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Iterative Stereospecific Reagent-Controlled Homologation of Pinacol Boronates by Enantioenriched α-Chloroalkyllithium Reagents

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Generally applicable iterative methods for the programmed assembly of complex molecules are largely limited to constructs involving the formation of carbon−heteroatom bonds. Some such methods, particularly those directed at the synthesis of important classes of biopolymers, e.g., polypeptides and oligonucleosides, are highly sophisticated and have been successfully automated.[1] By contrast, similarly versatile technologies for the synthesis of molecules via carbon−carbon bond formation are limited.[2] Implicit to any general solution of this multifaceted problem must be a means to arbitrarily control substitution pattern and absolute stereochemical features during molecular assembly. In an earlier report,[3] we advanced a simple unifying concept for synthesis based on the stereospecific chain extension of organometallic substrates **1** by enantioenriched main-group chiral carbenoid reagents **2** (Scheme 1). Envisioned to proceed via 1,2-metalate rearrangement of intermediate ate-complexes (**3** → **4**),[4] iterative application of this so-called "stereospecific reagent controlled homologation" (StReCH) process would in principle allow for the programmed assembly of polysubstituted alkyl moieties with total command over stereochemistry and constitution (e.g., **4** → **5**).

Full realization of the reductionist synthetic paradigm presented by StReCH would require satisfaction of three basic conditions,[3] while its practical implementation would necessitate the ready availability of enantioenriched chiral carbenoid reagents **2** and the existence of suitable (isolable) organometallic substrates **1**. Seminal guiding contributions from Hoffmann[5] and Matteson[6] led us to select a StReCH manifold of $M^1 = B(OR)_2$ and $M^2 =$ MgCl for initial consideration. Proof-of-concept experiments established that an enantioenriched Mg-carbenoid, generated in >98%ee by sulfoxide ligand exchange,[5,7] effected chain extension of catechol and neopentyl glycol boronic esters with modest stereochemical fidelity; however, it was later discovered that a putative Li-carbenoid generated in near identical fashion gave dramatically improved results.[3] Herein, we report a significant extension of this work to robust pinacol boronate substrates and describe the first demonstration of iterative StReCH cycles for the programmed synthesis of molecules containing multiple stereogenic centers.[8]

In a departure from earlier work, we employed a Jackson−Ellman−Bolm catalytic enantioselective sulfoxidation[9] in concert with Yamakawa chlorination[10] to efficiently prepare the scalemic α-chloroalkyl sulfoxides **8** of interest as carbenoid precursors (Table 1). For both steps, the isomeric purity of products was enhanced by recrystallization wherever possible.

Alkyllithium-effected sulfoxide ligand exchange from α-protio-α-haloalkyl sulfoxides is complicated by deprotonation.[3,7] Prior to attempting the deployment of putative Li-carbenoids **2** (M^2 = Li, X = Cl) generated from precursors **8** via this means in StReCH reactions, we therefore sought to identify reaction conditions which might best favor the desired sulfoxide−lithium interchange process over any competing pathways. Following a survey of reaction variables,[11] a combination of *t*-BuLi in PhMe solvent was revealed to be optimal for effecting sulfoxide ligand exchange from substrates of type **8**. Initial comparison of the *t*-BuLi−PhMe carbenoid generation system (method B) to the *n*-BuLi−THF system (method A), used previously for StReCH extension of neopentyl glycol boronates,[3] revealed no advantage (Table 2, entries 1−4). However, when we next examined the feasibility of essentially identical StReCH reactions from analogous pinacol boronates, the *t*-BuLi−PhMe system was demonstrably superior (entries 5−8). The fact that StReCH reactions with Li-carbenoids are successful from pinacol boronates is highly significant. In contrast to neopentyl glycol-derived boronic esters, pinacol boronates are stable toward aerial oxidation, resist hydrolysis, and may be subjected to silica gel chromatography without significant loss. Isolation of product pinacol boronates from StReCH cycles is therefore potentially straightforward, enabling ready iteration of the chain extension process (vide infra).

Up to this point, all of the attempted StReCH reactions had employed a putative Li-carbenoid (**13**) related to Hoffmann's Mg-carbenoid[5] and substituted by a benzyl group (**2**, R^2 = Bn, X = Cl). It was then established that the scope of StReCH is not limited

Scheme 1. Stereospecific Reagent-Controlled Homologation

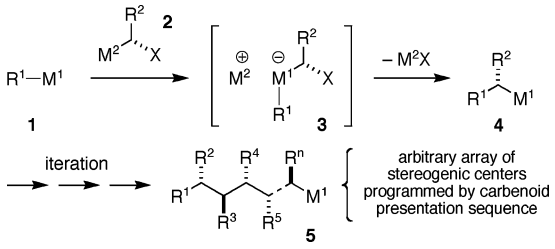
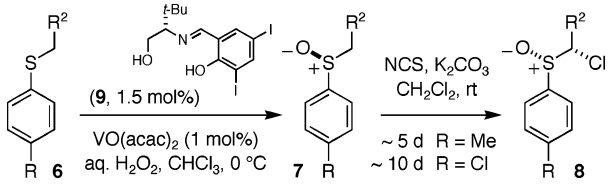


Table 1. Synthesis of α-Chlorosulfoxide Carbenoid Precursors



	sulfide **6**		sulfoxide **7**[a]		chlorosulfoxide **8**[a]	
entry	R	R^2	% yield	% ee	% yield	% ee
1	Me	Bn	45	99	67	99
2	Me	Me	83	99[b]	77	66[b]
3	Cl	Et	77	99	72	nd[c]
4	Me	*i*-Pr	85	71	28	40
5	Me	*i*-Bu	52	98	41	99
6	Me	CH_2Bn	70	99	53	99

[a] Isolated yield and % ee (HPLC, Daicel OD column) data are those following recrystallization (to give pure *syn* diastereoisomers in case of **8**). [b] Not recrystallized. [c] Enantiomers not resolvable by HPLC method.

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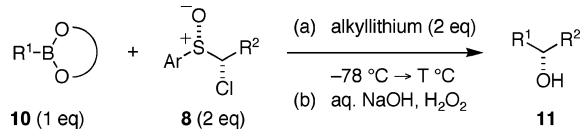
Table 2. Stereospecific Reagent-Controlled Homologation (StReCH) of Neopentyl Glycol (neo) and Pinacol (pin) Boronates with Putative α-Chloroalkyllithiums Generated by in Situ Sulfoxide Ligand Exchange



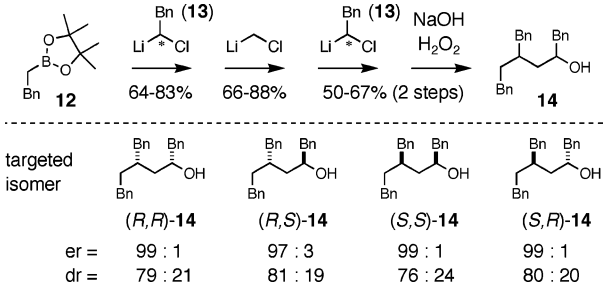
	boronate **10**[a]		sulfoxide **8**[b]				carbinol **11**[d]	
entry	R^1	B(O⌒O)	R^2	% ee	cond.[c]	*T* °C	% yield	% ee
1[e]	$BnCH_2$	neo	Bn	99	A	0	70	96
2	$BnCH_2$	neo	Bn	99	B	0	79	90
3[e]	c-hex	neo	Bn	99	A	0	86	87
4	c-hex	neo	Bn	99	B	0	61	88
5	$BnCH_2$	pin	Bn	99	A	rt	35	84
6	$BnCH_2$	pin	Bn	99	B	rt	76	92
7	c-hex	pin	Bn	99	A	rt	24	88
8	c-hex	pin	Bn	99	B	rt	67	82
9	$BnCH_2$	pin	Me	66	B	rt	23	60
10	$BnCH_2$	neo	Et	nd[f]	B	rt	29	98
11	$BnCH_2$	pin	Et	nd[f]	B	rt	31	76
12	$BnCH_2$	pin	*i*-Pr	40	B	Δ	0	na
13	$BnCH_2$	pin	*i*-Bu	99	B	rt	64	92
14	$BnCH_2$	pin	$BnCH_2$	99	B	Δ	46	na
15	c-hex	neo	$BnCH_2$	99	B	rt	26	86
16	c-hex	pin	$BnCH_2$	99	B	rt	71	44

[a] neo = $B(OCH_2CMe_2CH_2O)$, pin = $B(OCMe_2CMe_2O)$. [b] Ar = *p*-Tol or *p*-ClC_6H_4. [c] Reaction conditions: A = *n*-BuLi in THF, B = *t*-BuLi in PhMe. [d] Isolated yields, % ee determined by HPLC (Daicel OD column). [e] Data previously reported in ref 3 (enantiomeric series was opposite to that illustrated). [f] % ee could not be determined by chosen HPLC method.

to the original test system (Table 2, entries 9−16). Thus, enantioenriched Li-carbenoids bearing R^2 groups of varying steric demand (Me, Et, *i*-Pr, *i*-Bu, $BnCH_2$) were generated via method B from their appropriate precursors **8**, and observed to homologate boronic esters in the desired manner (with the notable exception of R^2 = *i*-Pr). Stereochemical fidelity was generally excellent; however, the yield of the chain extension varied widely, and some reactions required heating prior to oxidative quench to obtain the desired product **11**. It is unlikely that variations in efficacy are due solely to intrinsic reactivity differences between the various carbenoids. Significantly, it was discovered that sulfoxide ligand exchange from **8** (R^2 = Bn) is more effective than the comparable reaction from **8** (R^2 = Me) under the conditions of method B.[12]

The good tolerance of pinacol boronates toward handling and chromatographic purification allowed for the successful execution of iterative StReCH cycles from boronic ester **12** (Scheme 2). The substrate was extended by two treatments with enantioenriched chiral carbenoid **13** (generated via method B in either (*R*)- or (*S*)-configuration), interspersed by an homologation step with chloromethyllithium (generated via I/Li exchange from ICH_2Cl),[13] to yield carbinols **14** following oxidation. Intermediate boronates[14] were isolated between successive extension cycles, and all four stereoisomers of **14** were separately targeted by deployment of the appropriate carbenoid presentation sequences (e.g., (*R*)-**13**, CH_2LiCl, (*R*)-**13** to target (*R*,*R*)-**14**, etc.). The targeted alcohols **14** were produced with uniformly excellent enantiopurity and were accompanied in each case by a minor diastereomeric coproduct generated with low enantiomeric excess (typically <20% ee). This outcome is an expected artifact of stereospecific reagent control; a

Scheme 2. Programmed Synthesis of a Stereodiad Motif by Iterative Stereospecific Reagent-Controlled Homologation



second StReCH cycle effectively up-grades the enantiopurity of the intended ultimate product by preferentially converting the unwanted minor enantiomer from the first StReCH cycle into a compound belonging to a different diastereomeric series.[15]

In summary, it has been demonstrated that pinacol boronates are chain extended with generally excellent stereochemical fidelity by enantioenriched Li-carbenoid species generated in situ by sulfoxide ligand exchange phenomena. Repeated application of this "StReCH" process enabled the programmed assembly of all stereoisomers of a simple stereodiad model system. Extension of the synthetic principle outlined herein to the elaboration of more complex molecular systems is under active investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org

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