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Lewis acid-catalyzed Mannich type reactions with potassium organotrifluoroborates

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Abstract—Three-component Lewis acid-catalyzed Mannich type reactions using potassium organotrifluoroborates (aryl, vinyl, and allyl reagents) has been developed as an extension of the standard Petasis reaction.

With the ultimate goal of preparing a library of small molecules having either an allylic or a benzylic amine moiety for biological targets evaluation, we turned our attention to the Petasis reaction[1] as an attractive alternative to the reductive amination reaction.[2] The Petasis reaction is a three-component boronic Mannich-type reaction that would allow us to have rapid access to a wide range of molecular diversity, as illustrated below (Fig. 1).

However, as previously observed by Petasis and Akritopoulou[1a] we also found that arylboronic acids are particularly less reactive than alkenylboronic acids, especially when $R^3 = H$ (Fig. 1). In a model reaction, we established that the reaction between 4-benzylpiperidine and paraformaldehyde in the presence of phenylboronic acid was rapidly inhibited and produced the desired compound **1** only in very low yield since side product **2**[3] was formed in various quantities (Scheme 1). Depending on the reaction conditions (solvent, temperature, and additives) side product **2** can be the predominant product. Though the exact nature of the postulated intermediates **3a** and **3b** are not well defined in the Petasis reaction,[1] the formation of **2** could arise from the reduction of either the iminium intermediate via an Eschweiler–Clarke type methylation[4] or the postulated boronate complex intermediates **3a** or **3b** by a hydride source competing with the expected intramolecular aryl group transfer.

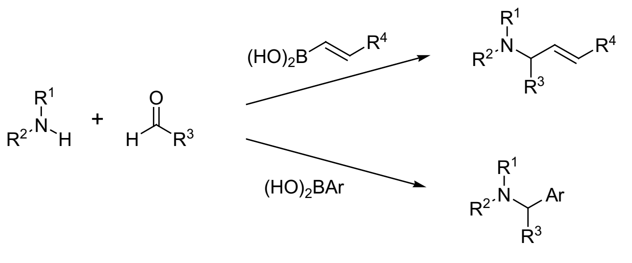

Figure 1. The Petasis reaction.

Consequently, in order to increase the formation of the desired compound **1** and minimize the production of the methylated amine **2** we decided to investigate the use of potassium organotrifluoroborates, which are known to be more reactive after activation by a Lewis acid[5] or an organometallic catalyst.[6] Moreover, they can be either purchased or easily prepared from the corresponding boronic acids according to a known procedure.[7] To the best of our knowledge, the use of potassium aryl-, alkenyl-, and allyltrifluoroborates, in the presence of a catalytic amount of Lewis acid, in the Petasis reaction has not been reported. Although the use of potassium β-styryltrifluoroborate in the presence of a slight excess of trimethylsilyl chloride has already been disclosed by Bryce and co-workers,[8] the study was incomplete and resulted in low to moderate yields of Mannich-type product. Herein we describe our results of an efficient Lewis acid-catalyzed three-component Mannich type reaction using potassium organotrifluoroborates in this modified Petasis reaction.

Thus in a first set of experiments, when phenylboronic acid was replaced by potassium phenyltrifluoroborate

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Keywords: Mannich reaction; Petasis reaction; Potassium organotrifluoroborates; Lewis acids.

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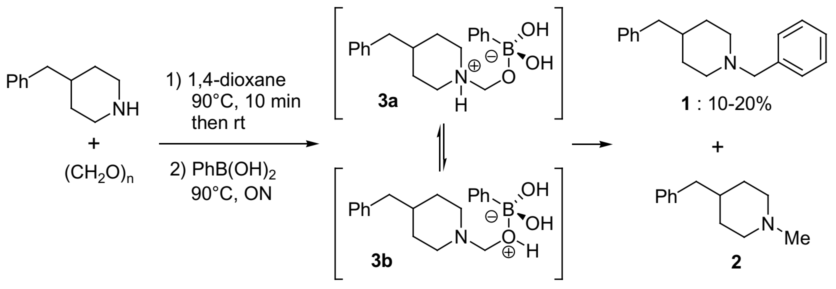
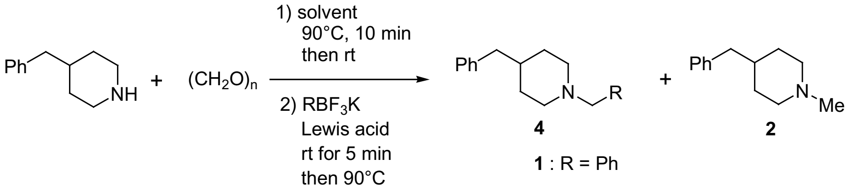


Scheme 1.



Scheme 2.

(1.2 equiv) in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ (20–25 mol%) in 1,4-dioxane (0.14 M) at 90 °C, we were pleased to observe the formation of **1** as the major product in 50–60% isolated yield (Scheme 2). Gratifyingly, the formation of the side product **2** was drastically reduced in these new conditions (a trace amount by MS). With this encouraging preliminary result in hand, we decided to carry out a study of the parameters that influence this reaction (solvent and temperature, Lewis acid, additive, reactant, etc).

We first examined the effect of the solvent and the temperature on the three-component Mannich type reaction (Scheme 2). We rapidly noticed in our standard conditions described above that no reaction occurred after step 2 at room temperature and it was very sluggish at 60 °C. Actually, the reaction only proceeded well at $T > 80\,°C$ using high boiling solvents with very small dielectric constants such as 1,4-dioxane, 1,2-dichloroethane or toluene, which are not able to dissociate charged substrates. The desired product **1** was isolated in 60%, 70%, and 75% yields, respectively, with these solvents. Using THF, DME, and acetic acid as the solvent resulted in incomplete reaction and gave a lower yield of **1**. On the other hand, we established that solvents having a high dielectric constant such as CH_3CN, DMF, and DMSO, which are able to dissociate charged substrates, gave exclusively the side product **2** as the major product. Thus, toluene was deemed the solvent of choice for this transformation allowing the reaction to proceed very cleanly and rapidly at 90 °C ($t < 1$ h).

We next investigated the influence of common Lewis acids (Scheme 2, Table 1) in the three-component Mannich type reaction.[9] First, it is worthwhile to mention that in contrast to the conventional Petasis reaction using boronic acids as the nucleophile, no reaction occurred with potassium organotrifluoroborates in the absence of a Lewis acid (entry 1). This result suggests that the in situ generation of the organoboron difluoride[7] (RBF_2) is a critical component of this reaction as this active species is derived from Lewis acid activation of the potassium organotrifluoroborate. Secondly, a catalytic as well as a stoichiometric amount of $BF_3{\cdot}OEt_2$ catalyzes the reaction in moderate to good yield (entries 2–4). However, we observed that the reaction was cleaner and therefore easier to purify when using only a catalytic amount (25 mol%) of $BF_3{\cdot}OEt_2$. On the other hand, an excess of this Lewis acid completely inhibits the formation of **1** (entry 5). Although the majority of Lewis acids do in fact catalyze the three-component Mannich type reaction affording the desired product **1** in moderate to excellent yield [e.g., $Zn(OTf)_2$, $Cu(OTf)_2$, $Sn(OTf)_2$, $La(OTf)_3$, $Y(OTf)_3$, $Sc(OTf)_3$, TMSCl, $MgBr_2{\cdot}OEt_2$], Lewis acids having only one trifluoromethane sulfonate moiety (Tf) (e.g., *n*-Bu_2BOTf, AgOTf, TMSOTf) or strong Lewis acids such as $SnCl_4$ or $AlMe_3$ led to either a mixture of products or the degradation of the reaction mixture. In this study, TiF_4 was found to be the best Lewis acid for this transformation since it resulted in the highest conversion to the desired product **1** (entry 6). Although TiF_4 was found to be the best LA, the subsequent study was done using $BF_3{\cdot}OEt_2$.

Table 1. Effect of the Lewis acid on the formation of **1** by the three-component Mannich type reaction

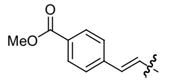
Entry[a]	Lewis acid[b]	Isolated yield for **1** (%)[c]
1	No	No reaction
2	$BF_3{\cdot}OEt_2$ (10 mol%)	59
3	$\mathbf{BF_3{\cdot}OEt_2}$	**75**
4	$BF_3{\cdot}OEt_2$ (1 equiv)	78
5	$BF_3{\cdot}OEt_2$ (2 equiv)	No reaction
6	$\mathbf{TiF_4}$	**90**

[a] 4-Benzylpiperidine (1.0 equiv), paraformaldehyde (1.2 equiv), $PhBF_3K$ (1.2 equiv), anhydrous toluene (0.14 M), 90 °C for 5 h.

[b] A catalytic amount of Lewis acid (20–25 mol%) was used if not specified.

[c] After work-up and flash chromatography on silica gel.

Table 2. Effect of potassium organotrifluoroborates on the formation of **4** by the three-component Mannich type reaction

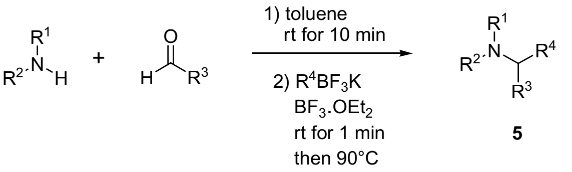
Entry[a]	RBF_3K	Yield for **4** (%)[b]
1	1-Naphthyl	86
2	4-Biphenyl	81
3	4-Vinylphenyl	75
4	3,4-Dimethoxyphenyl	85
5	4-Tolyl	67
6	4-Fluorophenyl	79
7	4-Methoxycarbonylphenyl	43[c]
8	β-Styryl	90
9[11]		91
10	3-Thienyl	82
11	1-Benzothiophen-2-yl	98
12	Allyl	40

[a] 4-Benzylpiperidine (1.0 equiv), paraformaldehyde (1.2 equiv), RBF_3K (1.2 equiv), $BF_3{\cdot}OEt_2$ (25 mol%), anhydrous toluene (0.14 M), 90 °C for 5 h.

[b] After work-up and flash chromatography on silica gel.

[c] AcOH (1 equiv) was added as an additive.

We also studied the effect of potassium organotrifluoroborates on the formation of **4**[10] by the three-component Mannich type reaction (Scheme 2, Table 2). In general, electron rich aryls (entries 1–6), heteroaryls (entries 10 and 11), and vinyltrifluoroborates (entries 8 and 9) were successful as nucleophiles following BF_3 activation and provided moderate to excellent yields. Although the electron poor aryltrifluoroborates resulted in a low yield in this reaction, it was found that addition of either a catalytic or a stoichiometric amount of acetic acid in the reaction medium increased the production of the desired product **4** to a moderate yield (entry 7).



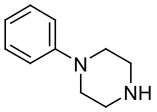
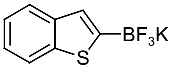
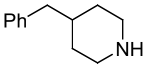
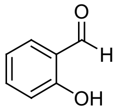
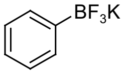
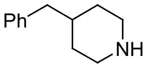
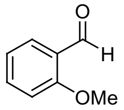
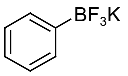
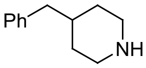
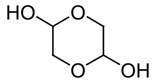
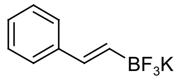
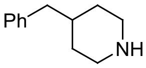
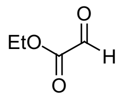
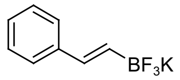
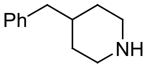
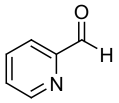
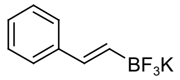
Scheme 3.

Interestingly, potassium allyltrifluoroborate, developed by Batey et al.[5a,b] provided the desired homoallylic amine in moderate yield (entry 12) under nonoptimized conditions.

Finally, the scope of this three-component Mannich type reaction was further investigated by variations of the aldehyde reactant (Scheme 3, Table 3). It was found that only the aldehydes having an α or an *ortho* activating group successfully underwent this reaction, which agrees with results from Petasis and Akritopoulou[1,8] (e.g., entry 2 vs 3). Consequently, Lewis acid activated organotrifluoroborates behave and follow the same type of postulated mechanism pathway as the boronic acids in the Petasis reaction.

In conclusion, we showed that less reactive boronic acids (e.g., aryl) in the standard Petasis reaction, when paraformaldehyde is used, can be easily replaced by potassium organotrifluoroborates in the presence of a catalytic amount of Lewis acid. Moreover, we found that the formation of the desired product under these new conditions is highly dependent on the effect and nature of the solvent, the Lewis acid itself, and finally the reaction temperature used. Ultimately, we have successfully developed a Lewis acid-catalyzed Mannich

Table 3. Effect of aldehydes on the formation of **5** by the three-component Mannich type reaction

Entry[a]	R^1R^2NH	R^3CHO	R^4BF_3K	Yield for **5** (%)[b]
1		$(CH_2O)_n$		95
2				75
3				No reaction
4				78
5				21
6				58

[a] R^1R^2NH (1.0 equiv), R^3CHO (1.1–1.2 equiv), R^4BF_3K (1.2 equiv), $BF_3{\cdot}OEt_2$ (25 mol%), anhydrous toluene (0.14 M), 90 °C for 1 h.

[b] After work-up and flash chromatography on silica gel.

type reaction using potassium organotrifluoroborates (aryl, vinyl, and allyl reagents) as an extension of the standard Petasis reaction. We are currently working on the optimization of the reaction conditions using potassium allyl- and crotyltrifluoroborates^4 to prepare homoallylic amines and in addition, an asymmetric version of this three-component transformation using chiral Lewis acids.

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3. Compound **2** was isolated, purified by flash chromatography, and characterized. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.29–7.22 (m, 2H), 7.19–7.11 (m, 3H), 3.12–3.03 (m, 2H), 2.53–2.42 (m, 7H), 1.67–1.56 (m, 3H), 1.47–1.33 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 140.04, 129.23, 128.51, 126.21, 54.43, 44.45, 42.45, 36.21, 30.47; MS (EI): 190.2 [M+H]$^{+\cdot}$.
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9. Representative procedure for the preparation of **1**: A stirred suspension, under nitrogen, of 4-benzylpiperidine (0.1 mL, 0.55 mmol, 1.0 equiv) and paraformaldehyde (20 mg, 0.65 mmol, 1.2 equiv) in anhydrous toluene (4 mL) was heated at 90 °C for 10–15 min. The resulting solution was allowed to cool down to rt, and PhBF$_3$K (125 mg, 0.68 mmol, 1.2 equiv) and BF$_3$·OEt$_2$ (0.02 mL, 0.14 mmol, 25 mol %) were successively added. After 5 min, the reaction mixture was heated to 90 °C for 5 h. Then, the reaction was allowed to cool down to rt, and the reaction mixture was neutralized with a saturated aqueous solution of NH$_4$Cl (10 mL). After shaking for 30 min, the reaction mixture was successively basified with 2 N NaOH (20 mL), extracted with CH$_2$Cl$_2$, and the combined organic layer was dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (4% NH$_4$OH in MeOH/CH$_2$Cl$_2$: 2/98 $\rightarrow$ 5/95) to give the desired product **1** (112 mg, 0.42 mmol) in 75% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.34–7.12 (m, 10H), 3.51 (s, 2H), 2.90 (br d, $J = 11.7$ Hz, 2H), 2.57 (d, $J = 7.0$ Hz, 2H), 1.94 (tr d, $J = 11.7$, 2.3 Hz, 2H), 1.69–1.60 (m, 2H), 1.59–1.50 (m, 1H), 1.39 (dd, $J = 12.4$, 3.6 Hz, 1H), 1.33 (dd, $J = 11.7$, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 140.55, 138.95, 129.23, 128.91, 128.37, 127.02, 126.00, 63.21, 54.05, 43.32, 38.34, 32.74; MS (EI): 266.4 [M+H]$^{+\cdot}$.
10. All compounds **4** and **5** have been characterized by ^{1}H and ^{13}C NMR, and MS.
11. This potassium organotrifluoroborate was prepared in five steps from methyl 4-bromobenzoate according to known reactions.