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B(OCH₂CF₃)₃-mediated direct amidation of pharmaceutically relevant building blocks in cyclopentyl methyl ether†

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The use of B(OCH₂CF₃)₃ for mediating direct amidation reactions of a wide range of pharmaceutically relevant carboxylic acids and amines is described, including numerous heterocycle-containing examples. An initial screen of solvents for the direct amidation reaction suggested that cyclopentyl methyl ether, a solvent with a very good safety profile suitable for use over a wide temperature range, was an excellent replacement for the previously used solvent acetonitrile. Under these conditions amides could be prepared from 18 of the 21 carboxylic acids and 18 of the 21 amines examined. Further optimisation of one of the low yielding amidation reactions (36% yield) *via* a design of experiments approach enabled an 84% yield of the amide to be obtained.

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Introduction

Amides are highly important in pharmaceuticals and it is well documented that amidation is one of the most commonly used processes in the synthesis of medicinally relevant compounds.¹ Amides are typically synthesised either *via* preparation of a highly reactive acyl derivative (acyl chloride, mixed anhydride, *etc.*) or *via* use of a coupling reagent.² These processes are not without significant drawbacks, however, as they often involve the use of toxic reagents or solvents and lead to the generation of large quantities of waste products. As a consequence of this, there has been considerable interest in the development of alternative methods for achieving direct amidation between carboxylic acids and amines, a process which formally only requires the removal of a molecule of water.³ Notable developments have included the identification of numerous catalysts for mediating amidation reactions under dehydrating conditions (*e.g.* Dean-Stark water removal or molecular sieves) including systems based around boron,⁴ group IV metals,⁵ or other inorganic compounds.⁶ Progress has also been made on the improvement of direct thermal amidation reactions without a catalyst.⁷ However, these

methods are largely limited to more reactive carboxylic acids and amines (*e.g.* simple relatively lipophilic alkyl or aryl systems), with very few successful reactions of functionalised compounds being reported. The synthesis of pharmaceutically relevant compounds inherently requires the amidation of such polar functionalised molecules,⁸ however, with heterocyclic compounds in particular being an essential component of many drug molecules. These highly polar heterocycle-containing acids and amines often show low reactivity in direct amidation reactions (*e.g.* electron-deficient amino-heterocycles are typically very poor nucleophiles), and the presence of co-ordinating heteroatoms is incompatible with many of the catalytic amidation systems reported to date. In our previous work, we have shown that borate esters⁹ such as B(OMe)₃ and B(OCH₂CF₃)₃ are effective amidation reagents,^{10,11} and that purification of the amide products can be achieved using a simple filtration work-up in many cases, without any need for chromatography or aqueous work-up.¹¹ In this paper we report new conditions for direct amidation using a simple borate ester that are effective with a wide range of pharmaceutically relevant carboxylic acids and amines.

Results and discussion

Solvent screen

In our original report of borate-mediated amidation reactions we screened a selection of different solvents for the B(OMe)₃-mediated reaction between phenylacetic acid **1a** and benzylamine **2** to give amide **3a**.¹⁰ From this initial screen, aceto-

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nitrile was selected as a solvent for further study and this was employed for subsequent amidation reactions with other borate esters from which $B(OCH_2CF_3)_3$ emerged as the most promising reagent, especially for less reactive substrates. However, no subsequent screen of solvents using $B(OCH_2CF_3)_3$ was carried out. In general, amidation reactions with less reactive substrates were observed to proceed more effectively at higher temperatures, but using acetonitrile as solvent, this led to the need to carry out reactions of particularly difficult substrates at 100 °C in a sealed tube. Even under these conditions, very unreactive substrates such as the poorly nucleophilic 2-aminopyridine gave <20% yield of the corresponding amide.¹¹ Before challenging our amidation method with a set of highly functionalised acids and amines, we therefore elected to carry out a further solvent screen to determine whether other solvents might be more suitable for carrying out $B(OCH_2CF_3)_3$ -mediated amidation reactions (Scheme 1 and Table 1).¹² As in our previous work, we used the reaction of phenylacetic acid and benzylamine as a benchmark to screen the different solvents. The amidation product in this case can easily be isolated rapidly *via* a filtration work-up, without the need for aqueous work-up or chromatography.

Dimethylsulfoxide (entry 2), selected as it readily dissolves most polar acids/amines, was a poor solvent for the reaction. Ethereal solvents (entries 3–8) proved particularly promising, however, although it should be noted that there was considerable variation in yield within this class of solvent. *tert*-Amyl methyl ether (TAME, entry 3) and cyclopentyl methyl ether (CPME, entry 4)¹³ were both excellent solvents for the amidation reaction, whereas the use of 4-methyltetrahydropyran (entry 5) resulted in only a moderate yield of the product. Notably, in this latter solvent immediate precipitation was observed on mixing the acid/amine suggesting that salt formation is particularly favourable. This was not the case in the

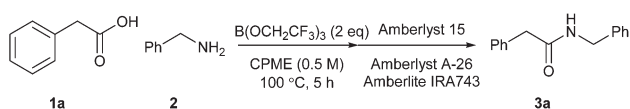
other solvents examined. Other ether solvents including THF, 2-MeTHF and TBME gave the amide in moderate yield, as did ethyl acetate. The latter example elegantly demonstrates the compatibility of esters with the reaction conditions. We selected CPME for further use as it has a relatively high boiling point (bp 106 °C), providing scope for increasing the reaction temperature when studying the amidation of less-reactive substrates. Preliminary studies suggested that whilst many heterocyclic acids/amines may not readily dissolve in CPME at room temperature, they typically dissolve and react at higher temperatures.

Application to pharmaceutically relevant carboxylic acids and amines

In order to challenge the scope of the $B(OCH_2CF_3)_3$ -mediated direct amidation reactions we studied the reaction of sets of 21 carboxylic acid and 21 amines specifically selected by researchers in the pharmaceutical industry as ‘difficult substrates’ which can often prove incompatible with newly developed synthetic methodology.¹⁴ Standard reaction conditions (2 eq. $B(OCH_2CF_3)_3$, CPME, 100 °C, 5 h) were examined with all of the compounds in the first instance, with the temperature or the reaction time being increased if required for less reactive examples.

Screen of functionalised carboxylic acids

In order to provide a good comparison of the reactivity, the acids were all examined in direct amidation reactions with benzylamine as the nucleophile (Scheme 2). Pleasingly the standard procedure worked well for the vast majority of carboxylic acids tested (18/21). Unless otherwise indicated, the amide product could be isolated *via* a simple solid phase filtration procedure without the need for aqueous work-up or chromatography. Substrates containing free alcohols readily gave the corresponding amides in good yield (**3b**, **3c**, **3l**). 3-Fluorophenylacetic acid **1d** was notably less reactive than the parent compound **1a**, giving only 69% of amide **3d**. Pleasingly, a wide range of heterocyclic carboxylic acids underwent amidation in excellent yield, including acids containing a pyridine (**3e**), a pyrazine (**3f**), a 7-azaindole (**3h**), an indazole (**3i**) and a pyrazole (**3j**), although with the less reactive examples the reaction temperature had to be increased to 125 °C. The 2-pyridone/2-hydroxypyridine substrate **1g** gave only a moderate yield of the amide **3g** even at this higher reaction temperature, however. With some of the amides containing basic nitrogen heterocycles, purification *via* the standard solid-phase work-up was not possible due to absorption of the product on the Amberlyst 15 resin. However, in some cases replacement of this strongly acidic resin with Amberlite IRA86 carboxylic acid resin enabled the products to be isolated without chromatography (**3e–3f**). In other cases, purification by chromatography was necessary (**3g–3j**). Functionalised aliphatic carboxylic acids also underwent amidation efficiently including substrates containing acetamides (**3k**, **3l**), free hydroxyl groups (**3c**, **3l**, **3m**) and a lactam (**3n**). The amino-acid derivatives *N*-acetylhydroxyproline (**3m**), *L*-pyroglutamic acid (**3n**), Boc-pipe-



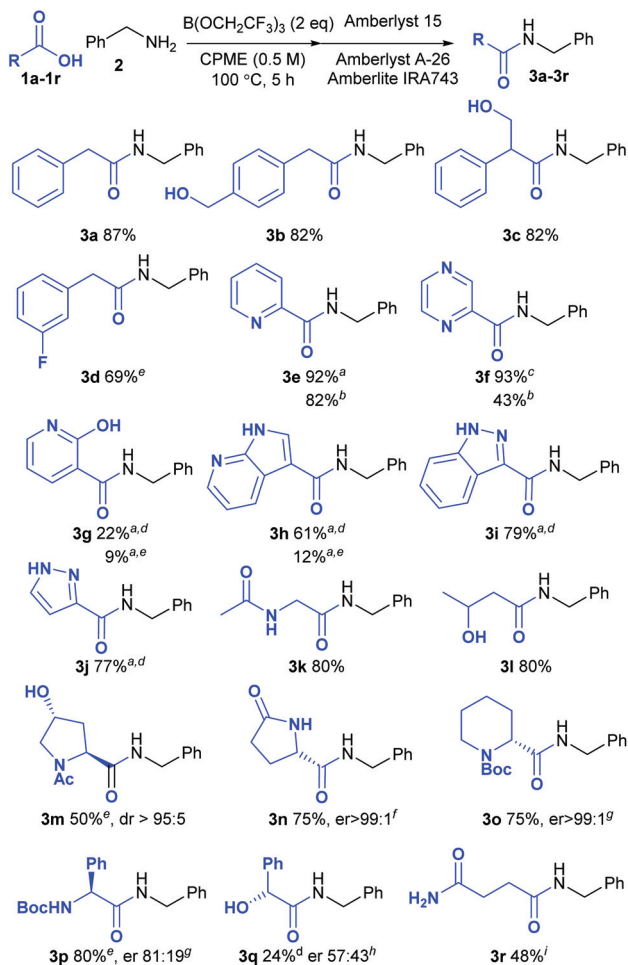
Scheme 1 Direct amidation between phenylacetic acid and benzylamine.

Table 1 Direct amidation between **1a** and **2** in a variety of solvents

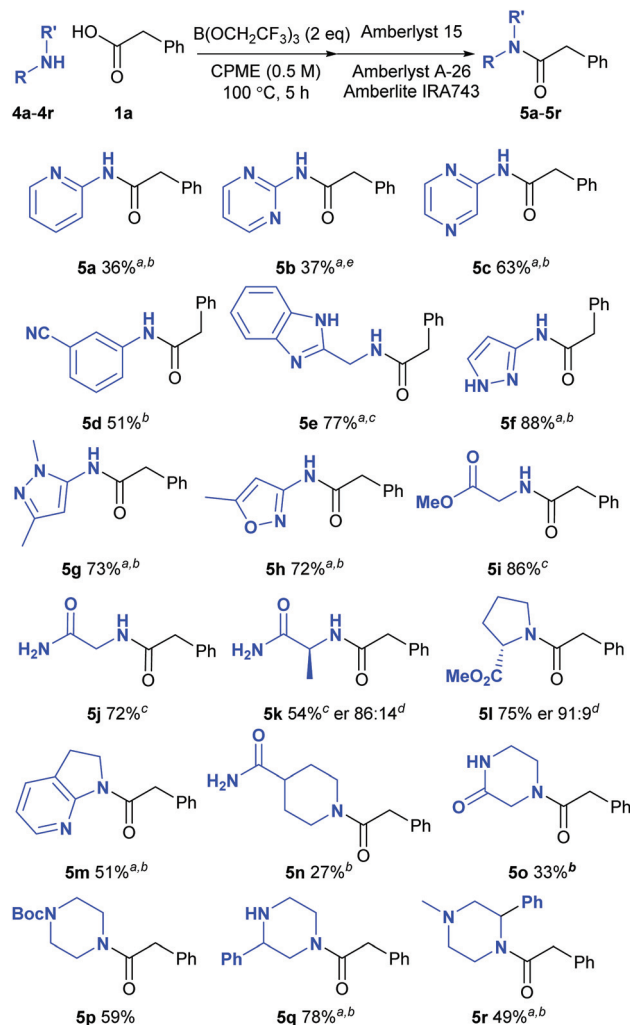
Entry	Solvent	Temperature	Yield ^a
1	MeCN	80	87%
2	DMSO	80	35%
3	<i>tert</i> -Amyl methyl ether (TAME)	80	88%
4	Cyclopentyl methyl ether (CPME)	80	87%
5	4-Methyltetrahydropyran	80	43%
6	Tetrahydrofuran (THF)	80	58%
7	2-Methyltetrahydrofuran (2-MeTHF)	80	56%
8	<i>tert</i> -Butyl methyl ether (TBME)	80	53%
9	Ethyl acetate (EtOAc)	80	50%

^a Isolated yields.





Scheme 2 Direct amidation reactions of functionalised carboxylic acids; ^aPurified by column chromatography; ^bAmberlite IRA86 (CO₂H) resin used instead of Amberlyst 15; ^cAmberlyst 15 resin was not used; ^d24 h, 125 °C; ^e24 h; ^fDetermined using an organic chiral shift reagent;¹⁵ ^gDetermined by derivatisation with Marfey's reagent;¹⁶ ^hDetermined by HPLC using a chiral stationary phase;¹⁷ ⁱPurified by recrystallisation; no solid-phase work-up.



Scheme 3 Direct amidation reactions of functionalised amines; ^aPurified by column chromatography; ^b125 °C, 24 h; ^cAmine hydrochloride salt was used; Et₃N was added to the reaction; ^dDetermined by HPLC using a chiral stationary phase;¹⁷ ^e24 h.

colic acid (**3o**) and Boc-phenylglycine (**3p**) were all good substrates for the amidation with only the latter compound undergoing any significant degree of racemisation under the reaction conditions. Mandelic acid (**3q**) gave only 24% yield of the amide, however, and underwent almost complete racemisation during the amidation process. The primary amide in succinic acid monoamide **1r** was compatible with the reaction conditions, although the resulting amide **3r** appeared to undergo cyclisation to the corresponding *N*-benzylsuccinimide during the solid-phase work-up procedure. As a consequence, this compound was purified by recrystallisation to give the amide **3r** in 48% yield.

Screen of functionalised amines

We next went on to examine the amidation of a set of pharmaceutically relevant amines (Scheme 3). In a similar fashion to

the carboxylic acids above, we chose to study their reaction with a standard reaction partner (phenylacetic acid **1a**) in order to provide a good understanding of their comparative reactivity. Heterocyclic amines are notoriously unreactive substrates for amidation reactions as the strongly electron-withdrawing nature of many nitrogen heterocycles makes the adjacent amine an extremely poor nucleophile. Low yields of amide were obtained from 2-aminopyridine (**5a**) and 2-aminopyrimidine (**5b**), but the corresponding 2-aminopyrazine underwent amidation effectively (**5c**). An electron-deficient aniline bearing a cyano group also gave a reasonable yield of the corresponding amide **5d**. Pleasingly, amines containing a benzimidazole (**5e**), a pyrazole (**5f–5g**) and an oxazole (**5h**) all gave the amide derivatives in good yield. Relatively unreactive aliphatic amines such as glycine methyl ester (**5i**), glycylamide (**5j**), alaninamide (**5k**) and proline methyl ester (**5l**) were also fairly good substrates, with some racemisation being observed



with the two chiral substrates. Moderate to good yields of amides were obtained from other challenging substrates including a cyclic aminopyridine (**5m**), an amide-containing piperidine (**5n**), piperazin-2-one (**5o**) as well as a series of piperazine derivatives (**5p–5r**). 2-Phenylpiperazine **4q** reacted selectively at the least hindered amine to give amide **5q**, with no diamidated product being isolated from the reaction. Amines which were supplied as hydrochloride salts could also be used directly in the amidation reaction, with triethylamine being added to liberate the free amine from the salt (**5e**, **5i–5k**). In a similar manner to the reactions of the carboxylic acids described above, amide products containing basic nitrogen atoms could not be purified *via* the solid-phase work-up procedure.

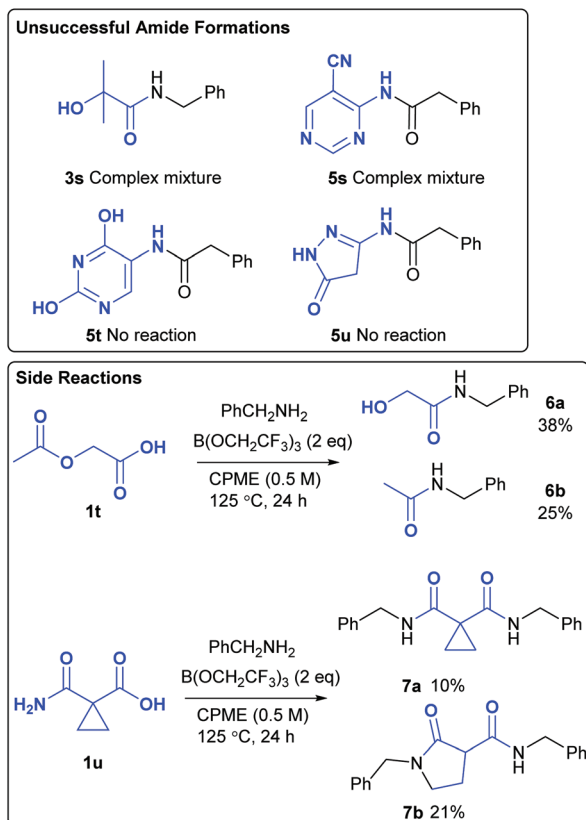
Unsuccessful amidation reactions

Amide **3s**, derived from 2-hydroxyisobutyric acid could not be obtained from the amidation reaction, with a complex mixture of products being formed (Scheme 4). Attempted formation of amide **5s** also gave a complex mixture of products due to numerous side-reactions. The formation of amides **5t** and **5u** was unsuccessful as the corresponding amines **4t–4u** were insoluble in the reaction mixture. Although acetoxyacetic acid **1t** did undergo amidation of the carboxylic acid group, this was accompanied by amidation of the acetoxy group to give amides **6a/6b** in moderate overall yield. Given the fact that the

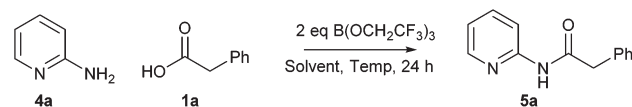
borate-mediated amidation reaction is compatible with esters (Table 1, entry 9), this suggests that reaction of this acetate group is probably assisted by co-ordination of the adjacent amide or carboxylic acid group to the boron atom. Cyclopropyl malonate derivative **1u** gave a mixture of products **7a** and **7b** in moderate overall yield. Thus, direct amidation of the carboxylic acid competes with transamidation of the primary amide as well as ring opening of the highly activated cyclopropane. Heating cyclopropane **7a** on its own or in the presence of $B(OCH_2CF_3)_3$ with/without benzylamine did not result in the formation of **7b**, suggesting that these products were formed *via* divergent competing reaction pathways in the original amidation reaction.

Design of Experiments optimisation of the reaction of 2-aminopyridine with phenylacetic acid

In order to further demonstrate the utility of this amidation method, we sought to take one of the less efficient amidation reactions and optimise the procedure to give good yields of the amide product. We selected the reaction between 2-aminopyridine **4a** and phenylacetic acid **1a** to give amide **5a** as this reaction gave only a moderate yield of product (Scheme 5 and Table 2). Indeed, under our original conditions (MeCN, 100 °C), only a 12% yield of the amide was obtained (entry 1).¹¹ As can be seen above, switching the solvent to CPME and raising the temperature led to a significant improvement, giving a 36% yield of the amide (entry 2). In an initial investigation, we explored whether dropwise addition of one or more reagents to the reaction could lead to improved yields of the product. Dropwise addition of the borate reagent to a mixture of acid/amine led to a small improvement in the yield (entry 3, 39%), whilst dropwise addition of a mixture of acid/borate to the amine gave a similar yield (entry 4, 40%). Interestingly, a significant improvement in yield (entry 5, 60%) was observed by addition of the borate reagent dropwise to a mixture of acid, amine and triethylamine suggesting that



Scheme 4 Unsuccessful amidation reactions.



Scheme 5 Reaction of 2-aminopyridine **4a** and phenylacetic acid **1a**.

Table 2 Study of the effect of different experimental procedures on the yield of amide **5a**

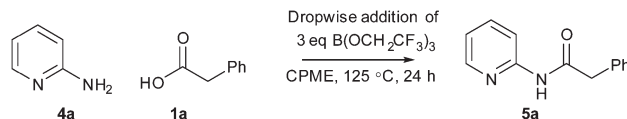
Entry	Conditions	Yield ^a
1	MeCN, 100 °C	12%
2	CPME, 125 °C	36%
3	CPME, 125 °C, dropwise addition of borate	(39%)
4	CPME, 125 °C, dropwise addition of borate/acid	(40%)
5	CPME, 125 °C, 1 eq. Et ₃ N, dropwise addition of borate	(60%)

^a Isolated yields; NMR yields in parentheses.

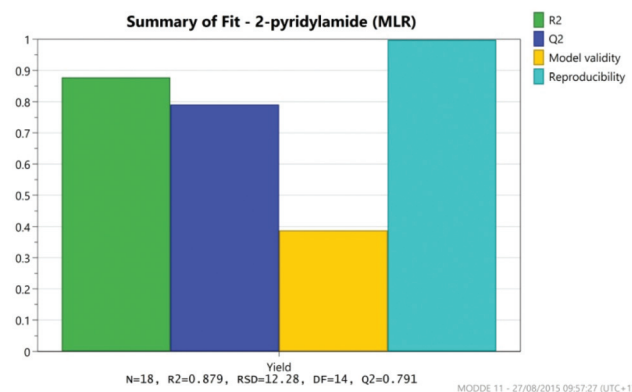
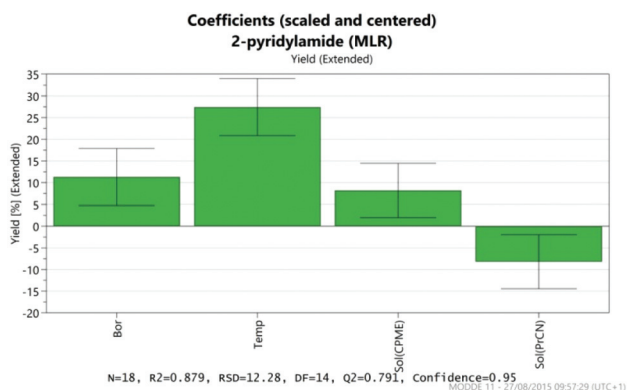


Table 3 Factors and ranges covered in the 'Design of Experiments' optimisation of the formation of amide **5a**^a

Variable	Low	High
(eq. amine 4a)-(eq. acid 1a)	-2	+2
eq. B(OCH ₂ CF ₃) ₃	0.5	3
eq. Et ₃ N	0.1	3
Solvent volume in borate solution	0.5 mL	2 mL
Solvent volume in reaction vessel	0.5 mL	2 mL
Addition rate (syringe pump)	0.254 mL h ⁻¹	13 mL h ⁻¹
Temperature	80 °C	125 °C

^a For full details of the Design of Experiments study, see the ESI.**Scheme 6** Reaction of 2-aminopyridine **4a** and phenylacetic acid **1a** to give amide **5a** under optimised conditions.**Table 4** 'Optimised' methods for the formation of amide **5a**

Entry	Conditions	Yield ^a
1	3 eq. Et ₃ N	58%
2	3 eq. 4a , 0.1 eq. Et ₃ N	84%
3	3 eq. 1a ; 3 eq. Et ₃ N	83%
4	3 eq. Et ₃ N, Bu ₂ O, 140 °C	74%

^a Isolated yields; 1 eq. **4a** and 1 eq. **1a** used unless otherwise stated.**Fig. 1** Model fit for DoE.**Fig. 2** Coefficient plot showing the most important factors in the amidation reaction.

keeping the borate concentration low and the overall reaction mixture basic is advantageous.

With this information in hand, we then went on to carry out a 'Design of Experiments' optimisation of this reaction using the conditions where a solution of borate was added dropwise to a mixture of amine/acid/Et₃N as our starting point. 'Design of Experiments' is a statistical approach to reaction optimisation which enables the variation of multiple

factors simultaneously in order to evaluate the important parameters in a reaction using a relatively small number of experiments.¹⁸ For the DoE optimisation, seven different continuous variables were chosen for the study, and two solvents were evaluated: CPME and propionitrile (EtCN), the latter being chosen as a higher boiling point equivalent to MeCN. The parameters were investigated *via* a Resolution IV design consisting of 16 experiments plus two centre points. The factors studied and the ranges covered are shown in Table 3.

The results were analysed using MODDE 10 software,¹⁹ and a model was generated to fit the data using multiple linear regression (MLR) which provided a good fit to the data (Fig. 1). The important factors in the reaction are shown in the coefficient plot in Fig. 2. By far the most significant factor in the reaction was temperature with the higher temperature giving, on average, a ~27% increase in the reaction yield. The addition of more borate reagent was also beneficial to the outcome, as was the use of CPME as solvent rather than EtCN. None of the other factors were found to be significant across the ranges explored and there were no significant interactions between the factors. The factor (amine-acid) explored the use of an excess (3 eq.) of either the amine or the acid relative to the other component. The design suggested that there was no particular benefit in using either an excess of the amine or the acid, though it should be noted that the highest yields in the DoE study were obtained with either an excess of acid or amine at high temperature and with high borate loading in CPME. The centre points of the DoE which employed equimolar quantities of acid and amine gave considerably lower yields. In further studies we observed that an excess of one reagent or the other was important in order to obtain a good isolated yield of the amide (*vide infra*, Table 4).

Following on from the DoE study, we then determined the isolated yield of amide **5a** obtained under various sets of 'optimised' conditions (Scheme 6 and Table 4). With equimolar equivalents of acid and amine, the best isolated yield obtained



was 58% using three equivalents of triethylamine (entry 1). However, with an excess of either the amine (entry 2) or the acid and triethylamine (entry 3) >80% isolated yield of amide **5a** was obtained. The ability to carry out the amidation reaction of a poorly reactive substrate with either an excess of the acid or the amine provides flexibility in cases where one of the coupling partners is particularly valuable. Furthermore, switching the solvent to dibutyl ether (Bu₂O), which has similar properties to CPME but a higher boiling point, enabled a 74% isolated yield to be obtained using equimolar quantities of amine **4a** and acid **1a** at 140 °C. This correlates well with the prediction of the DoE model that reaction temperature is by far the most important factor affecting the yield of amide obtained.

Conclusions

An improved procedure has been developed for direct amidation reactions with B(OCH₂CF₃)₃ using CPME as the solvent. The method was successfully applied to a wide variety of pharmaceutically relevant carboxylic acids and amines with only 6 of the 42 substrates failing to undergo the desired amidation process. More than half of the amides could be isolated *via* a simple filtration work-up without the need for chromatographic purification. Furthermore, it was demonstrated that optimisation of the amidation protocol for one of the lower yielding substrates enabled the isolated yield of the amide to be increased from 36% to 84%.

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