti* (37 : 63); ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 1.17 (d, 3H, J=6.9 Hz), 2.03 (s, 3H), 4.48 (d, 0.63H, J=6.9 Hz), 4.65 (br s, 1H), 4.73 (d, 0.37H, J=5.0 Hz), 6.49—6.56 (m, 2H), 6.68—6.73 (m, 1H), 7.08—7.15 (m, 2H), 7.21—7.28 (m, 2H), 7.45—7.47 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 15.7, 29.9, 53.7, 60.5, 114.3, 118.6, 121.5, 128.6, 129.2, 131.9, 142,3, 147.1, 212.5. HR-MS (ESI) Calcd for $C_{17}H_{19}BrNO$ $[M+H]^+$ 333.2429, Found 333.2339.

5-[(Phenyl)(phenylamino)]pantan-3-one (6b) Eluent: ethyl acetate : hexane (1 : 9). Yield 81%. Yellow solid, mp 87—88 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.04 (t, 3H, J=6.9 Hz), 2.38—2.39 (m, 2H), 2.95 (d, 2H), 4.40 (br s, 1H), 4.92 (t, 1H, J=5.8 Hz), 6.60—6.64 (m, 2H), 6.67—6.72 (m, 1H), 7.14—7.16 (m, 2H), 7.29—7.31 (m, 1H), 7.38—7.41 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 7.4, 36.9, 49.9, 54.5, 113.6, 117.5, 126.3, 127.3, 128.8, 129.1, 141.4, 146.9, 212.4. HR-MS (ESI) Calcd for $C_{17}H_{20}NO$ $[M+H]^+$ 254.3468, Found 254.3446.

3-Methyl-4-[(phenyl)(phenylamino)]butan-2-one (7b) Eluent: ethyl acetate : hexane (1 : 9). Yield 81%. Yellow solid, mp 87—88 °C. *Syn* : *anti* (46 : 54); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.15—1.20 (m, 3H), 2.05 (s, 3H), 3.00—3.07 (m, 1H), 4.57 (d, 0.55H, *J*=6.9 Hz), 4.74 (br s, 1H), 4.83 (d, 0.45H, *J*=3.8 Hz), 6.60—6.64 (m, 2H), 6.67—6.72 (m, 1H), 7.14—7.16 (m, 2H), 7.29—7.31 (m, 1H), 7.38—7.41 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 15.1, 29.3, 53.5, 60.5, 113.5, 117.7, 126.9, 127.3, 128.8, 129.1, 142.7, 146.9, 209.8. HR-MS (ESI) Calcd for $C_{17}H_{20}NO$ $[M+H]^+$ 254.3468, Found 254.3446.

5-[(4-Methoxyphenyl)(phenylamino)]pantan-3-one (6c) Eluent: ethyl acetate : hexane (1 : 9). Yield 84%. Yellow solid, mp 82—83 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.03 (t, 3H, *J*=7.0 Hz), 2.37 (q, 2H, *J*=7.0, 6.4 Hz), 2.92 (d, 2H, *J*=5.1 Hz), 3.79 (s, 3H), 4.67 (br s, 1H), 4.89 (t, 1H, J=5.9 Hz), 6.62—6.65 (m, 2H), 6.70—6.77 (m, 1H), 6.91 (d, 2H, *J*=7.6 Hz), 7.14—7.18 (m, 2H), 7.24—7.35 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 7.4, 36.8, 49.9, 53.8, 55.1, 113.7, 114.0, 117.6, 127.3, 129.0, 134.6, 146.9, 158.7, 209.8. HR-MS (ESI) Calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.3728, Found 284.3721.

3-Methyl-4-[(4-methoxyphenyl)(phenylamino)]butan-2-one (7c) Eluent: ethyl acetate : hexane (1 : 9). Yield 84%. Yellow solid, mp 82—83 °C. *Syn* : *anti* (28 : 72); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.17 (d, 3H, *J*=6.6 Hz), 2.07 (s, 3H), 2.98—3.00 (m, 1H), 3.79 (s, 3H), 4.53 (d, 0.72H, *J*=7.2 Hz), 4.67 (br s, 1H), 6.62—6.65 (m, 2H), 6.70—6.77 (m, 1H), 6.91 (d, 2H, *J*=7.6 Hz), 7.14—7.18 (m, 2H), 7.24—7.35 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), *anti* isomer, δ: 15.0, 29.0, 53.5, 59.8, 113.7, 114.0, 117.6, 127.3, 129.0, 134.6, 146.9, 158.7, 212.4. HR-MS (ESI) Calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.3728, Found 284.3721.

5-[(3-Bromophenylamino)(4-methoxyphenyl)]pantan-3-one (6d) Eluent: ethyl acetate : hexane (1 : 9). Yield 82%. White solid, mp 81—82 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.99 (t, 3H, *J*=7.2 Hz), 2.30—2.36 (m, 2H), 2.88 (d, 2H, *J*=6.0 Hz), 3.79 (s, 3H), 4.70 (br s, 1H), 4.77 (t, 1H, *J*=6.0 Hz), 6.47 (d, 1H, *J*=7.9 Hz), 6.71—6.72 (m, 1H), 6.78 (d, 1H, *J*=7.9 Hz), 6.85—6.88 (m, 2H), 6.91—6.96 (m, 1H), 7.24—7.27 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 7.5, 37.1, 49.7, 53.9, 55.3, 112.1, 114.3, 116.5, 120.5, 123.1, 127.4, 130.7, 134.0, 148.3, 159.0, 209.9. HR-MS (ESI) Calcd for $C_{18}H_{21}BrNO_2$ $[M+H]^+$ 363.2689, Found 363.2795.

1,3-Diphenyl-3-phenylaminopropan-1-one (8a) Eluent: ethyl acetate : hexane (1 : 9). Yield 74%. White solid, mp 162—164 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.39—3.56 (m, 2H), 4.57 (br s, 1H), 5.01—5.03 (m, 1H), 6.58 (d, 2H, *J*=7.5 Hz), 6.65—6.70 (m, 1H), 7.10 (t, 2H, *J*=7.0 Hz), 7.25—7.27 (m, 1H), 7.34 (t, 2H, *J*=6.9 Hz), 7.45—7.47 (m, 4H), 7.55—7.59 (m, 1H), 7.92 (d, 2H, *J*=7.3 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 46.4, 55.0, 114.0, 117.9, 126.5, 127.5, 128.3, 128.8, 128.9, 129.2, 133.5, 136.9, 143.1, 147.1, 198.4. HR-MS (ESI) Calcd for $C_{21}H_{20}NO$ $[M+H]^+$ 302.3896, Found 302.3883.

3-(4-Nitrophenyl)-1-phenyl-3-phenylaminopropan-1-one (8b) Eluent: ethyl acetate : hexane (1 : 9). Yield 61%. Yellow solid, mp 104—106 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.41 (d, 2H, *J*=5.9 Hz), 4.59 (br s, 1H), 5.02 (t, 1H, *J*=5.8 Hz), 6.43 (d, 2H, *J*=7.7 Hz), 6.60 (t, 1H, *J*=7.2 Hz), 7.01 (t, 2H, *J*=7.3 Hz), 7.33—7.38 (m, 2H), 7.45—7.54 (m, 3H), 7.81 (d, 2H, *J*=7.6 Hz), 8.05 (d, 2H, *J*=8.2 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 45.4, 53.9, 113.5, 118.1, 123.7, 127.2, 127.8, 128.5, 128.9, 133.4, 136.1, 146.0, 146.9, 150.5, 196.9. HR-MS (ESI) Calcd for $C_{21}H_{19}N_2O_3$ $[M+H]^+$ 347.3872, Found 347.3825.

3-(4-Bromophenyl)-1-phenyl-3-phenylaminopropan-1-one (8c) Eluent: ethyl acetate : hexane (1 : 9). Yield 58%. White solid, mp 138—140 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.45—3.47 (m, 2H), 4.59 (br s, 1H), 5.00 (t, 1H, *J*=5.8 Hz), 6.57 (d, 2H, *J*=7.7 Hz), 6.71 (t, 1H, *J*=7.0 Hz), 7.13 (t, 2H, *J*=7.3 Hz), 7.34—7.36 (m, 2H), 7.45—7.49 (m, 4H), 7.57—7.61 (m, 1H), 7.92 (d, 2H, *J*=7.5 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 46.1, 54.3, 114.0, 118.2, 121.1, 128.2, 128.3, 128.8, 129.3, 132.0, 133.6, 136.7, 142.2, 146.8, 197.9. HR-MS (ESI) Calcd for $C_{21}H_{19}BrNO$ $[M+H]^+$ 381.2857, Found 381.2856.

1,3-Diphenyl-3-(4-methylphenylamino)propan-1-one (8d) Eluent: ethyl acetate : hexane (1 : 9). Yield 76%. White solid, mp 164—166 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.20 (s, 3H), 3.43—3.50 (m, 2H), 4.43 (br s, 1H), 5.00 (t, 1H, *J*=6.0 Hz), 6.51 (d, 2H, *J*=7.4 Hz), 6.92 (d, 2H, *J*=7.6 Hz), 7.22—7.27 (m, 1H), 7.31—7.36 (m, 2H), 7.45—7.47 (m, 4H), 7.55—7.59 (m, 1H), 7.92 (d, 2H, *J*=7.6 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 20.5, 46.5, 55.2, 114.2, 126.5, 127.1, 127.4, 128.3, 128.8, 128.9, 129.7, 133.5, 136.9, 143.3, 144.8, 198.4. HR-MS (ESI) Calcd for $C_{22}H_{22}NO$ $[M+H]^+$ 316.4162, Found 316.4172.

Results and Discussion

Silica-supported heterogeneous catalysts have received considerable attention as inexpensive and recyclable catalysts for various organic transformations and in most of these catalysts strong toxic acids are employed. Thus, in order to overcome the above mentioned problems, we have first time prepared a non-toxic catalyst, silica-supported boric acid (H_3BO_3–SiO_2) and it was characterized by X-ray diffraction (XRD) and IR spectroscopy. The IR spectrum of prepared H_3BO_3–SiO_2 showed stretching and bending vibration bands for borosiloxane linkage (Si–O–B) at 875 and 720 cm^{-1}, respectively, and a band at 1345 cm^{-1} was observed for B–O stretching vibration of borosiloxane. The other bands were observed at 3400 (SiO–H_{str}), 3221 (BO–H_{str}), 2260 (B–$OH_{combination}$), 1200 (B–OH_{bend}), 1100 (Si–O_{str}), 960 (Si–OH_{str}) and 800 (Si–O–Si_{bend}) cm^{-1}. XRD pattern of H_3BO_3–SiO_2 (Fig. 1) showed only one broad peak at 2θ *ca.* 22° which indicates the amorphous nature of catalyst. The absence of reflection at 2θ *ca.* 28° for free boric acid[40,41] indicated that boron atoms are mainly engaged in the formation of borosiloxane bridges in the catalyst. The borosiloxane linkage in catalyst was further confirmed by comparison with reported XRD pattern.[40,41]

The catalytic efficiency of H_3BO_3–SiO_2 catalyst was evaluated by conducting a three-component model Mannich reaction of benzaldehyde, aniline and cyclohexanone under different catalytic conditions such as boric acid, silica-gel and H_3BO_3–SiO_2 and also under catalyst free conditions (Table 1). The progress of reaction was studied by thin layer chromatography. The model reaction without catalyst under solvent free condition afforded product in very low yield. When boric acid, silica gel and boric acid+silica gel were used as catalysts under solvent free condition, the yield was not increased even after a very long period of time (Table 1, entries 1—4). The reaction with H_3BO_3–SiO_2 in absence of solvent at room temperature, gave only 35% yield even after 12 h (Table 1, entry 5). Therefore, in order to find out the effect of temperature on yield, this reaction was carried out at elevated temperatures *i.e.* 50, 80 and 120 °C with conventional as well as microwave (MW) heating (Table 1, entries 6—11). At 50 °C, the yield was increased to 40% under conventional heating, while at 80 and 120 °C, the yield was reduced and other undesired byproducts were formed in all the six heating conditions. The aldol condensation product was observed as the major byproduct which was characterized by high resolution (HR)-MS and NMR analysis.

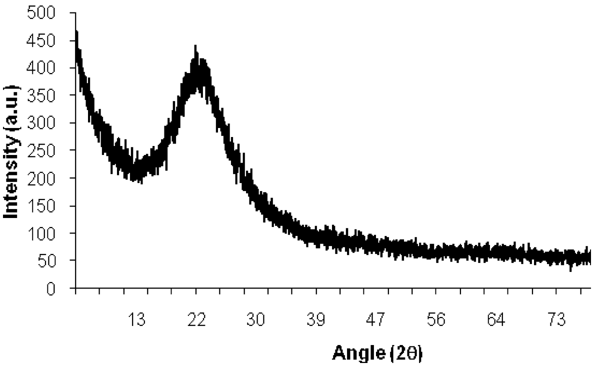
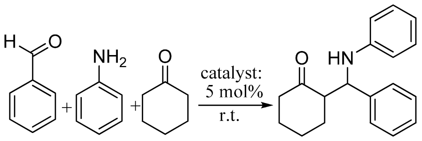


Fig. 1. XRD Spectrum of H_3BO_3–SiO_2

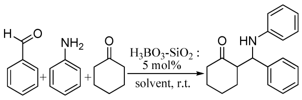
Table 1. Optimization of Reaction Conditions in Different Catalytic Systems[a)]



Entry	Catalyst	Time (h)	Yield (%)[b)]
1	Without catalyst	12	10
2	H_3BO_3	12	12
3	SiO_2	12	10
4	$H_3BO_3+SiO_2$	12	14
5	$H_3BO_3-SiO_2$	12	35
6	$H_3BO_3-SiO_2$[c)]	12	40
7	$H_3BO_3-SiO_2$[d)]	12	28
8	$H_3BO_3-SiO_2$[e)]	12	15
9	$H_3BO_3-SiO_2$[c,f)]	2	30
10	$H_3BO_3-SiO_2$[d,f)]	2	32
11	$H_3BO_3-SiO_2$[e,f)]	2	24
12	IL[g)]	12	38
13	H_3BO_3+IL	12	48
14	SiO_2+IL	12	39
15	$H_3BO_3+SiO_2+IL$	12	50
16	$H_3BO_3-SiO_2+IL$	0.5	94

a) Reaction was carried out with 1.0 mmol each of benzaldehyde and aniline, and 3.0 mmol of cyclohexanone. *b*) Yield of isolated product. *c*) Reaction was carried out at 50 °C. *d*) Reaction was carried out at 80 °C. *e*) Reaction was carried out at 120 °C. *f*) Reaction was carried out under MW irradiation. *g*) IL = ionic liquid.

Table 2. Optimization of Reaction Conditions in Various Solvents[a)]

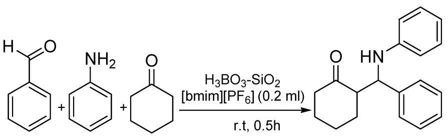


Entry	Solvent	Time (h)	Yield (%)[b)]
1	Neat	12	35
2	H_2O	12	52
3	EtOH	12	58
4	EtOH : H_2O (1 : 1)	12	53
5	THF	12	60
6	DMSO	12	62
7	MeCN	12	55
8	[bmim][PF_6]	0.5	94
9	Without catalyst and neat	12	10

a) Reaction was carried out with 1.0 mmol each of benzaldehyde and aniline, and 3.0 mmol of cyclohexanone. *b*) Yield of isolated product.

Next, the effect of different solvent media on the model reaction in presence of H_3BO_3–SiO_2 was studied. Solvents such as water, ethanol, ethanol : water (1 : 1), tetrahydrofuran, dimethylsulfoxide, acetonitrile proved to be good, but in these solvents extended periods of time were required and also, full conversion of reactants was not achieved (Table 2, entries 2—7). Interestingly, in presence of ionic liquid, [bmim][PF_6], high yield of the Mannich product was obtained (Table 2, entry 8). Encouraged by these observations, model reaction was carried out with catalytic amount of boric acid, silica gel and boric acid + silica gel separately in [bmim][PF_6] (Table 1, entries 13—15). The results clearly demonstrated that H_3BO_3–SiO_2 with ionic liquid, [bmim][PF_6], was the best catalytic system for three-component Mannich reaction. From these observations, it has been anticipated that [bmim][PF_6] is synergistically enhancing the catalytic activity of H_3BO_3–SiO_2.

Table 3. Optimization of the Amount of Catalyst



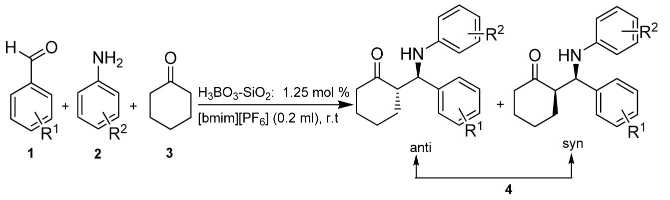
Entry	Catalyst (mol%)	Yield (%)
1	0.25	36
2	0.50	44
3	0.75	59
4	1.00	93
5	1.25	95
6	1.50	93
7	1.75	94

Further, the amount of catalyst required for the reaction was optimized (Table 3) by initially starting with 0.25 mol% of catalyst and gradually increased the amount up to 1.75 mol%. It was observed that initially the yield increased with the amount of catalyst and maximum yield was obtained with 1.25 mol% of catalyst (Table 3, entry 5). Further increase in the amount of catalyst neither increased the yield nor the rate of the reaction.

It should be mentioned here that methods reported earlier for this model reaction required longer time and use of toxic catalytic system such as $Zn(OTf)_2$[42)] and $Bi(OTf)_3 \cdot 4H_2O$[43)] Although in some cases non-toxic catalytic system was used (boric acid/glycerol), a very long reaction time (30—45 h) and low yield limit the scope of the method.[29)]

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to find the generality and scope of this new protocol, various aldehydes and amines were used. The results (Table 4) clearly demonstrated that H_3BO_3–SiO_2 in presence of ionic liquid, [bmim][PF_6], is an excellent catalytic system for Mannich reaction. Generally, excellent yields of Mannich products were obtained for a variety of aldehydes including those bearing an electron-withdrawing group (Table 4, entries 4, 6, 7, 9). Some of the earlier reported methods were not capable of giving Mannich products from aldehydes substituted with –NO_2 group.[28,35)] However, in present case excellent yield of product was obtained with 4-nitrobenzaldehyde (Table 4, entries 6, 9). Furthermore, several electron-rich aromatic aldehydes led to the desired products in good yield with moderate to good "*anti*" diastereoselectivity in most of the cases. *Syn* : *anti* ratio was determined by ^{1}H-NMR analysis of product. The scope of method was extended to other amines also. In case of amines having an electron-donating group, such as 4-methylaniline the corresponding amino ketones were obtained in good yields. Amines with electron-withdrawing group, such as, 3-bromo, 4-nitro and 3-chloroaniline, gave the desired product in good yields (Table 4, entries 3, 8, 10). Generally, the Mannich reaction of 4-methoxybenzaldehyde, 4-nitroaniline and cyclohexanone is very difficult because of the presence of electron-donating and electron-withdrawing groups in aldehyde and amine, respectively[43)] and also, no report exists in literature for the synthesis of Mannich product from these substrates. However, in present case, excellent yield of prod-

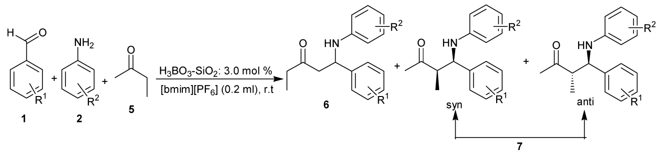
Table 4. Mannich Reaction of Aromatic Aldehydes, Amines and Cyclohexanone[a)]



Entry	R^1	R^2	Product	Time (min)	Yield (%)$^{b)}$	*syn* : *anti*$^{c)}$	mp (°C)
1	H	H	**4a**	30	95	9 : 91	141—142
2	4-OCH_3	H	**4b**	30	94	0 : 100	134—136
3	4-OCH_3	3-Br	**4c**	35	96	37 : 63	Oily
4	4-Cl	H	**4d**	25	98	26 : 74	133—135
5	H	4-CH_3	**4e**	40	97	32 : 68	116—117
6	4-NO_2	H	**4f**	35	98	59 : 41	Oily
7	4-Br	H	**4g**	20	96	39 : 61	Oily
8	4-OCH_3	4-NO_2	**4h**	60	95	59 : 41	63—65
9	4-NO_2	4-CH_3	**4i**	25	98	34 : 66	120—122
10	4-CH_3	3-Cl	**4j**	30	97	nd$^{d)}$	122—123

a) Reactions were carried out with 1.0 mmol each of aldehyde and amine, and 3.0 mmol of cyclohexanone. *b*) Yield of isolated products. *c*) *Syn* : *anti* ratio was determined by ^{1}H-NMR analysis of product. *d*) nd: not determined due to overlapping signals in ^{1}H-NMR spectrum.

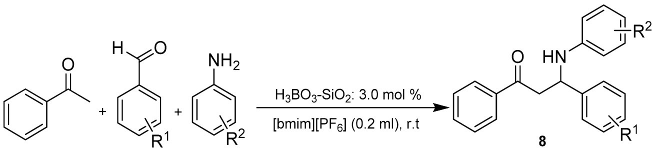
Table 5. Mannich Reaction of Aromatic Aldehydes, Amines and Ethyl Methyl Ketone[a)]



Entry	R^1	R^2	Product (**6**, **7**)	Regioselectivity (**6** : **7**)	Time (h)	Yield (%)$^{b)}$	*syn* : *anti*$^{c)}$	mp (°C)
1	4-Br	H	**6a**, **7a**	48 : 52	6	88	37 : 63	Oily
2	H	H	**6b**, **7b**	32 : 68	8	81	46 : 54	87—88
3	4-OMe	H	**6c**, **7c**	49 : 51	7.5	84	28 : 72	82—83
4	4-OMe	3-Br	**6d**, **7d**	100 : 0	7	82	—	81—82

a) Reactions were carried out with 1.0 mmol each of aldehyde and amine, and 3.0 mmol of ethyl methyl ketone. *b*) Yield of isolated products. *c*) *Syn*/*anti* ratio was determined by ^{1}H-NMR analysis of product.

Table 6. Mannich Reaction of Aromatic Aldehydes, Amines and Acetophenone[a)]



Entry	R^1	R^2	Product (**8**)	Time (h)	Yield (%)$^{b)}$	mp (°C)
1	H	H	**8a**	8.5	74	162—164
2	4-NO_2	H	**8b**	7.0	61	104—106
3	4-Br	H	**8c**	8.0	58	138—140
4	H	4-CH_3	**8d**	9.0	76	164—166

a) Reactions were carried out with 1.0 mmol each of aldehyde and amine, and 3.0 mmol of acetophenone. *b*) Yield of isolated product.

uct was obtained from these substrates (Table 4, entry 8).

The high yield, simple reaction protocol, and originality of this novel process prompted us to investigate the reaction on other ketones under these conditions (Tables 5, 6). Thus, the three component coupling reactions were carried out with acyclic ketones such as ethyl methyl ketone and acetophenone. The expected products were obtained in moderate to good yields under these conditions. Acyclic ketones were less reactive than cyclohexanone and needed much more catalyst to afford the desired products. The regioselectivity was determined by ^{1}H-NMR spectroscopy and by comparison with the literature NMR values.[44—47)] In general, "*anti*" selectivity was observed when ethyl methyl ketone was used.

Another characteristic feature of the present protocol is the

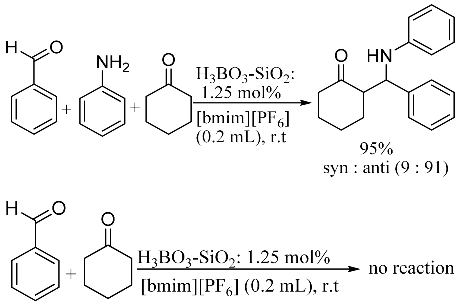


Chart 1. Reaction of Cyclohexanone with Aldimine in Preference to aldehyde

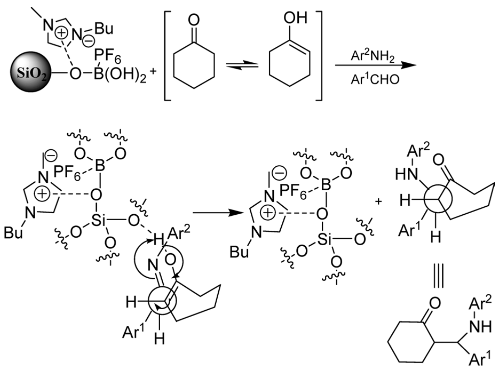


Fig. 2. Plausible Mechanism for Silica-BA-IL Catalyzed Reaction of Cyclohexanone with Aldimine Leading to *anti*-Product

high chemoselectivity of cyclohexanone toward aldimines, prepared *in situ* from the reaction of aldehydes and amines, in preference to aldehydes as shown in Chart 1. Generally, conventional Lewis acids activate aldehydes preferentially towards aldol reaction. However, in present reaction conditions *i.e.* H_3BO_3–SiO_2/ionic liquid the aldol product was not observed at all. The high chemoselectivity is rationalized by considering the higher basicity of nitrogen over oxygen. A related phenomenon was reported in the reactivity between aldimines and aldehydes by the use of proline, HBF_4, and dibutyltin dimethoxide.[48—50] The recyclability of the catalytic system was also checked. The catalytic system was recovered from the reaction mixture and reused successfully for seven times without any considerable effect on yield of the product.

Further, in order to check the kinetic or thermodynamic control of diastereoselectivity under present reaction conditions, the model Mannich reaction was carried out at three different temperatures *i.e.* 0 °C, room temperature and 80 °C. The dominance of *anti* product at lower temperatures (0 °C and room temperature) and its decrease at higher temperature *i.e.* 80 °C indicated kinetically controlled *anti* product formation.[29]

As far as the mechanism of the reaction is concerned, it has been presumed that oxygen of borosiloxane (Si–O–B) bond in H_3BO_3–SiO_2 interacts with imdazolium cation of ionic liquid resulting in polarization of Si–O and Si–O–B bonds with subsequent stabilization by anion of ionic liquid. Polarized Si–O bonds interact with O–H bond of enol to form desired product (Fig. 2).

Conclusion

In conclusion, a new solid supported environmentally benign catalyst has been developed and used efficiently with ionic liquid for diastereoselective synthesis of β-amino carbonyl compounds. This is the first report for the preparation of H_3BO_3–SiO_2 catalyst and its use in Mannich reaction. This procedure offers several advantages including low loading of catalyst, improved yields, clean reaction and use of unmodified ketones, which makes it a useful and attractive strategy for the multi-component reactions of combinatorial chemistry. In addition, a very easy workup procedure has been realized. When the products were solid, the pure products were obtained directly by crystallization from ethanol. Chromatographic separation was not necessary in some cases. Current efforts in our research group are attempting to expand the application of this silica-supported boric acid catalyst for other reactions.

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