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Rh-Catalyzed Desymmetrization of α-Quaternary Centers by Isomerization-Hydroacylation

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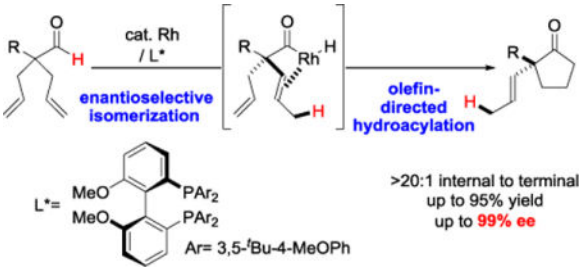
Abstract

We describe a Rh-catalyzed desymmetrization of all-carbon quaternary centers from α,α-bis(allyl)aldehydes by a cascade featuring isomerization and hydroacylation. This desymmetrization competes with two other novel olefin functionalizations that are triggered by C–H bond activation, including carboacylation and bisacylation. A BIPHEP ligand promotes enantioselective formation of α-vinylcyclopentanones. Mechanistic studies support irreversible and enantioselective olefin-isomerization followed by olefin-hydroacylation.

Graphical abstract



Introduction

Desymmetrization has emerged as a way to access chiral quaternary-carbon motifs, which are among the most challenging stereocenters to generate with enantiocontrol.[1–4] Strategies involving C−H bond activation are especially promising yet rare.[5,6] Given this challenge, we propose that prochiral aldehyde **1** could isomerize to scaffolds bearing quaternary centers *via* two possible pathways triggered by aldehyde C–H bond activation (Figure 1). Herein, we communicate Rh-catalyzed olefin functionalizations, including hydroacylation and carboacylation from a common aldehyde. This initial report focuses on hydroacylation of bis(allyl)aldehydes to generate α-vinylcyclopentanones **2** bearing quaternary stereocenters.[7]

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Electronic supplementary information (ESI) available: Materials and methods, reaction procedures, characterization data. CCDC 1056687, 1062118. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/x0xx00000x

Mechanistic studies reveal a cascade process featuring an enantioselective olefin-isomerization followed by olefin-hydroacylation.

The use of oxygen, nitrogen, and sulfur-based functional groups has allowed breakthroughs in enantioselective Rh-catalyzed hydroacylation.[8] These heteroatoms act as directing groups by binding to rhodium and favoring C−H bond activation while accelerating hydroacylation over competitive pathways, such as decarbonylation or catalyst decomposition.[9] Fu demonstrated intramolecular hydroacylation of alkynals bearing β-methoxy groups (Figure 2a).[10] Our laboratory reported intermolecular hydroacylation of cyclopropenes using chelating aldehydes, specifically salicylaldehyde derivatives (Figure 2b).[5] Given their ability to bind Rh, we reasoned that olefins could be used as directing groups for hydroacylation.[11] We were encouraged that Tanaka and Suemune reported desymmetrization of β-bis(alkenyl) aldehydes (Figure 2c).[12] Although not proposed, we reason that the pendant olefin in their substrate could be acting as a directing group. These previous desymmetrizations by hydroacylation generate ketones bearing β-quaternary stereocenters. Given this limitation, we chose to develop a complementary desymmetrization of α-trisubstituted aldehydes, which represents a sterically hindered and thus, challenging substrate class.[13b–c,14] If successful, our strategy would allow access to cyclopentanones bearing α-quaternary centers, whereby the pendant olefin serves as both a directing group and versatile handle for further elaboration.

Results and Discussion

To test our proposal, we studied the desymmetrization of model **1a**, which can be prepared in one-step from commercially available phenylacetaldehyde.[15] Aldehyde **1a** was subjected to cationic Rh(I)-catalysts and various bidentate phosphine ligands that are known to promote formyl C–H bond activation.[16] We imagined that oxidative addition followed by alkene insertion would generate metallacycle **5**, which could diverge into various scaffolds (Table 1). The choice of phosphine ligand had a dramatic impact on product outcome and enabled chemoselective formation of two major products, cyclopentanone **2a** and bicyclo[2.2.1]heptanone **3a**.

With a BINAP-ligated rhodium catalyst, we observed formation of both **2a** and **3a** in 61% and 19% yields, respectively (entry 1). We discovered that the hydroacylation product, cyclopentanone **2a**, bears an internal olefin, which presumably results from isomerization of the terminal olefin. Carbometallation of the pendant olefin from **5** results in intermediate **7**, which undergoes reductive elimination to form bicycloheptanone **3a** as a minor product. Use of BzDPPB ligand, however, favors the carboacylation pathway to generate **3a** as the major product in 56% yield with high diastereoselectivity (>20:1, entry 2). This unique olefin functionalization takes advantage of C−H activation rather than strained C−C activation to achieve carboacylation.[17] While our study was in progress, Aïssa reported a related carbocyclization using pyridyl directing groups.[18] We also observed bicyclo[3.2.1]octadione **4a** as a minor product in 10% yield (entry 2). The molecular structure of this homologated ketone **4a** was confirmed by X-ray crystallography (see ESI.). We believe that the second carbonyl arises from a disproportionation process where a second equivalent of aldehyde **1a** undergoes decarbonylation to generate CO.

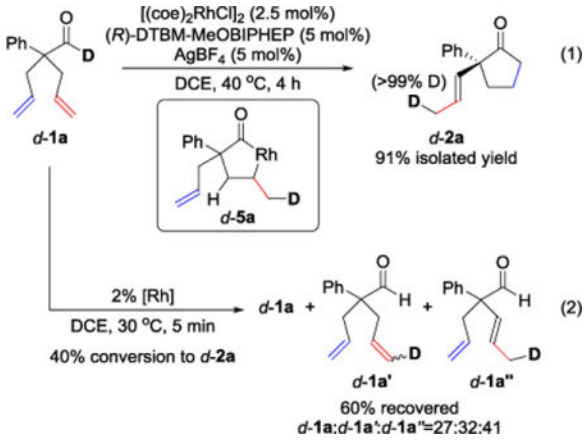
With these promising leads in hand, we plan to further study each pathway and develop enantioselective variants. Towards this goal, we realized that electron-donating aromatic groups on phosphines enhance selectivity for **2a**. Among the ligands evaluated, (*R*)-DTBM-MeOBIPHEP provided the best reactivity and enantioselectivity for **2a** (entry 3). The absolute configuration of cyclopentanone **2a** was determined by elaboration with 2,4-dinitrophenylhydrazine to hydrazone **9**, in which the molecular structure was established by X-ray crystallographic analysis (Figure 3).

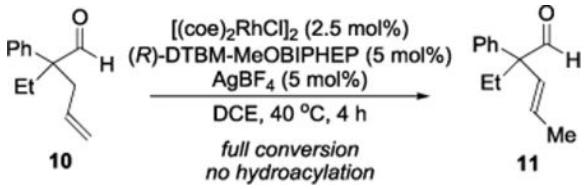
With this protocol, we prepared eleven cyclopentanones bearing various α-quaternary stereocenters (Table 2). Aldehydes with aromatic substituents (**1a**–**1g**) undergo desymmetrization in 83–91% yields and high enantioselectivities (95–99% *ee*). Ether, aryl halide, and acetal functional groups are well-tolerated. Heteroaromatic aldehyde (**1h**) as well as aldehydes bearing aliphatic substituents (**1i–1k**) rearrange to the corresponding cyclopentanones in excellent enantioselectivities albeit using increased catalyst loading at lower temperature.[19,20]

To understand the mechanism, we performed a deuterium-labelling study with *d*-**1a**. Desymmetrization of *d*-**1a**, under standard reaction conditions, led to exclusive formation of *d*-**2a** where the deuterium label was incorporated into the methyl group of the α-propenyl substituent (eq 1). This result indicates that isomerization of one allyl group takes place first through an endocyclic β-hydride elimination of a 5-membered rhodacycle *d*-**5a**.[21] Our observations corroborate Aïssa's recent report on the isomerisation of 4-pentenals.[22] Although β-hydride eliminations of this type are uncommon, it has been predicted that binding of a pendant alkene to the metal center significantly lowers the barrier to this process.[23]

When the reaction of *d*-**1a** was quenched at an early stage (40% conversion to *d*-**2a**), we recovered three deuterated aldehydes, *d*-**1a**, *d*-**1a′** and *d*-**1a″** (eq 2). The observation of *d*-**1a′** suggests that olefin-insertion is reversible. Yet, the deuterium is incorporated into only the methyl group of the α-propenyl unit in product *d*-**2a**. This lack of deuterium scrambling on the cyclopentanone ring suggests that Rh-D insertion occurs with high enantioselecivity (with the olefin shown in red). Thus, the insertion step is both reversible and highly enantioselective.[24]

Further experiments support the notion that the α-vinyl group (formed from initial isomerization) directs hydroacylation. For example, α-trisubstituted aldehyde **10** (with only one allyl group) does not undergo hydroacylation. Instead, this aldehyde undergoes isomerization to generate α-vinyl aldehyde **11** (eq 3).[22] In addition, subjecting α-allylcyclopentanone **12a** to the optimized reaction conditions results in trace formation of α-vinylcyclopentanone **2a** (eq 4). Thus, the cyclopentanones obtained in Table 2 must arise from an isomerization that occurs prior to hydroacylation. In contrast, we discovered that aldehyde **1l**, containing an acetal group, yields α-allylcyclopentanone **12l** as the major product (eq 5). In this case, we reason that the acetal acts as an oxygen-directing group which promotes hydroacylation over olefin isomerization.





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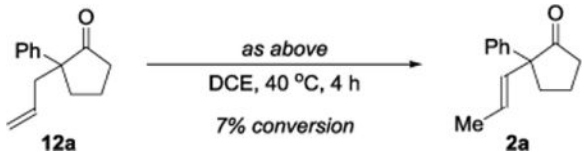
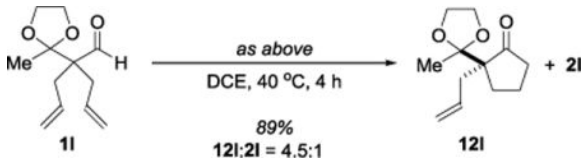


(4)



(5)

On the basis of literature reports and our own observations, we propose a mechanism starting with cationic Rh(I)-complex activating the aldehyde C–H bond of **1** to form acyl-Rh(III)-hydride **13** (Scheme 1). Insertion of the olefin into Rh(III)-hydride **13** leads to formation of the more thermodynamically stable 5-membered metallacycle **5**.[25] A rare endocyclic β-hydride elimination takes place to produce isomerized acyl-Rh(III)-hydride **14**. The allyl olefin inserts into the Rh(III)-hydride to form a 6-membered rhodacycle **6**. Finally,

reductive elimination affords the cyclopentanone product **2** and regenerates the Rh(I)-catalyst.

Conclusions

We have demonstrated a Rh-catalyzed enantioselective synthesis of α-quaternary cyclopentanones. Studies on the scope and mechanism support an olefin-assisted isomerization[23] and olefin-directed hydroacylation cascade. While endocyclic β-hydride elimination has been proposed in the literature on the basis of theoretical studies,[21] our results provide experimental evidence for this elementary step. The use of a BIPHEP ligand enables high selectivity for one out of four possible rearrangements, all initiated by the activation of aldehyde C−H bond. Insights from these studies will guide efforts to understand and expand the power of the related carboacylation and bisacylation as routes to scaffolds containing chiral all-carbon stereocenters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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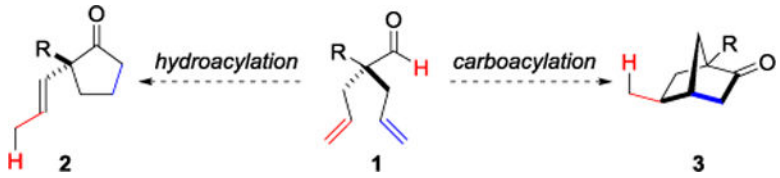


Figure 1.
Two pathways to quaternary-carbon motifs from desymmetrization of **1**.

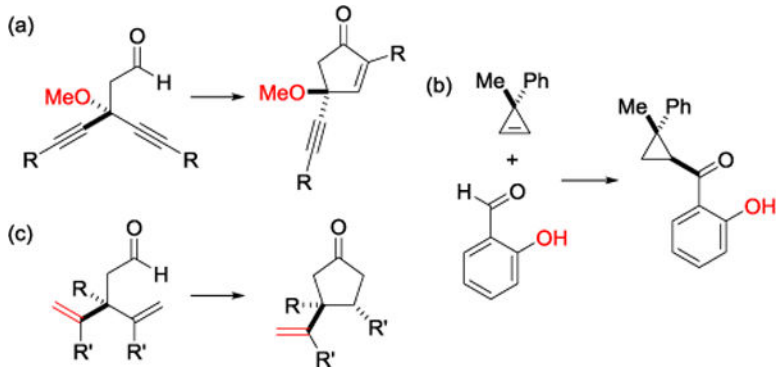


Figure 2.

Previous desymmetrizations by hydroacylation result in ketones bearing β-quaternary stereocenters.

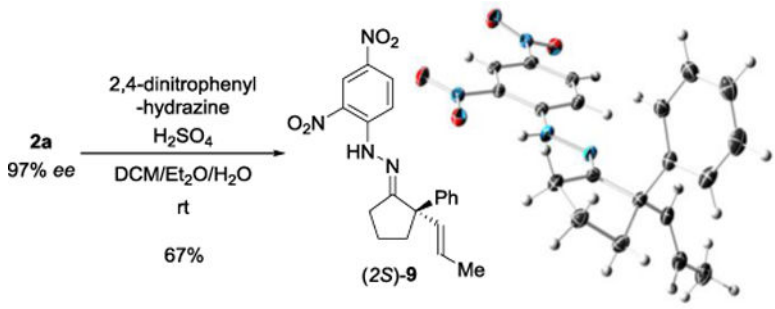
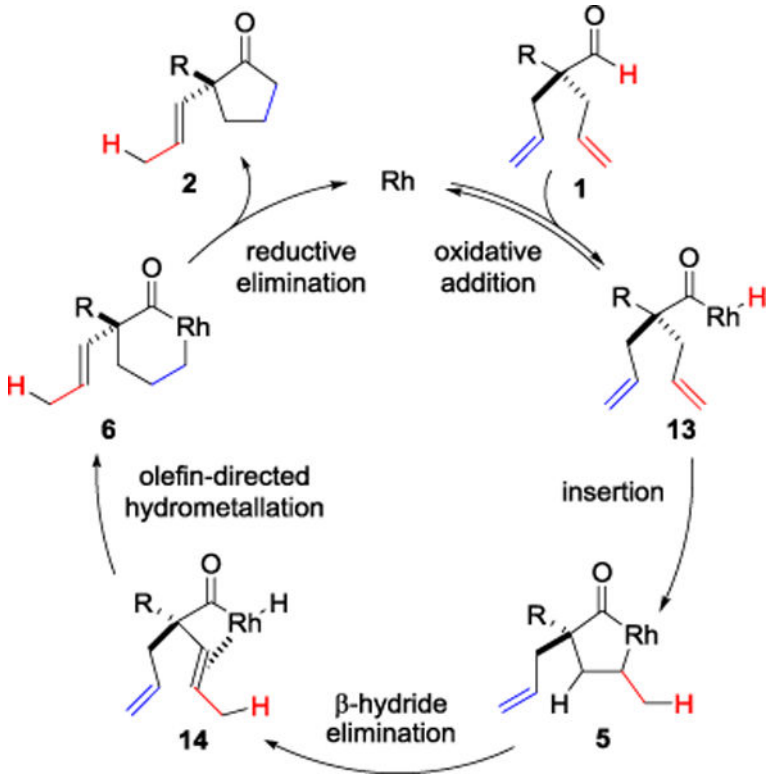


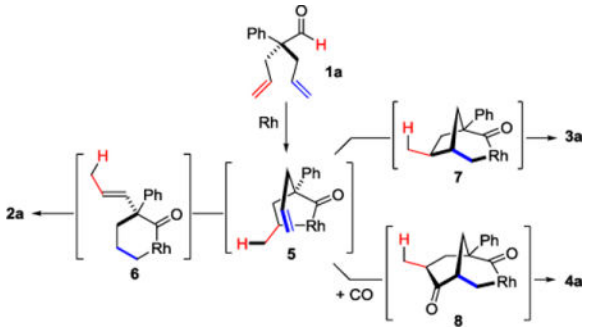
Figure 3.
Determination of the absolute configuration of **2a** and X-ray crystal structure of (*2S*)-**9**

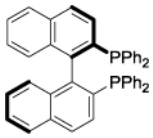
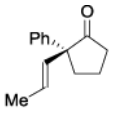
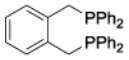
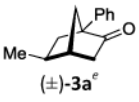
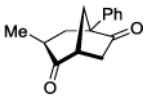
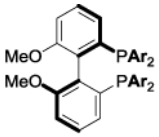
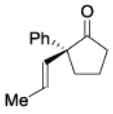


Scheme 1.
Proposed Mechanism for Rh-Catalyzed Cascade

Table 1

Divergent Pathways for Desymmetrization of **1a** Based on Ligand-Choice



Entry	Ligand	Major Product, yield[c]	Minor Product(s), yield[d]
1	 (*R*)-BINAP	 (*S*)-**2a** 61%, 31% *ee*	**3a** 19%, 33% *ee*
2	 BzDPPB	 (±)-**3a**[e] 56%	 (±)-**4a**, 10%[e] (±)-**2a**, 7%
3[b]	 (*R*)-DTBM-MeOBIPHEP	 (*S*)-**2a** 91%, 97% *ee*	**3a** and **4a** not observed

[a] Reaction conditions: $[(coe)_2RhCl]_2$ 5 mol%, ligand 10 mol%, $AgBF_4$ 10 mol%, DCE (0.2 M), 40 °C, 36 h,

[b] $[(coe)_2RhCl]_2$ 2.5 mol%, ligand 5 mol%, $AgBF_4$ 5 mol%, 40 °C, 4 h,

[c] Isolated yield,

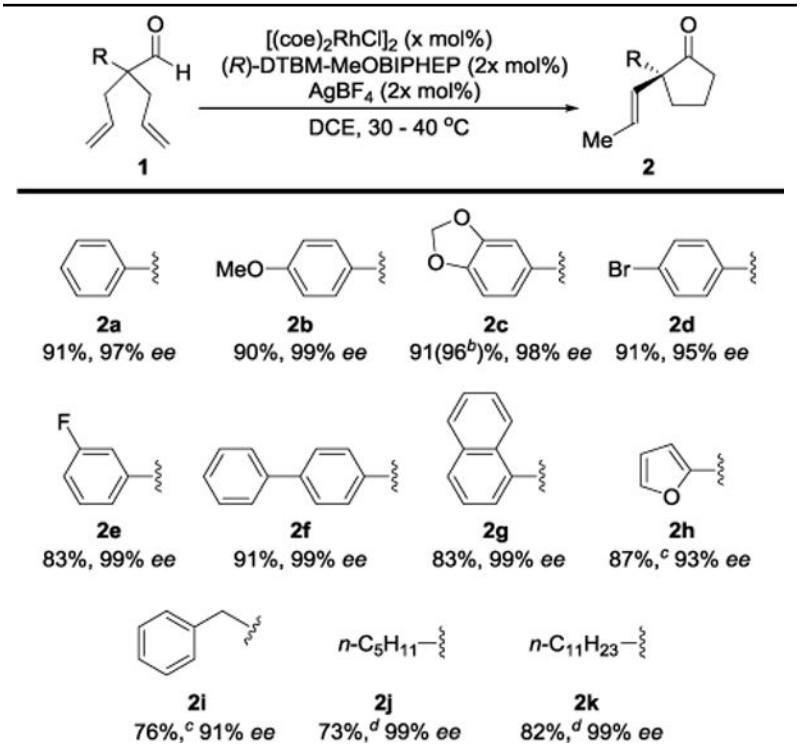
[d] Determined by GC-FID.

[e] >20:1 *dr*, determined by ^1H NMR.

[f] one equivalent of **1a** was used as a CO donor. DTBM: 3,5-di(*tert*-butyl)-4-methoxyphenyl

Table 2

Desymmetrization of α-Quaternary Aldehyde **1** by Isomerization-Hydroacylation[a]



[a]Reaction conditions: 0.1 mmol **1**, x = 2.5 mol%, DCE (0.2 M), 40 °C, 4 h,

[b]1 mmol **1c** used,

[c]x = 5, DCE (0.33 M), 30 °C, 2 h,

[d]x = 6, DCE (0.33 M), 30 °C, 2 h.