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Asymmetric Hydroacylation Involving Alkene Isomerization for the Construction of C_3-Chirogenic Center

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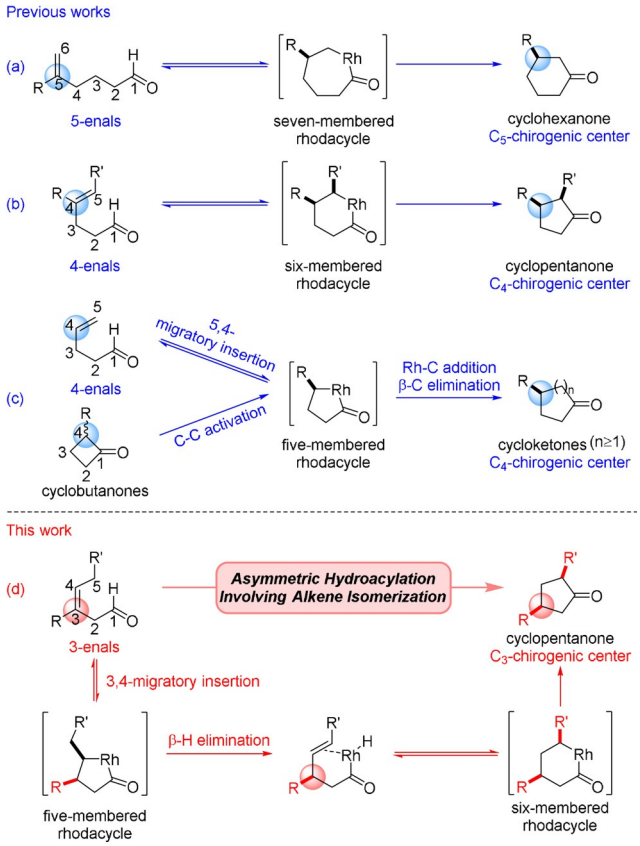
Abstract: *A new transformation pattern for enantioselective intramolecular hydroacylation has been developed involving an alkene isomerization strategy. Proceeding through a five-membered rhodacycle intermediate, 3-enals were converted to C_3- or C_3,C_5-chirogenic cyclopentanones with satisfactory yields, diastereoselectivities, and enantioselectivities. A catalytic cycle has been theoretically calculated and the origin of the stereoselection is rationally explained.*

Introduction

Chiral ketones are ubiquitous skeletons in natural products and synthetic pharmaceuticals.[1] Among the various developed methods, the enantioselective hydroacylation of alkenes is one of the most efficient and atom-economic approaches for the construction of these valuable compounds.[2] Since the pioneering work of James and Young,[3] the area of metal-catalyzed asymmetric intramolecular hydroacylations for the generation of chiral cycloketones has seen considerable progress, especially for methodologies focused on 5-substituted 5-enals and 4-substituted 4-enals (Scheme 1 a,b).[4] Since the corresponding seven- and six-membered rhodacycle intermediates tend to undergo reductive elimination, they can only provide a single pattern of transformation, which results in limitations to the construction of C_5- and C_4-dominated chirogenic centers (numbered from the formyl group). Recently, Dong has reported the efficient creation of C_2-chirogenic center via an asymmetric desymmetrization strategy.[5] However, to the best of our knowledge, research on the efficient generation of only C_3-chirogenic center via asymmetric hydroacylation of alkenes still remains a great challenge.[6] In order to expand the capacity and diversity of asymmetric hydroacylation, it is still highly desirable to develop distinctive transformation patterns and reaction strategies.



Scheme 1. Different formations and enantioselective transformations of rhodacycle intermediates.

Compared to the commonly utilized seven- and six-membered rhodacycle intermediates, the five-membered rhodacycle intermediate is too thermodynamically stable to achieve reductive elimination. In turn, it provides the possibility to realize transformation diversity through dynamically feasible sequential reactions such as Rh-C addition and β-C elimination.[7] To date, five-membered rhodacycle intermediates are mainly produced from 5,4-migratory insertion of 4-enals or C–C activation of cyclobutanones (Scheme 1 c).[7] However, the alternative route via 3,4-migratory insertion of 3-enals, which could generate the challenging C_3-chirogenic center, remains unexplored (Scheme 1 d).

In order to further transform the five-membered rhodacycle intermediate, we envisaged that an external β-H elimination could be introduced to enable the final synthesis of C_3-chirogenic cyclopentanones via a six-membered rhodacycle intermediate (Scheme 1 d). The key strategy for this

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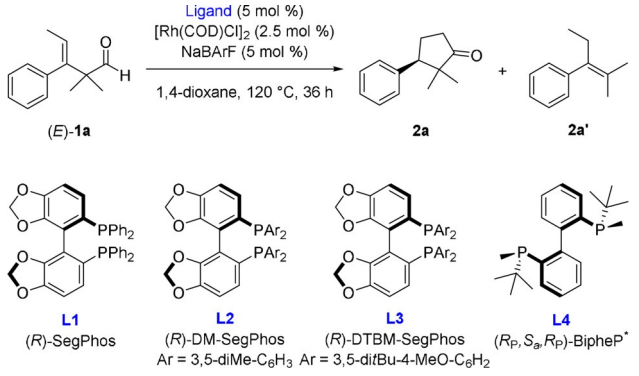
transformation is an unusual "alkene isomerization" from the thermodynamically favored 3-position to the thermodynamically unfavored 4-position, which is completely different from the reported examples in asymmetric hydrogenations, hydroborations, and hydrosilylations.[8] In addition, in combination with our previous findings by using an internal 4-enals,[9] an extra C_5-chirogenic center could be constructed during the last reductive elimination step. This work provides a new transformation pattern for asymmetric hydroacylations, as well as a new reaction strategy for the construction of C_3-chirogenic center.

Results and Discussion

With this hypothesis in mind, (*E*)-2,2-dimethyl-3-phenylpent-3-enal ((*E*)-**1a**) was chosen as the model substrate for condition optimization (Table 1, Table S1 and S2 in SI). Solvents and ligands play critically important roles in this reaction. The desired product **2a** could only be obtained in 1,4-dioxane. Additionally, only the bulky *t*Bu substituted bisphosphine ligands, DTBM-SegPhos (**L3**) and BipheP* (**L4**),[10] could afford **2a** (entries 1–4 and Table S1 in SI). The latter gave the desired product in 24% yield (remainder being unreacted (*E*)-**1a**) and 64/36 er, while the former provided a promising result of 76% yield (with the rest of the material being the decarbonylated byproduct **2a′**[11]) and 98/2 er. Changing the counterions of the catalyst precursors from $BArF^-$ to SbF_6^- had almost no effect on the reaction (entry 5). However, using the comparatively smaller counterion, BF_4^-, and other coordinating ions resulted in no reaction (entry 6 and Table S2 in SI). Shortening the reaction time from 36 to 24 h and further lowering the reaction temperature from 120 to 110 °C suppressed the side reaction and increased the yield of the desired product from 76% to 98% and the enantioselectivity from 98/2 to 99/1 er (entries 7,8). Further lowering the temperature to 100 °C dramatically reduced the reactivity with no product detected (entry 9).

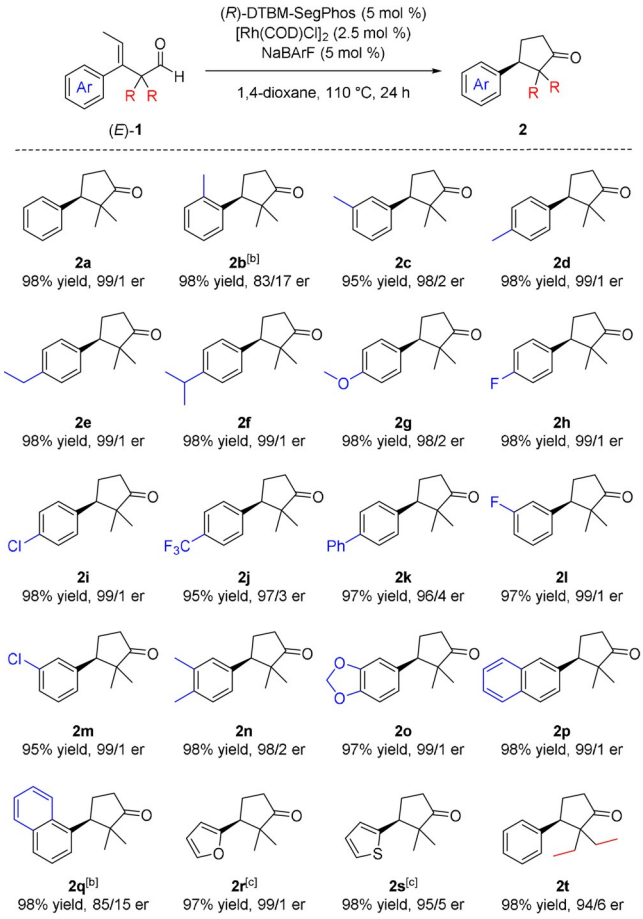
With an optimized protocol prepared, we evaluated a wide range of (*E*)-2,2-dialkyl-3-arylpent-3-enals containing different substituents on the aromatic ring (Scheme 2). Substrates ((*E*)-**1a**,**c**–**p**) bearing substituents at the *meta*- and *para*-positions underwent hydroacylation smoothly to give the desired products in 95–98% yield and with 96/4–99/1 er, regardless of the presence of electron-withdrawing/electron-donating substituents, or mono-/di-substituted groups on the aromatic ring. The hydroacylation of substrates with an *ortho*-substituted group ((*E*)-**1b**,**q**) requires a higher catalyst loading (10 mol%) to give the corresponding products in excellent yields (both are 98%), but with moderate enantio-

Table 1: Condition optimization for (*E*)-**1a**.



Entry[a]	Ligand	Yield [%][b]	er [%][c]
1	**L1**	trace	–
2	**L2**	trace	–
3	**L3**	76	98/2
4	**L4**	24	64/36
5[d]	**L3**	73	98/2
6[e]	**L3**	NR	–
7[f]	**L3**	78	98/2
8[f,g]	**L3**	**98**	**99/1**
9[f,h]	**L3**	NR	–

[a] Conditions: (*E*)-**1a** (0.2 mmol), ligand (5 mol%), $[Rh(COD)Cl]_2$ (2.5 mol%), NaBArF (5 mol%), 1,4-dioxane (2 mL), 120 °C, 36 h, unless otherwise noted. [b] Isolated yields of **2a**. [c] The er values of **2a** were determined by HPLC using a chiral AS-H column. [d] $[Rh(COD)_2]SbF_6$ (5 mol%) used instead of $[Rh(COD)Cl]_2$ and NaBArF. [e] $[Rh(NBD)_2]BF_4$ (5 mol%) used instead of $[Rh(COD)Cl]_2$ and NaBArF. [f] Reaction time is 24 h. [g] 110 °C. [h] 100 °C.



Scheme 2. Substrate scope of (*E*)-3-enals. [a] Conditions: (*E*)-**1** (0.2 mmol), (*R*)-DTBM-SegPhos (5 mol%), $[Rh(COD)Cl]_2$ (2.5 mol%), NaBArF (5 mol%), 1,4-dioxane (2 mL), 110 °C, 24 h, unless otherwise noted. Isolated yields. The er values were determined by HPLC using chiral columns. [b] Catalyst loading is 10 mol%. [c] The configuration of **1r**,**s** is *Z*.

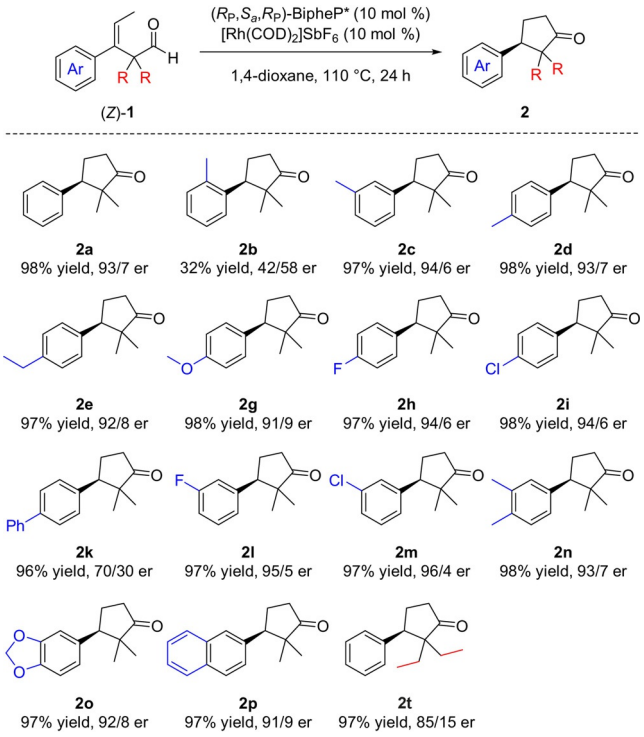
selectivities (83/17 and 85/15 er, respectively). The heteroaromatic substrate (*Z*)-**1r** and (*Z*)-**1s** is tolerated under the reaction conditions to form the corresponding product **2r** and **2s** in excellent results. By replacing the methyl to ethyl at the 2-position, the substrate (*E*)-**1t** could also give its corresponding product with satisfactory results (98% yield and 94/6 er).

After achieving excellent performance with (*E*)-substrates, we turned our attention to exploration with (*Z*)-substrates (Table S3 and S4 in SI). Taking (*Z*)-2,2-dimethyl-3-phenylpent-3-enal ((*Z*)-**1a**) as a model substrate, the bulky *t*Bu substituted bisphosphine ligand BipheP* (**L4**) gave positive results. With an optimized protocol for (*Z*)-**1a** in hand, the substrate scope of the (*Z*)-2,2-dialkyl-3-arylpent-3-enals was explored (Scheme 3). In most cases, the corresponding products were obtained quantitatively with 91/9–96/4 er, especially for substrates bearing *meta*-F and *meta*-Cl substituents. However, a Me-substituent at the *ortho*-position of aromatic ring significantly reduced the reactivity and enantioselectivity ((*Z*)-**1b**), and substrates possessing *para*-Ph and 2-Et substituents gave relatively poor results ((*Z*)-**1k**,**t**). These are consistent with the results obtained with the (*E*)-substrates.

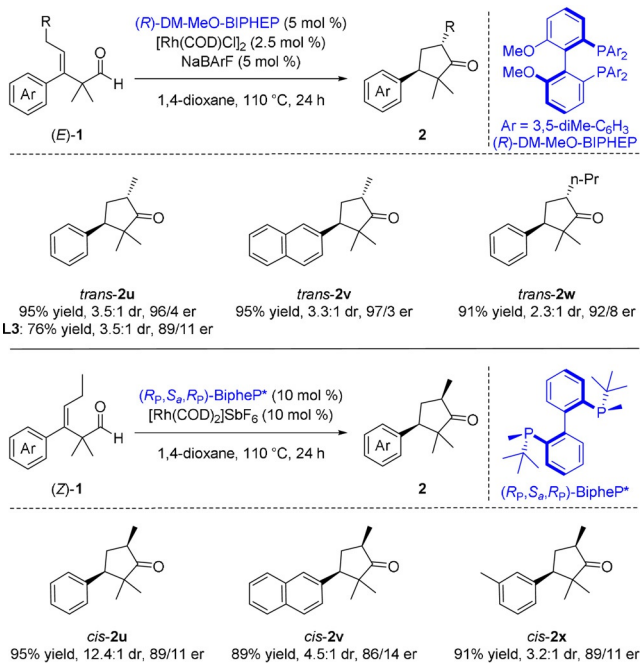
In order to verify the feasibility of this catalyst system for the construction of discontinuous C_3-,C_5-chirogenic cyclopentanones, a number of 3-enals bearing long alkyl substituents were chosen as the substrates (Scheme 4). By using DTBM-SegPhos (**L3**) as the ligand, (*E*)-2,2-dimethyl-3-phenylhex-3-enal ((*E*)-**1u**) was successfully converted to the desired product *trans*-**2u** in 76% yield and moderate enantio- and diastereoselectivity (3.5:1 dr, 89/11 er). When the ligand was changed to DM-MeO-BIPHEP, the *trans*-cyclopentanone was obtained with promising results (95% yield, 3.5:1 dr, 96/4 er). According to substrate scope, substituents at the *meta*- and *para*-positions of the aromatic skeleton have little impact on the catalytic performance. As expected, the hydroacylation of (*E*)-**1v** occurred to form the corresponding *trans*-**2v** with excellent results (95% yield, 3.3:1 dr, 97/3 er). The absolute configuration of this product was confirmed to be (*R*,*S*) according to the single crystal XRD analysis (see SI for details). Another substrate, (*E*)-**1w**, also afforded its corresponding product *trans*-**2w** with acceptable results (91% yield, 2.3:1 dr, 92/8 er). Similar results are also observed for (*Z*)-substrates. To our delight, contrary to the *trans*-products derived from (*E*)-substrates, the chiral cyclopentanones were obtained with a *cis*-configuration using BipheP* as the ligand (Scheme 4). The highest dr value of 12.4:1 was obtained during the hydroacylation of (*Z*)-**1u**, giving the desired product *cis*-**2u** with 89/11 er. Another two substrates, (*Z*)-**1v** and (*Z*)-**1x**, also gave the desired *cis*-products with comparable yields, diastereoselectivities, and enantioselectivities.

To gain insight into the mechanism, we prepared deuterium-labeled substrates (*E*- and *Z*-**1a**-*d*) and performed the hydroacylation reactions under the optimized conditions (Scheme 5). These experiments showed that the proton on the C_3-chirogenic center originates completely from the aldehyde group, which gave the evidence for the oxidative addition of CO-H to rhodium and Rh-H addition to the C_3-position.

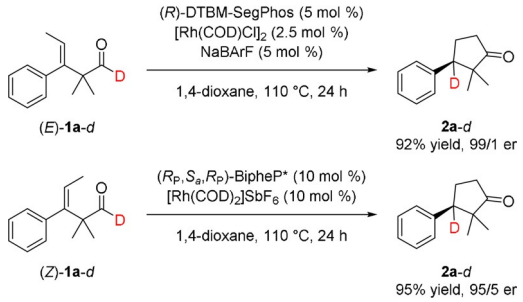
In order to gain a clearer insight into the reaction mechanism and stereocontrol mode, the catalytic cycle and corresponding energies of the intermediates and transition



Scheme 3. Substrate scope of (*Z*)-3-enals. [a] Conditions: (*Z*)-**1** (0.2 mmol), $[Rh(COD)_2]SbF_6$ (10 mol%), (R_P,S_a,R_P)-BipheP* (10 mol%), 1,4-dioxane (2 mL), 110°C, 24 h. Isolated yields. The er values were determined by HPLC using chiral columns.



Scheme 4. Asymmetric construction of C_3,C_5-chirogenic cyclopentanones.



Scheme 5. Deuteration experiments.

states were calculated as shown in Figure 1. Coordination of the prochiral substrate to the catalyst is endergonic, and provides the catalyst-substrate complexes **1*R*** and **1*S***. Subsequent oxidative addition of the aldehyde group to the metal affords the corresponding hydrides **2** which are capable of transferring the hydride to the prochiral carbon, thus producing chelating diastereomeric complexes **3*R*** and **3*S***. Note that this step is stereoselective favoring the formation of the *S*-stereocenter thermodynamically. The next stage, being also stereoselective, is also rate-limiting due to the high activation barriers of the rearrangements bringing the methyl groups on the opposite site of the chelate cycle of **3*R*** and **3*S***

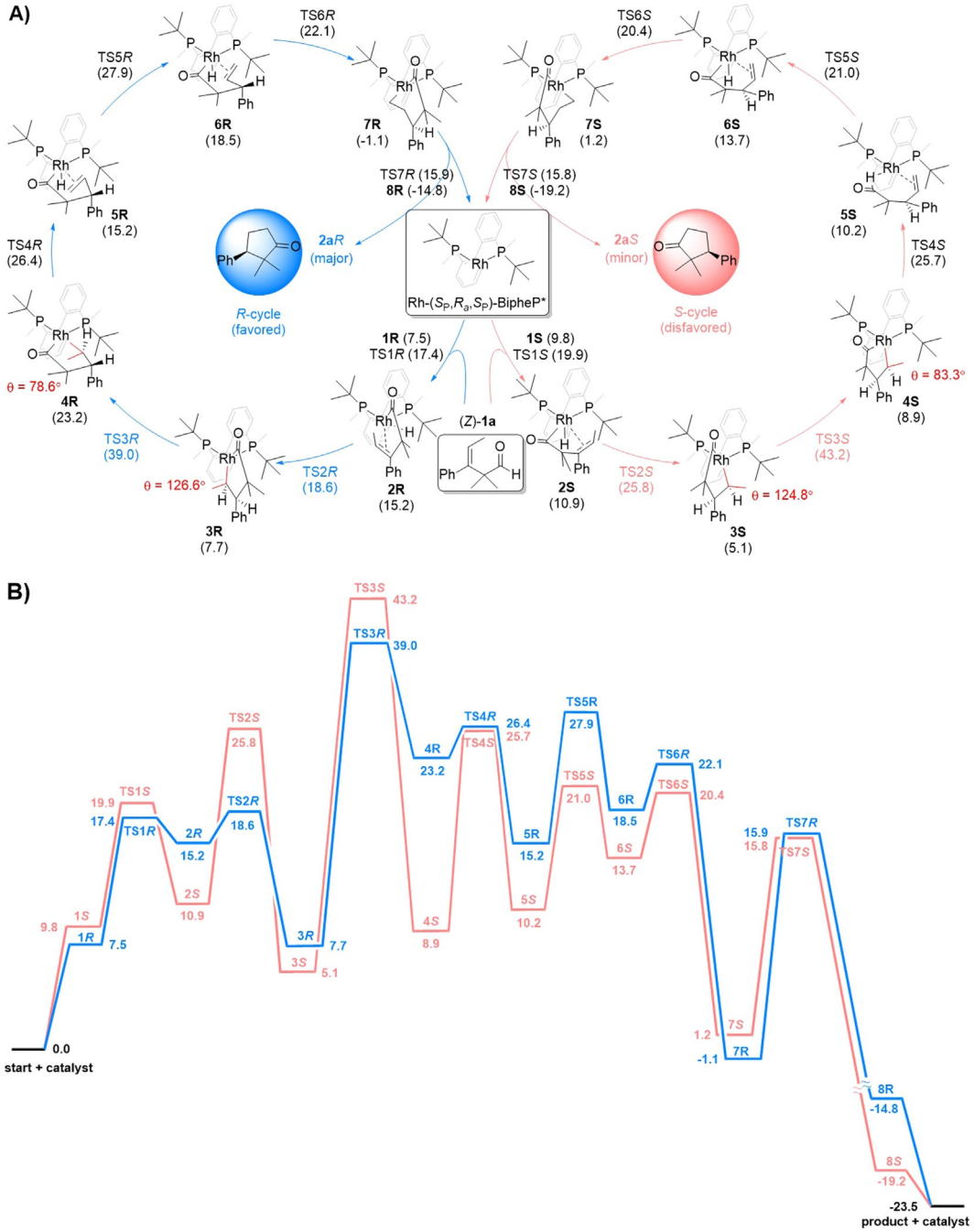


Figure 1. A) Computed catalytic cycle and B) potential energy profile.

into a proper position to enable abstraction of a hydride. The angles of Rh-C-CH_3, which correspond to the distance between Rh···β-H, have been shown as θ in **3*R*/4*R*** and **3*S*/4*S***. The β-H elimination will occur only when this angle is small enough. The **TS3*S*** is 4.2 kcal mol^{-1} less stable than **TS3*R***, strongly indicating the stereoselective formation of the *R*-enantiomer. The Rh-P bond in the **TS3*S*** must dissociate to effectuate the hydride transfer, since otherwise the methyl group of the substrate would overlap with the methyl group of the catalyst. This is additionally illustrated by the opposite relative stabilities of **4*R*** and **4*S***: while in the latter the rhodacycle is closed, the former cannot form a proper Rh–C bond due to the potential overlap of the $CHCH_3$ group with the *t*-Bu group of the catalyst.

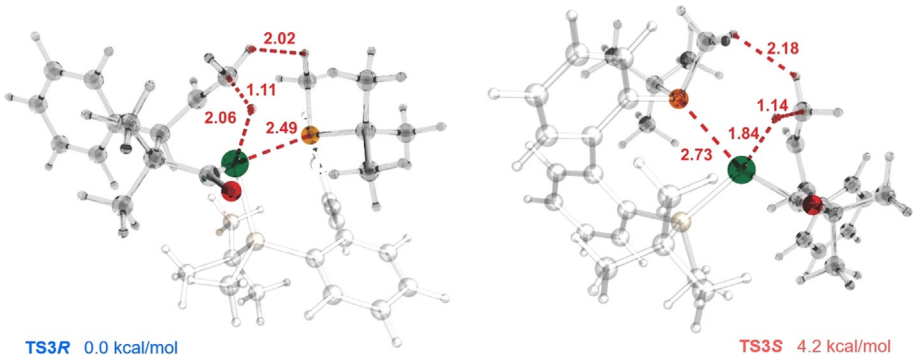


Figure 2. Optimized structures for the competing transition states.

Further rearrangements are necessary to place the newly formed Rh-H and C=C bonds in a proper position for the hydrorhodation resulting in **7**. There are numerous possibilities that are illustrated by computing different rearrangements leading to **7** for the *R* and *S* pathways. In the transformations computed for the *R*-pathway, β-H elimination of the agostic intermediate **4*R*** results in the Rh hydride **5*R*** with the coplanar Rh-H and C=C bonds. However, to avoid the reverse transformation via hydrorhodation, the double bond must first rotate via **TS5*R*** yielding **6*R***. The latter gives the rhodacycle **7*R*** in a hydrorhodation via **TS6*R***, and after reductive elimination provides the reaction product **2 a*R*** and releases the catalyst. For the *S*-pathway another consequence for the catalytic steps was computed. The agostic intermediate **4*S*** can undergo β-H elimination and reductive elimination providing a coordinated 4-enals. Rotation of the aldehyde group or small relocation would give **6*S*** upon hydrorhodation via **TS6*S*** yielding **7*S***, and eventually the reaction product **2 a*S***. It can be seen that the free energies of either of the computed pathways are much lower than those of the transition states of the rate-limiting steps. Hence, they do not affect the origin of the stereoselection.

The optimized structures with selected interatomic distances for the competing transition states **TS3*S*** and **TS3*R*** has been shown in Figure 2. In **TS3*S***, approach of the methyl group of the catalyst to the Rh atom (to enable further hydride transfer) requires dissociation of the catalyst chelate cycle leading to an increase in one of the Rh-P interatomic distances to 2.73 Å. In **TS3*R***, this interatomic distance is only 2.49 Å (i.e. it is 0.24 Å shorter). Maintaining the same Rh-P distance in the **TS3*S*** would require the methyl groups of the catalyst and the substrate to approach at 1.94 Å (2.18–0.24), and it is known that a weak attraction between two aliphatic protons in the range 2.3–2.7 Å switches to repulsion if they are closer than 2.1 Å.[12]

Conclusion

In summary, we have realized the first enantioselective intramolecular hydroacylation reaction of 3-enals for the construction of C_3-chirogenic cyclopentanones. The reaction proceeds through alkene isomerization via a five-membered rhodacycle intermediate. The C_3-chirogenic and C_3,C_5-chirogenic products are obtained with satisfactory yields, diastereoselectivities, and enantioselectivities (up to 99/1 er). We have also proposed a catalytic mechanism for the reaction and have rationalized the outcome of the enantioselectivity based on theoretical calculation.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: β-H elimination · alkene isomerization · cycloketones · hydroacylation · rhodacycle

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