Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 64 (2008) 2441–2455
www.elsevier.com/locate/tet

Enantioselective addition of β-functionalized allylboronates to aldehydes and aldimines. Stereocontrolled synthesis of α-methylene-γ-lactones and lactams

Isabelle Chataigner*,†, Françoise Zammattio, Jacques Lebreton, Jean Villiéras

Université de Nantes, Nantes Atlantique Université, CNRS, Faculté des Sciences et des Techniques, Laboratoire de Synthèse Organique (LSO), UMR CNRS 6513, 2 rue de la Houssinière, BP 92208, F-44322 Nantes Cedex 3, France

Received 12 November 2007; received in revised form 19 December 2007; accepted 20 December 2007
Available online 15 January 2008

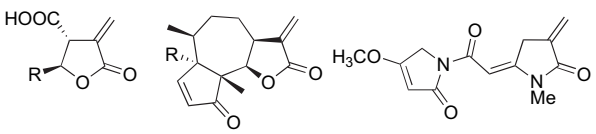
Abstract

We report results regarding the development of condensations of chiral β-alkoxycarbonylallylboronates on aldehydes and imines. These allylboronates add in a highly enantioselective and diastereospecific manner to afford biologically and synthetically useful chiral α-methylene-γ-butyrolactones and lactams. The nature of the electrophile (aldehyde vs imine) is shown to have a dramatic influence on the mechanism of the reaction, probably directing the stereoselectivity of the process through different transition states.

1. Introduction

The α-methylene-γ-butyrolactone framework is widely found in naturally occuring compounds (Fig. 1).[1] In 1985, Hoffmann already reported that more than 2000 natural derivatives featured this moiety and evaluated that 10% of the registered products contained this structural motif.[1a] The ability of the methylene group of the γ-lactone to act as a highly reactive Michael acceptor is the basis of its role as a physiologically important building block. Nucleophiles such as L-cysteine or sulfhydryl containing enzymes add in vivo to the unsaturated lactone part, thus inhibiting the incorporation of several aminoacids into proteins.[1,2] The toxicity often associated to their significant in vivo activity has, however, limited the clinical use of these products.[3] Modulations are thus needed to improve the pharmacological properties and decrease the toxicity. In this context, the isosteric replacement of the oxygen by a nitrogen atom is of interest, as it leads to a less reactive and hopefully more selective system. In addition, the supplementary nitrogen atom allows for a large variety of modulations by its substitution with electron-withdrawing groups or lipophilic chains for instance. Even if known in the natural world, the α-methylene-γ-butyrolactam moiety is much scarcer than the lactone one (Fig. 1).[1c,4]

Various synthetic strategies have described an access to these molecules in literature.[1,5] A classical route is based on the α-methylenation of a preformed lactone.[5b] Alkoxycarbonylallylation reactions have also been largely studied to



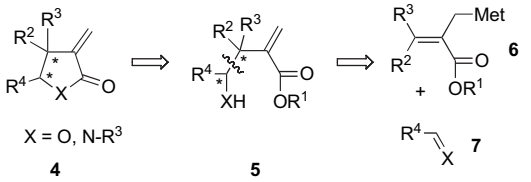
1a: R = C_5H_{11} **2a**: R = H **3**
1b: R = $C_{13}H_{27}$ **2b**: R = CH_3

Figure 1. Examples of naturally occuring α-methylene-γ-lactones and lactams: methylenelactocin (**1a**), protolichesterinic acid (**1b**), ambrosin (**2a**), parthenin (**2b**), and pukelimid E (**3**).

* Corresponding author.
E-mail address: isabelle.chataigner@univ-rouen.fr (I. Chataigner).
† Present address: Université de Rouen, INSA de Rouen, CNRS UMR 6014, C.O.B.R.A., I.R.C.O.F., 1 rue Tesnières, 76131 Mont Saint Aignan Cedex, France.

0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.12.046

assemble these frameworks (Scheme 1). The latter approach is clearly attractive since it provides a convenient and attractive route to both the methylene-lactone and -lactam skeletons by simply changing the electrophilic partner from an aldehyde to an aldimine substrate.



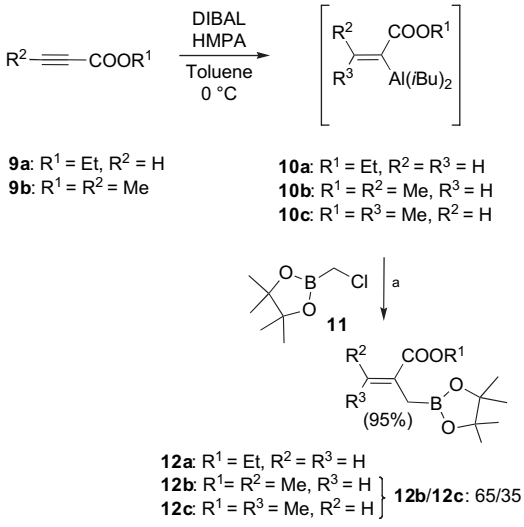
Scheme 1.

The asymmetric versions of this allylation reaction have been mainly envisaged by introduction of the chiral part on the alkoxycarbonyl group of the organometallic or on the electrophile.[6] The inherent lack of flexibility of these strategies and the increasing efficiency of chiral allylmetals has led to the development of substrates bearing a chiral auxiliary on the metal center. This attractive route avoids the long and sometimes tedious deprotection of substrates and allows for the recycling of the chiral inductor. Among allylmetal reagents, organoboranes have proven their efficiency in the stereocontrolled construction of several adjacent chiral centers and have become invaluable tools in the organic chemists' toolbox.[7] In this context, we have been interested, for several years, in the development of chiral β-alkoxycarbonylallylboronates and have studied their reactivity toward various electrophiles such as aldehydes and aldimines.[8] We report herein results regarding the stereochemical course of these condensations and show that the mechanism involved in the process depends on the nature of the electrophile.

2. Results and discussion

2.1. Preparation of β-functionalized allylboronates

A few methods of β-alkoxycarbonylallylboronates preparation have been reported in literature.[8a,9] In 1993, we first described the synthesis of the achiral allylboronate **12a** by condensation of a vinylalane derivative on pinacol chloromethylboronate in the presence of HMPA.[8a] More recently, Hall et al. have described the related reaction between vinylcopper(I) intermediate and iodomethylboronate to yield γ,γ′-disubstituted allylboronates.[9a,b] Ramachandran and Kabalka have independently developed an alternative strategy based on a palladium-catalyzed SN_2' reaction of allylacetates with bisdiboron compounds.[9c,d] Our own methodology relies on treatment of ethylpropiolate **9a** with diisobutylaluminium hydride in the presence of HMPA leading to a vinylalane intermediate **10a**, which in turn was reacted in situ with pinacol chloromethylboronate **11** to furnish pinacol β-ethoxycarbonylallylboronate **12a**, isolated in 95% yield (Scheme 2). In contrast to the unfunctionalized allylboronate derivatives, known to be sensitive species, **12a** eventually proved to be stable enough to be purified either by distillation under reduced pressure or by flash chromatography on neutralized silica.



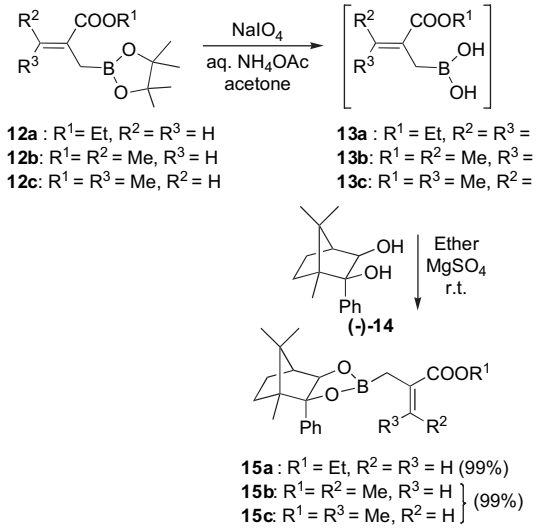
[a] MeCu was added in the case of **10b** and **10c**.

Scheme 2.

The γ-substituted crotylboronate derivatives could be accessed in a similar way, starting from methyl but-2-ynoate. DIBAL reduction of methyl but-2-ynoate **9b** expectedly furnished the *E*-vinylalane **10b**, in accordance with Tsuda's work.[10] The presence of the supplementary methyl substituent, however, significantly reduced the reactivity of the vinylalane intermediate and after treatment with **11**, the corresponding crotylboronate was isolated in poor yield. This problem was circumvented by addition of a catalytic amount of MeCu that allowed to increase the overall yield to 95%. The pinacol β-methoxycarbonylcrotyl-boronates **12b** and **12c** were isolated as a mixture of diastereomers in a 65:35 (*Z*/*E*) ratio (Scheme 2).

We next studied the replacement of the achiral pinacol moiety by a chiral diol. Roush and Chemler have extensively proven the efficiency of tartrate derivatives in enantioselective allylations involving unfunctionalized boronates.[7a] However, disappointing results had been observed in the β-alkoxycarbonyl series with these chiral auxiliaries, as well as with the commercially available pinanediol (ee=6–20% in the condensation on aldehydes).[8b] We have thus turned our attention to other chiral diols and have considered (−)-(1*R*,2*R*,3*R*,4*S*)-2-*endo*-phenyl-2,3-bornanediol **14**,[8c–e,9a] initially described by Hoffmann (Scheme 3).[11] Thus, boronates **12** were cleaved into the corresponding acids **13** by oxidative treatment of the pinacol ester compounds using sodium periodate in a water/acetone mixture. This procedure involves a concomitant oxidation of the liberated pinacol, preventing its interference in the following steps. Problems of reproducibility led us to consider the modified procedure described by Coutts et al., who replaced water by an aqueous solution of ammonium acetate.[12] Under these conditions, acids **13** proved unstable but their immediate esterification with diol **14** afforded

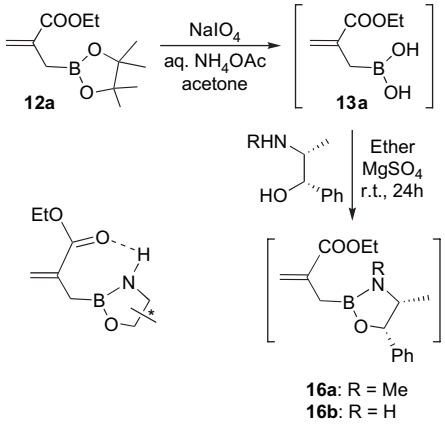
chiral β-alkoxycarbonylallylboronates **15** in excellent yields (Scheme 3). Once again, these boronates revealed quite robust and were purified by chromatography on neutralized silica. It allowed the concomitant separation of the *Z*/*E* mixture, in the crotylboronate series, giving access to each diastereomer **15b** and **15c**.



Scheme 3.

2.2. Preparation of β-functionalized allyloxazaborolidines

As Reetz and Itsuno have reported good results for similar reactions when using unfunctionalized allyloxazaborolidine derivatives,[13] we decided to extend our method to the preparation of chiral β-alkoxycarbonyl substituted allyloxazaborolidines. The synthetic strategy used to access the chiral boron species was similar to the one described above with chiral diols. Thus, boronate **12a** was cleaved with sodium periodate and the resulting boronic acid **13a** was immediately reacted with ephedrine in the presence of magnesium sulfate. Disappearance of **13a** and generation of a new product was monitored by TLC. Mass spectrometry analysis of the crude mixture indicated the formation of the expected allylboron derivative **16a** (Scheme 4). We anticipated that the use of free aminoalcohols could be beneficial to the chiral induction by freezing the conformation of the chiral species through intramolecular hydrogen bonding (Scheme 4). Thus, the chiral substrate derived from norephedrine, **16b**, was prepared in a similar manner. These new β-allyloxazaborolidine derivatives **16a**,**b**, however, proved unstable and were thus used as such in the following step without further purification.



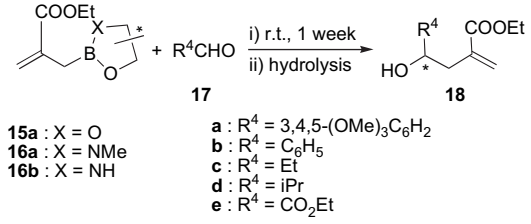
Scheme 4.

Having successfully synthesized various chiral allylboron reagents, enantioselective allylboration reactions of aldehydes and imines were next undertaken.

2.3. Reactivity of chiral β-ethoxycarbonylallylboron reagents: the case of achiral aldehydes

2.3.1. Case of ephedrine as chiral auxiliary

Reacting the chiral allyloxazaborolidine **16a** with 3,4,5-trimethoxybenzaldehyde **17a**, chosen as a model substrate, led to the formation of the expected homoallylic alcohol **18a**, isolated in 60% overall yield (Scheme 5 and Table 1, entry 1). With this β-ethoxycarbonyl substituted allylboron derivative, the condensation required one week at room temperature to reach completion and confirmed its sluggish character when compared to reactions in the unfunctionalized series. Conjugation of the allyl unit to the ester, by lowering the nucleophilicity of the allylboron moiety, may account for this fact. Acidic catalyses (both by Lewis and Brønsted acids) of similar condensations have been recently reported in the literature.[14–16] They have proven highly efficient on accelerating the reaction and diminishing reaction times to one day. However, they have also shown detrimental effects on the stereoselectivity of the process, especially on the enantioselectivity.[14b] In our case, the enantioselectivity of the



Scheme 5.

Table 1
Reaction between chiral allylboron substrates and achiral aldehydes

Entry	Allylboron substrate	R^4CHO	Solvent	Adduct	Yield (%)	ee[a] (%)
1	**16a**	**17a**	Toluene	**18a**	60	6
2	**16b**	**17a**	Toluene	**18a**	60	30
3	**15a**	**17a**	Toluene	**18a**	88	82
4	**15a**	**17a**	CH_2Cl_2	**18a**	63	82
5	**15a**	**17a**	THF	**18a**	91	80
6	**15a**	**17a**	Et_2O	**18a**	99	76
7	**15a**	**17a**	Pentane	**18a**	89	71
8	**15a**	**17b**	Toluene	**18b**	95	80
9	**15a**	**17c**	Toluene	**18c**	99	78
10	**15a**	**17d**	Toluene	**18d**	80	72
11	**15a**	**17e**	Toluene	**18e**	90	78

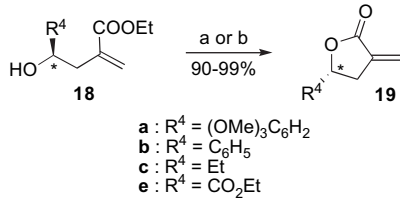
[a] Enantiomeric excess.

uncatalyzed process, evaluated by ^{1}H NMR of the derived *O*-methylmandelic and *O*-acetylmandelic esters,[17] led to the conclusion that ephedrine was a poor chiral inductor for this reaction. Condensing **16b** on **17a** led to a significant increase of the enantiomeric excess (ee) (entry 2) and came to support the initial hypothesis on the positive impact of the free amino group on the rigidity of the reactive conformation. However, in both cases, the enantioselectivities remained modest, possibly because of the remote position of the chiral centers with respect to reactive sites.

2.3.2. Case of the (−)-(1R,2R,3R,4S)-2-endo-phenyl-2,3-bornanediol chiral auxiliary

We were pleased to find that chiral allylboronate **15a** bearing a phenylbornanediol as chiral auxiliary provided good level of enantioselectivity in the allylation reactions of aldehyde **17a** (Table 1, entry 3). After the reaction, chiral diol auxiliary **14** could be recovered in quantitative yields. The absolute stereochemistry, reliably assigned by ^{1}H NMR spectrometry after derivatization of the alcohols into mandelate esters,[17] showed an *R* configuration for the major enantiomer. Note that important solvent effects had been observed in the unfunctionalized series.[11b,18] The influence of this parameter on the course of the reaction revealed insignificant when using the β-ethoxycarbonyl substituted derivatives (compare entries 3–7). Toluene proved, however, to be the solvent of choice, leading to the best yields and selectivities. Condensing the chiral allylboronate **15a** on benzaldehyde led to similar results, leading to **18b** in 95% yield and 80% ee (entry 8). Examination of the reactivity of **15a** included the study of the condensation with aliphatic aldehydes. Thus, using *n*-propanal **17c** furnished alcohol **18c**, isolated in excellent yield and 78% ee (entry 9). More hindered isobutyraldehyde **17d** led to a small decrease in enantioselectivity (entry 10). Finally, the condensation of **15a** on an ester substituted aldehyde **17e** furnished **18e** in 90% yield and 78% ee (entry 11). We thus showed that the nature of the aldehydic component has only little influence on the course of the allylboration reaction. In contrast to tartrate or pinanediol derived allylboronates, results observed here with **14** are comparable to the ones reported in the unfunctionalized series,[11b] and remain the best enantioselectivities observed for condensations involving achiral aldehydes and β-alkoxycarbonylallylboronate reagents with chirality borne by the boron atom.[19,8c–e,9a]

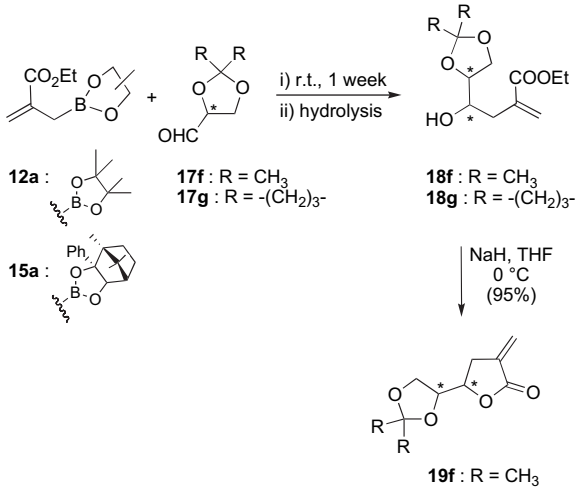
The homoallylic alcohols **18** were then easily cyclized to furnish the corresponding α-methylene-γ-butyrolactones **19** in high yields (Scheme 6). Lactonizations were run either under basic (**18**–**c**) or acidic (**18e**) conditions. Comparison of the optical rotation of lactone **19b** ($[\alpha]_D$ −15.2 (*c* 1, $CHCl_3$)) with the literature data[20] confirmed the *R* absolute configuration of the major enantiomer.



Scheme 6. Reagents and conditions: (a) NaH, THF, 0 °C (**18a**–**c**); (b) PTSA, Toluene, Δ (**18e**).

2.4. Reactivity of chiral β-ethoxycarbonylallylboronate: the case of chiral aldehydes

The double asymmetric induction phenomenon was also examined by means of reaction with chiral aldehydes (Scheme 7, Table 2). L and D-glyceraldehyde acetonide derivatives **17f** and **17g** were chosen as model chiral electrophiles since these aldehydes have been used as classical probes.[21] Both *R* and *S* enantiomers were prepared in two steps starting, respectively, from D-mannitol and L-gulonolactone, according to Schmidt and Bradley's procedure.[22,23]



Scheme 7.

Reacting the achiral β-ethoxycarbonylallylboronate **12a** with aldehyde (*R*)-**17f** in toluene furnished homoallylic alcohol **18f**, isolated in 89% yield (Scheme 7) (Table 2, entry 1). The reaction showed moderate diastereoselectivity (40% de), the major diastereomer having an (*S*,*R*) configuration.[24] Similarly, condensation of **12a** on the (*S*)-**17g** led to an increased but still modest stereoselectivity (entry 2). Reaction between chiral boronate **15a** and chiral aldehyde **17f** of (*R*) configuration led to a poorer diastereoselectivity, showing that these two chiral entities have opposite stereochemical influences (entry 3). In contrast, the reaction between **15a** and aldehyde **17f**

Table 2
Reaction between chiral allylboron substrates and chiral aldehydes

Entry	Allylboron substrate	Aldehyde	Adduct	Yield (%)	de[a] (%)
1	**12a**	(***R***)-**17f**	**18f**	89	40
2	**12a**	(***S***)-**17g**	**18g**	99	56
3	**15a**	(***R***)-**17f**	**18f**	99	30
4	**15a**	(***S***)-**17f**	**18f**	99	>95
5	**15a**	(***S***)-**17g**	**18g**	97	>95

[a] Diastereomeric excess.

possessing an (*S*) configuration led to the formation of a unique diastereomer **18f** bearing an (*R*,*S*) configuration (entry 4). The phenomenon was confirmed when condensing boronate **15a** on chiral (*S*)-**17g** (entry 5). Both chiral entities have thus fully synergical effects in these cases and allow for a totally diastereoselective process. The resulting homoallylic alcohol **18f** was then cyclized into the corresponding lactone **19f** in high yield (Scheme 7).

2.5. Reactivity of chiral (*E*)-β-methoxycarbonylcrotylboronate: the case of achiral aldehydes

Reacting chiral (*E*)-**15c** with benzaldehyde **17b** in toluene furnished the corresponding homoallylic alcohol **20a** in 95% yield (Scheme 8) (Table 3, entry 1). The diastereoselectivity of the reaction was complete and expectedly the *syn* diastereomer was found to have formed, on basis of the ^{1}H NMR (vide infra). While, the acid-catalyzed condensations have been shown to lead to mixtures of diastereomers, no isomerization was observed under these non-acidic reaction conditions.[14d,15a,b] A lower enantioselectivity was observed here, probably because of the steric hindrance imposed by the methyl group; this decrease in the asymmetric induction when comparing allylboron with crotylboron reagents had already been observed in the case of unfunctionalized reagents.[7a,25] Next, (*E*)-crotylboronate **15c** was reacted with aldehyde **17c**. Similar results were observed in terms of yield and diastereoselectivity but the level of asymmetric induction was significantly increased with this aliphatic aldehyde (entry 2). In contrast, the condensation of **15c** on glyoxylic aldehyde **17e** appeared less enantioselective (entry 3).

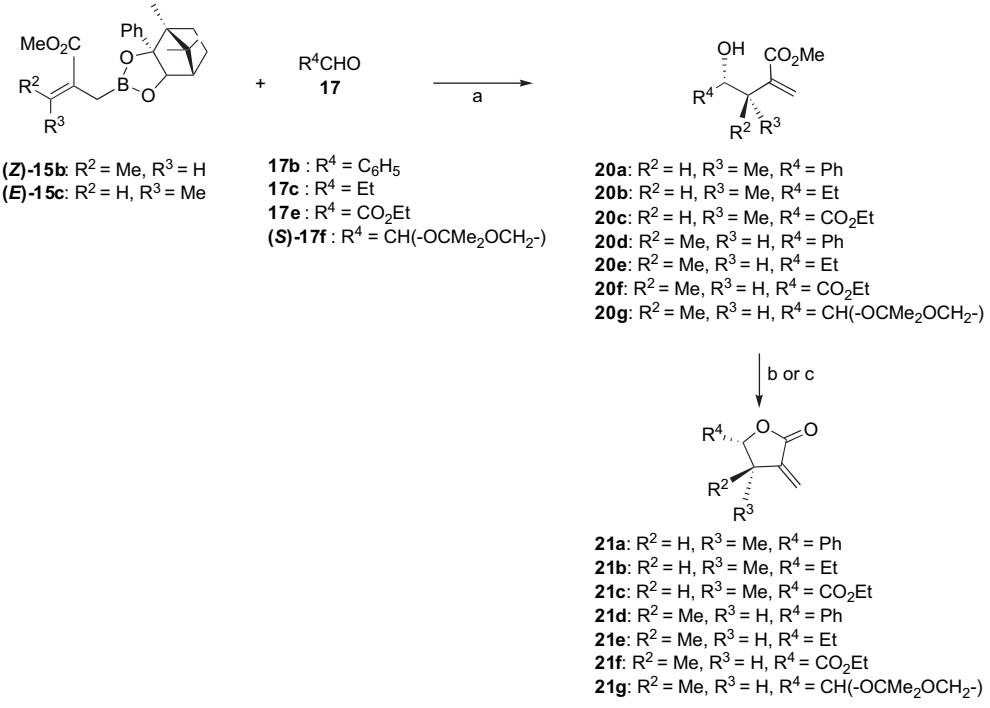
Table 3
Reaction between chiral crotylboron substrates and aldehydes

Entry	Allylic substrate	R^4CHO	Adduct	Yield (%)	dr[a] *syn*:*anti*	Select.[b] (%)
1	**15c**	**17b**	**20a**	95	>19:1	50[c]
2	**15c**	**17c**	**20b**	85	>19:1	80[c]
3	**15c**	**17e**	**20c**	92	>19:1	35[c]
4	**15b**	**17b**	**20d**	86	>1:19	75[c]
5	**15b**	**17c**	**21e**	90	>1:19	85[c]
6	**15b**	**17e**	**20f**	92	>1:19	70[c]
7	**15b**	(*S*)-**17f**	**20g**	85	>1:19	>95[d]

[a] Diastereomeric ratio determined by ^{1}H NMR on the crude mixture.
[b] Enantiomeric excess or diastereomeric excess.
[c] Enantiomeric excess determined by ^{1}H NMR spectrometry of the derived mandelic esters.
[d] Diastereomeric excess.

2.6. Reactivity of chiral (*Z*)-β-methoxycarbonylcrotylboronate: the case of aldehydes

Reacting chiral (*Z*)-crotylboronate **15b** with aldehydes in toluene furnished the expected homoallylic alcohols **20d–g** and corresponding cyclized lactones **21d–g** (Scheme 8). The diastereoselectivity of the reaction also appears to be complete, leading to *anti*-alcohols **20d–g** and corresponding *trans*-lactones **21d–g** (vide infra).[26] Enantiomeric excesses were higher with this (*Z*)-crotylboronate stereoisomer and values appeared similar to those obtained previously in the allylic series, in the 70–85% range (Table 3, entries 4–6). Condensation of boronate **15b** on chiral aldehyde (*S*)-**17f** similarly led to a completely diastereoselective reaction, giving access to the (3*R*,4*R*,5*S*) enantiomer of alcohol **20g**, isolated in 85% yield (entry 7).



Scheme 8. Reagents and conditions: (a) toluene, rt; (b) NaH, THF, 0 °C (**20a**,**b**,**d**,**e**,**g**); (c) PTSA, toluene, Δ (**20c–f**).

Lactonization of homoallylic alcohols **20a–g** was effected in conditions similar to those described above (Scheme 8). The cis/trans stereochemistry of the obtained lactones **21a–g** was assigned on the basis of NMR spectrometry and comparison with previously reported data.[14,15,27] Accordingly, the respective *syn*/*anti* stereochemistry of the corresponding precursory alcohols **20a–g** could be attributed.

The process thus appears to be stereospecific: the geometry of isomeric crotylboronates (*E*)-**15b** and (*Z*)-**15c** was transfered, respectively, into diastereomeric *anti*- and *syn*-homoallylic alcohols and further into *trans*- and *cis*-lactones with no apparent loss of selectivity. This constitutes the first enantioselective version of condensations of crotylboronates bearing an alkoxycarbonyl moiety in β-position. While the enantioselectivity of this process is moderate with (*E*)-crotylboronate, it reaches values in 80% range with (*Z*)-crotyl species.

We have then tried to understand the sense of asymmetric induction observed in these allylation reactions. A two-step mechanism is generally proposed: after coordination of the aldehydic oxygen to the boron, condensation happens with allylic transposition (SE_2'), involving a six-membered cyclic Zimmermann–Traxler type transition state.[7a] The first coordination step is the one that allows for discrimination of both prochiral faces of the aldehyde and thus sets the enantioselectivity of the process. When cyclic boronates are considered, Roush proposed a prefered 'axial' coordination of the aldehydic oxygen to boron atom, which could lead to a conformation stabilized by n–σ* interactions between the axial lone pairs of boronate oxygen atoms and the forming B–O bond, evoking an anomeric effect centered on boron.[28] A possible attractive interaction between the aldehydic proton and the oxygen atom borne by boron,[29] associated to steric effects led us to consider that the aldehydic hydrogen atom should be positioned toward the oxygen boronate. Taking into account these considerations, two complexes **A** and **B** are to be considered (Fig. 2). Hoffmann hypothesized that induction observed with unfunctionalized allylboronates derived from phenylbornanediol is based on aldehydic C=O double bond that should be parallel to the phenyl moiety, the aldehydic hydrogen being positioned on the phenyl side to avoid disfavored interactions with the camphor moiety.[11b] In our case, this would lead to a preferred complexation of the aldehyde on its *Si* face (complex **A** on Fig. 1).

Once this discriminative complexation has occurred, the complex evolves to the reactive conformation. A chair-like transition state **C**, for which the aldehydic R^4 moiety adopts a preferred *pseudo*-equatorial orientation in order to avoid 1,2-interactions, can thus account for the enantioselectivity

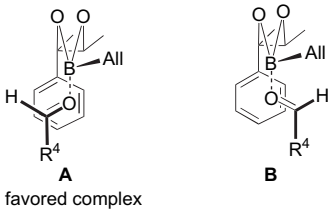
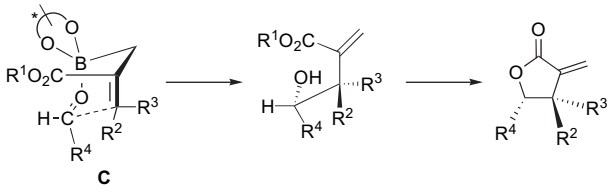


Figure 2.

observed in all these allylation reactions (Scheme 9). The diastereoselectivities observed in the case of double asymmetric induction are in complete agreement with the proposed transition state. Assuming that C–O bonds of the dioxolane and the forming C–C bond are antiperiplanar,[21b] a mismatched effect is expected when using an *R* aldehyde, while the aldehyde of *S* configuration should lead to synergical effects and formation of a unique diastereomer. The complete diastereoselectivity observed in the case of crotylboronate species is also in full agreement with the proposed mechanism, since the (*Z*)-crotylboronate leads to the formation of *anti*-homoallylic alcohols and corresponding *trans*-lactones, while the (*E*)-crotylboronate furnishes *syn*-alcohols and corresponding *cis*-lactones. In the latter case, a disfavoring 1,2-interaction between the methyl moiety of the crotylboronate and the R substituent of the aldehyde can account for the lower selectivity observed in some cases.



Scheme 9.

2.7. Reactivity of chiral β-ethoxycarbonylallylboronate: the case of aldimines

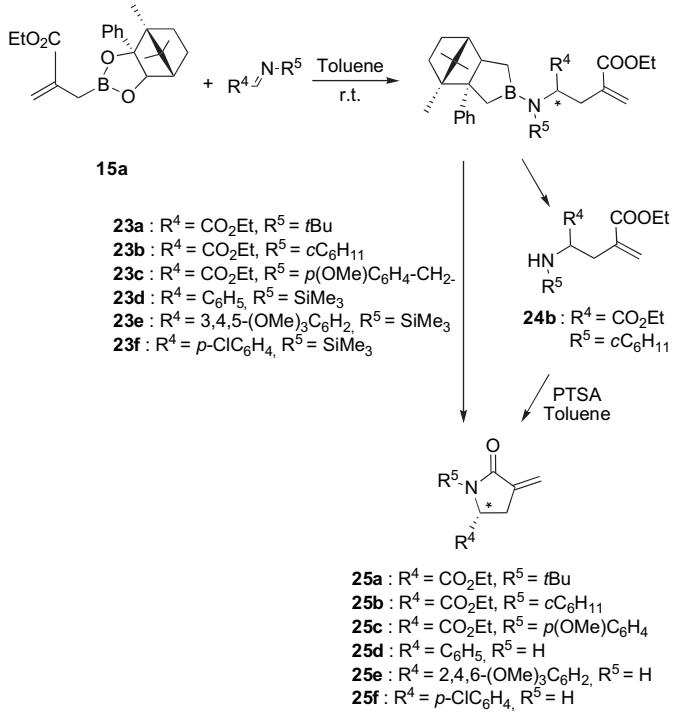
Reports on allylboration reactions with aldimines are much seldom reported in the literature.[30] This is probably due to their trans-geometry that imposes the coordination of the nitrogen atom *syn* to the R^4 group and, consequently, their poor reactivity in allylation reactions. Interestingly, catalytic asymmetric alkoxycarbonylallylstannation of aldimines was recently reported in the presence of chiral bis-π-allylpalladium complex.[31] In our case, this reaction would lead to functionalized α-methylene-γ-lactams of interest.[4] Furthermore, imines derived from glyoxylate would produce chiral α-aminoesters bearing a functionalized allylic moiety. Reacting chiral allylboronate **15a** with imines led to a set of results summarized in Table 4 (Scheme 10). No reaction was found to occur with the sterically hindered imine **23a**, bearing a *tert*-butyl moiety (entry 1). In contrast, condensation of **15a** on imine **23b**, derived from glyoxylate led to the expected α-aminoester **24b** in good yield (entry 2). The lower reactivity of aldimines when compared to aldehydes explains that the reaction required two weeks to reach completion. This inertness was, however, beneficial to enantioselectivity that reached 94%, a value higher than that measured in the case of achiral aldehydes (compare entries 3, 8–11 of Table 1 with entries 2, 3 of Table 4). The generated homoallylic amine could be cyclized in 93% yield using PTSA in toluene. Condensation of allylboronate **15a** on aldimine **23c**, bearing a *p*-methoxybenzyl group on the nitrogen atom directly led to lactam **25c** (entry 3). Enantioselectivity proved even higher in this case and led

Table 4
Reaction between chiral allylboron **15a** and aldimines

Entry	Imine	Adduct	Yield (%)	ee[a] (%)
1	**23a**	—	—	—
2	**23b**	**24b**	73	94
3	**23c**	**25c**	65	>95
4	**23d**	**25d**	92	>95
5	**23e**	**25e**	58	>95
6	**23f**	**25f**	61	>95

[a] Enantiomeric excess determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift.

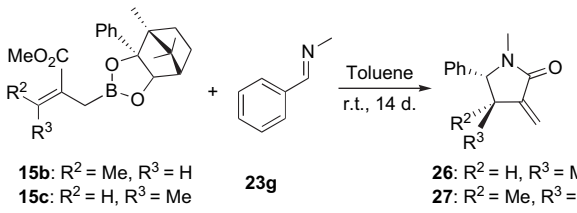
to the isolation of a single enantiomer (ee>95%). The use of silylated aldimines was also envisaged since they would have the advantage of furnishing directly N-deprotected derivatives after hydrolysis of the medium. Highly sensitive aldimines **23d–f** were accessed by condensing hexamethyldisilylazane amide on the corresponding aromatic aldehydes.[32] Reacting these silylated imines on chiral allylboronate **15a** directly led to the corresponding secondary lactams **25d–f** after acidic hydrolysis of the reaction medium (entries 4–6). Here again, the condensations proved efficient and completely enantioselective (ee>95%), leading to only one detectable enantiomeric secondary lactam. Optical rotations of lactams **25d** and **25e** were indicative of their *R* configuration.[33]



Scheme 10.

2.8. Reactivity of chiral β-methoxycarbonylcrotylboronate: the case of aldimines

Reacting chiral (*Z*)-crotylboronate **15b** with aldimine **23g** in toluene furnished lactam **26** (Scheme 11). The diastereomeric excess was determined by NMR spectrometry on the crude sample and showed the formation of only one stereoisomer, which proved to be the *trans*-lactam by comparison with reported data.[34] Additionally, condensing (*E*)-crotylboronate **15c** with **23g** led to the unique formation of the *cis*-lactam **27**. The enantiomeric excess of lactams **26** and **27**, determined by NMR spectrometry in the presence of Eu(hfc)$_3$, proved to be superior to 95% in both cases, confirming the good chiral transfer mentioned above with imines. This latter pair of examples highlights the power of this approach at affording excellent diastereo- and enantiocontrol in the formation of α-methylene-γ-butyrolactams.



Scheme 11.

The formation of lactams of *R* absolute configuration involves an exclusive attack at the *Re* face of the aldimine and thus contrasts dramatically with the similar reaction Involving aldehydes. A different pathway is to be considered here. Because of the *s-trans* nature of imines, their coordination to the boron atom may occur in a different manner, as described in Figure 3. Steric and electronic repulsions between the R^4 group and phenyl group of the chiral auxiliary on one side and between R^5 and the bornanediol moiety on the other side may greatly disfavor the formation of complex **D**.

Two transition states are then to be considered, involving either a chair-like or a boat-like conformation (Scheme 12). The respective formation of the *trans*- and *cis*-lactams from the (*Z*)- and (*E*)-crotylboronate suggests that a boat-like transition state may be preferred in this case. A strong 1,3-diaxial interaction between the ester group of the allylboronate and the R^4 group on the imine may, in this case, greatly disfavor the chair-like conformation **E** over the boat-like one **F**. This is in agreement with some results from the literature, which propose boat-like transition states in the allylboration of imine.[35] These results, however, contrast with those previously obtained in these laboratories with β-alkoxycarbonyl crotylzinc derivatives, which furnish, respectively, *cis*- or *trans*-lactam from (*Z*) or (*E*) substrates[34] and thus furnishes a complementary methodology to access α-methylene-γ-lactams on demand.

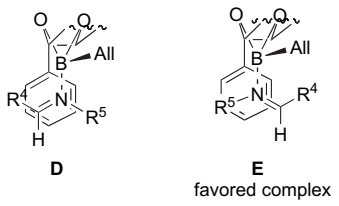
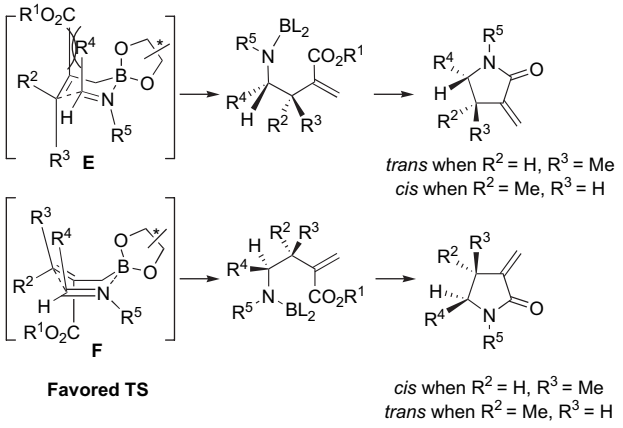


Figure 3.



Scheme 12.

3. Conclusion

Asymmetric β-alkoxycarbonylallylboration reactions offer an easy and rapid access to chiral α-methylene-γ-butyro-lactones and lactams. The presence of an ester function in β-position of the nucleophilic allylic species, however, introduces severe constraints as compared to classical unfunctionalized allylmetal reagents, leading to less reactive reagents. The reactions are thus rather slow but they are operationally simple. Phenylbornanediol constitutes, to date, the best chiral auxiliary for β-alkoxycarbonylallylboration reactions and allows a good to complete enantioselection and quantitative recycling of the chiral entity. Discriminative complexation of aldehydes to boron implicates a reaction on its *Si* face. In the case of aldimines, addition of a substituent on the heteroatom induces new steric constraints and completely modifies the system, the reaction taking place at the *Re* face of the imine. The process appears to be completely stereospecific, depending on the stereochemistry of the starting allylboronate species. (*E*)- and (*Z*)-Crotylboronate, respectively, lead to *cis*- and *trans*-lactones when reacted with aldehydes and a classical chair-like transition state is proposed to account for these results. In contrast, the interaction of imines with (*E*)- and (*Z*)-crotylboronate yields *cis*- and *trans*-lactam, suggesting a boat-like transition state in this case. This methodology will now be used in the synthesis of natural products and will be reported in due time.

4. Experimental section

4.1. General

Unless otherwise stated, ^{1}H NMR (400 or 200 MHz) and ^{13}C NMR (100 or 50 MHz) spectra were recorded in deuterated chloroform relative to $(CH_3)_4Si$ and $CDCl_3$, respectively. Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded on a H.P. 5889 A spectrometer. IR spectra were recorded on a Bruker IFS WHR spectrometers.

4.1.1. Synthesis of ethyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)acrylate (**12a**)

To a stirred solution of HMPA (37 mL, 210 mmol) in dry toluene (230 mL) was added dropwise at 0 °C a 1 M solution of DIBAL in toluene (113 mL, 110 mmol). The mixture was stirred at this temperature for 2 h. Ethylpropiolate (6.82 g, 71 mmol) was additioned dropwise and the reaction mixture was stirred at 0 °C overnight. Pinacol chloromethylboronate **11** (15 g, 85 mmol) was introduced and stirring was maintained at room temperature for 24 h. After dilution with ether (230 mL), the reaction mixture was quenched with a 1 M solution of HCl (60 mL). The organic layer was then successively washed with 1 M HCl (60 mL, three times), saturated sodium bicarbonate (60 mL), and water (60 mL, twice). After drying over $MgSO_4$ and evaporation of the solvents the product was purified by distillation under reduced pressure (Eb=80–85 °C/1 mmHg) to give a colorless liquid (16.2 g, 95%). ^{1}H NMR (200 MHz) 1.25 (s, 12H), 1.29 (t, 3H, *J*=7.1), 1.91 (br s, 2H), 4.19 (q, 2H, *J*=7.1), 5.54 (dt, 1H, *J*=1.5, 1.4), 6.09 (dt, *J*=1.5, 0.8). ^{13}C NMR (50 MHz) 14.2, 17.2, 24.7 (4C), 60.7, 83.4 (2C), 124.1, 137.8, 167.3. MS (EI) *m/z*: 240, 225, 182, 153, 141, 83. IR (film, cm^{-1}): 1720, 1625, 1350.

4.1.2. Synthesis of methyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)but-2-enoate (**12b** and **12c**)

To a stirred solution of CuI (192 mg, 1 mmol) in dry THF (10 mL), cooled down to −30 °C, was added a 1 M solution of methyllithium in ether (1 mL, 1 mmol). After 20 min stirring at this temperature, dry toluene (20 mL) and HMPA (3.4 mL, 19.6 mmol) were added to this mixture. A 1 M solution of DIBAL in toluene (15 mL, 15 mmol) was then additioned dropwise and the reaction mixture was stirred at −30 °C for 2 h. Methyl but-2-ynoate (1 mL, 10 mmol) was added and the reaction mixture was stirred at −20 °C for an additional 5 h. A solution of pinacol chloromethylboronate **11** (2.12 g, 12 mmol) was introduced and stirring was maintained at room temperature overnight. After dilution with ether (30 mL), the reaction mixture was slowly quenched with a 1 M solution of HCl (10 mL). The organic layer was then successively washed with 1 M HCl (10 mL, three times), saturated sodium bicarbonate (10 mL), and water (10 mL, twice). After drying over $MgSO_4$ and evaporation of the solvents, a colorless liquid (2.28 g, 95%) was obtained as 35:65 mixture of *E*/*Z* diastereomers. Major diastereomer, **12b**: ^{1}H NMR (200 MHz) 1.24 (s, 12H), 1.83 (br s, 2H), 2.00 (dt, 3H, *J*=7.3, 1.2), 3.71 (s, 3H), 6.06 (qt, 1H, *J*=7.3, 1.3). ^{13}C NMR (50 MHz) 15.8, 24.7 (4C), 51.0, 83.1 (2C), 128.7, 137.7, 168.2. Minor diastereomer, **12c**: ^{1}H NMR (200 MHz) 1.24 (s, 12H), 1.78 (dt, 3H, *J*=7.0, 0.8), 1.85 (br s, 2H), 3.71 (s, 3H), 6.83 (qt, 1H, *J*=7.0, 1.1). ^{13}C NMR (50 MHz) 14.4, 24.7 (4C), 51.5, 83.2 (2C), 129.9, 135.7, 168.3. MS (EI) *m/z* (%): 368 (1), 285 (7), 258 (100), 141 (64), 82 (52). IR (film, cm^{-1}): 2956, 1721, 1644, 1350, 1197.

4.1.3. Synthesis of ethyl 2-[4-methyl-4,7-[dimethylmethano-1,3-dioxo-2-boraperhydroinden-2-yl]methyl]prop-2-enoate (**15a**)

Sodium periodate (3.85 g, 18 mmol) was added to a mixture of pinacol allylboronate **12a** (1.44 g, 6 mmol) in acetone (160 mL) and 0.1 M solution of aqueous ammonium acetate

(130 mL). Stirring was maintained at room temperature for 24 h. Acetone was removed and the aqueous layer was extracted three times with ether. The organic layer was dried over $MgSO_4$ and partially evaporated until 40 mL of ether are left. Phenylbornandiol **14** (1.086 g, 6 mmol) in ether (40 mL) and $MgSO_4$ (2 g) were added to this solution. After 24 h stirring, the magnesium sulfate was filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc/Et_3N 95:5:0.001) to give **15a** as a colorless oil (2.2 g, quantitative yield). ^1H NMR (200 MHz) 0.80–1.90 (m, 4H), 0.92 (s, 3H), 0.93 (s, 3H), 1.02 (t, 3H, J=7.1), 1.23 (s, 3H), 1.93 (br s, 2H), 2.13 (d, 1H, J=5.2), 3.84 (dq, 1H, J=−10.8, 7.1), 3.98 (dq, 1H, J=−10.8, 7.1), 4.72 (s, 1H), 5.44 (dd, 1H, J=1.4, 2.9), 5.44 (d, 1H, J=1.4), 7.20–7.50 (m, 5H). ^{13}C NMR (50 MHz) 9.3, 13.8, 17.1, 20.7, 23.5, 24.6, 29.5, 48.7, 50.1, 51.9, 60.4, 88.7, 95.7, 124.0, 126.6 (2C), 127.1, 127.3 (2C), 137.0, 141.6, 167.2. MS (EI) *m/z* (I%): 368 (1), 258 (100), 230 (28), 141 (34), 105 (21), 95 (19), 68 (23). IR (film, cm^{-1}): 3060, 2984, 2963, 2898, 1718, 1635, 1372. $[\alpha]_D$ 46.2 (*c* 1.59, $CHCl_3$). Anal. Calcd for $C_{22}H_{29}BO_4$: C, 71.75; H, 7.94. Found: C, 71.79; H, 7.88.

*4.1.4. Synthesis of methyl 2-[4-methyl-4,7-[dimethylmethano-1,3-dioxo-2-boraperhydroinden-2-yl]-methyl]but-2-enoate (**15b** and **15c**)*

Sodium periodate (2.77 g, 12.9 mmol) was added to a 65:35 mixture of pinacol crotylboronate **12b/12c** (1.037 g, 4.3 mmol) in acetone (57 mL) and 0.1 M solution of aqueous ammonium acetate (48 mL). Stirring was maintained at room temperature overnight. Acetone was removed and the aqueous layer was extracted three times with ether. The organic layer was dried over $MgSO_4$ and partially evaporated until 30 mL of ether are left. Phenylbornandiol **14** (1.65 g, 4.3 mmol) in ether (30 mL) and $MgSO_4$ (10 g) were added to this solution. After 24 h stirring, the $MgSO_4$ was filtered and the solvent removed under reduced pressure to give a colorless oil (1.58 g, quantitative yield) containing a 65:35 mixture of *Z*/*E* diastereomers. They were separated by flash chromatography on silica (hexane/EtOAc/Et_3N 98:2:0.001) to give **15b** and **15c** as colorless oils. Major diastereomer, first eluted, **15b**: ^1H NMR (200 MHz) 0.90–1.25 (m, 4H), 0.92 (s, 3H), 0.94 (s, 3H), 1.21 (s, 3H), 1.82 (br s, 2H), 1.98 (dt, 3H, J=7.2, 1.2), 2.13 (d, 1H, J=5.1), 3.26 (s, 3H), 4.72 (s, 1H), 5.98 (qt, 1H, J=7.2, 1.3), 7.20–7.50 (m, 5H). ^{13}C NMR (50 MHz) 9.2, 14.6, 19.5, 20.8, 23.5, 24.6, 29.4, 48.7, 50.1, 50.4, 51.8, 88.6, 95.8, 126.6 (2C), 127.1, 127.3 (2C), 128.3, 137.5, 141.8, 167.8. $[\alpha]_D$ 95.5 (*c* 1.0, $CHCl_3$). Minor diastereomer, second eluted, **15c**: ^1H NMR (200 MHz) 0.90–1.25 (m, 4H), 0.92 (s, 3H), 0.93 (s, 3H), 1.22 (s, 3H), 1.70 (d, 3H, J=7.0), 1.87 (br s, 2H), 2.12 (d, 1H, J=5.2), 3.39 (s, 3H), 4.71 (s, 1H), 6.81 (q, 1H, J=7.0), 7.20–7.50 (m, 5H). ^{13}C NMR (50 MHz) 9.2, 11.4, 14.3, 20.7, 23.5, 24.6, 29.4, 48.7, 50.1, 51.1, 51.8, 88.7, 95.6, 126.6, 127.1, 127.3, 129.5, 135.6, 141.7, 168.2. $[\alpha]_D$ 58.7 (*c* 1.0, $CHCl_3$). MS (EI) *m/z*: 368 (1), 285 (7), 258 (100), 141 (64), 82 (52). IR (film, cm^{-1}): 2956, 1721, 1644, 1350, 1197.

*4.2. General procedure for the synthesis of homoallylic alcohols **18** (typically on 1 mmol scale)*

The desired aldehyde (1 equiv) was added to a stirred solution of phenylbornandiol 2-ethoxycarbonylallylboronate **15a** (1 mmol) in the appropriate solvent (2 M). Stirring was maintained at room temperature under inert atmosphere for one week (monitored by TLC). The reaction mixture was quenched with water and extracted three times with ether. After drying over $MgSO_4$, solvents were removed under reduced pressure. The residue was purified by flash chromatography, allowing separation of the chiral auxiliary (quantitative recovering yield) and the desired homoallylic alcohol (63–99% yield).

*4.2.1. Ethyl 4-hydroxy-2-methylene-4-(3,4,5-trimethoxyphenyl) butanoate (**18a**)*

^1H NMR (200 MHz) 1.32 (t, 3H, J=7.1), 2.64 (ddd, 1H, J=0.6, 8.2, −14.0), 2.76 (br s, 1H), 2.80 (ddd, 1H, J=0.9, 4.0, −14.0), 3.83 (s, 3H), 3.87 (s, 6H), 4.23 (q, 2H, J=7.1), 4.83 (dd, 1H, J=4.0, 8.2), 5.65 (m, 1H, J=0.6, 0.9, 1.4), 6.26 (d, 1H, J=1.4), 6.60 (s, 2H). ^{13}C NMR (50 MHz) 13.9, 42.3, 55.8 (2C), 60.5, 60.8, 72.9, 102.4, 127.8 (2C), 137.0, 139.8, 152.9 (3C), 167.5. MS (EI) *m/z* (I%): 310 (5), 264 (68), 197 (100). IR (film, cm^{-1}): 3510–3420, 3006, 2940, 1710, 1620. Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.57; H, 7.38.

*4.2.2. Ethyl 4-hydroxy-2-methylene-4-phenyl butanoate (**18b**)*

^1H NMR (200 MHz) 1.31 (t, 3H, J=7.1), 2.66 (ddd, 1H, J=0.9, 8.2, −13.9), 2.70 (br s, 1H), 2.80 (ddd, 1H, J=1.1, 4.3, −13.9), 4.22 (q, 2H, J=7.1), 4.89 (dd, 1H, J=4.3, 8.2), 5.59 (m, 1H, J=0.9, 1.1, 1.3), 6.23 (d, 1H, J=1.3), 7.2–7.4 (m, 5H). ^{13}C NMR (50 MHz) 14.0, 42.2, 60.8, 72.8, 125.6 (2C), 127.2, 127.9, 128.1 (2C), 137.0, 143.9, 167.5. MS (EI) *m/z* (I%): 220 (1), 203 (20), 174 (14), 107 (100). IR (film, cm^{-1}): 3510–3420, 3006, 2980, 1710, 1620. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.47; H, 7.43.

*4.2.3. Ethyl 4-hydroxy-2-methylenehexanoate (**18c**)*

^1H NMR (200 MHz) 0.97 (t, 3H, J=7.4), 1.31 (t, 3H, J=7.1), 1.50 (m, 2H, J=7.4), 2.29 (br s, 1H), 2.33 (ddd, 1H, J=0.9, 8.3, 14.0), 2.59 (ddd, 1H, J=1.1, 3.7, −14.0), 3.66 (m, 1H, J=3.7, 8.3), 4.22 (q, 2H, J=7.1), 5.66 (m, 1H, J=0.9, 1.1, 1.5), 6.25 (d, 1H, J=1.5). ^{13}C NMR (50 MHz) 9.9, 14.1, 29.9, 39.9, 60.9, 71.9, 127.3, 137.8, 167.7. MS (EI) *m/z* (I%): 172 (1), 126 (10), 59 (100). IR (film, cm^{-1}): 3510, 2980, 2962, 1710, 1620. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.59; H, 9.50.

*4.2.4. Ethyl 4-hydroxy-5-methyl-2-methylene hexanoate (**18d**)*

^1H NMR (400 MHz) 0.96 (d, 6H, J=6.7), 1.30 (t, 3H, J=7.1), 1.67 (m, 1H), 2.29 (dd, 1H, J=9.4, −14.0), 3.50 (ddd, 1H, J=1.0, 2.7, −14.0), 3.50 (ddd, 1H, J=2.7, 5.3, 9.4), 4.22 (q, 2H, J=7.2), 5.66 (m, 1H), 6.25 (d, 1H, J=1.4). ^{13}C NMR (50 MHz) 14.1, 17.3, 18.5, 33.6, 37.2, 60.9, 75.4,

127.1, 138.3, 167.8. MS (CI NH_3) *m/z*: 187. IR (film, cm^{-1}): 3520, 2950, 1710, 1620.

4.2.5. Ethyl 4-hydroxy-2-methylene penta-1,5-dioate (**18e**)

^1H NMR (200 MHz) 1.29 (t, 3H, *J*=7.1), 1.30 (t, 3H, *J*=7.1), 2.64 (dd, 1H, *J*=8.0, −14.0), 2.86 (ddd, 1H, *J*=0.9, 4.5, −14.0), 3.16 (d, 1H, *J*=6.6), 4.23 (q, 4H, *J*=7.1), 4.39 (ddd, 1H, *J*=4.5, 6.6, 8.0), 5.72 (m, *J*=0.9, 1.2 Hz), 6.29 (d, *J*=1.2). ^{13}C NMR (50 MHz) 13.5 (2C), 36.5, 60.3, 60.7, 69.0, 127.5, 135.4, 166.3, 173.6. MS (CI CH_4) *m/z*: 217. IR (film, cm^{-1}): 3470, 2980, 1740, 1630.

4.2.6. Ethyl 2,2′-dimethyl-1′,3′-(dioxolan-4-yl)-4-hydroxy-2-methylene butanoate (**18f**)

(*R*,*S*) or (*S*,*R*) isomer: ^1H NMR (400 MHz) 1.21 (t, 3H, *J*=7.1), 1.25 (s, 3H), 1.32 (s, 3H), 2.26 (ddd, 1H, *J*=0.9, 8.6, −14.3), 2.61 (ddd, 1H, *J*=1.1, 3.3, −14.3), 3.6–4.0 (m, 4H), 4.12 (q, 2H, *J*=7.1), 5.63 (m, 1H), 6.18 (d, 1H, *J*=1.4). ^{13}C NMR (50 MHz) 14.2, 25.3, 26.2 36.2, 61.1, 66.7, 71.2, 78.3, 109.4, 128.0, 137.2, 168.0. (*R*,*R*) or (*S*,*S*) isomer: ^1H NMR (400 MHz) 1.21 (t, 3H, *J*=7.1), 1.26 (s, 3H), 1.34 (s, 3H), 2.34 (ddd, 1H, *J*=0.9, 8.4, −14.2), 2.40 (ddd, 1H, *J*=1.0, 4.1, −14.2), 3.6–4.0 (m, 4H), 4.11 (q, 2H, *J*=7.1), 5.62 (m, 1H), 6.17 (d, 1H, *J*=1.4). ^{13}C NMR (50 MHz) 14.2, 25.3, 26.3, 36.7, 60.9, 66.7, 71.2, 78.5, 109.2, 127.8, 137.9, 167.3. MS (EI) *m/z* (I%): 244 (1), 229 (37), 199 (4), 143 (100), 113 (16), 123 (98), 73 (24). IR (film, cm^{-1}): 3471, 2980–2920, 1714, 1632, 1066.

4.2.7. Ethyl 4-(1,4-dioxaspiro [4,5] decanyl)-4-hydroxy-2-methylene butanoate (**18g**)

(*R*,*S*) or (*S*,*R*) isomer: ^1H NMR (400 MHz) 1.32 (t, 3H, *J*=7.1), 1.35–1.75 (m, 10H), 2.39 (ddd, 1H, *J*=0.7, 8.5, −14.3), 2.72 (ddd, 1H, *J*=0.9, 3.4, −14.3), 3.66–4.00 (m, 4H), 4.23 (q, 2H, *J*=7.1), 5.74 (m, 1H), 6.29 (d, 1H, *J*=1.4). ^{13}C NMR (50 MHz) 14.0, 23.6 (2C), 25.0, 34.7 (2C), 36.1, 60.9, 65.6, 71.2, 77.6, 109.6, 127.8, 137.0, 167.8. (*R*,*R*) or (*S*,*S*) isomer: ^1H NMR (400 MHz) 1.31 (t, 3H, *J*=7.1), 1.35–1.75 (m,10H), 2.48 (ddd, 1H, *J*=0.7, 8.0, −14.0), 2.51 (ddd, 1H, *J*=0.9, 4.0, −14.0), 3.63–4.00 (m, 4H), 4.22 (q, 2H, *J*=7.1), 5.73 (m, 1H), 6.28 (d, 1H, *J*=1.5). ^{13}C NMR (50 MHz) 14.0, 23.0 (2C), 24.8, 34.7 (2C), 35.7, 60.9, 65.1, 69.4, 79.4, 110.0, 127.8, 137.0, 168.0. MS (CI NH_3) *m/z*: 302 ($M+NH_3+1$). IR (film, cm^{-1}): 3470, 2972–2920, 1716, 1628, 1100.

4.3. General procedure for the synthesis of α-methylene-γ-lactones **19**

A solution of the hydroxyester **18** (1 equiv) in dry THF (1 M solution) was added dropwise to a cooled (0 °C) suspension of sodium hydride (1.1 equiv) in THF (1 M solution). The reaction mixture was stirred for several minutes (monitored by TLC), then worked up with a phosphate buffered solution (pH=7). After extraction with ether (three times), drying over $MgSO_4$, and evaporation of the solvents, the residue was purified by flash chromatography to give a white solid (95% yield).

4.3.1. 3-Methylene-5-(3′,4′,5′-trimethoxyphenyl) tetrahydrofuran-2-one (**19a**)

^1H NMR (200 MHz) 2.88 (m, 1H, *J*=2.6, 2.9, 6.9, −17.0), 3.40 (m, 1H, *J*=2.0, 2.6, 8.0, −17.0), 3.84 (s, 3H), 3.86 (s, 6H), 5.45 (dd, 1H, *J*=6.9, 8.0), 5.70 (dd, 1H, *J*=2.0, 2.6), 6.30 (dd, 1H, *J*=2.6, 2.9 Hz), 6.52 (s, 2H). ^{13}C NMR (50 MHz) 36.4, 56.3 (2C), 60.9, 78.0, 122.5, 133.7 (2C), 134.4 (3C), 138.3, 153.7, 168.2. MS (EI) *m/z* (I%): 264 (11), 97 (100), 197 (73). IR (film, cm^{-1}): 3040, 2972, 1760, 1560.

4.3.2. 3-Methylene-5-phenyl tetrahydrofuran-2-one (**19b**)

^1H NMR (200 MHz) 2.91 (dddd, 1H, *J*=2.5, 2.9, 6.5, −17.1), 3.41 (dddt, 1H, *J*=2.5, 2.9, 8.0, −17.1), 5.53 (dd, 1H, *J*=6.5, 8.0), 5.69 (dd, 1H, *J*=2.5, 2.9), 6.31 (dd, 1H, *J*=2.5, 2.9 Hz), 7.20–7.40 (m, 5H). ^{13}C NMR (50 MHz) 36.1, 77.9, 122.3, 125.3 (2C), 128.5, 128.7 (2C), 134.2, 139.8, 167.9. MS (EI) *m/z* (I%): 174 (8), 97 (100), 77 (18), 68 (38). IR (film, cm^{-1}): 3020, 2960, 1772, 1642.

4.3.3. 3-Methylene-5-ethyl tetrahydrofuran-2-one (**19c**)

^1H NMR (200 MHz) 1.00 (t, 3H, *J*=7.3), 1.72 (qd, 2H, *J*=7.3, 7.4), 2.58 (dddd, 1H, *J*=2.6, 2.9, 6.2, −17.0), 3.06 (dddd, 1H, *J*=2.0, 2.6, 7.6, −17.0), 4.70 (ddd, 1H, *J*=6.2, 7.4, 7.6), 5.63 (dd, 1H, *J*=2.0, 2.6), 6.21 (dd, 1H, *J*=2.6, 2.9). ^{13}C NMR (50 MHz) 8.9, 29.0, 32.9, 78.6, 121.7, 134.7, 162.2. MS (EI) *m/z* (I%): 126 (21), 97 (100), 69 (48). IR (film, cm^{-1}): 2980, 2962, 1772, 1645.

4.3.4. 3-Methylene-5-ethoxycarbonyltetrahydrofuran-2-one (**19e**)

To a solution of the hydroxyester **18e** (216 mg, 1 mmol) in toluene (5 mL) was added a catalytic quantity of monohydrated PTSA (19 mg, 0.1 mmol). The reaction mixture was heated to reflux overnight and the water trapped in a Dean-Stark apparatus. The solution was quenched with water, extracted with CH_2Cl_2, dried over $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography (hexane/EtOAc 60:40) to give **19e** (168 mg, 99% yield). ^1H NMR (200 MHz, $CDCl_3$) 1.31 (t, 3H, *J*=7.2), 3.01 (dddd, 1H, *J*=2.4, 2.8, 4.7, −17.5), 3.28 (dddd, 1H, *J*=2.4, 2.8, 9.3, −17.5), 4.26 (q, 2H, *J*=7.2), 4.96 (dd, 1H, *J*=4.7, 9.3), 5.73 (dd, 1H, *J*=2.4, 2.8), 6.30 (dd, 1H, *J*=2.4, 2.8). ^{13}C NMR (50 MHz) 13.6, 30.7, 61.7, 72.5, 122.9, 131.5, 168.9, 169.3. MS (EI) *m/z* (I%): 170 (1), 141 (7), 124 (18), 97 (100), 69 (43), 41 (46). IR (film, cm^{-1}): 2981 (C–H), 1783, 1748, 1654. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.02; H, 6.20.

4.3.5. 5-(2,2′-Dimethyl-1,3-dioxolan-4-yl)-3-methylene-tetrahydro-2-furanone (**19f**)

(*R*,*S*) or (*S*,*R*) isomer: ^1H NMR (400 MHz) 1.26 (s, 3H), 1.34 (s, 3H), 2.83 (dddd, 1H, *J*=2.6, 2.9, 4.9, −17.5), 2.97 (dddd, 1H, *J*=2.6, 2.9, 8.1, −17.5), 3.80–3.85 (m, 1H), 3.95–4.10 (m, 2H), 4.34 (ddd, 1H, *J*=4.9, 6.9, 8.1), 5.59

(dd, 1H, J=2.6, 2.9), 6.17 (dd, 1H, J=2.6, 2.9). ^{13}C NMR (50 MHz) 24.9, 26.5, 29.8, 66.6, 76.6, 76.7, 110.1, 122.7, 133.6, 169.8. (*R*,*R*) or (*S*,*S*) isomer: ^{1}H NMR (400 MHz) 1.36 (s, 3H), 1.39 (s, 3H), 2.83 (m, 1H), 2.97 (dddd, 1H, J=2.6, 2.9, 8.1, −17.5), 3.70−4.10 (m, 3H), 4.35−4.50 (m, 1H), 5.56 (dd, 1H, J=2.6, 2.9), 6.16 (dd, 1H, J=2.6, 2.9). ^{13}C NMR (50 MHz) 25.3, 25.9, 29.5, 65.0, 75.1, 76.9, 110.2, 121.9, 133.8, 170.0. MS (EI) *m/z* (I%): 198 (1), 183 (24), 123 (16), 101 (41), 43 (100). IR (film, cm^{-1}): 2980−2920, 1774, 1667.

*4.4. General procedure for the synthesis of homoallylic alcohols **20** (typically on 1 mmol scale)*

The desired aldehyde (1 equiv) was added to a stirred solution of the desired phenylbornandiol 2-methoxycarbonyl-crotyl-boronate **15b** or **15c** (1 mmol) in dry toluene (2 M). Stirring was maintained at room temperature under inert atmosphere for one week (monitored by TLC). The reaction mixture was quenched with water and extracted three times with ether. After drying over $MgSO_4$, solvents were removed under reduced pressure. The residue was purified by flash chromatography, allowing separation of the chiral auxiliary (quantitative recovering yield) and the desired homoallylic alcohol (85−95% yield).

*4.4.1. syn-Methyl 4-hydroxy-3-methyl-2-methylene-4-phenylbutanoate (**20a**)*

^{1}H NMR (400 MHz) 0.97 (d, 3H, J=7.2), 2.71 (d, 1H, J=4.4), 3.06 (m, 1H), 3.71 (s, 3H), 4.64 (dd, 1H, J=8.0, 4.4), 5.60 (m≈d, 1H, J=0.8), 6.23 (m, 1H), 7.31 (m, 5H). ^{13}C NMR (50 MHz) 16.5, 43.5, 52.0, 78.1, 125.7, 126.6 (2C), 127.7, 128.2 (2C), 136.6, 142.9, 168.3. MS (EI) *m/z* (I%): 220 (7), 114 (100), 79 (47). IR (film, cm^{-1}): 3481, 3064, 3029, 2973, 1772, 1715.

*4.4.2. syn-Methyl 4-hydroxy-3-methyl-2-methylene-hexanoate (**20b**)*

^{1}H NMR (200 MHz) 0.93 (t, 3H, J=7.4), 1.06 (d, 3H, J=7.2), 1.43 (m, 2H), 2.20 (br s, 1H), 2.80 (m, 1H), 3.52 (m, 1H), 3.73 (s, 3H), 5.60 (s, 1H), 6.23 (s, 1H). ^{13}C NMR (50 MHz) 10.4, 12.8, 27.4, 40.0, 51.8, 74.6, 125.3, 143.2, 168.0. MS (CI, NH_3) *m/z*: 190, 173. IR (film, cm^{-1}): 3453, 2978, 2966, 1718, 1636.

*4.4.3. syn-1-Ethyl 5-methyl 2-hydroxy-3-methyl-4-methyl-enepentanedioate (**20c**)*

^{1}H NMR (400 MHz) 1.10 (d, 3H, J=7.2), 1.27 (t, 3H, J=7.2), 3.65 (m, 1H), 3.71 (s, 3H), 4.16 (dq, 1H, J=7.2, −10.8), 4.21 (dq, 1H, 7.2, −10.8), 4.45 (d, 1H, J=5.9), 5.73 (s, 1H), 6.30 (s, 1H). ^{13}C NMR (100 MHz) 13.9, 16.1, 38.6, 51.1, 61.1, 73.3, 126.9, 140.0, 169.0, 174.0. MS (CI, NH_3) *m/z* 234, 217.

*4.4.4. anti-Methyl 4-hydroxy-3-methyl-2-methylene-4-phenylbutanoate (**20d**)*

^{1}H NMR (200 MHz) 1.32 (d, 3H, J=6.7), 2.96 (m, 1H), 3.71 (s, 3H), 4.91 (d, 1H, J=7.6), 5.59 (dd, 1H, J=3.2, 1.1), 6.31 (ddd, 1H, J=3.2, 0.9, 0.9), 7.38 (m, 5H). ^{13}C NMR (50 MHz) 15.7, 24.7, 51.4, 85.8, 120.9, 125.8, 128.7 (4C), 136.6, 140.4, 170.0. MS (EI) *m/z* (I%) 220 (2), 114 (100), 107 (72), 79 (79). IR (film, cm^{-1}): 3481, 3040−3029, 2976, 2940, 1772, 1718, 1636.

*4.4.5. anti-1-Ethyl 5-methyl 2-hydroxy-3-methyl-4-methyl-enepentanedioate (**20f**)*

^{1}H NMR (400 MHz) 1.31 (t, 3H, J=7.2), 1.40 (d, 3H, J=6.9), 3.56 (m, 1H), 3.71 (s, 3H), 4.16 (dq, 1H, J=7.2, −10.8), 4.21 (dq, 1H, J=7.2, −10.8), 4.34 (d, 1H, J=6.3), 5.65 (d, 1H, J=2.5), 6.31 (d, 1H, J=2.8). ^{13}C NMR (100 MHz) 12.6, 18.6, 38.2, 51.1, 61.8, 71.9, 126.3, 140.9, 168.6, 174.0. MS (CI, NH_3) *m/z* 234, 217. IR (film, cm^{-1}): 3487, 2981, 1777, 1719, 1628.

*4.5. General procedure for the synthesis of α-methylene-γ-lactones **21***

A solution of the hydroxyester **20** (1 equiv) in dry THF (1 M solution) was added dropwise to a cooled (0 °C) suspension of sodium hydride (1.1 equiv) in THF (1 M solution). The reaction mixture was stirred for several minutes (monitored by TLC), then worked up with a phosphate buffered solution (pH=7). After extraction with ether (three times), drying over $MgSO_4$, and evaporation of the solvents, the residue was purified by flash chromatography on silica to give the desired lactone (90−99% yield).

*4.5.1. cis-4-Methyl-3-methylene-5-phenyl-dihydrofuran-2(3H)-one (**21a**)*

^{1}H NMR (400 MHz) 0.76 (d, 3H, J=7.1), 3.42 (m, 1H), 5.55 (d, 1H, J=2.6), 5.60 (d, 1H, J=8.1), 6.29 (d, 1H, J=3.2), 7.30−7.40 (m, 5H). ^{13}C NMR (50 MHz) 15.4, 38.9, 82.1, 121.7, 126.0 (2C), 128.4, 128.5 (2C), 136.6, 140.0, 170.1. MS (EI) *m/z* (I%) 188 (10), 143 (30), 82 (100), 54 (95). IR (film, cm^{-1}): 2968, 2932, 1769, 1752, 1663.

*4.5.2. cis-5-Ethyl-4-methyl-3-methylene-dihydrofuran-2(3H)-one (**21b**)*

^{1}H NMR (400 MHz) 1.03 (t, 3H, J=7.4), 1.23 (d, 3H, J=6.8), 1.68 (m, 2H), 2.68 (m, 1H), 3.93 (m, 1H), 5.52 (d, 1H, J=2.8), 6.20 (d, 1H, J=3.1). ^{13}C NMR (50 MHz) 9.5, 17.2, 27.7, 39.4, 86.2, 120.7, 141.1, 170.3.

*4.5.3. cis-Ethyl 3-methyl-4-methylene-5-oxo-tetrahydrofuran-2-carboxylate (**21c**)*

^{1}H NMR (400 MHz) 1.24 (t, 3H, J=7.1), 1.33 (d, 3H, J=6.9), 3.06 (m, 1H), 4.04 (q, 2H, J=7.1), 4.40 (d, 1H, J=5.9), 5.60 (m, 1H), 6.25 (m, 1H). ^{13}C NMR (50 MHz) 14.6, 18.7, 38.3, 66.8, 80.0, 122.8, 138.1, 169.0, 172.7.

*4.5.4. trans-4-Methyl-3-methylene-5-phenyl-dihydrofuran-2(3H)-one (**21d**)*

^{1}H NMR (400 MHz) 1.32 (d, 3H, J=6.7), 2.95 (m, 1H), 4.90 (d, 1H, J=7.6), 5.59 (d, 1H, J=2.9), 6.31 (d, 1H, J=3.2), 7.30−7.42 (m, 5H). ^{13}C NMR (100 MHz) 15.9,

43.4, 85.9, 121.0, 125.9 (2C), 128.7, 128.8 (2C), 136.4, 140.5, 170.0. MS (EI) *m/z* (I%) 188 (6), 143 (23), 82 (100), 54 (89). IR (film, cm^{-1}): 3068, 3035, 2968, 2932, 1766, 1693.

*4.5.5. trans-5-Ethyl-4-methyl-3-methylene-dihydrofuran-2(3H)-one (**21e**)*

^1H NMR (200 MHz) 1.05 (t, 3H, J=7.4), 1.25 (d, 3H, J=6.8), 1.68 (m, 2H), 2.70 (m, 1H), 3.95 (m, 1H), 5.55 (d, 1H, J=2.7), 6.23 (d, 1H, J=3.1). ^{13}C NMR (50 MHz) 9.2, 17.0, 27.4, 39.2, 86.0, 120.4, 140.9, 170.0. MS (EI) *m/z* (I%) 140 (1), 111 (33), 82 (100), 54 (59). IR (film, cm^{-1}): 2968, 2935, 2881, 1762, 1685.

*4.5.6. trans-Ethyl 3-methyl-4-methylene-5-oxo-tetrahydrofuran-2-carboxylate (**21f**)*

^1H NMR (400 MHz) 1.23 (t, 3H, J=7.1), 1.36 (d, 3H, J=6.9), 3.12 (m, 1H), 4.20 (q, 2H, J=7.1), 4.44 (d, 1H, J=6.0), 5.61 (m, 1H), 6.24 (m, 1H). ^{13}C NMR (50 MHz) 14.0, 18.7, 38.3, 62.1, 79.4, 123.0, 137.9, 168.9, 172.7.

*4.5.7. trans-5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-methyl-3-methylene-dihydrofuran-2(3H)-one (**21g**)*

^1H NMR (400 MHz) 1.33 (d, 3H, J=6.9), 1.35 (s, 3H), 1.44 (s, 3H), 3.01 (m, 1H), 3.88–4.19 (m, 4H), 5.61 (d, 1H, J=2.6), 6.26 (d, 1H, J=3.0). ^{13}C NMR (50 MHz) 19.1, 24.9, 26.6, 37.2, 66.8, 77.1, 83.9, 110.0, 122.0, 140.0, 169.6. MS (EI) *m/z* (I%) 213 (1), 197 (87), 101 (81), 43 (100). IR (film, cm^{-1}): 2940, 2901, 1770, 1726.

*4.6. General procedure for the synthesis of ethylglyoxylate derived imines **23a–c** (typically on 10 mmol scale)*

To a 0.5 M solution of ethylglyoxylate (1 equiv) in dry ether was added $MgSO_4$. A solution of the corresponding amine (1 equiv) in ether (0.5 M) was then added. The mixture was stirred overnight under inert atmosphere at room temperature before filtration and removal of the solvent. When necessary, the imine was purified by flash chromatography on neutralized silica (90% yield).

*4.6.1. Ethyl N-tert-butyl-imino-ethanoate (**23a**)*

^1H NMR (200 MHz) 1.23 (s, 9H), 1.30 (t, 3H, J=7.2), 4.30 (q, 2H, J=7.2), 7.60 (s, 1H). ^{13}C NMR (50 MHz) 13.9 (3C), 28.7, 61.3, 65.5, 148.5, 171.3. MS (EI) *m/z* (I%): 157 (1), 142 (2), 84 (15), 57 (100), 29 (18). IR (film, cm^{-1}): 2972–2874, 1752, 1748, 1648.

*4.6.2. Ethyl N-cyclohexyl-imino-ethanoate (**23b**)*

^1H NMR (200 MHz) 1.00–2.00 (m, 10H), 1.35 (t, 3H, J=7.2), 3.27 (m, 1H), 4.35 (q, 2H, J=7.2), 7.73 (s, 1H). ^{13}C NMR (50 MHz) 14.2, 24.4 (2C), 25.4, 33.5 (2C), 61.7, 69.8, 151.4, 164.4. MS (EI) *m/z* (I%) 183 (1), 154 (11), 137 (14), 100 (30), 83 (100). IR (film, cm^{-1}): 2984–2857, 1747, 1723, 1646, 1242.

*4.6.3. Ethyl N-p-methoxybenzyl-imino-ethanoate (**23c**)*

^1H NMR (200 MHz) 1.36 (t, 3H, J=7.2), 3.81 (s, 3H), 4.34 (q, 2H, J=7.2), 4.81 (d, 2H, J=1.7), 6.80–7.20 (m, 4H), 7.69 (t, 1H, J=1.7). ^{13}C NMR (50 MHz) 14.1, 55.3, 61.8, 63.9, 114.2 (2C), 129.9 (2C), 153.9, 157.5 (2C), 171.3. MS (EI) *m/z* (I%) 221 (15), 192 (17), 148 (53), 121 (100). IR (film, cm^{-1}): 2978, 2936, 2836, 1745, 1634.

*4.7. General procedure for the syntheis of silylated imines **23d–23f** (typically on 15 mmol scale)*

To a solution of hexamethyldisilylazane (1 equiv) in dry THF (0.25 M) was added dropwise at room temperature a 2 M *n*-BuLi solution in hexanes (1.25 equiv). The reaction mixture was stirred at room temperature for 1 h before being cooled to 5 °C. The freshly distilled aldehyde (1 equiv) was added dropwise and after 1 h stirring at 5 °C, the reaction mixture was filtered over Celite under inert atmosphere and then over a classical filter to remove the salts. Evaporation of the solvents led to the crude imine used for allylation reaction (70% yield).

*4.7.1. N-Trimethylsilyl benzylidenamine (**23d**)*

^1H NMR (200 MHz) 0.20 (s, 9H), 7.38 (m, 3H), 7.74 (m, 2H), 8.92 (s, 1H). ^{13}C NMR (50 MHz) −1.2 (3C), 128.4 (2C), 128.5, 131.2 (2C), 138.8, 168.5. MS (EI) *m/z* (I%) 177 (44), 162 (100), 135 (27), 73 (53), 59 (81), 45 (14).

*4.7.2. N-Trimethylsilyl-3,4,5-trimethoxybenzylidenamine (**23e**)*

^1H NMR (200 MHz) 0.25 (s, 9H), 3.74 (s, 3H), 3.93 (s, 6H), 7.06 (s, 2H), 8.86 (s, 1H). ^{13}C NMR (50 MHz) −1.3 (3C), 56.0 (2C), 60.6, 131.5, 134.3 (2C), 140.7, 153.2, 157.8, 168.5.

*4.7.3. N-Trimethylsilyl-4-chlorobenzylidenamine (**23f**)*

^1H NMR (400 MHz) 0.25 (s, 9H), 7.40 (d, 2H, J=7.0), 7.73 (d, 2H, J=7.0), 8.92 (s, 1H). ^{13}C NMR (50 MHz) −1.3 (3C), 128.8 (3C), 129.6 (2C), 137.2, 166.8. MS (EI) *m/z* (I%) 211–213 (1), 196–198, 169–171, 139–141, 73 (68), 59 (100).

4.8. General procedure for the synthesis of homoallylic amines

The desired imine (1.1 mmol) in dry toluene (0.5 mL) was added to a solution of 2-ethoxycarbonylallylboronate **15a** (240 mg, 1 mmol) in toluene (0.5 mL). The reaction mixture was stirred under inert atmosphere at room temperature for two weeks (monitored by TLC), before being hydrolyzed with water. After extraction with ether, drying over $MgSO_4$ and evaporation of the solvents, the residue was purified by flash chromatography, allowing separation of the chiral auxiliary **14** (quantitative recovering yield) and the desired homoallylic amine (73% yield).

*4.8.1. Ethyl N-cyclohexylamine-2-methylenepenta-1,5-dioate (**24b**)*

^1H NMR (400 MHz) 0.80–2.00 (m, 10H), 1.27 (t, 3H, J=7.1), 1.33 (t, 3H, J=7.1), 2.37 (m, 1H), 2.51 (dd, 1H, J=7.5, −13.7), 2.69 (ddd, 1H, J=0.9, 7.1, −13.7), 3.64 (dd,

1H, J=7.1, 7.5), 4.14 (q, 2H, J=7.1 Hz), 4.22 (q, 2H, J=7.1), 5.60 (dd, 1H, J=0.9, 1.5), 6.19 (d, 1H, J=1.5). ^{13}C NMR (50 MHz) 14.1 (2C), 24.5, 24.8, 25.9, 32.7, 34.0, 36.7, 55.0, 57.5, 60.4, 60.6, 126.9, 137.0, 165.6, 175.2. MS (EI) *m/z* (I%) 298 (100), 224 (15), 184 (8), 96 (5), 55(6), 29 (47). IR (film, cm^{-1}): 2982, 2940, 1742, 1640. Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15. Found: C, 64.46; H, 9.09.

*4.8.2. 1-Cyclohexyl-5-ethoxycarbonyl-3-methylene pyrrolidin-2-one (**25b**)*

To a solution of the homoallylic amine **24b** (297 mg, 1 mmol) in toluene (5 mL) was added a catalytic quantity of PTSA (19 mg, 0.1 mmol). The reaction mixture was heated to reflux overnight and the water trapped in a Dean-Stark apparatus. The solution was quenched with water, extracted with CH_2Cl_2, and dried over $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography to give **25b** (93% yield). ^{1}H NMR (200 MHz) 1.00–1.83 (m, 10H), 1.29 (t, 3H, J=7.1), 2.69 (dddd, 1H, J=2.1, 2.1, 4.2, −17.0), 3.00 (dddd, 1H, J=3.0, 3.0, 9.4, −17.0), 3.96 (tt, 1H, J=3.7, 12.0), 4.17 (qd, 1H, J=7.1, −14.2), 4.23 (qd, 1H, J=7.1, −14.2), 4.24 (dd, 1H, J=4.2, 9.4), 5.33 (m, 1H), 6.01 (m, 1H). ^{13}C NMR (50 MHz) 14.0, 25.5, 25.6, 29.2, 30.0, 30.3, 30.4, 52.9, 55.0, 61.6, 115.7, 137.9, 168.0, 172.9. MS (EI) *m/z* (I%): 251 (14), 178 (100), 96 (91), 53 (19). IR (film, cm^{-1}): 2975, 2932, 1740, 1734, 1669.

*4.9. General procedure for the synthesis of lactams **25***

The desired imine (2 equiv) was added to a solution of 2-ethoxycarbonylallylboronate **15a** (1 equiv) in dry toluene (2 M). Stirring was maintained at room temperature under inert atmosphere for one week (monitored by TLC). The reaction mixture was quenched with water and extracted with ether. When homoallylic amine remained, an acido-basic treatment of the crude mixture (HCl/NaOH) led to completion of the cyclization. After drying of the organic layer over $MgSO_4$ and removal of the solvents, the residue was chromatographed, allowing separation of the chiral auxiliary **14** (quantitative recovering yield) and the desired lactam (58–92% yield).

*4.9.1. (−)-(R)-5-Ethoxycarbonyl-3-methylene-1-(4-methoxybenzyl) pyrrolidin-2-one (**25c**)*

^{1}H NMR (400 MHz) 1.18 (t, 3H, J=7.1), 2.68 (dddd, 1H, J=2.2, 2.6, 3.4, −17.2), 2.89 (dddd, 1H, J=2.2, 2.6, 9.4, −17.2), 3.72 (s, 3H), 3.90 (dd, 1H, J=3.4, 9.4), 4.00 (d, 1H, J=−14.7), 4.08 (qd, 2H, J=7.1, 1.8), 5.02 (d, 1H, J=−14.7), 5.32 (dd, 1H, J=2.2, 2.2), 6.01 (dd, 1H, J=2.6, 2.6), 6.77 (d, 2H, J=8.6), 7.08 (d, 2H, J=8.6). ^{13}C NMR (50 MHz) 13.8, 28.8, 55.0, 55.5, 61.3, 74.6, 113.9, 116.5 (2C), 127.2, 129.8 (2C), 137.0, 159.1, 167.7, 170. MS (EI) *m/z* (I%): 289 (8), 216 (10), 121 (100). IR (film, cm^{-1}): 3470, 2981, 2937, 1740, 1734, 1669. $[\alpha]_D$ −85.2 (*c* 2.03, $CHCl_3$).

*4.9.2. (−)-(R)-3-Methylene-5-phenyl pyrrolidin-2-one (**25d**)*

Mp: 191 °C, ^{1}H NMR (400 MHz) 2.68 (dddd, 1H, J=2.7, 2.7, 4.7, −17.1), 3.30 (dddd, 1H, J=2.4, 2.4, 8.2, −17.1), 4.75 (dd, 1H, J=4.7, 8.2), 5.37 (m, 1H), 6.04 (dd, 1H, J=2.4, 2.7), 6.55 (br s, 1H), 7.2–7.8 (m, 5H). ^{13}C NMR (100 MHz) 36.8, 54.8, 116.6, 125.7 (2C), 128.0, 129.0 (2C), 138.7, 142.6, 170.8. MS (EI) *m/z* (I%): 173 (69), 144 (20), 104 (33), 68 (49), 40 (100). IR (film, cm^{-1}): 3220, 1690, 1665, 1640. $[\alpha]_D$ −15.0 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40. Found: C, 76.38; H, 6.41.

*4.9.3. (−)-(R)-3-Methylene-5-(3,4,5-trimethoxyphenyl) pyrrolidin-2-one (**25e**)*

Mp: 141 °C, ^{1}H NMR (400 MHz) 2.69 (dddd, 1H, J=2.4, 2.8, 4.9, −17.2), 3.30 (dddd, 1H, J=2.4, 2.4, 8.1, −17.2), 3.83 (s, 3H), 3.85 (s, 6H), 4.69 (dd, 1H, J=4.9, 8.1), 5.40 (m, 1H), 6.08 (dd, 1H, J=2.7, 2.4), 6.29 (br s, 1H), 6.48 (s, 2H). ^{13}C NMR (50 MHz) 36.7, 55.0, 56.0 (2C), 60.7, 102.4 (2C), 116.3, 138.3, 138.8 (3C), 153.5, 170.8. MS (EI) *m/z* (I%): 263 (100), 232 (62), 204 (13), 40 (24), 28 (24). IR (film, cm^{-1}): 3158, 3074, 2885, 1704, 1666. $[\alpha]_D$ −20.0 (*c* 1.20, $CHCl_3$).

*4.9.4. (−)-3-Methylene-5-p-chlorophenyl pyrrolidin-2-one (**25f**)*

^{1}H NMR (400 MHz) 2.64 (dddd, 1H, J=2.3, 2.7, 4.6, −17.2), 3.31 (dddd, 1H, J=2.3, 2.7, 8.2, −17.2), 4.74 (dd, 1H, J=4.6, 8.2), 5.40 (dd, 1H, J=2.3, 2.3), 6.07 (dd, 1H, J=2.7, 2.7), 6.73 (s, 1H), 7.22 (ddd, 2H, J=2.0, 2.4, 8.5), 7.34 (ddd, 2H, J=2.0, 2.4, 8.5). ^{13}C NMR (50 MHz) 36.7, 54.2, 116.9, 127.1 (2C), 129.1 (2C), 133.6, 138.3, 141.2, 170.8. MS (EI) *m/z* (I%): 209–207 (63), 172 (100), 138 (29), 68 (74). IR (film, cm^{-1}): 3237, 3090, 2925, 1697, 1676. $[\alpha]_D$ −21.9 (*c* 0.64, $CHCl_3$).

*4.9.5. 1,4-Dimethyl-3-methylene-5-phenylpyrrolidin-2-one (**26**)*

^{1}H NMR (200 MHz) 1.26 (d, 3H, J=7.0), 2.71 (m, 1H), 2.74 (s, 3H), 3.96 (d, 1H, J=5.1), 5.29 (d, 1H, J=2.4), 6.07 (d, 1H, J=2.8), 7.3 (m, 5H). ^{13}C NMR (50 MHz) 18.0, 28.8, 42.3, 70.5, 114.7, 127.0 (2C), 128.6, 129.3 (2C), 140.1, 145.2, 168.7. MS (EI) *m/z* (I%): 201 (100), 124 (69). $[\alpha]_D$ −21.0 (*c* 1.50, $CHCl_3$).

*4.9.6. 1,4-Dimethyl-3-methylene-5-phenylpyrrolidin-2-one (**27**)*

^{1}H NMR (200 MHz) 0.75 (d, 3H, J=7.1), 2.82 (s, 3H), 3.28 (m, 1H), 4.60 (d, 1H, J=8.3), 5.22 (d, 1H, J=2.9), 6.07 (d, 1H, J=3.1), 7.00 (m, 2H), 7.30 (m, 3H). ^{13}C NMR (50 MHz) 14.2, 28.8, 35.6, 66.5, 114.5, 126.9, 127.4, 128.1, 128.6 (2C), 136.9, 144.6, 168.8. MS (EI) *m/z* (I%): 201 (100), 124 (69). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.55; H, 7.17. $[\alpha]_D$ −59.0 (*c* 0.32, $CHCl_3$).

Acknowledgements

We thank the 'Centre National de la Recherche Scientifique', the 'Ministère de l'Education Nationale de la Recherche

et de la Technologie' for a doctoral fellowship for I.C. and the 'Université de Nantes' for supporting this work.

References and notes

1. For reviews on α-methylene-γ-lactones, see: (a) Hoffmann, H. M.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110; (b) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43–72; (c) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rosalski, M. *J. Med. Chem.* **2005**, *48*, 3516–3521.
2. (a) Kupchan, S. M.; Fessler, D. C.; Eakin, M. A.; Giacobbe, T. J. *Science* **1970**, *168*, 376–378; (b) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147–1152.
3. Howie, G. A.; Stamos, I. K.; Cassady, J. M. *J. Med. Chem.* **1976**, *19*, 309–313.
4. (a) Cardellina, J. H.; Moore, R. E. *Tetrahedron Lett.* **1979**, *20*, 2007–2010; (b) Tronchet, J. M.; Gentile, B. *Helv. Chim. Acta* **1979**, *62*, 977–984; (c) Kornet, M. J. *J. Heterocycl. Chem.* **1985**, 129–130.
5. For reviews on the synthesis of α-methylene-γ-lactones, see: (a) Grieco, P. A. *Synthesis* **1975**, 67–82; (b) Petragnani, N.; Ferraz, H. M.; Silva, G. V. *Synthesis* **1986**, 157–183.
6. (a) Tanaka, K.; Yoda, H.; Isobe, Y.; Kaji, A. *Tetrahedron Lett.* **1985**, *26*, 1337–1340; (b) Tanaka, K.; Yoda, H.; Isobe, A.; Kaji, A. *J. Org. Chem.* **1986**, *51*, 1856–1866; (c) Nishitani, K.; Yamakawa, K. *Tetrahedron Lett.* **1991**, *32*, 387–390; (d) Csuk, R.; Schröder, C.; Hutter, S.; Mohr, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1411–1429.
7. (a) Chemler, S. R.; Roush, W. R. *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chapter 11, pp 403–490; (b) Kennedy, J. W. J.; Hall, D. G. *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005, Chapter 6, pp 241–277.
8. (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; (c) Chataigner, I.; Lebreton, J.; Zammattio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719–3722; (d) Chataigner, I.; Zammattio, F.; Lebreton, J.; Villiéras, J. *Synlett* **1998**, 275–276; (e) Draillard, K.; Lebreton, J.; Villiéras, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4281–4284.
9. (a) Kennedy, J. M. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898–899; (b) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066–6069; (c) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481–484; (d) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807–5809.
10. (a) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540; (b) Tsuda, T.; Yoshida, T.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 1624–1627; (c) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037–1040.
11. (a) Herold, T.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 768–769; (b) Herold, T.; Schrott, U.; Hoffmann, R. W. *Chem. Ber.* **1981**, *114*, 359–374; (c) Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375–383.
12. Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. J. *Tetrahedron Lett.* **1994**, *35*, 5109–5112.
13. (a) Reetz, M. T.; Zierke, T. *Chem. Ind.* **1988**, 663–664; (b) Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 109–110.
14. (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587; (b) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412–4428; (c) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808–12809; (d) Elford, T. G.; Arimura, Y.; Yu, S. H.; Hall, D. G. *J. Org. Chem.* **2007**, *72*, 1276–1284.
15. (a) Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Org. Lett.* **2006**, *8*, 3877–3879; (b) Ramachandran, P. V.; Pratihar, D. *Org. Lett.* **2007**, *9*, 2087–2090.
16. Kabalka, G. W.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 7325–7328.
17. (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkorec, M.; Baldwin, J. J.; Christy, M. E.; Ponticello, S. L.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374; (b) Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villiéras, J. *Tetrahedron Lett.* **1998**, *39*, 1759–1762.
18. Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109–4117.
19. Double asymmetric induction using chiral units on both the boron atom (phenylbormanediol **14**) and the ester group (8-(phenyl)mentoxy) have led to enantioselectivities >95%. See Ref. 9a.
20. Bravo, P.; Resnati, G.; Viani, F. *Tetrahedron Lett.* **1985**, *26*, 2913–2916.
21. (a) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H. J. *Carbohydr. Res.* **1983**, *123*, 320–325; (b) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966–3979; (c) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422–3424; (d) Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117–4126.
22. Schmidt, C. R.; Bradley, D. A. *Synthesis* **1992**, 587–590.
23. The oxidative cleavage involved in the second step was performed in the presence of potassium hydrogenocarbonate in order to avoid the formation of by-products responsible for the polymerization of the generated aldehydes. See: Jackson, D. J. *Synth. Commun.* **1988**, *18*, 337–341.
24. Stereochemistry was assigned on the basis of NMR spectrometry data collected on the corresponding lactone derivatives.
25. (a) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306–307; (b) Garcia, J.; Kim, B. M.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831–4832; (c) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535–1538; (d) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Haltermann, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348; (e) Sato, M.; Yamamoto, Y.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7071–7074.
26. Lactone derivatives were obtained as major compounds in several cases. As the enantioselectivity of the process was evaluated by ^{1}H NMR spectrometry of the *O*-methylmandelic esters derived from homoallylic alcohol precursors, the condensation was prematurely quenched in the required cases in order to dispose of sufficient amount of alcohols **20d–g** to effect the derivatization. We assume, here, that the reaction is under kinetic control, as reported with unfunctionalized derivatives. See: Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123–130.
27. (a) Lambert, F.; Kirschleger, B.; Villiéras, J. *J. Organomet. Chem.* **1991**, *406*, 71–86; (b) Fouquet, E.; Gabriel, A.; Maillard, B.; Peyrere, M. *Bull. Soc. Chim. Fr.* **1995**, *132*, 590–598.
28. (a) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979–3982; (b) Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 7167–7172.
29. (a) Corey, E. J.; Rohde, J. J.; Fisher, A.; Azimiora, M. *Tetrahedron Lett.* **1997**, *38*, 33–36; (b) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37–40; (c) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 1699–1702.
30. (a) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131–1132; (b) Wuts, P. G. M.; Jung, Y. W. *J. Org. Chem.* **1991**, *56*, 365–372; (c) See Ref. 13b; (d) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946; (e) El-Shehawy, A. A.; Omara, M. A.; Ito, K.; Itsuno, S. *Synlett* **1998**, 367–368; (f) Itsuno, S.; Watanabe, K.; Matsumoto, T.; Kuroda, S.; Yokoi, A.; El-Shehawy, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2011–2016; (g) Sebelius, S.; Szabo, K. J. *Eur. J. Org. Chem.* **2005**, 2539–2547; (h) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551–5553; (i) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691; (j) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646–9647.
31. Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3562–3564.
32. (a) Hart, D. J.; Kanai, K.-I.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289–294; (b) Cainelli, G.; Giacomini, D.; Galetti, P. *Synlett* **1996**, 657–658; (c) Cainelli, G.; Giacomini, D.; Galetti, P. *Synthesis* **1997**, 886–890.
33. (a) Kornet, M. J. *J. Pharm. Sci.* **1979**, 350–353; (b) Belaud, C.; Roussakis, C.; Letouneux, Y.; El-Alami, N.; Villiéras, J. *Synth. Commun.* **1985**, *15*,

1233–1243; (c) Klutchko, S.; Hoefle, M. L. *J. Med. Chem.* **1981**, *24*, 104–109.
34. Nyzam, V.; Belaud, C.; Zammattio, F.; Villiéras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835–1843.
35. (a) Evans, D. A.; Nilson, J. V.; Taber, T. R. *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley-Interscience: New York, NY, 1982; Vol. 13, p 1; (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115–3121; (c) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778–7786; (d) Li, Y.; Paddon-Row, P.-R.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481–493; (e) Goodma, J. M.; Kahn, S. D.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3295–3303; (f) Bernardi, A.; Gennari, C.; Raimondi, L.; Villa, M. B. *Tetrahedron* **1997**, *53*, 7705–7714.