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Organocatalysis

Organocatalytic Enantioselective Vinylcyclopropane-Cyclopentene (VCP-CP) Rearrangement

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Abstract: We have demonstrated that the catalytic and enantioselective vinylcyclopropane-cyclopentene rearrangement can be carried out on (vinylcyclopropyl)acetaldehydes through activation via enamine intermediates. The reaction makes use of racemic starting materials that, upon ring opening facilitated by the catalytic generation of a donor-acceptor cyclopropane, deliver an acyclic iminium ion/dienolate intermediate in which all stereochemical information has been deleted. The final cyclization step forms the rearrangement product, showing that chirality transfer from the catalyst to the final compound is highly effective and leads to the stereocontrolled formation of a variety of structurally different cyclopentenes.

Introduction

Early reports in the 1950's already demonstrated that vinylcyclopropanes undergo ring expansion to provide cyclopentenes under thermal conditions (the so-called vinylcyclopropane-cyclopentene rearrangement).[1] The utility of this transformation in synthesis has remained very limited for many years due to the harsh reaction conditions required, that typically involved very high temperatures.[2] For this reason, intense research has been carried out in order to find alternatives that enable carrying out this transformation under milder conditions, which has been essentially achieved either by incorporating a specific substitution pattern at the vinylcyclopropane scaffold, by making use of the ability of transition metals to activate the vinylcyclopropane scaffold or by carrying out his reaction photochemical activation.[3] Remarkably, with respect to the possibility of performing the vinylcyclopropane rearrangement to provide a chiral cyclopentene product with a defined absolute configuration, all attempts have been limited to enantiospecific reactions, in which enantiomerically enriched vinylcyclopropanes are used as starting materials.[4] Despite these elegant approaches, the possibility of performing a catalytic and enantioselective vinylcyclopropane rearrangement that converts racemic starting materials into enantioenriched cyclopentenes is still elusive.

In this context, Christmann and co-workers recently reported an elegant example of enantiospecific divinylcyclopropane-cycloheptene rearrangement using catalytically generated dienamine-substituted divinylcyclopropane intermediates.[5] The authors demonstrated that, despite the fact that a chiral catalyst had to be used for the reaction to proceed with good yields, the absolute configuration of the final products relied exclusively on the starting chiral cyclopropane reagent, being impossible to control the stereochemical outcome of the process using chiral secondary amines as catalysts (Scheme 1a). On the contrary, we wish to report herein that catalyst-controlled enantioselective vinylcyclopropane-cyclopentene rearrangement is a feasible process using (vinylcyclopropyl)acetaldehydes as starting materials (Scheme 1b).[6] These compounds can generate an enamine adduct (**EN** intermediate on Scheme 1b) upon activation with a chiral secondary amine, having the structure of a donor-acceptor cyclopropane if an electron-withdrawing substituent is placed at the terminal position of the vinyl moiety.[7] The synergistic character of the enamine donor and the electron-poor olefin acceptor moieties facilitates a ring-opening event that can generate a stabilized

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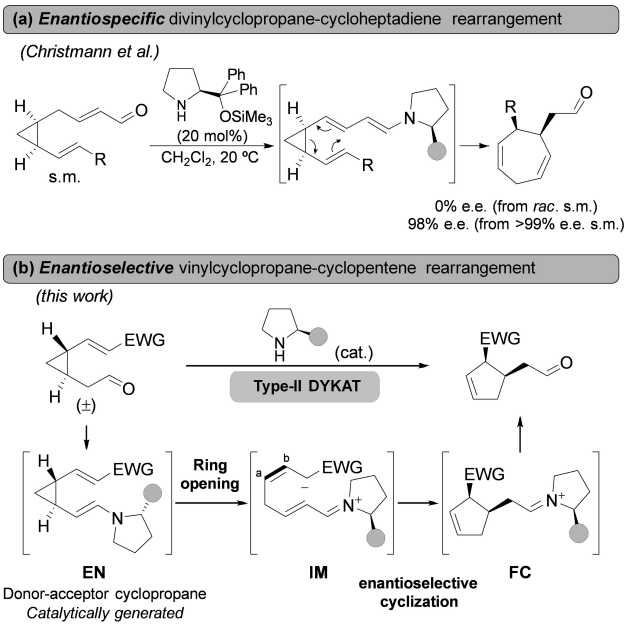


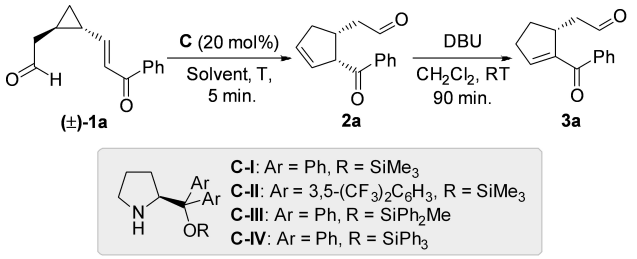
Scheme 1. Vinylcyclopropane rearrangements through (a) dienamine and (b) enamine activation manifolds. (EN = Enamine intermediate, IM = Iminium ion intermediate, FC = Ring closure intermediate.

iminium/dienolate intermediate (**IM** intermediate on Scheme 1b) in which all the stereochemical information form the starting cyclopropane reagent has been lost.[8] Finally, this intermediate has the potential to undergo ring-closure with the catalyst being engaged in controlling the stereochemical outcome of this cyclization, forming the cyclopentene scaffold (**FC** intermediate on Scheme 1b) in a stereoselective manner. The final rearrangement product would be obtained after catalyst release by hydrolysis. The overall reaction can therefore be classified as a type II DYKAT (Dynamic Asymmetric Transformation) process.[9]

Results and Discussion

In our first experiments, we initially verified the ability of chiral secondary amines to participate as potential catalysts for the reaction using cyclopropylacetaldehyde **1a** as model substrate (Table 1). We focused on diarylprolinol-type compounds as archetypical catalysts for enamine activation,[10] starting with *O*-trimethylsilyl-protected diphenylprolinol **C-I**. Under these conditions, a remarkably fast reaction took place (starting material was consumed in 5 min.) and the rearrangement product could be isolated in moderate yield, although as a mixture of diastereosiomers (entry 1). Isomerization of this mixture in the presence of DBU (DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene) led to the clean formation of cyclopentene **3a**, which was isolated with a promising 72 % e.e.[11] We next evaluated catalyst **C-II** with bulkier aryl substituents, observing that the reaction proceeded similarly, with only a slight increase in the enantioselectivity (entry 2). However, when catalysts incorporating bulkier SiR_3 substituents **C-III** and **C-IV** were used

Table 1: Screening for the best experimental reaction conditions.[a]



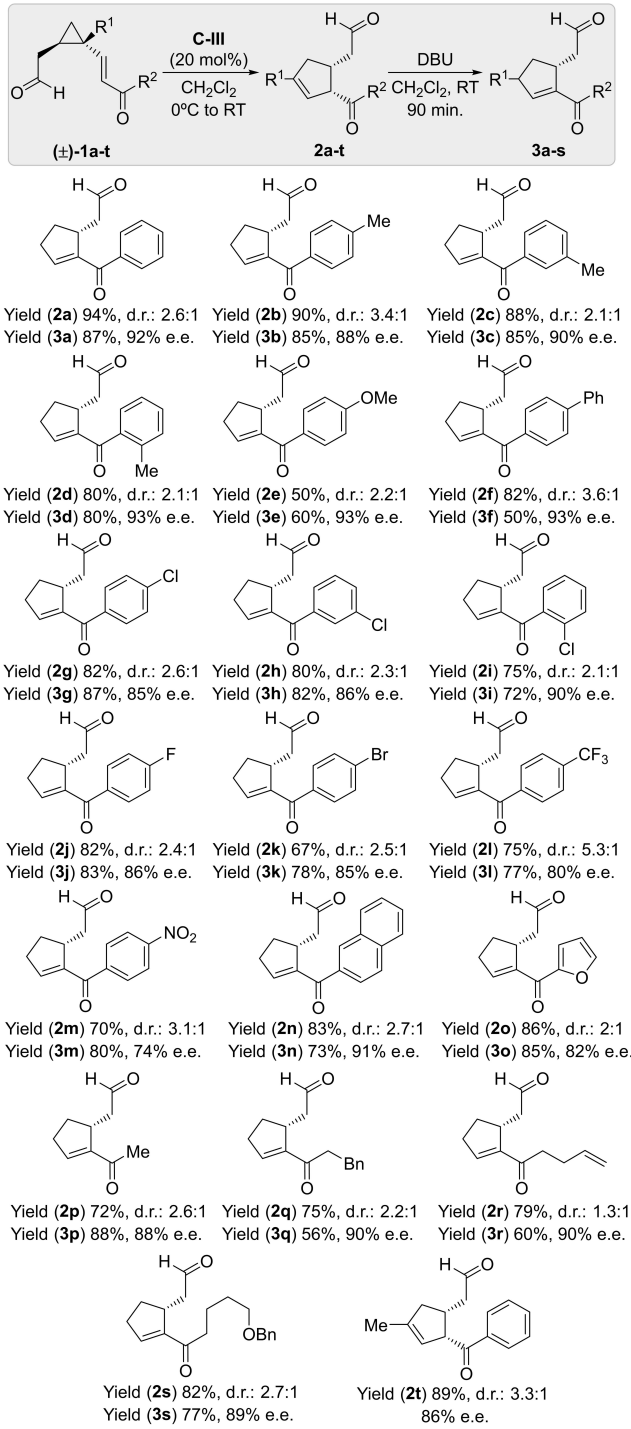
Entry	Cat.	Solvent	T	Yield **2a** [%][b]	d.r. **2a**[c]	Yield **3a** [%][d]	e.e. **3a** [%][e]
1	**C–I**	$CHCl_3$	RT	44	1.4:1	78	72
2	**C–II**	$CHCl_3$	RT	22	2.1:1	82	82
3	**C–III**	$CHCl_3$	RT	64	2.5:1	80	88
4	**C–IV**	$CHCl_3$	RT	68	2.5:1	81	84
5	**C–III**	THF	RT	90	3.5/1	80	65
6	**C–III**	Toluene	RT	67	3.0:1	84	75
7	**C–III**	$Cl(CH_2)_2Cl$	RT	81	2.6:1	83	88
8	**C–III**	CH_2Cl_2	RT	86	2.6:1	82	88
9	**C–III**	CH_2Cl_2	0 °C	94	2.6:1	87	92
10[f]	**C–III**	CH_2Cl_2	0 °C to RT	90	2.6:1	86	92
11[g]	**C–III**	CH_2Cl_2	0 °C to RT	–	–	72	91

[a] Reaction carried out in a 0.1 mmol scale of **1a**, using 20 mol% of catalyst in the indicated solvent and temperature. [b] Combined yield of both diastereoisomers after flash column chromatography purification. [c] Determined by NMR analysis of crude reaction mixture. [d] Isolated yield of **3a** after flash column chromatography purification. [e] Determined by HPLC analysis on a chiral stationary phase. [f] Reaction carried out in a 1.00 mmol scale of **1a**. [g] The rearrangement step was carried out under the conditions shown in entry 10 and DBU was added at once to the crude mixture after consumption of starting material had been observed (5 min.). DBU = 1,8-diazabicyclo-(5.4.0)undec-7-ene.

a remarkable improvement in the yield of the reaction was observed, still maintaining high enantioselectivity (entries 3 and 4). With best catalyst **C-III** in hand, solvent effects were evaluated (entries 5–8), obtaining an excellent yield and stereocontrol when the reaction was carried out in CH_2Cl_2 (entry 8) and even increasing the enantioselectivity working at lower temperature (entry 9). Under these conditions, the reaction still was observed to be remarkably fast, observing full conversion after 5 min. Finally, we also verified the excellent performance of the reaction on a higher 1.00 mmol scale of **1a**, (entry 10). For this experiment, the reagents were added at 0 °C and the mixture was allowed to reach to RT, during the 5 min. required for the full consumption of the starting materials. Under these conditions, **3a** was obtained with similarly high yield and enantioselectivity. We also carried out the complete vinlycyclopropane-cyclopentene rearrangement followed by the isomerization sequence in a one pot manner, obtaining the final product **3a** with a similar overall yield and enantioselectivity (entry 11).

With a robust experimental protocol for the reaction in hand, we next explored the ability of differently substituted cyclopropanes to undergo this new transformation, starting by evaluating the influence of the substituent R at the enone moiety (Table 2). All substrates were found to undergo this reaction with good efficiency in terms of both chemical yield

Table 2: Scope of the reaction using vinylcyclopropanes **1a–t**.



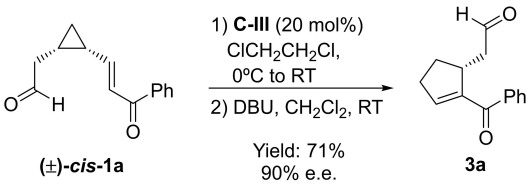
[a] For reaction conditions see Table 1 and Supporting Information.

and enantiocontrol. Importantly, the moderate diastereoselectivity obtained for the formation of cyclopentenes **2b–s** was inconsequential, as both isomers were easily converted into the same products **3b–s**.

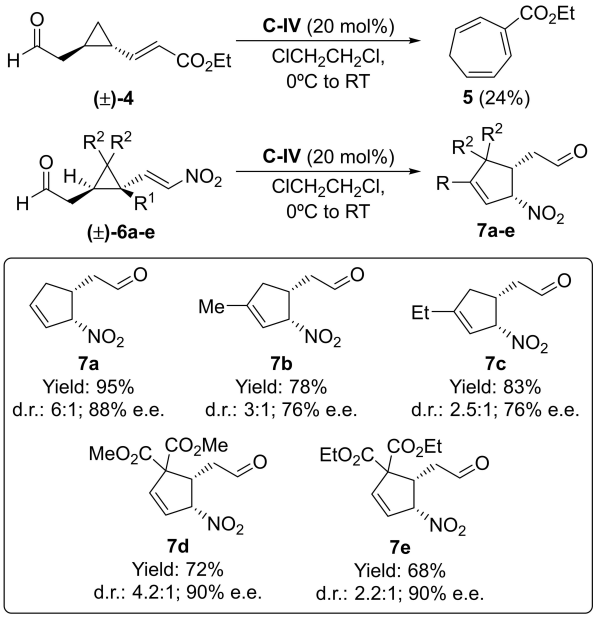
In particular, electron-donating substituents at different positions in the aryl moiety (**1b–f**) were well-tolerated offering good yields and enantioselectivities in the final adducts (**3b–f**). Similarly, substituents with electron-withdrawing properties in different positions (substrates **1g–m**) were also evaluated, observing higher yields in general, which can be attributed to a more polarized donor-acceptor cyclopropane intermediate. On the contrary, slightly lower enantioselectivities were also obtained in many of these substrates, most likely because of a possible competing uncatalyzed background reaction. In a different context, naphthyl-substituted cyclopropyl enone **1n** behave similarly as those evaluated before and, importantly, this reaction could also be extended to heteroaryl substituted enone **1o**, which led to cyclopentene **3o** in good yield and enantioselectivity. Moreover, enones bearing an alkyl or functionalized alkyl substituent at R^2 position (**1p–s**) also performed well in the reaction for all cases tested. Finally, we also evaluated the possibility of placing an additional substituent at the C-2 position of the cyclopropylacetaldehyde scaffold (R^1 substituent, substrate **1t**). This compound also reacted efficiently, providing cyclopentene **2t** with good yield and enantioselectivity. It should be pointed out that, in this particular case, the DBU-mediated isomerization of **2t** into **3t** did not take place under the optimized conditions, only observing the clean conversion of compound **2t** into its thermodynamically more stable *trans*-configured diastereoisomer (see Supporting Information for details). The absolute configuration of compound **2k** was established by X-ray analysis after reduction/benzoylation (see Supporting Information for details) and the stereostructure of all other compounds obtained was established based on mechanistic analogy.[12]

In a different experiment, we also decided to study the behavior of the *cis*-configured cyclopropane substrate **(±)-*cis*-1a** on the rearrangement/isomerization sequence under the optimized reaction conditions. As it can be seen in Scheme 2, this substrate underwent clean conversion into **3a** with comparable overall yield and similar enantioselectivity to that observed for its diastereoisomer **1a** (see entry 11 on table 1). NMR analysis of the crude reaction mixture obtained after the rearrangement process also showed that intermediate **2a** had been formed with comparable diastereoselectivity (d.r. = 2.7:1) to the one observed with the reaction starting from **1a** and we also verified that the *cis*-configured diastereoisomer was the major one being formed before the DBU-promoted **2a** to **3a** isomerization step.

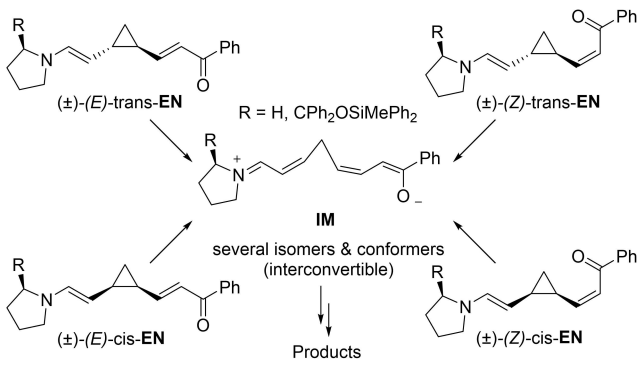
We also evaluated the use of other electron-poor vinyl substituents through cyclopropanes **4** and **6a–e** as representative compounds (Scheme 3).[13] Initially we investigated



Scheme 2. Vinylcyclopropane-cyclopentene rearrangement under optimized reaction conditions using a *cis*-configured cyclopropane substrate.



Scheme 3. Influence of the electron withdrawing vinyl substituent on the reaction outcome.



Scheme 4. Transformation of configurational information into conformational information and *vice versa*. All isomers are connected with the same intermediate **IM** in which all the stereochemical information coming from the cyclopropane starting material had been removed.

the possibility of using an ester as activating substituent on the vinyl moiety (substrate **4**). In this particular case, the desired rearrangement compound was not observed, isolating cycloheptatriene **5** as the major product, which can be explained by a competitive divinylcyclopropane-cycloheptadiene rearrangement.[5b] On the other hand, when a stronger electron-withdrawing substituent at the vinyl chain such as the nitro group was incorporated (substrates **6a–e**), the vinylcyclopropane-cyclopentene rearrangement took place smoothly, providing compounds **7a–e** in good yields and high enantiomeric excesses[14] In these particular cases, the ring-closing event also took place with good diastereoselectivity.

We also decided to study the mechanism of the reaction using computational tools. In particular, we focused on the transformation of **EN**, derived from **1a**, into **FC** through intermediate **IM** (See Scheme 1). In this intermediate, all the configurational information of the starting enamine, including the configuration of the cyclopropane ring (*cis/trans)* and that of the double bond (*E/Z*), has been lost as the configurational information has been transformed into conformational information and *vice versa*, thus causing the possibility of interconversion between all isomers and conformers of **IM**. Consequently, and as it is shown in Scheme 4, it could be possible to connect both *cis* and *trans* isomers bearing *(E)* and *(Z)*-C=C double bonds, through the same achiral intermediate (R = H), *predicting identical results whatever isomer of the cyclopropane **1** is used*, as it had been demonstrated experimentally through the experiment shown in Scheme 2.

Moreover, in the particular case of **IM**, only the intermediates with *(Z)*-configuration in the Ca–Cb double bond can cyclize to **FC** and therefore only the ring-opening in the appropriate conformation (*s-cis* between C-a and C-b in **EN**) will lead to productive species. Interestingly, when using the chiral catalyst **C-III**, **IM** (R = $CPh_2OSiMePh_2$) is a unique chiral intermediate from which different enantiomers can be obtained, representing a typical Type II DYKAT.[9a] Initially, we studied the achiral reaction (using a simple pyrrolidine as catalyst, Figure 1). Any attempt of locating

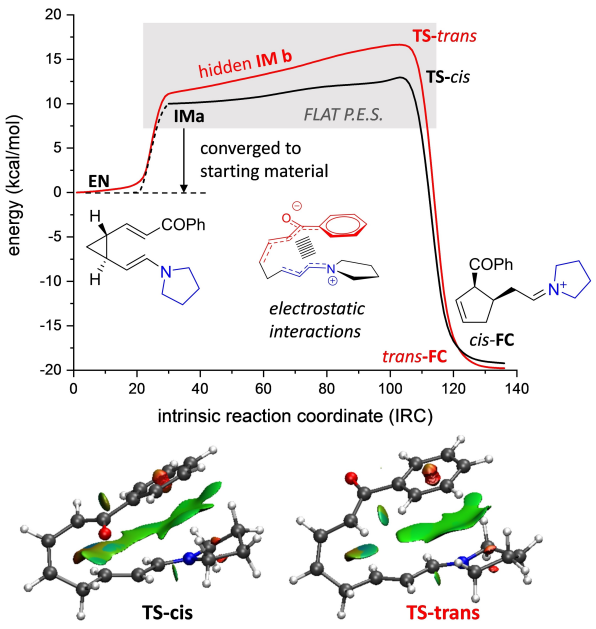


Figure 1. Top: Intrinsic reaction coordinates of the most stable transition structures corresponding to the attack by the two different diastereotopic faces leading to *cis*-**FC** (**TS-*cis*** (Re_{IM}*-Si_{ENOL}*) and *trans*-**FC** (**TS-*trans*** (Re_{IM}*-Re_{ENOL}*). Dashed line indicates a complementary relaxed scan from the starting point of the IRC for **TS-*cis*** (**INb**). Note that both the relaxed scan and the final point converged, after optimization, to the starting **EN**. Bottom: Optimized geometries (wb97xd/def2svp/smd = CH_2Cl_2) of **TS-*cis*** and **TS-*trans*** showing a NCI analysis representing the electrostatic interactions between the two parts of the intermediate: Green surface indicates cooperative interactions. As it can be observed qualitatively, **TS-*cis*** has a continuous surface greater than **TS-*trans*** which have a smaller interrupted surface, in agreement with a higher stability of the former.

transition structures corresponding to the cyclopropane ring-opening failed, suggesting a flat potential energy surface (PES) that could lead to a typical situation of a very asynchronous concerted mechanism with a single transition state but with two stages clearly defined.[15] After an exhaustive examination of the PES[16] close to the formation of **FC** we located the two transition structures leading to *cis*-(**TS-*cis***) and *trans*-isomers (**TS-*trans***). The corresponding intrinsic reaction coordinate plots corroborated the flatness of the PES either showing **IM** very close in energy to the transition structure or directly connecting the reagent **EN** with the product **FC** through a long reaction coordinate having a shoulder typical of hidden intermediates and transition structures.[17] After the ring-opening event, a very polar system is formed, whose stability depends on the electrostatic interactions between the two parts of the molecule oppositely charged. These interactions are also responsible of the stability of the corresponding transition structures as it is inferred from the analysis of non-covalent interactions (NCI) (See Figure 1).[18]

Transition structures **TS-*cis*** and **TS-*trans*** present an *(E)*-configuration and a *s-trans* conformation for the eniminium ion system, and *(Z)*-configuration and *s-cis* conformation for the dienolate. The difference in energy between these transitions structures accounts for the predicted diastereoselectivity. Accordingly, greater differences in energy between **TS-cis** and **TS-trans** should result in better diastereoselectivities. These could be achieved, for instance, by introducing a second electron-withdrawing group in the double bond connecting with the initial electron-withdrawing group. Actually, **IMa** (as extracted from the IRC) and **IMb** are different conformations of the same achiral species (for details see Supporting Information).

Next, we studied the real system (using chiral catalyst **C-III**) by introducing the C-2 substituent of the pyrrolidine moiety into the achiral model. Hayashi et al.[19] have demonstrated that catalyst **C-III** leads to highly energetically favored *s-trans-(E,E)*-eniminium ions in which the exocyclic C–C bond adopts a *sc-exo* conformation. So, we keep those configuration and conformation in our models and grew **TS-*cis*** to **TSa**-(1*R*,2*S*) and **TSa**-(1*S*,2*R*) respectively. Transition structure **TS-*trans*** was also grown to **TSb**-(1*R*,2*R*), and **TSb**-(1*S*,2*S*) (Figure 2).[20] The calculated relative energies predicted a diastereomeric ratio of 4:3 in favor of the *cis* isomer, in good agreement with that observed experimentally (*cis/trans* 2.6:1). The predicted enantioselectivity is essentially complete, also in excellent agreement with previous calculations for other reactions,[21] and with the experimental observations (90 % e.e.).

Calculations not only explain the observed enantioselectivity due to steric factors and diastereoselectivity mainly due to electrostatic interactions, but also predicts the same ratio of products when started from any configurational isomer of **1a**. This is a consequence of the presence of a hidden intermediate (evidenced in the IRC analyses) in which all the configurational information has been transferred to interchangeable conformational information, resulting -when the chiral catalyst is used- into a type II DYKAT. Calculations also revealed the negligible difference in energy between the transition state corresponding to the cyclopropane ring-opening and the open intermediates resulting in formal highly asymmetric concerted reaction (only one transition structure is located) in which two stages (ring-opening and cyclization) are clearly defined.

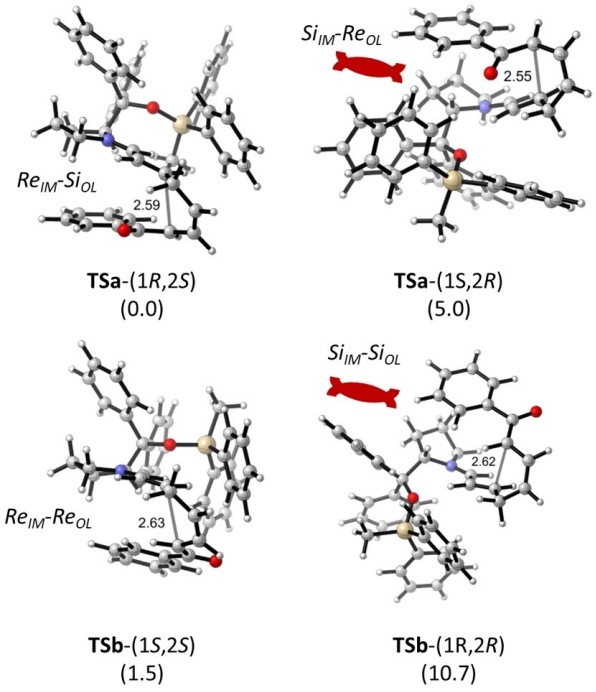


Figure 2. Optimized geometries (wb97xd/def2svp/smd = CH_2Cl_2) for transition structures corresponding to the real model. Relative energies are given in kcal mol^{-1}. The diastereofaces involved in the reaction are indicated (IM for iminium; OL for enolate). Whereas **TSa**-(1*R*,2*S*) and **TSb**-(1*S*,2*S*) correspond to the reaction of enolate moiety through the lees hindered face of the iminium moiety, **TSb**-(1*S*,2*R*) and **TSb**-(1*R*,2*R*) correspond to the reaction of the enolate moiety through the more hindered face of the iminium moiety. For NCI calculations see Supporting Information.

Conclusion

In conclusion, we have developed a very convenient catalytic and enantioselective vinylcyclopropane-cyclopentene (VCP-CP) rearrangement that converts racemic vinylcyclopropane-acetaldehydes into substituted cyclopentenes promoted by a chiral Jørgensen-Hayashi type catalyst. This enantioselective reaction is possible due to the disappearance of the chiral information present in the initial cyclopropane **1** during the reaction outcome, being governed exclusively by catalyst **C-III**, in a type II DYKAT process. Computational studies identified the electrostatic interactions between the two parts of the molecule that are developing opposite charges during the ring-opening step and the steric hindrance of the chiral catalyst as the key elements that explain the observed high diastereo- and enantioselectivities, respectively.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Catalysis · Cyclopropanes · DYKAT · Organocatalysis · Rearrangement

[1] N. P. Neureiter, *J. Org. Chem.* **1959**, *24*, 2044–2046.

[2] For some reviews: a) M. Meazza, H. Guo, R. Rios, *Org. Biomol. Chem.* **2017**, *15*, 2479–2490; b) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197–1212; c) S. C. Wang, D. J. Tantillo, *J. Organomet. Chem.* **2006**, *691*, 4386–4392; d) Z. Goldschmidt, B. Crammer, *Chem. Soc. Rev.* **1988**, *17*, 229–267; e) T. Hudlicky, T. M. Kutchan, S. Naqvi, *Org. React.* **1985**, *33*, 247–335; f) H. R. Sonawane, N. S. Bellur, D. G. Kulkarni, J. R. Ahuja, *Synlett* **1993**, 875–884.

[3] For an excellent discussion on the historical evolution of the development of this reaction, see: T. Hudlicky, J. W. Reed, *Angew. Chem. Int. Ed.* **2010**, *49*, 4864–4876.

[4] a) S. Clergue, O. Rousseau, T. Delaunay, G. Dequirez, T.-V. Tran, S. El Aakchioui, G. Barozzino-Consiglio, R. Robiette, *Chem. Eur. J.* **2018**, *24*, 11417–11425; b) J. Wu, J. Becerril, Y. Lian, H. M. L. Davies, J. A. Porco Jr., J. S. Panek, *Angew. Chem. Int. Ed.* **2011**, *50*, 5938–5942; c) K. Hiroi, Y. Yoshida, Y. Kaneko, *Tetrahedron Lett.* **1999**, *40*, 3431–3434; d) C. Doubleday, M. Nendel, K. N. Houk, D. Thweatt, M. Page, *J. Am. Chem. Soc.* **1999**, *121*, 4720–4721; e) J. E. Baldwin, S. J. Bonacorsi Jr., R. C. Burrell, *J. Org. Chem.* **1998**, *63*, 4721–4725; f) J. E. Baldwin, S. J. Bonacorsi Jr., *J. Am. Chem. Soc.* **1996**, *118*, 8258–8265; g) H. Weng, Q. Sheik, H. D. Roth, *J. Am. Chem. Soc.* **1995**, *117*, 10655–10661; h) L. A. Asuncion, J. E. Baldwin, *J. Am. Chem. Soc.* **1995**, *117*, 10672–10677; i) K. Hiroi, Y. Arinaga, *Tetrahedron Lett.* **1994**, *35*, 153–156; j) J. E. Baldwin, S. J. Bonacorsi Jr., *J. Am. Chem. Soc.* **1993**, *115*, 10621–10627; k) T. Hudlicky, M. G. Natchus, *J. Org. Chem.* **1992**, *57*, 4740–4746; l) H. R. Sonawane, B. S. Nanjundiah, V. G. Shah, D. G. Kulkarni, J. R. Ahuja, *Tetrahedron Lett.* **1991**, *32*, 1107–1108; m) T. Hudlicky, N. Heard, A. Fleming, *J. Org. Chem.* **1990**, *55*, 2570–2572; n) T. Hudlicky, A. Fleming, L. Radesca, *J. Am. Chem. Soc.* **1989**, *111*, 6691–6707; o) S. D. Larsen, *J. Am. Chem. Soc.* **1988**, *110*, 5932–5934; p) T. Hudlicky, G. Sinai-Zingde, M. G. Natchus, B. C. Ranu, P. Papadopoulos, *Tetrahedron* **1987**, *43*, 5685–5721; q) E. J. Corey, A. G. Meyers, *J. Am. Chem. Soc.* **1985**, *107*, 5574–5576; r) L. Higgs, M. Kavka, B. C. Ranu, T. Hudlicky, *Tetrahedron Lett.* **1984**, *25*, 2447–2450; s) T. Hudlicky, T. M. Kutchan, S. R. Wilson, D. T. Mao, *J. Am. Chem. Soc.* **1980**, *102*, 6351–6353.

[5] a) C. Apel, S. S. Hartmann, D. Lentz, M. Christmann, *Angew. Chem. Int. Ed.* **2019**, *58*, 5075–5079; For a general reviews of vinylcyclopropane-cycloheptene rearrangement, see: b) T. Hudlicky, R. Fan, J. W. Reed, K. G. Gadamasetti, *Org. React.* **1992**, *41*, 1–129.

[6] For a previous example on the enamine activation of cyclopropylacetaldehydes from our group, see: a) E. Sanchez-Diez, D. L. Vesga, E. Reyes, U. Uria, L. Carrillo, J. L. Vicario, *Org. Lett.* **2016**, *18*, 1270–1273; From other groups, see: b) J. Blom, A. Vidal-Albalat, J. Jørgensen, C. L. Barløse, K. S. Jessen, M. V. Iversen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2017**, *56*, 11831–11835; c) S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.* **2015**, *137*, 1685–1691.

[7] For some selected reviews on donor-acceptor cyclopropanes, see: a) S. J. Gharpure, L. N. Nanda, *Tetrahedron Lett.* **2017**, *58*, 711–720; b) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655–671; c) R. A. Novikov, Y. V. Tomilov, *Mendeleev Commun.* **2015**, *25*, 1–10; d) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818; e) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523; f) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano, J. Waser, *Chem. Commun.* **2014**, *50*, 10912–10928; g) M. Ya. Mel'nikov, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, *Mendeleev Commun.* **2011**, *21*, 293–301.

[8] For an early report proposing the formation of ring-opened zwitterionic intermediates in vinylcyclopropane-cyclopentene rearrangement involving donor-acceptor cyclopropanes, see: a) M. Buchert, H. U. Reissig, *Liebigs Ann.* **1996**, 2007–2013; For a previous report on a vinylcyclopropane-cyclopentene rearrangement involving donor-acceptor cyclopropanes, see: b) D. F. Harvey, M. F. Brown, *Tetrahedron Lett.* **1991**, *32*, 2871–2874.

[9] a) J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, *14*, 8060–8072; b) K. Faber, *Chem. Eur. J.* **2001**, *7*, 5004–5010.

[10] a) D. McLeod, M. K. Thøgersen, N. I. Jessen, K. A. Jørgensen, C. S. Jamieson, X.-S. Xue, K. N. Houk, F. Liu, R. Hoffmann, *Acc. Chem. Res.* **2019**, *52*, 3488–3501; b) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860–13874; c) S. Meninno, A. Lattanzi, *Chem. Commun.* **2013**, *49*, 3821–3832; d) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248–264; e) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880; f) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922–948.

[11] Partial isomerization from **2a** to **3a** was also observed upon standing for a prolonged time at r.t. or when the product remained in contact with silica for a long time during chromatographic purification.

[12] Deposition number 2240978 contains 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.

[13] For those substrates **6a**–**e**, the reaction proceeded with higher yields when **C–IV** was used as catalyst and in 1,2-dichloroethane as solvent. See Supporting Information for details.

[14] The absolute configuration of compound **7a** was established by X-ray analysis after reduction/intramolecular reductive amination (see Supporting Information for details). Deposition

number 2240977 contains 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..

[15] For two recent examples from our laboratories see: a) E. Capel, M. Rodriguez-Rodriguez, U. Uria, M. Pedron, T. Tejero, J. L. Vicario, P. Merino, *J. Org. Chem.* **2022**, *87*, 693–707; b) A. Ortega, R. Manzano, U. Uria, L. Carrillo, E. Reyes, T. Tejero, P. Merino, J. L. Vicario, *Angew. Chem. Int. Ed.* **2018**, *57*, 8225–8229.

[16] A total of 16 approaches were optimized leading to ten different transition structures from which three of them accounts for 100 % of Boltzmann distribution. See Supporting Information for details.

[17] a) S. Alvi, D. A. Singleton, *Org. Lett.* **2021**, *23*, 2174–2177; b) E. Kraka, D. Cremer, *Acc. Chem. Res.* **2010**, *43*, 591–601.

[18] a) E. R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506; b) J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan, W. Yang, *J. Chem. Theory Comput.* **2011**, *7*, 625–632.

[19] Y. Hayashi, D. Okamura, T. Yamazaki, Y. Ameda, H. Gotoh, S. Tsuzuki, T. Uchimaru, D. Seebach, *Chem. Eur. J.* **2014**, *20*, 17077–17088.

[20] Additional exploratory calculations of models with less stable conformations and configurations according to ref. [19] confirmed the prediction and led to transition structures higher in energy without any contribution to the reaction. On the other hand, we considered the conformational variability at the chiral substituent, which Hayashi et al. mentioned to provide different conformers.

[21] A. Orue, U. Uria, D. Roca-López, I. Delso, E. Reyes, L. Carrillo, P. Merino, J. L. Vicario, *Chem. Sci.* **2017**, *8*, 2904–2913 and references cited therein.

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