



# Rapid “high” temperature batch and flow lithiation-trapping of *N*-Boc pyrrolidine<sup>☆</sup>



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## ABSTRACT

The development of suitable reaction conditions for the rapid “high” temperature lithiation-trapping of *N*-Boc pyrrolidine under batch and flow conditions is described. For optimisation of batch conditions, the lithiation-trapping was explored using *s*-BuLi at temperatures of  $-30$  to  $20$  °C. Two new batch lithiation conditions were discovered using the biomass-derived, sustainable solvent, 2-MeTHF: diamine-free lithiation in 2-MeTHF gave  $\alpha$ -substituted pyrrolidines in 50–69% yields at  $-20$  °C or  $0$  °C. The requirement for very short lithiation times is explained by the chemical instability of the lithiated intermediate at high temperatures. A practical flow chemistry reaction manifold (*s*-BuLi, TMEDA, THF,  $0$  °C,  $5$  s) has been developed which delivered an  $\alpha$ -substituted pyrrolidine in 59% yield. This flow process opens up new opportunities for scaling-up of lithiation-trapping reactions of *N*-Boc heterocycles.

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## 1. Introduction

Heterocycles such as pyrrolidines, piperidines, piperazines and morpholines are amongst the most common saturated ring systems in blockbuster drug molecules [1,2]. In this context, there are a growing number of marketed pharmaceuticals that contain the  $\alpha$ -substituted pyrrolidine motif, including the anti-cancer and antiviral agents Larotrectinib [3], Acalabrutinib [4] and Telaprevir [5] (Fig. 1A). The lithiation-trapping of *N*-Boc heterocycles, first introduced by Beak in 1989 (using *s*-BuLi/TMEDA in Et<sub>2</sub>O at  $-78$  °C) [6], is a useful route to  $\alpha$ -substituted saturated nitrogen heterocycles [7] and continues to be exploited in the synthesis of potential drugs by medicinal and process chemists [5,8,9]. For example, lithiation-carboxylation of  $\sim 100$  kg of a bicyclic *N*-Boc pyrrolidine was carried out by process chemists at Vertex in the synthesis of the hepatitis C drug Telaprevir [2]. Similarly, at Merck, a lithiation-transmetallation-Negishi cross-coupling reaction was carried out on  $\sim 1$  kg scale starting from *N*-Boc pyrrolidine *en route* to a glucokinase activator (Fig. 1A) [8]. In both examples, *s*-BuLi and a bispidine diamine in *tert*-butyl methyl ether were used for the lithiation step and the reaction temperature was maintained at  $-75$

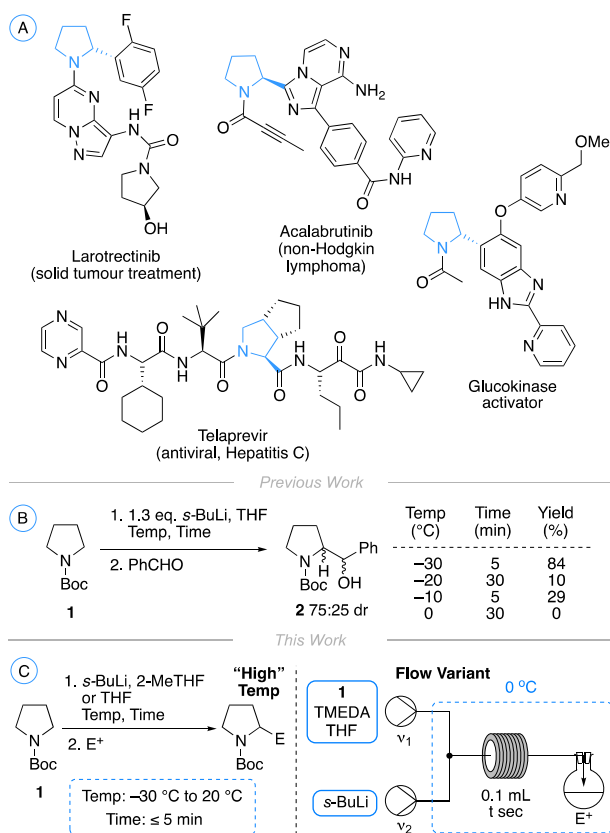
to  $-68$  °C for 2.5–3 h, a not-inconsiderable task and expense given the scale involved [10].

As part of our ongoing work on the synthesis of  $\alpha$ -substituted saturated nitrogen heterocycles [11], we have previously reported a diamine-free, “high” temperature lithiation-trapping protocol for *N*-Boc pyrrolidine **1** which, using PhCHO, delivered  $\alpha$ -trapped product **2** (75:25 dr) in 84% yield (Fig. 1B) [12,13]. The lithiation was accomplished using *s*-BuLi in THF at  $-30$  °C for just 5 min. Despite the improvement on both reaction temperature and lithiation time compared to Beak's original report ( $-78$  °C, 3.5 h, TMEDA required), we were not entirely satisfied with these reaction conditions and hypothesised that it might be possible to push the lithiation temperature even higher than  $-30$  °C. However, our previously reported attempts at this were somewhat discouraging: lithiation of *N*-Boc pyrrolidine **1** in THF at  $-20$  °C for 30 min,  $-10$  °C for 5 min and  $0$  °C for 30 min followed by PhCHO trapping gave  $\alpha$ -substituted pyrrolidine **2** in 0–29% yield (Fig. 1B) [12]. We had previously concluded that these lower yields were due to consumption of more *s*-BuLi by  $\alpha$ -lithiation of the THF solvent [14], facilitated by the higher temperatures. On reflection, we began to consider an alternative explanation, namely that the lithiated *N*-Boc pyrrolidine is chemically unstable if left for  $\geq 5$  min at these higher temperatures. This idea ultimately led us to revisit lithiation temperatures above  $-30$  °C, due to the potential energy savings associated with large-scale (e.g. kg-scale) reactions. Furthermore, we also wished to fully explore 2-MeTHF as a reaction solvent. The advantages of using 2-MeTHF are that it is a biomass-derived, sustainable solvent

<sup>☆</sup> This paper is dedicated with much respect to the memory of Professor Jonathan M. J. Williams, a wonderfully creative synthetic chemist who was sadly taken too soon.

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**Fig. 1.** A. Exemplar pharmacologically active  $\alpha$ -substituted pyrrolidines. B. Previous work: Diamine-free lithiation-trapping of *N*-Boc pyrrolidine **1**. C. This work: High yielding lithiation-trapping of *N*-Boc pyrrolidine **1** at temperatures above  $-30$  °C and a flow variant using *s*-BuLi and TMEDA in THF at  $0$  °C.

and it is less water-miscible than THF making it preferable to THF for working-up reactions, especially on scale [15,16]. With both of these key aspects in mind, we explored the lithiation-trapping of *N*-Boc pyrrolidine **1** at  $-30$  °C and above with reaction times of 5 min or less (batch conditions, Fig. 1C). Ultimately, this led to new “high” temperature lithiation-trapping conditions (2-MeTHF at  $-20$  °C or  $0$  °C) for *N*-Boc pyrrolidine **1**.

As a final aim, having developed a lithiation protocol that required a very short reaction time (5 s) at  $0$  °C, we also wished to explore an increasingly popular method for working with organolithium intermediates that are unstable at “high” temperatures, namely the use of continuous flow technology. The topical nature of flow organolithium chemistry is highlighted by the fact that four excellent review articles, authored by Nagaki [17], Piccardi [18], Nagaki/Luisi [19] and McGlacken [20], have appeared in the last two years. Although a wide range of reactions proceeding via organolithium intermediates have now been carried out using flow chemistry [17–21], it is notable that this technology has not previously been applied to a lithiation-trapping reaction of a *N*-Boc heterocycle. Herein, we describe both batch and flow lithiation-trapping of *N*-Boc pyrrolidine **1** at temperatures above  $-30$  °C.

## 2. Results and discussion

To start, the lithiation-trapping of *N*-Boc pyrrolidine **1** was carried out under different reaction conditions. Thus, 1.3 equiv. of *s*-BuLi was used to lithiate *N*-Boc pyrrolidine **1** (1 mmol scale) in four solvent systems: (a) THF alone, (b) 2-MeTHF alone, (c) 2-MeTHF with 1.3 equiv. of TMEDA and (d) Et<sub>2</sub>O with 1.3 equiv. of TMEDA.

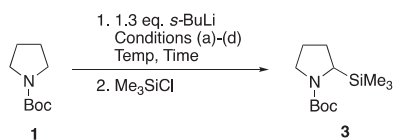
The lithiations were conducted at temperatures ranging from  $-30$  °C to  $20$  °C for  $\leq 5$  min before trapping with Me<sub>3</sub>SiCl. The % yield of silyl pyrrolidine **3** isolated after purification by chromatography was used to compare the efficiencies of the different conditions. The four sets of lithiation conditions were chosen based on our previously reported diamine-free, “high” temperature lithiations in THF (Fig. 1B) and Beak’s original conditions (Et<sub>2</sub>O, TMEDA) [6] as well as the desire to explore analogous reactions in 2-MeTHF (with and without added TMEDA). The full results under a range of lithiation temperatures and times are presented in Table 1.

Lithiations at  $-30$  °C for 5 min before reaction with Me<sub>3</sub>SiCl delivered silyl pyrrolidine **3** in yields of 66–76% under the four sets of conditions (entry 1), clearly indicating that all were suitable for synthetic applications. A similar profile in % yields of **3** was found at  $-20$  °C for 5 min (57–71%, entry 2) and at  $-20$  °C for 2 min (52–70%, entry 3). In THF or 2-MeTHF at  $-20$  °C for 2 min, yields of **3** were 65% and 52% respectively (entry 3). However, lower yields of **3** (particularly for the reaction in 2-MeTHF) were obtained at  $-10$  °C for 2 min (entry 4). To account for this, as proposed in the Introduction, we suspected that the generated lithiated *N*-Boc pyrrolidine is chemically unstable at temperatures above  $-20$  °C. As a result, even shorter lithiation times for reactions at  $-10$  °C and above were explored (entries 5–9). For example, lithiating *N*-Boc pyrrolidine **1** at  $-10$  °C for 30 s gave a satisfactory yield profile (46–74%, entry 6). However, at this high temperature, it was noticeable that reactions in the presence of TMEDA (69–74%) were higher yielding than those without TMEDA (46–47%). We ascribe this to a better chemical stability of the TMEDA-complexed lithiated *N*-Boc pyrrolidine which is supported by a more detailed study of chemical stability under different conditions (*vide infra*). Finally, lithiation at  $0$  °C was explored but an extremely short lithiation time of 5 s was required to obtain synthetically useful yields (50–63%, entry 8). Lithiations at  $0$  °C for just 2 s led to disappointing yields of **3** (16–33%, entry 9). Clearly, attempts to push the reaction temperature as high as possible had reached their limit and we do not recommend the use of  $20$  °C for these types of lithiations.

Next, we explored the chemical stability of the lithiated *N*-Boc pyrrolidine at  $0$  °C using the four sets of conditions. Our plan was to generate the intermediate organolithium by lithiation of *N*-Boc pyrrolidine **1** with 1.3 equiv. of *s*-BuLi at  $-30$  °C over 5 min in each of the four solvent systems (a)–(d) from Table 1. Then, the lithiated species would be incubated at  $0$  °C for 5 min or 30 min before trapping with Me<sub>3</sub>SiCl to give silyl pyrrolidine **3**. The % yield obtained after purification by chromatography would then be used as a reporter on the chemical stability of the lithiated *N*-Boc pyrrolidine at  $0$  °C. The results obtained from these incubation experiments are shown in Table 2.

The % yields of silyl pyrrolidine **3** obtained by direct trapping after lithiating at  $-30$  °C for 5 min in the four different solvent systems are shown in entries 1, 4, 7 and 10 in Table 2 as points of reference. In all four conditions, lower yields of silyl pyrrolidine **3** were obtained after incubation at  $0$  °C for 5 min (compare entries 1/2, 4/5, 7/8 and 10/11). Furthermore, extending the incubation time at  $0$  °C to 30 min led to extremely low or no isolated yields of silyl pyrrolidine **3** (0–4%, entries, 3, 6, 9 and 12). Taken together, these results implicate chemical instability of the lithiated *N*-Boc pyrrolidine as the source of low yields under “high” temperature lithiation conditions over longer lithiation times. Indeed, this provides an explanation for the very low yielding results for the lithiation-trapping of *N*-Boc pyrrolidine **1** obtained in THF at temperatures of  $-20$  °C or above from our earlier study [12] (Fig. 1B).

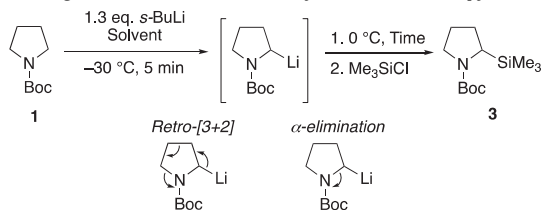
The results in Table 2 also highlight two additional points. First, lithiated *N*-Boc pyrrolidine appears to be more chemically unstable in 2-MeTHF than in THF (compare entries 2/5). Second, TMEDA

**Table 1**Investigation of reaction conditions for the lithiation-trapping of *N*-Boc pyrrolidine **1** to give silyl pyrrolidine **3**.

Entry	Temp (°C)	Time	(a) THF Yield of <b>3</b> (%) <sup>a</sup>	(b) 2-MeTHF Yield of <b>3</b> (%) <sup>a</sup>	(c) 2-MeTHF + TMEDA <sup>b</sup> Yield of <b>3</b> (%) <sup>a</sup>	(d) Et <sub>2</sub> O + TMEDA <sup>b</sup> Yield of <b>3</b> (%) <sup>a</sup>
1	−30	5 min	66	69	76	73
2	−20	5 min	64	57	69	71
3	−20	2 min	65	52	68	70
4	−10	2 min	53	28	—	—
5	−10	1 min	58	35	—	67
6	−10	30 s	47	46	74	69
7	0	10 s	—	31	—	55
8	0	5 s	59	50	63	53 <sup>c,d</sup>
9	20	2 s	22	33	16	30

<sup>a</sup> Yield after purification by chromatography.<sup>b</sup> 1.3 equiv. of TMEDA.<sup>c</sup> The % yield of **3** in Et<sub>2</sub>O alone was 20%, probably due to a slower rate of lithiation in the absence of TMEDA.<sup>d</sup> The % yield of **3** in TBME with TMEDA was 67% (14% in absence of TMEDA).

appears to have a minor stabilising effect on the stability of lithiated *N*-Boc pyrrolidine (compare entries 5/8). Of note, the use of THF or Et<sub>2</sub>O/TMEDA appear to stabilise the lithiated *N*-Boc pyrrolidine to the highest degree (entries 2 and 11). Unfortunately, we have not been able to identify a pathway for the chemical instability of lithiated *N*-Boc pyrrolidine. At first, we considered that lithiation of the solvent by the generated lithiated *N*-Boc pyrrolidine may be occurring. For example,  $\alpha$ -lithiation of THF and 2-MeTHF and  $\beta$ -lithiation-elimination of Et<sub>2</sub>O by organolithiums are known processes [14,22]. However, the lack of formation of significant amounts of *N*-Boc pyrrolidine **1** after incubation at 0 °C for 30 min did not fit with that proposal. Instead, we imagine that lithiated *N*-Boc pyrrolidine decomposes either *via* a retro-[3 + 2] cycloaddition (in an analogous way to lithiated THF [14]) or *via*  $\alpha$ -elimination to

**Table 2**Investigation of the chemical stability of lithiated *N*-Boc pyrrolidine.

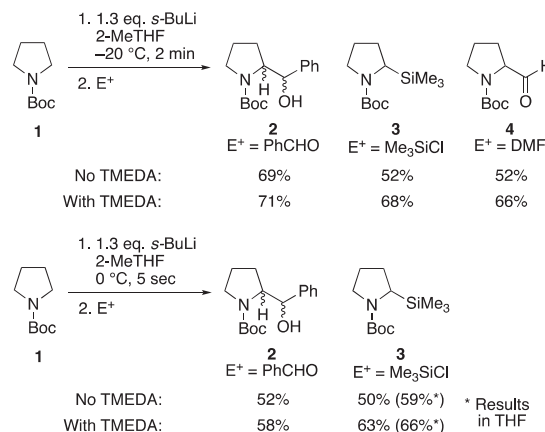
Entry	Solvent)	Time (min)	Yield of <b>3</b> (%) <sup>a</sup>
1	THF	n.a.	66 <sup>c</sup>
2	THF	5	51
3	THF	30	4
4	2-MeTHF	n.a.	54 <sup>c</sup>
5	2-MeTHF	5	18 <sup>d</sup>
6	2-MeTHF	30	2 <sup>e</sup>
7	2-MeTHF + TMEDA <sup>b</sup>	n.a.	76 <sup>c</sup>
8	2-MeTHF + TMEDA <sup>b</sup>	5	25
9	2-MeTHF + TMEDA <sup>b</sup>	30	2
10	Et <sub>2</sub> O + TMEDA <sup>b</sup>	n.a.	73 <sup>c</sup>
11	Et <sub>2</sub> O + TMEDA <sup>b</sup>	5	52
12	Et <sub>2</sub> O + TMEDA <sup>b</sup>	30	0 <sup>f</sup>

<sup>a</sup> Yield after purification by chromatography.<sup>b</sup> 1.3 equiv. of TMEDA.<sup>c</sup> This experiment was not incubated at 0 °C; % yield obtained after trapping directly after 5 min at −30 °C.<sup>d</sup> 6% of starting material **1** also isolated.<sup>e</sup> 24% of starting material **1** also isolated.<sup>f</sup> 20% of starting material **1** also isolated.

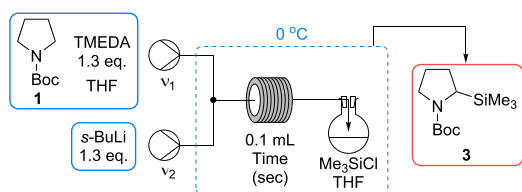
give a carbene (Table 2), both processes that could be facilitated by higher temperatures. Disappointingly, despite careful analysis of the <sup>1</sup>H NMR spectra of the crude reaction mixtures and attempted isolation of any by-products, we have been unable to identify any products from either of these proposed pathways. For that reason, these two suggested decomposition pathways must be treated as speculative at this point.

Based on the results presented in Table 1 and the conclusions from Table 2, two useful sets of reaction conditions for carrying out the racemic lithiation-trapping of *N*-Boc pyrrolidine **1** in 2-MeTHF can be identified: (i) −20 °C for 2 min (Table 1, entry 3) and (ii) 0 °C for 5 s (Table 1, entry 8). Using each of these conditions, better % yields of silyl pyrrolidine **3** were obtained with added TMEDA. However, even diamine-free lithiation-silylation in 2-MeTHF delivered useful % yields of approximately 50%. Two other electrophiles (PhCHO and DMF) were explored under our recommended conditions and the results in 2-MeTHF with and without TMEDA present are summarised in Scheme 1. When using these reaction conditions in synthetic applications on a small-scale, the conditions at −20 °C for 2 min or 0 °C for 5 s will be suitable for batch reactions.

At this stage, it was clear that these new “high” temperature conditions were unlikely to be suitable for larger-scale batch reactions. Furthermore, given the inherent instability of lithiated *N*-

**Scheme 1.** Lithiation-trapping of *N*-Boc pyrrolidine **1** in 2-MeTHF at −20 °C and 0 °C.

**Table 3**  
Optimisation of continuous flow synthesis of silyl pyrrolidine **3**.



Entry	$\nu_1/\text{mL min}^{-1}$	$\nu_2/\text{mL min}^{-1}$	Time (sec)	Yield of <b>3</b> (%) <sup>a</sup>
1	0.50	0.10	10	34
2	1.00	0.20	5	53
3	1.25	0.25	4	59
4	1.67	0.33	3	59

<sup>a</sup> Yield after purification by chromatography.

Boc pyrrolidine at 0 °C (see Table 2), performing such lithiation reactions on scale will be practically challenging due to the need for fast addition of the *s*-BuLi and issues with mixing and heat dissipation. We therefore turned our attention to the development of a continuous flow process [17–21] for the synthesis of silyl pyrrolidine **3** at 0 °C. As shown in Scheme 1, using *s*-BuLi/THF or *s*-BuLi/TMEDA in THF at 0 °C for 5 s gave the best batch yields of silyl pyrrolidine **3** (59% and 66% respectively). Thus, suspecting that using THF as the solvent and employing TMEDA helps to stabilise the lithiated *N*-Boc pyrrolidine, we employed these conditions and investigated the effect of reaction time on the isolated yield of silyl pyrrolidine **3** (Table 3).

Using a Uniqsis FlowSyn system (see ESI for set-up) fitted with a T-mixer, a pre-cooled stream of *N*-Boc pyrrolidine **1** and TMEDA were mixed with *s*-BuLi at 0 °C, before flowing through a 0.1 mL microtube reactor. Subsequent trapping with Me<sub>3</sub>SiCl in THF solution in a flask at 0 °C resulted in formation of silyl pyrrolidine **3** (Table 3). With a residence time of 10 s, silyl pyrrolidine **3** was isolated in a disappointing 34% yield after chromatography (entry 1). Reducing the residence time to 5 s led to a significantly improved yield of 53% of silyl pyrrolidine **3** (entry 2). Further reduction in residence time to 4 s or 3 s gave silyl pyrrolidine **3** in 59% yield (entries 3 and 4). These last two results are comparable with the diamine-free batch synthesis of silyl pyrrolidine **3** for 5 s at 0 °C (see Table 1, entry 8). However, of significance, the continuous flow process will be amenable to scale-up. The results presented in Table 3 represent the first example of a lithiation-trapping reaction of a *N*-Boc heterocycle using flow chemistry.

### 3. Conclusion

In conclusion, an exploration of temperatures of –30 °C and above for the rapid “high” temperature lithiation-trapping of *N*-Boc pyrrolidine **1** has led to the identification of two new sets of reaction conditions. Diamine-free lithiation in 2-MeTHF works well at either –20 °C (2 min) or 0 °C (just 5 s) delivering  $\alpha$ -substituted pyrrolidines **2**, **3** or **4** in 50–69% yields. From a green chemistry perspective, these conditions represent significant improvements on those previously used as the temperatures are higher (and so there would be less energy required to cool larger-scale reactions) and the petroleum-derived solvents Et<sub>2</sub>O and THF have been replaced by the biomass-derived, sustainable solvent, 2-MeTHF. From a mechanistic perspective, we have also shown that lower yields at higher temperatures and/or longer lithiation times are due to the chemical instability of lithiated *N*-Boc pyrrolidine. Most importantly, however, we have demonstrated that lithiation-trapping of *N*-Boc heterocycles is possible at 0 °C (in THF using *s*-

BuLi/TMEDA) using continuous flow methods and this opens up new opportunities for these lithiation-trapping processes, including the potential for scale-up.

## 4. Experimental

### 4.1. General

All non-aqueous reactions were carried out under oxygen-free Ar atmosphere using flame-dried glassware. Et<sub>2</sub>O and THF were freshly distilled from sodium and benzophenone. 2-MeTHF, TMEDA and Me<sub>3</sub>SiCl were purified by short-path distillation over CaH<sub>2</sub> before use. Benzaldehyde was purified by Kugelrohr distillation. DMF was used directly from the Pure Solv. MD-7 purification system. *s*-BuLi was titrated against *N*-benzylbenzamide before use [23]. Flash column chromatography was carried out according to standard techniques using silica gel (60 Å, 220–440 mesh particle size 40–63 µm) purchased from Sigma-Aldrich or Fluka silica gel, 35–70 µm, 60 Å and the solvent system as stated. Thin layer chromatography was carried out using Merck TLC Silica gel 60G F254 aluminium backed plates (100390 Supelco). Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in CDCl<sub>3</sub>, chemical shifts are quoted in parts per million relative to CHCl<sub>3</sub> ( $\delta_{\text{H}}$  7.26) and CDCl<sub>3</sub> ( $\delta_{\text{C}}$  77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in hertz. Infrared spectra were recorded on a PerkinElmer UATR 2 FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. *N*-Boc pyrrolidine **1** was prepared according to the literature procedure [24].

### 4.2. General procedure A: lithiation-trapping in THF or 2-MeTHF

*s*-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (1.0 eq.) in THF or 2-MeTHF (7 mL) at the specified temperature (–30 °C–20 °C) under Ar. The resulting solution was stirred at the specified temperature for the specific time (2 s–5 min). Then, the electrophile (Me<sub>3</sub>SiCl, PhCHO or DMF) (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated NH<sub>4</sub>Cl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 mL) and the combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Table 1.

### 4.3. General procedure B: lithiation-trapping in 2-MeTHF or Et<sub>2</sub>O with TMEDA

*s*-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (1.0 eq.) and TMEDA (1.3 eq.) in 2-MeTHF or Et<sub>2</sub>O (7 mL) at the specified temperature (–30 °C–20 °C) under Ar. The resulting solution was stirred at the specified temperature for the specific time (2 s–5 min). Then, the electrophile (Me<sub>3</sub>SiCl, PhCHO or DMF) (2.0 eq.) was added. The resulting solution was stirred at the specified temperature for 10 min and then allowed to warm to rt over 1 h. Saturated NH<sub>4</sub>Cl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 mL) and the combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Table 1.



#### 4.4. General procedure C: lithiation-trapping in THF or 2-MeTHF followed by incubation

*s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175  $\mu$ L, 1.0 mmol) in THF or 2-MeTHF (7 mL) at  $-30^{\circ}\text{C}$  under Ar. The resulting solution was stirred at  $-30^{\circ}\text{C}$  for 5 min. The reaction flask was transferred to a  $0^{\circ}\text{C}$  bath and stirred at  $0^{\circ}\text{C}$  for 5 or 30 min. Then,  $\text{Me}_3\text{SiCl}$  (218 mg, 256  $\mu$ L, 2.0 mmol) was added. The resulting solution was stirred at  $0^{\circ}\text{C}$  for 10 min and then allowed to warm to rt over 1 h. Saturated  $\text{NH}_4\text{Cl}_{(\text{aq})}$  (10 mL) was added and the two layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude product. [Table 2](#).

#### 4.5. General procedure D: lithiation-trapping in 2-MeTHF or $\text{Et}_2\text{O}$ with TMEDA followed by incubation

*s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (171 mg, 175  $\mu$ L, 1.0 mmol) and TMEDA (151 mg, 195  $\mu$ L, 1.3 mmol) in  $\text{Et}_2\text{O}$  or 2-MeTHF (7 mL) at  $-30^{\circ}\text{C}$  under Ar. The resulting solution was stirred at  $-30^{\circ}\text{C}$  for 5 min. The reaction flask was transferred to a  $0^{\circ}\text{C}$  bath and stirred at  $0^{\circ}\text{C}$  for 5 or 30 min. Then,  $\text{Me}_3\text{SiCl}$  (218 mg, 256  $\mu$ L, 2.0 mmol) was added. The resulting solution was stirred at  $0^{\circ}\text{C}$  for 10 min and then allowed to warm to rt over 1 h. Saturated  $\text{NH}_4\text{Cl}_{(\text{aq})}$  (10 mL) was added and the two layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude product. [Table 2](#).

#### 4.6. 2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid tert-butyl ester *syn*-2 and *anti*-2

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175  $\mu$ L, 1.0 mmol) in 2-MeTHF (7 mL) at  $-20^{\circ}\text{C}$  for 2 min and benzaldehyde (228 mg, 203  $\mu$ L, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 98:2  $\text{CH}_2\text{Cl}_2$ -acetone as eluent gave pyrrolidine *syn*-**2** (119 mg, 43%) as a colourless oil,  $R_F$  (98:2  $\text{CH}_2\text{Cl}_2$ -acetone) 0.4;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38–7.27 (m, 5H, Ph), 5.93 (br s, 1 H, OH), 4.53 (br d,  $J = 7.5$  Hz 1H, OCH), 4.09 (td,  $J = 7.5, 5.0$  Hz, 1H, NCH), 3.50–3.42 (m, 1H, NCH), 3.39–3.28 (m, 1H, NCH), 1.78–1.65 (m, 2H, CH), 1.65–1.56 (m, 2H, CH), 1.52 (s, 9H,  $\text{CMe}_3$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  158.5 (C=O), 141.3 (*ipso*-Ph), 128.8 (Ph), 128.6 (Ph), 127.2 (Ph), 81.1 (OCH), 79.5 ( $\text{CMe}_3$ ), 65.5 (NCH), 47.9 (NCH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 28.7 ( $\text{CMe}_3$ ), 24.0 (CH<sub>2</sub>), a 65:35 mixture (by  $^1\text{H}$  NMR spectroscopy) of pyrrolidine *anti*-**2** and *syn*-**2** (4 mg, 1%) as a colourless oil and pyrrolidine *anti*-**2** (70 mg, 25%) as a colourless oil,  $R_F$  (98:2  $\text{CH}_2\text{Cl}_2$ -acetone) 0.3;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) (75:25 mixture of rotamers)  $\delta$  7.41–7.22 (m, 5H, Ph), 5.49 (br s, 0.75H, OH), 5.17 (br s, 0.25H, OH), 4.86 (br s, 0.75H, OCH), 4.32 (br s, 0.75H, NCH), 3.97 (br s, 0.25H, OCH), 3.57 (br s, 0.25H, NCH), 3.30 (br s, 1H, NCH), 2.81 (br s, 0.75H, NCH), 2.30 (br s, 0.25H, NCH), 2.04–1.87 (m, 1H, CH), 1.86–1.66 (m, 1H, CH), 1.57 (br s, 3.5 H,  $\text{CMe}_3$ ), 1.52 (br s, 5.5 H,  $\text{CMe}_3$ ), 1.20–1.09 (m, 1H, CH), 0.93–0.79 (m, 1H, CH);  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  159.8 (C=O), 157.4 (C=O), 141.9 (*ipso*-Ph), 141.3 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.1 (Ph), 127.4 (Ph), 127.1 (Ph), 126.1 (Ph), 80.5 ( $\text{CMe}_3$ ), 80.4 ( $\text{CMe}_3$ ), 76.3 (COH), 63.3 (NCH), 47.9 (NCH<sub>2</sub>), 47.7 (NCH<sub>2</sub>), 28.6 ( $\text{CMe}_3$ ), 27.5 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 23.6 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>). Spectroscopic data consistent with those reported in the literature [\[25\]](#). The total yield of *syn*-**2** and *anti*-**2** is 69%. [Scheme 1](#).

#### 4.7. 2-Trimethylsilyl pyrrolidine-1-carboxylic acid tert-butyl ester 3

Using general procedure A, *s*-BuLi (2.0 mL of a 2.6 M solution in hexanes, 2.6 mmol) and *N*-Boc pyrrolidine **1** (342 mg, 350  $\mu$ L, 2.0 mmol) in 2-MeTHF (10 mL) at  $-20^{\circ}\text{C}$  for 2 min and  $\text{Me}_3\text{SiCl}$  (326 mg, 381  $\mu$ L, 3.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol- $\text{Et}_2\text{O}$  as eluent gave silyl pyrrolidine **3** (254 mg, 52%) as a colourless oil,  $R_F$  (8:2 petrol- $\text{Et}_2\text{O}$ ) 0.4;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.56–3.41 (m, 1H, NCH), 3.29–3.23 (m, 1H, NCH), 3.19–3.12 (m, 1H, NCH), 2.06–1.95 (m, 1H, CH), 1.82–1.72 (m, 3H, CH), 1.45 (s, 9H,  $\text{CMe}_3$ ), 0.04 (s, 9H,  $\text{SiMe}_3$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ) (rotamers)  $\delta$  154.6 (C=O), 79.2 ( $\text{CMe}_3$ ), 78.3 ( $\text{CMe}_3$ ), 47.6 (NCH), 47.0 (NCH<sub>2</sub>), 46.6 (NCH<sub>2</sub>), 28.5 ( $\text{CMe}_3$ ), 27.9 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 24.9 (CH<sub>2</sub>),  $-2.2$  ( $\text{SiMe}_3$ ). Spectroscopic data consistent with those reported in the literature [\[26\]](#). [Table 1](#), entry 3(b) and [Scheme 1](#).

#### 4.8. *N*-(tert-Butoxycarbonyl)pyrrolidine-2-carboxaldehyde 4

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol) and *N*-Boc pyrrolidine **1** (171 mg, 175  $\mu$ L, 1.0 mmol) in 2-MeTHF (7 mL) at  $-20^{\circ}\text{C}$  for 2 min and DMF (146 mg, 155  $\mu$ L, 2.0 mmol) gave the crude product. Purification by flash column chromatography on silica with 1:1 hexane- $\text{Et}_2\text{O}$  as eluent gave aldehyde **4** (105 mg, 52%) as a colourless oil,  $R_F$  (1:1 hexane- $\text{Et}_2\text{O}$ ) 0.3;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) (60:40 mixture of rotamers)  $\delta$  9.56 (d,  $J = 2.0$  Hz, 0.4H, CHO), 9.46 (d,  $J = 3.0$  Hz, 0.6H, CHO), 4.24–4.17 (m, 0.4H, NCH), 4.05 (ddd,  $J = 8.5, 6.0, 3.0$  Hz, 0.6H, NCH), 3.61–3.38 (m, 2H, NCH), 2.20–1.74 (m, 4H, CH), 1.48 (s, 4H,  $\text{CMe}_3$ ), 1.43 (s, 5H,  $\text{CMe}_3$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ) (rotamers)  $\delta$  200.7 (C=O, CHO), 200.5 (C=O, CHO), 154.0 (C=O, Boc), 80.6 ( $\text{CMe}_3$ ), 80.2 ( $\text{CMe}_3$ ), 65.0 (NCH), 64.8 (NCH), 46.8 (NCH<sub>2</sub>), 46.7 (NCH<sub>2</sub>), 28.4 ( $\text{CMe}_3$ ), 28.2 ( $\text{CMe}_3$ ), 28.0 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 23.9 (CH<sub>2</sub>). Spectroscopic data consistent with those reported in the literature [\[27\]](#). [Scheme 1](#).

#### 4.9. General procedure E: continuous flow synthesis of 2-trimethylsilyl pyrrolidine-1-carboxylic acid tert-butyl ester 2

A Uniqsis FlowSyn system fitted with a T-mixer and a 0.1 mL reaction tube (0.5 mm ID  $\times$  50 cm PTFE tubing) was flushed with anhydrous THF (100 mL) under  $\text{N}_2$  and the pre-mixer tubing, mixer and reaction tubing was cooled to  $0^{\circ}\text{C}$ . The end of the reaction tubing was added to a 2-neck RBF containing  $\text{Me}_3\text{SiCl}$  (761  $\mu$ L, 6.0 mmol, 2.0 eq.) at  $0^{\circ}\text{C}$  under  $\text{N}_2$ . A solution of *N*-Boc pyrrolidine **1** (526  $\mu$ L, 3.0 mmol, 1.0 eq., 0.20 M) and TMEDA (585  $\mu$ L, 3.9 mmol, 1.3 eq., 0.26 M) in anhydrous THF (15 mL) under  $\text{N}_2$  was pumped through the FlowSyn system at a flow rate between 0.5 and 1.67 mL  $\text{min}^{-1}$ . Simultaneously, *s*-BuLi (1.3 M solution in hexanes, 3.0 mL, 3.9 mmol, 1.3 eq.) was pumped through the FlowSyn system at a flow rate between 0.10 and 0.33 mL  $\text{min}^{-1}$  from a 3 mL injection loop placed after the peristaltic pump. After 9–30 min, the flow reactor was stopped and the reaction was quenched with saturated  $\text{NH}_4\text{Cl}_{(\text{aq})}$  (10 mL).  $\text{Et}_2\text{O}$  (20 mL) was added and the two layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $2 \times 20$  mL) and the combined organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude product.

#### 4.10. 2-Trimethylsilyl pyrrolidine-1-carboxylic acid tert-butyl ester 3

Using general procedure E, *N*-Boc pyrrolidine **1** (526  $\mu$ L, 3.0 mmol, 1.0 eq., 0.20 M) and TMEDA (585  $\mu$ L, 3.9 mmol, 1.3 eq., 0.26 M) at 1.25 mL  $\text{min}^{-1}$ , *s*-BuLi (1.3 M solution in hexanes, 3.0 mL, 3.9 mmol, 1.3 eq.) at 0.25 mL  $\text{min}^{-1}$  and  $\text{Me}_3\text{SiCl}$  (761  $\mu$ L, 6.0 mmol,

2.0 eq.) for a total time of 12 min gave the crude product. Purification by flash column chromatography on silica with 85:15 hexane-Et<sub>2</sub>O as eluent gave silyl pyrrolidine **3** (433 mg, 59%) as a colourless oil. Table 3, entry 3.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tet.2020.131899>.

### References

- [1] R.D. Taylor, M. MacCoss, A.D.G. Lawson, *J. Med. Chem.* 57 (2014) 5845–5859.
- [2] E. Vitaku, D.T. Smith, J.T. Njardarson, *J. Med. Chem.* 57 (2014) 10257–10274.
- [3] R.C. Doebele, L.E. Davis, A. Vaishnavi, A.T. Le, A. Estrada-Bernal, S. Keysar, A. Jimeno, M. Varella-Garcia, D.L. Aisner, Y. Li, P.J. Stephens, D. Morosini, B.B. Tuch, M. Fernandes, N. Nanda, J.A. Low, *Canc. Discov.* 5 (2015) 1049–1057.
- [4] J. Wu, M. Zhang, D. Liu, *J. Hematol. Oncol.* 9 (2016) 21.
- [5] G.J. Tanoury, M. Chen, Y. Dong, R. Forslund, V. Jurkauskas, A.D. Jones, D. Belmont, *Org. Process Res. Dev.* 18 (2014) 1234–1244.
- [6] P. Beak, W.-K. Lee, *Tetrahedron Lett.* 30 (1989) 1197–1200.
- [7] K. Kasten, N. Selig, P. O'Brien, in: *Enantioselective Lithiation—Substitution of Nitrogen—Containing Heterocycles*, vol. 100, John Wiley & Sons, Inc., 2019, pp. 255–328.
- [8] A. Klapars, K.R. Campos, J.H. Waldman, D. Zewge, P.G. Dormer, C. Chen, *J. Org. Chem.* 73 (2008) 4986–4993.
- [9] (a) D. Xiao, B.J. Lavey, A. Palani, C. Wang, R.G. Aslanian, J.A. Kozlowski, N.-Y. Shih, A.T. McPhail, G.P. Randolph, J.E. Lachowicz, R.A. Duffy, *Tetrahedron Lett.* 46 (2005) 7653–7656; (b) B. Le Bourdonnec, A.J. Goodman, T.M. Graczyk, S. Belanger, P.R. Seida, R.N. DeHaven, R.E. Dolle, *J. Med. Chem.* 49 (2006) 7290–7306.
- [10] L.S. Bennie, W.J. Kerr, M. Middleditch, A.J.B. Watson, *Chem. Commun.* 47 (2011) 2264–2266.
- [11] (a) G. Carbone, P. O'Brien, G. Hilmersson, *J. Am. Chem. Soc.* 132 (2010) 15445–15450; (b) D. Stead, G. Carbone, P. O'Brien, K.R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* 132 (2010) 7260–7261; (c) G. Barker, J.L. McGrath, A. Klapars, D. Stead, G. Zhou, K.R. Campos, P. O'Brien, P. O'Brien, *J. Org. Chem.* 76 (2011) 5936–5953; (d) N.S. Sheikh, D. Leonori, G. Barker, J.D. Firth, K.R. Campos, A.J.H.M. Meijer, P. O'Brien, I. Coldham, *J. Am. Chem. Soc.* 134 (2012) 5300–5308; (e) P.J. Rayner, P. O'Brien, R.A. Horan, *J. Am. Chem. Soc.* 135 (2013) 8071–8077; (f) M. Lüthy, M.C. Wheldon, C. Haji-Cheteh, M. Atobe, P.S. Bond, P. O'Brien, R.E. Hubbard, I.J.S. Fairlamb, *Bioorg. Med. Chem.* 23 (2015) 2680–2694; (g) D. Stead, P. O'Brien, A. Sanderson, *Synlett* 26 (2015) 2381–2384; (h) D.J. Firth, P. O'Brien, L. Ferris, J.D. Firth, P. O'Brien, L. Ferris, *J. Am. Chem. Soc.* 138 (2016) 651–659; (i) J.D. Firth, P. O'Brien, L. Ferris, *J. Org. Chem.* 82 (2017) 7023–7031; (j) J.D. Firth, G. Gelardi, P.J. Rayner, D. Stead, P. O'Brien, *Heterocycles* 97 (2018) 1288–1303; (k) T.D. Downes, S.P. Jones, H.F. Klein, M.C. Wheldon, M. Atobe, P.S. Bond, J.D. Firth, N.S. Chan, L. Waddelove, R.E. Hubbard, D.C. Blakemore, C. De Fusco, S.D. Roughley, L.R. Vidler, M.A. Whatton, A.J.A. Woolford, G.L. Wrigley, P. O'Brien, *Chem. Eur. J.* 26 (2020) 8969–8975.
- [12] G. Barker, P. O'Brien, K.R. Campos, *Org. Lett.* 12 (2010) 4176–4179.
- [13] For asymmetric lithiation-trapping of *N*-Boc heterocycles at temperatures as high as –20 °C, see: G. Gelardi, G. Barker, P. O'Brien, D.C. Blakemore, *Org. Lett.* 15 (2013) 5424–5427.
- [14] R.B. Bates, L.M. Kroposki, D.E. Potter, *J. Org. Chem.* 37 (1972) 560–562.
- [15] (a) D.F. Aycok, *Org. Process Res. Dev.* 11 (2007) 156–159; (b) V. Antonucci, J. Coleman, J.B. Ferry, N. Johnson, M. Mathe, J.P. Scott, J. Xu, *Org. Process Res. Dev.* 15 (2011) 939–941.
- [16] For a review on the use of 2-MeTHF as a solvent for organometallic reactions, see: S. Monticelli, L. Castoldi, I. Murgia, R. Senatore, E. Mazzeo, J. Wackerlig, E. Urban, T. Langer, V. Pace, *Monatsch Chem* 148 (2017) 37–48.
- [17] A. Nagaki, *Tetrahedron Lett.* 60 (2019) 150923.
- [18] T. Zhao, L. Micouin, R. Piccardi, *Helv. Chim. Acta* 102 (2019), e1900172.
- [19] M. Colella, A. Nagaki, R. Luisi, *Chem. Eur. J.* 26 (2020) 19–32.
- [20] M. Power, E. Alcock, G.P. McGlacken, *Org. Process Res. Dev.* 24 (2020) 1814–1838.
- [21] For Recent Examples, See: (a) S. Seghers, T.S.A. Heugebaert, M. Moens, J. Sonck, J.W. Thybaut, C.V. Stevens, *ChemSusChem* 11 (2018) 2248–2254; (b) A. Mambri, D. Gori, C. Kouklovsky, H. Kim, J. Yoshida, V. Alezra, *Eur. J. Org. Chem.* 2018 (2018) 6754–6757; (c) T. von Keutz, F.J. Strauss, D. Cantillo, C.O. Kappe, *Tetrahedron* 74 (2018) 3113–3117; (d) M.A. Ganiek, M.V. Ivanova, B. Martin, P. Knochel, *Angew. Chem. Int. Ed.* 57 (2018) 17249–17253; (e) M. Köckinger, T. Ciaglia, M. Bersier, P. Hanselmann, B. Gutmann, C.O. Kappe, *Green Chem.* 20 (2018) 108–112; (f) C. Stueckler, P. Hermsen, B. Ritzén, M. Vasiliou, P. Poehlauer, S. Steinhöfer, A. Pelz, C. Zinganel, U. Felfer, S. Boyer, M. Goldbach, A. de Vries, T. Pabst, G. Winkler, V. LaVopa, S. Hecker, C. Schuster, *Org. Process Res. Dev.* 23 (2019) 1069–1077; (g) J.Y.F. Wong, J.M. Tobin, F. Vilela, G. Barker, *Chem. Eur. J.* 25 (2019) 12439–12445; (h) A.L. Dunn, D.C. Leitch, M. Journet, M. Martin, E.A. Tabet, N.R. Curtis, G. Williams, C. Goss, T. Shaw, B. O'Hare, C. Wade, M.A. Toczko, P. Liu, *Organometallics* 38 (2019) 129–137; (i) P. Sagmeister, J.D. Williams, C.A. Hone, C.O. Kappe, *React. Chem. Eng.* 4 (2019) 1571–1578; (j) G. Vilé, G. Schmidt, S. Richard-Bildstein, S. Abele, *J. Flow Chem.* 9 (2019) 19–25.
- [22] A. Maercker, *Angew. Chem. Int. Ed.* 26 (1987) 972–989.
- [23] A.F. Burchat, J.M. Chong, N. Nielsen, *J. Organomet. Chem.* 542 (1997) 281–283.
- [24] R.K. Dieter, S. Li, *J. Org. Chem.* 62 (1997) 7726–7735.
- [25] J.L. Bilke, S.P. Moore, P. O'Brien, J. Gilday, *Org. Lett.* 11 (2009) 1935–1938.
- [26] P. Beak, S.T. Kerrick, S. Wu, J. Chu, *J. Am. Chem. Soc.* 116 (1994) 3231–3239.
- [27] P. Beak, W.K. Lee, *J. Org. Chem.* 58 (1993) 1109–1117.