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Lewis Acid Catalyzed Allylboration: Discovery, Optimization, and Application to the Formation of Stereogenic Quaternary Carbon Centers

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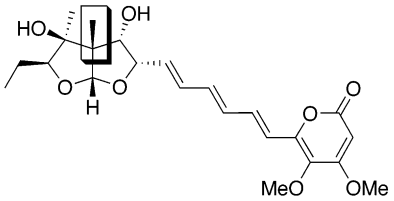
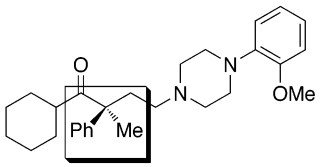
A full account of the development of the first catalytic manifold for the additions of allylboronates to aldehydes is described. The thermal additions (both diastereospecific and enantioselective) of 2-carboxyester 3,3-disubstituted allylboronates **1** to both aromatic and aliphatic aldehydes give biologically and synthetically important *exo*-methylene butyrolactones **2** containing a β-quaternary carbon center. Although the thermal reaction requires 14 d at room temperature to reach completion, the presence of certain metal salts allows for a 12−16 h reaction while preserving the diastereospecificity observed in the uncatalyzed process. Preliminary mechanistic studies on the origin of the catalytic effect are described as well as stereoselective transformations of lactones **2** into cyclic and acyclic stereotriads with potential usefulness as synthetic intermediates.

Introduction

Despite the major advances made in synthetic organic chemistry over the past several decades, the construction of quaternary carbon centers (i.e., carbons bearing four carbon substituents) remains a significant challenge.[1−9] Part of this synthetic challenge derives from the congested nature of these structural units, which makes unfavorable steric interactions unavoidable along the reaction pathway leading to these centres. The preparation of these sterically demanding centers is important not only because of the intellectual challenge that they present to modern synthetic chemists but also because they are present in many interesting natural products and synthetic drugs (e.g., asteltoxin and LY426965 below).[10] Since quaternary carbons in synthetic targets often bear four nonequivalent substituents, the challenge is further amplified by the need to prepare these centers in a stereocontrolled fashion.

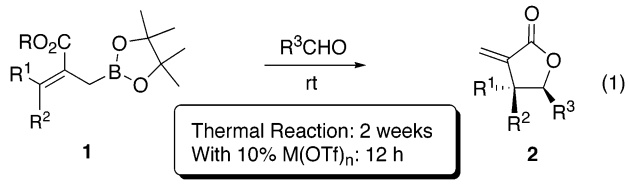


Asteltoxin



LY426965

The addition of 3,3-disubstituted allylboronates to aldehydes is a particularly effective route to stereodefined quaternary carbon centers due to the high diastereoselectivities usually observed in these reactions. This approach is made more attractive by the fact that the stereochemical outcome of these additions is generally and reliably predicted from simple Zimmerman−Traxler models. Hoffmann and Schlapbach were among the first to show that 3,3-disubstituted allylboronates could be used to generate stereodefined quaternary carbon centers.[11a] Although these allylboronates reacted with aldehydes in the expected manner, the reactions were notably slower than those involving less substituted allylboronates, requiring 5−8 days at room temperature to reach completion. The authors also noted that the diastereomeric purity of the homoallylic alcohol products was lower than the purity of the initial allylboronates. A comparable stereochemical leakage was reported by Suzuki and co-workers during similar studies on the reactions of 3,3-disubstituted allylboronates.[11b] This lower level of stereocontrol, accompanied by the long preparation of the required 3,3-disubstituted allylboronates, have hampered the wide spread use of this method for the preparation of quaternary carbon centers.



While other allylation reagents have been used to prepare stereogenic quaternary carbon centers (e.g., allylstannanes[12a] and allylzincs[12b]), to date the bench-

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mark method in this field belongs to Denmark and coworkers, who can prepare quaternary carbon centers with high levels of diastereo- and enantiocontrol using a chiral bisphosphoramide-catalyzed allylsilation system.[13] However, a significant limitation to this chemistry is that it is currently only applicable to aromatic aldehydes because aliphatic aldehydes fail to undergo the desired allylation.

As reported in a previous communication,[14a] 2-carboxyester-3,3-disubstituted allylboronates **1** undergo a diastereospecific allylation with aldehydes to yield synthetically and biologically useful α−methylene butyrolactones **2** which bear a β−stereogenic quaternary carbon center (eq 1). In retrospect, this preparation presented us with two significant challenges. The first was the preparation of the allylboronates **1**; previously published routes to allylboronates either offered poor prospects of diastereocontrol and substrate generality[15] or were long and cumbersome.[11,16] We solved this problem by developing a general and efficient, two-step, one-pot preparation of these important starting materials via the carbocupration of alkynoate esters.

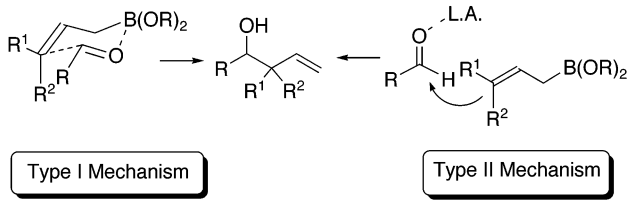

FIGURE 1. Type I and II allylation mechanisms.[18]

The second challenge encountered in this methodology was the low reactivity of the 2-carboxyester allylboronates **1**. Conjugation of the allyl unit to the ester lowers the nucleophilicity of these allylboronates, and consequently, aldehyde additions with **1** were quite sluggish. This reactivity problem prompted us to explore the possibility of using an external Lewis acid to catalyze the allylboration.[17] Allylboronates are self-activating Type I reagents, where the allylation reaction is promoted by internal coordination of the aldehyde to the boron atom (Figure 1).[18] Because of this internal activation, there would appear to be no need for an external promoter. Furthermore, an external Lewis acid might compete with the boron atom for the aldehyde, leading to a switch from the highly diastereoselective, cyclic, Type I mechanism to the less selective, open-chain Type II mechanism. However, this concern turned out to be unfounded, and in the end we were able to develop the first successful catalytic system that allows for the diastereospecific allylation of both aliphatic and aromatic aldehydes with allylboronates under mild conditions in reasonable time frames.[14b]

Here we report the full account of the discovery and optimization of the Lewis acid catalyzed allylboration, focusing in particular on the use of this methodology for the challenging preparation of quaternary carbon centers. Efforts toward a novel attempt to control the absolute stereochemistry of the allylboration using a single, carboxyester-based chiral auxiliary will be described. The results of a scope and limitations study on the Lewis acid catalyzed allylboration reaction are presented, along with a new catalytic protocol which greatly improves the efficiency of the addition reaction with aliphatic aldehydes. Finally, we describe the extension of this methodology to the preparation of highly substituted butyrolactones with three contiguous stereogenic carbons.

Results and Discussion

1.1. Preparation of Tetrasubstituted Allylboronates and Optimization of *E*/*Z* Selectivity. Inspired by the work of Hoffmann and Schlapbach,[11a] we decided to explore a route to tetrasubstituted allylboronates starting from the carbocupration of alkynoate esters (Scheme 1). Here, treatment of an alkynoate ester (**3**) with a dialkylcuprate would yield alkenylcopper inter-

(1) (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419−460. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146.

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(8) Fukuda, Y.-i.; Sasaki, H.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2002**, *43*, 2047−2049.

(9) Enders, D.; Knopp, M.; Runsink, J.; Raabe, G. *Liebigs Ann.* **1996**, 1095−1116.

(10) For some examples, see: (a) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186−4188. (b) Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951−1953.

(11) (a) Hoffmann, R. W.; Schlapbach, A. *Liebigs. Ann. Chem.* **1990**, 1243−1248. (b) Sato, M.; Yamamoto, Y.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7071−7074.

(12) (a) Nishigaichi, Y.; Takuwa, A. *Tetrahedron Lett.* **1999**, *40*, 109−112. (b) Skulte, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776−11777.

(13) (a) Denmark, S. E.; Fu, J. P. *Chem. Commun.* **2003**, 167−170. (b) For a specific example on the preparation of a quaternary carbon centre, see: Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951−1953.

(14) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898−899. (b) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586−11587.

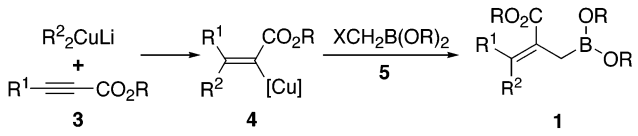
(15) Roush, W. R. In *Stereoselective Synthesis: Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21b, pp 1410−1486.

(16) For some alternate preparations of allylboronates, see: (a) Falck, J. R.; Bondlela, M.; Ye, J. H.; Cho, S. D. *Tetrahedron Lett.* **1999**, *40*, 5647−5650. (b) Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2000**, *122*, 7122−7123. (c) Yamamoto, Y.; Kurihara, K.; Yamada, A.; Takahashi, M.; Takahashi, Y.; Miyaura, N. *Tetrahedron* **2003**, *59*, 537−542. (d) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413−416. (e) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807−810. (f) Touré, B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. Eur. J.* **2003**, *9*, 466−474. (g) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308−9309. (h) Pietruszka; J. Schöne, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5638−5641. (i) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481−484.

(17) For a recent review on the activation of allylsilanes and allylboronates, see: Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732−4739.

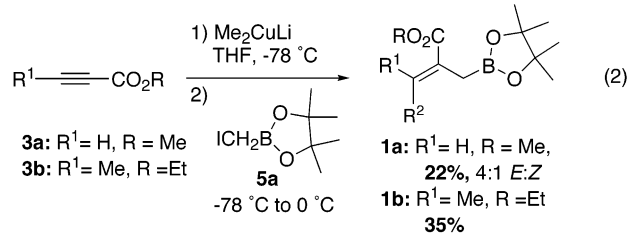
(18) For a discussion of the different types of allylating reagents, see: (a) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655−1660. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2001; pp 299−401.

SCHEME 1



mediate **4**, which would subsequently be trapped by a halomethaneboronate (**5**) to give the tetrasubstituted allylboronate **1**. This route appeared promising because the carbocupration of alkynoate esters is known to proceed stereospecifically to give one isomer of the alkenylcopper species **4**.[19] Another attractive feature of this strategy is that a large number of alkynoate esters and cuprates are available, which allows for a wide variety of R^1 and R^2 groups in the products **1**. However, the alkenylcopper intermediate **4** is notoriously unreactive and is typically only trapped by very active electrophiles.[20] At the outset of these studies, we wondered if electrophile **5** would be sufficiently reactive to trap this intermediate or, if not, whether conditions could be found which would allow for effective trapping. Also, the 1-alkoxycarbonylalkenylcopper intermediate **4** is configurationally unstable at temperatures above −30 °C,[21] and any alkylation conditions would have to contend with this potential pitfall.

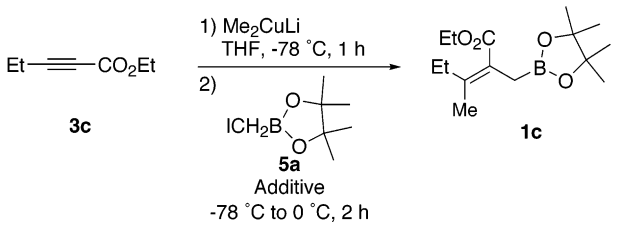
Initial experiments following the procedure of Deslongchamps and co-workers yielded promising, if somewhat modest, results.[20b] Methyl propionate **3a** and ethyl 2-butynoate **3b** were both successfully converted into their respective allylboronates **1a** and **1b** (eq 2). Unfortunately, the yields for both compounds were low, and the *E*/*Z* selectivity for **1a** was poor.



(2)

A breakthrough came when we discovered that adding small amounts of hexamethylphosphoramide (HMPA) prior to the electrophilic quench allowed for the formation of tetrasubstituted allylboronates **1** in good yield and excellent diastereoselectivity (Table 1). In this model study, the data show that at least 9 equiv of HMPA is required to achieve a highly selective reaction (entry 1) and that selectivity erodes as the amount of HMPA decreases (entries 2 and 3). Although attempts were made to find a replacement for the carcinogenic HMPA, no other additive tried to date rivals HMPA in its efficiency at providing good yields of highly stereopure products. Although DMPU comes the closest, it must be used in much larger amounts in order to achieve the same results (entry 4).

TABLE 1. Effect of Different Additives on the Carbocupration−Alkylation Sequence[a]

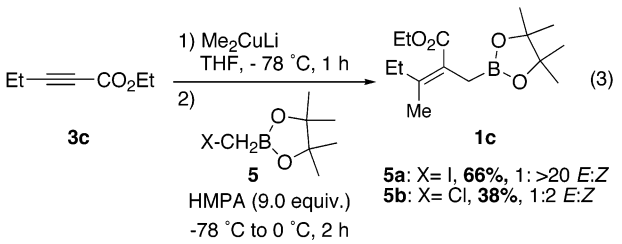


entry	additive	equiv	yield (%)	*E*/*Z* selectivity
1	HMPA	9	68	1:17
2	HMPA	3	(100)	1:12
3	HMPA	1	(100)	1:4
4	DMPU	40[b]	(69)	1:>20
5	DMPU	9	34	1:10
6	DMEU	9	54	1:12
7	TMEDA	7	0	

[a] Reactions done on 1 mmol scale in 5 mL of THF. *E*/*Z* ratio determined by ^{1}H NMR of the crude reaction mixture. Yields in parentheses are from unpurified products. [b] DMPU used as a 1:1 cosolvent with THF.

Recently, a more thorough study of the role of additives in this carbocupration−alkylation sequence was performed in our research group.[22] This study showed that HMPA plays a dual role in the alkylation step: it stabilizes the alkenylcopper intermediate by sequestering lithium cations from solution, and it enhances the alkylation process itself. This study also showed that excellent yields and diastereoselectivities are obtained with as little as 2 equiv of HMPA provided that 1 equiv of 12-crown-4 is included in the electrophilic quench.

Finally, we demonstrated that the chloromethane boronate **5b** is not as effective as the iodoelectrophile **5a** in this reaction (eq 3).[23]



(3)

We were pleased to find that a large number of tetrasubstituted allylboronates could be prepared using this convenient, one-pot, two-step procedure (Table 2). Initially, the allylboronates **1** were assumed to be too sensitive to purify, and consequently, some of the yields below are compiled from crude products. However, these boronates eventually proved to be quite robust, and they could be readily purified by flash chromatography on silica gel.

As can be seen from Table 2, cuprates derived from either alkyllithium or Grignard reagents may be used. Branched organometallic reagents are also effective in the reaction, although the stereoselectivity of the product

(19) (a) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851−1852. (b) Siddall, J. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 1853−1854.

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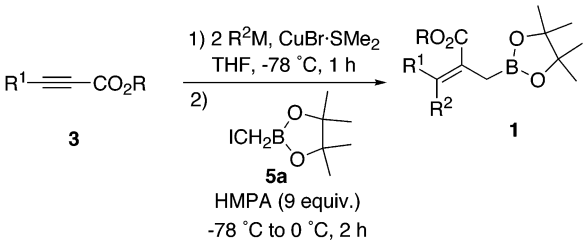
(21) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051−2058.

(22) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066−6069.

(23) Chloromethaneboronate **5b** can be prepared according to: Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137−141.

TABLE 2. Yields and Diastereomeric Ratios of Prepared Allylboronates 1[a]



entry	alkynoate	boronate	R^1	R^2M	yield (%)	*E*/*Z*
1[b]	**3a**	**1a**	H	MeLi	60	>20:1
2	**3b**	**1b**	Me	MeLi	(99)	
3	**3c**	**1c**	Et	MeLi	68	1:17
4	**3d**	**1d**	Bu	MeLi	(99)	1:>20
5	**3b**	**1e**	Me	BuLi	78	>20:1
6	**3b**	**1f**	Me	*i*-BuMgCl	45	>20:1
7	**3b**	**1g**	Me	*s*-BuLi	58	>20:1
8	**3b**	**1h**	Me	*t*-BuLi	72	2:1
9[b]	**3c**	**1i**	Et	BuLi	60	>20:1
10	**3d**	**1j**	Bu	octylMgCl	24	>20:1
11	**3b**	**1k**	Me	allylMgCl	60	19:1
12	**3e**	**1l**	$TBDPSOCH_2$	MeLi	60	1:>20
13	**3f**	**1m**	$TBDPSO(CH_2)_2$	MeLi	(92)	1:>20
14	**3b**	**1n**	Me	$TMS(CH_2)_2OCH_2Li$	28	>20:1
15	**3g**	**1o**	Ph	MeLi	38	1:>20
16	**3h**	**1p**	TMS	MeLi	0	

[a] R = Me, Et. Yields in parentheses are for crude products, others are of compounds purified by flash chromatography. TBDPS = *tert*-butyldiphenylsilyl. [b] Allylboronate prepared from 2 equiv of **5a** and a room-temperature quench; see below for details.

decreases for sterically demanding reagents (cf. entries 5−8). Unsaturation may be present in the cuprate as long as it is not directly next to the copper. Thus, allyl groups are effectively transferred (entry 11), but vinyl- and phenylcuprates failed to provide the desired products. In these latter cases, the major product is the protonated olefin, suggesting that the problem originates in the electrophilic quench. A single, low-yielding example was obtained with a cuprate bearing a protected alcohol (entry 14).

Similarly, there are few limitations on the kind of alkynoate that may be used in this reaction. Alkynoates that are not commercially available are readily prepared by the reaction of terminal alkynes with methyl chloroformate.[24] So far, alkynoates where the R^1 group has been a primary, aliphatic chain have successfully been used, as well as alkynoates bearing protected hydroxyl groups (entries 12 and 13). There were, however, two substrates that did not perform well in this reaction sequence. Methyl 3-phenylpropiolate **3g** gave only a low yield of boronate **1o** along with significant amounts of unreacted alkynoate (entry 15), and the TMS-protected **3h** was recovered unchanged after reaction (entry 16). Performing the 1,4-addition of these alkynoates at a higher temperature (−40 °C) did not improve the outcome. Overall, these results show that this procedure is able to produce a relatively large scope of highly functionalized, tetrasubstituted allylboronates quickly and efficiently.

The stereochemistry of the products was reliably determined by analysis of the ^1H NMR spectrum. In all cases, the ^1H NMR signal of the *Z*-substituent (which is cis to the ester group) was found downfield from the *E*-substituent, presumably due to anisotropic deshielding from the ester. This deshielding of the *Z*-substituent has been noted before.[20] In addition, ^1H NOE experiments on boronate **1c** were consistent with the proposed structure.[25]

1.2. Optimization of Reagent Stoichiometry in the Preparation of Tetrasubstituted Allylboronates (1). One limitation to the sequence described above was the use of 3 equiv of electrophile **5a** in the alkylation step. Although the preparation of **5a** is not dificult,[26] a more effective and less wasteful use of this electrophile was desirable. Yields and selectivities using only 2 equiv of **5a** were comparable to those obtained when 3 equiv was employed as long as the electrophilic quench was performed at room temperature (Table 3, compare entry 2 with entry 4).

Interestingly, no allylboronate was formed at all if only 1 equiv of **5a** was used (entry 5). This result suggests that the first equivalent of iodomethaneboronate **5a** is consumed by preferential transfer of the methyl group over the alkenyl group from the mixed cuprate **4a** to the electrophile **5a** (Scheme 2) to give the putative ethylboronate **6**. Selectivity in the transfer of ligands from unsymmetrical cuprates has long been an issue in organocopper chemistry, and saturated ligands are generally transferred faster in substitution reactions than unsaturated groups.[27] Although this problem might be circumvented by using a cuprate bearing a nontransfer-

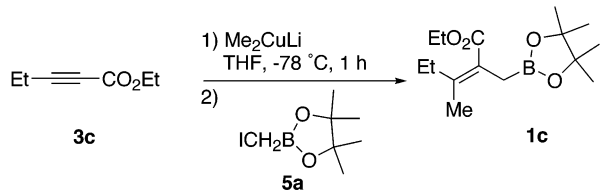
(24) Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70*, 2058−2064.

(25) See the Supporting Information for further details.

(26) Of the numerous preparations of iodomethaneboronate **5a** available, the one that we found to be the most convenient on large scale was: Phillion, D. P.; Neubauer, R.; Andrew, S. S. *J. Org. Chem.* **1986**, *51*, 1610−1612. For alternative preparations, see refs 44 and 23.

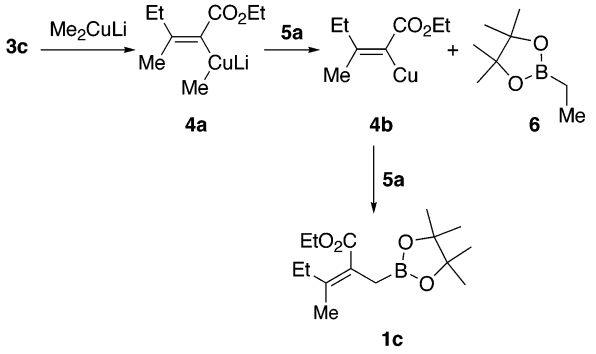
(27) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. A. *J. Org. Chem.* **1984**, *49*, 3928−3938.

TABLE 3. Optimization of the Preparation of 1c with Respect to Equivalents of 5a and Temperature



entry	equiv of **5a**	quench conditions	yield (%)	*E*/*Z* selectivity
1	4	0 °C, 3 h	72	1:>20
2	3	0 °C, 2 h	66	1:>20
3	2	0 °C, 4 h	27	1:>20
4	2	rt, 2 h	53	1:>20
5	1	0 °C, 4 h	0	

SCHEME 2



able group,[28] electrophile **5a** is too readily available to justify an extensive search for a suitable dummy ligand.

2.1. Quaternary Carbon Centers from Diastereoselective Allylborations. We were pleased to find that the tetrasubstituted allylboronates **1** underwent a smooth, if somewhat slow, reaction with aldehydes (Table 4). In contrast to previously reported allylations with 3,3-unsubstituted 2-carboxyester allylboronates,[29] the product from allylations with **1** was almost always lactone **2**, and the intermediate homoallylic alcohol **7** was only observed in the reaction of monosubstituted boronate **1a** (entry 1). This facile lactonization is likely a manifestation of the *gem*-dialkyl effect.[30]

These reactions are operationally extremely simple—the aldehyde and allylboronate are stirred together in toluene, dichloromethane, or even neat. Most aldehydes, both aromatic and aliphatic, are effective substrates in the reaction, and so far the only exceptions found are very hindered aldehydes (e.g., cyclohexanecarboxaldehyde, mesitaldehyde) and aldehydes with free amino groups (4-dimethylaminobenzaldehyde). The only drawback is that the reactions are quite sluggish. Similar to the results of Villiéras and co-workers,[29] reaction times are on the order of 2 weeks at room temperature but, in contrast to these published results, only 24 h in hot toluene.

The large rate differences seen between reactions with 2-carboxyester allylboronates and 3,3-disubstituted analogues that lack this ester substituent suggest that steric arguments alone cannot explain the low reactivity of **1**. This slow reaction is likely due to a reduction of the nucleophilicity of the γ-carbon in boronates **1** by conjugation to the carboxyester. In support of this theory, an unusually slow reaction is also observed with 3-alkoxyallylboronates,[31] where the alkoxy substituent can similarly reduce the nucleophilicity at this position by inductive effects. However, reaction times with allylboronates **1** are dramatically reduced under the new catalytic manifold (see below).

Previous reports of allylations with 3,3-disubstituted allylboronates that lack the 2-carboxyester group describe that these reactions proceed with high but not complete diastereoselectivity.[11] In contrast to these reports, additions with our allylboronates **1** are generally diastereospecific—the *Z*-group in boronate **1** (R^2, which derives from the cuprate) is almost always syn in lactone **2** to the group from the aldehyde (R^3).[32] Furthermore, the stereochemical purity of lactone **2** mirrors that of boronate **1**. Thus, if the initial boronate is a 20:1 mixture of *E*/*Z* isomers, then the lactone produced is correspondingly a 20:1 diastereomeric mixture. This effect was elegantly demonstrated by the preparation of the epimeric lactones **2i** and **2j** (Scheme 3). The only time that these reactions were not stereospecific is when aliphatic aldehydes are allylated at high temperatures. When reactions with these substrates are performed in refluxing toluene, the product lactones do show some erosion of stereoselectivity (see below). This erosion is not observed when the reactions are done at temperatures at or below 80 °C, nor are they observed with aromatic substrates at any temperature.

The diastereomer observed in these reactions is the same as that predicted from simple Zimmerman−Traxler models (Figure 2) where the R^3 group from the aldehyde occupies the pseudoequatorial position (transition state **A**). Reactions with 2-carboxyester allylboronates do not exhibit any stereochemical leakage, in contrast to allylations with 3,3-disubstituted allylboronates that lack the 2-carboxyester group (see above).[11] The reason for the improved selectivity is likely that in the competing transition state **B**, the formyl R^3 group and the 2-carboxyester group would experience an unfavorable 1,3-diaxial interaction in addition to the usual 1,3-interaction between the R^3 group and the axial boronate substituent. This additional steric interaction further favors transition state **A** over transition state **B**.

Finally, there remains to explain the erosion of stereochemical purity observed in the reactions of aliphatic aldehydes in refluxing toluene. One possible explanation is that the boronate undergoes reversible borotropic rearrangement at these temperatures,[15] thus leading to "isomerized" products after the allylboration. However, if that were the case, then aromatic aldehydes should also

(28) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437−447.

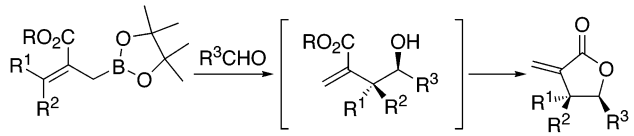
(29) (a) Nyzam, V.; Belaud, C.; Villiéras, J. *Tetrahedron Lett.* **1993**, *34*, 6899−6902. (b) Nyzam, V.; Belaud, C.; Zammattio, F.; Villiéras, J. *Bull. Soc. Chim. Fr.* **1997**, *134*, 583−592.

(30) For a discussion of this effect, see: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232.

(31) (a) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs. Ann. Chem.* **1985**, 2246−2260. (b) Hoffmann, R. W.; Metternich, R. *Liebigs. Ann. Chem.* **1985**, 2390−2402.

(32) The stereochemistry of the lactones **2** was unambiguously determined by ^{1}H NOE experiments on the diastereomeric lactones **2i** and **2j** as well as by X-ray crystallography of lactone **2n**. See the Supporting Information for details.

TABLE 4. Diastereospecific Allylborations with 3,3-Disubstituted Allylboronates 1[a]

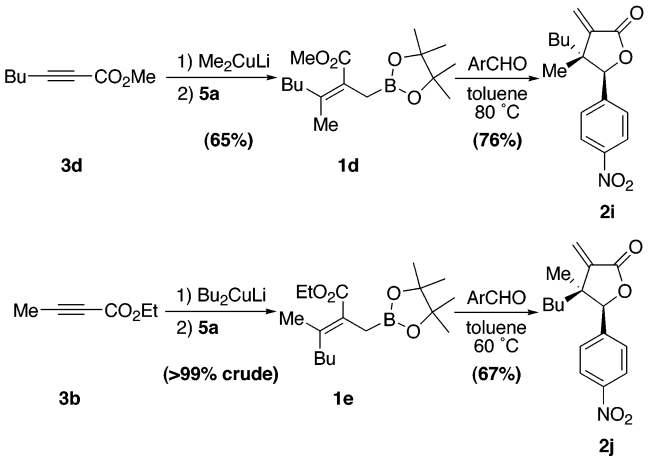


1 **7** **2**

entry	boronate	R^1	R^2	R^3	lactone	conditions[b]	yield (%)
1	**1a**	H	Me	Ph	**2a**	B	60
2	**1b**	Me	Me	Ph	**2b**	C	78
3	**1b**	Me	Me	TBDPSO$(CH_2)_2$	**2c**	E	92
4	**1b**	Me	Me	C_9H_{19}	**2d**	B	40
5	**1c**	Et	Me	C_9H_{19}	**2e**	A	68
6	**1c**	Et	Me	Ph	**2f**	A	60
7	**1c**	Et	Me	*p*-MeO-C_6H_4	**2g**	C	47
8	**1c**	Et	Me	*p*-NO_2-C_6H_4	**2h**	B	81
9	**1d**	Bu	Me	*p*-NO_2-C_6H_4	**2i**	B	76
10	**1e**	Me	Bu	*p*-NO_2-C_6H_4	**2j**	D	67
11	**1f**	Me	*i*-Bu	*p*-MeO-C_6H_4	**2k**	C	50
12	**1k**	Me	allyl	*p*-MeO-C_6H_4	**2l**	C	48
13	**1l**	TBDPSOCH_2	Me	*p*-NO_2-C_6H_4	**2m**	B	75
14	**1o**	Ph	Me	*p*-NO_2-C_6H_4	**2n**	B	26

[a] All butyrolactones **2** were isolated in >20:1 dr. TBDPS = *tert*-butyldiphenylsilyl. [b] Conditions: (A) toluene, rt, >12 d; (B) toluene, 60−80 °C, 16−120 h; (C) toluene, 110 °C, 16−24 h; (D) CH_2Cl_2, 40 °C, 48 h; (E) neat, rt, >12 d.

SCHEME 3



show some levels of erosion. Furthermore, recovered boronates from these reactions do not show evidence of isomerization. A more likely possibility is that other transition states become energetically attainable at these higher temperatures. This explanation was the one offered by Hoffmann and Schlapbach to rationalize the erosion of stereochemistry seen with their 3,3-disubstituted allylboronates.[11a] While transition state **B** in Figure 2 is the most likely candidate, we cannot exclude the possibility that boatlike transition states which lead to the other diastereomer of lactone **2** may also be operative.

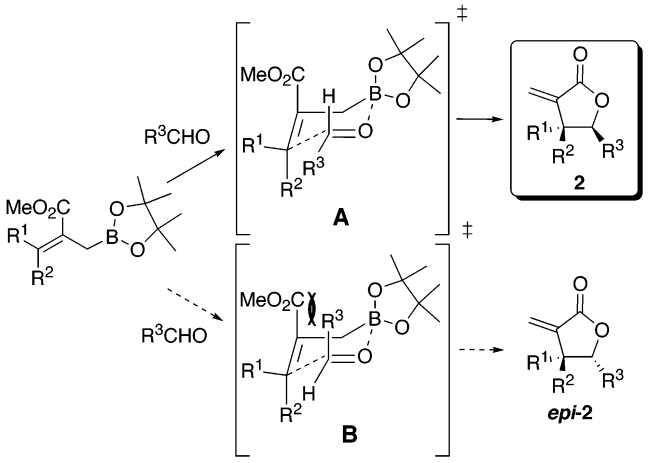


FIGURE 2. Proposed mechanistic pathway for diastereospecific allylborations with 2-carboxyester allylboronates **1**.

2.2. Quaternary Carbon Centers from Enantioselective Allylborations: Single Auxiliary Approach. The possibility of extending this methodology to enantioselective additions was next examined. Currently there is no widely applicable route to the enantioselective preparation of quaternary carbon centers using allylboration chemistry.[33] Inspection of the structure of boronate **1** reveals that there are two positions where a chiral auxiliary could be installed—either on the carboxyester or on the boronate. Since the Villiéras group had found that most known, boron-based, chiral diol directors were ineffective with 2-carboxyester allylboronates,[16i,29,34] we decided to explore the effectiveness of a carboxyester-based auxiliary.

The requisite chiral 2-carboxyester allylboronates **11** were prepared by the DCC mediated esterification[35] of 2-butynoic acid **8** with various chiral alcohols (**9**)[36] followed by carbocupration and trapping with **5a** as described above (Table 5).

Using aldehyde **12** as an aliphatic, nonvolatile, model substrate,[37] enantioselective allylborations with chiral

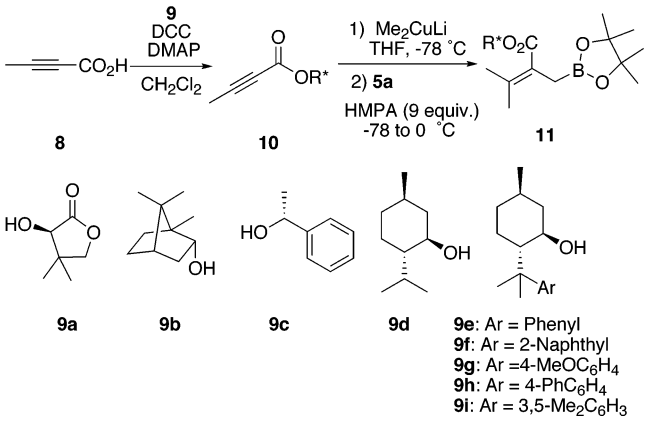
(33) For some pioneering studies on the enantioselective preparation of quaternary carbon centres from 3,3-disubstituted allylboronates, see: (a) Hoffmann, R. W.; Schlapbach, A. *Liebigs Ann. Chem.* **1991**, 1203−1206. (b) Yamamoto, Y.; Hara, S.; Suzuki, A. *Synlett* **1996**, 883−884.

(34) Chataigner, I.; Lebreton, J.; Zammattio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719−3722.

(35) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 4239−4254.

(36) Alcohols **9f**−**h** were prepared according to: Yang, D.; Xu, M.; Bian, M.-Y. *Org. Lett.* **2001**, *3*, 111−114. See also: (a) Ort, O. *Org. Synth.* **1987**, *65*, 203-213. (b) Potin, D.; Dumas, F. *Synth. Commun.* **1990**, *20*, 2805−2813.

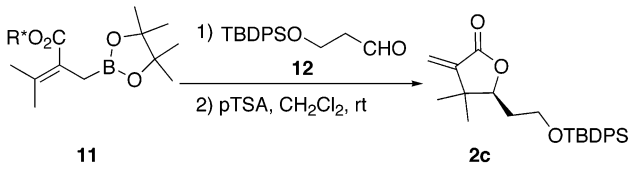
TABLE 5. Preparation of Chiral Alkynoates 10 and Allylboronates 11



entry	chiral alcohol	alkynoate	yield of **10** (%)	boronate	crude yield of **11** (%)[a]
1	**9a**	**10a**	89	**11a**	>99
2	**9b**	**10b**	80	**11b**	>99
3	**9c**	**10c**	79	**11c**	98
4	**9d**	**10d**	78	**11d**	94
5	**9e**	**10e**	89	**11e**	44[b]
6	**9f**	**10f**	82	**11f**	>99
7	**9g**	**10g**	65	**11g**	>99
8	**9h**	**10h**	35	**11h**	>99
9	**9i**	**10i**	43	**11i**	>99

[a] Crude yields recorded due to the presumed instability of the products. [b] Product purified by silica gel chromatography.

TABLE 6. Enantioselective Allylations with Chiral Allylboronates 11a−i[a]



entry	allylboronate	conditions	yield (%)	ee (%)
1	**11a**	neat, 8 d	89	22
2	**11b**	neat, 14 d	64	(−6)[b]
3	**11c**	toluene, 26 d[c]	70	10
4	**11d**	neat, 8 d	78	7
5	**11e**	toluene, 36 d[c]	51	80
6	**11f**	toluene, 14 d	(95)[d]	82
7	**11f**	CH_2Cl_2, 14 d	(86)[d]	75
8	**11g**	toluene, 14 d	74	56
9	**11h**	toluene, 14 d	24	66
10	**11i**	toluene, 14 d	6	62

[a] Yields calculated after silica gel chromatography. Selectivities were determined by Chiral HPLC. See the Experimental Section for details. The absolute configuration of **2c** is inferred from other results; see below for details. TBDPS = *tert*-butyldiphenylsilyl. [b] Major isomer is opposite to that in the other entries. [c] Excessively long reaction times due to the performance of the reaction over a Christmas vacation, and not due to a reactivity problem with boronates **11c** and **11e**. [d] Product contaminated with auxiliary. While this contamination gives an artificially high yield, it did not affect the chiral HPLC analysis.

allylboronates **11** were performed at room temperature over 10−14 days and the enantiomeric purity of the lactone products **2c** was determined by chiral HPLC (Table 6). Lactonization of the homoallylic alcohol was not spontaneous in reactions with the very large arylmenthol auxiliaries (entries 5−10), and the cyclization had to be promoted by treatment of the crude reaction mixture with mild acid.

Gratifyingly, we found that a carboxyester-based chiral auxiliary could effectively direct the stereochemical course of the reaction (Table 6). Although the simple chiral alcohols **9a**−**d** were not effective auxiliaries in this reaction (entries 1−4), the leap in enantioselectivity observed with the 8-arylmenthol auxiliaries **9e**−**i** is remarkable (entries 5−10). This increase is especially impressive given the poor performance of menthol **9d** (the parent compound, entry 4). A small solvent effect was also observed, where selectivities were higher when the reaction was performed in toluene rather than in dichloromethane (compare entries 6 and 7).

In view of the effectiveness of the 8-phenymenthol ester **11e** in the reaction (entry 5), it seemed only a matter of modifying the aromatic ring to find the auxiliary that would provide truly effective levels of stereoinduction. Unfortunately, enantioselectivities greater than 82% were not achieved, despite the use of a large number of different arylmenthols, and there currently seems to be no advantage to using auxiliaries other than the commercially available phenyl derivative **9e**.

In analogy to the results from the enantioselective additions with the dual auxiliary allylboronate **13a** (see next section), the (*S*)-configuration has been assigned to the major enantiomer of lactone **2c** produced in these reactions.

The power of 8-arylmenthol esters in stereoselective cyclizations,[36,38] Michael additions,[39] and allylsilations[40] is well documented, and their effectiveness is generally attributed to the ability of the aromatic ring to shield one face of the reacting olefin.[41] In the case of these allylborations, the phenyl ring presumably shields one of the faces of the allyl group. Indeed, an X-ray crystal structure of **11f** shows that the *β*-naphthyl group effectively covers the *Re*-face of the allylboronate (as determined from C2, Figure 3). This X-ray structure also reveals that there is no coordination between the boron and the carboxyester carbonyl. Similarly, ^{1}H NMR spectroscopy on **11f** shows that the signals for the protons on C4, C5, and C6 are all shifted significantly upfield compared to the analogous ethyl ester **1b**, an effect that would be expected from diamagnetic shielding from the naphthyl ring. Similar shielding effects are observed in other α,*β*-unsaturated arylmenthol esters.[41]

At this point in the study it would be premature to propose a transition state to explain the observed stereoselectivity, even with the crystal structure shown in Figure 3. Indeed, a simple Zimmerman−Traxler model with preferential *Si*-face approach of the aldehyde inaccurately predicts that (*R*)-**2c** should be the preferred

(37) Ndibwami, A.; Lamothe, S.; Guay, D.; Plante, R.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 695−713.

(38) (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908−6909. (b) Ohkata, K.; Miyamoto, K.; Matsumura, S.; Akiba, K.-y *Tetrahedron Lett.* **1993**, *34*, 6575−6578. (c) Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785−1788.

(39) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112−8114.

(40) D'Oca, M. G. M.; Pilli, R. A.; Pardini, V. L.; Curi, D.; Comninos, F. C. M. *J. Braz. Chem. Soc.* **2001**, *12*, 507−513.

(41) (a) Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500−503. (b) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293−2304.

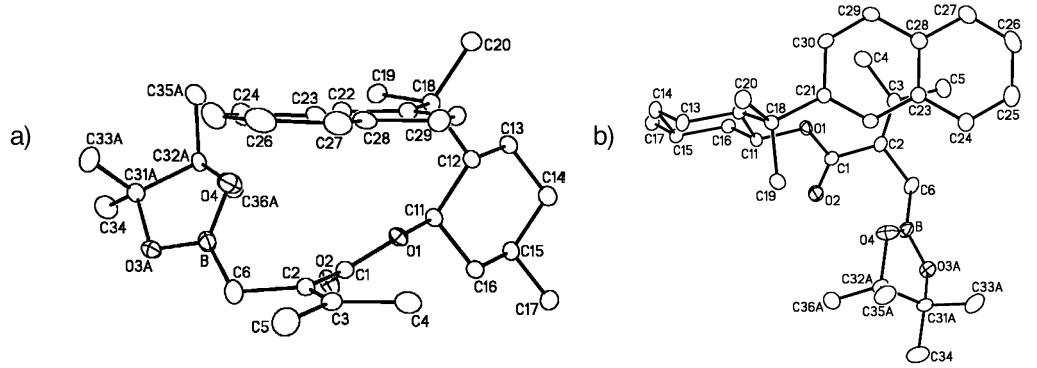


FIGURE 3. ORTEP diagrams of β-naphthylboronate **11f**: (a) view parallel to the plane of the β-naphthyl ring; (b) view perpendicular to this plane.

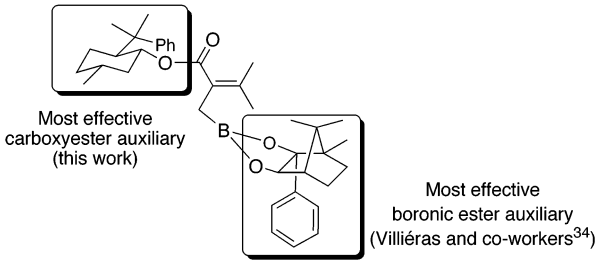


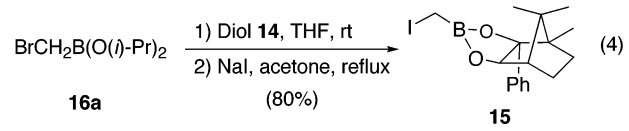
FIGURE 4. Design of the dual-auxiliary 2-carboxyester allylboronate **13a**.

isomer. Because of the uncertainty of the reactive conformation of the chiral allylboronate **11** at the transition state, any models that could currently be proposed would be purely speculative.

2.3. Quaternary Carbon Centers from Enantioselective Allylborations: Dual Auxiliary Approach. Since it was not possible to achieve sufficiently high levels of enantioselectivity with a single chiral auxiliary, we decided to explore a dual auxiliary approach (Figure 4). We envisaged that allylboronate **13a**, which bears chiral auxiliaries on both the carboxyester and boronic ester, would provide high levels of selectivity. Corey's 8-phenylmenthol **9e** and Hoffmann's bornanediol-derived **14**[42] were chosen for this study because these two auxiliaries were previously shown to be the most effective auxiliaries for 2-carboxyester allylboronates.[34]

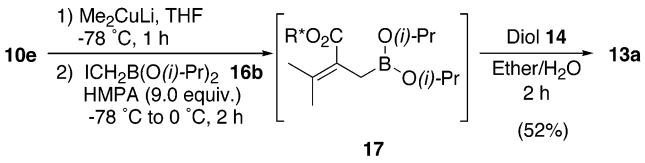
Several preparations of allylboronate **13a** were attempted before an effective route was finally developed. A simple preparation would entail replacement of the pinacol in allylboronate **11e** for diol **14**. However, despite literature precedents for this transformation,[29b,43] all attempts to transesterify the pinacol ester **11e** failed in our hands.

We next prepared chiral electrophile **15** by transesterification of the diisopropyl bromomethaneboronate **16a**[44] followed by halogen exchange on the resulting bromide (eq 4).[23] We hoped to use this electrophile in place of the pinacol electrophile **5a** in the carbocupration−alkylation sequence. Unfortunately, although the preparation of **15** was relatively straightforward, this chiral electrophile did not provide an effective quench in the subsequent carbocupration reaction.



Allylboronate **13a** was finally accessed by transesterification of the diisopropyl allylboronate **17**, which was prepared from alkynoate **10e** and electrophile **16b** (Scheme 4).[45] The diisopropyl allylboronate **17** was not

SCHEME 4



isolated but was rather treated with an ethereal solution of **14** in the workup, directly yielding the desired chiral allylboronate **13a**.

We were delighted to see that this dual auxiliary strategy did indeed afford a highly enantioselective allylating reagent. Stirring boronate **13a** in toluene with aldehydes for 2 weeks at room temperature followed by acid-catalyzed ring closure gave acceptable yields of highly enantioenriched lactones **2** (Table 7). Both model aliphatic and aromatic aldehydes were effective in this reaction. Although the requirement for two different auxiliaries might appear excessive, the enantioselectivities obtained are excellent. Furthermore, the methodology is partially redeemed by the facile removal of the auxiliaries from the product. Indeed, both auxiliaries are simultaneously removed in the ensuing lactonization, alleviating the need for separate cleavage steps.

Lactone **2o** was determined to have the (*S*)-configuration by X-ray crystallography (see the Supporting Information). The stereogenic centers in all other enantioenriched lactone products were assigned in analogy to this result. Chiral HPLC data confirmed that all of the

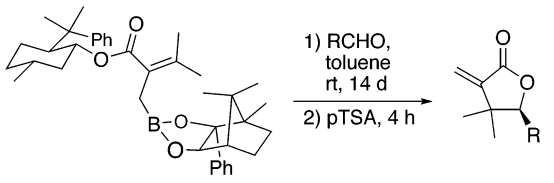
(42) Herold, T.; Schrott, U.; Hoffmann, R. W.; Schnelle, G.; Ladner, W.; Steinbach, K. *Chem. Ber.* **1981**, *114*, 359−374.

(43) (a) Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3250−3263. (b) Singh, R. P.; Matteson, D. S. *J. Org. Chem.* **2000**, *65*, 6650−6653.

(44) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631−632.

(45) Electrophile **16b** was prepared in a similar procedure as reported in ref 44. See also: (a) Brown, H. C.; Roy, C. D.; Soundararajan, R. *Tetrahedron Lett.* **1997**, *38*, 765−768. (b) Smil, D. V. Ph.D. Thesis, University of Toronto, 2001, p 94.

TABLE 7. Enantioselective Additions with Dual Auxiliary Allylboronate 13a[a]

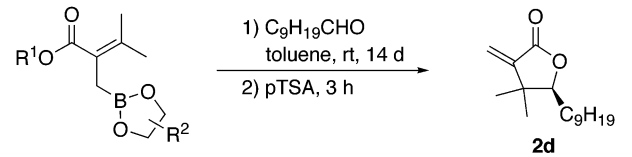


13a **2**

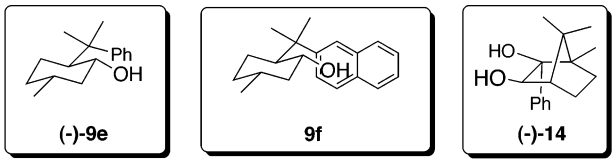
entry	lactone	R	yield (%)	ee (%)
1	**2b**	Ph	55	>95[b]
2	**2d**	C_9H_{19}	80	97
3	**2o**	*p*-Br-C_6H_4−	40	>95[b]

[a] Enantioselectivities determined by chiral HPLC. See the Experimental Section for details. [b] Selectivity uncertain because of poor baseline resolution of the enantiomers. 95% is the lowest, most conservative estimate.

TABLE 8. Matched and Mismatched Auxiliary Studies on Allylboronate 13a



2d



(-)-9e **9f** **(-)-14**

entry	allylboronate	R^1	diol	ee (%)
1	**13a**	(−)-**9e**	(−)-**14**	97
2	**18**	ethyl	(−)-**14**	50
3	**11f**	**9f**[a]	pinacol	82
4	**13b**	(−)-**9e**	(+)-**14**	<10

[a] Reaction performed with the *β*-naphthyl allylboronate **11f** and not the parent 8-phenylmenthol **11e**. Nevertheless, **11f** is an appropriate control substrate for this study since these two allylboronates gave comparable results in the single auxiliary study (see preceding section).

enantioselective allylborations in this study and the single auxiliary study (see above) led to the same major enantiomer of the lactone product.

These high selectivities are a result of a matched combination of the (−)-8-phenylmenthol **9e** and the (−)-isomer of bornanediol **14**. As seen in Table 8, the selectivities observed with these two auxiliaries are higher than selectivities observed with only one or the other (entries 2 and 3) and are much higher than the mismatched combination of (−)-8-phenylmenthol **9e** and the (+)-isomer of bornanediol **14** (entry 4).

At this stage of the project, it is not yet possible to offer an accurate transition state model that incorporates both the phenylmenthol auxiliary **9e** as well as the bornanediol **14** in the stereodifferentiating step. However, the simple model proposed by Villiéras and co-workers to explain the stereochemical outcome of reactions with boronates featuring only **14** accurately predicts that the (*S*)-isomer of lactones **2** is produced in these reactions (Figure 5).[34]

3.1. Lewis Acid Catalyzed Allylborations: Catalyst Search. Prior to our studies there were no catalytic

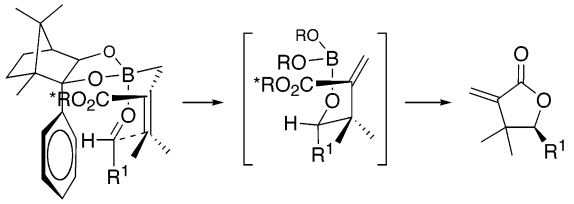
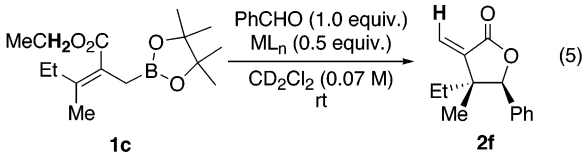


FIGURE 5. Model for stereoinduction proposed by Villiéras and co-workers.[34]

systems known to accelerate the addition of allylboronates to carbonyl compounds. The sluggish reactivity of the 3,3-disubstituted-2-carboxyester allylboronates **1** motivated us to look for a catalyst that could increase the efficiency of allylations with these reagents.[46] In addition to decreasing the reaction times, establishing a catalyzed allylboration reaction would open the door to enantioselective catalysis and the exciting possibility that enantiomerically pure quaternary carbon centers could be generated with a substoichiometric chiral director rather than with the two stoichiometric auxiliaries currently required.

The first step in our search for a catalyzed allylboration was to identify possible metals that might act as catalysts. Inspired by the study of Brown and co-workers,[47] we devised a simple, NMR spectroscopy based screen. The reaction between benzaldehyde and allylboronate **1c** in dilute CD_2Cl_2 with 0.5 equiv of potential catalyst (eq 5) was followed by ^{1}H NMR spectroscopy. Specifically, the disappearance of the ester CH_2 signal from **1c** (δ 4.18 pm, quartet) and the appearance of the signal for the *Z*-olefin proton in **2f** (δ 6.43 ppm, singlet) were monitored. All of the data presented below came from ^{1}H NMR experiments, despite the paramagnetic nature of some of the metals studied which complicated the spectra.



1c **2f** (5)

A wide variety of transition and lanthanide metal salts were then screened (see the graphs in the Supporting Information). To our surprise, a large number of metals were found to be capable of accelerating the allylboration reaction. However, two salts, scandium triflate and copper(II) triflate, displayed remarkable reactivity. In fact, half-life times for reactions in the presence of these salts were over 35 times shorter than those for uncatalyzed reactions. This large accelerating effect should be sufficiently high to eventually allow for effective enantioselective catalysis without significant competition from the racemic, background reaction.

(46) For the previously reported Lewis acid-catalyzed formation of a reactive difluoroborane (a reaction which marks the first formal catalysed allylboration), see: (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289−4292. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990−998. (c) Batey, R. A.; Quach, T. D.; Shen, M.; Thadani, A. N.; Smil, D. V.; Li, S. W.; MacKay, D. B. *Pure Appl. Chem.* **2002**, *74*, 43−55.

(47) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868−1874.

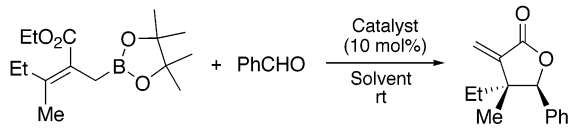
Most of the mixtures in this initial screening were heterogeneous, and we wondered if some of the catalysts were performing poorly due to low solubility of the metal salt in dichloromethane. Thus, a second screen was carried out on a selected group of metal salts in a more polar solvent system, 1:1 THF-d_8/CD_2Cl_2 (see the graph in the Supporting Information). Although many of the mixtures were still heterogeneous, this second screening identified ytterbium triflate as a viable lead catalyst. While this salt gave only a mediocre performance in the initial screening, it proved to be a remarkably effective catalyst in the presence of THF.

Following the identification of lead catalysts, preliminary optimization studies determined that the triflate salts of scandium and copper(II) were significantly more effective than either the chloride or the acetate salts. While $ScCl_3$ still showed some catalytic activity, both the acetate and chloride salts of copper were essentially inactive in the reaction. Also, a brief survey of solvents for the scandium triflate catalyzed reaction revealed that the reaction rates were similar in either toluene or dichloromethane but that coordinating solvents (e.g., acetonitrile, 1:1 THF/CH_2Cl_2) significantly retarded the reaction.

In light of these studies, we were able to determine that scandium triflate, copper(II) triflate, and ytterbium triflate would be the best catalysts for use in a catalytic allylboration reaction. However, before proceeding to preparative-scale reactions we wanted to ensure that the catalytic effect was truly due to the Lewis acidic metal. Thus, one final series of NMR experiments was performed.[25] The reaction using tetrabutylammonium triflate showed that triflate anion itself did not cause an observable rate enhancement. We also considered the possibility that the true catalyst might be triflic acid, generated in situ by adventitious water and the metal triflate. The reaction with tetrabutylammonium triflate cast doubt on this possibility, and aqueous solutions of rare earth metal triflates do not generate appreciable amounts of triflic acid.[48] Nevertheless, the ability of $Sc(OTf)_3$ to catalyze the reaction in the presence of an acid scavenger was evaluated by performing the reaction using a 1:1 mixture of $Sc(OTf)_3$/*i*-Pr_2NEt. This reaction was marginally, but not significantly, slower than the reaction without amine present, showing that the Lewis acid was able to catalyze the reaction without generating triflic acid. Diisopropylethylamine alone was not an effective catalyst.[49]

Following these NMR screening studies, it remained to show that the catalytic effect would hold on a preparative scale and with truly catalytic loadings. In particular, we hoped to achieve a reaction that was complete within 12−16 h at room temperature with a maximum of 10 mol % catalyst loading. Equally important was the issue of diastereoselectivity and whether the stereospecificity seen in the thermal allylboration would be preserved or not. Pleasingly, the Lewis acid catalyzed allylboration satisfied all three of these conditions, and both aromatic and aliphatic aldehydes proved to be effective substrates in this catalytic manifold. However, both kinds of aldehydes show minor differences in their reactivity, and for this reason they will be discussed separately below.

TABLE 9. Lewis Acid Catalyzed Allylborations with Benzaldehyde and Allylboronate 1c



1c **2f**

entry	catalyst	reaction conditions	reaction time (h)	yield (%)
1	$Sc(OTf)_3$	0.5 M in toluene	20	71
2	$Sc(OTf)_3$	1 M in toluene	24	93
3	$Sc(OTf)_3$	1 M in CH_2Cl_2	24	78
4	$Cu(OTf)_2$	0.5 M in toluene	20	67
5	$Cu(OTf)_2$	1 M in toluene	16	73
6	$Yb(OTf)_3$	0.5 M in toluene	20	91
7	$Yb(OTf)_3$	1 M in CH_2Cl_2	16	93
8	none	toluene, 80 °C	16	60

3.2. Catalytic Allylboration with Aromatic Aldehydes. The initial catalytic reactions with benzaldehyde showed a dramatic improvement over the thermal reactions (Table 9). Reactions with all three lead catalysts under practical conditions (10 mol % loading, 0.5−1 M concentrations, 12−24 h) gave excellent yields of the lactone **2f**. Although the reactions are often complete after 12 h, they were generally left overnight for practical reasons. Most importantly, the stereospecificity of the thermal reaction was preserved, and lactone **2f** was formed stereochemically pure in all catalyzed reactions. It is remarkable that these catalytic reactions show the same yields and reaction times as the uncatalyzed processes (Table 4), except at a much lower temperature (cf. control reaction, entry 8).

A noteworthy difference was observed in the water tolerance of scandium triflate and copper triflate as catalysts. Copper triflate lost all catalytic ability in the presence of one equivalent of added water, but catalysis could be restored to these reactions by adding molecular sieves to the reaction mixture. However, reactions with scandium triflate retained their catalytic effect in the presence of up to one equivalent of added water, but showed no catalysis at all in the presence of molecular sieves. The reasons why sieves shut down catalysis with scandium triflate are not clear at the moment, but this tolerance to water led us to use scandium triflate as the catalyst in most future allylborations.

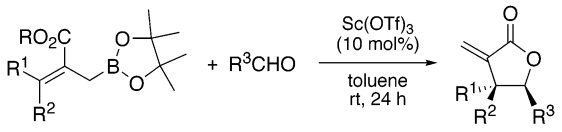
This catalytic effect was extended to the reaction of other allylboronates with a variety of aromatic aldehydes (Table 10), including a sterically demanding aldehyde (entry 6). As above, all of the lactone products were isolated with a stereochemical purity reflecting that of the allylboronate used.

One major limitation to this catalytic manifold is that certain aldehydes do not give stereochemically pure products (Table 11). To date, this problem has only been observed with electron rich aromatic aldehydes and α,β-unsaturated aldehydes. This stereochemical scrambling is observed with all three lead catalysts in several different solvents, and we have yet to find conditions that allow for the effective, catalytic allylation of these alde-

(48) Kobayashi, S. *Synlett* **1994**, 689−701.

(49) While the difference in reaction rates between the scandium-catalyzed reactions in the presence and absence of diisopropylethylamine might be due to a sequestering of the catalyst by the amine, it might also be due to competitive coordination of the amine to the boronate.

TABLE 10. Catalytic Allylborations with Aromatic Aldehydes[a]

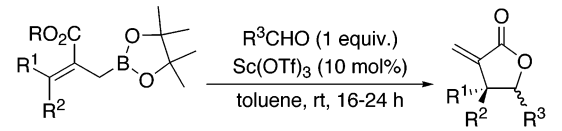


1 2

entry	boronate	lactone	R^1	R^2	R^3	yield (%)
1[b]	**1b**	**2o**	Me	Me	4-Br-C_6H_4	62
2[b]	**1c**	**2q**	Et	Me	4-AcO-C_6H_4	57
3[c]	**1e**	**2r**	Me	Bu	3-I-C_6H_4	48
4[c]	**1e**	**2s**	Me	Bu	C_6F_5	47
5[b]	**1e**	**2t**	Me	Bu	4-NO_2-C_6H_4	58
6[b]	**1e**	**2u**	Me	Bu	1-naphthyl	44
7[c]	**1e**	**2v**	Me	Bu	4-Me-C_6H_4	75

[a] All boronates and lactones were >20:1 dr. R = Et or Me. [b] 1 equiv of aldehyde used. [c] 1.5 equiv of aldehyde used.

TABLE 11. Lewis Acid Catalyzed Allylborations with Problematic Unsaturated Aldehydes[a]



1 2

entry	lactone	R^1	R^2	R^3	yield (%)	dr of **2**
1[b]	**2w**	Et	Me	2-MeO-C_6H_4	66	2:1
2	**2x**	Et	Me	*E*-2-(4-NO_2-C_6H_4)-1-ethenyl	nd	2.8:1[c]
3[d]	**2y**	Me	Bu	4-MeO-C_6H_4	39	1.8:1
4[d]	**2z**	Me	Bu	*E*-1-propenyl	61	1:1
5	**2aa**	Et	Bu	2-furyl	45	2.5:1[e]
6	**2ab**	Et	Bu	4-MeS-C_6H_4	69[f]	2.5:1

[a] All allylboronates **1** were >20:1 dr except as noted. nd = yield not determined. R = Me or Et. [b] Initial boronate was of 10:1 dr. [c] Thermal reaction gave the product as one isomer in 80% yield. [d] 1.5 equiv of aldehyde used. [e] Thermal reaction gave the product as one isomer in 74% yield. [f] Reaction run for 7 days.

hydes. However, all of these substrates give the expected, stereochemically pure products in the uncatalyzed, thermal reaction (see above).

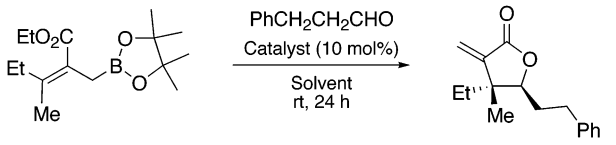
We excluded the possibility that the loss of stereoselectivity arises from a competing Zimmerman−Traxler transition state because this problem has not been observed with sterically less demanding aldehydes (butanal) or with aldehydes that could coordinate to the catalyst (benzyloxyacetaldehyde). This process appears to be quite sensitive to the electronic nature of the aldehyde; 4-acetoxybenzaldehyde does not suffer from this epimerization problem (entry 2, Table 10) and may be used as a substitute for the problematic 4-methoxybenzaldehyde (entry 3, Table 11).

We sought to gain evidence for this hypothesis by attempting to induce epimerization of a stereochemically pure sample of lactone **2x** with scandium triflate. However, no epimerization of the lactone could be detected by ^{1}H NMR spectroscopy, even after several days in dilute solution and overnight in concentrated solution.

Currently the cause of this epimerization remains unknown, and it may possibly occur at the stage of the borate intermediate prior to the lactonization.[50]

3.3. Catalytic Allylboration with Aliphatic Aldehydes. We next focused on the extension of this catalytic

TABLE 12. Solvent and Catalyst Survey for Catalytic Allylboration of Aliphatic Aldehydes with 1c[a]

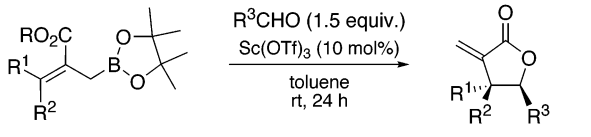


1c 2ac

entry	catalyst	solvent	yield (%)
1	$Sc(OTf)_3$	toluene	64
2	$Cu(OTf)_2$	toluene	63
3	$Yb(OTf)_3$	toluene	66
4	$Sc(OTf)_3$	CH_2Cl_2	62
5	$Cu(OTf)_2$	CH_2Cl_2	52
6	$Yb(OTf)_3$	CH_2Cl_2	38

[a] Reaction performed with 1.5 equiv of aldehyde and 0.5 M concentration.

TABLE 13. Lewis Acid Catalyzed Allylborations with Aliphatic Aldehydes[a]



1 2

entry	boronate	R^1	R^2	R^3	lactone	dr	yield (%)
1	**1c**	Et	Me	$BnOCH_2$	**2ad**	19:1	53
2	**1c**	Et	Me	*i*-Bu	**2ae**	>20:1	46[b]
3[c]	**1c**	Et	Me	*c*-Hex	**2af**	10:1[d]	54
4	**1e**	Me	Bu	*c*-Hex	**2ag**	>20:1	32
5	**1e**	Me	Bu	*i*-Pr	**2ah**	>20:1	32
6	**1e**	Me	Bu	*i*-Bu	**2ai**	>20:1	61
7	**1e**	Me	Bu	Bu	**2aj**	>20:1	62
8	**1a**	H	Me	$BnOCH_2$	**2ak**	>20:1	33[b]

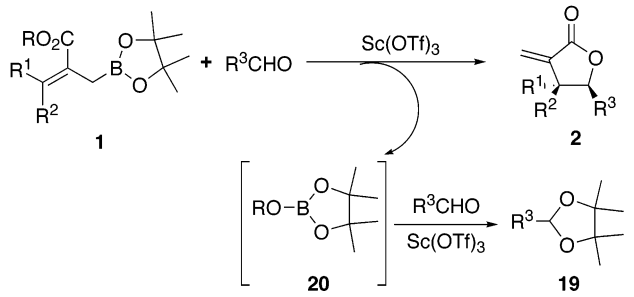
[a] R = Me or Et. [b] 1 equiv of aldehyde used. [c] Reaction performed using $Cu(OTf)_2$ as catalyst. [d] Allylboronate of 12:1 dr used in the reaction.

manifold to the allylboration of aliphatic aldehydes. Using hydrocinnamaldehyde as a model substrate, we performed a brief solvent and catalyst survey using slightly different conditions than those described for the allylation of aromatic aldehydes (Table 12). Like reactions with aromatic aldehydes, these reactions were complete in reasonable time frames at room temperature. All three lead catalysts gave effective allylation in toluene, and scandium triflate was clearly the most effective catalyst in dichloromethane solvent. To maintain consistency with the catalyzed reactions with aromatic aldehydes, scandium triflate in toluene was chosen as the general allylboration conditions.

A wide variety of aldehydes could be effectively allylated using these established conditions (Table 13). While the catalyzed reaction of aromatic aldehydes showed a marked improvement over the thermal reaction, the improvement seen in reactions with aliphatic aldehydes was even more impressive. As above, the reaction times were much shorter at lower temperatures and the stereospecificity of the thermal reaction was also

(50) There have been reports of the generation of carbocation intermediates from allylic and benzylic alcohols by Lewis acids. See: (a) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-i. *J. Org. Chem.* **1997**, *62*, 6997−7005. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580.

SCHEME 5

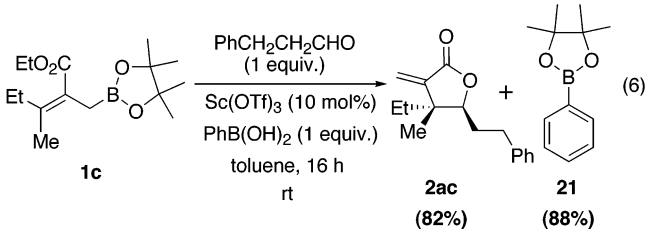


preserved. Furthermore, since these reactions are run at temperatures well below 110 °C, the stereochemical erosion sometimes observed with aliphatic aldehydes in the thermal reactions is completely suppressed here.

The most significant advance of this new catalytic manifold over the traditional thermal conditions is that it allowed for the formation of allylation products from hindered aldehydes (entries 3−5), substrates which previously failed to give effective thermal reactions. Although catalyzed reactions at room temperature with these hindered substrates were sluggish, gentle heating allowed for reactions to reach completion within 16 h.

Unlike reactions with aromatic aldehydes, the initial catalytic reactions with aliphatic aldehydes were plagued by low yields of lactones **2** and the competition of several side reactions. Consequently, significant optimization was required. First, the reactions with aliphatic aldehydes were best run at a concentration of 0.5 M in order to avoid self-condensation of the aldehyde. While reactions run at 1 M concentration only showed small amounts of self-condensation, this side reaction was completely suppressed under the more dilute conditions. More importantly, however, is that the aldehyde must be used in excess in order to obtain acceptable yields. The use of excess aldehyde is required because of the formation of significant amounts of the pinacol acetal **19** from the apparent reaction of unreacted aldehyde with the borate byproduct **20** (Scheme 5). Although Lewis acids are known to catalyze acetal formation,[51] the presence of this acetal side product was quite surprising because it was completely absent in the reactions with aromatic aldehydes.

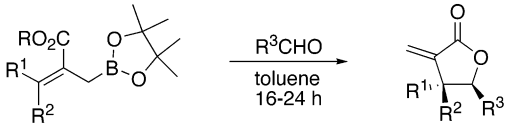
Although the addition of excess aldehyde can compensate for this side reaction, a more practical solution would be to find conditions to completely suppress it. Not only is the use of excess aldehyde wasteful (especially with expensive or noncommercially available aldehydes), in many cases this acetal impurity is difficult to remove from the desired lactone product. Fortunately, the problem can be solved by the addition of a stoichiometric amount of phenylboronic acid to the reaction mixture (eq 6). This boronic acid acts as a pinacol scavenger by trapping the troublesome diol as the boronic ester **21**. Under these conditions, acetal formation is almost completely suppressed and reasonable yields of lactone products are obtained from only 1 equiv of aldehyde. In all cases studied to date, the phenylboronic pinacolate **21** is easily removed from the lactone products by flash chromatography.



A comparison of the various methods for the allylboration of aliphatic aldehydes is shown in Table 14. From this table, it is clear that the catalytic reaction with $PhB(OH)_2$ scavenging (entries 2, 5, and 7) is superior to both the thermal reaction (entry 3) or the use of scandium triflate without $PhB(OH)_2$ (entries 1, 4, and 6).

3.4. Catalyzed Enantioselective Allylborations. Although a route to enantiopure lactones had already been established, it was hampered by the inefficiency of requiring two separate chiral auxiliaries for effective stereoinduction (see above). The first attempt to increase the efficiency of the enantioselective preparation of lactone **2d** was to apply the new catalytic manifold to the reaction of an allylboronate bearing only one chiral auxiliary (Table 15). However, these reactions were not successful, and they generally gave lower yields and selectivities than those obtained under the thermal,

TABLE 14. Comparison of Methods for the Allylboration of Aliphatic Aldehydes with 1[a]



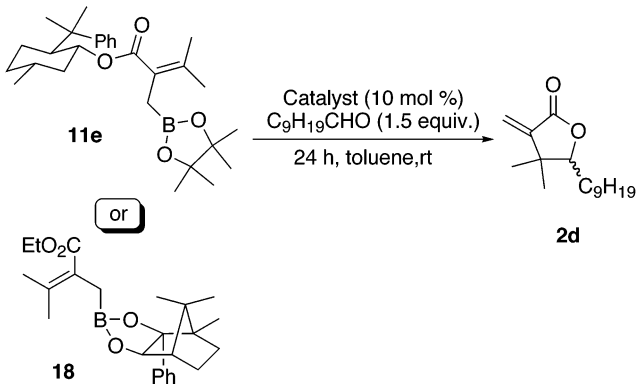
1a: R^1= H, R^2= Me
1c: R^1= Et, R^2= Me

2ad: R^1= Et, R^2= Me, R^3= $BnOCH_2$
2ae: R^1= Et, R^2= Me, R^3= (*i*)-Bu
2ak: R^1= H, R^2= Me, R^3= $BnOCH_2$

entry	allylboronate	lactone	equiv of R^3CHO	conditions[b]	yield (%)	dr
1	**1c**	**2ad**	1.5	$Sc(OTf)_3$	53	>20:1
2	**1c**	**2ad**	1.0	$Sc(OTf)_3$/$PhB(OH)_2$	54	>20:1
3	**1c**	**2ad**	1.5	thermal	33	9.5:1[c]
4	**1c**	**2ae**	1.0	$Sc(OTf)_3$	46	>20:1
5	**1c**	**2ae**	1.0	$Sc(OTf)_3$/$PhB(OH)_2$	66	>20:1
6	**1a**	**2ak**	1.0	$Sc(OTf)_3$	33	>20:1
7	**1a**	**2ak**	1.0	$Sc(OTf)_3$/$PhB(OH)_2$	66	>20:1

[a] R = Me or Et. [b] Conditions used: $Sc(OTf)_3$ (10 mol %) and/or $PhB(OH)_2$ (1 equiv), rt; thermal: refluxing toluene. [c] Initial boronate was >20:1 pure.

TABLE 15. Catalyzed Allylborations with Chiral Allylboronates 11e and 18[a]



entry	allylboronate	catalyst	yield (%)	ee (enantiomer)
1	**11e**	$Sc(OTf)_3$	29	10% (*R*)
2	**11e**	$Cu(OTf)_2$	93	71% (*S*)
3	**11e**	$Yb(OTf)_3$	30	31% (*S*)
4	**18**	$Sc(OTf)_3$	53	3% (*R*)
5	**18**	$Cu(OTf)_2$	31	13% (*R*)
6	**18**	$Yb(OTf)_3$	37	21% (*R*)

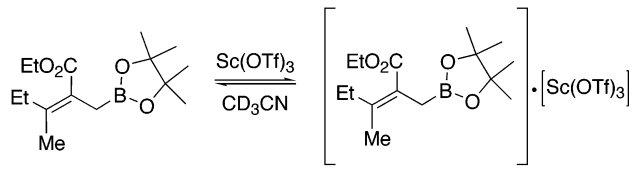
[a] Noncatalyzed reaction with the *β*-naphthyl analogue of **11e** gave 82% ee for the (*S*)-enantiomer; noncatalyzed reaction with **18** gave 51% ee for the (*S*)-enantiomer (cf. Table 8).

noncatalyzed conditions. Interestingly, the enantiomer produced in the catalyzed reaction was often the opposite to that generated in the thermal reaction. These results contrast sharply with the highly selective scandium-catalyzed reactions of allylboronates derived from bornanediol **14** but which lack the 2-carboxyester substituent.[52]

The ultimate goal is to eventually find a chiral catalyst that allows for the control of the absolute stereochemistry of the lactone products using no chiral auxiliary. Although Miyaura and co-workers reported modest success in the catalyzed addition of allyl and *E*-crotylboronates,[53] there is currently no catalyst system that provides preparatively useful levels of enantioinduction in these reactions. A preliminary evaluation of known chiral scandium catalysts[54] failed to reveal an effective catalyst. The general problem encountered is that the allylboration reaction is suppressed in the presence of the large, chiral ligands used in these catalytic systems.

4.1. Preliminary Mechanistic Studies: NMR Evidence for the Formation of a Boronate/Scandium Complex. Aside from satisfying our scientific curiosity, a better mechanistic understanding of this novel catalytic process could potentially allow for a rational and more effective approach to further optimization of the reaction, especially in the search for enantioselective catalyzed variants. To this end, the effect of various amounts of scandium triflate on the NMR spectrum of allylboronate **1c** in the absence of aldehyde was studied. The aim of this study was to find evidence for the possible formation of an activated boronate/scandium complex. The catalyst, solvent, and substrate were all carefully chosen for this study. Scandium(III) is not a paramagnetic nucleus and its presence would not interfere with the NMR spectra of other nuclei. The allylboronate **1c** was chosen because it is unsymmetrical about the *γ*-carbon and would allow us to determine if the olefin geometry remains intact under the catalytic conditions, and acetonitrile was used as solvent because it gave homogeneous mixtures.

TABLE 16. Titration of a Solution of Boronate 1c with $Sc(OTf)_3$[a]



1c **22**

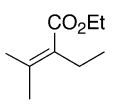
entry	equiv of $Sc(OTf)_3$	**22**/**1c** ratio
1	0.5	0.5:1
2	1	1.2:1
3	1.5	3:1
4	2	10:1

[a] Product ratio determined by ^{1}H NMR (400 MHz, CD_3CN).

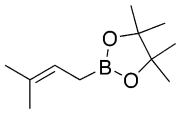
Titration of an NMR solution of allylboronate **1c** with $Sc(OTf)_3$ led to a very clean spectrum showing only two species, the free allylboronate **1c** and the putative complexed boronate **22** (Table 16). The amount of complex formed was directly related to the amount of scandium added, with one equivalent of complex formed for every two equivalents of scandium added. At present, it is not clear if this 1:2 relationship reflects the stoichiometry of the complex or the position of the equilibrium between bound and free boronate.

The amount of free and complexed scandium could not be determined by ^{45}Sc NMR spectroscopy because of the poor resolution of the spectra. The ^{19}F NMR spectra showed only a single, sharp peak, suggesting either the formation of a complex where all of the triflate anions are equivalent or that complexed and free triflate anions are equilibrating very rapidly.

To determine the importance of the boronic ester group in the formation of this complex, we conducted a control experiment with tetrasubstituted acrylate **23**. Treatment of this α,*β*-unsaturated ester with scandium triflate showed no evidence for the formation of a complex; the ^{1}H NMR spectrum of **23** was virtually unchanged even after the addition of one full equivalent of scandium triflate. This result shows that the boronic ester is essential for complex formation between scandium triflate and **1c**, and it lends credence to the presence of a metal−boronate interaction.



23



24

Attempts to perform a similar study with an allylboronate that lacked the 2-carboxyester group (e.g., **24**)

(51) Fukuzawa, S.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077−1078.
(52) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160−10161.
(53) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414−12415.
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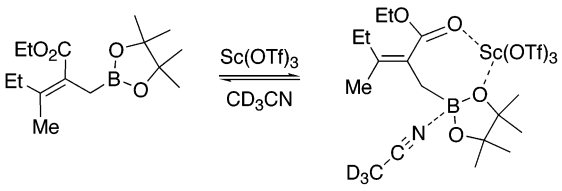
TABLE 17. ^{11}B NMR Shifts for Free and Complexed Allylboronate 1c[a]



1c **22a**

free allylboronate **1c**	complexed allylboronate **22a**
33.8	12.8 (major) 2.8 (minor)

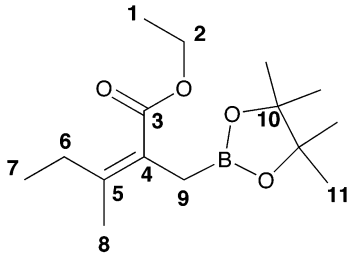
[a] Spectra taken in CD_3CN at 64 MHz. The structure of the scandium/boronate complex **22a** is hypothetical.

failed because the reagent generally decomposed at room temperature in the presence of scandium triflate. While it is not yet known if a boronate/scandium complex forms in the absence of a carboxyester group, there is ample evidence to show that this ester group is not required for catalysis to occur. Studies from our group[52] and Miyaura's[53] have shown that boronates that lack this 2-carboxyester group also undergo a metal-catalyzed allylboration reaction, although the magnitude of the catalysis observed at room temperature is much smaller with these boronates (approximately a 3-fold rate increase for **24**) than with boronate **1c** (35-fold increase).[14b] This result might simply reflect the large difference in reactivity between boronates **1c** and **24** (reaction with **24** is complete within a couple of hours rather than days). Alternatively, it might suggest that the ester in **1c** acts as a second coordination site for the catalyst, thereby increasing the binding of the boronate to the catalyst and allowing for greater activation to occur.

NMR techniques were then employed to probe the structure of the complex formed between boronate **1c** and scandium triflate. The most interesting result came from the ^{11}B NMR spectrum of the complex (Table 17). While the spectrum of **1c** displayed a single peak at 33.8 ppm in the absence of scandium triflate, the spectrum of the complex showed two new signals, both upfield of the original signal. The larger of these new signals resonates at 12.8 ppm, and is consistent with the formation of a tetrahedral complex, likely with acetonitrile as ligand (**22a**).[55] This upfield signal does not form in the absence of $Sc(OTf)_3$, nor is it observed if the spectrum is taken in CD_2Cl_2. The third signal, a small, sharp peak at 2.8 ppm, has yet to be assigned. These results may be interpreted to mean that while the boron in **1c** is normally not sufficiently electrophilic to bind to acetonitrile, formation of the boronate:scandium complex **22a** activates the boron enough so that it can accept the nitrile as a ligand.

The ^{1}H and ^{13}C NMR signals for the free and complexed boronate **1c** are shown in Table 18. The downfield shifts seen in the ^{13}C resonances for the carbons in the unsaturated ester (especially carbons 2, 3, and 5) are consistent with the binding of the ester carbonyl to the scandium metal.[56] However, the resonances of the carbons and protons around the boron are not as easily interpreted. Whereas the chemical shifts for the pinacol carbons (10 and 11) hardly change at all, the carbon α to the boron (carbon 9) shifts 5 ppm downfield and the protons attached to this carbon (protons 9) shift 0.2 ppm upfield. This difference in behavior for the carbon and the protons next to the boron may be explained by considering the putative acetonitrile adduct **22a**. Binding of the scandium to one or both of the boronate oxygen should make the boron atom more electron deficient by disrupting the overlap between the oxygen lone pair electrons and the empty p-orbital on the boron. Inductive effects would then shift the carbon signal downfield. Meanwhile, the methylene protons might experience a pronounced shielding effect from the p-orbital of the boron, which becomes filled after coordination of the acetonitrile, or from anisotropic effects of the proximal ester or nitrile groups.

TABLE 18. ^{1}H and ^{13}C NMR Shifts for Allylboronate 1c in the Presence of $Sc(OTf)_3$[a]



	^{13}C NMR (100 MHz)		^{1}H NMR (400 MHz)	
signal	free **1c**	complexed **1c**	free **1c**	complexed **1c**
1	14.6	14.2	1.23	1.43
2	60.8	70.5	4.09	4.62
3	170.0	181.2		
4	124.7	123.6		
5	147.2	167.8		
6	30.0	29.8	2.33	2.60
7	13.3	13.0	1.00	1.07
8	20.3	23.9	1.74	1.98
9	14.2	19.6	1.76	1.56
10	84.0	84.2		
11	25.0	24.3	1.19	1.36
				6.92[b]
				7.96[b]

[a] Spectra taken in CD_3CN. Assignments confirmed by 2D NMR techniques. [b] Broad signals due to coordinated water not present in the absence of scandium triflate.

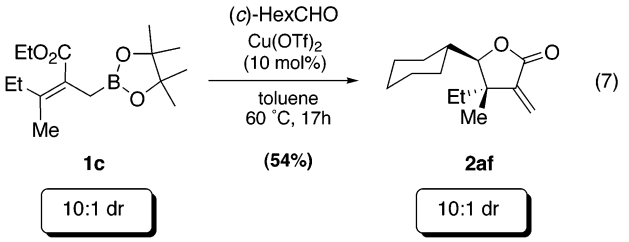
Many of the peaks in the NMR spectrum of the complex were significantly broadened, especially the pinacol methyl peaks. If scandium is capable of coordinating to one (or both) of the pinacol oxygens, then the four methyl groups on the pinacol ring should become nonequivalent. While the broadened peak for the pinacol protons could not be resolved into separate peaks, even at low temperatures, the fact that the broadening increases as the temperature decreases is consistent with this theory.

One intriguing result from this NMR study was that a long-range correlation was observed between the tertiary carbon on the pinacol group (carbon 10) and a coordinated water. This HMBC correlation suggests that water might be involved in the coordination of scandium to the boronate, and might help to explain why no catalysis is observed with scandium triflate in the presence of molecular sieves.

(55) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1999**, *38*, 3666−3669.
(56) (a) Clapham, G.; Shipman, M. *Tetrahedron Lett.* **1999**, *40*, 5639−5642. (b) Clapham, G.; Shipman, M. *Tetrahedron* **2000**, *56*, 1127−1134.

4.2. Issue of Type I or Type II Mechanism. One of the first mechanistic questions to address is whether the reaction follows the pattern of a closed, Type I mechanism or an open, Type II mechanism (Figure 1). The strongest evidence for one mechanism over the other comes from the stereochemistry of the products of the allylations. The Type I mechanism involves the transfer of stereochemistry of the allylboronate to the product, and thus the diastereoisomer of the product formed in these reactions depends on the *E*/*Z* geometry of the starting material used. In contrast, the Type II allylation pathway tends to be stereoconvergent, and the same isomer of product dominates regardless of the *E*/*Z* stereochemistry of the starting material.[18b]

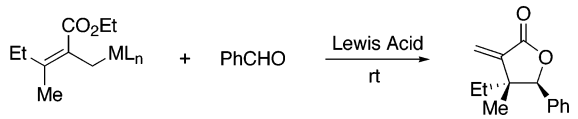
The stereospecificity observed in the catalyzed allylborations is consistent with that of the Type I mechanism. The reaction of an allylboronate of moderate stereochemical purity is especially telling (eq 7). This result confirms that the high stereochemical purity generally observed in the products of the catalyzed allylboration reaction comes from a transfer of stereochemistry from stereochemically pure allylboronates and not from a stereoconvergent process that favors one isomer of the product over another. Although not impossible, it is unlikely that an open transition state would allow for such a perfect transfer of stereochemistry from the allylboronate **1c** to the lactone **2af**.



Further evidence that the catalyzed allylboration is consistent with a Type I process comes from the reaction of benzaldehyde with allylstannane **25** and allylsilane **26** (Table 19).[57] Reactions of these known Type II reagents with benzaldehyde gave significantly different stereochemical results than the analogous allylboronate **1c**, strongly suggesting that the allylboronate **1c** does not behave like a Type II reagent in the presence of an external Lewis acid.

4.3. Possible Origins of the Activation Effect. All of the evidence obtained thus far supports the hypothesis that the catalyzed allylboration reaction proceeds via a closed, cyclic transition state following the formation of a scandium−allylboronate complex. However, there are still several different ways that the formation of this complex could cause the catalytic effect. For example, coordination of the scandium ion both to the boronate and the ester might cause the latter to twist out of conjugation with the olefin, thus rendering the γ-carbon (carbon 5 in Table 18) more nucleophilic in the complex than in the free boronate. However, the ^{13}C NMR spectrum of the complex showed that the signal for the γ-carbon shifts downfield by 20 ppm in the complex compared to the free boronate, suggesting that this carbon is significantly more electron deficient in the complex than in the free boronate. This data is not consistent with an increase in nucleophilicity of this carbon, and consequently it is unlikely that ester deconjugation is the root of the observed catalytic effect. Furthermore, the presence of a carboxylic ester is not required for catalysis to occur.[14a,52,53]

TABLE 19. Comparison of the Reactions of Allylboronate 1c with Those of the Analogous Allylstannane 25 and Allylsilane 26



entry	allylmetal	ML_n	Lewis acid	conditions	yield (%)	dr of **2f**
1	**1c**		$Sc(OTf)_3$ 10 mol%	toluene 24 h	93	19:1
2	**25**	$SnBu_3$	$Sc(OTf)_3$ 50 mol%	CH_2Cl_2 24 h	21	4:1
3	**26**	$SiMe_3$	$TiCl_4$ 300 mol%	toluene 14 d	21	3:1

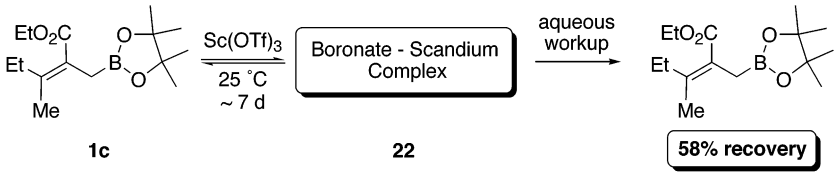
Another possibility is that the enhanced reaction rate is due to the formation of a new, highly reactive allylscandium species following a transmetalation process. While some catalyzed allylstannation reactions are reported to proceed via a transmetalation of the initial allylmetal to a more reactive allylmetal species,[18b] there are no known examples of an allylboration that proceeds via a similar mechanism, nor have there been any reports of a boron to scandium or ytterbium transmetalation. In this current study, we were able to treat a solution of allylboronate **1c** with excess scandium triflate, find evidence for the formation of a complex between the metal and the boronate by NMR, and then afterward recover the boronate unchanged and in good yield (Scheme 6). This recovery suggests that transmetalation of the boronate under the catalytic conditions is unlikely. Further evidence against a transmetalation mechanism is the fact that catalyzed allylborations with allylboronates bearing chiral diol auxiliaries showed appreciable levels of stereoselectivity (see above). If the reaction proceeded via transmetalation, these reactions in the presence of an achiral Lewis acid should have shown no selectivity at all.

Consolidating all of the evidence presented above, the most reasonable proposal for the mode of activation currently is the electrophilic activation of boron by coordination of scandium to one of the boronate oxygens (Figure 6). This coordination may be direct (transition state **A**) or mediated by water (transition state **B**).[58] Formation of this complex would increase the Lewis acidity of the boron atom, which then leads to enhanced

(57) Zhu, N. M.Sc. Thesis, University of Alberta, 2003, pp 36−50.

(58) Analogously, Aggarwal and co-workers reported that the rate enhancement in the lanthanum triflate catalysed Baylis−Hillman reaction derives from enhanced hydrogen bonds between the substrate and coordinated hydroxyl groups on the Lewis acid rather than from direct binding of the lanthanide to the substrate. See: Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183−7189.

SCHEME 6



allylboration with an aldehyde via the usual Zimmerman−Traxler transition state. Binding of the Lewis acid to one of the boronate oxygens would disrupt the $n_O \rightarrow p_B$ overlap, making the boron atom more electron deficient, and would increase the strength of the boron−carbonyl coordination and in turn lower the activation energy of the transition state. Molecular calculations have shown that the strength of this coordination is the main factor in lowering the activation energy of an allylboration reaction.[59] This proposal is also in line with the empirical study of Brown and co-workers who concluded that the reactivity of a given allylboronate is directly related to the availability of the lone pair electrons on the boronate substituents.[47]

5.1. Further Functionalization of Lactones 2. The *exo*-methylene butyrolactone products of the allylboration reactions are related to a family of biologically active natural products, which have shown promise as potential therapeutics in the treatment of a variety of ailments, ranging from cancer[60] to alcoholism.[61] The activity of these compounds is proposed to derive primarily from their ability to act as Michael acceptors for suitable biological nucleophiles (e.g., the thiol of a cysteine residue).[61,62] However, most of these compounds are too toxic for clinical use, and the need for analogues has spurred interest in establishing synthetic routes to these butyrolactones.[63,64]

Notwithstanding the inherent value of this class of compounds, the primary focus of our research was the generation of stereodefined quaternary carbon centers. We believed that our methodology would find wider application and use if the resulting quaternary carbon centers were not necessarily confined to a five-membered ring. To this end, both the ester functionality and the exocyclic olefin provide useful handles for the transformation of the lactones into other structures

We first investigated the simple hydrogenation of the exocyclic double bond in **2**. Although the product of this reduction is still a cyclic structure, it contains three contiguous stereogenic centers, and we expected that the cyclic nature of the substrate might help control the stereochemistry of the hydrogenation. In the event, this reduction exceeded our expectations, and the olefin underwent a highly selective reduction under mild conditions to give only one diastereomer of the α-methyl

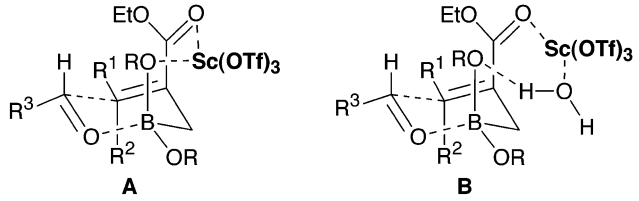
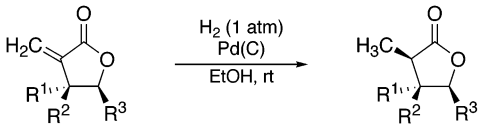


FIGURE 6. Possible transition states for the Lewis acid catalyzed allylboration.

TABLE 20. Diastereoselective Hydrogenation of Lactones 2



2 **27**

entry	lactone	product	R^1	R^2	R^3	yield (%)
1	**2e**	**27a**	Et	Me	C_9H_{19}	85
2	**2f**	**27b**	Et	Me	Ph	86
3	**2k**	**27c**	Me	*i*-Bu	4-$MeOC_6H_4$−	81
4	**2ac**	**27d**	Et	Me	$PhCH_2CH_2$−	88

lactone **27** (Table 20). No other isomer of the product could be detected by ^{1}H NMR spectroscopy. Pleasingly, no benzylic C−O cleavage was observed with the aromatic lactones under these conditions (entries 2 and 3).

The stereochemistry of the lactone **27c** was unambiguously determined by X-ray crystallography, showing that the hydrogen had added from the face opposite to the R^3 group (see the Supporting Information). The stereochemistry of the other products was then inferred from this result.

The reductive opening of butyrolactone **27** would lead to an acyclic stereochemical triad, a structural motif found in many natural products. The generation of multiple contiguous stereogenic centers is still a challenge in synthetic chemistry, especially when one of these centers is a quaternary carbon.[65] In the present case, after extensive investigation of several hydride reagents, butyrolactone **27a** was found to undergo reduction with Red-Al to give diol **28** in a nonoptimized yield of 80% (eq 8). This reaction illustrates the broad synthetic potential of the stereochemically pure lactones produced by this methodology. The investigation of other transformations of lactones **2** is ongoing in our laboratory.

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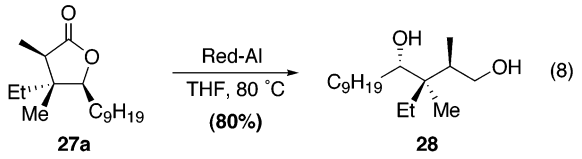
(64) For recent preparations, see: (a) Knochel, P.; Sidduri, A. R. *J. Am. Chem. Soc.* **1992**, *114*, 7579−7581. (b) Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209−3246. (c) Paquette, L. A., Méndez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301−4304. (d) Xu, M.-H.; Wang, W.; Xia, L.-J., Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953−3962. (e) Dumeunier, R.; Leclercq, C.; Markó, I. E. *Tetrahedron Lett.* **2002**, *43*, 2307−2311. (f) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584−1586.



27a 28 (8)

Conclusion

This paper described the efficient generation of stereogenic quaternary carbon centers via the stereospecific reaction of 2-carboxyester-3,3-disubstituted allylboronates (**1**) with aldehydes. This reaction generates diastereomerically pure *exo*-methylene butyrolactones **2** that embed the desired quaternary carbon center. These products can also be formed in enantiopure fashion using a dual-auxiliary strategy. In addition to being biologically interesting targets in their own right, these highly functionalized butyrolactones can undergo further useful transformations (e.g., reduction to a 1,4-diol bearing three contiguous stereogenic centers). The inherent utility of these lactones coupled with the relative ease and expedience of their preparation suggest that they are well suited to find use as synthetic intermediates in natural product synthesis.

The most important advance to come from this study is the development of the Lewis acid catalyzed carbonyl allylation with allylboronates. Under this new catalytic manifold, reactions with **1** that previously took 2 weeks at room temperature are now complete within 12 hours at room temperature. This catalysis not only provides a large rate enhancement over the noncatalyzed process but also broadens the scope of aldehydes that may be used as substrates. Crucially, the diastereospecificity observed in the thermal reaction of 2-carboxyester allylboronates is preserved in the Lewis acid catalyzed reaction.

With the development of the catalytic allylboration reaction comes the promise of an enantioselective, catalyzed version. Preliminary studies with some common chiral catalysts have yet to reveal an effective catalyst for these reactions. While a systematic survey of other catalysts and ligands might eventually lead to a successful, substoichiometric enantioselective allylboration system, a deeper understanding of the reaction mechanism would allow for a more effective and rational approach to solving this problem. Recent mechanistic studies addressed the origin of this catalytic effect in the case of 2-unsubstituted allylboronates.[66] These results give credence to the hypothesis that allylboronates **1** are subject to electrophilic activation of the boron atom following formation of a boronate-Lewis acid complex. It also raises the intriguing idea that this kind of boronate activation could be a general phenomenon that might find applications outside the realm of allylboration chemistry.

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Supporting Information Available: Full experimental details for catalyst screening and for the preparation of all compounds; ^{1}H and ^{13}C NMR spectra for previously unreported products; technical details for the collection of the X-ray crystallography data; structural confirmation (NOE data, X-ray structures) for allylboronate **1c** and lactones **2i**, **2j**, **2n**, **2o**, and **27c**; spectra and details of ^{1}H, ^{13}C, and ^{11}B NMR studies of the **1c**:$Sc(OTf)_3$ complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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(65) For some examples of products containing three or more contiguous stereogenic centers, see: (a) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *Perkin Trans. 1* **1998**, 9−39. (b) Yoda, H.; Katoh, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 7661−7665. (c) López-Alvarado, P.; García-Granda, S.; Álvarez-Rúa, C.; Avendaño, C. *Eur. J. Org. Chem.* **2002**, 1702−1707. (c) Harrowven, D. C.; Luca, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, *40*, 4443−4444. (d) Cassayre, J.; Zard, S. Z. *J. Organomet. Chem.* **2001**, *624*, 316−326. (e) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999−15016.

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