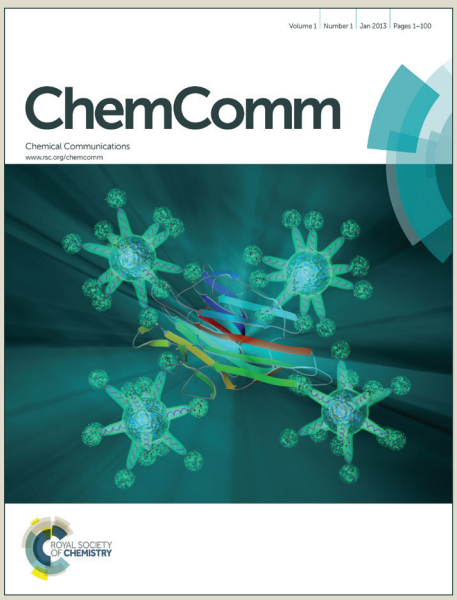
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

MCF-supported boronic acids as efficient catalysts for direct amide condensations of carboxylic acids and amines

Cite this: DOI: 10.1039/x0xx00000x

Received ooth January 2012,
Accepted ooth January 2012

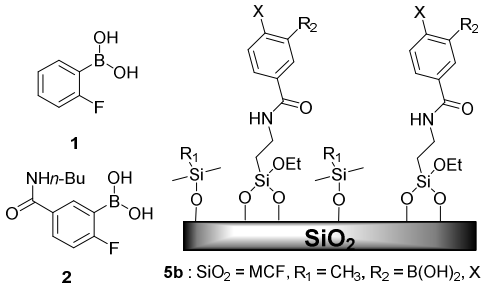
DOI: 10.1039/x0xx00000x

www.rsc.org/

Liuqun Gu,†* Jaehong Lim,† Jian Liang Cheong, and Su Seong Lee*

For efficient direct amide condensations, a new class of catalysts are developed by immobilizing boronic acids on mesocellular siliceous foam. Associated with its large pores, the microenvironments surrounding the immobilized active species greatly influence the catalytic activity. The fluoroalkyl moieties on silica surface significantly enhance the catalytic performance along with easy recovery and reuse. This approach proposes a potential way to optimize various types of silica-supported catalysts.

Amide bond formation is frequently used in the synthesis of pharmaceuticals and proteins.[1,2] The current industrial synthetic procedures are usually involved with stoichiometric use of acylation reagents, such as thionyl chloride, or coupling agents, such as 1-hydroxybenzotriazole (HOBt) and 1,1'-carbonyldiimidazole (CDI), for activation of carboxylic acids, from which hefty amount of wastes are generated.[3] Although much effort has been made to develop alternative coupling agents for more efficient formation of amide bonds, most methods still suffer from poor atom economy and high costs.[4] In search of novel methods that avoid employing such reagents, boron-based organocatalysts[5] as well as some metal-based catalysts[2,6] were investigated for direct amide condensations. These methods are significantly more environment-friendly and atom-economical with only water produced as a co-product. However, the drawbacks such as moderate reactivity and difficulty in catalyst recovery hampered those methods for industrial application. Recently, several inorganic heterogeneous catalysts[7-12] and polystyrene-bound 4-boronopyridinium salts[5b] were reported for direct amide bond formation. These findings indicate that heterogeneous catalysts are promising candidates despite remaining challenges such as high reaction temperature, long reaction time and azeotropic removal of *in situ* generated water. Herein, we report on silica-supported boronic acid catalysts for direct amide condensations. Mesocellular siliceous foam (MCF) was mainly investigated as support material due to its large (> 20 nm) and interconnected internal pores, which significantly facilitate the diffusion of substrates.[13] Moreover, the two-dimensional silica surface of MCF can be easily manipulated to control the microenvironments of immobilized catalysts. Indeed, we were delighted to observe that the MCF-supported boronic acids optimized with fluoroalkyl capping groups showed considerably enhanced catalytic activity compared with its homogeneous counterparts, not to mention bare MCF and trimethylsilyl (TMS)-capped MCF alone.



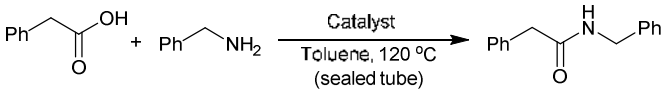
5b : SiO_2 = MCF, R_1 = CH_3, R_2 = $B(OH)_2$, X = F
6 : SiO_2 = MCF, R_1 = $(CH_2)_2CH_3$, R_2 = $B(OH)_2$, X = F
7: SiO_2 = MCF, R_1 = $(CH_2)_2CH_3$, R_2 = $B(OH)_2$, X = F
8a : SiO_2 = MCF, R_1 = $(CH_2)_2CF_3$, R_2 = $B(OH)_2$, X = F
8d : SiO_2 = MCF, R_1 = $(CH_2)_2CF_3$, R_2 = $B(OH)_2$, X = H
4 : SiO_2 = MCF, R_1 = $(CH_2)_2CF_3$, R_2 = H, X = H
9 : SiO_2 = SBA-16, R_1 = $(CH_2)_2CF_3$, R_2 = $B(OH)_2$, X = H\
10 : SiO_2 = commercial silica, R_1 = $(CH_2)_2CF_3$, R_2 = $B(OH)_2$, X = H

Fig. 1 Silica-supported boronic acids and their homogeneous counterparts. Commercial silica indicates Silica gel 60 (0.040-0.063 mm), Merck KGaA.

As depicted in Fig. 1, various silica-supported boronic acids were prepared by using our previously reported immobilization method (see SI, Scheme S1).[13] The sequential treatments began with the pre-capping of free silanol groups by a sub-stoichiometric use of hexamethyldisilazane (HMDS) or other dialkyltetramethyldisilazane, partially and uniformly. Onto the remaining active silanol groups, a desired amount of 3-aminopropyltriethoxysilane (APTES) was introduced in anhydrous toluene at 100 °C for 20 h to give the amine-functionalized MCF. The degree of pre-capping was determined depending on the amount of APTES to load. To prepare 0.2 mmol/g of APTES moiety, for example, 0.8 mmol/g of HMDS was used for pre-capping, which amounts to slightly more than half of the maximal TMS capping of *ca.* 1.5 mmol/g[13b]. After complete anchoring of APTES, ^{1}H NMR spectrum of the concentrated filtrate did not show any organic

compound, which confirmed that the added APTES groups were completely incorporated. Cross-polarization magic angle spinning (CPMAS) ^{29}Si NMR spectra clearly showed T^2 and T^3 peaks from the anchored APTES (see SI, Fig. S5). The still remaining silanol groups were thoroughly capped by further treatment with the corresponding dialkyltetramethyldisilazane. Although these steps can be sequentially conducted in one pot, a vapour-phase reaction under reduced pressure at 80 °C is carried out for the more efficient post-capping with HMDS.[13] The resulting amine-functionalized MCF then became available to immobilize carboxyphenylboronic acids through a typical coupling reaction. It is apparent that the pre-capping method beneficially minimizes the adverse interactions between the amine groups of APTES and silica surface during the grafting step. Kaiser test and CPMAS ^{13}C NMR spectra of the elaborated catalysts showed successful coupling of the boronic acids to the amine groups on MCF (see SI, Fig. S2 and S5). The surface area and pore volume of MCF slightly decreased over the immobilization process, which also supports the successful sequential anchoring of pre-capping agent, APTES and boronic acid (see SI, Fig. S1 and Table S1).

Table 1 Amide condensations of phenylacetic acid and benzylamine with various catalysts under sealed conditions[a]



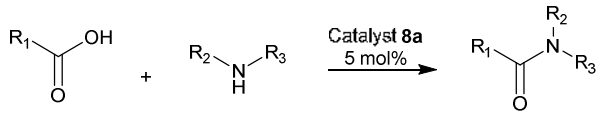
Entry	Catalyst (mol%)	Time (hr)	Yield (%)[b]
1	**1** (10)	2	74
2	**2** (10)	2	78
3	bare MCF[c]	2	23
4	**4** (5)	2	11[d]
5	**5b** (10)	2	71
6	**6** (10)	2	98
7	**7** (10)	2	88
8	**8a** (10)	2	>98
9	**8d** (10)	2	84
10	**6** (5)	1	55
11	**8a** (5)	1	82
12	**9** (5)	1	28
13	**10** (5)	1	42

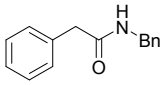
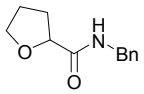
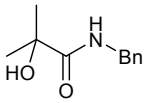
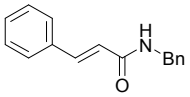
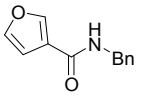
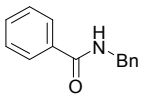
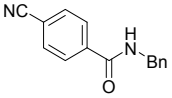
[a]Conditions: catalyst (10 or 5 mol%), phenylacetic acid (0.5 mmol), benzylamine (0.5 mmol), toluene (2 ml), 120 °C; [c]250 mg, dried under high vacuum at 120 °C for 15 hr; [d]Azeotropic removal of water.

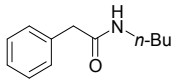
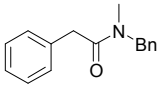
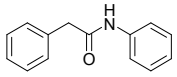
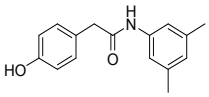
The catalysts in Fig. 1 were investigated in amide condensation of phenylacetic acid and benzylamine in a sealed tube using toluene as a solvent (Table 1). To our surprise, the MCF-supported boronic acid catalysts **8a** capped with fluoroalkyl moieties showed the best performance with even higher catalytic activity than the homogeneous counterparts **1** and **2** (Entry 1, 2 and 8). Interestingly, the introduction of fluoroalkyl moiety in the capping propyl group significantly improved the catalytic efficiency. The isolated yield produced by **8a** reached up to 82%, remarkably from 55% by the fluoro-free derivative **6** (Entries 9 and 10), presumably due to the beneficial role of the fluoroalkyl group as a Lewis base[14] or a better water-repelling agent (or both). Similar halogen group effects were also observed in the aromatic substituent of the boronic acid. Supported on the identical microenvironments, the fluoro-free catalyst **8d** led to lower catalytic activity than the fluoroalkyl derivative **8a** (Entries 8 and 9). The background reaction using bare MCF and **4** afforded the product with 23% and 11% yield, respectively. These results firmly proved that the boronic acid played a key role in the catalysis. It is noteworthy that the homogeneous catalyst **5** was inhibited by the presence of TMS-capped MCF (see SI, Table S3). The isolated yield (27%) became only comparable to that of TMS-capped MCF alone (20%). These phenomena might be attributed to strong interactions between free boronic acid and silica surface capped with the simple TMS group.

The importance of the post-capping is best demonstrated by the significantly decreased catalytic activity resulting from a catalyst prepared by pre-capping with slightly less amount of the fluoroalkyl moieties (0.5 mmol/g) and no post-capping (see SI, **8b** in Table S3). This might be caused by strong interactions between the anchored boronic acid and silica surface. The loading density of the boronic acid affected the catalytic activity. High loading significantly hampered the catalytic activity presumably due to the internal interactions amongst the immobilized boronic acids (see SI, Table S3). The pore size of the support material is another key factor to affect the catalytic activity. MCF with large pores (23.8 nm) showed much higher activity than SBA-16 (**9**) and a commercial silica (**10**) with smaller pores (3.7 nm and 4.7 nm, respectively) possibly due to diffusion issue (Entries 11-13).[15]

Table 2 Direct amide condensations of various carboxylic acids and amines by **8a**[a]



Entry	Product	Solvent	Temp (°C)	Time (hr)	Yield (%)[b]
1		toluene	120	2	>98
2		toluene	120	3	89
3[c]		*o*-xylene	155	5	94
4		*o*-xylene	155	5	97
5		*o*-xylene	155	5	95
6		*o*-xylene	155	15	83
7		*o*-xylene	155	5 15	59 51

8[d]		toluene	120	3	96
9		toluene	120[e]	17	68
10		*o*-xylene toluene	155 120[e]	16 23	35 98
11		*o*-xylene	155[e]	48	70[f]

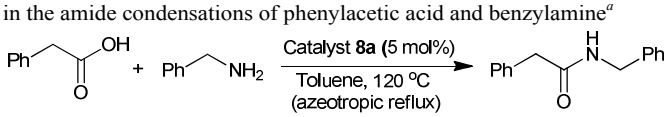
[a]Conditions: catalyst **2** (5 mol%), phenylacetic acid (0.55 mmol), benzylamine (0.5 mmol), solvent (2 ml); [b]Isolated yield; [c]0.75 mmol of the acid was used; [d]0.75 mmol of the amine was used; [e]Azeotropic removal of water; [f]By one-time recycled catalyst, 10 mmol scale.

Next, we examined the scope and limitations of the best catalyst **8a**. In the presence of 5 mol% of **8a**, various carboxylic acids reacted with benzylamine to produce the corresponding amides in good to excellent yields (Table 2). Aliphatic carboxylic acids turned out more reactive than aromatic derivatives, especially in the case of those containing electron-withdrawing groups. Functionalities including hydroxyl, alkene and furan groups were tolerant under these relatively mild conditions (Entries 3-5). Significant decrease in conversion was observed in the case of 4-cyanobenzoic acid compared to that with benzoic acid (Entries 6 and 7).

For amines, a similar trend was also observed that the aliphatic amines reacted with phenylacetic acid faster than the aromatic derivatives (Entries 8-10). A sterically encumbered substrate affected the reaction to result in only moderate yield (68%) with N-methylbenzyl amine even with a prolonged reaction time and azeotropic removal of water (Entries 1 and 9). The less reactive aniline was converted into the corresponding amide in a relatively low yield, whereas nearly full conversion could be achieved under azeotropic removal of water (Entry 10). With one-time recycled catalyst, an active pharmaceutical ingredient (API) intermediate[16] was synthesized in a moderate isolated yield (Entry 11) on a relatively large scale (10 mmol).

The catalyst **8a** was successfully reused for 5 times without any substantial loss of catalytic activity (Table 3). The ^{13}C solid-state NMR spectrum of **8a** after 6 repeated uses revealed the rise of peaks in the aromatic region, which we speculate might be caused by strong interactions between aromatic boronic acid moiety and phenylacetic acid[17].

Table 3 Recycling use of the MCF-supported boronic acid catalyst **8a** in the amide condensations of phenylacetic acid and benzylamine[a]



Run	1	2	3	4	5	6
Yield[b]	91%	94%	> 98%	> 98%	> 98%	> 98%

[a]Conditions: catalyst **2** (5 mol%), phenylacetic acid (2.5 mmol), benzylamine (2.5 mmol), toluene (5 ml), 120 °C, azeotropic removal of water, 2 hr; [b]Isolated yield.

In summary, a new class of MCF-supported boronic acid catalysts were developed in conjunction with a simple and efficient pre-capping and post-capping method. The catalytic activity was greatly enhanced by tuning the microenvironments that surround the immobilized boronic acid. The well-defined two-dimensional nature of silica surface facilitated such manipulations of the heterogeneous catalysts. The optimized catalyst with the fluoroalkyl capping group showed greatly enhanced catalytic activity in direct amide condensations of various sorts of carboxylic acids and amines. The stable heterogeneous catalysts could be easily recovered by simple filtration and reused for multiple times without loss of activity. Although it is still a long and challenging way to apply these catalysts to industrial productions, the developed immobilization strategy would provide an insight in the future development of reusable heterogeneous catalysts.

This work was supported by the Institute of Bioengineering and Nanotechnology (Biomedical Research Council, Agency for Science, Technology and Research Singapore).

Notes and references

Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669. E-mail: gulq@imre.a-star.edu.sg, sslee@ibn.a-star.edu.sg; Fax: +65-6478-9080
†*Both authors contributed equally to this work*
† Electronic Supplementary Information (ESI) available: Experimental procedures, results from testing all the catalysts, BET data and NMR specatra. See DOI: 10.1039/b000000x/

1 V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471-479.
2 (*a*) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405-3415; (b) H. Lundberg, F. Tinnis, N. Selander and H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 2714-2742.
3 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411–420.
4 E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606–631.
5 (*a*) K. Ishihara, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196–4197; (*b*) T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5043–5046; (*c*) K. Arnold, A. S. Batsanov, B. Davies and A.Whiting, *Green Chem.*, 2008, **10**, 124–134; (*d*) R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem., Int. Ed.*, 2008, **47**, 2876–2879.
6 (*a*) C. L. Allen, A. R. Chhatwal and J. M. J. Williams, *Chem.Commun.*, 2012, **48**, 666–668; (*b*) M. Hosseini-Sarvari and H. Sharghi, *J. Org. Chem.*, 2006, **71**, 6652–6654; (*c*) A. C. Shekhar, A. R. Kumar, G. Sathaiah, V. L. Paul, M. Sridhar and P. S. Rao, *Tetrahedron Lett.*, 2009, **50**, 7099–7101; (*d*) J.-G. Kim and D. O. Jang, *Synlett*, 2000, 1231–1234.
7 J. W. Comerford, J. H. Clark, D. J. Macquarrie and S. W. Breeden, *Chem. Commun.*, 2009, 2562–2564.
8 P. S. Chaundhari, S. D. Salim, R. V. Sawant and K. G. Akamanchi, *Green Chem.*, 2010, **12**, 1707–1710.
9 K. Komura, Y. Nakano and M. Koketsu, *Green Chem.*, 2011, **13**, 828-831.
10 J. Cossy and C. Palegrosdemange, *Tetrahedron Lett.*, 1989, **30**, 2771-2774.
11 L. J. Gooßen, D.M. Ohlmann and P. P. Lange, *Synthesis*, 2009, 160-164.
12 K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith and A. Whiting, *Adv. Synth. Catal.*, 2006, **348**, 813–820.
13 (a) S. S. Lee, S. Hadinoto, J. Y. Ying, *Adv. Synth. Catal.* 2006, **348**, 1248-1254; (b) J. Lim, S. N. Riduan, S. S. Lee, J. Y. Ying, *Adv. Synth. Catal*. 2008, **350**, 1295–1308.
14 T. Marcelli, *Angew. Chem., Int. Ed.*, 2010, **49**, 6840–6843.
15 For more details, see Supporting Information, Fig. S4 and Table S2.
16 P. J. Dunn, K. K. Hii, M. J. Krische, M. T. Williams, *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*, 2013, pp. 112-113.
17 K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.*, 2006, **348**, 813–820