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Regio- and Enantioselective Intermolecular Hydroacylation: Substrate-Directed Addition of Salicylaldehydes to Homoallylic Sulfides

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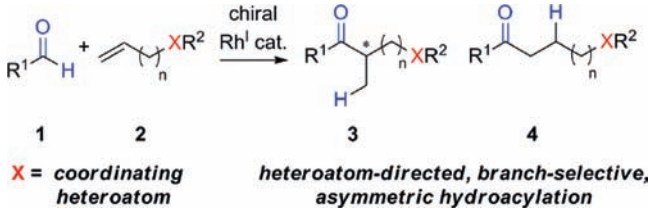
Abstract: We report a Rh-catalyzed, regio- and enantioselective intermolecular olefin hydroacylation under mild conditions. Hydroacylations between homoallylic sulfides, containing a substrate-bound directing group, and salicylaldehyde derivatives occur in the presence of a spiro-phosphoramidite ligand, (*R*)-SIPHOS-PE, to give α-branched ketones in >20:1 selectivity and up to 97% ee. Our conditions are also applicable to the asymmetric intermolecular hydroacylation of 1,2-disubstituted olefins.

Rhodium-catalyzed olefin hydroacylation is an atom-economical method for preparing enantioenriched ketones from readily available aldehyde and olefin precursors.[1] While many highly asymmetric intramolecular hydroacylations leading to cyclic ketone products have been developed,[2] intermolecular variants are much less common. Asymmetric intermolecular hydroacylation has been achieved with strained alkenes (e.g., norbornadienes,[3] cyclopropenes[4]), allenes,[5] and 1,1-disubstituted acrylamides,[6] while simple olefins[7] remain a challenging class of substrates. Indeed, asymmetric hydroacylation of 1,5-hexadiene has been pursued, but the resulting product was produced with moderate enantioselectivity and poor regioselectivity.[8] We present herein an intermolecular hydroacylation that uses a substrate-bound directing group in combination with a chiral phosphoramidite ligand to functionalize simple olefins with high levels of both enantio- and regiocontrol.

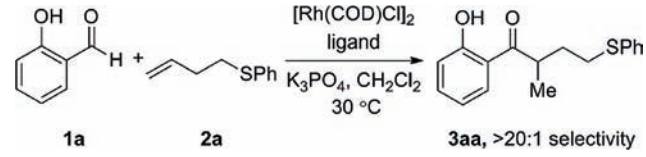
Scheme 1. Proposed Regio- and Enantioselective Synthesis of Ketones via Substrate-Directed Intermolecular Hydroacylation

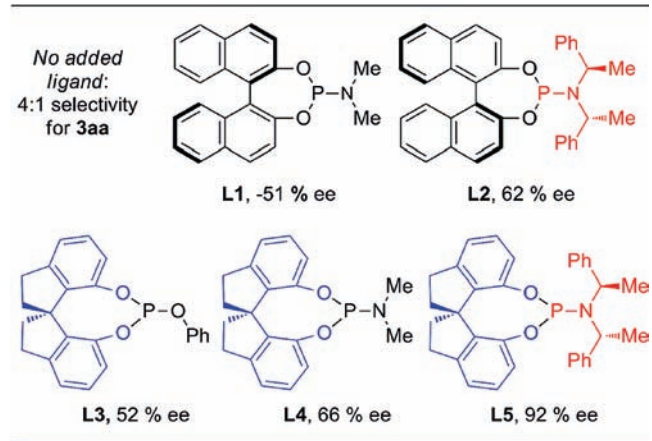


While reactive in Rh-catalyzed intermolecular hydroacylation, terminal olefins tend to give achiral, linear products or mixtures of regioisomers.[9,10] Our previous studies on enantioselective *intramolecular* hydroacylation revealed that by adjusting the tether length between a Lewis basic heteroatom and olefin, in combination with an appropriate phosphine ligand, we could direct the formation of α-branched cyclic ketones.[2c] As shown in Scheme 1, we proposed applying this heteroatom direction to achieve regio- and enantioselective *intermolecular* hydroacylation. Aldehyde **1** could thus react with terminal olefin **2**, bearing a coordinating heteroatom, to produce the chiral, α-branched ketone **3** in favor of linear product **4**.

Our initial studies were guided by Suemune's "double-chelation" assisted hydroacylation between salicylaldehydes and dienes, which produced branched ketones with various levels of regiocontrol.[10a] In this transformation, chelation by both the diene and salicylaldehyde[11] substrates was required for reactivity and regioselectivity. We thus began to probe the reaction of salicylaldehyde **1a** with homoallylic sulfide[12] **2a** using $[Rh(COD)Cl]_2$ as the catalyst precursor in the presence of K_3PO_4 at ambient temperature (Table 1). In the absence of ligand, the reaction was sluggish and rather unselective (4:1 selectivity for **3aa**). Bolm's report of intermolecular hydroacylation of norbornadienes with chiral monodentate phosphoramidites prompted us to explore these as ligands in an attempt to improve selectivity and achieve enantioinduction in **3aa**.[3] We were pleased to find that (*R*)-MonoPhos (**L1**) furnished the branched hydroacylation product **3aa** with much improved selectivity (>20:1) and in 51% enantiomeric excess (ee). We proceeded to explore various monodentate phosphoramidite ligands and found that they all led to high levels of branch selectivity for **3aa** in variable ee's (**L2**−**L5**).

Table 1. Ligand Effects in Regio- and Enantioselective Intermolecular Hydroacylation[a]





[a] Conditions: salicylaldehyde **1a** (1.0 equiv), olefin **2a** (1.5 equiv), $[Rh(COD)Cl]_2$ (5 mol %), ligand (10 mol %), K_3PO_4 (0.2 equiv), CH_2Cl_2, 30 °C. Selectivities for **3aa** over linear regioisomer were determined via ^{1}H NMR analysis of crude reaction mixtures. Ee's of **3aa** were determined by chiral HPLC analysis.

Our screen identified spiro (*R*)-SIPHOS-PE (**L5**) as the optimal ligand for our intermolecular hydroacylation, furnishing product **3aa** in >20:1 regioselectivity and 92% ee. Prior to this, spiro-based compounds were an unexplored class of ligands for hydroacyla-

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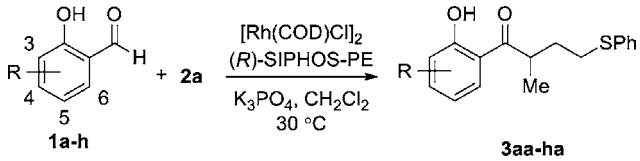
tion.[13] It is notable that the combination of the spiro-backbone and di-1-phenylethyl substituted nitrogen in (*R*)-SIPHOS-PE is required for high levels of enantioinduction; the absence of either component leads to inferior enantioselectivities (cf. **L5** to **L2** and **L4**). Interestingly, using bidentate ligand (*S*,*S*)-BDPP under these conditions completely inhibited the reaction.[14,15]

We further optimized conditions by reducing the loadings of Rh, ligand, and base[16] to 5 mol % and explored the substrate scope of this transformation (Table 2). Under these conditions, branched product **3aa** was obtained in 97% yield and 92% ee (entry 1).[17] Substitution of electron-withdrawing (−F, −Cl, $-CO_2Me$) or methyl groups at the 5-position in salicylaldehydes **1b**−**1e** had little effect on the reaction outcome, furnishing branched products in excellent yields and ee's (entries 3−6). 5-Methoxysalicylaldehyde **1f** required increased catalyst loading to achieve similar results (entry 7). 3-Methoxysalicylaldehyde **1g** furnished product **3ga** in 91% yield and 92% ee (entry 8), while 6-methylsalicylaldehyde required heating at 40 °C (entry 10) to obtain comparable yields. The addition of a silver salt, $AgClO_4$,[10a,18] had almost no effect on the reaction yield and ee (cf. entries 1 and 2) nor did increasing the number of equivalents of **2a** to 2.0 (cf. entries 8 and 9).

Table 2. Regio- and Enantioselective Intermolecular Hydroacylation: Salicylaldehyde Variation[a]

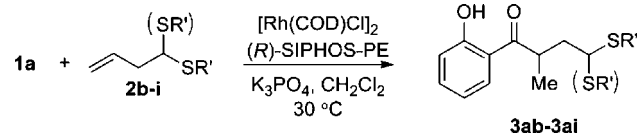


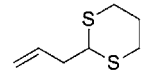
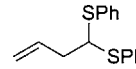
entry		R	product	time (h)	% yield[b]	% ee[c]
1	**1a**	H	**3aa**	18	97	92
2[d]	**1a**	H	**3aa**	18	97	93
3	**1b**	5-F	**3ba**	18	93	92
4	**1c**	5-Cl	**3ca**	18	95	92
5	**1d**	5-CO_2Me	**3da**	19	97	92
6	**1e**	5-Me	**3ea**	24	90	93
7[e]	**1f**	5-OMe	**3fa**	18	93	93
8	**1g**	3-OMe	**3ga**	18	91	92
9[f]	**1g**	3-OMe	**3ga**	18	91	93
10[e,g]	**1h**	6-Me	**3ha**	18	94	84

[a] Conditions: salicylaldehyde (1.0 equiv), olefin **2a** (1.5 equiv), $[Rh(COD)Cl]_2$ (2.5 mol %), (*R*)-SIPHOS-PE (5 mol %), K_3PO_4 (5 mol %), CH_2Cl_2, 30 °C. [b] Isolated yields of branched regioisomers. Regioselectivities of >20:1 were observed via ^{1}H NMR analysis of crude reaction mixtures. [c] Determined by chiral HPLC analysis. [d] With 5 mol % $AgClO_4$; isolated yield of both regioisomers (>20:1 selectivity). [e] Using 5 mol % $[Rh(COD)Cl]_2$, 10 mol % (*R*)-SIPHOS-PE, and 10 mol % K_3PO_4. [f] Using 2.0 equiv of **2a**. [g] Reaction temperature of 40 °C.

We then investigated the effect of varying the electronic and steric properties of the sulfide in our intermolecular hydroacylation (Table 3). 1-Naphthyl substituted **2b** provided the product in 95% ee, albeit with sluggish reactivity (entry 1), while 2-naphthyl-derived olefin **2c** reacted similarly to **2a** [96% yield, 92% ee (entry 2)]. *Ortho*- and *para*-substitution with electron-withdrawing groups (2-CO_2Me, 4-Cl) on **2d** and **2e** gave **3ad** and **3ae** in high yields and ee's (entries 3 and 4). A pronounced effect on the enantioselectivity was observed upon testing *para*-methoxy substituted sulfide **2f**, which produced **3af** in a reduced 87% ee (entry 5). More electron-rich cyclohexyl substituted sulfide **2g** underwent hydroacylation to give product **3ag** in a much lower 55% ee (entry 6). While ee's were variable across these olefin substitution patterns, the reaction remained highly regioselective, delivering the branched isomers in excellent selectivities (>20:1) and yields in all cases. We tested dithiane **2h** to access a protected 1,4-dicarbonyl equivalent.[19] While

Table 3. Regio- and Enantioselective Intermolecular Hydroacylation: Variation of Electronic and Steric Properties of Sulfides[a]



entry		substrate	product	time (h)	mol % [Rh/**L5**]	% yield[b]	% ee[c]
1	**2b**	R' = 1-naphthyl	**3ab**	96	10	74	95
2	**2c**	R' = 2-naphthyl	**3ac**	18	5	96	92
3	**2d**	R' = 2-CO_2Me-C_6H_4	**3ad**	24	10	92	97
4	**2e**	R' = 4-Cl-C_6H_4	**3ae**	26	10	99	92
5	**2f**	R' = 4-OMe-C_6H_4	**3af**	18	5	90	87
6	**2g**	R' = Cy	**3ag**	26	10	99	55
7[d]	**2h**		**3ah**	18	10	84	36
8	**2i**		**3ai**	22	5	95	95

[a] Conditions: salicylaldehyde **1a** (1.0 equiv), olefin (1.5 equiv), K_3PO_4 (equimolar to ligand), CH_2Cl_2, 30 °C. [b] Isolated yields of branched regioisomers. Regioselectivities of >20:1 were observed via ^{1}H NMR analysis of crude reaction mixtures. [c] Determined by chiral HPLC analysis. [d] Regioselectivity of 7:1.

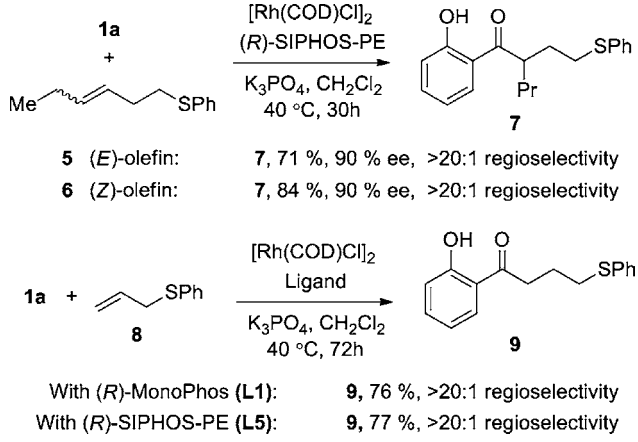
reactive under our standard conditions, giving product **3ah** in 84% yield, both regio- and enantioselectivites were lower than those of other substrates tested (7:1 and 36%, respectively, entry 7). We were pleased to find that selectivities could be restored using (*S*,*S*)-diphenyl acetal **2i**, which furnished masked-aldehyde **3ai** in 95% yield and 95% ee.

Unstrained 1,2-disubstituted olefins have also remained relatively unexplored in enantioselective intermolecular hydroacylation, despite their potential utility in accessing various enantioenriched, α-substituted ketones.[20] Given that substrate chelation is known to enhance reactivity, we wondered whether our conditions could be applied to the hydroacylation of these traditionally unreactive olefins. We were thus pleased to find that (*E*)-disubstituted olefin **5** underwent hydroacylation with **1a** to give α-propyl-substituted product **7** in >20:1 selectivity by crude NMR analysis (Scheme 2). Moreover, **7** was produced in 71% yield and 90% ee. (*Z*)-Olefin **6** also underwent hydroacylation to furnish **7** in 84% yield and 90% ee.[21] In contrast to homoallylic sulfides, allylic sulfide **8** undergoes hydroacylation with either (*R*)-MonoPhos (**L1**) or (*R*)-SIPHOS-PE (**L5**) to give linear product **9** in >20:1 selectivity by ^{1}H NMR analysis (Scheme 2; cf. Table 1, **L1**, **L5**).

We prepared an analogue of **2a** containing a methylene subunit in place of the sulfur atom. After subjecting it to the conditions used in Table 1, with (*R*)-SIPHOS-PE as the ligand, we observed less than 5% conversion after 4 days. The sulfur atom is thus a crucial element for both selectivity and reactivity under these conditions.[22] As has been demonstrated in other transition-metal catalyzed transformations, as opposed to poisoning the metal catalyst, sulfur can act as a highly effective control element that can increase reactivity and override inherent reaction selectivities.[23]

We provide a rationale for the observed regioselectivities with the substrates and ligands investigated in this study (Scheme 3). After oxidative addition, coordination sites on the Rh(III)-hydride can be occupied by two chelating substrates. Under the conditions

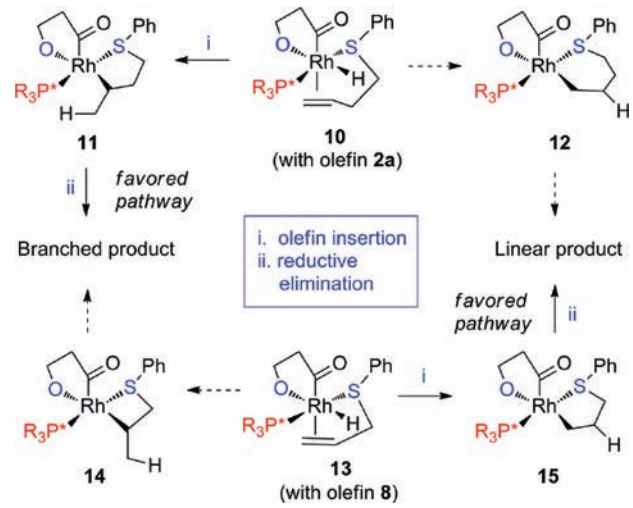
Scheme 2. Effects of Olefin Structure on Regioselectivity[a]



[a] Conditions: salicylaldehyde **1a** (1.0 equiv), olefin (1.5 equiv), $[Rh(COD)Cl]_2$ (5 mol %), ligand (10 mol %), K_3PO_4 (0.2 equiv), CH_2Cl_2, 40 °C; isolated yields.

investigated, the resulting hydride intermediates preferentially undergo hydroacylation via five-membered rhodacycles, rather than four- or six-membered rings. Thus, **10**, which contains chelating homoallylic sulfide **2a**, reacts via five-membered **11** to yield the branched ketone product. In comparison, **13**, which contains allylic sulfide **8**, undergoes hydroacylation via **15**, rather than the four-membered rhodacycle **14**, to give the linear product.[24,25] The monodentate phosphoramidite ligands used in this study likely aid in accommodating the high degree of coordination at Rh from the double-chelating substrates.

Scheme 3. Rationale for Observed Regioselectivities[a]



[a] The aromatic backbone of salicylaldehyde **1a** has been omitted.

This regio- and enantioselective intermolecular hydroacylation reaction does not require high temperatures, which can increase unwanted decarbonylation pathways. Hydrogenating a precatalyst or preparing cationic Rh complexes is also not required, thus rendering the protocol simple to perform. Our study features the first intermolecular hydroacylation system that concomitantly addresses all of the aspects of reactivity, regioselectivity, and enantioselectivity of unstrained, nonconjugated olefins.[3−6,8]

Heteroatom-based directing groups have been used with great success to control regioselectivities in many other intermolecular olefin functionalizations, including the related hydroformylation reaction, but had yet to be applied in this capacity to intermolecular hydroacylation.[26] In this study, we have developed a regio- and enantioselective hydroacylation of unstrained terminal and disubstituted olefins under mild conditions based on the high directing potential of coordinating sulfur atoms and by identifying a highly enantioselective spiro-phosphoramidite ligand, (*R*)-SIPHOS-PE. Future studies will focus on expanding the concepts outlined in this report to other heteroatom-based and removable directing groups.

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

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(14) See the Supporting Information for complete details on ligand screening.
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(20) Tanaka attempted enantioselective hydroacylation of 1,2-disubstituted and trisubstituted acrylamides, but product racemization and low yields were observed; see ref 6.
(21) Both (*E*)-olefin **5** and (*Z*)-olefin **6** underwent hydroacylation to give the same enantiomer of **7**. See the Supporting Information for further discussion.
(22) Initial attempts at intermolecular hydroacylation between salicylaldehyde and olefins bearing other heteroatom-based directing groups were unsuccessful. See the Supporting Information for details.
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