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Synthesis of Tertiary and Quaternary Stereogenic Centers: A Diastereoselective Tandem Reaction Sequence Combining Mukaiyama and Free Radical-Based Allylation

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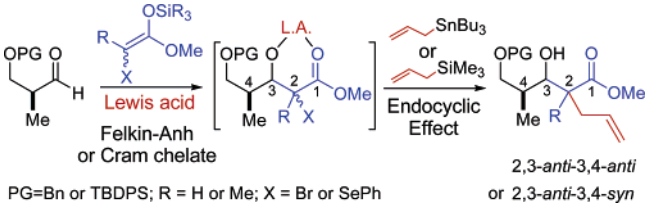
Received July 29, 2004



Reported herein is a strategy employing a Mukaiyama reaction in tandem with a free radical-based allyl transfer reaction for the elaboration of functionalized tertiary and quaternary centers. The appropriate choice of alcohol-protecting group on the starting α-methyl-*β*-hydroxyaldehyde and the nature of the Lewis acid used in the Mukaiyama reaction provided access to 3,4-*anti* and 3,4-*syn* aldolization products, precursors of the free-radical allylation reaction. After migration or exchange of the Lewis acid, the allyl transfer reaction with allyltributylstannane is then performed by taking advantage of the *endocyclic effect*, leading to the 2,3-anti relative stereochemistry. Importantly, ^{13}C NMR studies of the chelated intermediates are also reported and provide additional support for the *endocyclic effect*. In some cases, the remarkable reactivity of the aluminum-based Lewis acids allowed the use of allyltrimethylsilane, an interesting reagent from an ecological standpoint. The isolation of a key intermediate is also indicative of an atom transfer mechanism when the silicon-based reagent is employed.

Introduction

The synthesis of stereogenic centers on acyclic molecules is a topic of great importance in organic chemistry. Of particular interest is the asymmetric construction of quaternary centers[1] bearing substituents (e.g., ester, ketone, allyl groups) that could allow for a variety of chemical transformations with inter- and intramolecular processes. The stereocontrolled formation of isomers of *β*-hydroxy-α,α-disubstituted ester motifs, as in structures **1** and **2** (Figure 1) from a common acyclic precursor, is in this regard an interesting objective.

Recent notable contributions to the synthesis of such molecules illustrate the difficulties associated with these systems. For example, aldol-based strategies have been limited by the difficulties of accessing tetrasubstituted enolates of defined stereochemistry. It is therefore important to note the contributions of Gleason, who has successfully developed an aldolization method leading to *syn*-*β*-hydroxy-α,α-dialkyl esters **2** using α,α-disubstituted thioglycolates.[2] Similarly, one should note that Tanaka

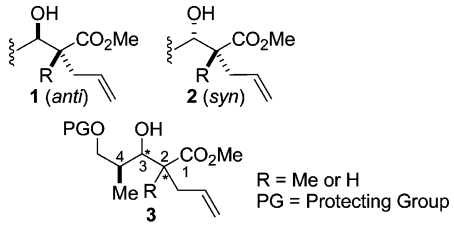


FIGURE 1. *β*-Hydroxy-α,α-disubstituted ester motifs.

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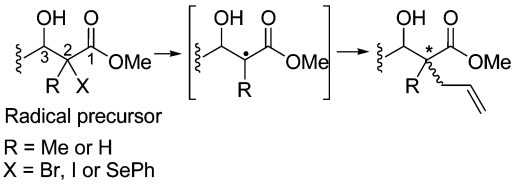
(1) For excellent reviews on the synthesis of quaternary centers, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem.* **1998**, *110*, 402. (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

10.1021/jo048687j CCC: $30.25
Published on Web 12/31/2004

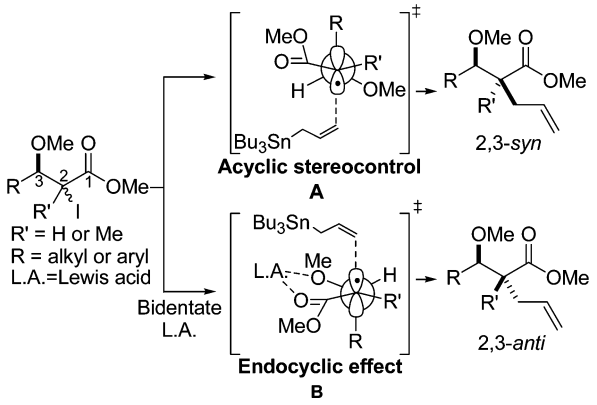
SCHEME 1



got access to *syn* and *anti* motifs based on the regioselective opening of chiral epoxides by an allyltitanium reagent, albeit in modest yield.[3] Finally, one should remember the Frater anionic alkylation,[4] although the low yields obtained in the case of quaternary centers and the strong basic conditions required can be limiting factors particularly when polyfunctionalized substrates are considered. A new approach that could potentially lead to either isomer should therefore complement the existing methodologies. In this regard, we embarked on the synthesis of molecules of general formula **3** in the context of this study.

We hypothesized that novel strategies to the synthesis of quaternary centers might capitalize on the intrinsically high reactivity of free radicals[5] as described in Scheme 1, wherein a carbon−carbon bond would be formed by reacting such intermediates with an appropriate radical trap.[6] We and others have shown that diastereoselectivity could be achieved with acyclic radicals, provided certain conditions.[5] Of particular interest to us is the reactivity of carbon-centered free radicals, flanked on one side by a stereogenic center bearing a heteroatom and on the other side by an ester, in carbon−carbon bond forming reactions. We have shown that tertiary and secondary iodides react with allyltributylstannane, whether in the presence of AIBN or Et_3B as initiator, to give the corresponding quaternary or tertiary centers in good yield, the major product having a 2,3-*syn* stereochemistry (Scheme 2).[7] Minimization of the allylic 1,3-strain[8] and intramolecular dipoles[9] and the stabilization of the

SCHEME 2



SOMO by σ-donation[10] in these planar radicals, as in transition state **A**, were found to be the controlling factors at the origin of the noted diastereoselectivity (termed acyclic stereocontrol).

Conversely, the addition of bidentate Lewis acids such as $MgBr_2{\cdot}OEt_2$ led to a reversal of stereoselectivity, the 2,3-*anti* product now being favored in excellent ratio and yield.[11,12] At the origin of the diastereoselectivity is the temporary entrapment of the carbon-centered radical in a ring formed through chelation of the Lewis acid by the ester carbonyl and the etheral oxygen at C-3 as in transition state **B** (termed *endocyclic effect*).[11] Of equal interest was the observation that the rate of the allylation reaction in the presence of a Lewis acid was significantly enhanced. The reactions were then performed at −78 °C whether iodide, bromide, or phenylselenide precursors were employed, as opposed to reactions in the absence of a Lewis acid that required being performed in refluxing hexanes. We took advantage of this apparent increase in reactivity of complexed free radicals in atom or group transfer reactions. Indeed β-alkoxy-α-halo esters, which were reacting very slowly with allyltrimethylsilane, became very good substrates when appropriate Lewis acids were added.[13] Collectively, these results suggested that the stereochemistry at C-2 (Scheme 2) of our targeted series could be controlled by using free radical intermediates. Thus, free radicals could be used to create the terminal quaternary center depicted in Figure 1, which possesses two substituents at different oxidation states (e.g. an alkene and an ester) that could be easily modified.

As a first approach to β-hydroxy-α,α-disubstituted esters, we decided to evaluate a substrate control-based strategy. Therefore, a reaction remained to be identified, which would utilize, for instance, a stereocenter at C-4 to induce the hydroxy at C-3 (Figure 1). The strategy proposed herein is based on the use of a Mukaiyama aldol reaction[14] in tandem with a free radical-based allylation, as described in Scheme 3. In this context, the radical

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(9) (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845. (b) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912. (c) Giese, B.; Bulliard, M.; Wetterich, F.; Zeitz, H. G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* **1993**, *34*, 5885.
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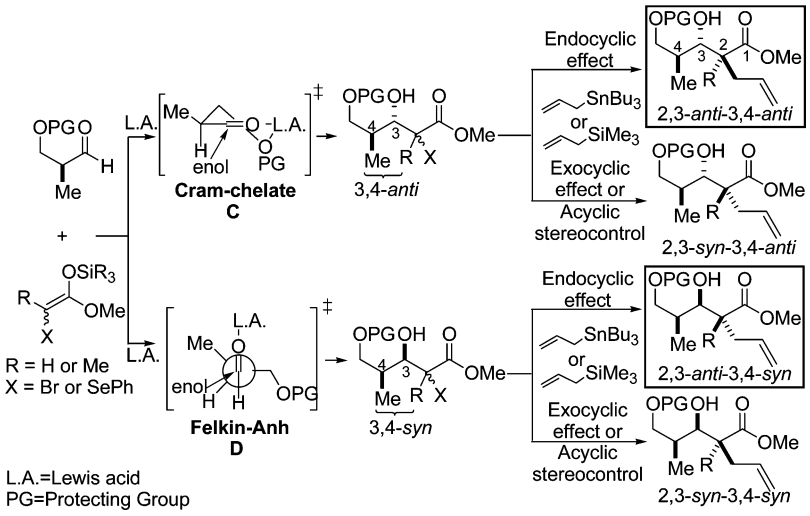
(13) (a) Reference 11b. (b) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1996**, *118*, 12528.

SCHEME 3



precursors would result from the addition of a mixture of heterosubstituted enoxysilanes (*Z*/*E*) on an activated α-methyl-*β*-alkoxyaldehyde. Activation of the aldehyde with bidentate Lewis acids would provide the 3,4-*anti* stereoisomer via a Cram chelate transition state (as in **C**), whereas the use of monodentate Lewis acids would yield the 3,4-*syn* adducts as predicted by the Felkin-Anh model (as in **D**).[15] As the C-2 stereochemistry of the tertiary halides or selenides was presumed to have little importance in the free radical step, we planned to use *E*/*Z* mixtures of enoxysilanes in the Mukaiyama step, thus avoiding the stumbling block (i.e., the stereoselective synthesis of tetrasubstituted enolates) that has plagued the "aldol" approach (vide supra). As discussed before, the Lewis acid will play a crucial role in determining the relative stereochemistry at C-2 during the allylation step, via the endocyclic effect or the acyclic stereocontrol. Therefore, the efficiency of this strategy relies on the appropriate selection of the Lewis acid for both chemical steps. Central to the present study is the use of free radical-based allylations under the control of the *endocyclic effect* on precursors originating from Cram chelate or Felkin-Anh-driven Mukaiyama reactions (Scheme 3).[16] We would therefore expect that the allyl substituent at the quaternary center, in this first study, be *anti* to the hydroxyl group at C-3 (Scheme 3), which relative stereochemistry to C-4 will vary depending on the conditions used for the aldol reaction. A secondary objective, yet important from a synthetic standpoint, will be the formation of tertiary centers[17] following the same strategy while using trisubstituted enoxysilanes.[18]

Results and Discussion

The Mukaiyama Reaction. For the first part of our study, we selected to react *β*-benzyloxyaldehyde **4**[19] with tri- or tetrasubstituted enoxysilanes bearing a phenylselenide substituent such as **6** and **7**. For reasons stated before, no efforts were invested in a stereoselective synthesis of these reagents. Bidentate Lewis acids were used to promote the addition of enoxysilanes to aldehydes to yield 3,4-*anti* adducts through the intermediacy of a Cram chelate complex. Our first attempts with Et_2BOTf[20] and Me_2AlCl[21] were unsuccessful (Table 1, entries 1 and 2). However, excellent results were observed with $TiCl_4$ and $MgBr_2{\cdot}OEt_2$, both in terms of yield and stereoselectivity, the *anti* products being favored whether the trisubstituted enoxysilane **6** (entries 3 and 6) or the tetrasubstituted enoxysilane **7** (entries 9 and 10) were used. Interestingly, specific experimental conditions had to be present. For instance, the order of addition of the reactants was found to be important. Indeed, precomplexing the aldehyde with the Lewis acid prior to the addition of the enoxysilanes **6** or **7** afforded, as stated

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(15) Open or extended transition state models have provided the best rationalization for the stereochemical results of the Mukaiyama reaction. (a) Nakamura, E.; Yamago, S.; Machii, D.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 2207. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032.

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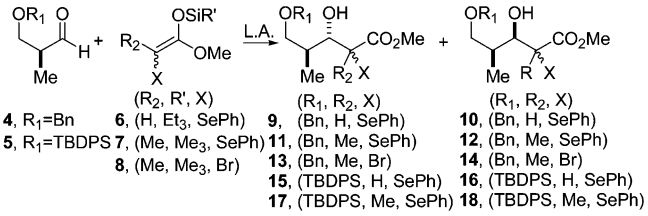
(18) A part of this work has already been reported. See ref 16a.

(19) For the preparation of aldehyde **4**, see: Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(20) Et_2BOTf was prepared following the procedure described by: Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(21) Good Cram-chelate selectivity has been observed with aldehyde **4** and Me_2AlCl; see: (a) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457. (b) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840.

TABLE 1. Mukaiyama Reactions[a]

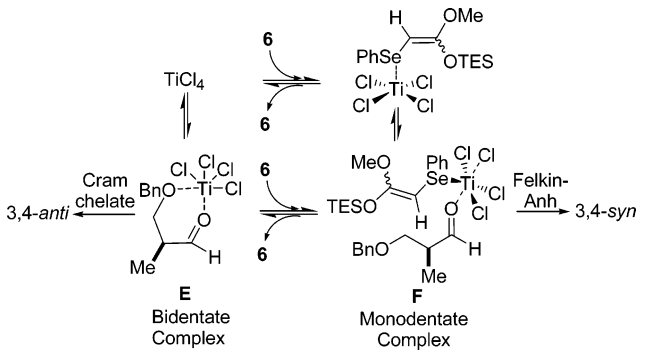


4, R_1=Bn ((R_2, R', X)) **6**, (H, Et_3, SePh) ((R_1, R_2, X)) **9**, (Bn, H, SePh) **10**, (Bn, H, SePh)
5, R_1=TBDPS **7**, (Me, Me_3, SePh) **11**, (Bn, Me, SePh) **12**, (Bn, Me, SePh)
8, (Me, Me_3, Br) **13**, (Bn, Me, Br) **14**, (Bn, Me, Br)
15, (TBDPS, H, SePh) **16**, (TBDPS, H, SePh)
17, (TBDPS, Me, SePh) **18**, (TBDPS, Me, SePh)

entry	**4** or **5** (enol)	Lewis acid (equiv)	products (ratio)[b] 3,4-(*anti:syn*)	2,3-(*anti:syn*)	yield (%)
1	**4** (**6**)	Et_2BOTf (1.2)	**9**:**10** (1:3)	ND	74
2	**4** (**6**)	Me_2AlCl (2.5)[c]	ND	ND	12[d]
3	**4** (**6**)	$TiCl_4$ (1.1)[c]	**9**:**10** (>20:1)	**9a**:**9b** (7:1)	71
4	**4** (**6**)	$TiCl_4$ (1.1)	**9**:**10** (3:1)	ND	63
5	**4** (**6**)	$MgBr_2{\cdot}OEt_2$ (7)	**9**:**10** (>20:1)	**9a**:**9b** (3:1)	97[e]
6	**4** (**6**)	$MgBr_2{\cdot}OEt_2$ (7)	**9**:**10** (>20:1)	**9a**:**9b** (11:1)	91
7	**4** (**6**)	$MgBr_2{\cdot}OEt_2$ (3)	**9**:**10** (>20:1)	**9a**:**9b** (9:1)	91
8	**4** (**6**)	$MgBr_2{\cdot}OEt_2$ (1)	**9**:**10** (>20:1)	**9a**:**9b** (3:1)	28
9	**4** (**7**)	$MgBr_2{\cdot}OEt_2$ (3)	**11**:**12** (>20:1)	**11a**:**11b** (>20:1)	81[f]
10	**4** (**7**)	$TiCl_4$ (1.1)[c]	**11**:**12** (>20:1)	**11a**:**11b** (3:1)	73[g]
11	**4** (**8**)	$MgBr_2{\cdot}OEt_2$ (5)	**13**:**14** (>20:1)	ND	65
12	**4** (**8**)	$TiCl_4$ (1.1)	**13**:**14** (>20:1)	ND	80
13	**5** (**6**)	$BF_3{\cdot}OEt_2$ (1.1)	**15**:**16** (1:12)	**16a:b** (1:10)	97
14	**5** (**6**)	Me_2AlCl (2.5)	**15**:**16** (1:12)	**16a:b** (1:2)	76
15	**5** (**7**)	$BF_3{\cdot}OEt_2$ (1.1)	**17**:**18** (1:11)	ND	85
16	**5** (**7**)	Me_2AlCl (2.5)	**17**:**18** (1:11)	ND	78

[a] Reagents and conditions: Aldehydes in CH_2Cl_2 (0.05 M with $MgBr_2{\cdot}OEt_2$ and 0.1 M with other Lewis acids) were treated at −78 °C with enoxysilane **6** (1.8 equiv; *E*:*Z* (8:1)), **7** (1.5 equiv with **4** and 2.0 equiv with **5**; *E*:*Z* (4:1)), or **8** (1.5 equiv; *E*:*Z* (4:1)) followed by the addition of the appropriate Lewis acid. [b] Ratios as determined by ^1H NMR spectroscopy of crude reaction isolates. [c] The aldehyde was precomplexed 2 min with Lewis acid prior the addition of enoxysilane. [d] Unknown products were observed. [e] The reaction was performed at 0 °C. [f] The reaction was performed at −40 °C. [g] The reaction was performed at −95 °C.

SCHEME 4



before, excellent diastereoselection. Conversely, when $TiCl_4$ was added to a solution containing the aldehyde and the enoxysilane, low selectivity was observed (entry 4). At first analysis, this intriguing result suggested two hypotheses: that the titanium complexes involved in these two reactions are not the same, and that the Felkin-Anh pathway has been activated in the later case, generating a significant amount of 3,4-*syn* product, thus eroding the *anti* preference. One possible scenario is illustrated in Scheme 4. As suggested by the work of Gau,[22] hexacoordinated complexes are preferred in the case of titanium. The sequence of bonding order for ligands toward titanium centers is *i*-PrO^- > Cl^- > THF > Et_2O > PhCOH > RCO_2Me, the strongest ligand being in a trans position relative to the weakest.[22] Complex **E** should therefore be involved in the Cram-chelate pathway as expected. In terms of the activation of the Felkin-Anh pathway (entry 4), this may suggest that when $TiCl_4$ is added to a solution of aldehyde and selenoenoxysilane, complex **F** (monodentate complex) may be one of the reacting species. To our knowledge, no crystal structures of titanium complexes involving a selenoether as a ligand have yet been reported. Our results would suggest that a selenoether has comparable ligand ability to an ether, a hypothesis that remains to be verified. The fact that preorganization of the Cram chelate complex with $TiCl_4$ and the aldehyde gave excellent diastereoselectivity suggests, as well, that the equilibrium between bidentate and monodentate complexes is slow. It should be mentioned that such an erosion of stereoselectivity has also been observed with methylthio-substituted enoxysilanes in $TiCl_4$-promoted Mukaiyama reactions.[23] Interestingly, precomplexation was not necessary to obtain 3,4-*anti* adducts with bromoenoxysilane **8** (entry 12), suggesting that the bromide would not be nucleophilic enough to compete with the chelate formation. Further work will be needed to test these hypotheses, including an evaluation of the reaction rates of the competing pathways.

It is noteworthy that at least 3 equiv of $MgBr_2{\cdot}OEt_2$ were required to obtain excellent yields (entries 6−8). As such, this is not surprising to us, since we have already observed that $MgBr_2{\cdot}OEt_2$ often contains significant amounts of CH_2Cl_2-insoluble material, probably $MgBr_2$, generally present in the commercially available Lewis acid.[11c] One will note that despite the low yield, the 3,4-*anti:syn* ratio is already very good with 1 equiv (entry 8).

Interestingly, 2,3-*anti* selectivity was noted by using both $TiCl_4$ and $MgBr_2{\cdot}OEt_2$ with the trisubstituted enoxysilane **6** (entries 3, 6, and 7) and $MgBr_2{\cdot}OEt_2$ with the tetrasubstituted enoxysilane **7** (entry 9). Mechanistic studies with pure stereoisomers of the trisubstituted enoxysilanes are underway to understand the origin of this unexpected stereocontrol.

We then turned our attention to the Felkin-Anh pathway that could be activated either by using a monodentate Lewis acid or by preventing chelation with the β-hydroxy group through an appropriate protecting group selection.[24,25] The β-silyloxy aldehyde **5** was therefore reacted with Lewis acids in the presence of the enoxysilanes **6** and **7**. As illustrated by entries 13 to 16, the 3,4-*syn* compounds were selectively obtained with $BF_3{\cdot}OEt_2$.

In these two selective Mukaiyama pathways, both $MgBr_2{\cdot}OEt_2$ and Me_2AlCl were particularly interesting to us, since they had been shown to be compatible with free radical-based allylation reactions,[11,26] thus suggesting that a potential tandem Mukaiyama-allylation sequence (Scheme 3) may be viable.

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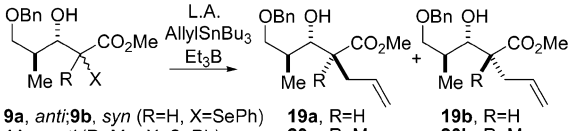
(23) Bernardi, A.; Cardani, S.; Colombo, L.; Poli, G.; Schimperna, G.; Scolasstico, C. *J. Org. Chem.* **1987**, *52*, 888.

(24) Activation of β-benzyloxyaldehyde **4** with $BF_3{\cdot}OEt_2$ led to low Felkin-Anh selectivity: 3,4-syn:3,4-anti (4:1).

(25) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778 and references therein.

TABLE 2. Free-Radical Allylation of Benzylated Substrates with Allyltributyltin[a]



9a, *anti*;**9b**, *syn* (R=H, X=SePh) **19a**, R=H **19b**, R=H
11a, *anti* (R=Me, X=SePh) **20a**, R=Me **20b**, R=Me
13a, *anti*; **13b**, syn (R=Me, X=Br)

entry	substrate	Lewis acid (equiv)	temp (°C)	2,3-(*anti:syn*) product (ratio)[b]	yield (%)
1	**9a**	none	−78 → rt	n.d.	0[c]
2	**9a**	BF_3·OEt_2 (1.1)	−78 → 0	**19a**:**19b** (3:1)	69
3	**9a**	$MgBr_2$·OEt_2 (5)	−40 → 0	**19a**:**19b** (>20:1)	62[c]
4	**9a**	Me_2AlCl (2.5)	−78	**19a**:**19b** (>20:1)	90
5	**9a**	$AlMe_3$ (2.5)	−78	**19a**:**19b** (>20:1)	80
6	**9b**	Me_2AlCl (2.5)	−78	**19a**:**19b** (2:1)	53
7	**9b**	$AlMe_3$ (2.5)	−40	**19a**:**19b** (6:1)	60
8	**11a**	$TiCl_4$ (1.1)	0	n.d.	0[c]
9	**11a**	Me_2AlCl (2.5)	0	**20a**:**20b** (8:1)	55[d]
10	**11a**	$AlMe_3$ (2.5)	0	**20a**:**20b** (>20:1)	58[d]
11	**13a**:**13b** (4:1)	$MgBr_2$·OEt_2 (5)	rt	**20a**:**20b** (>20:1)	40[c]
12	**13a**	$AlMe_3$ (2.5)	0	**20a**:**20b** (>20:1)	61[d]
13	**13b**	$AlMe_3$ (2.5)	0	**20a**:**20b** (>20:1)	60[d]

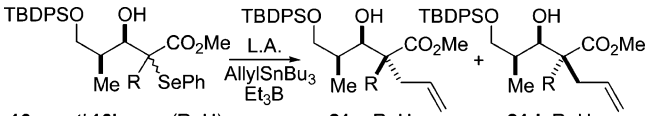
[a] Reagents and conditions: Substrates (0.05 M in CH_2Cl_2 when $MgBr_2$·OEt_2 is used and 0.1 M in CH_2Cl_2 with other Lewis acids) were pretreated with Lewis acid, allylSnBu$_3$ (2 equiv), Et_3B (0.2 equiv), and dry air (O_2). [b] Determined by ^1H NMR spectroscopy of crude reaction isolates. [c] Starting material was recovered. [d] Retro-Michael products were also observed (see the Supporting Information).

The Free Radical Allylation Step. Having the aldol adducts in hand, the evaluation of the allylation of these substrates under free radical conditions with Et_3B/O_2 as the initiator became our next objective. As stated before, the use of Lewis acid was planned to both activate the reaction and direct the diastereocontrol, as previously realized with β-methoxy-α-halo esters.[11,13] The present study, however, is fundamentally different, as it involves the reactions between Lewis acids and free alcohols to form σ-complexes that could competitively chelate various functionalities (e.g., benzyloxy vs ester).

We first investigated the allylation of 2,3-*anti*-3,4-*anti*-phenylselenide **9a** (Table 2), the major product obtained from the reaction of the trisubstituted enoxysilane **6** under Cram-chelate control. As seen in entry 1, no significant reaction was noted in the absence of Lewis acid, even at room temperature, the starting material being recovered. The addition of 1.1 equiv of BF_3·OEt_2 to the reaction mixture led to the allylated product in good yield (entry 2), but with low ratio favoring the 2,3-*anti* product, as expected. However, excellent stereoselectivity (>20:1) was observed in favor of the 2,3-*anti* product **19a** when bidentate Lewis acids such as $MgBr_2$·OEt_2, Me_2AlCl, or $AlMe_3$[27] were used (entries 3−5), suggesting the involvement of a chelated intermediate such as **B** (Scheme 2). Despite the high ratio observed with $MgBr_2$·OEt_2, this Lewis acid was less reactive in the allylation reaction than the aluminum-based Lewis acids. Indeed, the reaction of substrate **9a** was complete after 3.5 h with Me_2AlCl and $AlMe_3$ at −78 °C, affording **19** with excellent yields (entries 4 and 5), while the same reaction employing $MgBr_2$·OEt_2 was incomplete even after 9 h at higher temperatures, an average yield being obtained (entry 3).

Surprisingly, from a mechanistic standpoint, are the results observed with the minor product of the aldol reaction, the secondary syn selenide **9b**. As seen in entries 6 and 7, both Me_2AlCl and $AlMe_3$ gave low stereoselectivity, *anti:syn* ratios of 2:1 and 6:1 being respectively obtained.

TABLE 3. Free-Radical Allylation of Silyloxy Substrates with Allyltributyltin[a]



16a, *anti*;**16b**, *syn* (R=H) **21c**, R=H **21d**, R=H
18a, *anti*;**18b**, *syn* (R=Me) **22c**, R=Me **22d**, R=Me

entry	substrate	Lewis acid (equiv)	temp (°C)	2,3-(*anti:syn*) product (ratio)[b]	yield (%)
1	**16a**	Me_2AlCl (2.5)	−40	**21c**:**21d** (>20:1)	76
2	**16b**	Me_2AlCl (2.5)	−40	**21c**:**21d** (>20:1)	85
3	**18a**	Me_2AlCl (2.5)	0	**22c**:**22d** (>20:1)	50
4	**18b**	Me_2AlCl (2.5)	0	**22c**:**22d** (>20:1)	70

[a] Reagents and conditions: Substrates (0.1M in CH_2Cl_2) were pretreated with Me_2AlCl, allylSnBu$_3$ (2 equiv), Et_3B (0.2 equiv), and dry air (O_2). [b] Determined by ^1H NMR spectroscopy of crude reaction isolates.

The allylation of tertiary α-halo- or phenylselenoesters was then considered. No reactivity was observed with $TiCl_4$ (entry 8). A putative transmetalation of allyltributyltin may be at the origin of this absence of reactivity observed when $TiCl_4$ was used. However, a modest 8:1 (2,3-*anti:syn*) selectivity was obtained with Me_2AlCl (entry 9). We were pleased to note that both 2,3-anti phenylselenide **11a** and 2,3-*anti* bromide **13a** gave an excellent 2,3-*anti* selectivity (>20:1) during the allylation reaction under the control of the endocyclic effect with $AlMe_3$ (entries 10 and 12). Notably, the stereochemistry at C-2 was inconsequent in the case of tertiary halides as shown by the excellent 2,3-*anti* ratio observed, even for the allylation reaction of the 2,3-*syn* bromide **13b** (entry 13).

Excellent results in terms of yield and selectivity were also observed with Me_2AlCl when 3,4-*syn* phenylselenides **16** and **18**, obtained via Felkin-Anh control, were reacted with allyltributyltin (Table 3). Once again, both 2,3-*anti* (**16a** and **18a**) and 2,3-*syn* (**16b** and **18b**) selenides gave similar results (entries 1−4). Allylation of the less reactive tertiary selenides **18a**,**b** required higher temperature (entries 3 and 4). Interestingly, since Me_2AlCl is found to be an efficient Lewis acid in both the Mukaiyama and the allylation reactions, the prospect of a tandem sequence became a likely scenario.

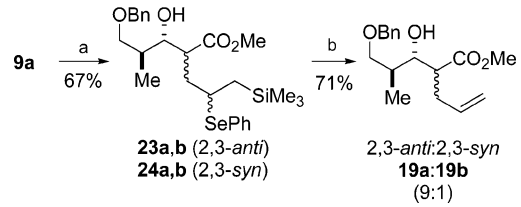
The evaluation of the allyltrimethylsilane as a less toxic allylating agent in the synthesis of our stereogenic centers became our next objective.[28] Many strategies have been used to compensate for the lack of reactivity of this reagent, mostly by lowering the SOMO energy of the radical. Malonates[29] and malononitriles[30] were found to be well suited to promote atom transfer reactions, since

(26) See ref 16a and references therein.

(27) Renaud and collaborators have already reported a chelation-controlled radical-based allylation of α-halo β-hydroxy esters with $AlMe_3$: Gerster, M.; Audergon, L.; Moufid, N.; Renaud, P. *Tetrahedron Lett.* **1996**, *37*, 6335.

(28) For other tin-free radical allylation methods see: (a) Schaffner, A.-P.; Renaud, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2658. (b) Usugi, S.-i.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* **2001**, *42*, 4535 and references therein. (c) Le Guyader, F.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 7410.

SCHEME 5[a]



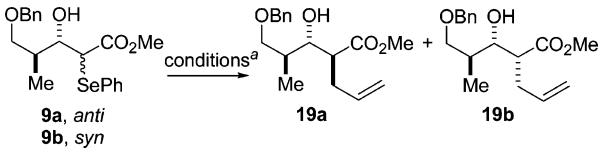
[a] Reagents and conditions: (a) Me_2AlCl (2.5 equiv), $AllylSiMe_3$ (2.0 equiv), Et_3B (0.2 equiv)/O_2, CH_2Cl_2, 0 °C. (b) TBAF (3.0 equiv), THF, 0 °C.

the radical can be delocalized toward two electronegative groups. In addition, we[13] and others[31,32] have shown that Lewis acids can be used to broaden the range of substrates that can undergo atom transfer reactions. This complexation to otherwise nonreactive α-haloesters led to productive reactions, the increased electron-withdrawing ability of the complexed ester being at the origin of this improvement in reactivity.

Therefore, the 2,3-*anti* α-selenoester **9a** was precomplexed with Me_2AlCl and reacted with allyltrimethylsilane in the presence of Et_3B at 0 °C (Scheme 5). A mixture of *β*-phenylselenosilanes **23** and **24** was isolated in 67% yield after flash chromatography. This result is consistent with an atom transfer mechanism, as generally recognized, when allyltrimethylsilane is used under free radical conditions.[13,31b,c] However, the isolation of this key intermediate is in contrast with the results normally obtained when a halide radical precursor is used, the unstable *β*-halosilane undergoing rapid *β*-elimination to the corresponding olefin.[13,31b,c] In our case, the *β*-phenylselenosilanes had to be submitted to a source of soluble fluoride ions in THF to get the allylated product in 71% yield.[33] An optimized one-pot sequence involving the atom transfer and the elimination reactions is illustrated in Table 4. One will note that generally lower yields are obtained compared to the parent reaction involving allyltributylstannane. The best ratio in favor of the allylated adduct **19a** was observed with $AlMe_3$ at −40 °C (entries 2 and 4), whereas selectivity was slightly lower with Me_2AlCl (entries 1 and 3). As was observed in tin-mediated allylation reactions, the secondary *anti* selenide precursor **9a** afforded higher stereoselectivity than the *syn* counterpart **9b** (cf. entries 1−2 and 3−4).

Unfortunately, all attempts to promote the allylsilane-mediated atom transfer reaction with secondary phenylselenides **16** or the tertiary phenylselenides and bromides **11**, **13**, and **18** led to decomposition and/or recovery of the starting material. Seemingly, substrates **16a** and **16b**, bearing a bulky silyl group on the primary alcohol, were less reactive, as this was the case for tertiary bromides **13** and tertiary phenylselenides **11a** and **18**.

TABLE 4. Free-Radical-Based Allylation with Allyltrimethylsilane[a]



entry	substrate	Lewis acid (equiv)	ratio[b] (**19a**:**19b**)	yield (%)
1	**9a**	Me_2AlCl (2.5)	15:1	67
2	**9a**	$AlMe_3$ (2.5)	>20:1	78
3	**9b**	Me_2AlCl (2.5)	3:1	42
4	**9b**	$AlMe_3$ (2.5)	6:1	31

[a] Reagents and conditions: Substrates (0.1 M in CH_2Cl_2) were pretreated with Lewis acid for 10 min at −40 °C, then $allylSiMe_3$ (2 equiv), Et_3B (0.2 equiv), and dry air (O_2) were successively added. 0.2 equiv of Et_3B was added every 30 min until completion by TLC. After workup, the crude reaction mixtures were dissolved in THF and treated with TBAF at 0 °C. [b] Ratios were determined by ^1H NMR spectroscopy of crude reaction isolates.

Mechanistic Considerations. Some of the results described in the previous section should be rationalized from a mechanistic standpoint. First, why were better yields observed with aluminum Lewis acids, as compared to $MgBr_2{\cdot}OEt_2$? This reactivity issue shall first be answered by using arguments derived from frontier molecular orbital theory. Indeed, additions to the HOMO of electron-rich olefins, such as allyltributylstannane and allyltrimethylsilane, should be facilitated by using carbon-centered free radicals of low SOMO energy (i.e. electron-deficient radical). Thus, rendering the ester more electron withdrawing through chelation with a Lewis acid should therefore decrease the SOMO energy of the radical, which was shown to be an effective strategy to promote the reaction of otherwise nonreactive α-halo- or selenoesters. Experimentally, the evaluation of the carbonyl activation in our proposed complexes was based on the previous work of Eliel. His group previously showed the ^{13}C chemical shift of carbonyls to be deshielded in the presence of Lewis acids, the deshielding and the reaction rate of organomagnesium addition being maximized when bidentate complexes were involved.[34] We conducted similar studies using substrates **9a** and **9b**, results of which are depicted in Table 5. As seen in entries 1 and 2, the addition of $MgBr_2{\cdot}OEt_2$ to a CD_2Cl_2 solution of *β*-hydroxy ester **9a** led to a downfield shift (+6.4 ppm) of the carbonyl signal. This shift was further increased to +10.3 ppm in the presence of $AlMe_3$ (entry 3). Similarly, this suggests that the carbonyl-conjugated free radical, when complexed with an aluminum-based Lewis acid, would be more reactive than when complexed with $MgBr_2{\cdot}OEt_2$ toward addition to an electron-rich olefin, as experimentally observed. In the case of the 2,3-*syn* selenoester **9b**, the +3.3 ppm shift noted with $AlMe_3$ (entry 4) suggested that the chelated complex was weaker

(29) (a) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826. (b) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(30) (a) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2157. (b) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9401.

(31) (a) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155. (b) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702. (c) Porter, N. A.; Zhang, G.; Reed, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773. (d) Feng, H.; Kavrakova, I. K.; Pratt, D. A.; Tellinghuisen, J.; Porter, N. A. *J. Org. Chem.* **2002**, *67*, 6050.

(32) Yang, D.; Yan, Y.-L.; Law, K.-L.; Zhu, N.-Y. *Tetrahedron* **2003**, *59*, 10465.

(33) For an example of conversion of a *β*-bromosilane to the corresponding olefin with TBAF, see: Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776.

(34) Chen, X.; Hortelano, R. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.

TABLE 5. ^{13}C NMR Studies of Complexes in CD_2Cl_2

entry	substrate	Lewis acid (equiv)	δ C=O (ppm)	$\Delta\delta^a$ (ppm)
1	**9a**	None	173.0	0
2	**9a**	$MgBr_2{\cdot}OEt_2$[b]	179.4	+6.4
3	**9a**	$AlMe_3$[c]	183.3	+10.3
4	**9b**	$AlMe_3$[c]	176.3	+3.3

[a] Chemical shift of the substrate complexed with Lewis acid − chemical shift of the substrate. [b] Substrate was pretreated with $MgBr_2{\cdot}OEt_2$ at 0 °C for 15 min. The solution was then filtrated and transferred into an NMR tube prior to recording the spectrum at 0 °C. [c] Substrates were pretreated with $AlMe_3$ at −40 °C for 15 min and ^{13}C NMR spectra were recorded at the same temperature.

than the one involving **9a**, probably due to steric effects (vide infra) between the *syn* substituents. This observation was experimentally reflected by a lower reactivity of **9b**, particularly with allyltrimethylsilane (cf. entries 2 and 4, Table 4), which bears an olefin of lower HOMO energy compared to allyltributylstannane.

A second question of interest should be answered: why is the relative 2,3-stereochemistry of phenylselenide precursors important in certain cases, as illustrated by the lower ratio noted for the secondary 2,3-*syn* phenylselenoester **9b**, as compared with 2,3-*anti* **9a**, in allylation reactions involving either allyltributylstannane (entries 5 and 7, Table 2) or allyltrimethylsilane (entries 2 and 4, Table 4)? The different results observed at times, during free radical-based allylations for different stereoisomeric precursors, could be considered counterintuitive at first.[35] Indeed, the formed tertiary (or quaternary) centers are the end products of the addition on a common radical intermediate, regardless of the stereochemistry of its selenide precursor. However, this statement needs to be reconsidered when more than one reaction pathway are in competition as is often the case of Lewis acid activated reactions (monodentate vs bidentate) where the potential involvement of various competing putative reacting complexes needs to be evaluated. In the context of this study, the Lewis acid reacts first with the hydroxyl group to form a covalent bond, yielding intermediates **A** and **A′** from **9a** and **9b**, respectively (Scheme 6). These new Lewis acids may then, for instance, chelate with the carbonyl. As stated before, complex **B** is likely to be more stable than **B′** for steric reasons. This, on first analysis, may affect the reaction rate of the homolytic bond cleavage of the selenide leading to the formation of the radical, which should have no consequence on the ratio noted after the addition of the radical trap, both **B** and **B′** leading to the same free-radical intermediates. The product distribution in this reaction pathway would be dependent on the difference of energy between transition states **G** and **H**, the former being favored for electronic and steric reasons. σ-Complexes **A** and **A′** could lead as well to intermediates **C** and **C′** through binding of the metal to the benzyloxy group. Complexes **C** and **C′** would obviously not be part of the reaction cascade due to the lack of reactivity of nonactivated carbonyls. However, these intermediates could in turn lead to complexes **D** and **D′** by complexation to an additional metal center. These could then react under the acyclic stereocontrol or the *exocyclic effect* to give *syn*-allylated compounds. These intermediates may be more populated under equilibration conditions in the reaction cascade involving the more congested **B′** as compared to **B**, thus favoring the noted erosion of diastereoselectivity in allylation of the *syn* precursor **9b**.[36]

One could hypothesize that the populations of intermediates **D** and **D′** would be significantly low in case of tertiary selenides for steric reasons, or when the primary alcohol protecting group is preventing chelation, as in the case of the silyl ether. This pathway should therefore be severely compromized as the steric hindrance increases in the new cycles **D** and **D′** (e.g., *syn* substituents or trisubstituted ring), a hypothesis that will be tested soon.

The Tandem Reaction Sequence. Encouraged by our results in the synthesis of tertiary and quaternary centers when the reactions were executed in an interrupted sequence, we decided to consider our main objective: the establishment of an experimental protocol, where both the Mukaiyama and allylation reactions would be achieved in tandem. Although separately optimizing two reactions as part of a planned sequence is a well-accepted approach to develop a tandem process, it is flawed with an important problem: the second reaction of the planned sequence is always under different conditions than the prototypic one, the side products and unreacted reagents of the first reaction being still present in the second step. From the onset, we realized that another, and even more important challenge was before us. Indeed, in the first step of the planned sequence, the β-benzyloxy aldehyde was best activated in a Cram-chelated pathway by $TiCl_4$ and $MgBr_2{\cdot}OEt_2$. However, in the allylation step, the aluminum-based Lewis acids were the most efficient activating agents, while $MgBr_2{\cdot}OEt_2$ had been found to give modest yields. One should note that $TiCl_4$ was precluded in the allylation step while Me_2AlCl did not work at all in the Mukaiyama reaction. Thus, we had to deal with the possibility that two different Lewis acids would have to be used sequentially. Our first reaction sequence involved $MgBr_2{\cdot}OEt_2$ as the Lewis acid. As indicated in Table 6, entry 1, reacting enoxysilane **6** and aldehyde **4** with $MgBr_2{\cdot}OEt_2$ (3 equiv) for 1 h, followed by the subsequent addition of allyltributylstannane and Et_3B, led to the creation of two stereogenic centers with high stereoselectivity. Once again, the low yield (35%) reflected the lack of reactivity of the magnesium complex with regards to the allylation reaction (entry 1). We then decided to add Me_2AlCl, after the first step, in the hope of improving the yield of the allylation reaction. Once again, high stereoselectivity was obtained but still in low yield (entry 2). Clearly, Lewis acid exchange did not take place. The addition of a Brønsted acid, such as acetic acid, was then envisaged to favor equilibrium between the reacting species and drive the formation of the aluminum complexes. Excitingly, the yield rose to 85% (entry 3), a result

(35) Previous results reported by our group indicated that severely hindered syn iodides reacted with lower selectivity than their anti counterparts when the *endocyclic effect* was required: see ref 11. For other examples showing the influence of the stereochemistry of the radical precursor see: Allylation: (a) Ishihara, T.; Mima, K.; Konno, T.; Yamanaka, H. *Tetrahedron Lett.* **2002**, *43*, 3493. (b) Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873. Reduction: (c) See ref 14.

(36) One should assume that the reaction kinetics involving B and D (and B′ and D′) is relatively similar allowing for these differences in population of intermediates to have an impact.

SCHEME 6

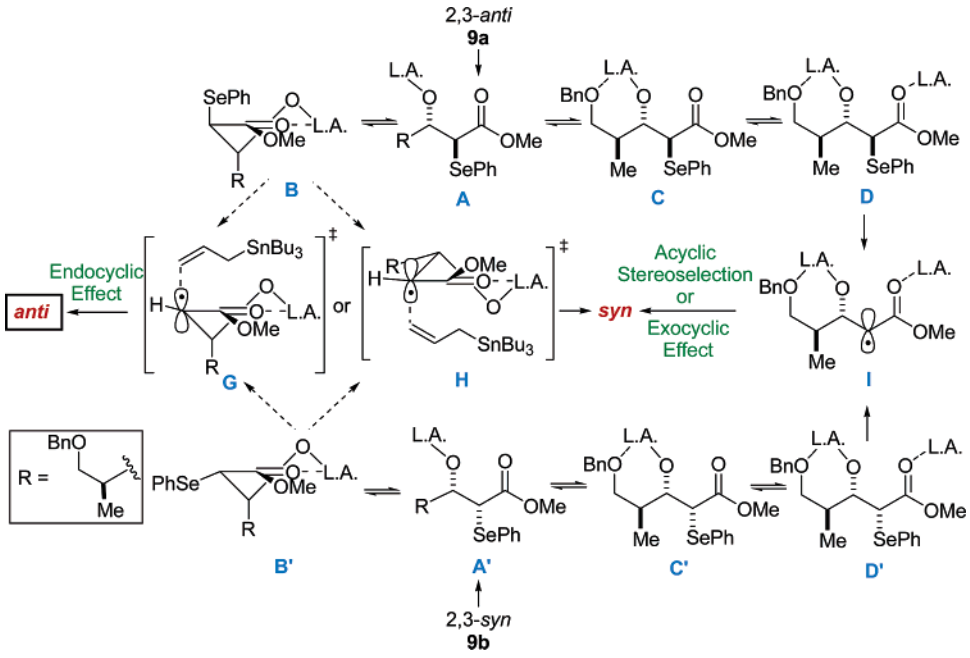
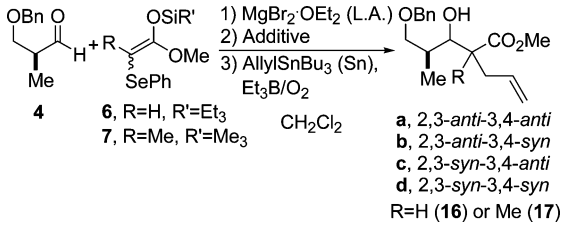


TABLE 6. Tandem Mukaiyama and Allylation Reactions with *β*-Benzyloxy Aldehyde 4[a]

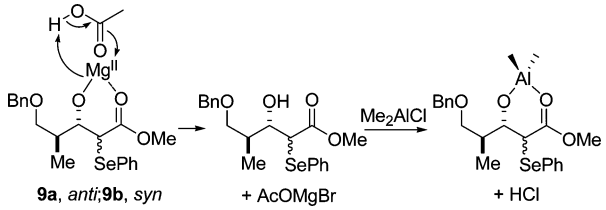


entry	**6** or **7** (equiv)	Lewis acid (equiv)	additive (equiv)	equiv of Sn	product (**a**:**b**:**c**:**d**)[b]	yield (%)
1	**6** (1.8)	**5**	none	4	**19** (>20:0:1:0)	35
2	**6** (1.8)	**5**	Me_2AlCl (3.5)	4	**19** (>20:0:1:0)	52
3	**6** (1.8)	**5**	CH_3COOH (1.2) Me_2AlCl (3.5)	4	**19** (>20:0:1:0)	85
4	**6** (1.8)	**3**	CH_3COOH (1.2) Me_2AlCl (3.5)	2	**19** (>20:0:1:0)	80
5	**7** (1.5)	**3**	CH_3COOH (1.2) Me_2AlCl (3.5)	2	**20** (>20:0:1:0)	52

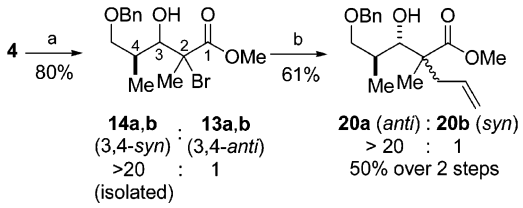
[a] Mukaiyama reagents and conditions: Substrates (0.05 M in CH_2Cl_2) were pretreated with enoxysilane **6** (1.8 equiv) at −78 °C or **7** (1.5 equiv) at −40 °C followed by $MgBr_2{\cdot}OEt_2$ until completion by TLC. Allylation reagents and conditions: The additive was added to the reaction mixture before the temperature was raised to −40 °C when **6** was used and to 0 °C when **7** was used. $AllylSnBu_3$ and Et_3B (0.2 equiv) were then added and the reaction mixture was exposed to dry air (O_2). [b] Ratios were determined by ^1H NMR spectroscopy.

suggesting that the O−Mg bond had been broken, which allowed the formation of an aluminum complex, as shown in Scheme 7. Performing the Mukaiyama reaction at −78 °C in the tandem sequence precluded the formation of **9b**, which had been found to be at the origin of a low-selective allylation reaction, as compared to **9a** (cf. Table 1, entries 5 and 6). The sequence was optimized by using 2 equiv of allyltributyltin and 3 equiv of $MgBr_2{\cdot}OEt_2$ (entry 4). These experimental conditions were then applied to the synthesis of compound **20a** bearing a quaternary center at C-2. Gratifyingly, it was produced

SCHEME 7



SCHEME 8 [a]



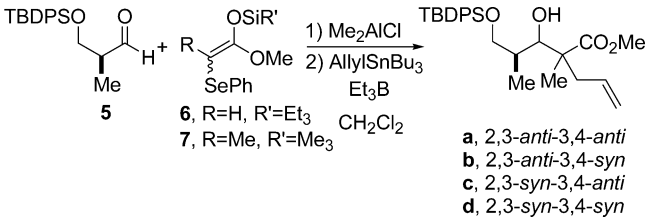
[a] Reagents and conditions: (a) $TiCl_4$ (1.1 equiv), **8** (1.5 equiv), CH_2Cl_2, −78 °C. (b) $AlMe_3$ (2.5 equiv), $AllylSnBu_3$ (2 equiv), Et_3B (0.2 equiv)/O_2, CH_2Cl_2, 0 °C.

as the only observable isomer in a 52% yield (entry 5), therefore realizing our first objective, the synthesis of two contiguous stereogenic centers, one being quaternary, from an α-substituted aldehyde.

Unfortunately, all attemps to synthesize **20a** from the tandem sequence involving bromoenoxysilane **8** failed. Indeed, the strategy employing acetic acid with $AlMe_3$, following the Mukaiyama reaction with $MgBr_2{\cdot}OEt_2$ (cf. Table 1, entry 12), led to unknown products and the recovery of Mukaiyama-derived intermediates **13a** and **13b**. Performing the sequence in two steps as an alternative ($TiCl_4$; $AlMe_3$) yielded 50% of the desired quaternary center with selectivity over 20:1 in favor of the 2,3-*anti*-3,4-*anti* adduct **20a** (Scheme 8).

The tandem sequences starting from *β*-silyloxyaldehyde **5** leading to the 2,3-*anti*-3,4-*syn* stereochemistry is conceptually simpler, given the fact that both the

TABLE 7. Tandem Mukaiyama and Allylation Reactions with β-Silyloxy Aldehyde 5[a]



entry	enol	temp (°C) Mukaiyama → allylation	product (ratio)[b]	yield (%)
1	**6**	−78 → −40	**21**, **a**:**b**:**c**:**d** (1:10:0:0)	40
2	**7**	−78 → 0	**22**, **a**:**b**:**c**:**d** (1:14:0:0)	55

[a] Mukaiyama reagents and conditions: Substrates (0.1 M in CH_2Cl_2) were pretreated with enoxysilane **6** (1.8 equiv) or **7** (1.5 equiv) followed by Me_2AlCl (2.5 equiv) until completion by TLC. Allylation reagents and conditions: The temperature was raised to the appropriate value prior to the addition of $AllylSnBu_3$ (2.0 equiv) and Et_3B (0.2 equiv) and the reaction was exposed to dry air (O_2). [b] Ratios were determined by ^1H NMR spectroscopy of the crude reaction isolates.

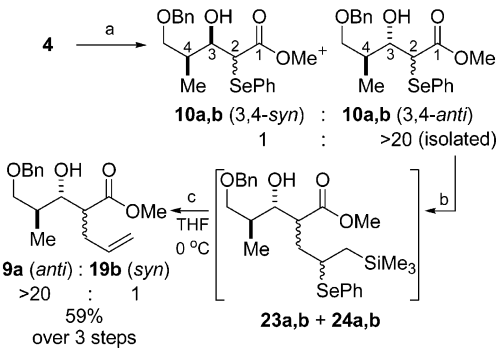
Mukaiyama and the free radical allylation reactions could be achieved by using the same Lewis acid, Me_2AlCl. Performing the one-pot sequence with Me_2AlCl under the optimized conditions for the separate reactions led, depending on the enoxysilane selected, to tertiary center **21b** or quaternary center **22b** with respective yields of 40% and 55% (Table 7, entries 1 and 2). As expected, the 2,3-*anti:syn* selectivities were above 20:1 for the allylation reaction and typical 3,4-*syn:anti* selectivities, obtained in the Mukaiyama step, of 10:1 and 14:1 were observed for products **21b** and **22b**, respectively. We therefore succeeded in the synthesis of tertiary and quaternary centers at C-2 having a 3,4-*syn* stereochemistry, where both stereogenic centers were induced successively under the influence of the same Lewis acid and from a common aldehyde as the only chiral source in this sequence.

As stated before, the sequence with allyltrimethylsilane over 3 steps gave an appreciable overall yield of 59% (Scheme 9). Facial diastereoselection was excellent, both for the Mukaiyama and for the allylation reactions, where the 2,3-*anti*-3,4-*anti* adduct prevailed with ratios over 20:1. However, trying to perform a tandem sequence with the optimized conditions previously documented in Table 5 resulted in low yield and diminished stereoselectivity.

Conclusion

The two-step Mukaiyama/radical-based allylation sequence allowed the stereoselective formation of synthetically useful molecules bearing a tertiary or a quaternary stereocenter. Two stereodefined carbon−carbon bonds can be created with good to excellent stereoselectivities, showing the efficiency of Lewis acids both in the anionic and in the radical steps. The 2,3-*anti* stereochemistry could be achieved in the free radical step, the aluminum-based Lewis acids giving the most reactive complexed radical intermediates. This increased reactivity also allowed the use of allyltrimethylsilane as the allylating agent through an atom transfer process. A complementary approach is currently under investigation to access if the 2,3-*syn* allylated adducts originate from the exocyclic effect or the acyclic stereoselection.

SCHEME 9[a]



[a] Reagents and conditions: (a) **6** (1.8 equiv), $MgBr_2{\cdot}OEt_2$ (3 equiv), CH_2Cl_2, −78 °C. (b) $AlMe_3$ (2.5 equiv), $AllylSiMe_3$ (2 equiv), Et_3B (0.2 equiv)/O_2, CH_2Cl_2, −40 °C. (c) Workup; TBAF (3.0 equiv), THF, 0 °C.

Acknowledgment. The authors wish to thank NSERC for its financial support as well as Dr. Daniel Chapdelaine and Ms. Georgia Bizoglou for their assistance in the preparation of this manuscript. Fellowship support from NSERC and FCAR (B.C.-D.) is also gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for compounds **15**, **16**, **19**−**22**, **23a**, and **25**; determination of relative configuration for compounds **15**, **16**, and **20**−**22**; experimental procedures and characterization data for lactones **26**−**30**; experimental procedure for ^{13}C NMR spectra of compounds **9a** and **9b** at low temperature with a Lewis acid; NMR spectra for compounds **15b**, **16a**, **19c**, **19d**, **21a**, **21b**, **21c**, **21d**, **22a**, **22b**, **22d**, **23a**, **25**, **26a**, **26b**, **27b**, **28b**, **28c**, **28d**, **29b**, **29c**, **29d**, **30a**, **30b**, **30c**, and **30d** and for compounds **9a** and **9b** in the presence of a Lewis acid; CIF data for compound **29a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048687J