A Computational Study of Radical Haloacetal Cyclizations Controlled by the Acetal Center

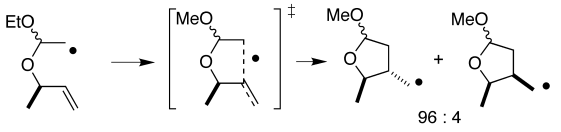
Olivier Corminboeuf,[a] Philippe Renaud,*[a] and Carl H. Schiesser*[b]

Abstract: The stereochemical outcome of the radical haloacetal cyclization reaction (Ueno–Stork reaction) has been examined by ab initio and other molecular orbital techniques. It was found that the stereochemistry of 5-*exo*- and 6-*exo* trig cyclizations can be accurately predicted from calculations using moderate levels of theory (UHF/6-311G** or B3LYP/6-311G**). A simplified computational procedure, easily run on a standard desktop computer, has been developed that provides excellent predictive ability for the stereochemical outcome for the reactions in question. Interestingly, a novel twist transition state has been identified for the first time in 5-*exo*-trig radical cyclization reactions.

Keywords: acetals · asymmetric synthesis · calculations · cyclizations · radical reactions

Introduction

Eighteen years ago, Ueno and Stork reported independently the very efficient 5-*exo* cyclization of bromoacetals.[1–6] This reaction is one of the most efficient radical reactions described to date and has been applied to the synthesis of a wide variety of molecules of interest.[7] It has been postulated that the allylic chiral center controls completely the stereochemical outcome of this reaction and that the second acetal stereogenic center does not influence the diastereoselectivity of the reaction [Eq. (1)].[1, 2, 8]



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On the other hand, there are several reports suggesting that the acetal center may well have an important influence[8–11] and, in some instances, it can provide some degree of stereocontrol.[12–19] In the preceding paper, we reported the full details of a systematic investigation of cyclization reactions where the acetal center is the unique stereogenic element and demonstrated that these reactions offer a highly diastereoselective route for the preparation of polysubstituted tetrahydrofurans and γ-lactones.[20] In order to provide a further level of understanding of this chemistry, we began to explore the mechanistic details of these radical ring closures using computational techniques. We now report that ab initio and other computational techniques are able to accurately predict the outcome of the reactions in question. These investigations have lead to the design of a simple computational procedure for predicting the stereochemical outcome of the Ueno–Stork reaction that can be applied readily on standard desktop computers. In addition, the calculation results stress the importance of the conformational anomeric effect. The presence of an unprecedented twist transition state has also been detected.

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Results and Discussion

The results presented here (see below) as well as those from other groups suggest that the simple and widely used Beckwith–Houk model[21–23] for radical cyclization of substituted hexenyl radicals is not applicable to the cyclization of haloacetals. It has been suggested that this failure is likely due to the anomeric effect stabilizing conformations where the exocyclic alkoxyl group occupies a pseudo axial position in the transition state for ring closure.[15–17] Consequently, methods that are based largely on steric interactions such as the simple molecular mechanics approach adopted by Beckwith and Schiesser[21] as well as Spellmeyer and Houk[23] are unlikely to give satisfactory results. The advent of faster, more

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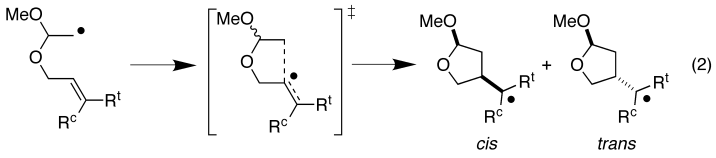
powerful computing facilities over the past decade or so has made possible the use of ab initio and other molecular orbital techniques to examine complex problems such as radical cyclization reactions of the type involved in Ueno–Stork chemistry.

Choice of the computational method—Cyclizations leading to 2-alkoxy-4-substituted tetrahydrofurans: In the preliminary phase of this study, a variety of computational methods ranging from semi-empirical to ab initio and density functional techniques were used to locate the *cis* and *trans* transition states involved in the cyclization of the simple radical **1a** leading to 2-alkoxy-4-substituted tetrahydrofurans [Eq. (2)]. In this manner, the computational methods best able to reproduce the experimentally observed stereoselectivities



1a: $R^c = R^t = H$
1b: $R^c = H$; $R^t = n$Pr
1c: $R^c = R^t = Me$

2a: $R^c = R^t = H$
2b: $R^c = H$; $R^t = n$Pr
2c: $R^c = R^t = Me$

for the reactions in question could be determined. In order to save computational cost, the methoxy substituted radical **1a** was used as a model for the ethoxy derivative used experimentally.[16, 20]

Five possible transition states were identified: a chair-axial, a twist-axial, a boat-axial, a chair-equatorial and a twist-equatorial (Figure 1). Interestingly, the twist transition state has not been reported so far. The existence of these transition states varied depending on the computational method employed; however, at any given level of theory, all structures located were fully characterized by harmonic frequency analysis which revealed the existence of only one imaginary frequency.

The boat-axial and twist-axial transition states are distinct only when the 3-21G basis set is used. At other levels of theory, these transition states collapse to the boat-axial (AM1) or the twist-axial (6-311G**) structures. Based on these results, it is clear that the boat and the twist transition states need to be considered separately (Table 1).

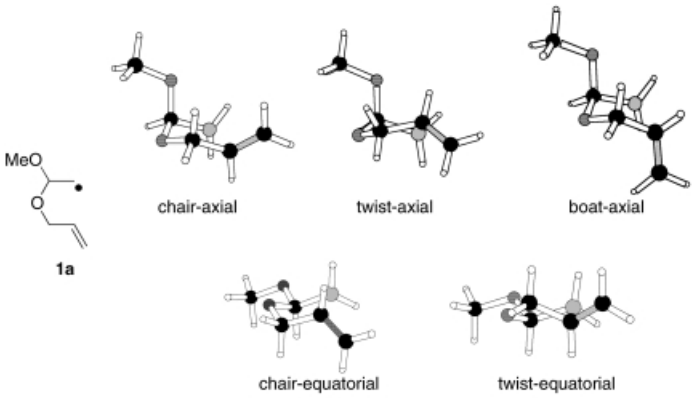


Figure 1. Calculated transition states for the cyclization of radical **1a**.

Inspection of the data in Table 1 also reveals that the two equatorial transition states (chair-equatorial and twist-equatorial) are much less stable than the axial structures by some 3–5 kcal mol^{-1}. Given that is it highly likely that this trend will continue in other series, transition states bearing equatorial anomeric methoxy groups are not considered in the rapid method (see below).

Toward a rapid computational method—Cyclizations leading to 2-alkoxy-4-substituted tetrahydrofurans: With the aim of developing a simple and rapid predictive tool for the evaluation of the stereochemical outcome during Ueno–Stork cyclizations, we considered fixing the transition state separations in other transition states of interest to values obtained for radical **1a**. Accordingly, the distance between the reacting centers in transition states involved in the ring closures of radicals **1b** and **1c**, was fixed at the value calculated for **1a** at the UHF/6-311G**//UHF/6-311G** and B3LYP/6-311G**//B3LYP/6-311G** levels of theory; these distances are listed in Table 2. The geometries of the remainder of these transition structures were then optimized

Table 2. Distance [Å] between the reacting centers at the transition states for cyclization of radical **1a**.

	chair-axial[a]	twist-axial	boat-axial
UHF/6-311G**//UHF/6-311G**	2.20	2.20	2.17
B3LYP/6-311G**//B3LYP/6-311G**	2.29	2.31	2.29

[a] These values have also been used for the boat-axial transition states as required.

Table 1. Relative energies[a] of the various transition states and calculated *cis*/*trans* diastereoselectivities of the cyclized product **2a** in the ring closure of radical **1a** (experimental *cis*/*trans* ratio for the cyclization of the ethoxy analogue of **1a**: $\geq$ 98:2).[20]

	Calculation method	chair-axial	twist-axial	boat-axial	chair-equatorial	twist-equatorial	*cis*/*trans*[c]
1	UHF/AM1//UHF/AM1	0	[b]	+0.69	[d]	[d]	86:14
2	UHF/PM3//UHF/PM3	0	[b]	+0.60	[d]	[d]	83:17
3	UHF/3-21G//UHF/3-21G	0	+0.45	+1.24	+5.29	+5.39	76:24
4	UHF/6-311G**//UHF/6-311G**	0	+1.37	[b]	+3.20	+5.04	97:3
5	MP2/3-21G//MP2/3-21G	0	+0.05	+1.98	[d]	[d]	54:46
6	MP2/6-311G**//MP2/6-311G**	0	+0.84	+2.30	[d]	[d]	90:10
7	B3LYP/3-21G//B3LYP/3-21G	0	+0.39	+1.82	[d]	[d]	73:27
8	B3LYP/6-311G**//B3LYP/6-311G**	0	+1.36	[b]	[d]	[d]	97:3

[a] Energies in kcal mol^{-1}. [b] Not located at this level of theory. [c] Determined at -78°C assuming identical entropy terms. [d] Not calculated.

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using the 3-21G basis set. In addition, higher-level single point calculations were performed on these optimized structures, the results of which are listed in Table 3.

Comparison of entries 1/2, 3/4, 5/6 and 7/8 in Table 3 reveals that minor changes in separation between reacting centers, as is observed between UHF/6-311G** and B3LYP/6-311G** calculations (Table 2), is not critical and that only minor changes in relative energy are observed. The most crucial parameter would appear to be the basis set used for the single point energy calculation. The best results are clearly obtained using the UHF/6-311G** and B3LYP/6-311G** methods for single-point energies (entries 3, 4, 7 and 8). For example, using B3LYP/6-311G**//B3LYP/3-21G[B3LYP/6-311G**],[24] an activation energy difference of 1.66 kcal mol^{-1} between *trans* and *cis* pathways during the ring closure of **1a** is predicted. This energy different translates into a 99:1 ratio at $-78\,^{\circ}C$, assuming identical entropy terms. When the smaller (3-21G) basis sets was used, the energy difference between the two most stable transition states was calculated to be substantially lower (entries 1, 2, 5 and 6), leading to significant underestimation of stereoselectivity during the ring closure of **1a**. To further test the validity of our calculations, the ring closure reactions of radicals **1b** and **1c** were investigated using both UHF/6-311G**//UHF/3-21G[UHF/6-311G**] and B3LYP/6-311G**//B3LYP/3-21G[B3LYP/6-311G**] methods, the results of which are also listed in Table 3 (entries 9–12). Once again, predictions made using these methods are in excellent agreement with available experimental data.[20]

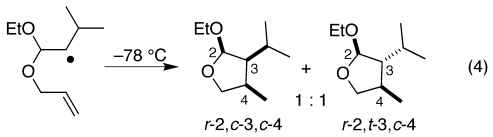
Cyclizations leading to 2-alkoxy-3,4-disubstituted tetrahydrofurans: The cyclization reactions of radicals **3**, leading to the 2-methoxy-3,4-disubstituted tetrahydrofurans **4** [Eq. (3)] were next examined using our previously described UHF/6-311G**//UHF/3-21G[UHF/6-311G**][25] rapid computational procedure.[26] These radicals strongly resemble the analogous ethoxy-substituted systems reported in the previous paper.[20] The relevant data are summarized in Table 4.

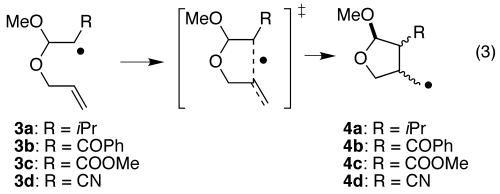
Table 4. Relative energies[a] of transition states involved in the cyclization of radicals **4** using the fixed distance approach.

	Radical	R	chair-axial-*cis*	chair-axial-*trans*	twist-axial-*cis*	twist-axial-*trans*	boat-axial-*cis*	boat-axial-*trans*
1	**3a**	*i*Pr	0	+0.05	+2.05	+1.16	+2.68	+1.46
2	**3b**	COPh	+6.80	0	+2.23	+6.38	+5.62	+8.83
3	**3c**	CO_2Me	+5.7	0	+2.23	+6.30	+2.23	+7.38
4	**3d**	CN	+0.99	0	+1.73	+1.66	+2.82	–

[a] Energies in kcal mol^{-1}.

Consideration of the various possible conformations available to transition states involved in these ring closure reactions reveals a possible six transition states and all six were located in the case of **3a** (Figure 2). Inspection of Table 4 reveals that the two chair-axial transition states are by far the most stable and possess very similar energies. Indeed, the calculated energy difference between the *trans* and *cis* pathways of only 0.05 kcal mol^{-1} is in excellent agreement the with 1:1 mixture of (*r*-2,*c*-3,*c*-4)[27] and (*r*-2,*t*-3,*c*-4) that were isolated in closely related experiments [Eq. (4)].[20] The





chair-axial-*trans* transition state involved in the ring closure of the benzoyl radical **3b** is by far the most stable of the transition states available to this radical, being some 2.23 kcal mol^{-1} lower in energy than its nearest rival (entry 2, Table 4). This value fits well with the available experimental data for **3b** that cyclizes with a diastereoselectivity in excess of

Table 3. Relative energies[a] and stereoselectivity calculated for the ring closure of radicals **1a**, **1b** and **1c** using the fixed distance approach [Eq. (1)].

		Method[b]	chair-axial	twist-axial	boat-axial	$\Delta E^{\ddagger}$(*trans*) – $\Delta E^{\ddagger}$(*cis*)	*cis*/*trans* calcd[c]	*cis*/*trans* exptl[d]
1	**1a**	UHF/3-21G//UHF/3-21G [UHF/6-311G**]	0	0.45	1.71	0.45	76:24	>98:2
2	**1a**	UHF/3-21G//UHF/3-21G [B3LYP/6-311G**]	0	0.42	1.65	0.42	75:25	>98:2
3	**1a**	UHF/6-311G**//UHF/3-21G[UHF/6-311G**]	0	1.55	1.93	1.55	98:2	>98:2
4	**1a**	UHF/6-311G**//UHF/3-21G[B3LYP/6-311G**]	0	1.63	2.12	1.63	99:1	>98:2
5	**1a**	B3LYP/3-21G// B3LYP/3-21G[UHF/6-311G**]	0	0.40	1.76	0.40	74:26	>98:2
6	**1a**	B3LYP/3-21G// B3LYP/3-21G[B3LYP/6-311G**]	0	0.32	1.80	0.32	70:30	>98:2
7	**1a**	B3LYP/6-311G**//B3LYP/3-21G[UHF/6-311G**]	0	1.44	2.26	1.44	98:2	>98:2
8	**1a**	B3LYP/6-311G**//B3LYP/3-21G[B3LYP/6-311G**]	0	1.66	2.50	1.66	99:1	>98:2
9	**1b**	UHF/6-311G**//UHF/3-21G[UHF/6-311G**]	0	1.40	1.90	1.40	97:3	92:8
10	**1b**	B3LYP/6-311G**//B3LYP/3-21G[B3LYP/6-311G**]	0	1.39	2.20	1.39	97:3	92:8
11	**1c**	UHF/6-311G**//UHF/3-21G[UHF/6-311G**]	0	1.25	0.43	0.43	77:25	78:22
12	**1c**	B3LYP/6-311G**//B3LYP/3-21G[B3LYP/6-311G**]	0	1.06	0.54	0.54	80:20	78:22

[a] Energies in kcal mol^{-1}. [b] Notation: B3LYP/6-311G**//B3LYP/3-21G[UHF/6-311G**] refers to a B3LYP/6-311G** single-point calculation performed on a B3LYP/3-21G-optimized structure with reacting centers fixed at the distance determined for **1a** at the UHF/6-311G** level of theory. [c] Determined at $-78\,^{\circ}$ assuming identical entropy terms. [d] Value for the ethoxy analogue.[20]

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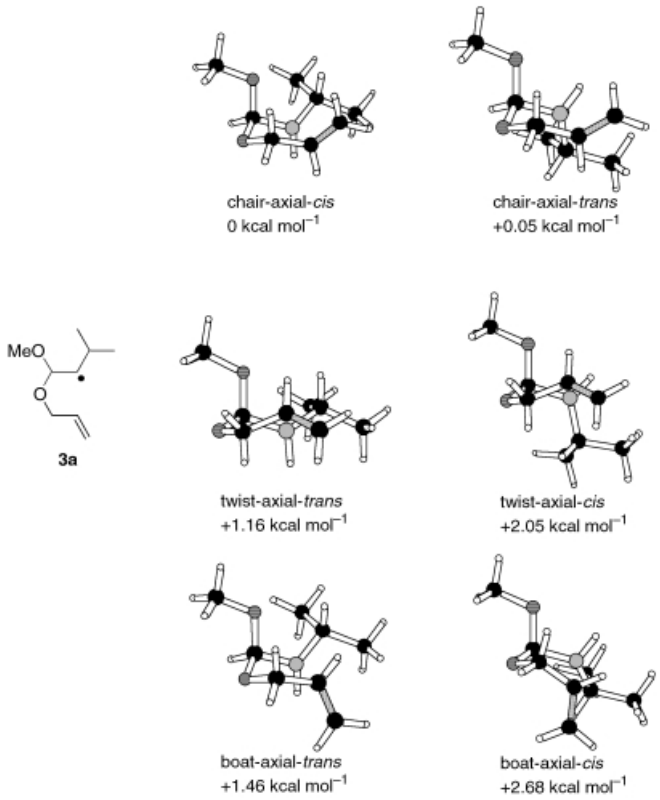
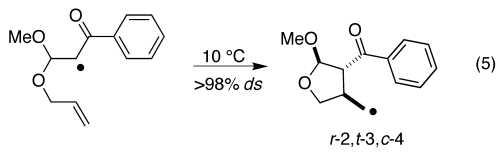


Figure 2. Optimized transition structuresfor the cyclization of radical **3a** (axial refers to the position of the 2-methoxy group and *cis*/*trans* to the relative position of the 3-*i*Pr and 4-Me group in the final product).

>98% [Eq. (5)].[20] A related example with complete stereocontrol has been reported by Stoodley.[19]

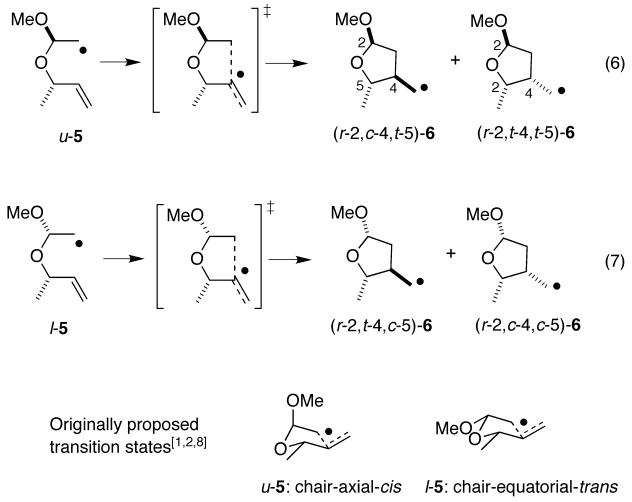


(5)

The corresponding ester and cyano substituted radical **3c** and **3d** were also investigated (Table 4, entries 3 and 4); in both cases, complete stereoselectivity in favor of the 2,3-*trans*-4,5-*trans* compound is predicted; this confirms the directional importance of electron withdrawing substituents in these reactions. No experimental data are available for comparison with these substrates.

Cyclizations leading to 2-alkoxy-4,5-disubstituted tetrahydrofurans: The cyclization of haloacetals derived from chiral allylic alcohols has been investigated in the original work of Ueno and Stork and it proved to be a very efficient method for the preparation of chiral lactones [Eq. (1)]. Models to rationalize the high *trans* stereoselectivities of these processes have been discussed based on the classical Beckwith–Houk transition states in which alkoxy substituents were occupying either axial or equatorial positions in chair and boat conformations.[1, 2, 8]

Based on our transition state calculations (see above), we believe that such models cannot provide an adequate description of this chemistry. It is apparent that transition state twist conformations have to be taken into account and that only structures in which the anomeric alkoxy groups are orientated in pseudo-axial positions are important. Calculations performed on the diastereomeric radicals *u*-**5** and *l*-**5** confirmed this hypothesis [Eqs. (6) and (7), Figure 3]. For



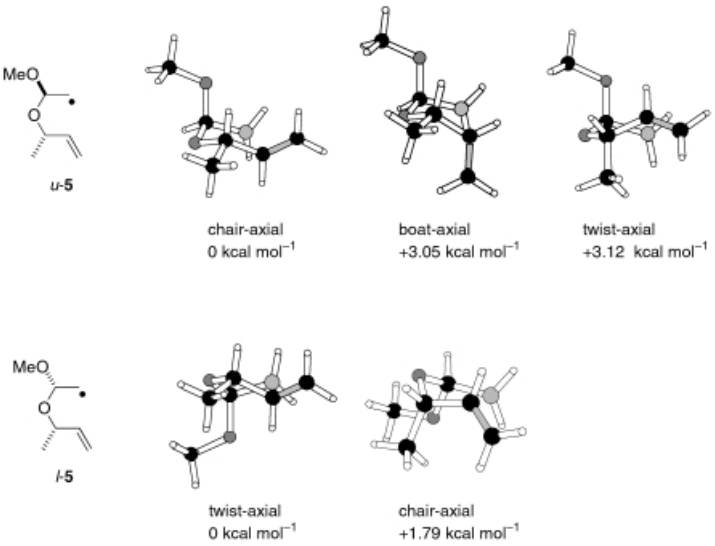


Figure 3. Calculated transition states for the cyclization of radicals *u*-**5** and *l*-**5**.

instance, in the case of radical *l*-**5**, no transition state bearing a pseudoequatorial methoxy group could be located after extensive searching. Indeed, starting structures bearing pseudoequatorial methoxy groups invariably collapsed to the twist axial transition state during optimization. For *u*-**5**, chair, boat and twist transition state conformations were found, with the chair-axial transition state being of lowest energy by more that 3 kcal mol^{-1}. This transition state leads to the formation of the 4,5-*trans* disubstituted tetrahydrofuran which is predicted to be formed with very high diastereomeric excess. For *l*-**5**, one chair and two twist transition states were found. The chair-axial transition state is predicted to be high in energy and the

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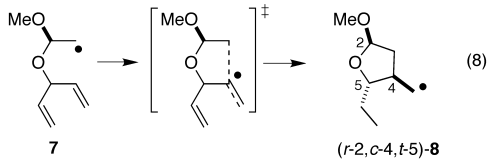
most stable transition state is found to be the twist-axial-*trans* (Figure 3). To the best of our knowledge, this is the first time that a twist transition state has been implicated in a 5-*exo* trig homolytic cyclization process. A second twist transition state leading to the 4,5-*cis* disubstituted tetrahydrofuran (twist-axial-*cis*) has also been detected but is significantly less stable. Interestingly, both diastereomeric radicals *u*-**5** and *l*-**5** are predicted to provide a tetrahydrofuran with *trans* orientation of substituents at positions 4 and 5. It is clear that the preferred transition state in the cyclization of *u*-**5** and *l*-**5** are quite different. It is therefore misleading to represent the transition state in a manner that depicts the forming ring as a simple chair with substituents in pseudo-axial or equatorial positions (e.g. chair-axial-*trans* and chair-equatorial-*trans*) since the only element of similarity between transition states such as *u*-**5** and *l*-**5** is the pseudo-axial alignment of the 2-alkoxy group.

The cyclization of ethoxy analogue of radical **5** has been reported by Ueno[1, 2] and Schäfer[8] [Eq. (1)]. The radical cyclization has been run with a 1:1 mixture of diastereomers and after oxidation of the acetal, the *trans* lactone was isolated as major isomer (*trans*/*cis* 96:4). This results fit very well with our calculations that predict at 50 °C a 94:6 ratio for *l*-**5**. We next chose to examine the ring closure of **7**; the analogous ethoxy-substituted radical that has been shown to cyclize to afford the tetrahydrofuran (*r*-2,*c*-4,*t*-5)-**8** with 98% diastereomeric excess at −78°.[20] Following our established procedure, the most stable transition state involved in this reaction was found to be the chair-axial-*trans* structure (Figure 4). The twist-axial-*trans* structure was calculated to be less stable by some 1.92 kcal mol^{-1} followed by the boat-axial-*cis* (+2.48 kcal mol^{-1}). Based on these data, a diastereoselectivity in excess of 99% is predicted at −78 °C, in excellent agreement with the experimental data [Eq. (8)].



Cyclizations leading to 2-alkoxy-3,4,5-substituted tetrahydrofurans: Transition states for the reactions depicted in Equation (9) were examined next. Experimental and calculated diastereoselectivities are reported in Table 5 and are in good agreement, except for entry 2 where the calculated diastereoselectivity is somewhat overestimated. However, this reaction is the only one that has been run under iodine atom transfer conditions. It cannot be excluded that under these conditions, partial epimerization of the acetal center due to traces of HI is occurring.

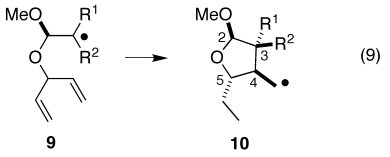
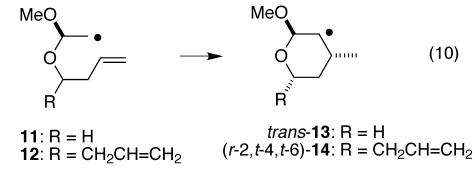


Table 5. Experimental and calculated diastereoselectivities for ring closures of radical **9** leading to 2-methoxy-3,4,5-substituted tetrahydrofurans [Eq. (9)].

	Radical[a]	R^1,R^2	T [°C]	Diastereoselectivity exptl[b] [%]	calcd [%]
1	**9a**	Me,Me	−78	>98	92
			0	8	85
2	**9b**	COOMe	10	77	98
3	**9c**	*i*Pr	−78	63	59

[a] Calculations performed on the methoxy-substituted analogue. [b] Values for the ethoxy analogue.[20]

Cyclizations leading to tetrahydropyrans: The 6-*exo*-trig cyclization of Equation (10) has also been investigated using the model developed for 5-*exo*-trig cyclizations. The strong anomeric effect observed in the five-membered rings allowed us to perform calculations only on the transition states possessing the axial alkoxy group. The results of the calculations for the ring closure of radicals **11** and **12** using our previously-described model are shown in Figures 5 and 6. In the former case, six different transition states **A**–**F** were located. The two most stable ones, **A** and **D**, ressemble the chair transition states involved in the formation of the previously discussed tetrahydrofurans. Transition state **A**, that leads to *trans*-**11**, is the most stable by 1.63 kcal mol^{-1}. These calculated data fit well with the experimental results reported by Beckwith and Page in which the *trans* ring-closed product was isolated with a diastereoselectivity of 74% at 80 °C.[15]



In the case of the ring-closure of radical **12**, our simplified method afforded transition

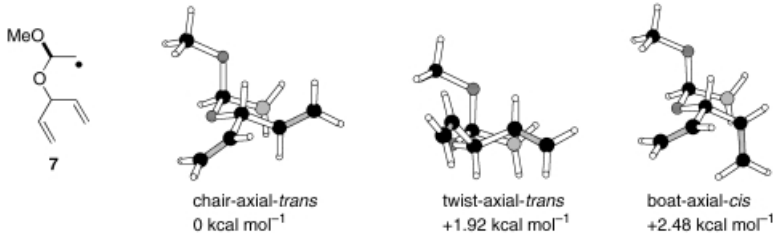


Figure 4. The three most stable transition states involved in the cyclization of **7** (axial refers to the position of the 2-methoxy group and *cis*/*trans* to the relative position of the 4-Me and 4-vinyl group in the final product).

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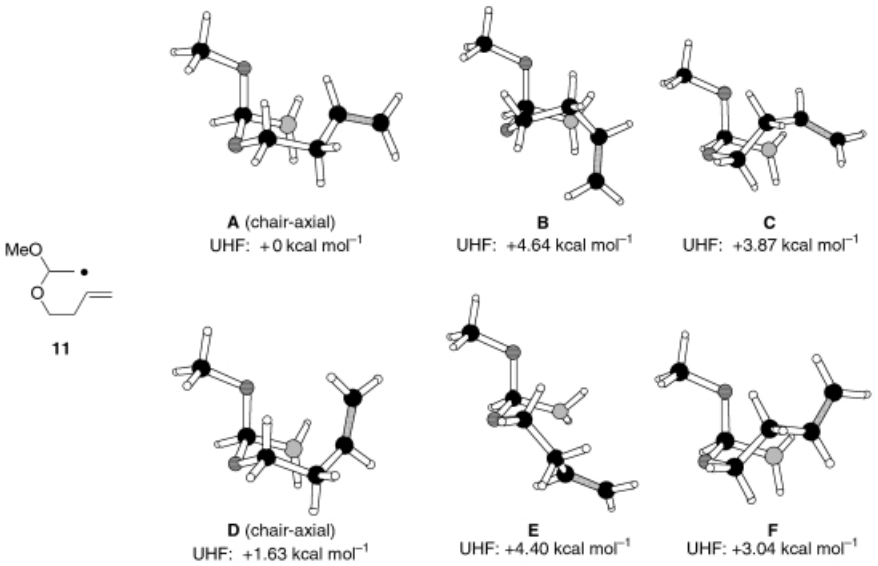

Figure 5. Transition states calculated for the 6-*exo*-cyclization of **11**.

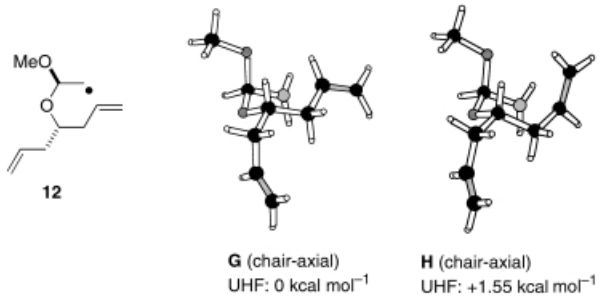

Figure 6. The two most stable transition states involved in the 6-*exo*-trig cyclization of **12**.

states very similar to those located for the cyclization of **11**. The two most stable transition states **G** and **H** are both chair axial (Figure 6). Inspection of Figure 6 reveals that **G** transition state is preferred over **H** by 1.55 kcal mol^{-1}, in excellent agreement with the experimentally observed exclusive formation of **14** at -78° in similar Ueno–Stork chemistry [Equation (11) in the previous paper[20]].

Conclusion

Cylizations of haloacetals represent a useful tool for asymmetric synthesis. The stereochemical outcome of 5-*exo*- and 6-*exo* trig cyclizations can be accurately predicted from calculation at moderate levels of theory (UHF/6-311G** or B3LYP/6-311G**). More interestingly, a simplified calculation procedure, easily run on a standard desktop computer, has been developed and gives excellent results, either for 5-*exo*- or for 6-*exo* trig cyclizations.

Based on these calculations, the high diastereoselectivity of the Ueno–Stork cyclization procedure is now better understood. The importance of the conformational anomeric effect is highlighted. The model used in these cyclizations differs from the classical Beckwith–Houk model not only by the preferential axial position of the alkoxy groups but also by the presence of twist transition states together with the well known chair and boat ones. These results support well the experimental data demonstrating that the acetal center can efficiently control the stereochemistry at C(4) of tetrahydrofurans during Ueno-Stork haloacetal cyclizations. The control of the C(3) and C(5) centers is also possible for a certain number of well designed substrates.

Computational methods

Calculations were generally performed either using the AM1 or PM3 (semiempirical) methods or with the 3-21G or 6-311G** basis sets at the unrestricted Hartree–Fock (UHF) or B3LYP level as implemented in the Spartan program package[28] or Gaussian 98 program package.[29] When MP2 calculations were employed, the frozen core approximation was used. Transition structures were characterized by harmonic frequency analysis at the level of optimization to ensure that all species had the correct number of imaginary frequencies. Optimized geometries of all optimized transition structures in this study are available as Supporting Information.

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[26] Transition states bearing equatorial anomeric methoxy groups were not considered since they were expected to be significantly less stable that the corresponding axial structures, if they existed at all. The fact that our computational data are in good agreement with experimental observations provides strong support for the unimportance of these structures.
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