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Mechanistic Insights into Lewis Acid-Controlled Torquoselective Nazarov Cyclization of Activated Dienones Bearing a Chiral Sulfoxide

Erwann Grenet,^[a] Raphaël Robidas,^[b] Arie van der Lee,^[c] Claude Y. Legault,^{*,[b]} and Xavier J. Salom-Roig^{*,[a]}

This work provides a switchable strategy to access, through a Nazarov cyclization, two diastereomeric disubstituted 3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-ones from an activated dienone bearing a chiral sulfoxide. The switch in the torquoselectivity is controlled by the nature of the Lewis acid used as promoter. From the four possible stereoisomers, only the two

trans were observed. The Lewis acids employed were achiral and the diastereoselectivities were dictated by the sulfinyl auxiliary. Density functional theory investigations shed light on the reaction mechanism. The experimental torquoselectivities were very closely reproduced and their inversion could be linked back to a change in the binding mode of the substrate.

Introduction

The 3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one scaffold (1, Figure 1) is present in Sterhirsutins A–D, bioactive heterodimeric sesquiterpenes, which were isolated from a strain of *Stereum hirsutum* (L515), a fungus collected in the region of Tibet Plateau. Sterhirsutins A, B and C show cytotoxicity against K562 and HCT116 cell lines.^[1] Scaffold 1 is also present in the structure of the strigolactone analogue PLO65 endowed with a remarkable activity as germination stimulant for seeds of the parasitic weeds *Orobanche aegyptiaca*.^[2]

In a previous communication,^[3] we described the Nazarov cyclization of activated dienones bearing a chiral sulfoxide as electron-withdrawing group (EWG) and chiral auxiliary and a dihydropyran moiety as electron-donating group (EDG), in which a torquoselectivity switch could be induced by changing the Lewis acid used as promoter. Thus, as outlined in Figure 2, both *trans* stereoisomers of the disubstituted 3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one 3 and 4 could be accessed from divinyl ketone sulfoxide 2 through this diastereodivergent reaction. In this paper, we report a mechanistic

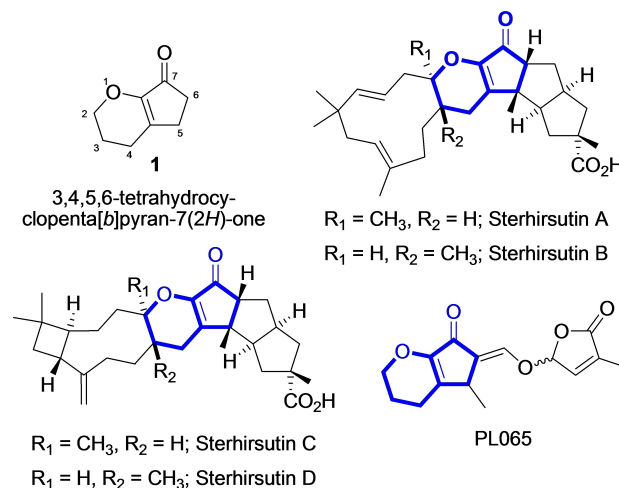


Figure 1. Bioactive compounds bearing scaffolds.

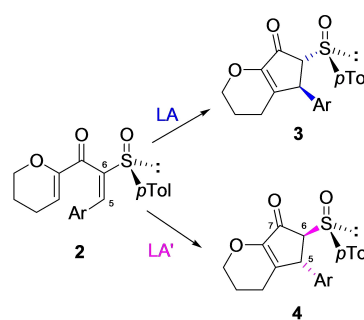


Figure 2. Switchable Nazarov cyclization.

proposal which accounts for the torquoselectivity switch and we broaden the scope of the cyclization to substrates bearing a cyclohexene moiety as EDG.

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Results and Discussion

We started our study with divinyl ketone **2a**, bearing a nucleophilic dihydrofuran moiety and a phenyl group as substituent at C-5 (Table 1), expecting that the chiral sulfoxide installed in the C-6 would impart torquoselectivity in the corresponding Nazarov cyclization and that it would be possible to modulate this torquoselectivity with the nature of the Lewis acid (LA) associated to the sulfoxide group. Our investigation began by identifying a suitable Lewis acid that provides the expected cyclopentenones. The direction and extent of the asymmetric induction was found to be dependent on the nature of the Lewis acid. Thus, a series of Lewis acids were screened and AlCl₃, TiCl₄ and ZnI₂ gave the best results.^[3] The optimal conditions for the use of AlCl₃ involve 0.25 equivalent of AlCl₃ at 0 °C during 3 hours of reaction, giving a 7:93 ratio of both *trans* adducts and 90% yield of the major stereoisomer **4a** (Table 1, entry 1). TiCl₄ provided stereoisomer **4a** as the major product after 2 hours of reaction at 0 °C, with 10:90 ratio (entry 2). Although promising, TiCl₄ proved to be problematic. Indeed, the reaction promoted by TiCl₄ afforded cyclopentenone **4a** in 71% yield. This yield was reduced by side-reactions, as evidenced by the presence of unidentified side-products in the reaction mixture. Shorter reaction times, lower temperature reactions and the use of sub-stoichiometric amounts of TiCl₄ did not allow the total conversion of substrate **2a**. Next, the substrate scope was evaluated for the use of AlCl₃ on diversely

Table 1. Scope of the Nazarov cyclization of dihydropyran substrates **2a–g** reported in our previous communication.^[3]

Entry	R ₅	Lewis acid	t [h]	d.r.(3:4) ^[f]	Yield 3 [%]	Yield 4 [%]
1	Ph (2a)	AlCl ₃ ^[a]	3	7:93	–	90
2	Ph (2a)	TiCl ₄ ^[b]	2	10:90	–	71
3	<i>p</i> -ClPh (2b)	AlCl ₃ ^[a]	3	7:93	–	88
4	<i>p</i> -MeOPh (2c)	AlCl ₃ ^[a]	3	7:93	–	90
5	<i>p</i> -NO ₂ Ph (2d)	AlCl ₃ ^[a]	3	10:90	–	90
6	<i>o</i> -NO ₂ Ph (2e)	AlCl ₃ ^[c]	24	8:92	–	90
7	3,4,5-TMPH (2f)	AlCl ₃ ^[c]	3	12:88	–	87
8	2-furfuryl (2g)	AlCl ₃ ^[a]	3	15:85	12	80
9	Ph (2a)	ZnI ₂ ^[d]	24	83:17	68	–
10	<i>p</i> -ClPh (2b)	ZnI ₂ ^[d]	24	85:15	69	14
11	<i>p</i> -MeOPh (2c)	ZnI ₂ ^[d]	24	51:49	19	19
12	<i>p</i> -NO ₂ Ph (2d)	ZnI ₂ ^[d]	24	77:23	70	18
13	<i>o</i> -NO ₂ Ph (2e)	ZnI ₂ ^[e]	24	70:30	65	–
14	3,4,5-TMPH (2f)	ZnI ₂ ^[d]	24	60:40	24	24
15	2-furfuryl (2g)	ZnI ₂ ^[d]	24	81:19	67	13

[a] Reaction conditions: 0.25 equivalents of AlCl₃ in 1,2-DCE (0.06 M) at 0 °C. [b] The reaction was performed at 0 °C. [c] The reaction was performed at r.t. [d] 1.1 equivalents of ZnI₂ in 1,2-DCE (0.06 M) at 0 °C. [e] The reaction was performed at 50 °C. [f] Diastereoisomeric ratio (d.r.) was determined by HPLC analysis or from the crude ¹H-NMR.

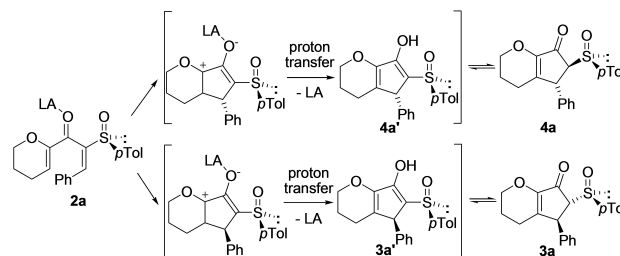
substituted dihydropyran substrates (**2b–g**) at C-5. The reaction proceeded with a complete conversion into the corresponding *trans* cyclopentenones **4b–g** and was compatible with both electron-donating and electron-withdrawing aryl substituents, as summarized in Table 1 (entries 3–8).

When the reaction was carried out with 1.1 equivalents of ZnI₂ at room temperature, a reversal of torquoselectivity was observed and a mixture of 83:17 *trans* diastereomers was obtained with 68% yield of the major stereoisomer **3a** (entry 9). With *p*-ClPh and 2-furfuryl substituents (entries 10 and 15) the d.r. and yield obtained were similar to those of the parent compound **2a** (entry 9). With a *p*-nitro substituent, the d.r. was slightly reduced (entry 12). An *o*-nitro (entry 13) and a 3,4,5-TMP (entry 14) substituents had a deleterious effect to the torquoselectivity. Yields of the isolated major stereoisomers (**3b**, **3d–e** and **3g**) were all in the range of 65 and 70%. No torquoselectivity was observed for substrate **2c** in these conditions (entry 11).

Theoretical insights

Considering the unique stereochemical outcome of our system, we resorted to a computational study to gain further insights on the reaction process. The calculations were performed using density functional theory (DFT) in Gaussian 16.^[4] More specifically, we used the M062X density functional^[5] in combination with the Def2TZVP basis set.^[6] The energy was corrected with dispersion interactions using the D3 empirical dispersion correction.^[7] Solvation was accounted for using the SMD implicit solvation model^[8] in combination with its parameters for 1,2-DCE. Conformational sampling was performed using xtb 6.4.1^[9] and CREST 2.11.1.^[10]

We chose **2a** as model substrate and aimed to study specifically the cyclisation step, as it is the stereodetermining step. We thus did not study in details the subsequent proton transfers leading to the final observed product. We assumed that the *anti* relationship between the phenyl group and the sulfoxide group is most likely due to thermodynamic control (Scheme 1). Indeed, the carbonyl and the sulfoxide groups increase the acidity of the α -proton, and the formation of the enol form should be possible at room temperature. Accordingly, our calculations indicate that the free energy of **3a'** is only 40 kJ/mol higher than that of **3a**, and thus energetically accessible in the reaction conditions.



Scheme 1. Pathways leading to the Nazarov cyclisation products **3a** and **4a**.

We first investigated the complexation of the three main Lewis acids (AlCl_3 , TiCl_4 , ZnI_2) as they provided the widest variations in selectivities. Many possible adducts were modelled, and the most significant ones involved the binding of Lewis acid to either the carbonyl, the sulfinyl oxygen, the ether oxygen, or both. We also performed conformational sampling on these adducts to obtain accurate free energies of complexation, which are presented in Table 2.

Intermediates were named according to the geometry of the alkene and an intermediate number. When an intermediate contained a Lewis acid, a lowercase suffix from *a* to *c* was used (see Table 2). Transition states were named from the intermediates directly leading up to them and suffixed by the label of the product (with the exception of the isomerization transition states).

As expected, chelation of the Lewis acid by the carbonyl and the sulfinyl oxygen (**Int-E1**) or by the ether and the carbonyl (**Int-E2**) is thermodynamically favorable. In the case of ZnI_2 and TiCl_4 , **Int-E1** is favored by 17 kJ/mol, and thus this form is strongly preferred over chelation by the ether and the carbonyl. Furthermore, AlCl_3 most favorably binds to a single Lewis basic site, namely the sulfinyl oxygen, to form **Int-E3**. Moreover, the complexation free energy of this Lewis acid is much more significant than those of the two other Lewis acids (−152 kJ/mol *versus* −76 kJ/mol and −35 kJ/mol). This suggests that the complexation of AlCl_3 is irreversible with respect to the

following reaction (*vide supra*), while it is reversible for TiCl_4 and ZnI_2 .

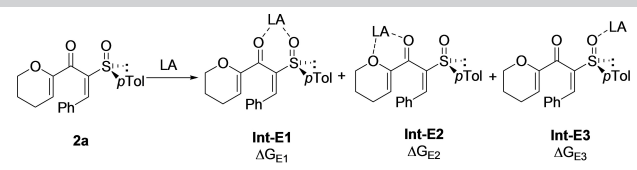
We then evaluated the possible reactions of those adducts (Table 3). The Nazarov reaction could occur directly from these adducts and lead to the observed products. However, it was previously reported by Frontier and co-workers that the alkene in similar substrates can isomerize to the *Z* isomer when activated by a Lewis acid.^[11] In that work, the isomerization was faster than the Nazarov reaction, leading to the same products regardless of the initial geometry of the alkene. We thus evaluated the barriers of the Nazarov reaction as well as the isomerization barrier for our model substrate with different Lewis acids.

As we can see in Table 3, the isomerization barriers are always much higher (>24 kJ/mol) than the barriers of the Nazarov reaction. This strongly supports that this substrate does not isomerize prior to the cyclization. Thus, assuming relatively rapid equilibration between the different conformers, the product selectivity must be caused by the difference in free energy of **TS-E2-3** and **TS-E2-4**.

The results in Table 4 strongly support this hypothesis in the case of ZnI_2 and TiCl_4 . Indeed, the experimental selectivities are reproduced within a range of only 0.3 kJ/mol. Moreover, the selectivities calculated from the isomerized substrate are very far (> 18 kJ/mol) from the experimentally observed selectivities.

However, the use of AlCl_3 leads to a more complex behavior. As seen in Table 4, the quantity of AlCl_3 used influences the selectivities significantly. The selectivity observed with 0.25 equivalent of this Lewis acid matches closely the calculated selectivity (+5.7 kJ/mol *exp. versus* +5.5 kJ/mol *calc.*). However, use of 1.1 equivalents of AlCl_3 results in a lower selectivity representing a difference between the transition states of +1.6 kJ/mol. This likely stems from the extremely favorable complexation of this Lewis acid to the substrate. Indeed, the complexation of a Lewis acid to the substrate could slow down equilibration between the different conformers. With the *E* alkene, the transition between the “pro-3” conformer and the “pro-4” conformer certainly possesses a certain barrier due to geometrical constraints. The complexation of a Lewis acid could increase this barrier. With ZnI_2 and TiCl_4 , this effect does not prevent pre-equilibration, as the complexation is reversible and fast compared to the Nazarov cyclization. The reversibility can

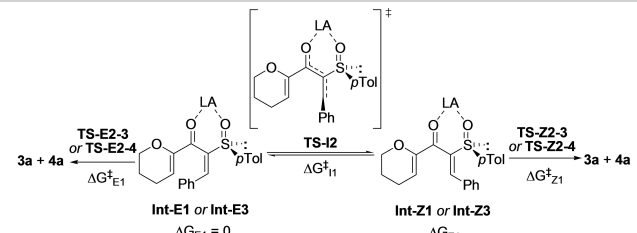
Table 2. Complexation free energies of Lewis acids to model substrate (**2a**).^[a]



Suffix	Lewis acid	ΔG_{E1}	ΔG_{E2}	ΔG_{E3}
a	ZnI_2	−35	−18	−
b	TiCl_4	−76	−59	−
c	AlCl_3	−140	−	−152

[a] Energies reported in kJ/mol.

Table 3. Evaluated reaction pathways.^[a]



Lewis acid	ΔG_{E1}^{\ddagger}	$\Delta G_{E11}^{\ddagger}$	ΔG_{Z1}^{\ddagger}	$\Delta G_{Z21}^{\ddagger}$
ZnI_2	108	132	+11	99
TiCl_4	86	111	+6	72
AlCl_3	90	140	+7	88

[a] Energies reported in kJ/mol.

Table 4. Comparison of the experimental and calculated product ratios with various Lewis acids.^[a]

Lewis acid	Experimental ratio 3:4	Experimental $\Delta\Delta G_{3-4}^{\ddagger}$	$\Delta\Delta G_{3-4}^{\ddagger}$ calc. from TS-E2	$\Delta\Delta G_{3-4}^{\ddagger}$ calc. from TS-Z2
ZnI_2 (1.1 equiv)	83:17	−3.9	−3.9	+14.0
TiCl_4 (1.1 equiv)	10:90	+5.4	+5.7	+32.0
AlCl_3 (1.1 equiv)	34:66	+1.6	+5.5	+0.2
AlCl_3 (0.25 equiv)	9:91	+5.7	+5.5	+0.2

[a] Energies reported in kJ/mol.

be justified by the calculated dissociation free energies, which are accessible at room temperature and lower than the activation barrier of the Nazarov reaction. However, the complexation of AlCl_3 is too exergonic to be reversible (-152 kJ/mol). The pre-equilibration is thus greatly slowed down, and we cannot apply a Curtin-Hammett regime as before. The stereo-determining step thus becomes the complexation of the Lewis acid, which is expected to have little discrimination between the different conformers. The small selectivity observed could be explained by multiple factors. It is possible that the equilibration is not completely prevented, but merely greatly slowed down. Thus, the transition state that is lower in free energy would be slightly favored, as observed. Moreover, the kinetics of complexation of the Lewis acid could contribute to this modest selectivity. While difficult to demonstrate computationally, there is no reason why the complexation should have the exact barrier for the pro-3 and the pro-4 conformers.

When using a catalytic amount of AlCl_3 , the observed selectivity matches the calculated one, implying fast equilibration again. This can be explained by exchange of the Lewis acid between molecules of substrate. Indeed, **Int-E3** can combine with a molecule of the substrate **2a** to form the dimers **Dim-1** and **Dim-2** (Figure 3). The formation of **Dim-1** is exergonic by -18 kJ/mol relative to **Int-E3** and **2a**, which suggests that this could be the main compound in solution in this case. The formation of **Dim-2** is endergonic by +8 kJ/mol, making it a second, less favored way to exchange the Lewis acid. This exchange allows molecules of substrate to be free of Lewis acid a part of the time, and thus to equilibrate between the different conformers. The system thus returns to a Curtin-Hammett regime.

These results show that complexation of two substrates by AlCl_3 is accessible, and even favorable in the case of **Dim-1**. We thus wondered if this could affect the selectivity, which is calculated from monomers. Indeed, binding Lewis bases to Lewis acids can actually increase the acidity of the latter, counter to intuition. This concept of *Lewis base catalysis* has been increasingly explored in recent years.^[12] In the case of our systems, it appeared possible that complexation of the sulfoxide group of a second molecule of substrate on AlCl_3 could lower the barrier of the Nazarov reaction. To study this possibility, we used a molecule of DMSO as a simplified model instead of a full second substrate molecule. This simplification keeps the system computationally tractable while yielding a very similar dimerization free energy.

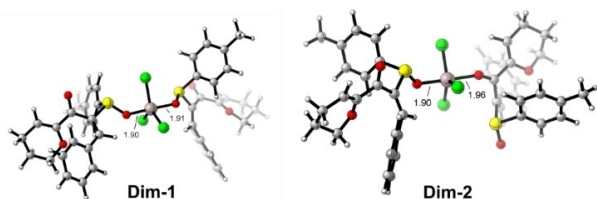


Figure 3. Possible dimers involved in the exchange of catalytic AlCl_3 .

We took the most significant transition states found previously with AlCl_3 and reoptimized them with a molecule of DMSO also binding to the Lewis acid. We obtained barriers that were 4–5 kJ/mol higher in free energy than the barriers of the reaction with the dissociated DMSO. However, the selectivity between **3** and **4** was quite similar, namely 4.8 kJ/mol (vs 5.5 kJ/mol) in favor of **4**. These results show that the reaction likely proceeds from the monomer, but that reaction from the dimer would not result in a significant change of selectivity.

Origin of the torquoselectivity of the Nazarov cyclization

Having demonstrated that the computational modelling quantitatively reproduces the experimental results, we sought to rationalize the inversion of torquoselectivity when going from AlCl_3 to ZnI_2 . We thus compared the transition states leading to both **3a** and **4a** in presence of these two Lewis acids (Figure 4).

One major difference between these two Lewis acids is that the most reactive complex with AlCl_3 is preferentially bound only to the carbonyl, while ZnI_2 is preferentially chelated by the carbonyl and the sulfinyl oxygen. In the latter case, the orientation of the sulfoxide is considerably constrained. Moreover, the torsion of the styryl group at the transition state influences the position of the sulfoxide group, and thus the orientation of the chelated ZnI_2 . In **TS-E2a-4**, this has the effect of inducing significant steric interactions between the iodine

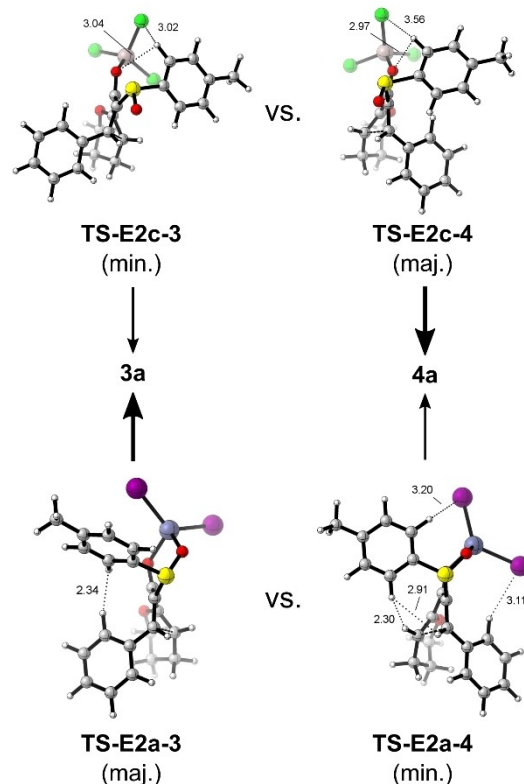


Figure 4. Comparison between the transition states of the Nazarov cyclization promoted by either AlCl_3 or ZnI_2 .

atoms and the hydrogen of the two aromatic rings. In **TS-E2a-3**, these steric interactions can mostly be avoided. ZnI_2 thus gives mainly product **3a**.

With $AlCl_3$, the sulfoxide group is free to rotate and thus can orient itself as to minimize the total molecular dipole (i.e. by opposing the carbonyl and S–O dipoles). However, in this position, the tolyl group is brought closer to the Lewis acid. Thus, depending on the position of the tolyl group, there can be steric interactions between the hydrogens and chlorine atoms. The Lewis acid positions itself opposite to the styryl group with respect to the bond in formation, and thus disfavors the representative transition state **TS-E2c-3** over **TS-E2c-4**.^[13]

It has been proven in the past that β -carbonyl sulfoxides assume a ground-state conformation, in which the carbonyl oxygen and sulfur-oxygen bonds are aligned roughly in opposition to minimize carbonyl-sulfoxide dipole interactions^[14] and this would be the case in dihydropyran substrates **2a–g**.

Finally, we elected to study the effect of removing the oxygen next to the carbonyl function by replacing the dihydropyran ring by a cyclohexene. Thus, substrates **5a** and **5b**^[15] were tested experimentally using the $AlCl_3$ and ZnI_2 conditions optimized for the dihydropyran derivatives. These compounds, less reactive than their oxygenated analogues, displayed marked differences in reactivity (Table 5). A stoichiometric amount of $AlCl_3$ was necessary to achieve the complete conversion of the substrates. Thus, reaction of **5a** with this promoter at room temperature yielded the *trans* stereoisomer **6** in 51% yield (entry 1), whereas at lower temperature (0 °C) the yield was 75% (entry 2). The absolute configuration of the new stereogenic centers in **6a** was confirmed by X-ray-analysis studies (Figure 5). Of great mechanistic significance is the fact that exposure of **5a** to ZnI_2 showed the same torquoselectivity

Table 5. Scope of the Nazarov cyclization of cyclohexene derivatives.						
Entry	Ar	Lewis acid	T (°C)	t (h)	Yield 6 (%)	
1	2,4,6-TMPH (5a)	$AlCl_3$	rt	24	51	
2	2,4,6-TMPH (5a)	$AlCl_3$	0	24	75	
3	2,4,6-TMPH (5a)	ZnI_2	60	15	73	
4	Ph (5b)	ZnI_2	60	15	No reaction	
5	Ph (5b)	$AlCl_3$	0	15	80 (6b + 7b)	

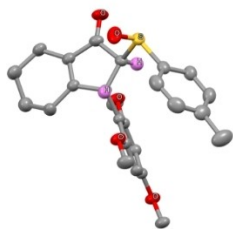
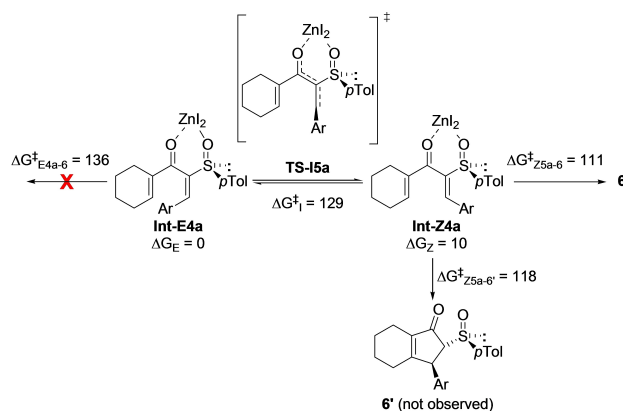


Figure 5. ORTEP plot of structure **6a**.



Scheme 2. Mechanistic insights into the Nazarov cyclization for **5** promoted by ZnI_2 (free energies in kJ/mol).

than the reaction with $AlCl_3$ leading also to the *trans* stereoisomer **6a** as major stereoisomer in 73% yield (entry 3).

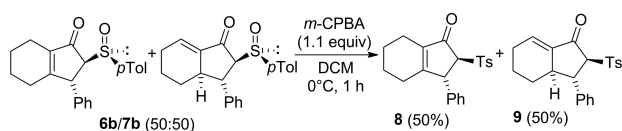
To gain a better understanding of this change in selectivity, we used DFT to investigate the reaction of **5a** with ZnI_2 . We found that the barriers of the Nazarov reaction with the *E* alkene were 136 kJ/mol and above, considerably higher than with **3a**. This can easily be explained by the lesser polarization between the two reactive carbons, due to the absence of the donating oxygen. However, the isomerization barrier remains similar to the previous case, being at 129 kJ/mol. Here, isomerization is favoured over the direct Nazarov reaction, although moderate heating is required to overcome this high barrier (Scheme 2). Following this step, the Nazarov reaction leading to products **6** and **7** is favoured by 7 kJ/mol (around 95:5) over the formation of the diastereoisomers, in accordance with experimental results.

On the other hand, following treatment of substrate **5b** with ZnI_2 (entry 4), no conversion was observed after 15 hours at 60 °C. In contrast, reaction with $AlCl_3$ furnished in 80% yield an inseparable 50/50 mixture of two products: the expected cyclopentenone **6b** and its regioisomer **7b** bearing a trisubstituted alkene and three contiguous new stereocenters (entry 5).

In order to confirm the structure of **7b**, the mixture of **6b** and **7b** was treated with *m*-CPBA giving rise to a mixture of the corresponding sulfones **8** and **9**, which could be quantitatively separated (Scheme 3). The absolute configurations of the three new stereogenic centers of **9** could be confirmed unambiguously by single-crystal X-ray diffraction analysis.

Conclusion

In conclusion, we have reported a switchable diastereodivergent strategy, which provides selective access, *via* a torquoselective Nazarov cyclization involving activated dienones bearing a chiral sulfoxide, to two *trans* disubstituted aryl cyclopentenones with an excellent diastereoselectivity and good torquoselectivity. As a special feature of our synthetic method, the



Scheme 3. Sulfoxide group oxidation of the 6b/7b mixture and ORTEP plot of structure 9.

asymmetric induction was dictated by the chiral sulfoxide auxiliary and could be switched according to the nature of the Lewis acid that was employed without introducing a new chiral parameter. We used DFT calculations to rationalize the Lewis acid-dependant torquoselectivity switch of the Nazarov cyclization. The results suggest that the binding mode of the Lewis acid controls the torquoselectivity due to differences in conformational flexibility and intramolecular interactions.

Experimental Section

General Procedure A for zinc iodide-promoted Nazarov cyclization

To a solution of ZnI_2 (1.1 equiv) in 1,2-DCE [0.12 M] under argon atmosphere was added a solution of the corresponding divinyl- β -ketosulfoxide **2a–g** (1 equiv) in 1,2-DCE [0.12 M]. After 24 h stirring at rt, the reaction mixture was quenched with brine (20 ml). The two layers were separated and aqueous layer was extracted with EtOAc (3×5 ml). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc; see *ratio* in the supporting information) to afford **3a–g**.

General Procedure B for aluminium chloride-promoted Nazarov cyclization

To a solution of $AlCl_3$ (0.25 equiv) in 1,2-DCE [0.12 M] under argon atmosphere was added a solution of the corresponding divinyl- β -ketosulfoxide **2a–g** (1 equiv) in 1,2-DCE [0.12 M]. After 3 h stirring at 0°C, the reaction mixture was quenched with brine (20 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (3×5 ml). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluent (cyclohexane/EtOAc; see *ratio* in the supporting information) to afford **4a–g**.

Crystallographic data

Deposition Numbers 2176271 (for **6a**) and 2176273 (for **9**) contain 2176271 (for **6a**) and 2176272 (for **9**) the supplementary crystallographic data for this paper. These data are provided free of charge

by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: Asymmetric synthesis · Chiral auxiliaries · Cyclization · Diastereoselectivity · Synthetic methods

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