Addressing the Configuration Stability of Lithiated Secondary Benzylic Carbamates for the Development of a Noncryogenic Stereospecific Boronate Rearrangement

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S *Supporting Information*

ABSTRACT: A practical noncryogenic process for the Aggarwal stereospecific boronate rearrangement with chiral secondary benzylic carbamates has been developed. The use of LDA instead of *sec*-BuLi combined with an *in situ* trapping of the unstable lithiated carbamate was critical to success. Furthermore, this new process increased the substrate scope to include the versatile aryl iodide and bromide substrates. The methodology was applied to a diverse array of substrates and was demonstrated on multikilogram scale.
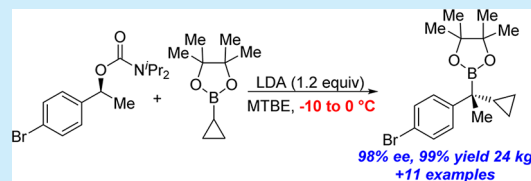
The search for new and improved methods for the efficient construction of complex chiral compounds is an ongoing endeavor in both academic and industrial settings. Since the seminal work of Matteson,[1] chiral boronic esters and boranes have emerged as an efficient handle for the rapid construction of diverse chiral synthons.[2] However, the large scale synthesis of pharmaceutically active compounds presents unique chemical challenges for these technologies.[3] The considerations of chemical robustness, safety, equipment suitability, and process and cost efficiency are important parameters for successful large scale batch operations.[4] In particular these considerations are imperative for asymmetric transformations. These constraints therefore serve as a test of the limitations of current chemical technologies and offer a medium for further advancement. In this regard, Aggarwal's stereoselective boronate rearrangement (Figure 1)[5,6] based on Hoppe's lithiated carbamates[7] is particularly attractive as the stereochemistry of the process is ultimately generated from a well precedented asymmetric reduction of a prochiral ketone.[8] However, the key boronate rearrangement requires cryogenic temperatures (i.e., −78 °C) that are not suitable for large scale synthesis where the considerations of reaction robustness, safety, and cost efficiency are important for commercial success (Figure 1).[9] Furthermore, the process is inherently unstable as the configurationally labile lithiated carbamate and boronate complexes are accumulated during the process. In addition, the use of alkyl lithium bases precluded[10] the use of the more versatile bromide analogue carbamate **1b**. Herein we wish to report the development of the
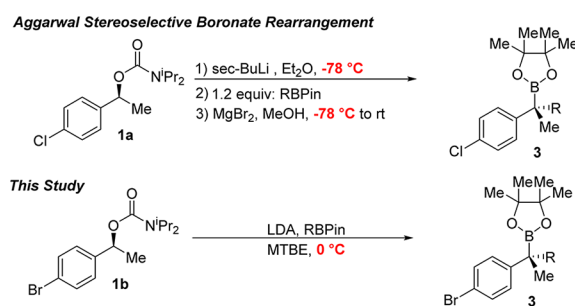

Figure 1. Boronate rearragements of chiral benzylic carbamates.

first robust and noncryogenic Aggarwal boronate rearrangement.[11]

The deprotonation of benzyl carbamates **1** utilizing *sec*-butyl lithium as the base is not compatible with the more versatile aryl bromide or iodide substrates, so the use of a hindered amide base was investigated. The stability of the resulting benzylic anions with respect to temperature over time was studied (Figure 2). Even at cryogenic temperatures (−78 °C) employing *sec*-butyl lithium (Et$_2$O) as the base, an appreciable erosion of enantiomeric excess was observed indicating the system is inherently unstable even at this low temperature. Furthermore, at the more practical −19 °C, the ee of the benzylic anion was completely eroded within 30 min. However, the rate of erosion of
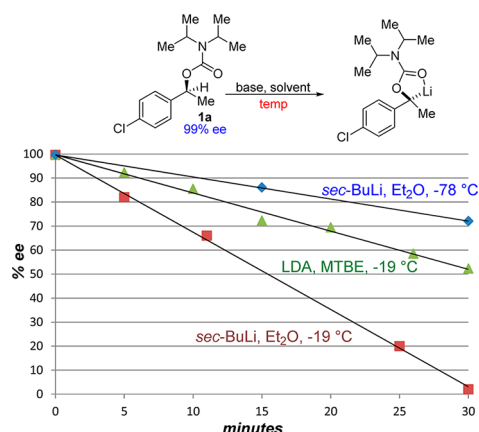
A

Figure 2. Rates of racemization under various reaction conditions.

the enantiomeric excess of the benzylic center with the use of LDA (MTBE) was found to be significantly less even at −19 °C. Within 5 min of aging the benzylic anion derived from *sec*-butyl lithium (−19 °C) a number of byproducts were observed, whereas the anion derived from the LDA process was found to be clean via HPLC analysis even after 30 min.

The nature of the derived anion with LDA was studied via deuterium trapping experiments (Figure 3). Deprotonation of
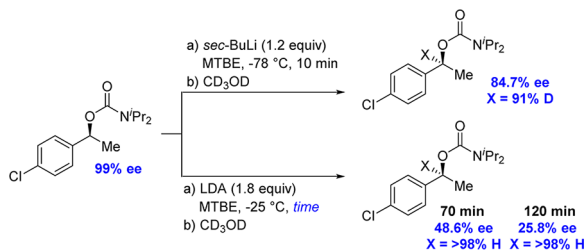

Figure 3. Deuterium trapping experiments for the deprotonation of Carbamate **1a** with *sec*-butyl lithium and LDA.

carbamate **1a** with *sec*-butyl lithium[7] formed a presumed anion of the carbamate which after aging for 10 min (−78 °C) was quenched with methanol-d_4. The resulting product had a minimal loss of ee (84.7% ee) and high deuterium incorporation (91%). However, repeating the same experiment with LDA as the base and aging for 70 and 120 min respectively (−25 °C) showed little to no deuterium incorporation while the derived products were obtained with significant ee erosion (48.6 and 25.8% ee) implying the benzylic anion is being accessed. One possibility is that the weaker base (LDA) does not outright deprotonate the carbamate substrate **1**, but instead the system is in a state of equilibrium between the LDA–carbamate complex and the deprotonated carbamate species, where the LDA–carbamate complex is thermodynamically preferred (Figure 4).[12] Thus, the LDA in the more stable LDA–carbamate complex would kinetically trap the deuterium from methanol-d_4 and preserve the carbamate benzylic proton. However, by employing an electrophile that is compatible with LDA (pinacol boronic esters), the thermodynamically less stable lithiated carbamate could be utilized for a productive transformation while benefiting from the increased stability afforded to the system by avoiding the accumulation of the deprotonated species. Based on the increased overall stability inherent in the LDA process, this system was further explored for the Aggarwal rearrangement process.
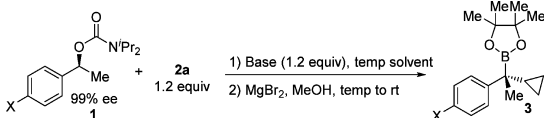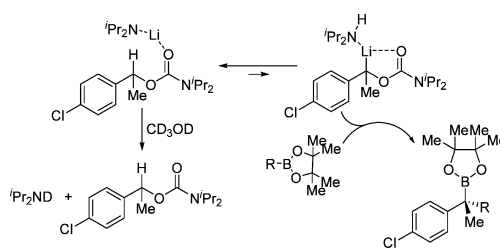

Figure 4. Equilibrium between the LDA−carbamate complex and the deprotonated/lithiated carbamate diisopropylamine complex.

In order to avoid the prolonged accumulation of the stereochemically unstable lithiated carbamate **4** the deprotonation of **1** was conducted in the presence of the boronic ester to quench the anion as it was formed (Table 1). Initial attempts at the *in situ* trapping using *sec*-butyl lithium provided no product, as the boronic ester kinetically traps the base prior to deprotonation. We were delighted to find that the use of LDA[13] for the *in situ* deprotonation (−78 °C) provided the desired adduct with 90% conversion with an erosion of only 4% ee (Table 1, entry 2). At more elevated reaction temperatures (−10 °C), lower conversion and higher ee erosion were observed. Eliminating THF from the system by utilizing LDA prepared in cyclopentyl methyl ether (CpOMe) allowed the reaction temperature to be increased to +4 °C while maintaining both high conversion (92%) and minimal loss of stereochemical integrity.

The LDA method described above as well as the original Aggarwal process was monitored in real time by ReactIR (Figures 5 and 6).[14] Treatment of the *p*-chloroaryl carbamate **1a** with *sec*-butyl lithium at −78 °C forms the thermally unstable lithiated carbamate **4** which is observed on the ReactIR plot (Figure 6a,b). The lithiation was shown to be very rapid and complete upon the addition of a base. The addition of the boronic ester **2b** instantly forms a new species (**5**) which is stable until the reaction is warmed to ∼0 °C, at which point the intermediate rearranges to the tertiary boronate product (30 min, Figure 6b). However, at the relatively high temperature required for the rearrangement, the dissociation process becomes competitive and provides a pathway for partial racemization. Aggarwal et al. presented an elegant solution to this issue by treating the boronate complex (−78 °C) with magnesium bromide in methanol to simultaneously accelerate the rearrangement and to trap the dissociated carbamate anion.[6] Indeed, the addition of MgBr$_2$/MeOH to the preformed boronate complex **5** formed a new complex (Figure 6a) which was observed to rearrange to the desired product **3b** upon warming. Yet, this solution would not be viable at noncryogenic temperatures where competitive dissociation is the major process, which would significantly reduce the yield. The rearrangement process would therefore need to be accelerated. Furthermore, at higher reaction temperatures the accumulation of the sensitive boronate complex would be bypassed altogether rendering the process inherently stable.

The LDA process was studied by ReactIR at low temperatures (Figure 7a). Treatment of a solution consisting of the carbamate with LDA at −78 °C caused a new peak to form which is presumed to be the LDA−carbamate complex.[15] The addition of the boronic ester **2b** did not alter the peak, but upon warming the resulting batch to −40 °C, the LDA−carbamate complex peak decreases and a new minor peak is formed which correlates with the boronate complex **5**. Upon warming the batch to −25 °C, the boronate complex peak decreased and the product **3b** was

Table 1. Survey of Bases for the *in Situ* Deprotonation and Boronate Rearrangement

entry	X	base	solvent	temp	conversion[a]	ee erosion[b]
1	Cl **1a**	*sec*-BuLi (1.2 equiv)	Et₂O	−30 °C	0%	*NA*
2	Br **1b**	LDA (2 M THF/Hept/EtPh)	CpOMe	−78 °C	90%	−4%
3	Br **1b**	LDA (2 M THF/Hept/EtPh)	CpOMe	−30 °C	80%	−4%
4	Br **1b**	LDA (2 M THF/Hept/EtPh)	CpOMe	−10 °C	50%	−10%
5	Br **1b**	LDA (1 M CpOMe)	CpOMe	−25 °C	91%	−0.8%
6	Br **1b**	LDA (1 M CpOMe)	CpOMe	−10 °C	96%	−1.0%
7	Br **1b**	LDA (1 M CpOMe)	CpOMe	4 °C	92%	−2.2%

[a]Molar conversion determined by HPLC analysis. [b]Measured by ee Erosion = ee Carbamate − ee Product. Ee determined by Chiral HPLC analysis.
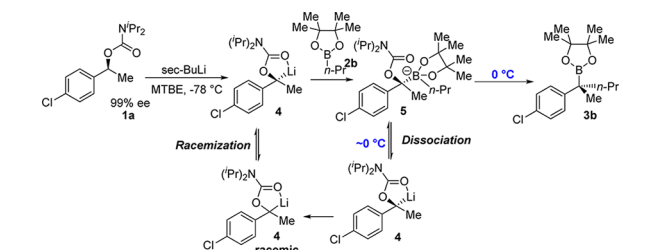

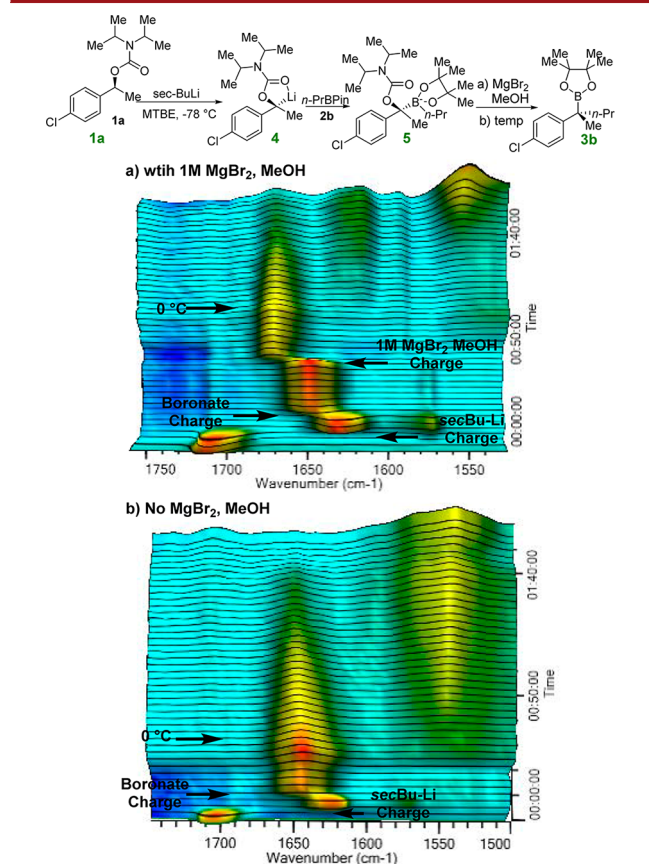**Figure 5.** Proposed mechanism for the Aggarwal boronate rearrangement process.

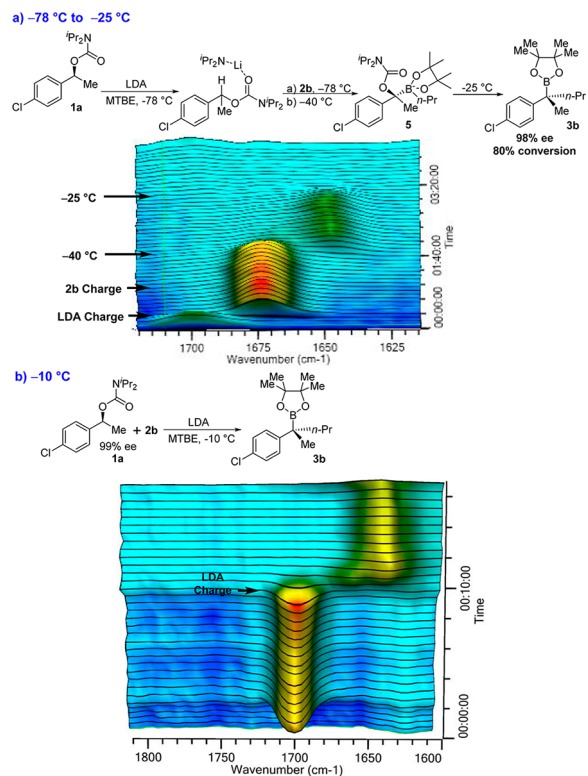**Figure 6.** ReactIR monitoring of the Aggarwal boronate rearrangement process.

Figure 7. ReactIR monitoring of the LDA process.

addition of LDA to the solution of both the boronic ester **2b** and carbamate **1a** (Figure 7b). In addition, with this noncryogenic approach, the system does not accumulate the configurationally labile lithiated carbamate **4** or the sensitive boronate complex **5**. The new LDA method is thus an inherently stable and robust process and suitable for large scale operations in commercial environments. Indeed, this chemistry, starting with bromoaryl cabamate **1b** was successfully scaled to provide 24 kg in a single batch of the tertiary boronic ester **3c** in near perfect yield (99%) and with excellent stereoretention (98.6% ee, Figure 8).

The LDA process was demonstrated to be general for a variety of alkyl boronic esters and substituted arene carbamates (Figure 9). Employing the previously incompatible aryl iodide or bromides, the corresponding tertiary boronic esters were obtained in good yield and >90% ee at a reaction temperature of 0 °C. Primary, secondary, and even allylic boronic esters are tolerated providing the products in 80−98% ee. The process was
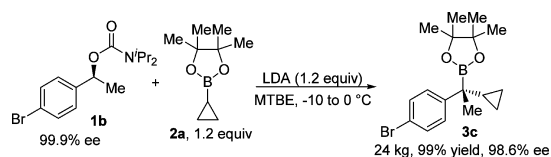
observed by HPLC analysis. When performing the reaction at −10 °C the process smoothly generates the product during the

Figure 8. Large scale and higher temperature LDA promoted Boronate rearrangement.
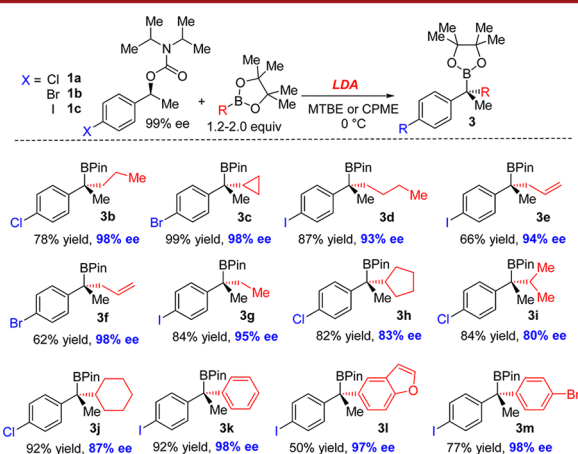

Figure 9. Substrate survey for the noncryogenic boronate rearrangement process.

also shown to be effective for the construction of chiral biaryl boronic esters (**3k–l**). In particular, the versatile aryl iodide aryl bromide **3m** was formed in 98% ee and 77% isolated yield.

In conclusion, an inherently stable and noncryogenic process for the Aggarwal stereoretentive boronate rearrangement process has been developed. By replacing *sec*-BuLi with LDA, using CpOME or MTBE as the solvent, and instituting an *in situ* trapping of the unstable lithiated carbamate, the process could be performed under noncryogenic conditions. By performing the chemistry under noncyrogenic conditions the reaction smoothly generates the desired boronate product which renders the reaction inherently stable by eliminating the accumulation of stereochemically sensitive intermediates. This new process increased the substrate scope of this reaction to include versatile aryl iodide and bromide substrates. The methodology was demonstrated on a diverse array of substrates and was demonstrated on multikilogram scale. This new method provides a valuable tool for the practical stereoselective construction of versatile chiral tertiary boronates.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and details including all associated spectra (^{1}H NMR, ^{13}C NMR, Chiral HPLC spectra). This information is free of charge via the Internet at http://pubs.acs. org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859−1885. (b) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535−1551.

(2) Scott, H. K.; Aggarwal, V. K. *Chem.—Eur. J.* **2011**, *17*, 13124−13132.

(3) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. Transition Metal Catalysts in the Pharmaceutical Industry. In *Applications of Transition Metal Catalysis in Drug Discovery and Development an Industrial Perspective*; Crawley, M. L, Trost, B. M., Eds.; Wiley: Hoboken, NJ, 2012.

(4) (a) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, 2000; p 354. (b) *Practical Process Development: Current Chemical and Engineering Challenges*; Blacker, J., Williams, M. T., Eds.; RSC Publishing: 2011; p 374.

(5) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24−39.

(6) (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778−782. (b) Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956−9960. (c) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142−5145. (d) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3760−3763.

(7) (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422−1424. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316.

(8) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734−2793.

(9) For general purpose large scale reactors the minimum preferred operational internal temperature is −10 to −20 °C.

(10) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1−46.

(11) Fandrick, K. R.; Gao, J. J.; Mulder, J. A.; Patel, N. D.; Zheng, X. Boehringer Ingelheim International GMBH, WO 2013/119751 A1, 2013.

(12) Another possibility exists where internal protonation of the deprotonated carbamate occurs from the diisopropylamine during the deuterium quench; see: Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390−5398.

(13) Matteson, D. S.; Soundararajan, R.; Ho, O. C.; Gatzweiler, W. *Organometallics* **1996**, *15*, 152−163.

(14) For selected examples of ReactIR used in process development, see: (a) Grabarnick, M.; Zamir, S. *Org. Process Res. Dev.* **2003**, *7*, 237−243. (b) Connolly, T. J.; Matchett, M.; McGarry, P.; Sukhtankar, S.; Zhu, J. *Org. Process Res. Dev.* **2006**, *10*, 391−397.

(15) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260−7261.