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Rhodium-Catalyzed Enantioselective Cycloisomerization to Cyclohexenes Bearing Quaternary Carbon Centers

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Supporting Information

ABSTRACT: We report a Rh-catalyzed enantioselective cycloisomerization of α,ω-heptadienes to afford cyclohexenes bearing quaternary carbon centers. Rhodium(I) and a new SDP ligand promote chemoselective formation of a cyclohex-3-enecarbaldehyde motif that is inaccessible by the Diels–Alder cycloaddition. Various α,α-bisallylaldehydes rearrange to generate six-membered rings by a mechanism triggered by aldehyde C–H bond activation. Mechanistic studies suggest a pathway involving regioselective carbometalation and endocyclic β-hydride elimination.

The cycloisomerization of dienes represents a powerful and atom-economical route to unsaturated carbocycles that remains relatively limited to the preparation of *five*-membered rings (Figure 1a).[1,2] Cycloisomerizations to *six*-membered rings have been challenging to achieve with high regio- and enantiocontrol.[1−4] Such strategies remain sought after due to the need for cyclohexenes as building blocks and their common occurrence in nature.[5] Inspired by natural products, including pinnatal, jerantiphylline A, and myricolal (Figure 1b),[6] we designed a metal-catalyzed isomerization to generate cyclohex-3-enecarbaldehydes bearing α-quaternary centers.[7] Herein, we disclose a desymmetrization of bisallylaldehydes **1** to generate cyclohexenes **4** via the desymmetrization of prochiral quaternary centers (Figure 1c, route A).[7−10] Our Rh-catalyzed method provides enantioselective access to the 3,5,5-trisubstituted cyclohexene motif that is inaccessible by the well-established Diels–Alder reaction and therefore complements conventional cycloadditions (Figure 1d).[11]

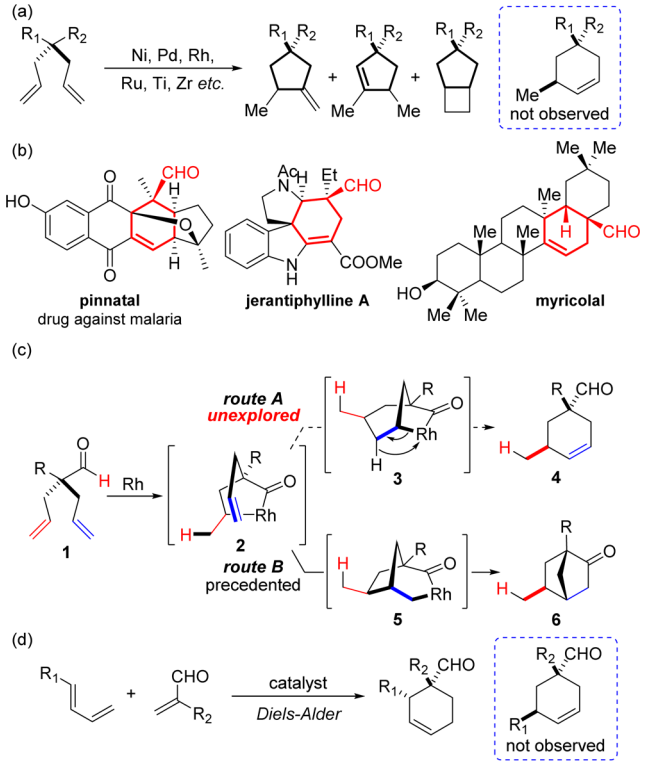

Figure 1. Inspiration for Rh-catalyzed cycloisomerization triggered by C–H bond activation.

The initial steps of our proposal rely on the well-precedented hydroacylation mechanism, namely aldehyde C–H bond activation and olefin insertion,[12,13] to form intermediate **2** (Figure 1c). Next, we imagined that a regioselective carbometalation of the pendant olefin could afford **3**, which upon endocyclic β-hydride elimination[13,14] would lead to the unprecedented cyclohexene **4** (Figure 1c, route A). Carbometalation could occur with the opposite regioselectivity to generate **5**, which upon reductive elimination would yield bicyclic heptanones **6** (Figure 1c, route B).[15a] On the basis of our previous study,[13] we realized that the key challenge would be to identify a catalyst to favor the proposed cycloisomerization, in preference to the known hydroacylation and carboacylation[15] pathways.

With this hypothesis in mind, we chose 2-allyl-2-benzylpent-4-enal (**1a**) as a model substrate for desymmetrization (Chart 1). In general, electron-donating bidentate phosphine ligands with bite angles ranging from 89° to 91° favored formation of the cyclopentanone **8a** via isomerization–hydroacylation pathways.[13,14,16] By focusing on ligands with bite angles ranging from 96° to 100°,[16] we discovered two ligand classes that resulted in formation of cyclohexenes **4a**/**7a**[17] and bicyclic heptanone **6a** via the carbometalation pathway. By tuning the aryl substituents on DPPF, we observed a modest increase in selectivity for the generation of cyclohexenes.

Zhou's rigid spiro-bisphosphine ligand, (*S*)-Ph-SDP,[18] gave the most promising lead as we obtained cyclohex-3-enecarbaldehyde **4a** in 71% yield as the major product (99% *ee*, >20:1 *dr*) with generation of **6a** in 23% yield. Transformation of **1a** with the Rh-SDP catalyst was efficient with a 2.5 mol % catalyst loading. By fine-tuning the aryl substituents on Zhou ligand, we observed a dramatic effect on the selectivity for **4a** over **6a**. Commercially available (*S*)-Ph-SDP and (*S*)-Xyl-SDP showed similar ca. 3:1 selectivity for **4a** over **6a**. By changing the *meta*-substituents on

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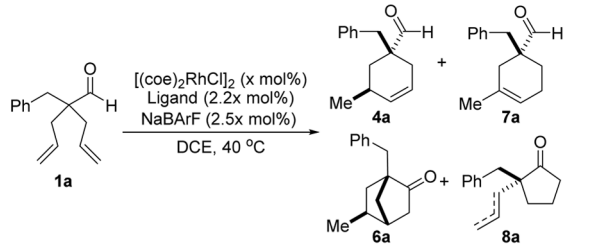
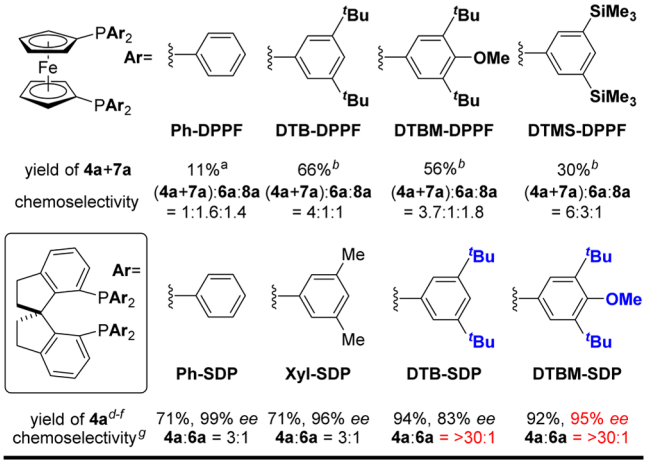
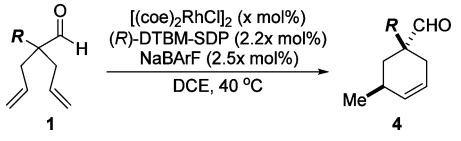
Chart 1. Ligand Effects on the Desymmetrization of α,α-Bisallylaldehyde towards Cyclohexenecarbaldehyde[a]

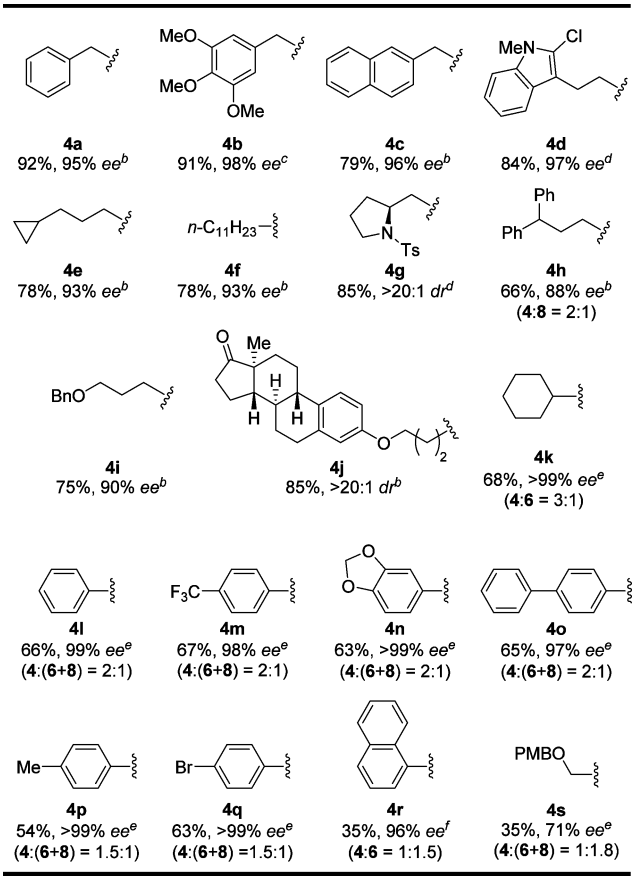




[a] x = 5, 18 h. [b] x = 2.5, 18 h. [c] x = 1.25, 12 h. [e] >20:1 *dr*, determined by ^{1}H NMR. [f] The aldehyde **4a** was reduced to its corresponding alcohol to determine *ee* by SFC analysis with a chiral stationary phase. [g] Trace amount of **7a** and **8a** was observed. Xyl: 3,5-Me-phenyl. DTB: 3,5-di(*tert*-butyl)-phenyl. DTBM: 3,5-di(*tert*-butyl)-4-methoxy-phenyl. DTMS: 3,5-di(trimethylsilyl)-phenyl.

Table 1. Enantioselective Cycloisomerization of α,α-Bisallylaldehydes[a]





[a]Isolated yields. The *ee* was determined by chiral SFC analysis after reducing the aldehydes with $NaBH_4$, and *dr* was determined by ^{1}H NMR. [b]Reaction conditions: x = 1.25, 40 °C, 4–12 h. [c]x = 1, rt, 2 h. [d]x = 1, 40 °C, 4 h. [e](*S*)- or (*R*)-SDP, x = 2.5, 40 °C, 18 h. [f](*S*)-Tol-SDP, x = 2.5, 40 °C, 18 h.

the phenyl group from methyl to *tert*-butyl ((*S*)-DTB-SDP), we observed **4a** as the predominant product. There was a drop in enantioselectivity from 96% *ee* to 83% *ee*. We prepared a novel analogue, (*R*)-DTBM-SDP, which bears an additional *para*-methoxy substituent. This designer ligand gave **4a** as the major product, with high enantio- and diastereoselectivity (95% *ee*, >20:1 *dr*).

Next, we used this protocol to prepare cyclohex-3-enecarbaldehydes bearing α-quaternary stereocenters (Table 1). Aldehydes with α-aliphatic substituents (**1a**–**1j**) underwent cycloisomerization in 66–92% yields with high enantio- and diastereoselectivities (up to 98% *ee*, >20:1 *dr*). Cyclopropyl groups (**1e**), nitrogen heterocycles (**1d** and **1g**), haloaromatics (**1d**), ethers (**1b**, **1i**, and **1j**), and ketones (**1j**) were well-tolerated under these conditions.

Aldehydes bearing more sterically encumbered α-substituents such as cyclohexyl (**1k**) and aromatic groups (**1l**–**q**) were challenging to cyclize. However, by using Ph-SDP as the ligand and applying a higher rhodium loading (5%), we obtained the corresponding cyclohexenecarbaldehydes (**4k** and **4l**–**q**) as the major products (about 2:1 chemoselectivity (**4**/(**6** + **8**)), 54–68% isolated yields, and 97–99% *ee*'s). Aldehyde **1r**, bearing the 1-naphthyl group, was unreactive with DTBM-SDP as the ligand, but could be cycloisomerized using the less bulky ligand, Tol-SDP. The aldehyde bearing a β-benzyloxy group (**1s**) transformed to the cyclohexene in only 35% yield because the γ-oxygen directing group promotes hydroacylation over cycloisomerization.[13,14] No reactivity was observed with more hindered, substituted olefin substrates.[19] While further catalyst development is warranted, our study represents a rare example of isomerization of α,ω-heptadienes to generate cyclohexenes with high enantiocontrol.

Aldehydes **4** can be easily oxidized or reduced to generate the corresponding acids or alcohols, respectively (Scheme 1). Depending on its oxidation state, the resulting cyclohexenes can undergo a number of selective transformations. For example, the aldehyde is necessary to initiate isomerization of the olefin to generate cyclohexenecarbaldehyde **7a** using a Rh(I)/dppf complex (Scheme 1a).[20] Subjecting ester **9** to the same reaction conditions resulted in no isomerization of the olefin (Scheme 1b). From this observation, we believe isomerization is triggered by aldehyde C–H bond activation, which generates the requisite Rh-hydride.[13,14,21] By Pinnick oxidation[22] of **4a**, we obtained the carboxylic acid derivative **10**. Iodolactonization of cyclohex-3-enecarboxylic acid **10** afforded [3.2.1]-bicyclic lactone **11** containing four stereogenic centers as a single regio- and diastereomer (Scheme 1c). Reduction of the aldehyde **4a** to the alcohol resulted in **4a-OH**. The alcohol

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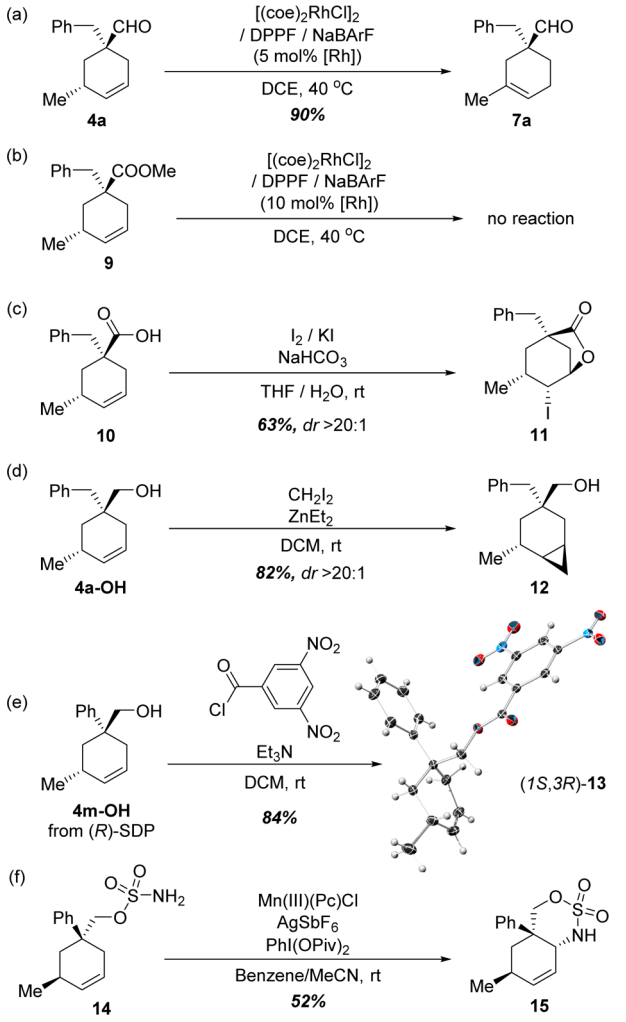
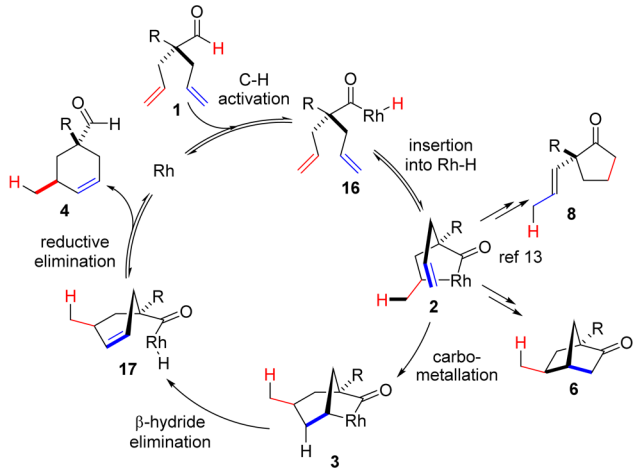
Scheme 1. Elaboration of Cyclohexenecarbaldehydes



Scheme 2. Proposed Mechanism

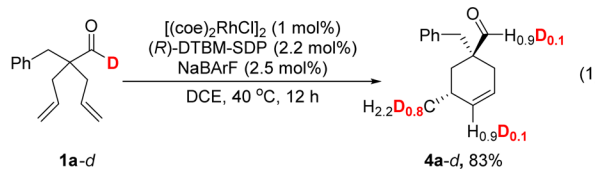


can be used to direct a diastereoselective cyclopropanation to form bicycloheptane **12** (Scheme 1d, *dr* > 20:1). Alcohol **4m-OH** can be acylated to generate ester **13** or sulfamylated to give sulfamate **14**. The molecular structure and absolute configuration of **13** was determined by X-ray crystallography (Scheme 1e).[23] By using White's protocol, sulfamate **14** can undergo a highly diastereoselective allylic C−H bond amination to afford **15** (Scheme 1f).[24] These simple derivatizations allow a number of different cyclohexanes and cyclohexenes to be prepared with substitution patterns that would otherwise be difficult to access.

On the basis of our observations and literature precedence, we propose the mechanism shown in Scheme 2. The cationic Rh(I)-complex activates the aldehyde C−H bond of **1** to form acyl-Rh(III)-hydride **16** which undergoes hydrometalation to generate rhodacycle **2**. Carbometalation onto the pendant olefin in rhodacycle **2** can occur to afford carbometalated intermediate **3**, which would then undergo *β*-hydride elimination to form acyl-Rh(III)-hydride **17**. Reductive elimination from **17** leads to formation of cycloisomerization product **4**. Reductive elimination from **2** or **3** would result in formation of a strained cyclobutanone, which is not observed. The carbometalation of rhodacycle **2** onto the pendant olefin with *opposite* regioselectivity would result in rhodabicycle **5** (Figure 1c), which undergoes reductive elimination to form **6**.

Our study reveals that the bite angle of the ligand is critical for promoting carboacylation in preference to isomerization−hydroacylation pathways. An electron-donating MeOBiphep ligand (bite angle: 90.6°) enables an enantioselective hydroacylation to afford cyclopentanone **8**.[13] Phosphine ligands with bite angles ranging from 96° to 99° promote formation of bicyclic heptanone **6**.[13] Yet, the rigid spiro-bisphosphine ligand, (*S*)-Ph-SDP (bite angle: 96.2°), favors a different carbometalation that leads to cyclohexene **4**.

To gain insight into the mechanism, we performed a deuterium-labeling study with **1a**-*d*. The reaction of **1a**-*d*, under standard reaction conditions, led to formation of **4a**-*d* where 80% of the deuterium label was incorporated into the 5-methyl group and 20% was scrambled between the aldehyde and the 4-position (eq 1). This deuterium scrambling suggests



that the olefin-insertion step (**16** → **2** in Scheme 2) is reversible. As a result, either carbometalation or *β*-hydride elimination is the rate-determining and enantiodetermining step.

We have demonstrated a Rh-catalyzed enantioselective cycloisomerization of *α*,*α*-bisallylaldehydes to form cyclohex-3-enecarbaldehydes. These products represent versatile intermediates that can be elaborated to a range of structures. Mechanistic studies support an aldehyde-assisted cycloisomerization followed by a regioselective carbometalation. The use of a novel SDP ligand enables high selectivity for cycloisomerization. Further experimental and theoretical studies are underway to elucidate the origin of chemoselectivity and guide development of other cycloisomerizations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01445.

Experimental procedures and spectral data for all new compounds (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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(17) Cyclohexene **7a** arises from olefin-isomerization of **4a**.

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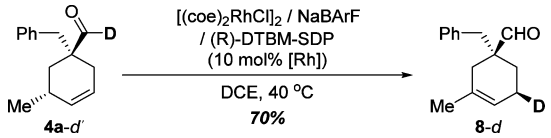
(19) Aldehydes bearing substituted α-allyl groups such as crotyl, cinnamyl, and methallyl groups were unreactive with the Rh/SDP catalyst. We did not observe the desired cycloisomerization product in the reaction of an α,α-bis(homoallyl)aldehyde.

(20) Only some ligands promote this isomerization. DPPF and DPEphos were effective (5% Rh/L, DCE, 40 °C). (*R*)-DTBM-SDP was less reactive even at a higher catalyst loading (10% Rh/L).

(21) When D-labeled **4a** (**4a**-*d*′) was subjected to the Rh^+/(*R*)-DTBM-SDP catalyst (10 mol%), we observed 70% conversion to **8** where the deuterium label was incorporated into the 4-position.



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(23) CCDC 1451888 contains the supplementary crystallographic data for compound **13**. See Supporting Information. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 879912, Union Road, Cambridge CB879952 879951EZ, U.K.; fax: +879944 871223 336033.

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