



Solid-supported *ortho*-iodoarylboronic acid catalyst for direct amidation of carboxylic acids



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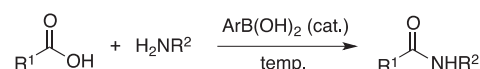
ABSTRACT

Amides are a ubiquitous class of organic compounds endowed with great utility. There is a need for simple and effective catalytic methods for their direct formation from carboxylic acids and amines as a way to avoid the use of coupling reagents. We have designed a recyclable resin-supported derivative of 5-methoxy-2-iodophenylboronic acid as a heterogeneous catalyst active in ambient conditions for promoting direct amidations of aliphatic carboxylic acids and amines. The optimal, practical procedure involves a simple double-filtration to isolate the amide product while separating the catalyst from residual molecular sieves.

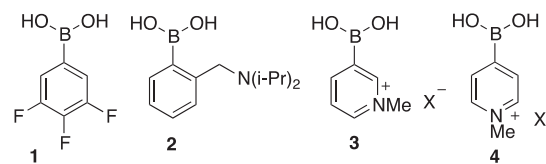
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Because of the great importance of amides as a ubiquitous class of compounds,^{1,2} there is significant interest in the development of simple methods for their direct formation from carboxylic acids and amines.^{3–5} A large number of sophisticated methods employing dehydrating-activating reagents have been developed for direct ('in situ') coupling of carboxylic acids and amines.^{3–5} Common coupling reagents such as carbodiimides, phosphonium or uronium salts are expensive, provide poor atom-economy, and are often toxic. All of these stoichiometric reagents and other additives, such as bases and supernucleophiles, are often required in a molar excess and generate large amounts of wasteful by-products that complicate the isolation of the desired amide product. An ideal direct amidation reaction between carboxylic acids and amines would be a waste-free, catalytic, and operationally simple process occurring at or near the ambient temperature. In this regard, boronic acids constitute an attractive alternative as catalysts for direct amidation reactions.⁶ Some of the most efficient boronic acid catalysts reported, such as 3,4,5-trifluorophenylboronic acid (**1**, Fig. 1),^{7,8} 2-diisopropylaminomethylphenylboronic acid (**2**),⁹ and the 3-¹⁰ and 4-pyridiniumboronic acids (**3** and **4**) tend to require high reaction temperatures. In contrast, we recently reported that *ortho*-iodophenylboronic acid (**5**) is a very efficient catalyst for direct amidation reactions under ambient conditions (Fig. 1).¹² Following this discovery, 5-methoxy 2-iodophenylboronic acid (**6**) was identified as a second-generation catalyst.¹³ Catalyst **6** was found to give higher yields within shorter reaction times for a wide range of aliphatic carboxylic acids and amines.¹³

The prospect of immobilizing a boronic acid catalyst could make this direct amidation methodology even more attractive. By allowing the rapid separation and recycling of the supported catalyst by a simple filtration, this boronic acid catalyzed amidation would afford a simple isolation of amide products after evaporation of the reaction solvent and the water by-product. Although pyridiniumboronic acid catalysts have previously been immobilized onto a solid support,^{10,11} we anticipated several benefits in immobilizing a derivative of catalyst **6** because of its high activity under practical conditions at ambient temperatures.¹³



Catalysts active at > 80 °C :



Catalysts active at rt to 50 °C :

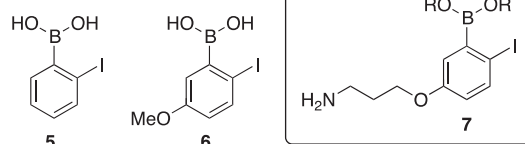
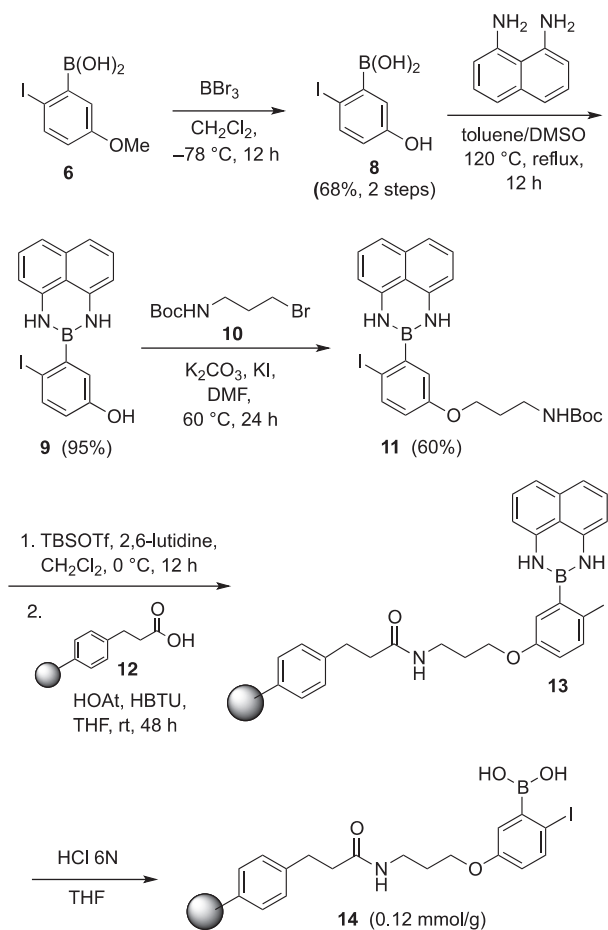


Figure 1. Known boronic acid catalysts for direct amidation reactions.

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Scheme 1. Synthesis of solid-supported boronic acid catalyst **14**.

In designing a suitable linker for attachment to solid supports, it was important to preserve the high activity of catalyst **6**. To this end, we realized that the 5-alkoxy substituent of **6** provides an opportunity for attachment to a solid support without modifying the optimal electronic characteristics of the catalytic unit. We opted for a 5-alkoxy linker functionalized with a terminal amine, which could be conjugated to carboxy-functionalized solid supports. The desired catalytic construct **7** (Fig. 1) was prepared using a sequence of chemoselective reactions made difficult by the presence of the boronyl group. Thus, according to a protocol previously reported by our group,¹⁴ commercially available 3-methoxyphenylboronic acid was first iodinated to give **6** using a combination of AgNO_3 and I_2 . This was followed by a demethylation with boron tribromide (BBr_3) at -78°C , giving phenol **8** in 68% yield over two steps (Scheme 1). Due to the basic conditions required for the alkylation step, the boronic acid moiety was protected. Several protecting groups were tested (*n*-butyldiethanolamine, pinacol ester, MIDA), and the 1,8-diaminonaphthalene unit reported by Suginome and coworkers was found to be the most efficient one.¹⁵ Easily introduced, stable under basic conditions and cleavable with aqueous acid, it furnished adduct **9**, which was easily purified by silica gel column chromatography. Compound **9** was thus obtained after a reaction time of 12 h under azeotropic water removal conditions in 95% yield. The linker arm **10** was prepared in one step by simple BOC protection of the corresponding free amine. It was then engaged in the alkylation step with phenol derivative **9** in the presence of K_2CO_3 and KI in DMF at 60°C to furnish the desired Boc-protected construct **11** in 60% yield after purification. At that stage, the initial idea was to deprotect both amine and boronic acid, and perform a simple autocatalytic amidation reaction with

the carboxylic acid group from the carboxyethyl polystyrene resin (**12**) using our reported process in the presence of molecular sieves.¹³ Unfortunately after many attempts it appeared extremely difficult to isolate the desired product **7** ($\text{R} = \text{H}$) with the free amine group. Then we switched to a one-pot sequence initiated by the use of TBSOTf and 2,6-lutidine, followed by a solid-phase amidation reaction using classical conditions with HOAt and HBTU to obtain the desired functionalized resin **13**. Finally, simple deprotection in the presence of HCl 6N in THF furnished the new solid-supported boronic acid catalyst **14** (0.1 mmol/g theoretical loading based on mass increase and analytical %N). Although only a fraction ($\sim 10\%$) of the sites of resin **12** were effectively functionalized, the final boronic acid loading of resin **14** was found to be sufficient for providing good catalytic activity. The large degree of incomplete functionalization implies that the heterogeneous support is probably functionalized with boronic acid units mainly at the surface of the resin beads. The internal carboxylic acid sites are less available for sequestering the amine reagent through salt formation, which avoids a decrease of amide product yields by depleting the amine. Moreover, the resulting salt interaction is reversible thus those amines could still be consumed.

As a preliminary test, we then evaluated solid-supported catalyst **14** with a number of model substrates that were previously tested with homogeneous catalyst **6**.¹³ Similar conditions were employed with the solid-supported catalyst **14**, including the use of 4A molecular sieves as water-trapping agent.¹⁶ Knowing that

Table 1
Substrate scope for the direct amide bond formation of carboxylic acids catalyzed by solid-supported catalyst **14**^a

Entry	Product	Time (h)	Yield ^b (%)
1		15 48	90
2		16 48	32 ^c
3		17 96	79 ^d
4		18 48	72
5		19 48	86

^a Reaction conditions: carboxylic acid (0.55 mmol, 1.1 equiv), solid-supported catalyst **14** (500 mg, 0.0485 mmol, ~ 10 mol %), and the amine (0.5 mmol, 1.0 equiv) were stirred at room temperature (25°C) in dry DCM (5 mL) containing powdered activated 4A molecular sieves (1.0 g).

^b Isolated yields following the simple filtration protocol and evaporation.

^c 29% of the desired product was obtained when the reaction time was extended to 6 days using DCM as solvent; 30% of the desired product was obtained after 48 h when the reaction was performed in toluene. Other compounds obtained are left-over starting materials.

^d Purified by silica gel column chromatography.

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