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Stereoselective Quaternary Center Construction via Atom-Transfer Radical Cyclization Using Silicon Tethers on Acyclic Precursors

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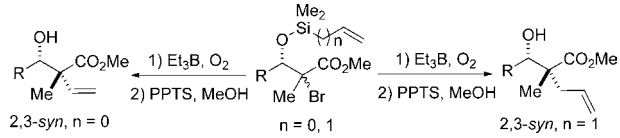
ABSTRACT



A novel strategy for the stereoselective construction of all-carbon quaternary centers on acyclic molecules using a two-step tandem process is reported. The first step involves an intramolecular and stereoselective atom transfer radical cyclization reaction from an allyl or vinyl subunit attached on a silyloxy, serving as a tether, to a tertiary radical α to an ester. A subsequent mild acidic elimination leads stereoselectively to a quaternary center bearing an allyl or a vinyl in high yield.

The construction of all-carbon stereogenic quaternary centers is a topic of great importance in chemistry.[1] A challenge of particular interest is the synthesis of stereogenic quaternary centers proximal to a chiral center on acyclic molecules such as the 2,3-*syn* and 2,3-*anti* allyl (**1**, **2**) or vinyl (**3**, **4**) motifs as depicted in Figure 1. Indeed, the intrinsic difficulty of creating quaternary centers is worsened by the presence of an α tertiary carbon and the increase in steric tensions.

These molecules are otherwise extremely interesting as potential synthons for the synthesis of natural products. The presence of an ester or an allyl (or vinyl) on the quaternary center as well as a hydroxyl on the neighboring carbon offers a large number of possibilities for further transformations.

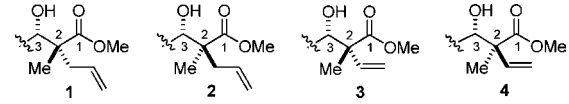


Figure 1. 2,3-*syn*- and 2,3-*anti*-β-hydroxy-α,α-disubstituted ester.

Notable scientific contributions toward the synthesis of these molecules have been realized. Fräter's anionic alkylation has led to molecules of general formulas **1** and **2**, although in low yields.[2] Mainly, the strong basic conditions required somewhat limited its use. Similarly, *syn* and *anti* motifs (**1** and **2**) could

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(1) For reviews, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *110*, 402. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943.

(2) (a) Fräter, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Fräter, G.; Mueller, U.; Guenther, W. *Tetrahedron* **1984**, *40*, 1269.

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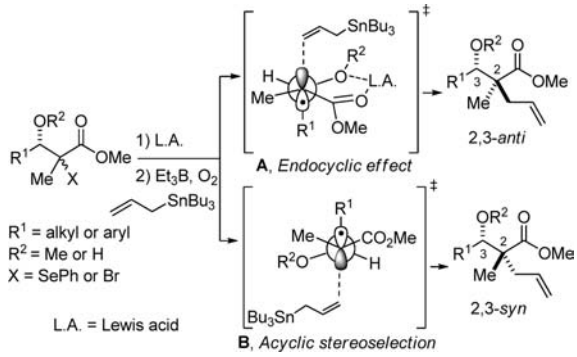
be obtained in modest yields through the regioselective opening of epoxides using an allyltitanium reagent.[3]

Although significant advancements have been reported recently,[4] aldol-based strategies have also been limited by the difficulty of accessing stereoselectively defined tetrasubstituted enolates.[5] More recently, silyl ketene imine has been used in the presence of chiral Lewis base and $SiCl_4$ to access diastereoselectively and enantioselectively the *anti* motif as in **2**, an aryl group replacing the methyl on the quaternary center.[6] Collectively, these results are exciting for their potential and serve to illustrate the difficulties in creating stereogenic quaternary centers.

In the past decade, we have explored the reactivity of carbon-centered free radicals on acyclic molecules in various transformations including carbon−carbon bond-forming reactions, as illustrated in Scheme 1. We have demonstrated that diastereo-

Scheme 1. Endocyclic Effect vs Acyclic Stereoselection



selectivity and high yields could be achieved in many of these reactions provided that certain conditions are present.[7]

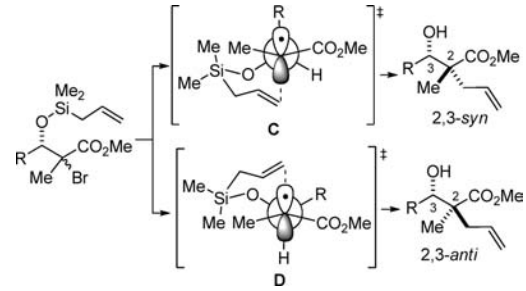
A critical first step en route to realize the objectives depicted previously was achieved when a radical precursor, flanked on one hand by an ester and on the other by a stereogenic center, was reacted with allyltributyltin in the presence of a bidendate Lewis acid ($MgBr_2$•OEt_2 or Me_2-AlCl). Entrapping the radical in a temporary chelated complex (transition state **A**, *endocyclic effect*) allowed the incoming reagent to attack on the bottom face of the radical leading to the stereospecific formation of the all-carbon quaternary centers with the 2,3-*anti* relative stereochemistry.[8]

We also observed that the balance of steric and stereoelectronic effects could influence the ground-state conformation of these radicals in the absence of Lewis acid (*acyclic stereoselection*).[9] As illustrated in **B**, the planar carbon-centered radical at C-2 should be delocalized in the ester. The induced allylic 1,3-strain has therefore to be alleviated as well as the intramolecular dipole−dipole effect between the alkoxy and the ester. Consequently, the C-3 hydrogen is at 30° of the ester while R^1 is close to be orthogonal to the plane of the radical.[10] We believe that this is also reflected in the early transition states of allylation reaction illustrated in **B** leading to the *syn* products. The observed diastereoselectivity was unfortunately decreased significantly when R^1 was a lower alkyl in the allylation reaction.[11] Although disappointing, the latter results served as a starting point for our present study and the exciting results reported herein.

Central to this study is our intention to explore intramolecular delivery of a radical trap on a tertiary carbon-centered free radical while taking advantage of the steric and electronic factors stated previously. The radical trap was planned to be linked to the oxygen at C-3 in order to benefit from this conformational bias.

Silicon-based tethers were chosen to link the radical traps to the oxygen at C-3 (Scheme 2). One should note that this

Scheme 2. Proposed Transition States: 2,3-*syn* and 2,3-*anti*



sequence is different from the previous strategy using (bromomethyl)dimethylsilyloxy ethers as tethered radical sources. These stabilized radicals have been involved successfully in various cyclizations including cascade reactions.[12] In our case, the silyl ether bears the olefin which will react on the acyclic tertiary radical. Examples of silyloxy ethers bearing vinyl, allyl, or ethynyl radical traps have been reported to react to cyclic secondary radicals,[13] but only isolated cases involving secondary acyclic radicals have been

(3) Ohno, H.; Hiramatsu, K.; Tanaka, T. *Tetrahedron Lett.* **2004**, *45*, 75.

(4) (a) Burke, E. D.; Gleason, J. L. *Org. Lett.* **2004**, *6*, 405. (b) Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, *8*, 1359.

(5) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005.

(6) Denmark, S. E.; Wilson, T. W.; Burke, M. T.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 14864.

(7) (a) Cardinal-David, B.; Guérin, B.; Guindon, Y. *J. Org. Chem.* **2005**, *70*, 776. (b) Cardinal-David, B.; Brazeau, J.-F.; Katsoulis, I.; Guindon, Y. *Curr. Org. Chem.* **2006**, *10*, 1939.

(8) For use of allylsilane reagent, see: (a) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1996**, *118*, 12528. (b) For use of allyltin reagent, see: Guérin, B.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W.; Guindon, Y. *Can. J. Chem.* **2000**, *78*, 852.

(9) (a) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27. (b) Guindon, Y.; Jung, G.; Guérin, B.; Ogilvie, W. W. *Synlett* **1998**, 213. (c) Brazeau, J.-F.; Mochirian, P.; Prévost, M.; Guindon, Y. *J. Org. Chem.* **2009**, *74*, 64.

(10) (a) Giese, B.; Bulliard, M.; Wetterich, F.; Zeitz, H. G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* **1993**, *34*, 5885. (b) Guindon, Y.; Benchequroun, M.; Bouzide, A. *J. Am. Chem. Soc.* **2005**, *127*, 554.

(11) A ratio of 4:1 in favor of *syn* was obtained when R^2 is a methyl and the allylation reaction done in refluxing hexanes (see ref 8b). In the case of R^2 = H, the ratio obtained was 6:1. The secondary hydroxyl group had to be protected in this case in a borinate and a monodentate Lewis acid used to activate the ester. (Cardinal-David B. Ph.D. Thesis, Université de Montréal, 2008).

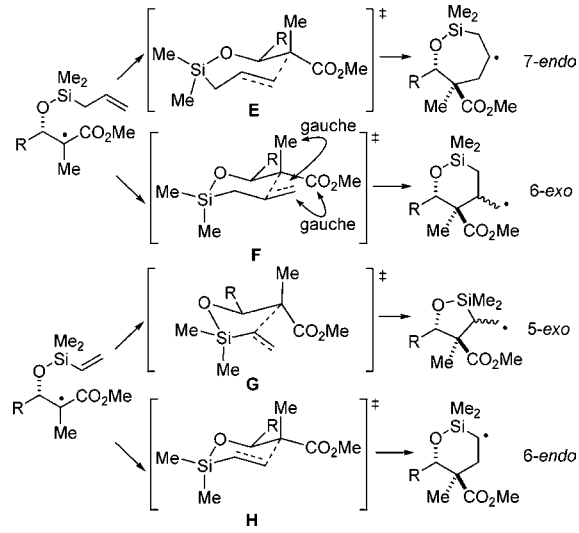
described with modest success.[14] The strength of our proposed methodology is the possibility to produce the allyl or vinyl products (as **1** and **3**, Figure 1) selectively. To our knowledge, neither of the methods described before allows the stereoselective formation of the *syn* products efficiently.

Our rationale to study these reactions is illustrated in Scheme 2. Minimization of the allylic 1,3-strain and intramolecular dipole−dipole effects are both alleviated in transition-state model **C**. Rotating the stereogenic center at C-3, in order to get access to the top face of the radical, leads to unfavorable transition state **D**. Two additional destabilizing interactions are now present: an allylic 1,3-strain between C−R with the ester and the presence of two bisecting functionalities C−O and C−R to the incoming double bond. On this basis, one will predict that the transition state **C** be of lower energy thus determining the relative stereochemistry of the quaternary center at C-2 versus the stereogenic center at C-3.

As stated before, our goal is the transfer of an allyl or a vinyl to the tertiary radical in order to generate the 2,3-*syn* stereogenic quaternary centers using a silicon-tethered radical trap. In order to reach the necessary cyclic β-bromosilyloxy intermediates that would lead to these products, regioselective 7-*endo-trig* or 5-*exo-trig* (see **E** and **G**, Scheme 3) cyclizations have to be favored over the competing 6-*exo-trig* and 6-*endo-trig* (**F** and **H**) pathways. The corresponding transition states are depicted in Scheme 3, the orientation of the planar carbon-centered radicals being consistent to the steric and electronic effects described above (Scheme 2). A priori it is problematic to predict the lowest energy transition states in those reactions using the Baldwin−Beckwith rules.[15] Indeed, the presence of silicon in the cyclizing chain of a number of reactions has generated different results from the ones expected.[16] The increases in bond lengths of O−Si and C−Si as compared to O−C and C−C bonds are probable causes of these variances, thus the need to evaluate those reactions experimentally.[17,18]

The synthesis in good yields of β-hydroxy-α-tertiary bromoesters, our precursors to the silyloxy ethers, have been realized by adding a mixture of *E*/*Z*-tetrasubstituted enoxysilane bearing a bromide atom to aldehydes activated by a Lewis acids.[19]

Scheme 3. Regioselectivity of the Radical Cyclization



The silylation reactions were achieved using well-known conditions. Chlorodimethylallylsilane or chlorodimethylvinylsilane was added to CH_2Cl_2 or DMF solutions of alcohol in the presence of pyridine or imidazole at room temperature. The resulting silyloxy ethers (substrates **5a**,**b** to **12a**,**b** and **29a**,**b** to **34a**,**b**) were subsequently isolated in excellent yields.

Solutions of the silyloxy ethers in benzene or toluene[20] bearing an allyl (Table 1) or a vinyl (Table 2) subunit were then exposed to free-radical conditions by adding 0.05 equiv of a solution of Et_3B at 0 °C. For optimal results, we added at 15−30 min intervals the same quantity of a solution of Et_3B for a period of 4 h or until the reactions were completed as indicated by TLC.[21] A mild acidic treatment leads to the elimination products and the formation of the quaternary centers bearing an allyl or a vinyl substituent.

As seen in Table 1, excellent to fair yields of the 2,3-*syn* products, in a ratio greater than 20:1, were obtained. Indeed, excellent ratios are noted even when lower alkanes are present (entries 1 and 2) as opposed to our previous protocol (vide supra). Our reactions are compatible with the presence of a phenyl group in the α position (entry 3) and with the usual protecting groups on hydroxyl groups on C-4 (entries 4 and 5). Of particular importance is the 2,3-*syn* diastereoselectivity noted regardless of the C-3−C-4

(12) See, for example: (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Am. Chem. Soc.* **1984**, *49*, 2298. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (c) Bogen, S.; Malacria, M. *J. Am. Chem. Soc.* **1996**, *118*, 3992. (d) Fensterbank, L.; Dhimane, A.-L.; Wu, S.; Lacôte, E.; Bogen, S.; Malacria, M. *Tetrahedron* **1996**, 11405, and references therein. (e) Blaszykowski, C.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2003**, *8*, 1341.

(13) Allyl: (a) Shuto, S.; Terauchi, M.; Yahiro, Y.; Abe, H.; Ichikawa, S.; Matsuda, A. *Tetrahedron Lett.* **2000**, *41*, 4151. (b) Kanazaki, M.; Ueno, Y.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 2422. (c) Terauchi, M.; Yahiro, Y.; Abe, H.; Ichikawa, S.; Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Potter, B. V. L.; Matsuda, A.; Shuto, S. *Tetrahedron* **2005**, *61*, 3697. (d) Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 5547. (e) Kodama, T.; Shuto, S.; Nomura, M.; Matsuda, A. *Chem.—Eur. J.* **2001**, *7*, 2332. (f) Sakaguchi, N.; Hirano, S.; Matsuda, A.; Shuto, S. *Org. Lett.* **2006**, *8*, 3291. (g) Stork, G.; Suk, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054. (h) Xi, Z.; Rong, J.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 5255. (i) Sukeda, M.; Ichikawa, S.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 4748. (j) Sukeda, M.; Ichikawa, S.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3465.

(14) Curran, D. P.; Ramamoorthy, P. S. *Tetrahedron* **1993**, *49*, 4841.

(15) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.

(16) (a) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281. (b) Saigo, K.; Tateishi, K.; Hiroshi, A.; Saotome, Y. *J. Org. Chem.* **1988**, *53*, 1572.

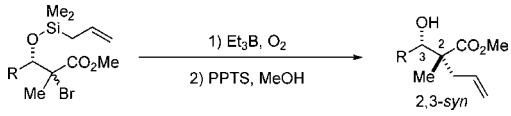
(17) Barton, T. J.; Revis, A. *J. Am. Chem. Soc.* **1984**, *106*, 3802.

(18) For references on the β-silicon effect (also called silicon hyperconjugation), see: (a) Ibrahim, M. R.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 819. (b) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183. (c) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173.

(19) Mochirian, P.; Cardinal-David, B.; Guérin, B.; Prévost, M.; Guindon, Y. *Tetrahedron Lett.* **2002**, *43*, 7067.

(20) The optimization of this reaction was initially performed in benzene to avoid benzylic bromination. However, few reactions done in toluene demonstrate that good yields and excellent diastereoselectivites can be obtained which represent a great alternative to benzene (entries 1, 4, 5, 7, and 8 in Table 1 and entry 2 in Table 2).

Table 1. Tandem Cyclization-Elimination Reaction−Allylation[a]



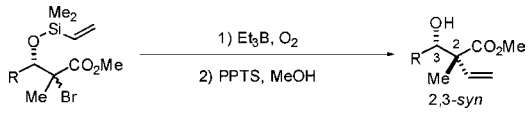
entry	substrate	R	product *syn:anti*	ratio	yield (%)
1[b]	**5a,b**	Et	**13:14**	>20:1	94
2[c]	**6a,b**	*i*Pr	**15:16**	>20:1	73
3[c]	**7a,b**	Ph	**17:18**	>20:1	76
4[b]	**8**	$BnOCH_2$	**19:20**	>20:1	72
5[b]	**9a,b**	$TBDPSOCH_2$	**21:22**	>20:1	79
6[c]	**10a,b**		**23:24**	>20:1	77
7[b]	**11**		**25:26**	>20:1	68
8[b]	**12a,b**		**27:28**	>20:1	66

[a] Conditions: Et_3B (0.05 equiv) was added every 15−30 min to the substrate in benzene or toluene at 0 °C until complete conversion by TLC. Treatment of the reaction mixture with PPTS (0.1 equiv) in MeOH for 1 h at room temperature led to the product. [b] Reaction was performed in toluene. [c] Reaction was performed in benzene.

relative stereochemistry (entries 6−8). The relative *syn* stereochemistry of the major compound **15** (entry 3) was proven through X-ray analysis of a *p*-nitrobenzoyl derivative.[22] The relative stereochemistry of the products **24** and **26** (entries 6 and 7) was confirmed through removal of the protecting groups, lactonization, and further X-ray and NMR (NOESY) analyses.[7a]

As seen in Table 2, similar results were noted in the vinylation reactions. Excellent yields and ratios were obtained favoring the 2,3-*syn* isomers, as in **3** (Figure 1). Once again,

Table 2. Tandem Cyclization-Elimination Reaction−Vinylation[a]



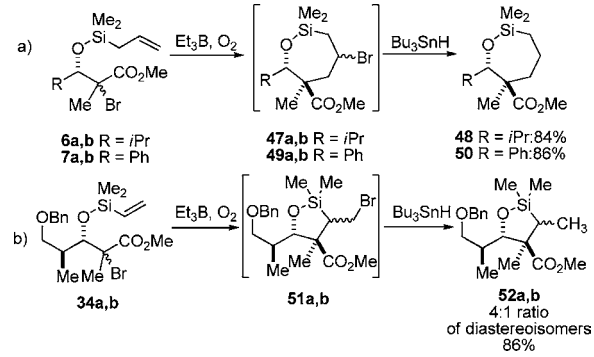
entry	substrate	R	product *syn:anti*	ratio	yield (%)
1[c]	**29a,b**	Et	**35:36**	>20:1	72
2[b]	**30a,b**	*i*Pr	**37:38**	>20:1	76
3[c]	**31a,b**	Ph	**39:40**	>20:1	87
4[c]	**32a,b**	$BnOCH_2$	**41:42**	>20:1	84
5[c]	**33a,b**	$TBDPSOCH_2$	**43:44**	>20:1	87
6[c]	**34a,b**		**45:46**	>20:1	83

[a] Conditions: Et_3B (0.05 equiv) was added every 15−30 min to the substrate in benzene or toluene, at 0 °C until complete conversion by TLC. Treatment of the reaction mixture with PPTS (0.1 equiv) in MeOH for 1 h at room temperature led to the product. [b] Reaction was performed in toluene. [c] Reaction was performed in benzene.

alkanes and aryls were compatible with our reactions (entries 1−3) as well as usual protecting groups (entries 4 and 5) and proximal stereogenic centers (entry 6). The relative *syn* stereochemistry of the major compound **45** was proven through X-ray analysis of a derivative.[22]

We proposed that, following initiation by Et_3B, an intramolecular cyclization occurs followed by atom transfer to give the corresponding 7-membered *β*-bromosilanes (**47**) which after elimination gave the corresponding 2,3-*syn*-allylated products. Similarly, 5-membered cyclic silyloxy ethers (**51a**,**b**) are proposed intermediates in the vinylation reactions.

Scheme 4. Proof of Structures: 5-*exo-trig* and 7-*endo-trig*



The presence of these intermediates (Scheme 4) has been supported from a number of experimental results, notably through hydrogen-transfer reactions. Indeed, at the end of the given allylation or vinylation reactions an equivalent amount of Bu_3SnH was added to the reaction mixtures. As seen in Scheme 4, 7-membered (**48** and **50**) and 5-membered rings (**52a**,**b**) were obtained in high yields, attesting to the presence of the proposed intermediates in these reactions.[23]

In conclusion, we have described herein the stereospecific construction of 2,3-*syn* allyl (as in **1**) or vinyl (as in **3**) subunits. The present intramolecular allylation on the tertiary free radical complement our previous allylation reaction under the control of the endocyclic effect (vide supra) making both stereoisomers **1** and **2** (Figure 1) now accessible.

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Supporting Information Available: Experimental procedures; crystallographic information files; complete spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The cyclic intermediates are unstable on silica. The allylated or vinylated products were observed in these cases.
(22) See the Supporting Information.
(23) See the Supporting Information for more details on the proof of structure of intermediates **48**, **50**, and **52a**,**b**.