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Rh-Catalyzed Intramolecular Olefin Hydroacylation: Enantioselective Synthesis of Seven- and Eight-Membered Heterocycles

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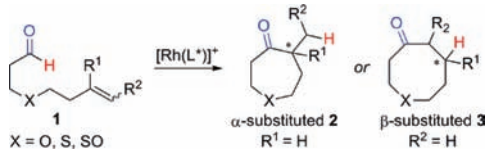
Medium-sized rings are motifs found in natural products[1] and regarded difficult structures to access in organic synthesis.[2] Through the use of transition-metal catalysts, formation of medium-sized rings has been achieved,[3] but developing enantioselective syntheses remains a goal.[4] In light of this goal, Rh-catalyzed hydroacylation appears an attractive approach because it is a mild, atom-economical, and selective C−H bond functionalizing process.[5] Indeed, a few variants of olefin hydroacylation produce seven- and eight-membered rings.[6] Enantioselective variants to form cyclic ketones larger than five-membered,[7] however, have yet to be realized. Herein, we describe a Rh-catalyzed hydroacylation to form medium-sized heterocyclic ketones, containing ether, sulfide, and sulfoxide functional groups, with high regio- and enantioselectivity.

It occurred to us that medium-sized heterocycles could be prepared by an enantioselective Rh-catalyzed hydroacylation of alkenals **1**, which are substrates bearing a functional group X (Scheme 1). Inspired by previous reports,[8,9] we expected coordination of X to Rh would help promote olefin hydroacylation over competing pathways, such as olefin isomerization, aldehyde decarbonylation, and catalyst decomposition. Hydroacylation of **1** could produce α-substituted ketones **2** or *β*-substituted ketones **3**; the regioselectivity would depend on the catalyst choice and substrate structure (i.e., X, tether length, and olefin substitution).

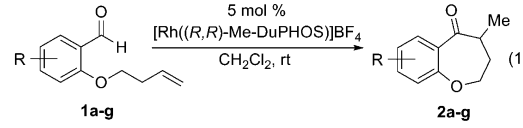
Scheme 1. Proposed Enantioselective Synthesis of Medium-Sized Heterocyclic Ketones by Intramolecular Olefin Hydroacylation

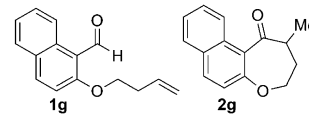


Initial experiments focused on finding an efficient Rh catalyst for intramolecular hydroacylation of substrate **1a**, which was readily prepared from salicylaldehyde. We discovered that [Rh((*R*,*R*)-Me-DuPHOS)]BF_4 catalyzed the cyclization of alkenal **1a** to seven-membered-ring ketone **2a** in 88% yield with 15:1 selectivity over its eight-membered-ring regioisomer.[7c] Moreover, this α-substituted ketone was produced in 98% enantiomeric excess (ee) (Table 1, entry 1). With this catalyst in hand, we prepared and tested six other aromatic aldehydes. Hydroacylation of both electron-deficient (fluoro- and chloro-substituted) and electron-rich (methyl- and methoxy-substituted) benzaldehydes produced corresponding seven-membered-ring ketones in high yields (80−95%) and ee's (96−98%) (entries 2−5 and 7). Naphthaldehyde **1g** underwent hydroacylation to form polycyclic **2g** in 86% yield and 98% ee (entry 8). At a reduced loading of 2.5 mol %, [Rh((*S*,*S*)-BDPP)]BF_4 furnished **2e** in high yield (90%) but slightly lower enantioselectivity (94% ee) than [Rh((*R*,*R*)-Me-DuPHOS)]BF_4 (entry 6).

Next, we focused on enantioselective hydroacylations with thioether substrates and observed strong ligand effects (Table 2).

Table 1. Enantioselective Synthesis of Medium-Sized Heterocyclic Ketones via Oxygen-Assisted Hydroacylation[a]



entry	substrate	product	% yield[b]	% ee[c]
1	**1a** R = H	**2a**	88	98
2	**1b** R = 5-F	**2b**	95	96
3	**1c** R = 5-Cl	**2c**	91	97
4	**1d** R = 5-Me	**2d**	89	98
5	**1e** R = 5-OMe	**2e**	86	96
6[d]	**1e** R = 5-OMe	**2e**	90	94
7[e]	**1f** R = 3-OMe	**2f**	80[f]	97
8[e]	 **1g**	**2g**	86	98

[a] Conditions: 5 mol % [Rh((*R*,*R*)-Me-DuPHOS)]BF_4, CH_2Cl_2, room temperature (rt), 1 day. [b] Isolated yield of seven-membered-ring ketone. ^{1}H NMR analysis of the crude reaction mixture showed a regioisomeric ratio of >15:1. [c] Determined by chiral HPLC or GC analysis. [d] Using 2.5 mol % [Rh((*S*,*S*)-BDPP)]BF_4. [e] Reaction time of 2 days. [f] Isolated yield of both regioisomers (>20:1 selectivity).

With (*R*,*R*)-Me-DuPHOS, **4** cyclized to form the seven-membered-ring compound **10** selectively in large ee (91% yield, 4:1 regioselectivity, 95% ee; entry 1). With (*S*,*S*)-BDPP, however, substrate **4** underwent hydroacylation to preferentially form eight-membered-ring heterocycle **11** (91% yield, >20:1 regioselectivity; entry 2).[10] Examples of asymmetric hydroacylation of 1,2-disubstituted alkenes are rare.[9b] However, by using (*R*)-DTBM-SEGPHOS as the ligand, we found hydroacylation of both (*E*)- and (*Z*)-disubstituted alkenes provided enantioenriched heterocycle **12** [89% yield, 97% ee (entry 3) and 97% yield, 93% ee (entry 4), respectively].[11] With 1,1-disubstituted alkenes, the length of the tether between the olefin and aldehyde determined the size of the medium ring formed. In the presence of (*R*,*R*)-Me-DuPHOS, cyclization of allylic thioether **7** formed seven-membered ring **13**, while cyclization of the homoallylic substrate **8** afforded eight-membered ring **14**. Notably, hydroacylation of these 1,1-disubstituted alkenes produced *β*-substituted ketones [85% yield, 99% ee (entry 5) and 86% yield, 93% ee (entry 6), respectively].

Sulfoxides have not been studied as directing groups for hydroacylation.[12] Thus, we were pleased to find that sulfoxide (±)-**9** underwent hydroacylation to generate *trans*-(±)-**15** in 87% yield with achiral dppp as the ligand (Table 2, entry 7). A single diastereomer was observed by ^{1}H and ^{13}C NMR spectroscopy, and the molecular structure of this diastereomer was confirmed by X-ray analysis. This unique transformation occurs with 1,4-induction of chirality and highlights the potential of sulfoxides for stereoselective hydroacylation.

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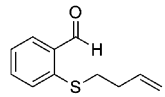
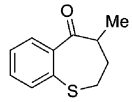
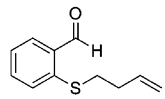
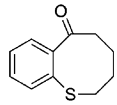
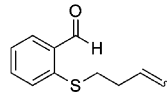
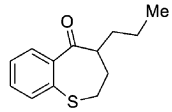
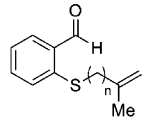
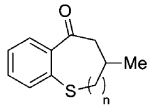
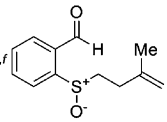
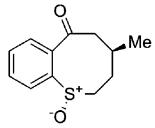
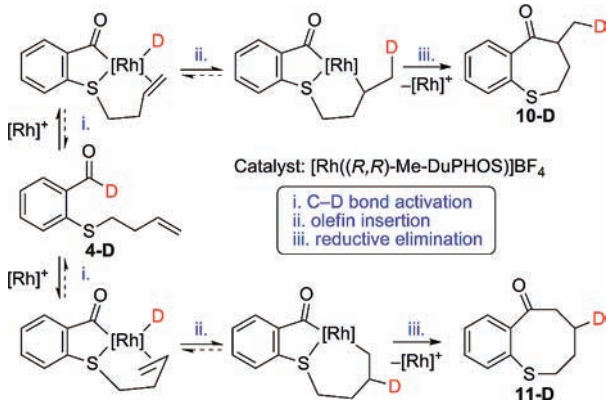
Table 2. Regio- and Enantioselective Formation of Medium Rings via Sulfide and Sulfoxide Chelation[a]

entry	substrate	ligand	product	% yield[b]	% ee[c]
1	 **4**	(*R*,*R*)-Me-DuPHOS	 **10**	91[d]	95
2	 **4**	(*S*,*S*)-BDPP	 **11**	91	-
3	 **5** (*E*)-olefin	(*R*)-DTBM-SEGPHOS	 **12**	89	97
4	**6** (*Z*)-olefin		**12**	97	93
5[e]	 **7** n = 1	(*R*,*R*)-Me-DuPHOS	 **13** n = 1	85	99
6[e]	**8** n = 2		**14** n = 2	86	93
7[e,f]	 (±)-**9**	dppp	 (±)-**15**, >20:1 dr	87	-

[a] Conditions: 2.5 mol % [Rh(ligand)]BF_4, CH_2Cl_2, rt, 1 day. [b] Isolated yields. [c] Determined by chiral HPLC or GC analysis. [d] Combined yield of **10** and **11** (4:1 selectivity). [e] 5 mol % [Rh(ligand)]BF_4. [f] Relative stereochemistry determined by X-ray analysis (see the Supporting Information for details).

Scheme 2. Proposed Mechanism and Deuterium Labeling Study: Incorporation of Deuterium with No Scrambling



Finally, we report preliminary studies that provide insight into the mechanism of this asymmetric hydroacylation. In agreement with our proposal, heteroatom coordination appears critical; subjecting an analogue of **4** (bearing carbon in place of sulfur) to our standard conditions resulted in no observable hydroacylation products. In addition, we performed an isotopic labeling experiment to probe the turnover-limiting step. As shown in Scheme 2, we envisioned that deuterium-labeled **4-D** would undergo hydroacylation by the well-established steps (C−D bond activation, olefin insertion, and reductive elimination) to produce seven- and eight-membered-ring regioisomers. In hydroacylation studies on different classes of substrates,[13,14] reductive elimination was implicated as turnover-limiting. If reductive elimination were turnover-limiting in our case, deuterium would be scrambled into the α-position of **11-D** (see the Supporting Information for a full discussion). However, we observed that products **10-D** and **11-D** had deuterium at only the β-position, as drawn. Analogous results were obtained using a deuterated analogue of **1a**. This lack of deuterium scrambling suggests that reductive elimination is not the turnover-limiting step in our catalytic system.

In summary, we have developed a highly asymmetric Rh-catalyzed synthesis of medium-sized heterocycles. Ether, sulfide, and sulfoxide groups function as directing moieties, and both α- and β-stereogenic centers can be produced. Further scope and mechanistic studies are underway.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, chiral chromatographic analyses, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Bendorf first reported hydroacylation of sulfur-containing alkenals with $Rh(PPh_3)_3Cl$, but an analogous oxygen-containing alkenal was unreactive (see ref 6a). (b) For an intramolecular oxygen-directed hydroacylation of ketones, see: Shen, Z.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 1077–1091.
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(10) It should be noted that this regioselectivity is opposite to that observed with oxygen-containing substrates **1a**−**g** (Table 1).
(11) In the presence of (*R*)-DTBM-SEGPHOS, alkenals **5** and **6** undergo hydroacylation to produce the same enantiomer of **12**.
(12) For applications of sulfoxides in transition-metal catalysis, see: Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3705.
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