A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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# Accepted Article

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**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.201911952
*Angew. Chem.* 10.1002/ange.201911952

**Link to VoR:** http://dx.doi.org/10.1002/anie.201911952
http://dx.doi.org/10.1002/ange.201911952

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10.1002/anie.201911952


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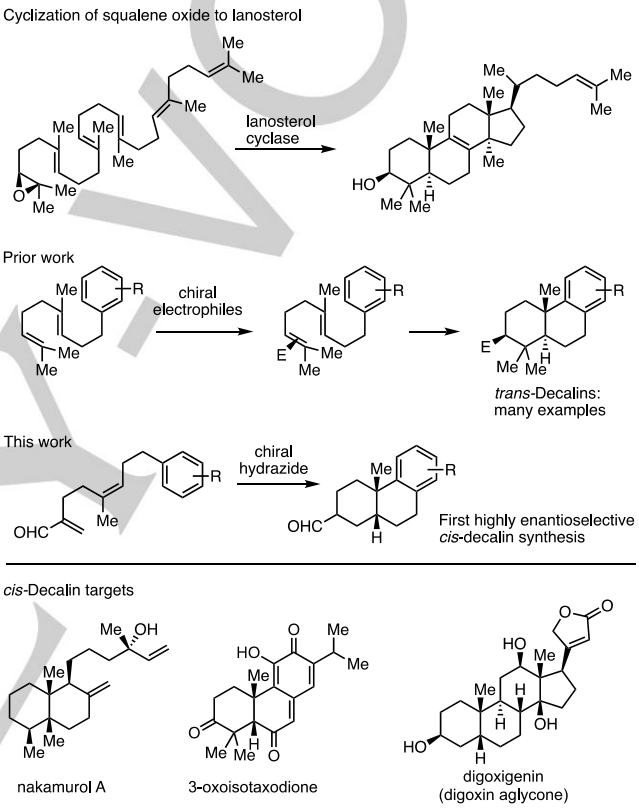
# Hydrazide-Catalyzed Polyene Cyclization: Asymmetric Organocatalytic Synthesis of *cis*-Decalins

Samuel J. Plamondon, Josephine M. Warnica, Dainis Kaldre and James L. Gleason*[a]

**Abstract:** Polyene cyclizations offer rapid entry into terpenoid ring systems. Although enantioselective cyclizations of (*E*)-polyenes to form *trans*-decalin ring systems are well precedented, highly enantioselective cyclizations of (*Z*)-polyenes to form the corresponding *cis*-decalins have not been reported. Here, we describe the first application of iminium catalysis to the initiation of polyene cyclizations. Ethyl 1,2-diazepane-1-carboxylate catalyzes the cyclization of polyenes bearing enal initiators. Moreover, chiral bicyclic hydrazides catalyze the cyclizations of (*Z*)-polyene substrates to form *cis*-decalins with enantioselectivities of up to 97:3 er. DFT calculations suggest the catalysts promote the reaction by stabilizing positive charge as it develops during the bicyclization.

The biosynthesis of steroids and other terpenoid natural products via polyene cyclization is a process which has inspired organic chemists for over 60 years. Since the proposals of Woodward, Stork and Eschenmoser,[1] numerous examples of biomimetic cyclizations have been reported, including many applications in total synthesis where polyene cyclization can afford rapid entry into complex polycyclic frameworks.[2] While the absolute stereochemistry of the epoxide in the prototypical substrate for steroid synthesis, 2,3-oxidosqualene (Scheme 1), is a defining influence on the subsequent polycyclic product,[2b, 3] in recent years there has been interest in initiating cyclizations via chiral catalysts on achiral precursors. The first examples by Yamamoto showed that chiral proton sources could initiate cyclizations directly on simple polyene substrates.[4] Enantioselective polyene cyclizations may also be initiated by chiral halogen/chalcogen sources[5] and $\eta^2$- and $\eta^3$-metal complexes.[6] In general, these methods activate one prochiral face of the terminal alkene in a fashion that mirrors the canonical epoxide initiation. Alternative strategies include the combination of protic acids with chiral ion binders[7] and using SOMO catalysis.[8] While many impressive advancements have been made, there are still areas ripe for development.

All highly enantioselective reactions reported to date have used (*E*)-olefin substrates that lead to *trans*-decalin ring junctions (Scheme 1). While most steroids possess *trans*-decalin junctions in the A/B rings (e.g. lanosterol), numerous terpenoids such as nakamurol A, 3-oxoisotaxodione and digoxin[9] possess *cis*-decalin ring junctions that would require cyclization of a (*Z*)-olefin substrate. While cyclizations of polyenes containing (*Z*)-alkenes do have ample precedent,[10] the few reported attempts at applying established enantioselective methods to (*Z*)-olefin substrates have resulted in significantly reduced enantioselectivity.[4b, 6a, 7] An additional challenge is that while concerted cyclizations will produce *cis*-decalins, reactions that proceed stepwise via an intermediate cyclohexyl cation are potentially vulnerable to ring-flip which can result in *trans*-decalin formation (c.f. Scheme 2B).[1c, 1d, 11]




**Scheme 1.** Enantioselective polyene cyclizations and *cis*-decalin-containing natural product targets.

In approaching this problem, we became interested in examining a potential alternative to direct alkene activation, specifically the use of LUMO-lowering iminium catalysis. We previously reported an iminium-catalyzed Cope rearrangement of 1,5-hexadiene-2-carboxaldehydes using cyclic hydrazides (e.g. **1**, Scheme 2A) as catalysts.[12] Preliminary calculations on this reaction suggested it proceeded in a stepwise fashion through a shallow cationic intermediate. Since polyene cyclizations bear a structural relationship to the Cope rearrangement, in that substrates for both possess 1,5-hexadiene units as core reactive functionality, we envisaged that hydrazide catalysts might also trigger polyene cyclizations (c.f. Scheme 2B). Here we report the successful implementation of this concept in the first iminium-catalyzed polyene cyclizations as well as the first highly enantioselective polyene cyclization of (*Z*)-polyenes to form *cis*-decalins, studies which reveal the ability of hydrazide catalysts to stabilize developing charge at remote locations.

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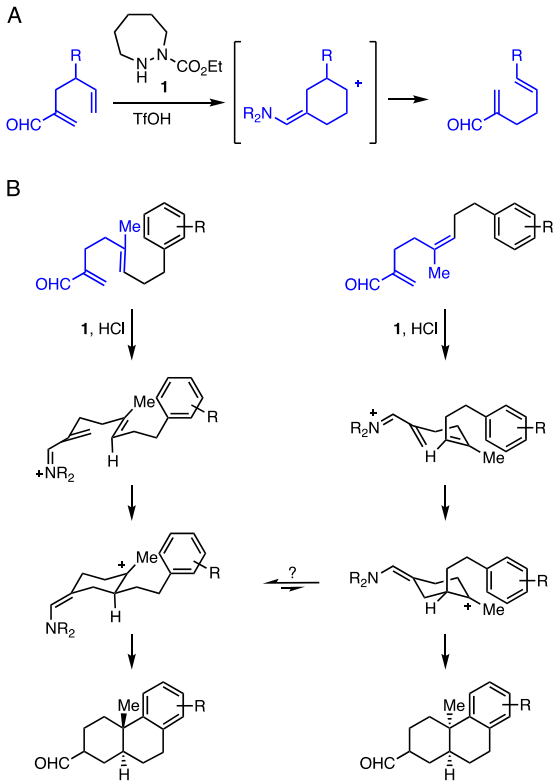
10.1002/anie.201911952

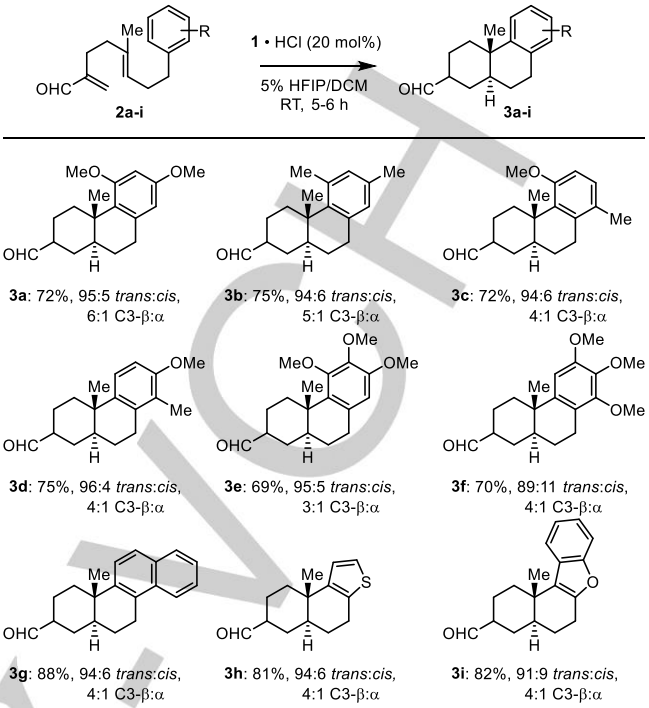




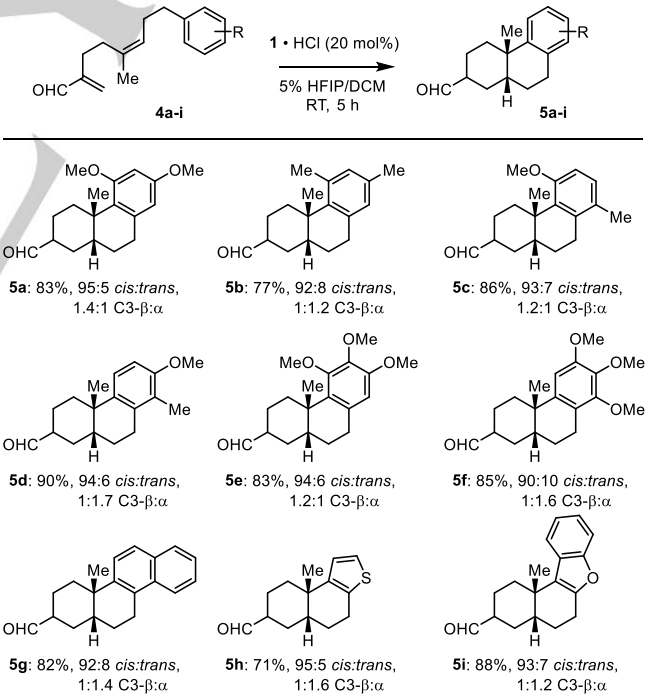

**Scheme 2.** A) An organocatalytic Cope rearrangement catalyzed by diazepane carboxylate. B) Polyene cyclization of (*E*)- and (*Z*)-polyene substrates to provide *trans*- and *cis*-decalin products.

As iminium catalysis has not been previously reported in polyene cyclizations, we first examined the cyclization of (*E*)-alkene substrates to generate *trans*-decalin products. We began by examining the cyclization of substrate **2a** (Scheme 3) and found that exposure to diazepane carboxylate hydrochloride (**1•HCl**)[13] in either 5% HFIP/DCM or EtOH afforded bicyclization adduct **3a**. The former solvent afforded higher yield, providing **3a** in 72% yield as a 95:5 mixture of *trans*- to *cis*-decalins in only 5 h. The aldehyde α-stereocenter at C3, formed by hydrolysis of the intermediate enamine in the final step, was generated as a thermodynamic mixture of 6:1 β/α. Reactions in ethanol were slightly more diastereoselective (97:3 *trans/cis*), but with diminished yield (42%) and requiring extended reaction time (24 h).[14] In addition, reactions in ethanol with less nucleophilic arenes, such as dimethylphenyl substrate **2b**, led to products resulting from trapping of the intermediate cyclohexyl cation by solvent. This observation, along with formation of minor amounts of the *cis*-decalin product, suggests some stepwise character to the reaction. Given the higher yields, faster reaction time and lack of intermediate trapping products, we examined the scope of the cyclization in 5% HFIP/DCM. We found that a range of (*E*)-polyene substrates possessing electron-rich aryl, naphthyl and heteroaryl terminating groups underwent bicyclization efficiently in consistently good yields and with ring fusion diastereoselectivities above 90:10 for all but one substrate, **2f**, which bears two *meta*-deactivating groups.

With iminium catalysis established for the polyene cyclization




**Scheme 3.** Polyene cyclization of (*E*)-hexadienes.




**Scheme 4.** Polyene cyclization of (*Z*)-hexadienes.

of (*E*)-olefin substrates, we next examined the extension to (*Z*)-olefins (Scheme 4). Gratifyingly, treatment of 3,5-dimethoxyarene substrate **4a** afforded *cis*-decalin **5a** in excellent yield (83%) and diastereoselectivity (95:5 *cis*/*trans*). As in the

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*trans*-decalin case, the aldehyde α-stereocenter was generated as a thermodynamic mixture, in this case 1.4:1 β/α due to the fluxional nature of the *cis*-decalin ring system. The bicyclization worked well across a range of (*Z*)-olefin substrates, affording high yields. Importantly, even though the results suggest at least some stepwise character to the bicyclization, scrambling from (*Z*)-olefin to *trans*-decalin via chair flip was minimal, leading to ring-fusion diastereoselectivities comparable to those in the (*E*)-olefin cyclization.

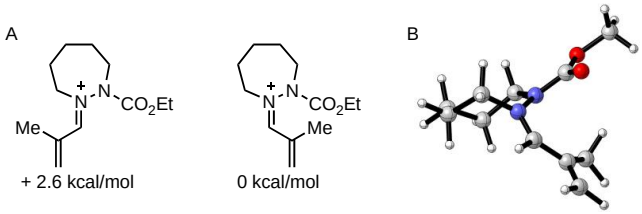
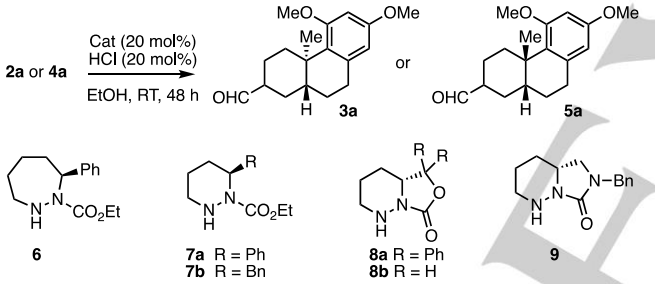



**Figure 1.** Diazepane carboxylate iminium ions calculated at the M06-2X/6-311G(d,p), SRCF=EtOH level. A) The (*Z*)-configuration is more stable than the (*E*)-configuration. B) Three-dimensional representation showing the twist along the N-N bond.

**Table 1.** Screening of chiral catalysts.



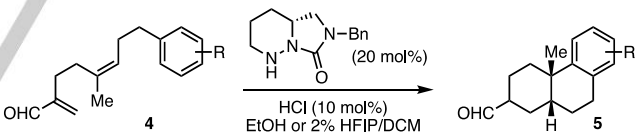

| Catalyst | 3a | | 5a | |
|---|---|---|---|---|
| | er[a] | Yield[b] | er[a] | Yield[b] |
| **6** | 75:25 | 36% | 74:26 | 52% |
| **7a**[c] | 53:47 | 42% | 84:16 | 61% |
| **7b** | 66:34 | 47% | 84:16 | 66% |
| **8a** | 44:56 | 38% | 86:14 | 51%[d] |
| **8b** | 59:41 | 35% | 90:10 | 49%[e] |
| **9**[f] | 64:34 | 35% | **94:6** | **74%**[d] |
| **9**[f,g] | ND | ND | **96:4** | **79%**[e] |

[a] Enantiomeric ratio, measured by reduction to corresponding primary alcohol and analysis by chiral HPLC. The er shown is the aggregate of C3 epimers for the major decalin isomer (*cis* or *trans*). [b] Isolated yield after TFA/$H_2O$/$CHCl_3$, 2h. [c] Catalyst **7a** was evaluated as its enantiomer, ent-**7a**. [d] 3 h. [e] 24 h. [f] 10 mol% HCl used. [g] Reaction at 0 °C.

With the racemic reaction established for both the (*E*)- and (*Z*)-alkene series, we next examined the potential for asymmetric catalysis. Computational studies predict that cyclic hydrazide iminium ions prefer the (*Z*)-configuration, with a twist along the N-N bond serving to relieve A-1,3 strain between the iminium and the carbamate (Figure 1). This suggests the positioning of the carbamate – twisted either above or below the plane of the iminium – might be harnessed for controlling enantioselectivity. We initially examined cyclic hydrazides with stereocenters adjacent to the carbamate group in order to gear the carbamate above or below the iminium. Catalysts were screened using substrates **2a**/**4a** in EtOH, as a solvent screen revealed that the highest enantioselectivities were observed in this solvent (see Supporting Information). Diazepane **6** afforded modest enantioselectivity (~75:25 er) for formation of both *cis*- and *trans*-decalins (Table 1). We then examined conformationally more rigid piperidazine carboxylates **7a** and **7b** which, intriguingly, displayed divergent behaviour with respect to (*E*)- and (*Z*)-olefins: enantioselectivity was improved for *cis*-decalin formation (84:16 er for both **7a** and **7b**) while enantioselectivity for *trans*-decalin formation was diminished. Given the previously noted lack of methods to impart high enantioselectivity in polyene cyclizations furnishing *cis*-decalins, we further optimized the selectivity for formation of **5a**.

As an alternative to the gearing of the carbamate in **6** and **7a**/**b**, we examined bicyclic hydrazides that would lock in its conformation. Initially, we observed that diphenyloxazolidinone **8a** afforded a modest improvement in enantioselectivity and significantly improved the reaction time (3 h vs 48 h) compared to the monocyclic hydrazides. The sense of enantioinduction for **8a** was the same as that observed with **7a/b**, even though it bears an inverted stereocenter, consistent with the carbamate being a significant stereocontrolling element. Somewhat surprisingly, removing the phenyl groups (**8b)** improved the

**Table 2.** Enantioselective cyclization of (*Z*)-polyenes.



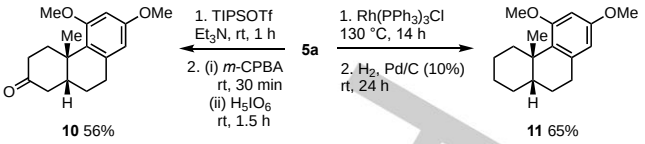

| Product | Cond.[a] | Time (h) | Yield (%) | C3-β/α | *cis*/*trans* | er[b] |
|---|---|---|---|---|---|---|
| **5a** | A | 24 | 79 | 1:3 | 97:3 | 96:4 |
| **5c** | A | 72 | 55 | 1:3 | 96:4 | 94:6[c] |
| **5e** | A | 48 | 60 | 1:3 | 96:4 | 97:3 |
| **5b** | B | 48 | 77 | 1:1.2 | 90:10 | 88:12 |
| **5d** | B | 48 | 83 | 1:1.8 | 93:7 | 93:7[c] |
| **5h** | B | 48 | 72 | 1:1.5 | 92:8 | 88:12 |
| **5i** | B | 48 | 77 | 1:1.2 | 92:8 | 90:10 |

[a] Conditions: A) EtOH, 0 °C; TFA/$H_2O$/$CHCl_3$, rt, 2 h. B) 2% HFIP/DCM, –10 °C. [b] Enantiomeric ratio measured by reduction to corresponding primary alcohol and analysis by chiral HPLC. The er shown is the aggregate of C3 epimers for the major *cis*-decalin isomer. [c] Product derivatized to corresponding ketone via two-step aldehyde dehomologation to assess er. The er shown is for the major *cis*-decalin isomer.

enantioselectivity to 90:10 er. Based on a developing model where electron donation from the carbonyl was important (*vide infra*), we next examined imidazolidinone **9** and found this improved the selectivity to 94:6 er. Given the high reactivity of the bicyclic hydrazides, the reaction using **9** could easily be conducted at 0 °C, affording the product in 79% yield in 24 h with an optimum enantioselectivity of 96:4 er.

With an optimized catalyst in hand, we examined the bicyclization of a range of (*Z*)-olefin substrates. Substrates bearing electron rich arenes performed well in EtOH, affording high er's and high *cis*-selectivity (Table 2). As with the racemic reaction, the cyclization of substrates bearing slightly less nucleophilic arenes resulted in byproducts arising from trapping of the intermediate cation. The use of 2% HFIP/DCM again eliminated all trapping products and only slightly attenuated enantioselectivity (94:6 er for **4a**→**5a** in 2% HFIP/DCM vs. 96:4 er in EtOH).[15] Using these conditions, 3,5-dimethylphenyl-, 3-methoxy-2-methylphenyl-, thiophenyl- and benzofuran-containing substrates afforded bicyclization products in high yields and enantioselectivities.

The bicyclization process leaves an aldehyde functional handle that may be used for further manipulation. Most steroids possess either oxygen or hydrogen at C3, and thus we developed methods to transform the aldehyde in these directions (Scheme 5). Oxidative degradation could be effected by formation of a silyl enol ether followed by mCPBA/$H_5IO_6$ treatment to form ketone **10**. Alternatively, if an ultimately traceless process is desired, decarbonylation could be achieved by treatment with Wilkinson's catalyst at reflux in xylenes, followed by hydrogenation of the resulting alkene to provide **11** in good yield.




**Scheme 5.** Transformations of polyene cyclization products.

In the enantioselective reaction, the catalyst is quite remote from the incipient stereocenter and the divergent effects of (*Z*)- and (*E*)-alkenes on this remote stereoinduction are highly intriguing. We sought to understand the origins of this stereocontrol using DFT. As noted above, at least some of the reactions appear to proceed in stepwise fashion. We thus began by modeling the initial cyclization step in a truncated system at the M06-2X/6-311G(d,p) level of theory using a PCM solvation model for EtOH.

As noted above, hydrazide iminium ions favour the (*Z*)-isomer. From this geometry, attack of the alkene on the s-*cis* and s-*trans* conformations of the α,β-unsaturated iminium may occur proximal or distal to the carbonyl group of the hydrazide. Of the four possible chair-like transition states, the lowest energy pathway results from proximal attack on the *s-trans*-iminium (Figure 2A). In this conformation, the hydrazide carbonyl is positioned below the carbon adjacent to the forming carbocation, allowing for electrostatic stabilization of the developing charge. In addition, NBO calculations identified an $n_O \rightarrow \sigma^*_{C\text{-}H}$ donation to the axial C-H bond, potentially as a means of direct donation of electron density into the electron-poor system. The disfavoured diastereomer results from proximal attack on the s-*cis* conformation and is 2.3 kcal/mol higher in energy. In this diastereomer, the proton is replaced by an alkyl group, forcing the carbonyl further from the developing cation, reducing

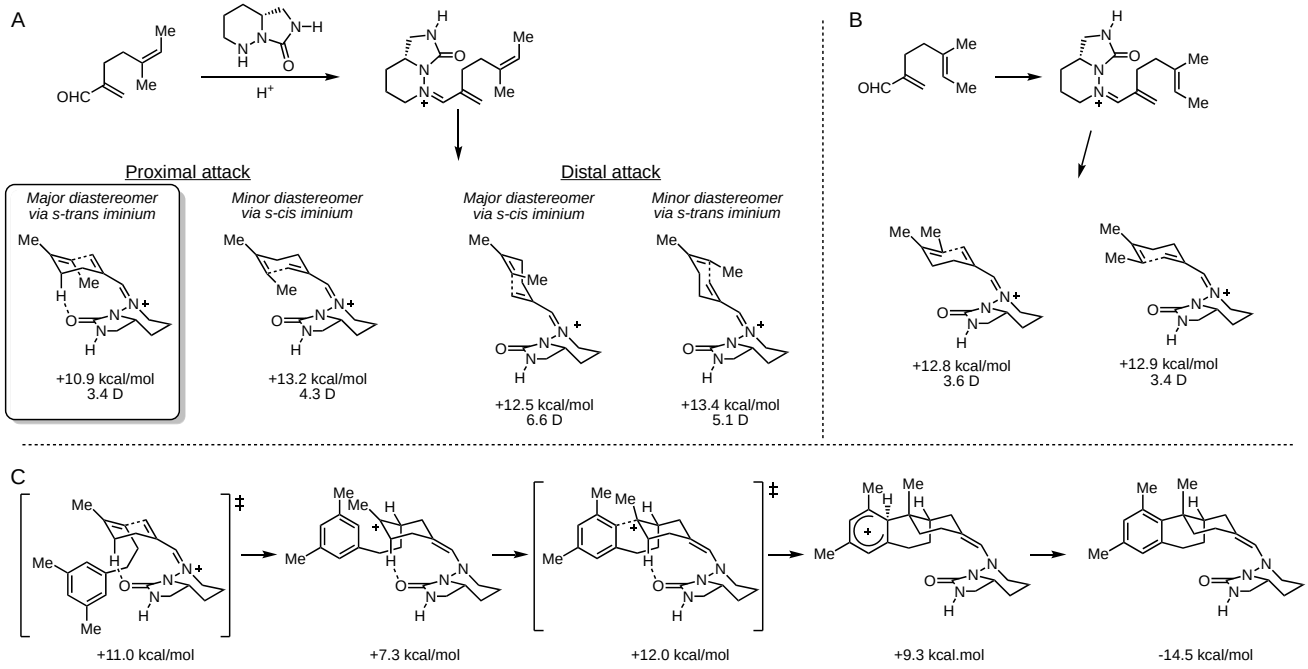



**Figure 2.** DFT Calculations at the M06-2X/6-311G(d,p), SCRF=EtOH level. A) Calculations on a truncated (*Z*)-alkene model showing the favoured pathway for cyclization. B) Calculations on (*E*)-substrates predict low selectivity. C) Extension of truncated model to full bicyclization pathway. All energies are relative to the initial iminium ion.

potential through-space electrostatic stabilization and disrupting direct donation. These changes are reflected in an increased dipole moment (4.3 D vs 3.4 D).[16] Distal attack is also less favoured, presumably due to increased distance between the forming cation and the carbonyl.[17] This model also explains the lack of selectivity observed with (*E*)-alkenes, as the alkyl group occupies an equatorial position in both proximal arrangements without disrupting the positioning of the carbonyl (Figure 2B).[18]

The model was then extended to the full bicyclization process (Figure 2C). For dimethylphenyl substrate **4b**, bicyclization from the iminium proceeds via the proximal, chair-like transition state ($\Delta G^{\ddagger}$ = 10.6 kcal/mol relative to the iminium) to give a discrete monocyclic intermediate cation, which then proceeds via electrophilic aromatic substitution ($\Delta G^{\ddagger}$ = 12.0 kcal/mol, +4.7 kcal/mol relative to the cation) to the eventual product. The corresponding pathway for the minor isomer was computed to have a 13.3 kcal/mol barrier for the cyclization step and 11.6 kcal/mol barrier for the trapping step. Intriguingly, calculations on the corresponding dimethoxy substrate **4a** suggest that its bicyclization may be a concerted, non-synchronous process (see Supporting Information). This potential change in mechanism is presumably due to the greater nucleophilicity of the arene which promotes a barrierless trapping and is consistent with the reduced amounts of (*Z*)→*trans* crossover and EtOH trapping products observed compared to **4b**.

In summary, we have developed the first iminium ion-catalyzed polyene cyclization and the first examples of highly enantioselective bicyclizations to form *cis*-decalins. Computations suggest that the enantioselectivity is influenced by the catalysts' ability to stabilize positive charge as it develops during the cyclization via electrostatics and/or direct σ-framework donation. This complements methods that use π-cation interactions to influence the reaction and will impact future catalyst design. Additionally, our studies highlight the remarkable differences that remote stereocenters can have on the outcome of polyene cyclizations and underscores the fact that olefin geometry must be carefully considered when developing asymmetric catalysts.

## Acknowledgements

The authors thank the Natural Sciences and Engineering Research Council of Canada for funding and Hayden Foy and Travis Dudding (Brock University) for help with AIM calculations.

**Keywords:** polyene cyclization • cis-decalin • hydrazide • organocatalysis • asymmetric catalysis

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[13] Reactions using stronger acids such as TfOH produced a greater proportion of byproducts and lower isolated yields.

[14] Reactions in EtOH form a mixture of aldehyde and diethyl acetal products. All acetals are hydrolyzed by treatment of the concentrated reaction mixture with TFA/$H_2O$/$CHCl_3$ prior to workup.

[15] The use of higher amounts of HFIP (e.g. 5%) resulted in decreased enantioselectivity.

[16] Although a steric component also seems possible, calculations on the corresponding saturated (neutral) cyclohexane predict that the diastereomer with the axial methyl group proximal to the carbonyl group

(as in the minor transition state) is slightly more stable than that which mimics the major transition state. See Supporting Information for details.

[17] Intermediates resulting from attack on a *trans*-imine were even higher in energy. See Supporting Information for details.

[18] Direct $n_O \rightarrow \sigma^*$C-H donation was not observed in the (*E*)-alkene calculations at the M06-2X/6-311G(d,p) level, but was observed with other basis sets (e.g. 6-31G*). Moreover, bond critical points were observed using AIM calculations. See Supporting Information for details.

10.1002/anie.201911952



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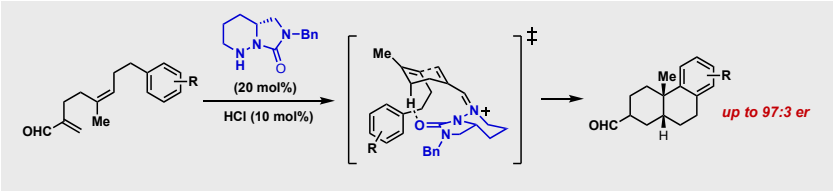
# COMMUNICATION




**Remote Stabilization:** Chiral bicyclic hydrazides catalyze cyclizations of (*Z*)-polyenes to *cis*-decalins by means of iminium-ion catalysis. High enantioselectivity results from remote stabilization of the developing cationic charge in the transition state by the hydrazide carbonyl.

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**Hydrazide-Catalyzed Polyene Cyclization: Asymmetric Organocatalytic Synthesis of *cis*-Decalins**