

# Programmed Synthesis of a Contiguous Stereotriad Motif by Triple Stereospecific Reagent-Controlled Homologation

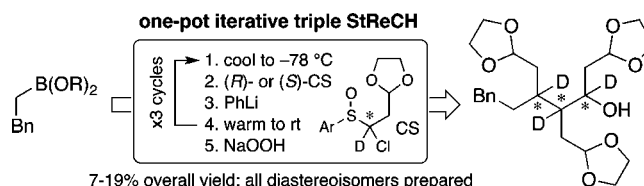
Xun Sun and Paul R. Blakemore\*

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003,  
United States

paul.blakemore@science.oregonstate.edu

Received July 19, 2013

## ABSTRACT



All distinct diastereoisomers of a contiguous stereotriad motif were separately targeted by a triple chain extension of *B*-phenethyl boronic esters using four unique presentation sequences of enantiomorphs of 1-[<sup>2</sup>H]-1-chloro-2-(1,3-dioxolan-2-yl)ethylolithium. The (*R*)- or (*S*)-configured chloroalkyllithium reagents were generated by sulfoxide–lithium exchange from the appropriate scalemic *p*-tolyl chloroalkyl sulfoxides using phenyllithium (THF, –78 °C). Stereotriad synthesis was accomplished in a single reaction vessel [7–19% yield, typical dr ≥ 74 (target):26 (Σ all other isomers)] and implemented by a simple algorithm consisting of reagent charging and temperature cycling events.

It is difficult to overstate the importance of controlling stereochemistry to the field of organic synthesis.<sup>1</sup> Indeed, molecules possessing multiple stereogenic centers, often chiral and in a nonracemic form, should be considered as the norm and not the exception when one contemplates the broad range of targets of primary interest to society. Few synthetic methods offer the means to install arbitrary stereochemical patterns, and the preparation of contiguous arrays of three, or more, stereogenic centers in any one of the many possible configurations remains a challenge.<sup>2</sup>

A potentially viable solution to this problem is offered by the nascent technique of iterative stereospecific reagent-controlled homologation (StReCH),<sup>3,4</sup> however, although double sequential StReCH of boronic acid esters has now been successfully applied to the elaboration of contiguous stereodiad motifs using a variety of carbenoid types,<sup>5,6</sup> the related programmed synthesis of higher-order contiguous stereochemical arrays by more than two iterative StReCH cycles has yet to be disclosed.<sup>7</sup> Such a demonstration, if convincing, would lend credence to the view that iterative StReCH is a truly unifying synthetic principle, and it may

(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; Wiley: New York, 2000. (b) Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds. *Stereoselective Synthesis*; Thieme: Stuttgart, 1995. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (d) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(2) By far the most work in this regard has focused on the generation of polypropionate-type domains found in polyketides characterized by contiguous arrays of stereogenic centers with an alternating pattern of alkyl and oxygenated substituents. For reviews, see: (a) Ward, D. E. *Chem. Commun.* **2011**, *47*, 11375–11393. (b) Li, J.; Menche, D. *Synthesis* **2009**, 2293–2315.

(3) (a) Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773–776. (b) Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068–3069.

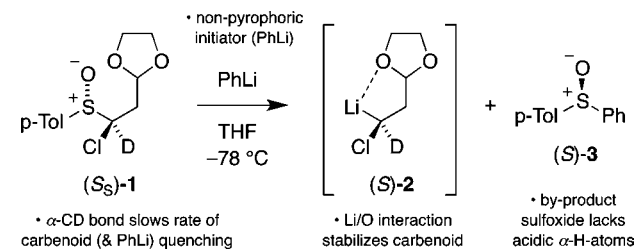
(4) For discourse on Matteson's related, but conceptually distinct, stereoinductive substrate-controlled homologation process using prochiral LiCHX<sub>2</sub> species, see: (a) Matteson, D. S. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 305–342. (b) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555–10607.

(5) For synthesis of contiguous stereodiads via double iterative StReCH using α-chloroalkyllithiums, see: (a) Emerson, C. R.; Zakharov, L. N.; Blakemore, P. R. *Org. Lett.* **2011**, *13*, 1318–1321. (b) Emerson, C. R.; Zakharov, L. N.; Blakemore, P. R. *Chem.—Eur. J.* **2013**, DOI: 10.1002/chem.201302511.

(6) For synthesis of contiguous stereodiads via double iterative StReCH using lithiated carbamates, see: (a) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491–7494. (b) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6317–6319. (c) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16798–16801.

(7) Double StReCH with lithiated oxirane and aziridine species leading to stereotriads and stereotetrad has been reported; however, see: (a) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165–168. (b) Schmidt, F.; Keller, F.; Vedrenne, E.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1149–1152.

**Scheme 1.** Favorable Attributes of the Putative  $\alpha$ -Chloroalkyl-Lithium Reagent (**2**) and the Carbenoid Generation Process Selected for Exploration of Iterative Triple StReCH



stimulate the wider adoption and further development of the technique. With this motivation in mind, we sought to prepare a nontrivial contiguous stereotriad motif by triple chain extension of a boronic ester using the operationally simple sulfoxide–metal exchange based StReCH manifold with  $\alpha$ -chloroalkyllithiums as homologation reagents.<sup>3,5</sup>

During our recent synthetic work on (–)-epibatidine,<sup>5</sup> it was discovered that a putative  $\alpha$ -chloroalkyllithium (**2**) generated from deuterated chlorosulfoxide **1** by sulfoxide–lithium exchange is among the most effective carbenoid reagents yet identified for StReCH. Two factors account for the heightened efficiency of StReCH with **1/2**: (1) the chemically labile carbenoid is stabilized by chelation of the Li atom to the proximal acetal moiety, and (2) any deleterious proton exchange between the basic  $\alpha$ -chloro-alkyllithium and its acidic  $\alpha$ -chlorosulfoxide precursor is retarded by a primary kinetic isotope effect. In addition to these favorable attributes (and others, as highlighted in Scheme 1), a priori carbenoid **2** was considered to be an ideal vehicle for exploration of stereotriad synthesis via triple StReCH because each new generation of chain extended adduct was anticipated to be significantly more polar than its predecessor, facilitating product separation and analysis. Herein, the programmed synthesis of all distinct diastereomers of a contiguous stereotriad motif (**10**) using four unique presentation sequences of (*R*)-**2** and (*S*)-**2** is reported; of note, it was found that triple StReCH was best executed in a one-pot fashion and that the isolation of intermediates was not required nor beneficial.<sup>8</sup>

Known *B*-phenethyl pinacol boronate **4**<sup>3b</sup> was selected as substrate and its single chain extension with carbenoid **2**, generated in situ from *anti*- $\alpha$ -chlorosulfoxide **1** under standard PhLi initiated Barbier conditions,<sup>5</sup> was examined first (Table 1). Systematic variation in the concentration of boronate revealed that values between 0.2 and 0.4 M were optimal for StReCH yield (entries 1–4). A longer dwell time at rt resulted in only a marginal gain in yield (cf. entries 5 and 2).<sup>9</sup> Given our interest in conducting multiple

**Table 1.** Effect of Concentration and Additives on the Single-Stage StReCH of Boronate **4**

entry	concn in <b>4</b> (M)	additive	time (h)	yield <b>5</b> (%)
1	0.75	none	1.5	61 <sup>a</sup>
2	0.38	none	1.5	78 <sup>a</sup>
3	0.19	none	1.5	70 <sup>a</sup>
4	0.08	none	1.5	65 <sup>a</sup>
5	0.38	none	14	84 <sup>b,c</sup>
6	0.38	( <i>S_S</i> )- <b>3</b> (2.5 equiv)	14	43 <sup>b</sup>
7	0.35	MgBr <sub>2</sub> ·OEt <sub>2</sub> (2.5 equiv)	1.5	90 <sup>b</sup>

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectral analysis after oxidative workup of the reaction mixture with NaOOH. <sup>b</sup> Isolated yield of (*S*)-**5**. <sup>c</sup> Enantiomeric excess of (*S*)-**5** ≥ 81% ee as determined by HPLC analysis of the derived carbinol (NaOOH) using a chiral stationary phase; this value represents a stereochemical fidelity of ≥92% given that % ee (**2**) ≤ 88% [since % ee (**2**) ≤ % de (**1**)]. Bpin = B[O(CMe<sub>2</sub>)<sub>2</sub>O].

StReCH cycles in a one-pot fashion, wherein by- and side-products cannot be removed before a subsequent stage is conducted (vide infra), the effect of deliberately adding sulfoxide–ligand exchange adduct **3** to the reaction mixture prior to initiation was investigated (entry 6). The presence of a 2.5 fold excess of **3** reduced the StReCH yield significantly (cf. entries 6 and 5), an effect attributed to competition between this compound and the short-lived carbenoid **2** for association with the boronate **4**. After further experimentation, a superlative StReCH yield was realized by doping freshly generated MgBr<sub>2</sub>·OEt<sub>2</sub> into the reaction mixture following ate-complex formation (entry 7). The exogenous Lewis acid presumably promoted 1,2-metalate rearrangement of the intermediate ate-complex by coordination to the Cl atom.<sup>10</sup>

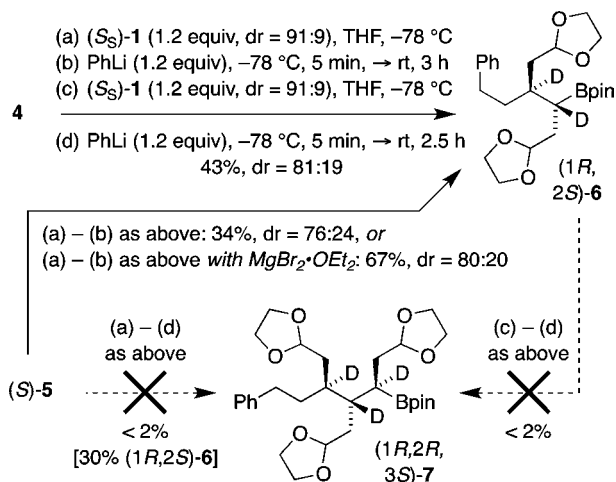
The one-pot double StReCH of boronate **4** using two sequential treatments with (*S\_S*)-**1**/PhLi was next evaluated (Scheme 2). Application of the straightforward protocol previously utilized for the synthesis of stereodiad motifs en route to (–)-epibatidine<sup>5</sup> led to the expected bisacetal **6** in good yield (43%) and with a dr (81:19) commensurate with the fact that the carbenoid precursor [(*S\_S*)-**1**] utilized exhibited dr = 91:9 about the  $\alpha$ -C atom.<sup>11</sup> The stereodiad motif was also prepared in a less convenient fashion by a single-stage StReCH reaction from boronate **5**; the use of added MgBr<sub>2</sub>·OEt<sub>2</sub> increased the yield of **6** significantly. Given the excellent results obtained up to this point, it was disappointing to discover that exposure of bisacetal **6** to a

(8) Sun, X.; Blakemore, P. R. *Abstracts of Papers*, 242nd ACS National Meeting & Exposition, Denver, CO, Aug 28–Sept 1, 2011; American Chemical Society: Washington, DC, 2011; ORGN-78.

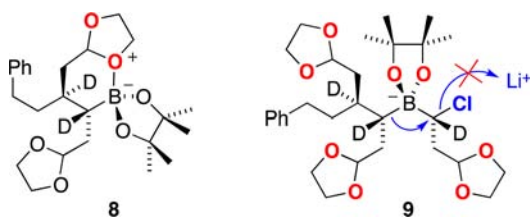
(9) Some warming of the reaction mixture is necessary to promote 1,2-metalate rearrangement of the ate-complex generated by the initial capture of the carbenoid reagent by the boronate substrate. See ref 3a for a discussion of the mechanism of StReCH and a list of general conditions that must be fulfilled for controlled chain extension.

(10) The beneficial effect of using Lewis acid additives to promote 1,2-metalate rearrangement of borate complexes was noted by Matteson et al., and ZnCl<sub>2</sub> is commonly used as an additive to improve the outcome of boronate homologation with LiCHCl<sub>2</sub>; see: Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078.

**Scheme 2.** Preparation of Stereodiad (1*R*,2*S*)-**6** by One-Pot Double StReCH from **4** or Single StReCH from (*S*)-**5** and Failed Attempts to Advance on Stereotriad Motif **7** from **5** and **6**



further dose of (*S*)-**1**/PhLi led to no more than a trace of the desired third-generation StReCH adduct **7**. Attempts to access the same contiguous stereotriad motif instead by one-pot double StReCH of the first-generation adduct (*S*)-**5** were also unsuccessful as were experiments to improve either of the two failed processes by use of  $\text{MgBr}_2 \cdot \text{OEt}_2$ . The difficulty of advancing beyond the second-generation StReCH adduct above is tentatively attributed to the high number of Lewis basic sites within boronate **6**; two issues are of some concern in this regard. First, a six-membered chelate from the  $\beta$ -dioxolanylmethyl unit to the B atom in **6** may block carbenoid and boronate assembly (as in **8**), and second, the high level of oxygenation in ate-complex **9** may preclude effective association of the Cl atom with  $\text{Li}^+$  (or  $\text{MgBr}_2$ ) and so prevent an adequate activation of the 1,2-metalate rearrangement.<sup>12</sup>

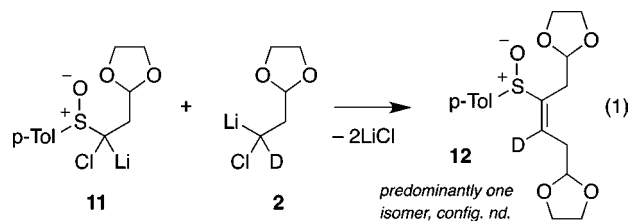


Whatever the reason for the difficult chain extension of boronate **6**, the one-pot triple StReCH of **4** was examined next with welcome results (Table 2, entries 1, 2, 4, 5). By

(11) The *er* of carbenoid **2** will not exceed the *dr* of its chlorosulfoxide precursor **1**; here, *er* (**2**)  $\leq$  91:9 (10:1). The anticipated *dr* for the stereodiad resulting from double StReCH using a reagent with this level of enantioenrichment is  $(10^2 + 1):(2 \times 10) = 83:17$ . See ref 5b for an explanation of the statistical effects that lead to this conclusion and the important corollary that *er* for the target diastereoisomer is boosted as compared to starting materials (calcd *er* =  $10^2:1$ ), while the minor diastereoisomer is anticipated to be racemic (calcd *er* = 10:10). For discourse on this kind of effect, see: Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, 29, 1055–1059.

(12) The Matteson chain extension process has likewise been noted to become sluggish, or to fail completely, when applied to boronates possessing a surfeit of Lewis basic sites within their structure; see: Matteson, D. S. *J. Organomet. Chem.* **1999**, 581, 51–65.

application of a simple algorithm of reagent charging and temperature cycling events, formation of the desired third-generation StReCH adduct **7**(**10**) now occurred with an average yield per transformation of up to 60% from **4** (for three StReCH cycles, followed by an oxidation). Product distributions were complex with triple (**10**,  $\leq 13\%$ ), double (**6**, 29–43%), and single (**5**, 30–34%) StReCH adducts all in evidence in addition to expected sulfoxide byproduct **3** (71–78%) and some recovered/epimerized chlorosulfoxide **1** (5–11%) (n.b. boronate **4** was fully consumed). Alkenyl sulfoxide **12**, isolated as its sulfone derivative for ease of purification, was also identified as a minor component ( $\sim 10\%$ ) of the product mixture. The origin of **12** lies in an association reaction between the persistent carbenoid (**11**) formed by unwanted deprotonation of **1** and the transient active homologation agent **2** (eq 1).<sup>13</sup> The outcome of the triple StReCH process was not improved by addition of  $\text{MgBr}_2 \cdot \text{OEt}_2$ , and we speculate that its success is due to the buildup of the LiCl byproduct generated at each stage.



Three out of the four unique carbenoid enantiomorph presentation sequences applied to boronate **4** emphatically yielded a triple StReCH adduct **7** (entries 1, 4, and 5). Boronates **7** could not be liberated from contaminants by chromatography and so were converted stereospecifically to the corresponding alcohols **10** before yield assessment and measurement of *dr* by  $^{13}\text{C}$  NMR spectral analysis. The major diastereoisomer formed from each successful reaction was clearly distinct, and the stereochemical outcome was assigned based on established precedent.<sup>3,5</sup> Assuming ideal StReCH behavior (complete stereochemical fidelity, absence of kinetic resolution), and with a knowledge of *er* for homologation reagents **2** used at each stage, a probability argument may be applied to estimate the anticipated *dr* for triple StReCH adducts.<sup>14</sup> When factoring in practical realities, such as the difficulty of isolating the delicate triacetals without any perturbation to native *dr*,<sup>15</sup> the observed stereoselectivity showed remarkable correlation with this simple calculation (see Table 2).

The need to isolate/purify intermediate stage boronates is of course obviated during one-pot iterative StReCH, and this fact afforded us the opportunity to explore a more

(13) For a review of the characteristic reactions of  $\alpha$ -chloroalkyllithiums, see: Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, 6, 41–52.

(14) See the Supporting Information for an illustration of the calculation.

(15) Products **10** are susceptible to transacetalization and other nefarious side reactions due to the presence of a free hydroxyl group and three acetals. The occurrence of any level of decomposition may perturb *dr* either for the better or for the worse, depending on which isomers are diminished faster. Triacetals **10** exhibited limited stability upon storage and were analyzed without delay following their isolation.

**Table 2.** Programmed Synthesis of All Four Distinct Diastereoisomers of a Contiguous Stereotriad Motif (**10**) by One-Pot Triple StReCH<sup>a,b,c,d,e</sup>

4 X = Bpin 4' X = Bneo	x3	(a) rt $\rightarrow$ $-78^{\circ}\text{C}$ , 10 min (b) ( $S_S$ )- or ( $R_S$ )- <b>1</b> (1.2 equiv), 10 min (c) PhLi (1.2 equiv), $-78^{\circ}\text{C}$ , 5 min (d) $-78^{\circ}\text{C} \rightarrow$ rt, 2 h	aq NaOOH	<b>7</b> X = Bpin <b>7'</b> X = Bneo <b>10</b> X = OH	<b>6</b> X = Bpin <b>6'</b> X = Bneo	<b>5</b> X = Bpin <b>5'</b> X = Bneo			
entry	carbenoid ( <b>2</b> ) presentation sequence <sup>a</sup>			boronate type	3rd gen. adduct <b>10</b>		2nd gen. <b>6/6'</b>		1st gen. <b>5/5'</b>
	1st cycle	2nd cycle	3rd cycle		yield <sup>b</sup>	obs. dr <sup>c</sup>	anticip. dr <sup>d</sup>	yield	obs. dr <sup>c</sup>
1				Bpin	7%	>94:02:02:02	79:07:07:07	29%	88:12
2				Bpin	<5%	nd	12:74:07:07	42%	67:33
3				Bneo	19%	05:80:09:06	12:64:12:12	27% <sup>e</sup>	78:22
4				Bpin	13%	09:10:74:08	12:07:74:07	43%	62:38
5				Bpin	10%	02:33:22:43	07:12:12:69	40%	21:79

<sup>a</sup> (*S*)-**2** generated in situ by addition of PhLi to (*S*)-**1**; (*R*)-**2** likewise from (*R*)-**1**; er (**2**) ≤ dr (**1**). <sup>b</sup> Isolated yield of carbinols **10** obtained by oxidation of boronates **7/7'** with NaOOH; indicated stereochemistry based on carbenoid enantiomorph presentation sequence and preceded stereochemical outcome of related StReCH reactions (see refs 3a, 5a, and 5b). <sup>c</sup> Determined by <sup>13</sup>C NMR spectral analysis. <sup>d</sup> Anticipated values based on maximal er for carbenoids **2** used in each StReCH cycle. <sup>e</sup> Isolated as NaOOH oxidation products. Bpin = B[O(CMe<sub>2</sub>)<sub>2</sub>O], Bneo = B[OCH<sub>2</sub>CMe<sub>2</sub>CH<sub>2</sub>O], R = CH<sub>2</sub>CH[O(CH<sub>2</sub>)<sub>2</sub>O].

chemically reactive substrate class in an attempt to access the remaining diastereoisomer of **10**. Thus, the carbenoid presentation sequence that had previously failed to yield a triple StReCH adduct from the robust pinacol boronate **4** (entry 2) was re-evaluated as applied to the less hindered neopentyl glycol boronate **4'** (entry 3). This reaction gave the highest yield yet encountered (an average of 66% per transformation), and the major isomer of **10** so produced belonged to a different diastereomeric series to the other principal triple StReCH adducts generated earlier. With this finding, the programmed synthesis of all diastereoisomers of the target contiguous stereotriad motif via StReCH was successfully completed.

In conclusion, it has been demonstrated that contiguous stereochemical arrays more complex than stereodiads can be made via iterative StReCH. Multiple chain extensions are realizable in a single reaction vessel, and the process is implemented by a simple algorithm that could, in principle, be automated. The method illustrated is not impervious to substrate effects, and in this case, the triacetal structure of the chosen target molecule

created difficulties that would probably not be relevant during elaboration of compounds possessing less Lewis basic sites. In moving forward, it is evident that α-chloroalkyllithiums are too reactive to be considered as broadly applicable homologation reagents; nonetheless, the operational simplicity and speed of the StReCH variant used herein are attributes worth retaining in future developments of this synthetic paradigm.

**Acknowledgment.** Financial support from the National Science Foundation is gratefully acknowledged (via grant CHE-0906409). The National Science Foundation (CHE-0722319) and the Murdock Charitable Trust (2005265) are also thanked for support of the OSU NMR facility.

**Supporting Information Available.** Experimental procedures, characterization data, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.