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Enantioselective *syn* and *anti* Homocrotylation of Aldehydes: Application to the Formal Synthesis of Spongidepsin

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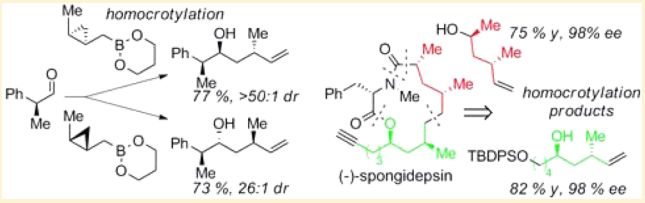
Supporting Information

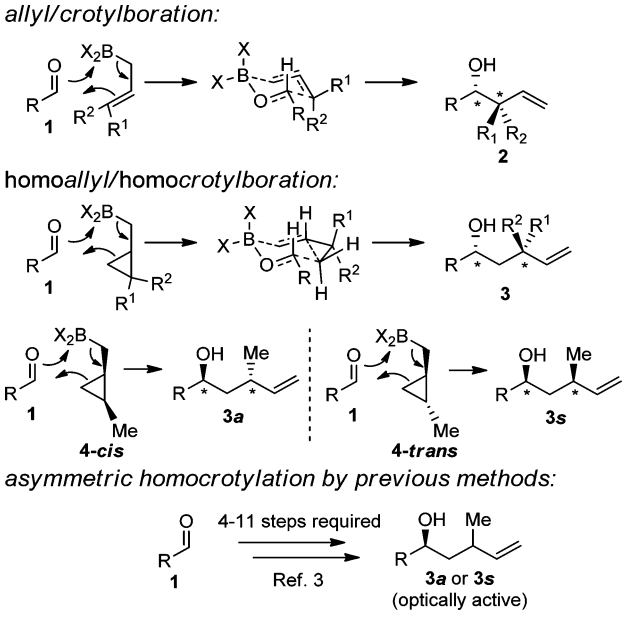
ABSTRACT: Whereas crotylboration has been a useful method for synthesis of stereochemically complex products, we have shown that *homo*crotylboration can be achieved with *cyclopropanated* crotylation reagents, and that the stereoselectivity of the reaction can be predicted by analogous models. This paper presents a full account of this work, including the first examples of asymmetric *anti* homocrotylation. The scope of this reaction is demonstrated with highly enantioselective homocrotylation of both aliphatic and aromatic aldehydes, as well as double diastereoselection studies. An application of the synthesis of the marine natural product spongidepsin is presented, as well as streamlined syntheses of homocrotylation reagents.



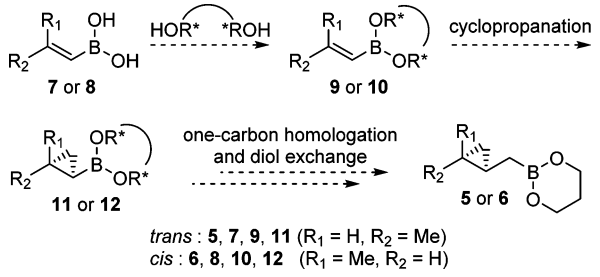
INTRODUCTION

Whereas asymmetric allyl- and crotylboration (Scheme 1, **1** → **2**) have been extensively developed and applied in synthesis,[1] methods for asymmetric *homo*allylation and *homo*crotylation (**1** → **3**) are still very limited.[2] Until recently, the seemingly simple aldehyde addition to produce optically pure **3*a*** or **3*s*** (*anti* or *syn*) has been accomplished only in sequences of 4−11 steps.[3] However, we have recently shown that **4**-*cis*/*trans* react stereospecifically to provide **3*a***/**3*s***, respectively.[4] This selectivity can be explained by a Zimmerman−Traxler model[5] in a manner analogous to allylboration. In a preliminary communication, it was shown that optically pure boronate reagent **5** (Scheme 2) enables asymmetric access to *syn* adducts of aliphatic aldehydes (**3*s***, Scheme 1).[4b] This paper is a full account of that work, detailing the enantioselective preparation of both *syn* and *anti* homocrotylation reagents **5** and **6** and their use in the asymmetric homocrotylation of both aliphatic and aromatic aldehydes, together with double diastereoselection studies on chiral aldehydes and a formal synthesis of a marine natural product, spongidepsin.[6] Additionally, background studies are presented for the stereoselective cyclopropanation en route to boronates **5** and **6**, as well as a second generation, large-scale route to prepare these reagents.

Scheme 1. Homoallylation through Allylation Mechanisms



Scheme 2. General Route to Optically Pure 5 and 6



RESULTS AND DISCUSSION

Initial Studies in Asymmetric Cyclopropanation of Vinylboronates. Reagents **5** and **6** can be prepared via straightforward one-carbon homologation of the corresponding

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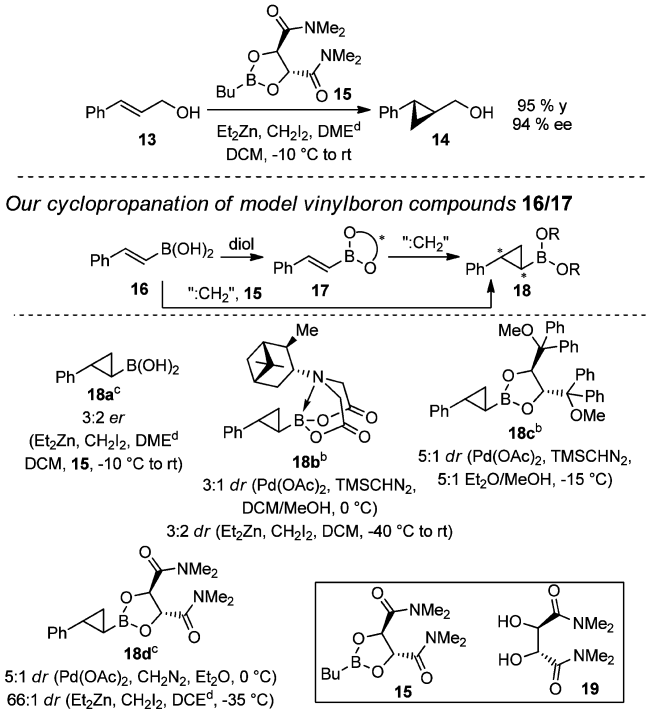
chiral cyclopropylboronates **11** and **12**, as outlined in Scheme 2. However, in the development of this route, some trial and error was required to achieve a highly stereoselective cyclopropanation yielding **11**/**12**. Although numerous enantioselective Rh- and Cu-catalyzed methods have been reported for asymmetric cyclopropanation using ester-substituted carbenoids ":CH(CO_2R)", asymmetric cyclopropanation with ":CH_2" remains a great challenge:[7] Charette's method using zinc carbenoid and a chiral director[8] (**15**, Scheme 3) is the only highly selective approach, and is itself limited to alkene substrates possessing an allylic hydroxyl (e.g., **13**). Hoping that the B(OH) moiety of a vinylboronic acid might fulfill the usual requirement for an allylic hydroxyl, we attempted Charette cyclopropanation directly on **16** (Scheme 3); however, this resulted in minimal selectivity for **18a** (3:2 er). Cyclopropanation was next attempted using Burke's[9] and Pietruszka's[10] auxiliaries (see **18b** and **18c**), but still obtained low to moderate selectivity, whether using zinc carbenoid, diazomethane, or TMS-diazomethane (selected conditions listed). However, in agreement with Deng's reports,[11] tartaramide auxiliary **19** promoted excellent stereoselectivity (97% de) in cyclopropanations using zinc carbenoid.

Although the styrenylboronates **17** used in these studies were convenient for comparison to previous reports, we next moved to the more challenging and relevant Me-substituted substrate **20c**, which had not been reported in Deng's studies (Table 1). Under the same conditions, the de of **21c** was lower than that for **21a,b**, and varied from 80 to 86%. Even when the reaction temperature was lowered to −78 °C, no improvement was observed.

Not only was the de of **21c** lower than desired, but the variability was of concern. As the crude tartaramide boronates **20** are used directly in the cyclopropanation (obtained by mixing of chiral diol with boronic acid, followed by simple drying over $MgSO_4$), we hypothesized that impurities such as water or small amounts of excess tartaramide diol **19** could influence the de of the cyclopropanation. Therefore, the effect of additives, including **19**, was investigated (Table 2).

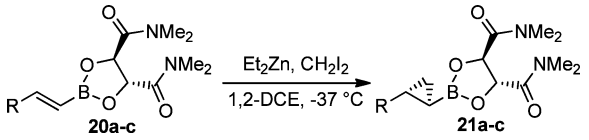
Selectivity was enhanced by addition of **19**, whereas water and other Lewis basic additives did not benefit the reaction. As described in our preliminary report,[4b] synthesis of **5** was then completed (Scheme 4) by one-carbon homologation of the pinacol boronate **23**, followed by conversion to the requisite propanediol derivative. Truncation of the synthetic route to **5** will be presented in Scheme 9 (vide infra).

Scheme 3. Preliminary Cyclopropanation[a]



[a]Selected er's/dr's are shown in the scheme. Product **18a** was prepared from cyclopropanation of **16**. Products **18b**−**d** were prepared from cyclopropanation of **17**. [b]dr's were measured by RP-HPLC. [c]er or dr corresponding to er measured by chiral HPLC after oxidation of **18d** with $NaBO_3{\cdot}4H_2O$. [d]DME = 1,2-dimethoxyethane; DCE = 1,2-dichloroethane.

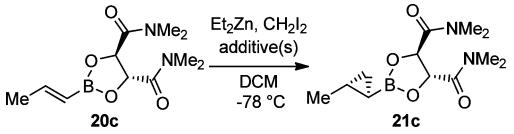
Table 1. Scope of Tartaramide-Directed Cyclopropanation under Deng's Conditions[a]



entry	R	de %
1	Ph (**21a**)	97[b]
2	Ph (**21a**)	95[bc]
3	Cy (**21b**)	93−94[d]
4	Me (**21c**)	80−86[de]

[a]All reactions were run at the concentration of 0.1 M. [b]de was measured by HPLC using a chiral stationary phase after oxidation of **21a** with $NaBO_3{\cdot}4H_2O$ to the corresponding alcohol. [c]DCM, −50 °C. [d]de was measured by HPLC using a chiral stationary phase after oxidation of **21b,c** with $NaBO_3{\cdot}4H_2O$ to the corresponding alcohol and benzoylated with BzCl and DMAP. [e]DCM, −78 °C.

Table 2. Effect of Additives on Cyclopropanation Stereoselectivity[a]



entry	additive(s)	amount (mol %)	de (%)[b]
1	none		82
2	**19**	20	91
3	**19**	30	95
4	**19**	40	96
5	**19**	50	97−98
6	**19** + H_2O	50 each	79
7	diethanolamine	5	81
8	H_2O	5	85
9	1,2-dimethoxyethane	5	84
10	1,4-dioxane	5	83

[a]Reactions were performed by adding the solution of **20c** mixed with additive(s) to the solution of 3 equiv of Et_2Zn and 4.5 equiv of CH_2I_2 at concentration of 0.1 M at −78 °C. [b]de's correspond to ee's measured by chiral HPLC after oxidation of **21c** to the corresponding alcohol followed by benzoylation.

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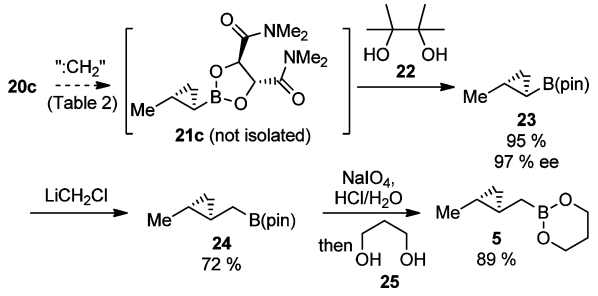
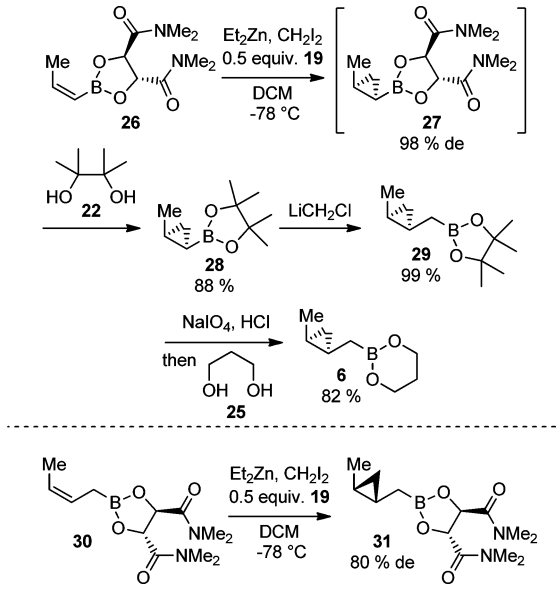
Scheme 4. Conversion of *trans* Cyclopropane to *syn* Homocrotylation Reagent 5



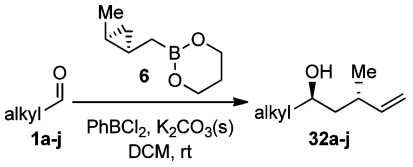
After obtaining **5**, we next turned to synthesis of **6**, starting with cyclopropanation of *cis* propenylboronate **26**[12] (Scheme 5). Pleasingly, the cyclopropanation under conditions optimized for *trans* boronate **20c** occurred with equally high stereoselectivity (98% de) in the case of **26**. Analogous homologation and diol exchange then afforded optically pure *anti* homocrotylation reagent **6** (Scheme 5). Interestingly, the opposite cyclopropane configuration was obtained when *Z-crotyl*boronate **30** was cyclopropanted under the same conditions, albeit the level of stereoselectivity was less useful (80% de).

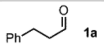
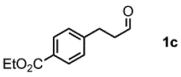
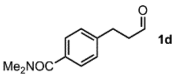
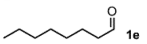
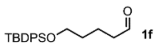
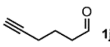
Scheme 5. Cyclopropanation of *cis* Propenylboronates and Preparation of *anti* Homocrotylation Reagent 6



anti* Homocrotylation of Aliphatic Aldehydes.** With optically pure *cis* boronate **6** in hand, asymmetric *anti* homocrotylation was tested on a range of simple aliphatic aldehydes. In the presence of $PhBCl_2$ activator and solid K_2CO_3 acid scavenger, we were pleased to see that the desired *anti* products **32a–j** were obtained in excellent yields and uniformly high enantio- and diastereoselectivity (Table 3). The reaction conditions are compatible with ester (entry 3), silyloxy (entry 6), and alkyne functionalities (entry 10), as well as enolization-prone aldehyde **1b** (entry 2), and branched substrates (entries 7–9). The lower yield observed with substrate **1d** (entry 4) is potentially due to deactivation of the PhBCl2 promoter by the more strongly Lewis basic amide group, which is also consistent with the markedly longer reaction time required for this substrate. *Overall, these results are significant in that no other method can provide optically active* anti *products* ***32a–j *from aldehydes in a single step.* These results complement the equally selective *syn* homocrotylations reported in our preliminary communication (Table 4).[4b]

Table 3. *anti* Homocrotylation of Aliphatic Aldehydes[a]



entry	aldehyde	time	product	yield (%)[b]	ee (%)[c]
1	 1a	3 h	**32a**	93	98
2	 1b	3 h	**32b**	87	96
3	 1c	3 h	**32c**	92	98
4	 1d	11 h	**32d**	56	98
5	 1e	3 h	**32e**	91	98
6	 1f	50 min	**32f**	82	98
7	 1g	1 h	**32g**	90	98
8	 1h	2 h	**32h**	66 (99)	98
9	 1i	23 h	**32i**	76 (96)	96
10	 1j	30 min	**32j**	74	95

[a]Reaction conditions: 3 equiv of **6**, 1.5 equiv of $PhBCl_2$, 1 equiv of aldehyde, and 6 equiv of K_2CO_3 (s). [b]Isolated yields, with NMR yields in parentheses in the case of volatile products. [c]ee's were measured by chiral HPLC. dr's > 20:1 by ^1H NMR for all entries.

Homocrotylation of Aromatic Aldehydes. The homocrotylation of aromatic aldehydes **1k–q** (Table 5) was also explored. Aromatic substrates reacted very rapidly, giving good yields as long as reactions were quenched shortly after full conversion. In nearly all cases, diastereo- and enantioselectivities were as high as with aliphatic substrates. Highest yields were obtained with substrates bearing strongly electron-withdrawing substituents (entries 1–3, 8–10). The potentially chelating *ortho* nitro group was also well tolerated (entry 2 and 9). Moreover, benzaldehyde (entry 4 and 11) and moderately electron rich *o*-tolualdehyde (entry 6 and 13) were homocrotylated in acceptable yields. However, homocrotylation of the very electron rich *p*-anisaldehyde (entry 7) afforded a ~ 1:1 mixture of *syn* and *anti* products after purification. GC-MS analysis revealed that the crude reaction product from homocrotylation of **1q** was largely benzylic chloride **35**, likely resulting from S_N1 decomposition of **34**, the homocrotylation product prior to aqueous workup (Scheme 6); alcohols **32q**/**33q** were then produced by hydrolysis of **35** during chromatography on alumina.[13]

Double Diastereoselection Studies. We next studied the selectivity conferred by reagents **5**/*ent*-**5** and **6**/*ent*-**6** in the presence of preexisting aldehyde stereochemistry (Scheme 7). For all aldehydes tested, either Felkin (*syn*/*anti*) or anti-Felkin (*anti*/*anti*) products could be obtained in high selectivity by choice of **6** or *ent*-**6**. *Together with* syn *homocrotylation reagents*

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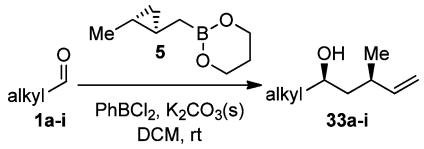
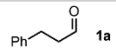
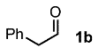
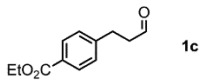
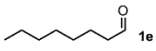
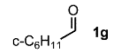
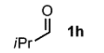
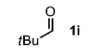
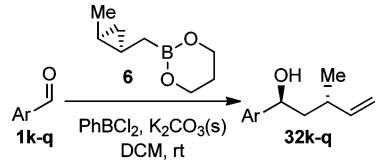
Table 4. *syn*-Homocrotylation of Aliphatic Aldehydes[a]

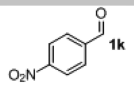
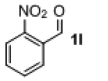
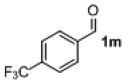
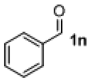
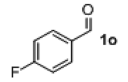
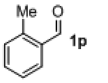
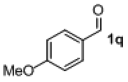


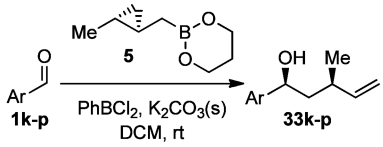
entry	aldehyde	time	product	yield (%)[b]	ee (%)[c]
1[d]	 1a	14 h	**33a**	83	97
2	 1b	14 h	**33b**	82	97
3	 1c	14 h	**33c**	89	97
4	 1e	14 h	**33e**	89	97
5	 1g	14 h	**33g**	89	97
6	 1h	50 h	**33h**	72 (83)	98
7	 1i	7 d	**33i**	62 (84)	98

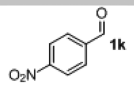
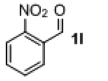
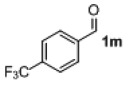
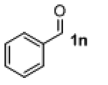
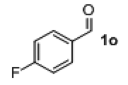
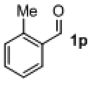
[a]Reaction conditions: 3 equiv of **5**, 1.5 equiv of $PhBCl_2$, 1 equiv of aldehyde, and 6 equiv of K_2CO_3 (s). [b]Isolated yields, with NMR yields in parentheses in the case of volatile products. [c]ee's were measured by chiral HPLC. dr's > 20:1 by ^1H NMR for all entries. [d]This reaction completed in 2 h.

Table 5. Homocrotylation with Aromatic Aldehydes[a]



entry	aldehyde	time	product	yield (%)[b]	ee (%)[c]
1	 1k	1 h	**32k**	95	98
2	 1l	1 h	**32l**	94	98
3	 1m	15 min	**32m**	95	98
4	 1n	15 min	**32n**	73	95
5	 1o	10 min	**32o**	66	98
6	 1p	15 min	**32p**	52	98
7[d]	 1q	45 min	**32q/33q**	90 (1:1 *syn*/*anti*)	N.D.



entry	aldehyde	time	product	yield (%)[b]	ee (%)[c]
8	 1k	1 h	**33k**	93	97
9	 1l	1 h	**33l**	93	97
10	 1m	15 min	**33m**	85	97
11	 1n	15 min	**33n**	68	95
12	 1o	10 min	**33o**	53	96
13	 1p	35 min[e]	**33p**	54	97

[a]Reaction conditions: 3 equiv of **5** or **6**, 1.5 equiv of $PhBCl_2$, 1 equiv of aldehyde, and 6 equiv of K_2CO_3. [b]Isolated yields. [c]ee's were measured by HPLC using a chiral stationary phase. In entries 1–6, no *syn* diastereomers were detected. In entries 8–13, no *anti* diastereomers were detected. The values in parentheses are dr, measured by NMR. [d]*rac*-**6** was used. Pentane, 4:1 pentane/DCM, and 1:4 pentane/DCM gave the same mixture. [e]This reaction was run at 0 °C.

5,[4b] *our reagents* ***6****/ent-****6*** *now provide reagent-controlled access to all possible stereotriads in products* **37** *and* **39**. Homocrotylation was next attempted with α- and β-silyloxy-substituted aldehydes **40** and **48**. Again, complete reagent control of stereochemistry was observed in all cases, but yields were low to modest, owing to competing desilylation and β-elimination. Although silyl protection is effective at positions remote from the carbonyl (Table 3, entry 6), positions closer to the carbonyl are apparently more sensitive. However, acetate, pivaloate, and particularly benzoate ester protection proved much more robust at these positions, affording good yields of products **45**–**47** and **51** without a significant decrease in selectivity.

Formal Synthesis of (−)-Spongidepsin. The utility of reagents **5** and **6** was next demonstrated in a short formal synthesis of spongidepsin (**52**), a cytotoxic natural product isolated from the Vanuatu marine sponge *Spongia* sp. (Scheme 8).[6] All previous syntheses[3,14] have proceeded through intermediates **53**, **54**, and **32f** (or *epi*-**32f**), assembling these pieces by a combination of esterification, amide bond formation and metathesis. However, in all of these studies, stereospecific preparation of **54** and **32f**/*epi*-**32f** has required very lengthy synthetic sequences (7–12 steps from commercial material for **54** and 6–14 steps for **32f**). In the present case, both **32f** and **54** should be accessible in a straightforward manner by asymmetric *anti* and *syn* homocrotylation of **1f** and **55**, respectively. *anti* Homocrotylation of **1f**[3c] with **6** (see Table 3, entry 6) afforded **32f** directly in 82% yield and 98% ee, as a single diastereomer. Acid **54** was then prepared from acetaldehyde (**55**). Despite the small size of acetaldehyde, *syn* homocrotylation using *ent*-**5** proceeded with undiminished diastereoselectivity to afford exclusively *syn* alcohol **56** in78% yield and 98% ee. Mesylation, cyanide displacement,[15] and hydrolysis of the resulting nitrile[16] afforded optically pure **54**. Fragments **32f** and **54** were then combined with commercial phenylalanine derivative **53**, according to Negishi's procedur-

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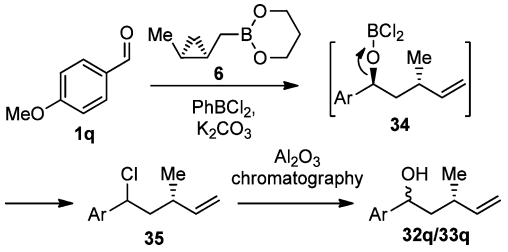
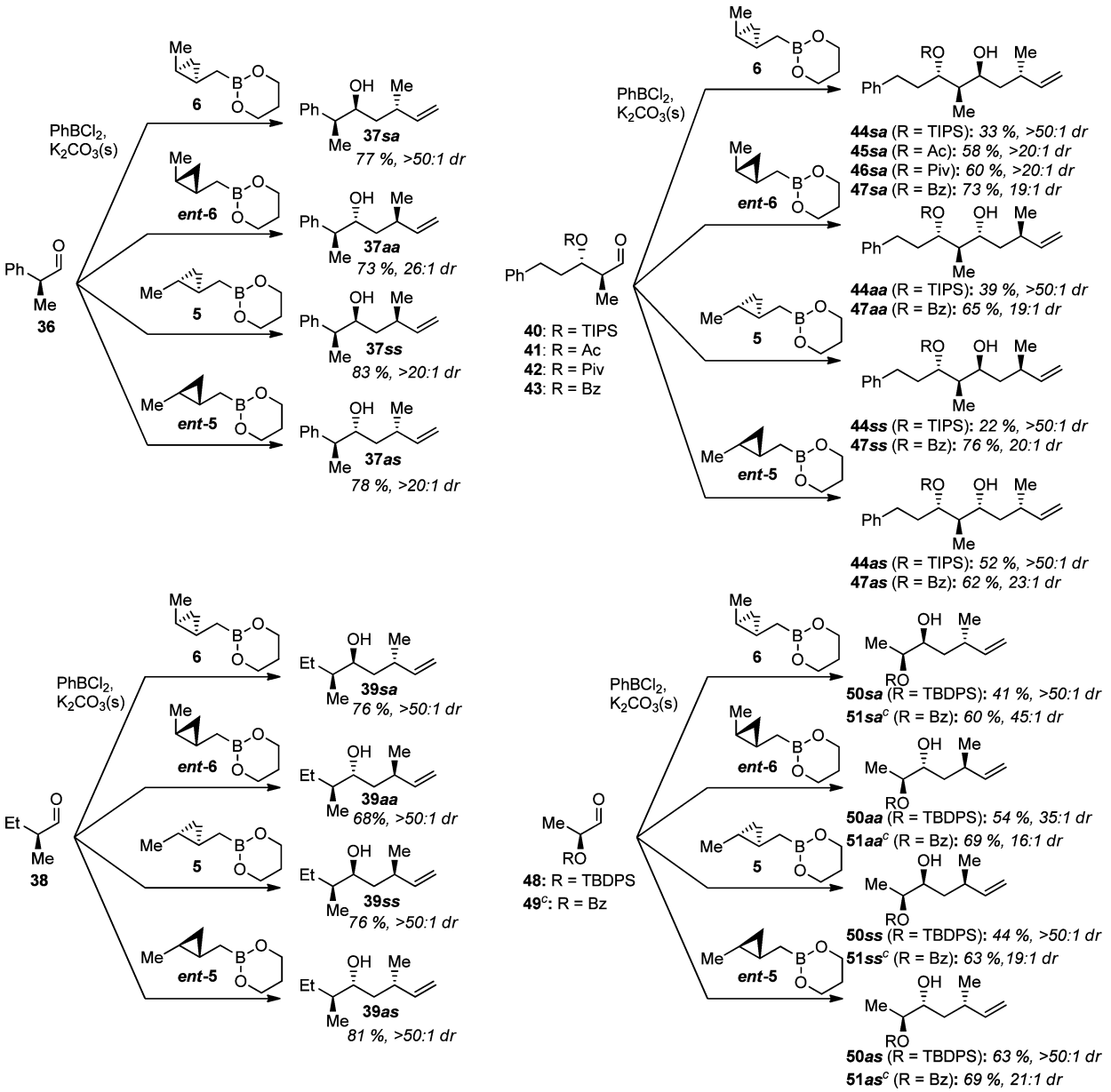
Scheme 6. Benzylic Chloride from Homocrotylation of Electron Rich Aldehyde 1q



es,[3c] to yield advanced intermediate **62**, whose spectroscopic data were identical to those previously reported.

Improved Large-Scale Route to Homocrotylation Reagents 5 and 6. Our original route to **5** (Scheme 9) was sufficient to yield several grams of reagent, but included several unnecessary interchanges of the boronate ester diol, merely to facilitate purification steps (recrystallization of **65** and chromatography of **23**, **24**) which turned out to be unnecessary. In our second-generation streamlined route, crude propenylboronic acid **64** from hydroboration of propyne[17] was condensed with diol **19**,[18] and the resulting unpurified **20c** could be cyclopropanated directly, followed by treatment with propanediol to yield boronate **66**.[19] Propanediol

Scheme 7. Reagent-Controlled Additions to Stereogenic α- and β- Substituted Aldehydes[a]



[a]Reaction conditions: 3 equiv of **5** or **6**, 1.5 equiv of $PhBCl_2$, 1 equiv of aldehyde, and 6 equiv of K_2CO_3. [b]dr's were measured on crude products prior to chromatography, using the following mehods: RP-HPLC for all **37**, **47**, **51**, GC for all **39**, **44**, and **50**, and ^1H NMR for **45**, **46**. See the Supporting Information for details. [c]For reactions **49** → **51**, the actual aldehyde and boronates used, and product structures produced, are the enantiomers of those depicted in this scheme.

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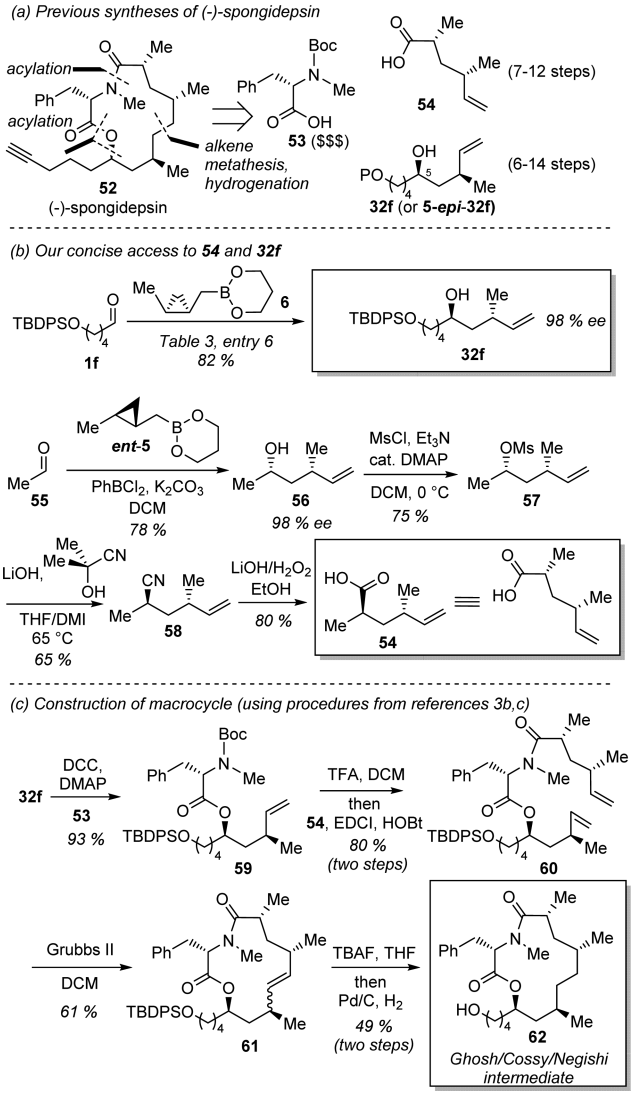
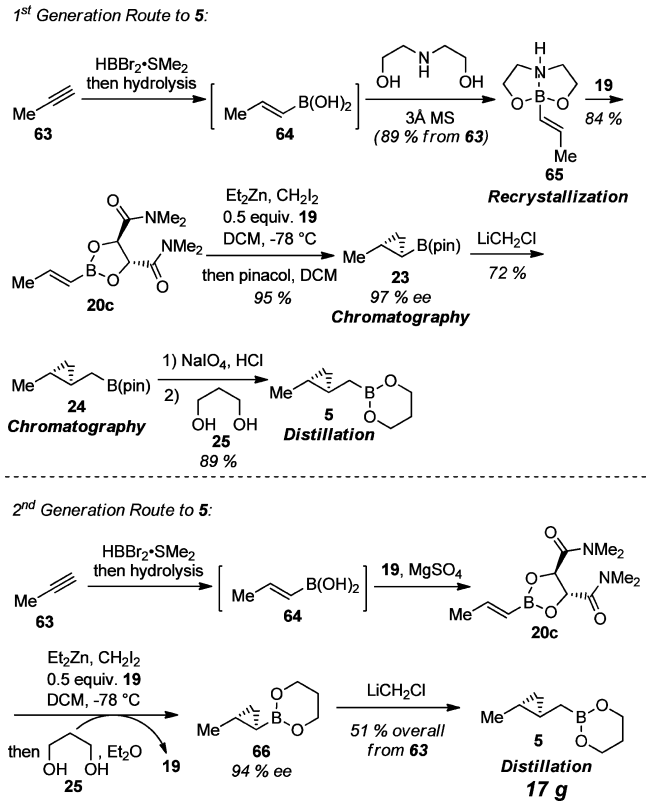
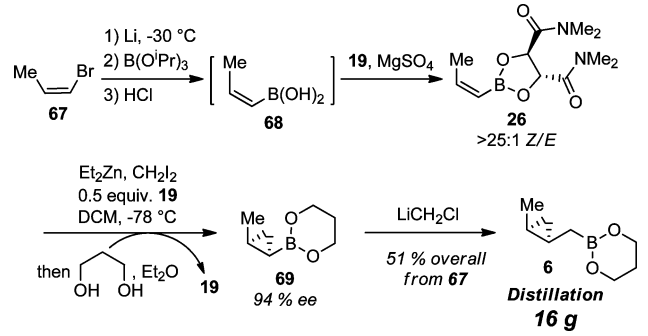
Scheme 8. Formal Synthesis of (−)-Spongidepsin



Scheme 9. First versus Second Generation Routes to 5



Scheme 10. Second Generation Route to 6



treatment is also accompanied by precipitation of **19**, allowing most of the auxiliary to be recovered. Finally, one-carbon homologation of **66** afforded **5** (17 g, 51% overall yield) after distillation, the only purification step in the sequence.

In the large scale preparation of **6**, the only substantially different step was preparation of the *cis* boronic acid **68**.[20] Lithiation of *cis*-1-bromopropene **67** under Whitesides conditions,[21] followed by trapping the intermediate *cis*-propenyl lithium with $B(O^iPr)_3$, hydrolysis and condensation with **19** gave boronate **26** with >25:1 *Z*/*E* selectivity. Subsequent steps were analogous to preparation of **5**. Large-scale cyclopropanation[19] of **26** and subsequent diol exchange and homologation afforded **6** (16 g, 51% overall yield) after distillation.

CONCLUSION

We have described the large-scale enantioselective preparation of asymmetric homocrotylation reagents **5** and **6**, and explored the scope their addition to a range of aliphatic and aromatic aldehydes including examples of double diastereoselection. The utility of this chemistry has been demonstrated in a very concise formal synthesis of (−)-spongidepsin, which could be readily be altered to provide materials for synthesis of any diastereomer of the natural product. Further studies to explore alternative boronate substitutions and other substrate classes, as well as development of milder and potentially enantioselective catalysts are under way and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08858.

Characterization data and NMR spectra (PDF)
Procedures for preparation of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) *trans*-Propenylboronic acid (**64**) is commercially available, but very expensive ($200/gram from Sigma-Aldrich). By contrast, it is prepared from propyne by this route at a materials cost of about $13/gram.

(18) D- and L-Tartaramide diols (**19**) are available from Sigma-Aldrich for $15/gram and $7/gram, respectively, but can be prepared from dimethyl tartrate and dimethylamine at a materials cost of about $1/gram and 60¢/gram, respectively, by the following procedure: Seebach, D.; Kalinowski, H.-O.; Langer, W.; Crass, G.; Wilka, E.-M. *Org. Synth.* **1983**, *61*, 24.

(19) It is noted that large-scale (∼200 mmol) cyclopropanations of **20c** and **26** proceeded with slightly diminished stereoselectivity: 94% compared with 97−98% for reactions performed on ∼ 30 mmol scale. Nevertheless, the selectivity obtained is synthetically useful and further optimization of this procedure is part of ongoing efforts.

(20) *cis*-Propenylboronic acid (**68**) is commercially available, but very expensive ($60/gram from Sigma-Aldrich); however, it is prepared from *cis*-propenylbromide by this route at a materials cost of about $11/gram.

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