Inter- and Intramolecular Crotyltitanation of Acetals: A Novel and Effective Route to Three- to Five-Membered Vinylcycloalkanes and Bicyclic Fused Compounds

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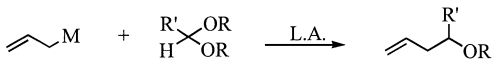
η^3-Crotyltitanocenes react with acetals to produce homoallylic ethers. The intramolecular coupling involving tethered dienyl acetals provides a convenient access to vinylcycloalkanes and bicyclic fused compounds. This new cyclization reaction proceeds with a total regioselectivity in the *exo* fashion, and with good to excellent diastereoselectivity depending especially on the tether chain length.

Introduction

The Lewis acid-induced addition of allylic organometallics to acetals represents a versatile method for the synthesis of homoallylic ethers, as shown in Equation (1).[1]

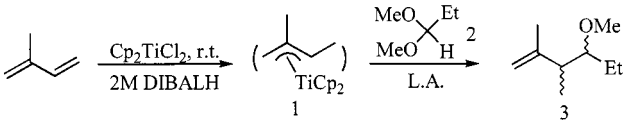


M (Si, Sn, Ge, B, Al)

In particular, the Sakurai reaction of allylic silanes with acetals, ketals and orthoesters has been developed.[2] Subsequently it was discovered that similar reactions employing allylic tin, germanium, boron, and aluminium reagents can also be performed with Lewis acid activation.[3] Two extreme mechanisms have been postulated for the cleavage of acetals involving the aforementioned η^1-allyl metal complexes: an S_N2-like reaction with a nucleophilic displacement of the Lewis acid-ether complex, and an S_N1 reaction via an oxocarbenium ion.[2c,2d,4] It has been shown that even moderate variations in the structure of the reactants and catalysts can influence the mechanism and the stereochemical outcome of these reactions.[2c]

The use of η^3-allyl complexes instead of the η^1-species could provide new mechanistic insights and be of synthetic interest. In this matter, η^3-crotyltitanocenes offer interesting opportunities. These allyl complexes, which can be readily obtained by hydrotitanation of the corresponding dienes,[5] add to aldehydes regiospecifically with, generally, a high *anti* stereoselectivity.[6] We have recently reported some new synthetic applications of η^3-crotyltitanocenes through the development of functionalized reagents,[7] introduction of new electrophiles,[6c,8] tandem reaction sequences,[9] and asymmetric procedures.[10] However, to the best of our knowledge, there are no precedents for the intramolecular cyclization involving an η^3-crotyltitanium entity tethered to an electrophile. In fact, the usual carbonyl- or imine-bearing electrophiles appear to be incompatible with the strongly reductive conditions needed to produce the crotyltitanium entity from a diene.[5] The acetal derivative could thus be used to overcome this difficulty.

In a preliminary communication,[11] we have already established the feasibility of performing intermolecular reactions of an η^3-crotyltitanocene reagent with acetals. Thus, a 1,2-dimethylallyl(tiglyl)titanium reagent (**1**) was prepared by reaction of Cp_2TiCl_2 with DIBALH (2 equiv.) and isoprene (1 equiv.).[12] Complex **1** reacted with propanal dimethyl acetal (**2**) in the presence of $TiCl_4$, $BF_3{\cdot}Et_2O$ or TMSOTf to afford the homoallylic ether **3** as an almost constant mixture of *anti* and *syn* diastereomers in 40%, 65% or 80% isolated yield, respectively (Scheme 1).



L.A.	% Yield
$TiCl_4$	40
$BF_3{\cdot}OEt_2$	65
TMSOTf	80

Scheme 1

Owing to the strikingly high yield in the reaction induced by TMSOTf, the reactions with some other acetals were next performed using an equimolar quantity of this Lewis acid as inductor.[13]

In the present work we further examine the effect of acetal structure on the course of the intramolecular reaction, and report on the new cyclization method based on the intramolecular coupling of tethered dienyl acetals.

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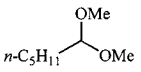
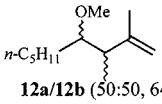
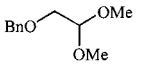
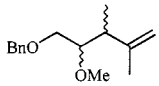
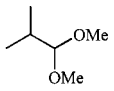
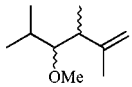
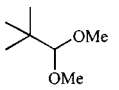
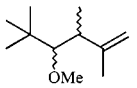
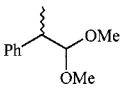
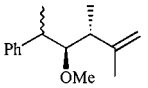
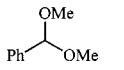
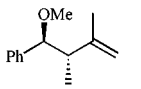
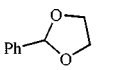
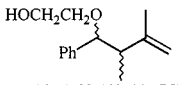
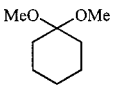
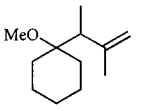
Results and Discussion

The intermolecular reactions involving a series of eight aliphatic and aromatic acetals (**4–11**) were performed, and the results are summarized in Table 1.

Table 1. Addition of tiglyltitanocene **2** to acetals and ketals **4–11** promoted by trimethylsilyl triflate

entry	acetal (ketal)	product *anti/syn*, % yield
1	 **4**	 **12a/12b** (50:50, 64)
2	 **5**	 **13a/13b** (55:45, 72)
3	 **6**	 **14a/14b** (78:22, 76)
4	 **7**	 **15a/15b** (85:15, 71)
5	 **8**	 **16a** (>98:2, 74)
6	 **9**	 **17a** (>98:2, 69)
7	 **10**	 **18a/18b**(60:40, 75)
8	 **11**	 **19**(60)

The crotyltitanation of the acetals **4**–**11** gave the homoallylic ethers **12–19** in good yield. As should be emphasized, all reactions appeared to proceed regiospecifically at the more substituted carbon atom of complex **1** similarly to the analogous reactions involving aldehydes.[6,14] The effect of modifying the acetal structure on the stereochemical course of the reaction could be deduced from the data in Table 1. The lack of diastereoselectivity for the aliphatic acetals bearing a linear carbon-chain was confirmed. Thus, neither the extension of the carbon chain in the acetal **4** (entry 1), nor the introduction of the potentially chelating β-alkoxy group into the acetal **5** (entry 2) significantly affects the stereoselectivity, which remains modest. In contrast, a spectacular increase of *anti* selectivity was observed by ramifying the alkyl chain at the α-carbon atom, as exemplified by acetals **6**, **7** and **8** (entries 3, 4 and 5). In these cases, the *anti* isomers were predominantly produced (*anti*/*syn* 8:2). Moreover, the reaction of **1** with an aromatic acetal, i.e. benzaldehyde dimethyl acetal (**9**) proceeded in a totally *anti* selective mode (entry 6). Surprisingly, the use of benzaldehyde dioxolane acetal (**10**) led to a pronounced loss of stereoselectivity (entry 7).

The structurally affected increase in *anti* stereoselectivity is noteworthy. This *anti* selectivity is opposite to the *syn* selectivity generally exhibited in the addition of allylic silanes (and other η^1-allyl complexes) to aliphatic acetals.[2,3] Moreover, the total *anti* selectivity observed in the reaction of **1** with the aromatic acetal **9** should not be directly associated with the increased *anti* selectivity in a similar reaction involving a *Z*-configured crotylsilane.[2a] In fact, type III η^3-crotyltitanocenes appear to be configurationally stable equivalents of (*E*)- [and not (*Z*)] η^1-crotylmetal reagents.[15] On the other hand, the stereochemical trend that we observed for the reactions of **1** with the acetals **4–10** differs from that exhibited in the analogous crotyltitanation of aldehydes, which is *invariably* highly *anti* selective for aliphatic aldehydes and a little less selective for the aromatic ones.[6,7] The stereochemistry of the reaction is indicative of a mechanism different from the S_N1- or S_N2-like mechanisms postulated for the reactions of η^1-allylmetal reagents with acetals,[2,3] as well as from the conventional Zimmerman-Traxler transition-state mechanism postulated for the crotyltitanation of aldehydes.[6b][7a] However, detailed mechanistic studies are needed to elucidate the course of these reactions.

Having investigated the feasibility of the intermolecular reaction we turned our attention to the intramolecular variant. We were interested in testing the scope of such a reaction, with the aim of developing a new useful procedure for the construction of small to medium-sized cyclic or bicyclic molecules. We will demonstrate below that the intramolecular crotyltitanation of tethered acetals can lead, in a substrate-controlled way, to 1-alkoxy-2-vinylcycloalkanes containing 3 to 5 carbon atoms in the ring.

The first series of experiments was directed towards the construction of monocyclic compounds. The starting dienyl acetals **20–24**[16] were chosen to test the dependence of the number of carbon atoms in the tether on the cyclization mode (Table 2). Thus, one two or three methylene groups separated the diene from the acetal function in the compounds **20–24**. The reactions were carried out as for the intermolecular series, using TMSOTf as promoter. As depicted in Table 2, the cyclization of **20–24** occurred in good yields to afford the 1-alkoxy-2-vinylcycloalkanes **25–29**. In all cases the cyclization appeared to be totally regioselective, proceeding exclusively in the *exo*-fashion.

The cyclopropane-derived products **25** and **26** should therefore be associated with the regioselective attack involving the C-4 and C-5 carbon atoms, respectively, of the corresponding complexes (entries 1 and 2).[17] The use of the

Table 2. Intramolecular crotyltitanation of tethered acetals promoted by TMSOTf

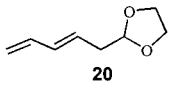
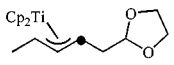
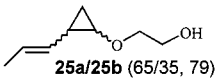
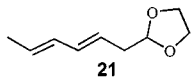
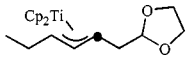
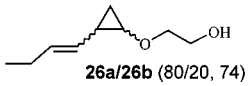
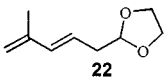
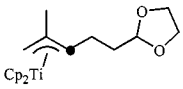
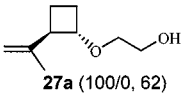
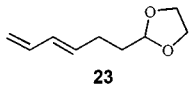
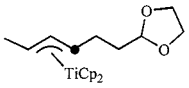
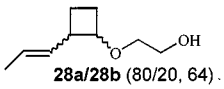
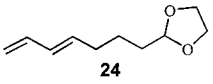
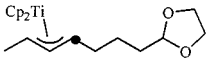
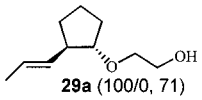
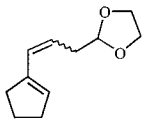
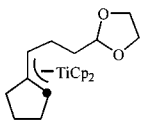
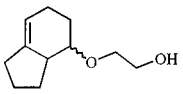
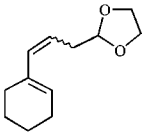
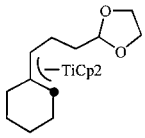
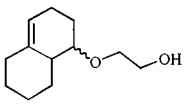
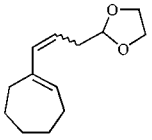
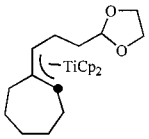
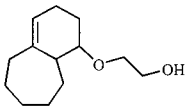
entry	dienyl acetal	complex	product (trans/cis, % yield)
1	 **20**		 **25a/25b** (65/35, 79)
2	 **21**		 **26a/26b** (80/20, 74)
3	 **22**		 **27a** (100/0, 62)
4	 **23**		 **28a/28b** (80/20, 64)
5	 **24**		 **29a** (100/0, 71)

Table 3. Synthesis of the bicyclic compounds **33–35** by intramolecular crotyltitanation of acetals **30–32**

entry	dienyl acetal	complex	product (trans/cis, % yield)
1	 **30**		 **33a/33b** (50/50, 75)
2	 **31**		 **34a/34b** (50/50, 61)
3	 **32**		 **35a** (100/0, 65)

dienyl acetal **22**, structurally resembling isoprene, led inevitably to the regioselective formation of the cyclobutane derivative **27** (entry 3). More interestingly, only one of the two possible regioisomers, i.e. the cyclobutane derivative **28**, was formed starting from the dienyl acetal **23**, with a tether chain of two methylene groups (entry 4). Furthermore, the addition of the supplementary methylene group in the tether resulted in the unique cyclopentane derivative **29** (entry 5).

The products **25–29** were shown to possess a unique *E* configuration of the double bond, regardless of the substrate structure. Moreover, the trans isomers are favored in all cases.[18] However, the stereoselectivity of the intramolecular reactions vary depending on the tether chain length, as well as on the substitution of the dienyl fragment. Thus, the introduction of a terminal methyl group in **21** prompted an increase of stereoselectivity (*trans*/*cis* = 80:20) over the non-substituted **20** (*trans*/*cis* = 65/35). Bringing the Me group closer to the reaction center contributed to a further increase of the trans selectivity, as exemplified by the analogous complexes derived from **23** and **22**. In fact, the cyclobutane derivative **28** was obtained as a mixture (*trans*/*cis* =

80:20) of stereoisomers starting from the former, whereas only the *trans*-configured cyclobutane derivative **27** was obtained starting from the latter (entries 3 and 4). The effect of varying the chain length on the stereoselectivity could be evaluated from the stereochemical outcome of the reactions employing the dienyl acetals **20**, **23** and **24** (entries 1, 4 and 5). From these compounds, structurally similar complexes were formed, having all terminal methyl groups and 1, 2 or 3 carbon atoms in the tether. They reacted to afford the corresponding cyclopropane (**25**), cyclobutane (**28**) and cyclopentane (**29**) derivatives, with an increasing *trans*/*cis* ratio (from 65:35 for **25** to 80.20 for **28** and 100:0 for **29**). The increase of stereoselectivity by introducing the substituent or by extending the tethered chain is noteworthy. The intramolecular coupling can also be applied to the construction of the bicyclic fused compounds (Table 3). The cyclic dienyl acetals **30–32,**[19] each bearing an *exo*- and an endocyclic double bond, were used as substrates. The intramolecular reactions were carried out as previously in the presence of TMSOTf. As can be seen from Table 3, all reactions appeared to occur regiospecifically at the ring carbon atom rather than at the side-chain atom.[10a,20] As a result, the bicyclic compounds **33–35** were obtained, bearing fused 6-membered and 5-, 6- and 7-membered rings.[18] The marked effect of the ring size on the stereoselectivity is exemplified by these reactions. In contrast to the lack of stereoselectivity for the dienyl acetals **30** and **31**, the total selectivity observed for **32** might be indicative of the operation of different mechanisms, prompted by the subtle structural changes.[21]

Conclusion

The Lewis acid induced inter- and intramolecular coupling of η^3-crotyltitanocenes with acetals was reported. The latter reaction provides a new synthetically useful route to small- and medium-sized vinylcycloalkanes, and also offers an opportunity to develop versatile entries to bicyclic fused compounds.

Experimental Section

General: All manipulations were carried out under argon, using vacuum-line techniques. The solvents used were distilled under Ar from sodium benzophenone ketyl. Titanocene dichloride,[22] acetals and dienyl acetals,[16,19] were prepared according to the published procedures. Other reagents were purchased from Aldrich Chemical Co. ^{1}H and ^{13}C NMR spectra were recorded at 200 or 500 and 50 MHz, respectively. Mass spectra were obtained by an EI (70 eV) technique. Column chromatography was performed on silica gel 60 (Merck).

General Procedure for the Intermolecular Reaction: The 1,2-dimethylallyl(tiglyl)titanium reagent **1** was prepared in situ at room temp. by reaction of Cp_2TiCl_2 (1.00 g, 4.03 mmol) with two equivalents of DIBALH (2 × 4 mL, 2 M solution in THF) and isoprene (0.6 mL, 6 mmol). The reaction was carried out by adding the acetal (1equiv.) at –40 °C to a solution of the preformed **1** in THF, followed by TMSOTf (0.8 mL; 4 mmol). The mixture was then stirred for 4 h at –40 °C. The cold mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL) and extracted with ether (3 × 100 mL). The combined organics were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The isomers were separated by chromatography eluting with a gradient of hexane/ether (40:1 v/v). The overall yields and spectral data of **3** and **12** to **19** are as follows:

3 (80%); **3a:** ^{1}H NMR ($CDCl_3$): δ = 4.76 (m, 2 H), 3.52 (s, 3 H), 3.19 (m, 1 H), 2.42 (qt, *J* = 7.3 Hz, 1 H), 1.71 (br. s, 3 H), 1.40 (m, 2 H), 1.06 (d, *J* = 7.3 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 143.1, 113.8, 83.1, 60.2, 44.2, 26.6, 23.1, 16.1, 10.1. – **3b:** ^{1}H NMR ($CDCl_3$): δ = 4.70 (m, 2 H), 3.54 (s, 3 H), 3.19 (m, 1 H), 2.29 (dq, *J* = 3.9, 7.3 Hz, 1 H), 1.82 (br. s, 3 H), 1.40 (m, 2 H), 0.97 (d, *J* = 7.3 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 143.1, 110.7, 79.2, 59.6, 43.3, 26.6, 21.1, 15.8, 9.6. – $C_9H_{18}O$ (**3a** + **3b**): calcd. C 76.00, H 12.76; found C 76.31, H 12.52.

12 (64%); **12a:** ^{1}H NMR ($CDCl_3$): δ = 4.78 (m, 2 H), 3.34 (s, 3 H), 3.14 (m, 1 H), 2.42 (qt, *J* = 7.3 Hz, 1 H), 1.71 (br. s, 3 H), 1.42–1.18 (m, 8 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 0.87 (t, *J* = 6.6 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 142.0, 110.8, 83.7, 57.7, 44.6, 32.1, 30.3, 25.2, 22.6, 21.1, 15.5, 14.0. – **12b:** ^{1}H NMR ($CDCl_3$): δ = 4.72 (m, 2 H), 3.31 (s, 3 H), 3.05 (m, 1 H), 2.31 (dq, *J* = 4.1, 7.3 Hz, 1 H), 1.68 (br. s, 3 H), 1.42–1.18 (m, 8 H), 0.97 (d, *J* = 7.3 Hz, 3 H), 0.87 (t, *J* = 6.6 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 141.2, 111.1, 83.1, 57.1, 42.8, 31.5, 29.7, 24.8, 22.6, 20.2, 15.5, 14.0. – $C_{12}H_{24}O$ (**12a** + **12b**): calcd. C 78.20, H 13.12; found C 78.02, H 12.99.

13 (72%); **13a:** ^{1}H NMR ($CDCl_3$): δ = 7.29–7.24 (m, 5 H), 4.71 (m, 2 H), 3.83–3.31 (m, 5 H), 3.29 (s, 3 H), 2.35 (dq, *J* = 7.9, 6.8 Hz, 1 H), 1.69 (br. s, 3 H), 1.07 (d, *J* = 6.8 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 147.9, 138.6, 128.4, 127.6, 127.5, 111.4, 81.3, 73.4, 72.1, 59.2, 43.4, 20.2, 15.7. – **13b:** ^{1}H NMR ($CDCl_3$): δ = 7.29–7.24 (m, 5 H), 4.52 (m, 2 H), 3.83–3.31 (m, 5 H), 3.24 (s, 3 H), 2.50 (dq, *J* = 5.9, 6.8 Hz, 1 H), 1.76 (br. s, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 147.6, 138.6, 128.4, 127.7, 127.5, 111.3, 81.2, 73.4, 71.1, 59.6, 42.6, 21.0, 15.4. – $C_{15}H_{22}O_2$ (**13a** + **13b**): calcd. C 76.88, H 9.46; found C 76.61, H 9.69.

14 (76%); **14a:** ^{1}H NMR ($CDCl_3$): δ = 4.75 (m, 2 H), 3.37 (s, 3 H), 2.81 (dd, *J* = 4.6, 7.6 Hz, 1 H), 2.36 (qt, *J* = 7.6 Hz, 1 H), 1.91–1.62 (m, 1 H), 1.73 (br. s, 3 H), 0.98 (d, *J* = 7.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 148.7, 111.2, 89.5, 61.3, 43.9, 30.5, 20.7, 16.8, 16.4, 12.5. – **14b:** ^{1}H NMR ($CDCl_3$): δ = 4.70 (m, 2 H), 3.43 (s, 3 H), 2.91 (dd, *J* = 4.4, 7.3 Hz, 1 H), 2.32 (qt, *J* = 7.3 Hz, 1 H), 1.91–1.62 (m, 1 H), 1.68 (br. s, 3 H), 1.07 (d, *J* = 7.3 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 147.1, 111.1, 89.1, 61.8, 44.3, 30.5, 20.6, 16.8, 16.4, 12.4. – $C_{10}H_{20}O$ (**14a** + **14b**): calcd. C 76.86, H 12.90; found C 76.65, H 12.72.

15 (71%); **15a:** ^{1}H NMR ($CDCl_3$): δ = 4.77 (m, 2 H), 3.40 (s, 3 H), 2.80 (d, *J* = 3.9 Hz, 1 H), 2.36 (dq, *J* = 3.9, 6.8 Hz, 1 H), 1.77 (br. s, 3 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 150.9, 110.2, 90.6, 61.8, 42.0, 37.3, 26.9, 21.3, 15.3. – **15b:** ^{1}H NMR ($CDCl_3$): δ = 4.75 (m, 2 H), 3.31 (s, 3 H), 2.85 (d, *J* = 2.7 Hz, 1 H), 2.50 (dq, *J* = 2.7, 7.1 Hz, 1 H), 1.79 (br. s, 3 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 0.93 (s, 9 H). – ^{13}C NMR ($CDCl_3$): δ = 150.9, 111.3, 88.4, 61.2, 41.4, 37.3, 26.2, 20.1, 13.6. – $C_{11}H_{22}O$ (**15a** + **15b**): calcd. C 77.58, H 13.02; found C 77.31, H 12.80.

16 (74%); **16a (*anti-anti*):** ^{1}H NMR ($CDCl_3$): δ = 7.39–7.08 (m, 5 H), 4.78 (m, 1 H), 4.74 (m, 1 H), 3.16 (s, 3 H), 3.13 (t, *J* = 7.0 Hz,

1 H), 2.85 (qt, J = 7.0 Hz, 1 H), 2.28 (qt, J = 7.0 Hz, 1 H), 1.77 (br. s, 3 H), 1.40 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 148.1, 145.1, 128.5, 127.9, 125.9, 111.6, 89.9, 61.2, 43.9, 42.7, 20.7, 19.3, 16.9. – **16a′** ***(anti-syn)*****:** ^{1}H NMR ($CDCl_3$): δ = 7.39–7.08 (m, 5 H), 4.77 (m, 1 H), 4.75 (m, 1 H), 3.13 (s, 3 H), 3.19 (dd, J = 5.1, 7.0 Hz, 1 H), 2.91 (dq, J = 5.1, 7.0 Hz, 1 H), 2.28 (qt, J = 7.0 Hz, 1 H), 1.71 (br. s, 3 H), 1.28 (d, J = 7.0 Hz, 3 H), 1.05 (d, J = 7.0 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 145.9, 145.1, 128.5, 127.9, 125.9, 111.8, 89.5, 61.1, 43.9, 41.8, 20.6, 17.0, 15.1. – $C_{15}H_{22}O$ (**16a** + **16a′**): calcd. C 82.52, H 10.16; found C 82.24, H 10.31.

17 (69%); **17a:** ^{1}H NMR ($CDCl_3$): δ = 7.40–7.19 (m, 5 H), 4.63 (m, 1 H), 4.60 (m, 1 H), 4.02 (d, J = 7.3 Hz, 1 H), 3.19 (s, 3 H), 2.44 (qd, J = 7.3, 7.3 Hz, 1 H), 1.58 (br. s, 3 H), 1.13 (d, J = 7.3 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 147.6, 141.3, 128.0, 127.4, 126.8, 111.7, 87.2, 57.0, 48.2, 21.0, 15.4. – $C_{13}H_{18}O$ (**17a**): calcd. C 82.06, H 9.53; found C 81.91, H 9.29.

18 (75%); **18a:** ^{1}H NMR ($CDCl_3$): δ = 7.27–6.94 (m, 5 H), 4.76 (m, 2 H), 4.14 (d, J = 8.8 Hz, 1 H), 3.71–3.24 (m, 4 H), 2.55 (dq, J = 8.8, 6.8 Hz, 1 H), 2.32 (br. s, D_2O exchangeable, 1 H), 1.78 (br. s, 3 H), 0.76 (d, J = 6.8 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 139.7, 127.8, 127.6, 127.3, 111.2, 85.5, 70.1, 61.9, 48.3, 20.9, 16.3. – **18b:** ^{1}H NMR ($CDCl_3$): δ = 7.27–6.94 (m, 5 H), 4.58 (m, 2 H), 4.17(d, J = 6.8 Hz, 1 H), 3.71–3.24 (m, 4 H), 2.47 (dq, J = 6.8, 6.8 Hz, 1 H), 2.31 (br. s, D_2O exchangeable, 1 H), 1.56 (br. s, 3 H), 1.15 (d, J = 6.8 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 141.2, 128.1, 127.9, 127.2, 111.7, 85.9, 70.3, 62.0, 47.9, 19.6, 15.7. – $C_{14}H_{20}O_2$ (**18a** + **18b**): calcd. C 76.33, H 9.15; found C 76.25, H 9.49.

19 (75%); ^{1}H NMR ($CDCl_3$): δ = 4.83 (m, 1 H), 4.71 (m, 1 H), 3.14 (s, 3 H), 2.47 (q, J = 6.8 Hz, 1 H), 1.76 (br. s, 3 H), 1.72–1.23 (m, 10 H), 0.98 (d, J = 6.8 Hz, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 147.5, 113.0, 92.9, 47.6, 44.6, 30.7, 30.5, 25.9, 22.9, 21.8, 21.6, 13.8. – $C_{12}H_{22}O$ (**19**): calcd. C 79.06, H 12.16; found C 79.35, H 12.06.

General Procedure for the Intramolecular Reaction: The complex was prepared in situ at room temp. by reaction of Cp_2TiCl_2 (1.00 g, 4.03 mmol) with two equivalents of DIBALH (2 × 4 mL, 2 M solution in THF) and dienyl acetal (4 mmol). The solution was then cooled to –40 °C, and TMSOTf (0.8 mL; 4 mmol) was slowly added. The mixture was then stirred for 4 h at –40 °C. The conventional basic workup ($NaHCO_3$, then extraction with ether), followed by chromatographic purification (hexane/ether = 1:1 v/v), afforded the homoallylic ether as a mixture of two diastereomers. The overall yields and spectral data of **25** to **29** and **33** to **35** are as follows.

25 (79%); **25a:** ^{1}H NMR ($CDCl_3$): δ = 5.35 (qd, J = 6.4, 15.3 Hz, 1 H), 5.05 (ddq, J = 15.3, 7.8, 1.4 Hz, 1 H), 3.70–3.59 (m, 2 H), 3.51–3.58 (m, 2 H), 3.11 (ddd, J = 3.3, 3.5, 6.4 Hz, 1 H), 2.45 (br. s, 1 H, D_2O exchangeable), 1.58 (dd, J = 1.7, 6.4 Hz, 3 H), 1.53 (dddd, J = 3.3, 3.5, 6.4, 7.8 Hz, 1 H), 0.95 (ddd, J = 9.3, 6.4, 3.3 Hz, 1 H), 0.64 (ddd, J = 9.3, 6.4, 3.5 Hz, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 130.4, 124.0, 71.6, 61.5, 60.4, 21.4, 17.6, 13.8. – **25b:** ^{1}H NMR ($CDCl_3$): δ = = 5.56 (qd, J = 6.3, 15.4 Hz, 1 H), 5.13 (ddq, J = 15.4, 7.8, 1.4 Hz, 1 H), 3.70–3.59 (m, 2 H), 3.58–3.51 (m, 2 H), 3.34 (dt, J = 3.7, 6.3 Hz, 1 H), 2.45 (br. s, 1 H, D_2O exchangeable), 1.64 (dd, J = 1.7, 6.3 Hz, 3 H), 1.45 (dddd, J = 3.3, 3.5, 6.4, 7.8 Hz, 1 H), 0.88 (ddd, J = 6.3, 6.4, 9.3 Hz, 1 H), 0.61 (ddd, J = 9.1, 9.3, 3.7 Hz, 1 H). – ^{13}C NMR ($CDCl_3$): δ = = 128.2, 125.3, 71.9, 61.5, 58.0, 20.6, 18.0, 12.8. – MS (**25a** + **25b**): m/z (%) = 142 (13) [M^+], 127 (12), 113 (5), 97 (14), 80 (44), 73 (81), 58 (54), 45 (100). – $C_8H_{14}O_2$ (**25a** + **25b**): calcd. C 67.57, H 9.92; found C 67.31, H 9.69.

26 (74%); **26a:** ^{1}H NMR ($CDCl_3$): δ = 5.48 (dt, J = 15.3, 6.2 Hz, 1 H), 5.07 (ddt, J = 15.3, 7.8, 1.4 Hz, 1 H), 3.78–3.63 (m, 2 H), 3.62–3.58 (m, 2 H), 3.15 (dt, J = 6.4, 3.2 Hz, 1 H), 2.60 (br. s, 1 H, D_2O exchangeable), 1.95 (ddq, J = 6.2, 1.4, 7.5 Hz, 2 H), 1.53 (dddd, J = 7.8, 6.3, 3.2, 3.2 Hz, 1 H), 0.93 (t, J = 7.5 Hz, 3 H), 0.95 (ddd, J = 9.3, 6.1, 3.2 Hz), 0.64 (ddd, J = 9.3, 6.3, 3.2 Hz, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 132.6, 128.2, 72.1, 61.6, 60.7, 25.5, 21.5, 14.0, 13.8. – **26b:** ^{1}H NMR ($CDCl_3$): δ = 5.64, (dt, J = 15.4, 6.4 Hz, 1 H), 5.23 (ddt, J = 15.4, 9.0, 1.4 Hz, 1 H), 3.78–3.63 (m, 2 H), 3.62–3.58 (m, 2 H), 3.39 (dt, J = 3.7, 6.3 Hz, 1 H), 2.60 (br. s, 1 H, D_2O exchangeable), 2.06 (ddq, J = 6.4, 1.4, 7.5 Hz, 2 H), 1.44 (dddd, J = 9.0, 6.3, 6.3, 3.2 Hz, 1 H), 0.98 (t, J = 7.5 Hz, 3 H), 0.88 (ddd, J = 9.3, 3.2, 3.7 Hz, 1 H), 0.62 (dt, J = 6.3, 9.3 Hz, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 130.8, 126.2, 69.2, 62.1, 58.2, 25.7, 20.7, 13.8, 13.0. – MS (**26a** + **26b**): m/z (%) = 156 (5) [M^+], 142 (11), 127 (10), 97 (9), 80 (24), 73 (54), 58 (38). – $C_9H_{16}O_2$ (**26a** + **26b**): calcd. C 69.19, H 10.32; found C 69.04, H 10.21.

27 (62%); **27a:** 1H NMR ($CDCl_3$): δ = = 4.85 (m, 1 H), 4.81 (m, 1 H), 4.16 (q, J = 6.4 Hz, 1 H) 3.69–3.61 (m, 2 H), 3.47–3.41 (m, 2 H), 3.08 (q, J = 6.4 Hz, 1 H), 2.11 (br. s, 1 H, D_2O exchangeable), 2.08–1.79 (m, 4 H), 1.82 (s, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 144.5, 111.0, 76.1, 69.7, 61.8, 47.4, 27.8, 22.5, 19.3. – MS: m/z (%) = 156 (3) [M^+], 141 (10), 128 (25), 113 (5), 94 (69), 84 (51), 79 (55), 67 (73). – $C_9H_{16}O_2$: calcd. C 69.19, H 10.32; found C 69.27, H 9.99.

28 (64%); **28a:** ^{1}H NMR ($CDCl_3$): δ = 5.46 (dq, J = 5.8, 15.4 Hz, 1 H), 5.37 (dd, J = 15.4, 7.9 Hz, 1 H), 3.69–3.62 (m, 3 H), 3.48–3.31 (m, 2 H), 2.69 (qt, J = 7.9 Hz, 1 H), 2.32 (br. s, 1 H, D_2O exchangeable), 2.08–1.74 (m, 2 H), 1.69 (d, J = 5.8 Hz, 3 H), 1.31–0.92 (m, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 133.1, 124.8, 78.8, 69.2, 61.7, 46.8, 26.7, 18.6, 17.7. – **28b:** ^{1}H NMR ($CDCl_3$): δ = 5.57 (dq, J = 5.8, 15.4 Hz, 1 H), 5.46 (dd, J = 15.4, 7.9 Hz, 1 H), 3.97 (qd, J = 7.3 Hz, 1 H), 3.69–3.62 (m, 2 H), 3.48–3.31 (m, 2 H), 3.06 (m, 1 H), 2.32 (br. s, 1 H, D_2O exchangeable), 2.08–1.74 (m, 2 H), 1.72 (d, J = 5.8 Hz, 3 H), 1.31–0.92 (m, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 129.9, 126.2, 74.8, 69.5, 61.7, 44.4, 28.0, 19.9, 17.7. – MS (**28a** + **28b**): m/z (%) = 156 (6) [M^+], 141 (11), 128 (25), 113 (10), 95 (100), 84 (27), 68 (81). – $C_9H_{16}O_2$ (**28a** + **28b**): calcd. C 69.19, H 10.32; found C 69.16, H 9.94.

29 (71%); **29a:** ^{1}H NMR ($CDCl_3$): δ = 5.58 (ddd, J = 15.3, 8.0, 1.3 Hz, 1 H), 5.49 (dq, J = 15.3, 6.1 Hz, 1 H), 3.77 (dt, J = 4.1, 4.4 Hz, 1 H), 3.73–3.64 (m, 2 H), 3.58–3.42 (m, 2 H), 2.45 (ddt, J = 8.0, 4.1, 5.6 Hz, 1 H), 2.34 (br. s, 1 H, D_2O exchangeable), 1.80–1.70 (m, 4 H), 1.68 (dd, J = 6.1, 1.3 Hz, 3 H), 1.66–1.53 (m, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 131.0, 125.5, 84.1, 70.2, 61.9, 47.7, 31.1, 29.8, 21.8, 18.1. – MS: m/z (%) = 170 (3) [M^+], 155 (10), 139 (15), 108 (55), 102 (54), 93 (100), 79 (59), 67 (86). – $C_{10}H_{18}O_2$: calcd. C 70.55, H 10.66; found C 70.49, H 10.46.

33 (75%); **33a:** ^{1}H NMR ($CDCl_3$): δ = 5.52 (m, 1 H), 4.08 (q, J = 7.3 Hz, 1 H), 3.63 (m, 2 H), 3.44 (m, 2 H), 3.27 (q, J = 7.3 Hz, 1 H), 2.43–2.06 (m, 9 H), 1.94–1.73 (m, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 147.2, 125.7, 75.4, 69.7, 61.8, 42.6, 34.6, 32.2, 28.6, 23.7, 18.9. – **33b:** ^{1}H NMR ($CDCl_3$): δ = 5.39 (m, 1 H), 3.81 (dt, J = 7.6, 8.5 Hz, 1 H), 3.68 (m, 2 H), 3.48 (m, 2 H), 2.87 (q, J = 8.5 Hz, 1 H), 2.35–1.51 (m, 11 H). – ^{13}C NMR ($CDCl_3$): δ = 145.5, 123.4, 77.6, 69.1, 61.8, 45.3, 33.2, 32.3, 26.8, 23.3, 17.9. – MS (**33a** + **33b**): m/z (%) = 182 (16) [M^+], 154 (25), 139 (21), 120 (59), 94 (100), 79 (92). – $C_{11}H_{18}O_2$ (**33a** + **33b**): calcd. C 72.49, H 9.95; found C 72.86, H 9.84.

34 (61%); **34a:** ^{1}H NMR ($CDCl_3$): δ = 5.49 (m, 1 H), 4.08 (dt, *J* = 5.4, 7.1 Hz, 1 H), 3.67–3.36 (m, 4 H), 3.01 (dt, *J* = 5.4, 6.1 Hz, 1 H), 2.07–1.24 (m, 13 H). – ^{13}C NMR ($CDCl_3$): δ = 136.8, 122.1, 79.2, 69.9, 62.0, 41.6, 34.7, 29.0, 26.4, 25.2, 22.0, 20.8. – **34b:** ^{1}H NMR ($CDCl_3$): δ = 5.44 (m, 1 H), 3.78 (dq, *J* = 7.0, 8.8 Hz, 1 H), 3.69–3.20 (m, 4 H), 2.68 (q, *J* = 8.8 Hz, 1 H), 2.31–1.49 (m, 13 H). – ^{13}C NMR ($CDCl_3$): δ = 139.1, 118.5, 82.1, 69.8, 62.2, 44.0, 35.2, 32.6, 27.7, 26.1, 25.1, 23.2. – MS (**34a** + **34b**): *m/z* (%) = 196 (2) [M^+], 184 (95), 181 (11), 173 (100), 168 (18). – $C_{12}H_{20}O_2$ (**34a** + **34b**): calcd. C 73.43, H 10.27; found C 73.16, H 10.43.

35 (65%); ^{1}H NMR ($CDCl_3$): δ = 5.65 (dt, *J* = 5.4, 1.5 Hz, 1 H), 4.11 (m,1 H), 3.69–3.34 (m, 4 H), 3.08 (q, *J* = 7.1 Hz, 1 H), 2.21–1.41 (m, 15 H). – ^{13}C NMR ($CDCl_3$): δ = 143.3, 126.6, 77.1, 69.4, 61.8, 48.7, 32.7, 32.6, 28.4, 27.2, 26.9, 26.6, 19.7. – MS: *m/z* (%) = 210 (5) [M^+], 182 (19), 167 (21), 148 (69), 122 (100), 107 (44), 93 (78), 81 (62). – $C_{13}H_{22}O_2$: calcd. C 74.24, H 10.54; found C 74.45, H 10.59.

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