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Synthesis of a P-Glycoprotein Inhibitor and Its High-Energy (*Z*)-Isomer by Carbenoid Eliminative Cross-Coupling

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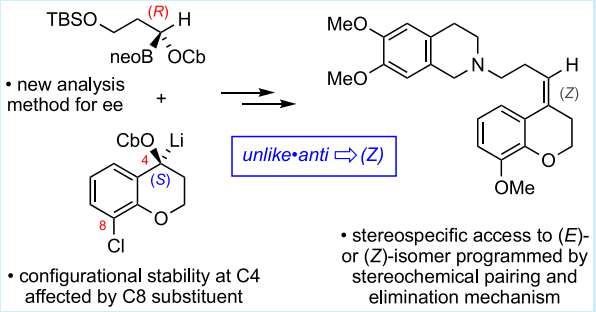
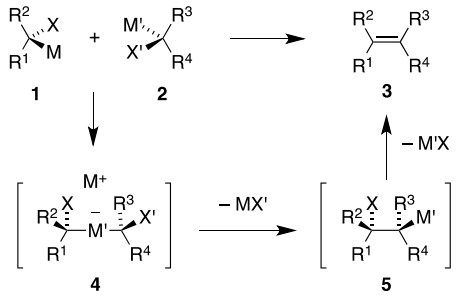
ABSTRACT: To gauge the feasibility of carbenoid eliminative cross-coupling for the synthesis of polyfunctional alkenes, a P-glycoprotein inhibitor containing an (*E*)-configured 4-chromanylidene-type trisubstituted olefin was prepared as well as its previously undescribed (*Z*)-isomer. Stereospecific alkene synthesis required generation of functionalized enantioenriched α-metalated carbamates [$R^1R^2CM(O_2CN\textit{i}\text{-}Pr_2)$, M = Li or Bneo], and problems associated with incorrect lithiation regioselectivity and unexpected organolithium configurational lability were encountered. Solutions to these difficulties are described together with a method for ee determination of α-carbamoyloxyboronates.



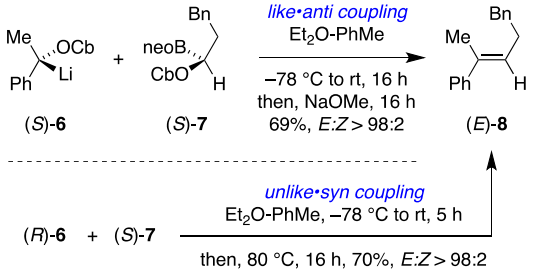
Transformations that generate alkenes in a connective and stereocontrolled fashion are of obvious strategic value for the synthesis of complex unsaturated molecules.[1] The usefulness of a particular method will be determined in large part by its functional group tolerance and olefin-forming reactions that are capable of linking together late-stage polyfunctional intermediates enjoy widespread application.[2] Eliminative cross-coupling of carbenoids is an unorthodox approach to alkene synthesis that offers stereospecific C=C double bond generation providing that the carbenoid substrates, **1** and **2**, are stereodefined and configurationally stable (Scheme 1).[3] Here, the stereochemical outcome is programmed by the choice of carbenoid "stereochemical pairing" (*like* or *unlike*) and, in cases where influence can be exerted, the type of elimination mechanism triggered (*syn* or *anti*). We introduced a viable implementation of this concept employing a combination of lithiated carbamates and α-carbamoyloxyboronates that allows for both types of control tactic to be exercised.[4−6] For example, (*E*)-styrene **8** could be obtained either by a *like*-pairing of organolithium (*S*)-**6** with boronate (*S*)-**7** and an *anti*-elimination mechanism (triggered by NaOMe) or by an *unlike*-pairing of (*R*)-**6** and (*S*)-**7** and a thermally triggered *syn*-elimination (Scheme 2). (*Z*)-**8** was similarly available (*E*/*Z* = 5:95) by an analogous *like*·*syn* eliminative cross-coupling reaction.[4] While this olefin construction is highly effective in model systems, how it might perform in a more complex "real-world" scenario was an open question. Accordingly, we elected to pursue the elaboration of a biologically active alkene target molecule that would require

Scheme 1. Eliminative Cross-Coupling of Carbenoids[a]



[a]Stereospecific alkene synthesis by eliminative cross-coupling illustrated with a terminating *anti* elimination step (**5** to **3**). M/M′ = electrofuge, X/X′ = nucleofuge.

Scheme 2. Exemplary Eliminative Cross-Couplings[a]



[a]Cb = *i*-$Pr_2NC(=O)$, Bneo = $B(OCH_2CMe_2CH_2O)$. Reference 4.

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installation of the necessary reactive carbenoid moieties within nontrivial functionalized fragments. Herein, we report realization of this endeavor with the synthesis of a P-glycoprotein inhibitor and its high-energy (*Z*)-isomer.[7]

A 4-chromanylidene derivative bearing a tethered tetrahydroisoquinoline nucleus [(*E*)-**9**] was selected as the vehicle for our study. This compound was discovered by Colabufo et al. to possess selective inhibitory activity against P-glycoprotein (Pgp).[8] Among other applications, P-gp inhibitors are potentially useful tools to measure the expression of Pgp which is a biomarker for the diagnosis of early stage Alzheimer's disease.[9] The initial plan to access (*E*)-**9** was straightforward and envisioned the target emerging directly from an eliminative cross-coupling reaction of a boron-based carbenoid (**10**) representing the azacycle propylidene domain and a lithium-based carbenoid (**11**) functioning likewise for the 4-chromanylidene moiety (Figure 1). Given the programmable nature of the approach, the previously unknown (*Z*)-isomer of (*E*)-**9**, a compound possessing significant allylic strain, was also pursued.

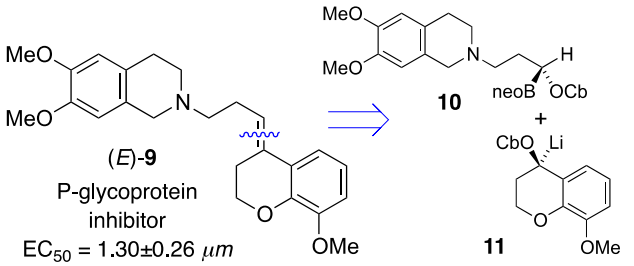
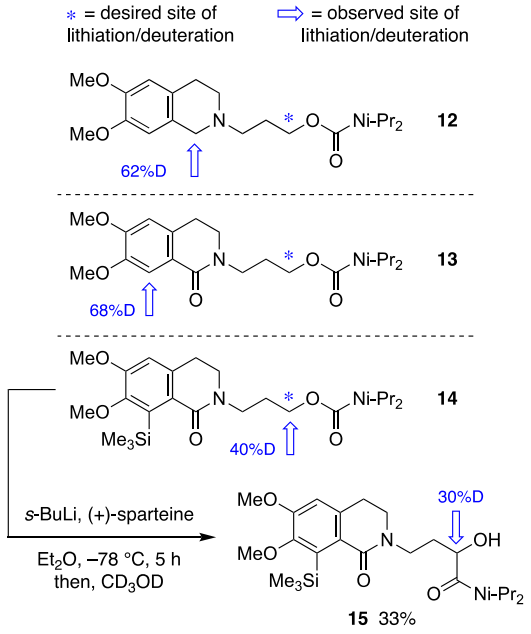


Figure 1. A P-glycoprotein inhibitor [(*E*)-**9**] and a pair of putative carbenoid intermediates (**10** and **11**) that could be used to access it via eliminative cross-coupling.

Attention was first directed to the synthesis of B-carbenoid **10**, or its synthetic equivalent. After failed attempts to access a compound related to **10** using Ito's catalytic enantioselective aldehyde borylation method,[10] **10** was targeted using Hoppe's sparteine-controlled lithiation–borylation chemistry.[11] For this approach to be successful within a polyfunctional molecule, it is necessary that the acidifying complex-induced proximity effect (CIPE)[12] caused by the chosen lithiation director (herein, *N,N*-diisopropylcarbamoyloxy, OCb) overrides those of other functional groups within the substrate and that subsequent thermodynamic equilibration does not reposition the site of lithiation following kinetic regioselective deprotonation.[13] Exposure of a potential direct precursor to **10** (**12**, prepared in 3 steps from homoveratrylamine) to Hoppe's standard conditions (as illustrated), followed by deuteration, revealed the net result of lithiation in the undesired benzylic position (Scheme 3).[14] Blocking of this site with a lactam carbonyl group, as in substrate **13**, exacerbated the regiocontrol problem, and lithiation was now observed to occur exclusively on the aromatic ring. Introduction of another blocking group to remove this second lithiation site, as in aryl silane **14**, had the desired effect, in that metalation now occurred adjacent to the carbamate; however, the resulting organolithium was unstable and experienced an unusually facile *O*-to-*C* acyl group migration to give α-hydroxyamide **15** as the major isolated product. Rearrangements of this type have seldom been documented to occur at such low temperatures, and it is speculated that the strained lactam carbonyl group in

Scheme 3. Lithiation Studies[a]

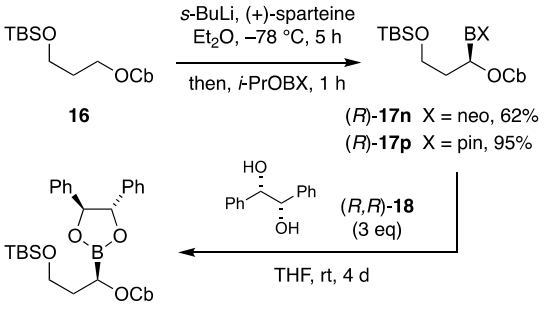


[a]Carbamates **12** and **13** were lithiated as indicated for **14** but quenched with CD_3OD after only 1 h at −78 °C.

14 is responsible for the peculiar reactivity of the lithiated carbamate.[15]

Given the difficulties of installing an α-carbamoyloxyboronate moiety in an *N*-alkyl 6,7-dimethoxytetrahydroisoquinoline, an alternate strategy toward targets (*E*)/(*Z*)-**9** was envisioned in which the azacyclic moiety would be added following olefin formation. For this purpose, B-carbenoids **17** containing pendant TBS ethers were prepared in straightforward fashion from 1,3-propanediol derivative **16** (Scheme 4).[14]

Scheme 4. Synthesis of α-Carbamoyloxyboronates 17 and Illustration of Indirect Er Analysis Method for 17n[a]



[a]Cb = *i*-$Pr_2NC(=O)$, Bneo = $B(OCH_2CMe_2CH_2O)$, Bpin = $B(OCMe_2CMe_2O)$.

The neopentyl glycol boronic ester **17n** is less stable than its pinacol congener **17p** toward chromatographic purification on silica gel, hence the lower isolated yield for the former. On the basis of Hoppe's precedent,[11] the compounds prepared were assumed to have (*R*)-configuration since (+)-sparteine was employed; however, it was important to ascertain their level of enantioenrichment since carbenoid ee is a critical determinant of stereoselectivity in eliminative cross-coupling.[3,4] Boronates **17** lack a UV chromophore to assist with application of chiral

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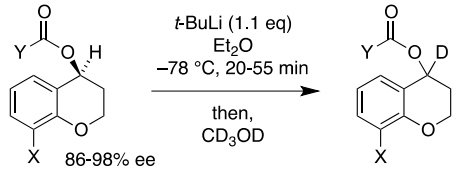
stationary phase (CSP) HPLC based er analysis, and so we developed a complementary NMR spectroscopy based method to achieve the same aim, as exemplified by the illustrated example. Thus, incubation of (*R*)-**17n** with commercially available diol (*R,R*)-**18** in THF solvent resulted in its transesterification to **19** with dr >97:3, as determined by integration of the ^{1}H NMR spectrum of the concentrated reaction mixture. That this dr represents the er of analyte (*R*)-**17n** (i.e., no kinetic resolution during transesterification) was confirmed by repeating the experiment with (±)-**18**, which gave **19** exhibiting dr = 50:50, measured as before. Although transesterification of pinacol boronates is sluggish, the same analysis method was also successfully applied to (*R*)-**17p** which was likewise revealed to be essentially enantiopure.

The results of eliminative cross-coupling reactions between lithiated carbamate **11** and boronates (*R*)-**17** were perplexing. Aside from the understandable finding that pinacol boronate **17p** lacked sufficient reactivity for effective alkene formation (yield olefin **23** ≤ 5% from **17p** vs 20−30% from **17n**), little else made sense, and it was impossible to correlate the outcome of a given experiment to the stereochemical pairing and the type of elimination protocol employed. The absence of stereochemical programmability was traced to the unexpected configurational lability of organolithium **11**. Thus, lithiation of an enantiopure sample of its precursor **20a** at −78 °C followed by deuteration 20 min later returned essentially racemic [^{2}H]-**20a** (Scheme 5).[14] The analogous lithiated TIB ester was likewise revealed to be inappropriate for our purposes by the same experiment from **20b**.

Scheme 5. Lithiation/Deuteration Experiments to Probe Configurational Stability of 4-Lithiochromans

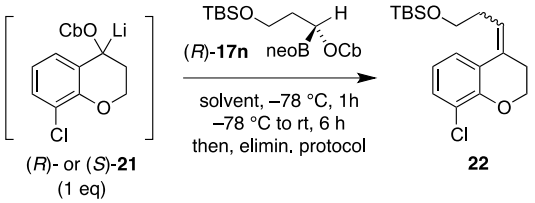


20a, X = OMe, Y = *i*-Pr$_2$N — [^{2}H]-**20a**, 87% D, 5% ee
20b, X = OMe, Y = 2,4,6-*i*-Pr$_3$C$_6$H$_2$ — [^{2}H]-**20b**, 96% D, 1% ee
20c, X = Cl, Y = *i*-Pr$_2$N — [^{2}H]-**20c**, 85% D, 97% ee

That lithiation of unsubstituted 4-chromanyl carbamate **20** (X = H, Y = *i*-Pr$_2$N) gave a well-behaved Li-carbenoid in our first report of eliminative cross-coupling[4] suggested that the MeO group present in **11** is responsible for its low configurational stability. Thus, an alternative C8-substituent was sought that could convey heightened configurational stability to the requisite Li-carbenoid while also being convertible to a MeO group at a later point in the synthesis. The higher halogens, Br and I, were ruled out for this purpose because of the likelihood of competing halogen−metal exchange during lithiation, and so a Cl-atom was evaluated. As shown by the lithiation/deuteration experiment from **20c**, this strategic device fulfilled its intended purpose; lithiation was chemoselective, and the resulting Li-carbenoid (**21**) maintained its stereochemical integrity at −78 °C. With this promising result, eliminative cross-couplings between (*R*)- or (*S*)-**21** and (*R*)-**17n** were explored (Table 1).

By contrast to the stereorandom nature of the reactions involving **11**, eliminative cross-couplings between **21** and **17n** led predominantly to the desired isomer of olefin **22** in all

Table 1. Eliminative Cross-Coupling between Li-Carbenoid 21 and B-Carbenoid 17n



no.[a]	**21**[b]	(*R*)-**17n**	solvent	elim.[c]	alkene **22** yield	alkene **22** *E*/*Z*
1	(*R*)	1.2 equiv	Et_2O	A2	30%	96:04
2	(*S*)	1.1 equiv	Et_2O−PhMe	S1	30%	96:04
3	(*S*)	1.5 equiv	Et_2O	S3	44%[d]	97:03
4	(*R*)	1.1 equiv	Et_2O−PhMe	S1	23%	45:55
5	(*R*)	1.1 equiv	Et_2O−PhMe	S2	16%	48:52
6	(*S*)	1.1 equiv	Et_2O−PhMe	A1	34%	29:71
7	(*S*)	1.2 equiv	Et_2O	A2	45%	12:88
8	(*S*)	1.5 equiv	Et_2O	A2	48%[e]	16:84

[a]Entries 1−3 target (*E*)-**22**, entries 4−8 target (*Z*)-**22**. [b]**21** generation: **20c**, *t*-BuLi (1.1 equiv), Et_2O, −78 °C, 20 min. [c]Elimination protocol: A1 = NaOH, MeOH, rt, 20 h; A2 = NaOH, MeOH, −10 °C, 20 h; S1 = 80 °C, 17 h; S2 = 40 °C, 46 h; S3 = PhMe added, 85 °C, 20 h. [d]20% (*S*)-**20c** recovered with 51% ee. [e]25% (*S*)-**20c** recovered with 57% ee.

cases. (*E*)-**22** was targeted by *like·anti* (entry 1) and *unlike·syn* (entries 2−3) type couplings with the latter proving to be superior. Use of pure Et_2O solvent for all but the final thermal elimination step (PhMe was added prior to heating) was found to be advantageous (entry 2 vs 3). The higher energy isomer (*Z*)-**22** was targeted by *like·syn* (entries 4−5) and *unlike·anti* (entries 6−8) couplings. The first reaction type barely gave a bias for the (*Z*)-alkene, and stereoselectivity was not improved by running the elimination at a lower temperature for a protracted time period (entry 4 vs 5). Here, it is likely that *anti* elimination triggered by an adventitious base/nucleophile (e.g., LDA formed from decarboxylation of LiOCb) competes against the desired high activation barrier *syn* elimination mechanism. Fortunately, the *unlike·anti* type reactions were more effective and an optimal stereochemical outcome was realized by operating the NaOH/MeOH triggered elimination at a lower temperature (entry 6 vs. 7). All putative intermediates involved in the most effective eliminative cross-coupling reactions above (entries 3 and 8) are illustrated in the Supporting Information.

With (*E*)-**22** and (*Z*)-**22** in hand, these stereodefined materials were next separately advanced to their respective targets, (*E*)-**9** and (*Z*)-**9**. As illustrated below for the (*Z*)-series (Scheme 6), the four-step sequence of transformations began with a Pd(0)-catalyzed etherification of the aryl chloride with basic methanol according to the method of Buchwald and co-workers.[16] No isomerization of the potentially sensitive olefin was observed during this critical operation. Further to uneventful conversion of the resulting TBS ethers (**23**) into alkyl chlorides (**24**), installation of the isoquinoline unit was achieved as in the original synthesis of **9**,[8] by direct amination with 6,7-dimethoxy-tetrahydroisoquinoline (**25**). Spectral data for the Pgp inhibitor (*E*)-**9** so-obtained agreed with those previously reported,[8] and characterization data collected for the new compound (*Z*)-**9** were fully consistent with the intended structure.

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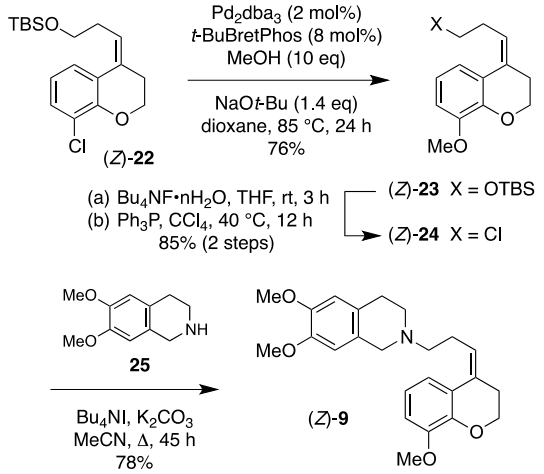
Scheme 6. Advancement of (Z)-22 to (Z)-9[a]



[a](E)-**22** was advanced to (E)-**9** using the same sequence of transformations which gave comparable yields in the (E)-series [overall yield of (E)-**9** from (E)-**22** was 38%, cf. 50% for above]. See Supporting Information for details.

In summary, carbenoid eliminative cross-coupling has been demonstrated for a stereochemically programmed synthesis of a nontrivial alkene within a bioactive molecule. The fact that the high-energy isomer of the target could also be prepared, an olefin not accessible in any quantity via the original approach,[17] is notable. Although elaboration of (E)- and (Z)-**9** was successful, this effort exposes that the generation of regio- and/or stereochemically defined organolithiums within polyfunctional molecules is not a trivial undertaking. For eliminative cross-coupling to emerge as a true rival to established methods for connective alkene synthesis, it will be important for additional types of carbenoids to be identified that can navigate the coupling mechanism while being both functional-group tolerant and easy to selectively install within complex fragments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00755.

Experimental procedures, characterization data, and $^{1}H/^{13}C$ NMR spectra for all compounds; details for the method to determine ee of α-carbamoyloxyboronates via transesterification with diol **18** and ^{1}H NMR spectral analysis (PDF)

FAIR data including NMR FID files for all compounds (ZIP)

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Notes

The authors declare no competing financial interest.

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(14) See Supporting Information for details concerning the synthesis of isoquinolinylpropanol derivatives **12**−**14**, 1,3-propanediol derivative **16**, and enantioenriched 4-hydroxychroman derivatives **20abc**.

(15) Known examples of *O*-to-*C* acyl migration from lithiated *O*-alkyl *N*,*N*-diisopropyl carbamates typically occur at 0 °C to rt; see: (a) Hémery, T.; Becker, J.; Fröhlich, R.; Hoppe, D. *Eur. J. Org. Chem.* **2010**, *2010*, 3711−3720. (b) Tomooka, K.; Shimizu, H.; Inoue, T.; Shibata, H. Nakai, T. *Chem. Lett.* **1999**, *28*, 759−760.

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(17) (*E*)-**24** was originally prepared by addition of *c*-C_3H_5MgBr to 8-methoxychroman-4-one followed by HCl mediated elimination (ref 8). In our hands, this procedure gave (*E*)-**24** in 35% yield (2 steps) and with no trace of (*Z*)-**24** observable by ^1H NMR spectroscopy. See Supporting Information for details.

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