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ARTICLE

How an Early or Late Transition State Impacts the Stereoselectivity of Tetrahydropyran Formation by Intramolecular oxa-Michael Addition

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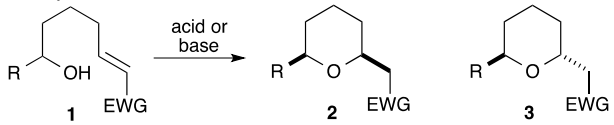
The intramolecular oxa-Michael addition giving tetrahydropyrans has been examined experimentally using both acidic and basic catalysis. With acidic catalysis, the diequatorial product is exclusively obtained in a kinetically controlled reaction in all cases. Under basic conditions at low temperature, the reaction is again under kinetic control, but formation of the axial-equatorial isomer is generally favoured with an (*E*)-Michael acceptor, although isomerisation to the diequatorial isomer is observed at higher temperatures. Computationally, it is found that the acid catalysed reaction has a late transition state and the kinetic favouring of the diequatorial isomer has a steric explanation. In contrast, under strongly basic conditions, an early transition state is found. Electrostatic effects are likely to be the main contributor to the stereoselectivity for the (*E*)-isomer and steric interactions for the (*Z*)-isomer.

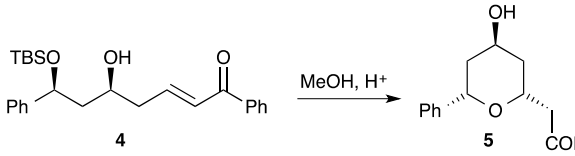
Introduction

The intramolecular oxa-Michael reaction is a widely used method for the formation of the tetrahydropyran (THP) ring (Scheme 1).[1] This method has gained particular utility with the advent of the alkene cross-metathesis reaction. There are numerous examples in the literature,[2] including a number from this laboratory.[3] The electron withdrawing group employed is often an ester, a ketone or a thioester. While the reaction is often base-catalysed, acid catalysis may also be used when the alkene is activated by a ketone group.[3a,c,d,f] In general esters do not cyclise under mild acidic conditions, unless forced.[2b]



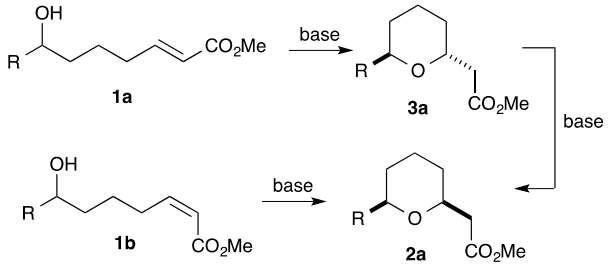
Scheme 1. The intramolecular oxa-Michael reaction; EWG = electron withdrawing group.

An important question concerns the stereochemical outcome. If the substrate **1** has a secondary alcohol as the nucleophilic group, either the 2,6-*cis* isomer **2** or the 2,6-*trans* isomer **3** may be formed. The 2,6-*cis* isomer **2**, with diequatorial substituents will, of course, be the thermodynamically favoured product as, for example, in Scheme 2.[3a] When the activating group is a ketone, then this isomer is always formed under acid catalysis.



Scheme 2. Acid catalysed formation of the 2,6-*cis* isomer in a synthesis of diospongin A.

In complete contrast, when the starting Michael acceptor has *E*-stereochemistry and basic catalysis is applied at a reduced temperature, then the major product is likely to be the 2,6-*trans* isomer **3a** (Scheme 3), an observation first made by Banwell *et al.*[2k] Upon prolonged exposure to base, or use of higher temperatures, epimerisation occurs via a retro-Michael-Michael mechanism, and the product is the 2,6-*cis* isomer **2a**. This strategy has been commonly used.[4] Banwell also made the contrasting observation that the corresponding *Z*-isomer **1b** of the Michael acceptor behaves differently, giving the *cis* isomer **2a** of the tetrahydropyran under basic conditions.[2k]



Scheme 3. Base catalysed formation of either isomer

It is pertinent to ask why the formation of the 2,6-*trans* isomer from the *E*-alkene should be kinetically favoured under basic

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Electronic Supplementary Information (ESI) available: experimental procedures for compounds **8**-**12** and **14**-**25**; ^{1}H and ^{13}C NMR spectra; X-ray crystallographic structures for compounds **cis-20**, **trans-19** and **trans-21**; comprehensive literature survey; computational details. See DOI: 10.1039/x0xx00000x

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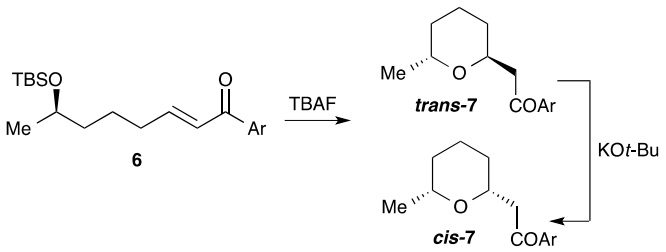
conditions. Chelation of the counter ion between the alkoxide oxygen atom and an oxygen atom of the ester group has been suggested although such a mechanism would invoke a ten membered ring containing a *trans* double bond.[5] On the other hand, in a synthesis of Curvulone B **7**, Takahashi employed an oxa-Michael addition to an α,β-unsaturated ketone of an alkoxide generated *in situ* by cleavage of a TBS ether **6** with TBAF (scheme 4). This process, in which chelation cannot be a factor, favoured the formation of the *trans* isomer and, therefore, required a second base catalysed equilibration step (in contrast to a closely related acid catalysed cyclisation[3f]). One of the first computational studies of this reaction was focused on a single complex polycyclic system and, therefore, may not be general.[6] Another early study examined a reaction which can also be an S_N' process.[7] Two studies are remarkably contrasting. In one of them, by Martín, "net TSs were not detected when the free enolates were used",[5] thus precluding proper consideration of whether the counter cation has a role. In the second, however, the role of the cation was disregarded![2i] In this latter study, the lower energy of the transition state leading to the *trans* isomer was attributed to a more favourable angle of nucleophilic attack. Clarke *et al.* reported a thorough experimental and computational study involving a hydroxylated thioether system.[8] Similarly, a careful study conducted as a part of a synthesis of herboxidiene focused on a related hydroxylated system.[2a] The δ-hydroxyl group was found to play an essential role through hydrogen bonding in both studies. Another early synthetic study concentrated on substrates with an oxygen substituent in the allylic position.[9] Thus, combined experimental and computational studies to probe the stereochemical outcome of the simplest form of this reaction are yet to be reported and the question of the cause of the *trans* selectivity remains open. In addition, to the best of our knowledge there has been no explanation of the behaviour of the *Z*-isomer and, to the best of our knowledge, only a single study of the acid catalysed reaction.[8]



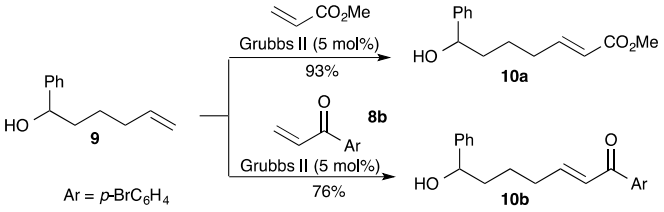
Scheme 4. Oxa-Michael addition in the synthesis of curvulone B with a non-coordinating counter ion.

The 2,6-substitution pattern has been the most widely employed. We believe that this reflects the ubiquity of this structure amongst THP containing natural products, itself a consequence of biosynthesis from acetate and propionate. However, in the era of diversity oriented synthesis,[10] the question of whether the same phenomena arise with other substitution patterns is worthy of investigation. Thus, we set out to study both the acid and base catalysed reactions using appropriate substrates and accessing all four substitution patterns, both experimentally and computationally, as well as addressing the question of the effect of the counter cation under basic conditions.

Results and discussion

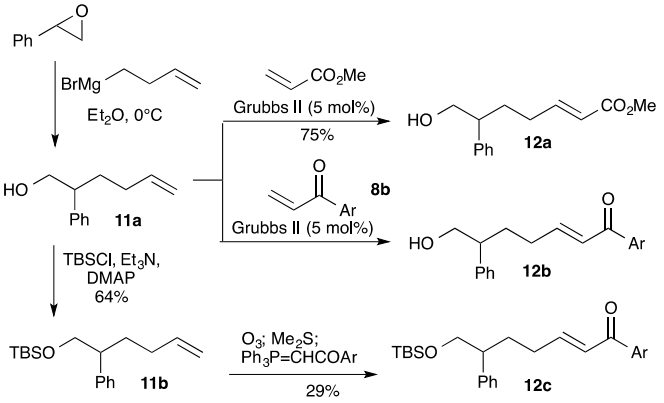
Synthesis of substrates

For the base catalyzed cyclisations, we selected a methyl ester group to activate the alkene as a Michael acceptor. For the acid catalyzed cyclisation reactions, we chose a *p*-bromobenzoyl group, partly in the hope that the compounds would display enhanced crystallinity, allowing the use of X-ray crystallography. For the substrates that would lead to the 2,6-disubstitution pattern, 1-phenylhex-5-en-1-ol **9** was subjected to cross metathesis with methyl acrylate and with *p*-bromophenylvinylketone **8b** to give the two desired substrates, **10a** and **10b**, without complication (Scheme 5).



Scheme 5. Synthesis of substrates leading to 2,6-disubstitution. Ar = *p*-BrC_6H_4.

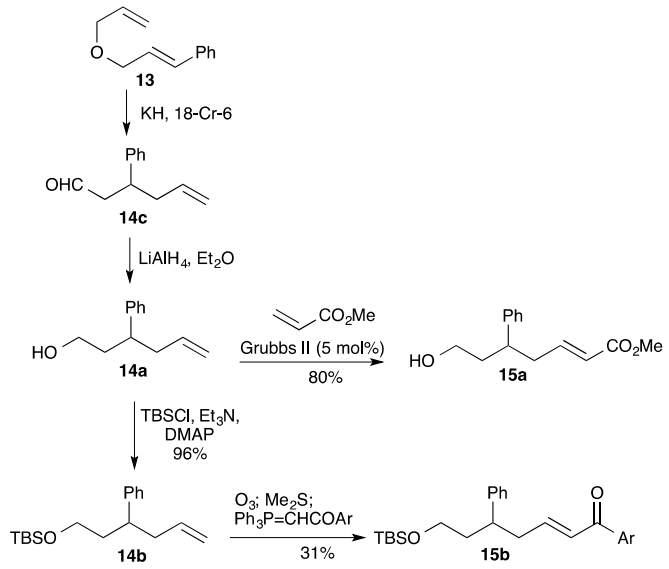
For the substrates that would lead to the 2,5-pattern, 2-phenylhex-5-en-1-ol was prepared in modest yield by ring opening of styrene oxide with the Grignard reagent derived from 4-bromobutene (Scheme 6).[11] While cross-metathesis with methyl acrylate proceeded uneventfully, cross-metathesis with enone **8b** provided a very low yield of the desired enone **12b**. An alternative and more conventional pathway involving protection, ozonolysis and a Wittig reaction delivered the corresponding TBS ether **12c**.[12]



Scheme 6. Synthesis of substrates leading to 2,5-disubstitution. Ar = *p*-BrC_6H_4.

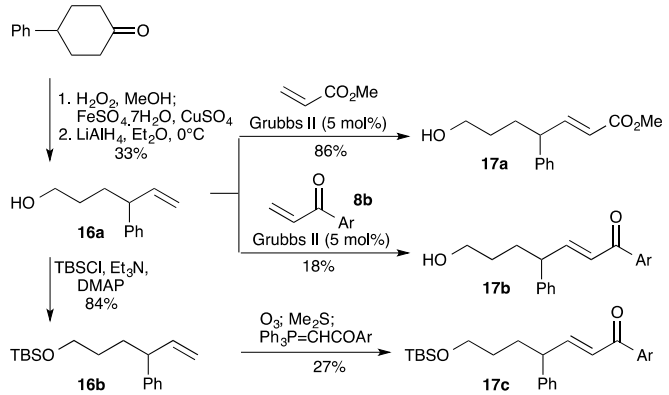
To access the substrates that would lead to the 2,4-pattern, allyl cinnamyl ether **13** was subjected to Wittig rearrangement, followed by reduction to give alcohol **14a** via the corresponding aldehyde **14c** (Scheme 7).[13] Again, cross-metathesis with methyl acrylate proceeded smoothly giving ester **15a**, while cross-metathesis with enone **8b** proceeded in disappointing yield. An

ozonolysis-Wittig procedure provided an alternative access to the corresponding TBS ether **15c**.



Scheme 7. Synthesis of substrates leading to 2,4-disubstitution. Ar = *p*-BrC_6H_4.

Finally, access to the substrates for the 2,3-pattern were obtained by oxidative ring opening of 4-phenylcyclohexanone (Scheme 8).[14] This yielded 4-phenylhex-5-enoic acid which could be reduced to the alcohol **16a**. Cross metathesis of alcohol **16a** with methyl acrylate yielded ester **17a** without any problems, despite the extra hindrance at the allylic position. Cross-metathesis with enone **8b**, however, gave only a poor yield of the desired ketone **17b**. An ozonolysis-Wittig sequence was employed, as before, to give the corresponding TBS ether **17c**.

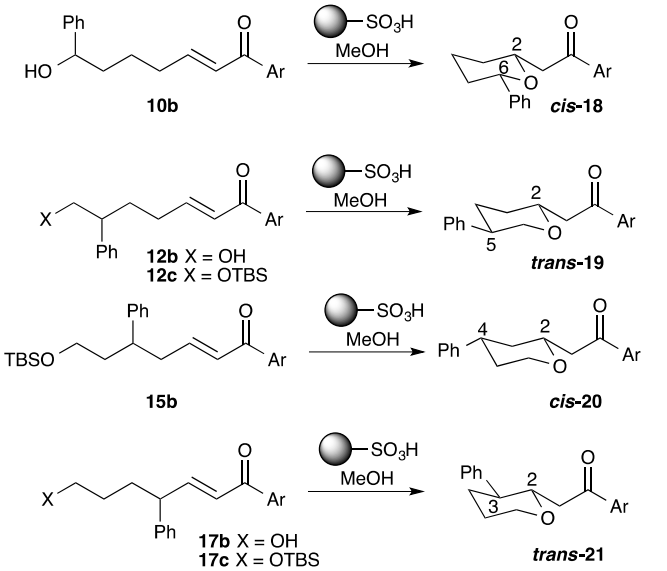


Scheme 8. Synthesis of substrates leading to 2,3-disubstitution. Ar = *p*-BrC_6H_4.

The Acid-catalysed oxa-Michael cyclisation

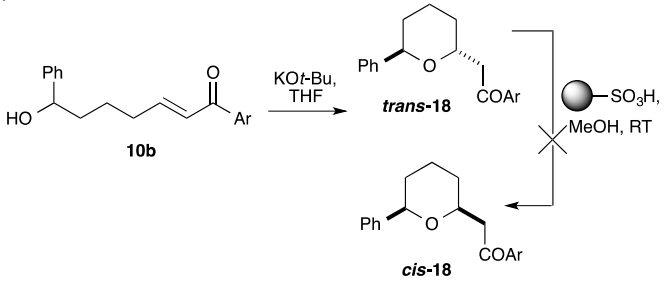
As a control experiment, ketone **10b** was exposed to acid (Amberlyst-15) in methanol and the product was found to give exclusively the 2,6-*cis* isomer ***cis*-18**, as expected (Scheme 9). The stereochemistry was determined by the observation of typical axial-axial coupling constants of 11 Hz in the signals of both H2 and H6, the protons α to the ring oxygen atom, in the ^{1}H NMR spectrum.

Similar treatment of ketones **12b, 12c**, **15b**, **17b** and **17c** gave the oxa-Michael products (Scheme 9). THP ***trans*-19** was determined to be the 2,5-*trans* isomer by observation of 10 Hz and 13 Hz coupling constants in the signals of H6 and H2 respectively. THP ***cis*-20** was found to be the 2,4-*cis* isomer by observation of a 15 Hz coupling constant between H2 and H3 and between H3 and H4. Indeed, H3, was found to be a 15 Hz triplet. THP ***trans*-21** was found to be the 2,3-*trans* isomer by observation of a 10 Hz coupling constant between H2 and H3. The stereochemistry of tetrahydropyrans ***trans*-19**, ***cis*-20** and ***trans*-21** was subsequently confirmed by X-ray crystallography.[15] All four of these tetrahydropyrans have a diequatorial substitution pattern and, thus, are in each case the thermodynamically more stable of the two possible products.



Scheme 9. Acid catalyzed cyclisation reactions. All reactions were carried out at room temperature. Ar = *p*-BrC_6H_4.

Even though these are the more stable products, it does not mean that they are formed for this reason. To test this, a 2:1 mixture of the 2,6-*cis* and 2,6-*trans* isomers of tetrahydropyran **18** was prepared by base catalysed cyclisation (Scheme 10). When this mixture was exposed to the same acidic conditions used for the cyclisation reactions, no change was observed. Therefore, these molecules do not equilibrate under these acidic conditions and the preference for the diequatorial products in the oxa-Michael addition is kinetic.



Scheme 10. Non-equilibration under acidic conditions. Ar = *p*-BrC_6H_4.

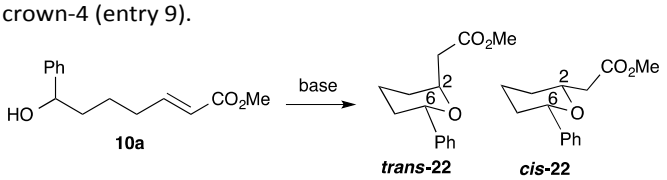
Strong base-catalysed oxa-Michael cyclisation

As Banwell pointed out, "a more extended survey of metal-ion effects seems warranted".[2k] Thus, for the base catalysed reaction, the role of the counter ion must first be addressed. If chelation is an important factor, then it would be expected that the stereoselectivity would be affected by the choice of cation. Therefore, a range of bases with varied counterions was tested. Alkoxide bases – principally *t*-butoxides – were used (Table 1).[16] In addition, some of these experiments were then repeated in the presence of excess of a crown ether. All initial studies were carried out using ester **10a**, giving the *cis* and *trans* tetrahydropyrans **22** (Scheme 11).

The stereochemistry could be determined by analysis of the coupling constants in the ^{1}H NMR spectra, as for the ketone analogs. For the isomer ***cis*-22** , the equatorial position of 2- and 6-substituents was apparent from the coupling constants of 11 Hz of the corresponding protons. The coupling constants of H2 in ***trans*-22** were observed to be 3 Hz and 7 Hz, while H6 was observed to be an apparent triplet with the coupling constant of 5.7 Hz. These values are consistent with *trans* stereochemistry.

With KO*t*-Bu in THF was used at -78°C, a ratio a little better than 5:1 in favour of the *trans* isomer was obtained (entry 1). A very similar result was obtained when this reaction was run in the presence of 5 equivalents (relative to K^+) of 18-crown-6 (entry 2). When the solvent was changed to toluene, a similar result was again obtained: KO*t*-Bu in toluene gave the same stereoselectivity, but a much slower reaction rate (entry 3). Only partial conversion was observed even after an extended reaction time. This is likely to be due to the low solubility of the alkoxide in toluene. Using 18-crown-6 with KO*t*-Bu in toluene gave complete conversion, and some slight erosion of selectivity (entry 4). When the base was changed to NaO*t*-Bu in THF, the result was very similar to that obtained with KO*t* -Bu (entry 5). In contrast however, the combination of NaO*t* -Bu and 15-crown-5 gave an increased proportion of the *cis* isomer (entry 6).[17] Use of sodium isopropoxide (entry 7) resulted in a similar level of stereoselectivity to NaO*t*-Bu, but a very slow reaction. No reaction was observed using NaO*i*-Pr at -78°C.

An obvious set of experiments involve lithium *t*-butoxide, as Li^+ is the most Lewis acidic cation in the group, and thus likely to promote chelation. When LiO*t*-Bu in THF was employed, we found that the reaction temperature had to be raised to -60°C (entry 8).[18] Even at this temperature, the reaction was slow compared to comparable reactions using K^+ and Na^+ counter ions. The low reactivity may be due to the tight binding of the lithium cation to the alkoxide oxygen.[19] The stereoselectivity was poor, although still favouring the *trans* isomer. Surprisingly, no reaction was observed using LiO*t*-Bu in the presence of 12-crown-4 (entry 9).



Scheme 11. Base catalyzed formation of the 2,6-disubstitution pattern.[20]

Table 1. The Intramolecular oxa-Michael addition (**10a** → **22**) using alkoxide bases[a,b]

entry	base	solvent	T/ °C	t/ h	conversion	selectivity *trans*:*cis*	additive
1	KO*t* -Bu	THF	-78	2	100%	5:1	none
2	KO*t* -Bu	THF	-78	2	100%	5:1	18-crown-6[c]
3	KO*t* -Bu	toluene	-78	15	27%	5:1	none
4	KO*t* -Bu	toluene	-78	15	100%	3.3:1	18-crown-6[c]
5	NaO*t* -Bu	THF	-78	2	100%	5:1	none
6	NaO*t* -Bu	THF	-78	2	100%	2:1	15-crown-5[c]
7	NaO*i*-Pr	THF-*i*-PrOH	-78	15	35%	5:1	none
8	LiO*t* -Bu	THF	-60	15	78%	1.4:1	none
9	LiO*t* -Bu	THF	-78-RT	15	0%	NA	12-crown-4[c]

a) 0.2 equivalents of the base was used; b) reactions were repeated in triplicate; c) 5 equivalents of crown ether relative to the base was used

The results thus far indicate no significant chelation effect. Most significant is the comparison of entries 1 and 2, showing almost no difference with and without addition of a crown ether. Comparison of entries 1 and 5 shows no difference on changing from K^+ to Na^+. The results with a lithium counter ion are harder to interpret as a different temperature is required. Nevertheless, the chelation argument would demand a higher proportion of the *trans* isomer with the more Lewis acidic counter ion, yet the opposite is observed in comparison of entry 8 with entries 1 and 5.

Mild base-catalysed oxa-Michael cyclisation

We were also interested to determine if other bases could be used (Table 2). K_2CO_3 and Cs_2CO_3 gave no conversion at RT; a modest conversion was observed using K_2CO_3 in THF at reflux, slightly favouring the *cis* isomer (entry 1). No reaction was observed using Et_3N, pyridine, TMEDA, *i*-Pr_2NEt, proton sponge

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or imidazole, even at reflux in THF for up to 15h. Only three nitrogen bases gave a respectable conversion. Use of tetramethylguanidine (TMG) in THF resulted in no reaction at RT, but slow cyclisation at reflux giving a mixture modestly favouring the *trans* isomer (entry 2). Employing the phosphazene P2-*t*-Bu base, after 15h at -78°C, a 50% conversion was observed, giving significant *trans* selectivity (entry 3). With DBU at RT in either THF or toluene, poor conversion was observed, but the *cis* isomer was now the major product (entries 4 and 5). Using DBU in refluxing THF or in refluxing toluene gave complete conversion (entries 6 and 7). Interestingly, all of these experiments employing DBU delivered almost the same stereoselectivity with a modest favouring of the *cis* isomer. It may be noted that when the *trans* isomer was resubmitted to these conditions, no equilibration was observed. Hence the partial selectivity for the *cis* isomer using DBU is kinetic. There is, therefore, a significant difference between basic conditions using alkoxides and basic conditions using amidines. The phosphazene, however, behaves more like an alkoxide. It is notable that, in the case of the phosphazene base, chelation is once again not feasible, yet the *trans* isomer is the major product. This result provides further support for the suggestion that chelation is not important. The results do suggest, however, that the transition state involving DBU is distinctly different. Given the lower basicity of DBU it may be suggested that no free alkoxide is formed and the DBU molecule remains closely associated.

Table 2 The Intramolecular oxa-Michael addition (**10a** → **22**) using non-alkoxide bases[a,b]

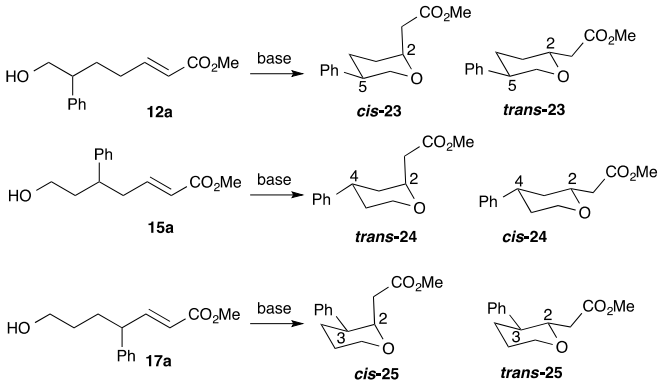
entry	base	solvent	T/ °C	t/ h	Conv-ersion	selectivity *trans*:*cis*
1	K_2CO_3	MeOH	reflux	15	ND	0.7:1
2	TMG	THF	reflux	15	29%	1.4:1
3	P2-*t*-Bu	THF	-78	15	50%	2.5:1
4	DBU	THF	rt	15	14%	2.5:1
5	DBU	toluene	rt	15	10%	2:1
6	DBU	THF	reflux	15	100%	2:1
7	DBU	toluene	reflux	15	100%	2.5:1
8	TBAF	THF	rt	15	100%	2:1
9	TBAF	THF	reflux	2.5	100%	*cis* only

a) 1 equivalent of the base was used; b) reactions were repeated in triplicate.

Mindful of Takahasi's curvulone synthesis,[2e] we examined the use of TBAF (entries 8 and 9). Complete cyclisation was observed in THF at room temperature, modestly favouring the *trans* isomer (entry 8). On the other hand, when this reaction was carried out in THF at reflux, the *cis* isomer was exclusively formed (entry 9). When the *trans* isomer was re-exposed to these conditions, no change was observed at room temperature, but complete conversion to the *cis* isomer was observed at reflux. The mixture obtained at RT, therefore, represents the kinetic distribution of products while fluoride is sufficiently basic to cause complete equilibration at reflux. The fact that the use of TBAF gives rise to the *trans* isomer as the major product is significant, as, again, no chelation is possible with the tetra-*n*-butylammonium counter ion.

oxa-Michael cyclisation of substrates with varied substitution pattern

It was of interest to see what happened if the substitution pattern was varied, as was done above in the ketone series. A series of experiments were carried out to investigate this (Table 3, Scheme 12).



Scheme 12. Base catalysed formation with the other disubstitution patterns.[20]

In the case of ester **12a** leading to the 2,5-isomer **23**, cyclisation using either TBAF or KO*t*-Bu was slower than for the 2,6-isomer. At -78°C, use of KO*t*-Bu gave significant selectivity in favour of the *cis* isomer (entry 1). As expected, the *trans* (diequatorial) isomer become the major product when the reaction was conducted at RT overnight (entry 2). A similar pattern was observed with TBAF: the *cis* isomer was by a small margin the major product at RT (entry 3); the *trans* isomer was the exclusive product when the reaction was conducted at reflux (entry 4). In *trans*-**23**, the equatorial position of the 2-substituent was verified by a coupling constant of 11 Hz for the corresponding proton. The equatorial position of the phenyl group was confirmed by observation of a 11 Hz coupling constants between the benzylic proton H5 and the axial proton at C6.

For ester **15a**, leading to the 2,4-isomer **24**, use of KO*t*-Bu in THF at -78°C gave the *trans* isomer exclusively (entry 5) – the highest selectivity that we have observed in the kinetically controlled series. At RT, the *cis* product became the major product (entry 6). With TBAF, the *cis* isomer was the major product at both RT and at reflux (entries 7 and 8). Turning to ester **17a**, leading to the 2,3 tetrahydropyrans **25**, use of KO*t*-Bu at low temperature gave useful selectivity in favour of the *cis* isomer (entry 9). At RT, the *cis* isomer remained the major isomer, but by a much smaller margin. With TBAF, cyclisation was very slow and both reflux and a higher catalyst loading were required. Again, the *cis* isomer was the major product (entry 10). It appears that the greater steric hindrance provided by having the phenyl group adjacent to the reacting centre slows down the chemistry.

The observation of a coupling constant of 10.4 Hz indicated the equatorial position of the 2-substituent in ***cis*-24**. Coupling constants 9.8 Hz and 2.3 Hz showed that the phenyl group was also in an equatorial position. The ^{1}H spectrum ***trans*-24** could not be entirely analysed as the two axial protons flanking the ring oxygen atom overlapped. However, the equatorial position of the phenyl group could be confirmed by the characteristic coupling constants of 8.5 Hz and 3.8 Hz.

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Table 3 The base catalysed intramolecular oxa-Michael addition for other substitution patterns

entry	SM, pattern	base	T/ °C	time/ h	selectivity *trans*:*cis*
1	**12a** 2,5	KO*t*-Bu[a]	-78	2	0.3:1
2	**12a** 2,5	KO*t*-Bu[a]	RT	overnight	2.5:1
3	**12a** 2,5	TBAF[b]	RT	overnight	0.8:1
4	**12a** 2,5	TBAF[b]	reflux	overnight	*trans* only
5	**15a** 2,4	KO*t*-Bu[a]	-78	2	*trans* only
6	**15a** 2,4	KO*t*-Bu[a]	RT	2	0.7:1
7	**15a** 2,4	TBAF[b]	RT	overnight	0.7:1
8	**15a** 2,4	TBAF[b]	reflux	2	0.5:1
9	**17a** 2,3	KO*t*-Bu[a]	-78	2	0.1:1
10	**17a** 2,3	KO*t*-Bu[a]	RT	3	0.6:1
11	**17a** 2,3	TBAF[b]	reflux	48	0.6:1

a) 0.2 eq. of base; b) 1 eq. of base

The coupling constant of 3.5 Hz was conclusive to verify the H_{eq}-H_{ax} relationship between H2 and H3 attached to Ph in ***cis*-25**. The coupling constant of 4.4 Hz associated with H3 was observed as a weighted average of conformers. In the case of the ***trans*-25**, H2 and H3 were found to be axial by observation of a 10 Hz coupling constant with one another.

Thus, a consistent pattern emerges that for all substitution patterns, under kinetic conditions, the isomer that is formed is the axial-equatorial isomer. Under forcing conditions, the major product is the diequatorial product, due to equilibration. As the earlier experiments (Tables 1 and 2) indicated that chelation is not a factor, we were interested to know what was causing the selectivity under kinetic conditions and, thus, turned to computational methods.

Computational Studies

We began the calculations by first obtaining the lowest energy conformers of the acyclic reactant. For the conformational analysis of the starting acyclic molecule, either protonated or deprotonated, we applied Monte Carlo sampling using the standard OPLS_2005 force field, which was carried out in the *MacroModel* software.[21] Next, all the distinct conformers within 10 kcal/mol were optimised using Density Functional Theory (DFT) with the *Gaussian* 09e suite of programmes.[22] The lowest-energy structure was used as a reference point for constructing the thermodynamic profile of the cyclisation. After due calibration using several other density functionals (see S.I. for more details), the ωB97X-D density functional was chosen in conjunction with the 6-311+G(d,p) basis-set.[23] The SMD implicit solvation model was used to model the global solvation effects.[24] Harmonic vibrational frequency calculations were performed to confirm the nature of the obtained structures. No imaginary frequencies were found for all the minima reported. For the transition states (TSs) only one imaginary frequency was found.

To verify that the TSs obtained indeed do describe the actual process, the following verifications were done:

(a) Animation of the imaginary frequency in order to verify that they genuinely describe the bond formation process for the *oxa*-Michael cyclisation.

(b) The connection between the reactant and the product through a corresponding transition state was further confirmed by optimizing slightly altered bond distance between the nucleophilic oxygen and the electrophilic β-carbon along the two directions which were associated with the imaginary frequency found in the vibrational frequency calculation.

(c) IRC calculations (starting from the TS) which confirmed that the desired internal cyclisation indeed did happen. These calculations thus aid us in ascertaining that the transition states correspond to the investigated intramolecular cyclisation.

Followed by geometry optimization, single point energies were calculated for all the structures applying the larger 6-311++G(3df,3pd) basis-set. The ultrafine integration grid was used to enhance the accuracy of the numerical integration in all the DFT calculations. The enthalpy was calculated according to the following formula:

H(corrected)=*E*(ωb97xd/6-311++G(3df,3pd)/SMD)+Thermal correction to Enthalpy (ωb97xd/6-311+G(d,p)/SMD). Thermal corrections to enthalpy were computed at 195.15 K for the base-catalysed cyclisation and at 298.15 K for the acid-catalysed cyclisation. Molecular structures were visualized using CYLview.[25]

An important technical point to note in this context is, for the acid catalysed reactions, the computed selectivities using the Gibbs free energies of activation are in qualitative agreement with those obtained experimentally i.e. the 2,6-cis isomer is the major product. However, the computed selectivities for the base catalysed reactions using the Gibbs free energies of activation results in selectivities opposite to that obtained experimentally. For instance, the enthalpies of activation and the free energies of activation in the stereoselectivity determining 1st step in Figures 1 and 2 (*vide* infra) are given below:

Acid-catalyzed cyclisation:
dr (experimentally): 1:0
$\Delta\Delta H^{\#}$ (computed) = 0.7 kcal/mol → dr (computed): 1:0.25
$\Delta\Delta G^{\#}$ (computed) = 0.4 kcal/mol → dr (computed): 1:0.4

Base-catalyzed cyclisation:
dr (experimentally): 1:0.25
$\Delta\Delta H^{\#}$ (computed) = 0.3 kcal/mol → dr (computed): 1:0.5
$\Delta\Delta G^{\#}$ (computed) = -0.3 kcal/mol → dr(computed): 0.5 1

This does not surprise us given that the error-bars associated with DFT energies are about 2-3 kcal/mol (the error-bar in energies even for the celebrated and computationally highly demanding CCSD(T)/CBS method is about 1 kcal/mol). The computation of enthalpy and free-energies involves even larger errors. Between enthalpy and free energies themselves, the error-bar is larger for the free-energies because of the additional approximations involved in the computation of the entropy. We suggest that such

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approximations affect our computed selectivities more severely in the case of the base-catalyzed reaction whose potential energy surface is flatter relative to the acid catalysed one. Therefore, when calculating selectivities (which are obtained by exponentiating the energies or free-energies or enthalpies), whose magnitudes are similar to those experimentally obtained in this work, it is to be expected that DFT calculations sometimes give values not in concordance with the experiments. This forms the basis for why we present the enthalpy profile in Figures 1 and 2, and do not use the free-energies.

Calculations for the acid catalysed cyclisation

The activation enthalpies of the acid-catalysed cyclisation were calculated to be 4.8 kcal/mol for the transition state **1.1-trans** leading to the *trans* isomer and 4.1 kcal/mol for the corresponding transition state **1.1-cis**, leading to the *cis* isomer (Figure 1). This is consistent with the observed experimental diastereoselectivity. We found that the O-protonated products formed, **1.2-cis** and **1.2-trans**, were stable intermediates (optimised minima at the (ωb97xd/6-311+G(d,p)/SMD) level of theory, the O(H)-C bond distance in the THP being 1.56 Å). The final products, **26-cis** and **26-trans**, are obtained via a simple proton transfer from the THP oxygen to, most likely, a solvent molecule (methanol).[26] The relative enthalpies of the final products (neutral) relative to the reactant (positively charged) plus the solvent molecule (methanol) are -7.0 and -5.2 kcal/mol (for neutral cis and trans 18 respectively). Note that in Figure 1 we only show the stereoselectivity determining step (1st step) leading to the formation of 1,3-cis and 1,3-trans, and we do not include how the final neutral products are formed. This is because there are several possibilities for the associated proton transfer/keto enol tautomerism, and computations cannot help here in deciphering how exactly they proceed nor would they be expected to have any impact on the step in which the stereochemical outcome is determined. Regardless, the main objective of our work - trying to understand the stereoselectivities is unambiguously shown in Figure 1.

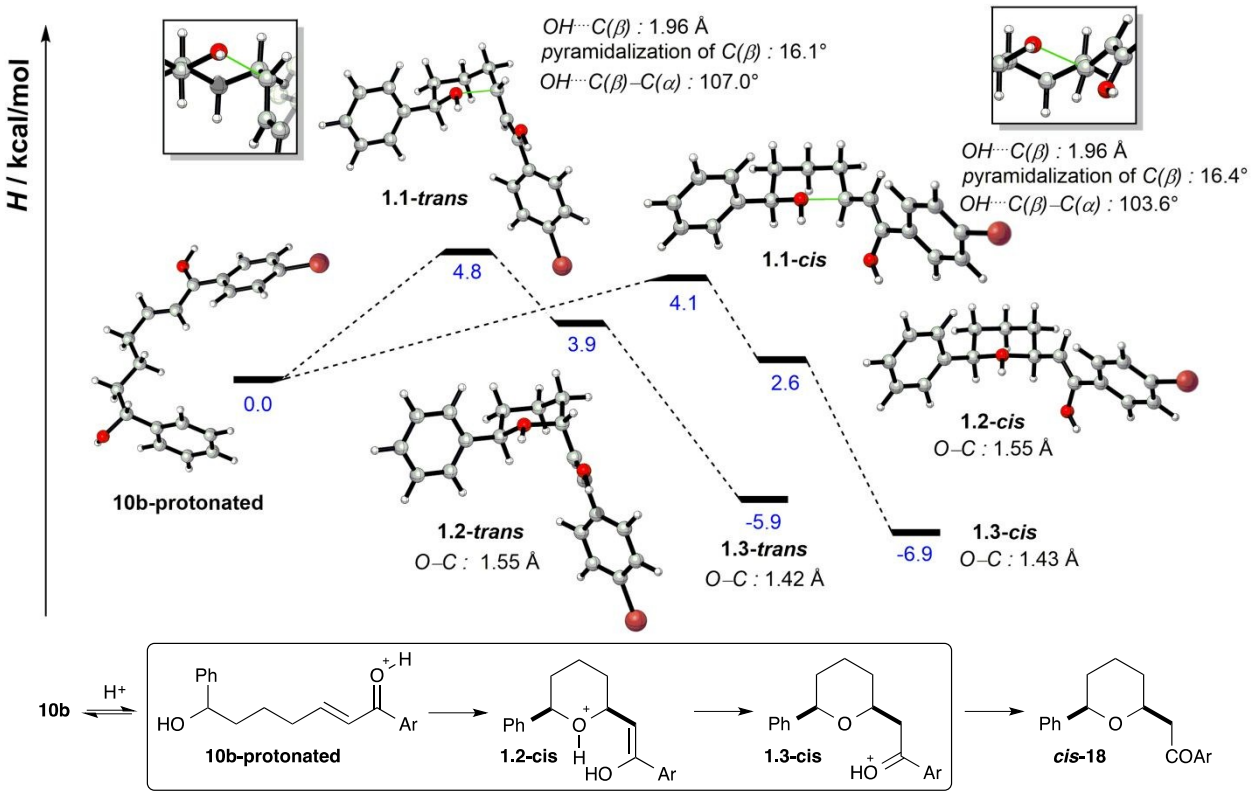

Figure 1. Enthalpy profile for the acid-catalysed *oxa*-Michael cyclisation for the formation of 1,3-cis and 1,3-trans.

Inspection of TS structures, **1.1-cis** and **1.1-trans**, reveals that the forming rings in both TSs for the acid-catalyzed cyclisation are orderly with chair-like conformations. Note that the intramolecular approaches of the nucleophiles follow very similar trajectories. In the case of both transition states, the trajectories are not very different from the Bürgi–Dunitz trajectory (about 2 degrees departure from the tetrahedral angle in **1.1-trans** and 5 degrees in **1.1-cis** – Figure 1). Hence, the stereoselectivities cannot be rationalized on the basis of the Bürgi–Dunitz trajectories alone. More significantly, in both transition states, **1.1-cis** and **1.1-trans**, the OH···C(*β*) distance was shortened down to 1.9 Å, starting from a considerably larger distance in the starting material, whereas, in the final enol structures, the OH···C(*β*) distances are around 1.56 Å. This reveals that the acid-catalyzed cyclisation takes place via a late-transition

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state as opposed to the base-catalyzed cyclisation (*vide infra*). At the TS, the carbon atom β to the carbonyl group was found to display extensive pyramidalization (16.4° for **1.1-cis**).[27] This is also consistent with a late transition state, as the β-carbon approaches sp^3 hydridisation.

As Clarke *et al.* have pointed out,[8] there has been no tangible explanation for the *cis* preference in the acid-catalysed *oxa*-Michael cyclisation. In their study, the energy difference between the *trans* and the *cis* TS was rationalized to be a result of an increased pseudo-1,3 diaxial steric clash between the hydrogen and the electrophilic Michael acceptor in the *trans* TS. This is in full agreement with our computational findings and explanation, however, this is only the case because of the relatively short bond-forming distance in the TSs and the consequent importance of the late-transition state. This, we believe, is the essence of understanding the origin of the stereocontrol for the acid catalysed reaction.

A noteworthy comment in this context is that, the terms "late" or "early" in this paper are meant to describe only the stereoselctivity determining step, and not the overall energy profile including proton-transfers and tautomerizations.

Lastly, we must also point out a possible limitation of the theoretical model we use: experimentally, it is evident that the acid catalysed reaction (Scheme 9) is under kinetic control. However, the difference in the computed activation enthalpies in the stereoselectivity determining step (Figure 1) is only 0.7 kcal/mol (which in principle is expected to be much large). This could perhaps be due to our model being unable to handle the co-ordination environment with precision.

Calculations for the base catalysed cyclisation

As our experimental results have clearly shown that the role of the cation is not significant in controlling the stereochemistry (*vide supra*), no cations were included in our computations. As can be seen in Figure 2, the transition state **2.1-trans** is 0.3 kcal/mol lower than the transition state **2.1-cis**, which adequately reflects the observed diastereoselectivity. Once bond-formation took place and the products were formed the relative stability became the opposite. In contrast to the trend in the TSs, enolate **2.2-cis** was found to be more stable than enolate **2.2-trans** by 0.9 kcal/mol. This is aligned with general chemical intuition and can be accounted for by the resultant 1,3-diaxial repulsion in the 2,6-*trans* THP ring. This also indicates that the applied computational method adequately predicts the relative stability of the entities in the case of base-catalyzed cyclisation as well. In this context, it may be noted that the geometry of the Michael acceptor greatly influences the order of the TSs. It was found that the transition states 3.1-cis and 3.1-trans in which the alkene and carbonyl group have an *s*-cis arrangement were lower in energy by 0.2 and 0.8 kcal/mol, respectively, compared to the corresponding transition states with an *s*-trans relationship. This may be due to 1,3-allylic strain between the methoxy group and the proton at the α-position (Figure 3).

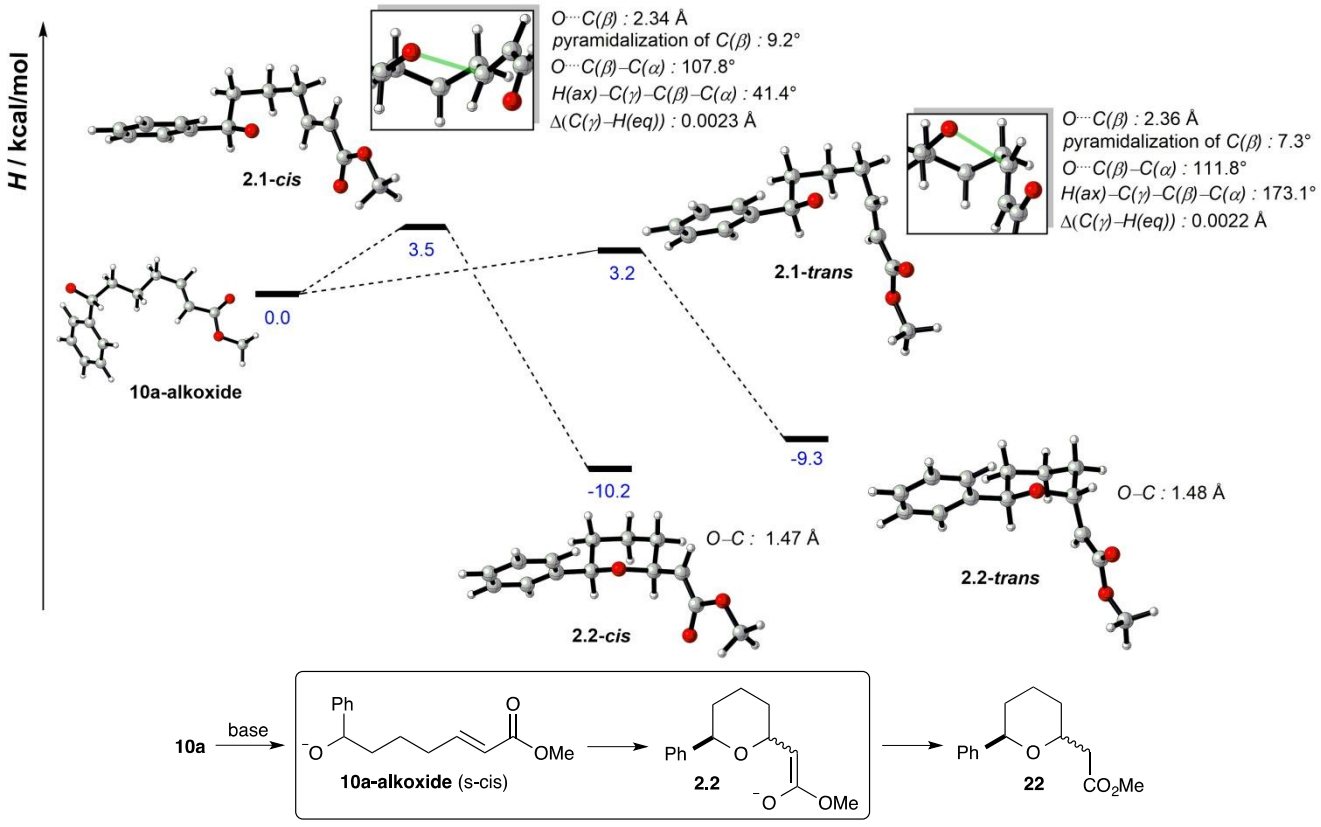

Figure 2. Enthalpy profile for the base-catalysed cyclisation for the formation of 2.2-cis and 2.2-trans

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Notably, the C•••O distances in all the transition states herein are long: 2.3-2.4 Å. This indicates an early transition state ($\Delta_{\text{bond length}}$(TS-product) = 0.9 Å, see Figure 2), which is consistent with the previously reported transition states.[2i, 6] Modest pyramidalization (7.3° in **2.1-trans**) of the carbon atom β to the carbonyl group in the TS is consistent with such an early TS. In comparison with the products, the early TSs in the base-catalyzed cyclisation are evidently much farther from the ideal chair conformation and also from the conformations identified in the acid-catalyzed TSs (Figure 1). Based on the long O(-)···C(*β*) distance and the experimental outcome, the 1,3-diaxial effect is arguably insignificant under kinetic control in the base catalysed cyclisation. This early transition state clearly explains why the *cis* product is not kinetically favoured. The question of why the *trans* product is favoured, however, still remains.

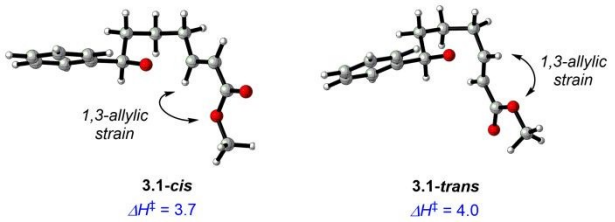

Figure 3. Transition states with s-trans Michael acceptors having 1,3-allylic strain and their relative enthalpies (in kcal/mol) with respect to SM-anion.

As part of answering this question, we realized that the Bürgi–Dunitz trajectory is closer to the tetrahedral angle in the transition state **2.1-cis** leading to the *cis* isomer.[28] This stands in contrast to the findings of the Schneider[2i] and the Yonemitsu[6] groups. We also examined the possibility of hyperconjugative interaction between the equatorial C(γ)-H and the double bond in both TSs.[9] However, we did not find any significant change in the bond length neither in comparison to the other two equatorial C-H bonds, nor between one another.

To see if any local orbital interactions played a role in determining selectivity, we performed NBO calculations. However, the second-order perturbative estimates (E(2) energy) of donor-acceptor interactions from NBO computations showed no tangible difference in the two investigated TSs, thereby ruling out such effects.

Wondering if, perhaps, these observations are mere artefacts of the fact that we did not include any cation in our calculations, we included the alkali metal cation also in our calculations. We found that the 2,6-*trans* arrangement **4.1-trans** remained the lowest energy transition state (Figure 4). Thus, the computational and experimental results are in agreement that the cation itself, which was suggested to be the reason for the *trans* selectivity due to chelation effects, does not play a crucial role in the selectivity.

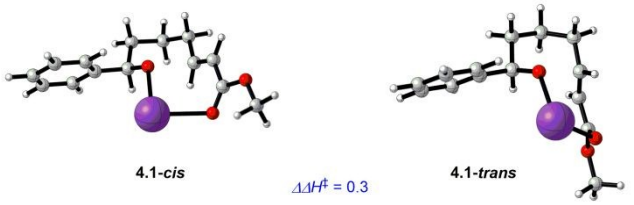

Figure 4. 2,6-*cis* and 2,6-*trans* transition states in the chelation model with potassium and the enthalpy difference (in kcal/mol) with respect to one other.

In a final attempt to understand the reason for *trans* selectivity under basic conditions, we examined electrostatic factors. In the transition states, **2.1-cis** and **2.1-trans**, leading to both the *cis* and *trans* isomers, the alkoxide oxygen atom and the carbon α to the carbonyl group bear charges of -0.88 and -0.45 or -0.46 respectively (NPA charges) (Figure 5). An electrostatic repulsion is, therefore, to be expected. The only significant difference between the two transition states appears to be the distance between the alkoxide oxygen and the α-carbon. In the TS leading to the *trans* isomer, **2.1-trans**, this distance is 0.1 Å longer than in **2.1-cis**, implying correspondingly less destabilisation of this transition state by electrostatic repulsion. The electrostatic repulsion between the carbonyl oxygen (NPA charges on oxygen: **2.1-cis**: -0.68, **2.1-trans**: -0.67) and the alkoxide oxygen also seems to play a role in a similar manner as, again, the atoms in question are further apart in the transition state leading to the *trans* product (4.06 vs 3.98 Å).[29] Thus, we propose that this electrostatic interaction may be one factor in the kinetic preference for the trans isomer, although additional factors, too small to be apparent, may also contribute.

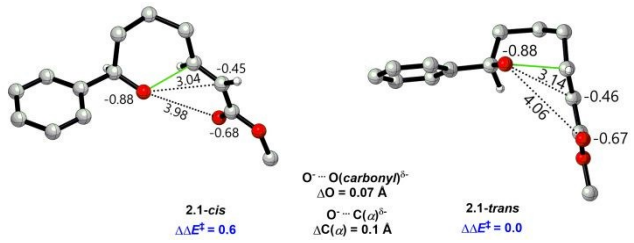

Figure 5. Electrostatic interactions in the TS of the base catalysed reaction. Distances in Å.

Note that we did not perform a similar electrostatics-based analysis for the acid-catalyzed transition states. That is because, with the acid catalyzed reactions, the classic Barton model[30] (invoking 1,3-diaxial interactions), adequately explains the selectivity, whereas it is with the base catalysed reaction that the Barton model is inadequate in explaining the selectivities.

Further, given the ~13 kcal/mol energy barrier of the reverse reaction, it is very unlikely the isomerisation into the *cis* isomer noticeably affects the overall selectivity at -78°C within the timeframe of our experiments. However, the isomerization reaction, which arises from the collapse of the enolate to afford the acyclic form, becomes rapidly predominant at higher temperature resulting in reverse selectivity. As can be seen in the enthalpy profile, the overall thermodynamic product of the cyclisation is the 2,6-*cis* enolate **2.2-cis**, which is 0.9 kcal/mol lower in energy in than the corresponding 2,6-*trans* isomer **2.2-trans**. These experimental and computational results are in accord with the idea that the cyclisation is under kinetic control at low temperature, particularly at -78°C, whereas thermodynamic control governs the stereochemical outcome at higher temperature, commonly above 0°C.

Such a change in the selectivity pattern at elevated temperature is easy to understand as occurring due to the unfavourable 1,3-diaxial interaction present in the *trans* product, for instance in the case of 2,6-tetrahydropyrans. This seems to be the major driving force for the isomerisation. The most striking aspect of this phenomenon is that it appears general irrespective of other substituents on the rest of the ring when a strong base is used (*see SI*).

The case of the (*Z*)-alkene

The remaining issue to be addressed is why the corresponding (*Z*)-isomer **1b** of the Michael acceptor delivers the *cis*-tetrahydropyran **2a**, even under kinetic conditions.[2k] This question appears to have been largely avoided up until now. With a verified model for the TS for the (*E*)-alkenes, we were able to examine this issue by calculating the corresponding transition states for the cyclisation of the (*Z*)-alkene (Figure 6). Again, early transition states were found, as judged by the length of the forming C-O bond (2.22 and 2.25 Å). The transition state **6.1-trans** leading to the *trans* isomer **3a** was found to be very significantly disfavoured compared to the transition state **6.1-cis** that leads to the *cis* isomer **2a**. This can be easily ascribed to a severe 1,3-interaction between the ester group and the pseudo-axial hydrogen atom at position 4 (THP numbering; δ relative to the carbonyl). Indeed, the distance between them is within the sum of their Van der Waals radii. The severity of this clash is in accordance with the very high diastereoselectivity (97:3) reported by Banwell.[2k]

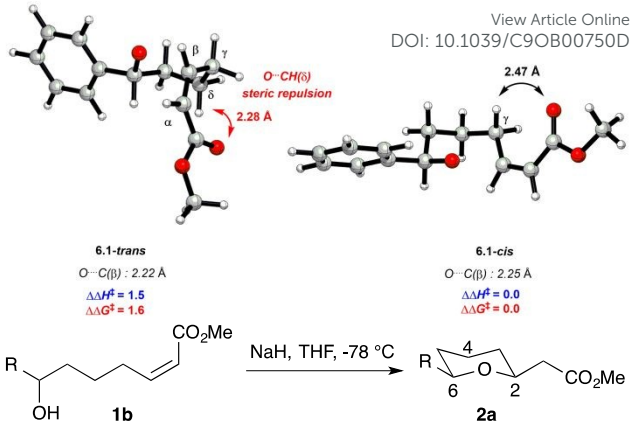

Figure 6. Transition states in the base catalysed cyclisation of the (*Z*)-Michael acceptor.

Conclusions

In the case of the cyclisation under mildly acidic conditions, the high preference for the formation of the 2,6-*cis* isomer is a kinetic phenomenon that arises from a late transition state with a relatively short C-O distance. The same concept holds true for the other substitution patterns, each delivering the diequatorial product.

Base catalysed cyclisation is more complex. The preference for formation of the 2,6-*trans* isomer from the (*E*)-Michael acceptor at lower temperatures is not due to chelation. Experiments involving varying the alkali metal cation and adding crown ethers, as well as employing TBAF and phosphazene bases, rule this out. That the 2,6-*cis* isomer is not favoured, as it is in the acid catalysed cyclisation, is explained by the early transition state with a relatively long C-O bond eliminating the significance of the classical 1,3-interactions. From inspection of the transition states it is not possible to identify a single effect that clearly controls the stereoselectivity of the reaction. Thus, the stereoselctivity appears to arise from a combination of minor factors working in concert, difficult to ascertain by theory or experiment. Amongst these effects, electrostatic repulsion between the α-carbon and the alkoxide oxygen, based upon the interatomic distances and the NPA charges, is likely to play a particular role. The same pattern holds for the three other isomers with the 2,5-, 2,4- and 2,3-substitution patterns, each giving mainly the equatorial-axial products under basic kinetic conditions.

In contrast, for the (*Z*)-Michael acceptor, a clear 1,3-interaction strongly disfavours the transition state leading to the 2,6-*trans* isomer, leaving the 2,6-*cis* isomer as the preferred product.

In this study, a comprehensive analysis of the literature precedents was carried out, which led us to recognize distinct selectivity patterns. However, in the absence of a focused study comparing the stereoselectivities under different conditions, a clear picture had not emerged pertaining to the origin of the selectivity. We hope that our contribution brings together all these stereo-determining

factors. Equally importantly, we hope that the present study will provide guidance for THP synthesis as well.

Conflicts of interest

There are no conflicts to declare.

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