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Enantioselective Rh-Catalyzed Hydroacylation of Olefins: From Serendipitous Discovery to Rational Design

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Abstract

Rh-catalysed hydroacylation allows the construction of chiral ketones from olefins and aldehydes. Since James' and Young's serendipitous discovery of the enantioselective 4-pentenal cyclisation, both intra and intermolecular variants have emerged that enable broader applications.

Hydroacylation enables the atom-economic synthesis of ketones by combining a chemoselective C–H bond activation with C–C bond formation. Sakai and coworkers reported the first Rh-mediated hydroacylation in 1972, which used stoichiometric amounts of Wilkinson's complex to cyclize 4-pentenals en route to prostanoids.[1] This study prompted a large body of work on Rh-catalysed hydroacylation that led to advances in catalyst development and a detailed understanding of reaction mechanism.[2] Driven by the abundance of chiral ketones in natural products and pharmaceuticals, stereoselective variants have been pursued. In this *Viewpoint*, the development of Rh-catalysed hydroacylation will be discussed with a focus on enantioselective methods, including 4-pentenal cyclisations, medium-ring syntheses, and intermolecular variants.

The first asymmetric hydroacylation was serendipitously discovered in 1983 by Brian R. James and Charles G. Young.[3a] While originally intending to resolve 4-pentenals by aldehyde decarbonylation, they instead observed an intramolecular hydroacylation that forged α-quaternary cyclopentenones in 40-50% yields and ee's up to 52% (Scheme 1).

Later studies revealed that ee's of up to 69% could be achieved at 17% conversion.[3b] Remarkably, the transformation used only 0.16 mol% of the Rh catalyst. A high temperature of 160 °C was required, likely due to the steric hindrance of the α-quaternary centre and the need for phosphine dissociation prior to hydroacylation.

Bosnich and co-workers made a breakthrough in 1988 by applying cationic Rh catalysts for 4-pentenal cyclisations.[4] These catalysts were highly selective for hydroacylation over aldehyde decarbonylation, and they enabled reactions at room temperature with catalyst loadings as low as 1 mol%. Both Bosnich and Sakai used chiral diphosphines in

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combination with cationic Rh to achieve asymmetric 4-substituted-4-pentenal cyclisation (Scheme 2).[5]

Carreira recently reported the use of a cationic Rh catalyst in combination with one P-olefin ligand and one monodentate phosphine for 4-pentenal cyclisations (Scheme 3).[6]

Both phosphines were required for reactivity and enantioselectivity. Of particular note is the high enantioselectivity (90-97% ee) obtained for the cyclisation of 4-aryl-substituted pentenals, which were previously cyclised in 65-78% ee with Me-DuPhos.

The development of cationic rhodium-diphosphine catalysts for 4-pentenal cyclisation set the stage for a variety of asymmetric cyclopentanone syntheses. More stereochemically complex 3,4-disubstituted cyclopentanones could be accessed by desymmetrizing processes and kinetic resolutions.[7] Similar catalysts have also been applied to cyclise 2-vinylbenzaldehydes and N-vinylindole-2-carboxaldehyes.[8]

Alkenals with homologated tethers tend to undergo hydroacylation with lower regio- and chemo-selectivity than 4-pentenals. To promote these reactions, several groups have used diene orvinylcyclopropanes acceptors, or tethers containing coordinating heteroatoms.[9] Dong and co-workers reported an asymmetric olefin hydroacylation to access 7- and 8-membered cyclic ketones that used a coordinating heteroatom (oxygen or sulphur) in the tether to promote hydroacylation over decarbonylation (Scheme 4).[10] Ligand-controlled regioselectivity was observed with terminal alkenes, which allowed access to either chiral 7-membered ketones or achiral 8-membered ketones. While 1,2-disubstituted alkenes were hydroacylated to give the 7-membered ketones, 1,1-disubsituted alkenes gave exclusively the 8-membered ketones.

Douglas and co-workers accessed 7-membered ketones without stoichiometric directing groups (Scheme 5).[11] Their strategy expanded on Jun's work on metal-organic cooperative catalysis.[12] A wide range of 7-membered ketones could be synthesized using the combination of 2-amino-3-picoline and PPh_3 as ligands. The 2-amino-3-picoline condenses with the aldehyde to form a 2-pyridylaldimine in situ that is reactive towards pyridine-directed hydroiminoacylation and subsequent hydrolysis. Low levels of enantioselectivity were observed when either of the ligands were replaced with a chiral variant (23% ee with 2-amino-3-picoline/**L2**, and 31 % ee with **L3**/PPh_3).

Compared to intramolecular processes, intermolecular olefin hydroacylation is more difficult and often results in aldehyde decarbonylation. To address these challenges, substrates are often designed with directing groups that stabilize the acyl-Rh intermediate and control regioselectivity. Additionally, strained or electron deficient olefins are commonly employed. A few notable exceptions have been reported by Jun[12] and Brookhart[13] for linear-selective olefin hydroacylation without substrate pre-activation. However, enantioselective variants are rare due to the lower reactivity of di- and tri-substituted olefins, and the lack of branched-selective methods. Asymmetric intermolecular olefin hydroacylation remains a developing field that holds promise for the synthesis of chiral ketones.

Bolm and co-workers published the first intermolecular variant of an asymmetric olefin hydroacylation in 2007 (Scheme 6).[14] Inspired by Suemune's previous study on a racemic version of this transformation,[15] salicylaldehydes were coupled with strained olefins—norbornadienes and norbornenes. The phenolic group of the salicylaldehyde is deprotonated by the acaccounterion to form a phenolate. This anionic group directs the initial C–H activation to form a metallacyclic acyl-Rh intermediate that is stable toward decarbonylation. Excellent exo selectivity and ee's up to 82% were obtained when a bidentate phosphine ligand was used. Conversely, endo selectivity and ee's up to 54% were observed with a monodentate phosphoramidite ligand. Presumably, the monodentate ligand allows the norbornadiene to coordinate in a bidentate fashion, which switches the diastereo selectivity.

Willis pioneered intermolecular hydroacylation with β-sulfur chelating aldehydes using cationic Rh catalysts, and developed an asymmetric variant in 2008 (Scheme 7).[16]

Me-DuPhos was used to achieve a highly regio- and enantio-selective hydroacylation of racemic allenes. This process can be described as a dynamic kinetic asymmetric transformation, where the alleneracemizes under the reaction conditions. Weller and Willis have established the utility of the thioether directing group by developing methods for its further elaboration, such as alkyne carbothiolation, cross-coupling, and desulfurization.[17 a-c] Furthermore, Weller and Willis have recently developed a $[Rh(C_6H_5F)(R_2PCH_2PR_2)]BAr^F{}_4$ catalyst for general linear-selective hydroacylation with β-sulfur chelating aldehydes.[17d,e]

A rare example of asymmetric intermolecular hydroacylation without the use of a chelating aldehyde was reported by Tanaka and co-workers in 2009 (Scheme 8).[18a]

Alkyl-substituted aldehydes underwent linear selective coupling with acrylamide acceptors in excellent enantioselectivity. The amide group was crucial for reactivity and was proposed to chelate to the metal during catalysis and stabilize the acyl-Rh intermediate. This work built upon a racemic variant previously reported by the same group, which also featured hydroacylations with aryl aldehydes and acrylates.[18b]

Olefins that are not electronically activated or strained are difficult substrates for intermolecular hydroacylation. To overcome this challenge, Suemune and co-workers used a double-chelating approach for the hydroacylation of 1,5-hexadienes with salicylaldehydes in 2009 (Scheme 9).[19]

In this strategy, the chelating aldehyde promotes C–H activation and suppresses decarbonylation, while the chelating dieneen forces the unusual branched regioselectivity. (*S*)-BINAP was used to make the process enantioselective, and an optimal ee of 84% was obtained with 1:1 regioselectivity. The authors invoked a bimetallic complex as the active catalyst based on their observation that a 2:1 ratio of Rh to (*S*)-BINAP was required for enantioselectivity. Up to 12:1 branched:linear regioselectivity was obtained in previous reports using achiral ligands.

In 2010, Dong and co-workers developed a method for branched-selective hydroacylation of unactivated olefins using a strategy that built upon their previous sulphide-directed

intramolecular hydroacylations (Scheme 10).[20] Homoallylic sulphides were coupled with salicylaldehydes, often with >20:1 regioselectivity for the branched ketones. By using a monodentate phosphoramidite ligand, a highly enantioselective protocol for hydroacylation of both terminal and 1,2-disubsituted olefins was achieved. The sulphur atom was crucial for reactivity, and no products were observed when the sulphur atom was replaced by a methylene unit. In a separate report, increasing the reaction temperature to 70 °C enabled a general linear-selective coupling of olefins with salicylaldehydes under otherwise identical reaction conditions.[21] Furthermore, the phenolic handle could be triflated and engaged in reduction, Suzuki-Miyauracross-coupling, or cyclocarbonylation.[21]

In the same year, the Dong group reported a desymmetrizing hydroacylation of cyclopropenes with salicylaldehydes (Scheme 11).[22]

The release of ring strain was thought to promote hydroacylation over competitive processes. This highly enantio- and diastereo-selective reaction tolerates a wide range of functionality on both the aldehyde and cyclopropene coupling partners, including a variety of substitution patterns and heterocycles.

Since James' and Young's original report of asymmetric 4-pentenal cyclisation, the development of cationic rhodium catalysts and chiral diphosphines have enabled excellent levels of reactivity and enantioselectivity for 4-pentenal cyclisation. Furthermore, with the recent advances in organocatalytic aldehyde α-allylation, complex 4-pentenals are now readily accessible, thus empowering intramolecular hydroacylation. Much work remains to be done in the synthesis of medium sized rings and intermolecular variants. While the major drawback of the current methods is the need for chelating aldehydes, there have been advances in intermolecular hydroacylation with non-chelating aldehydes for constructing racemic ketones using Rh,[23] Co,[24] and Ru.[25] N-heterocyclic carbene catalysed stetter reactions are an intriguing alternative that has seen much recent development as well. The discovery of better catalysts for intermolecular hydroacylation protocols continues to be an active field of research.

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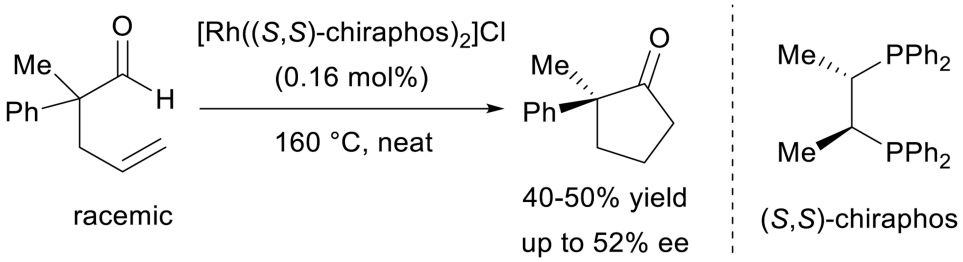
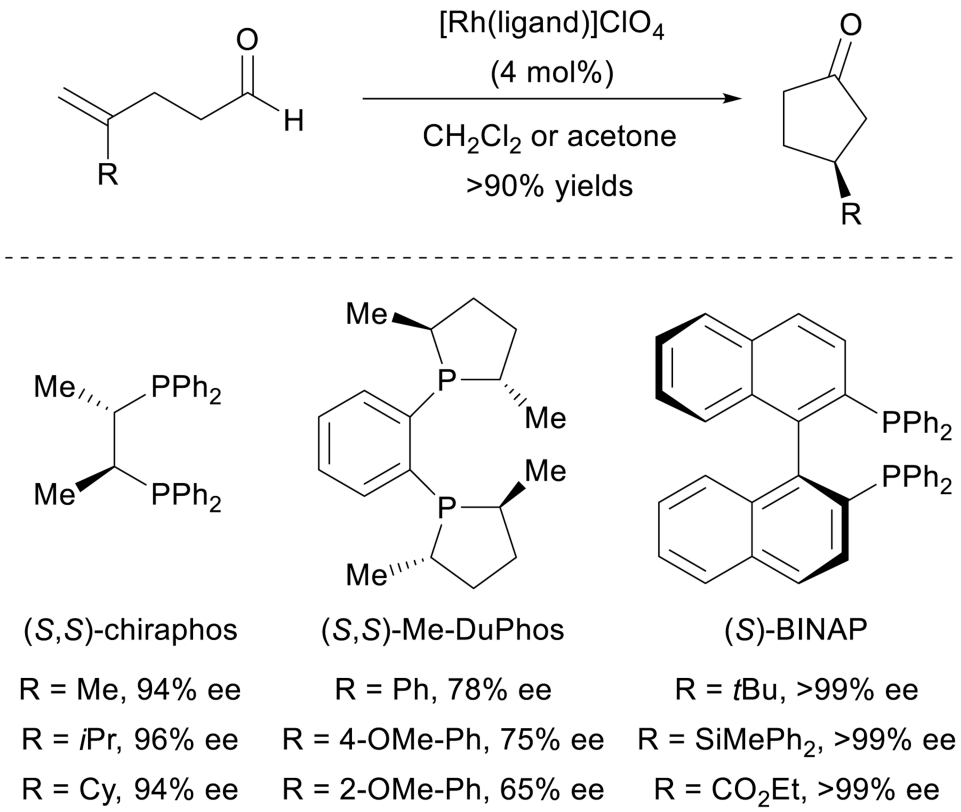
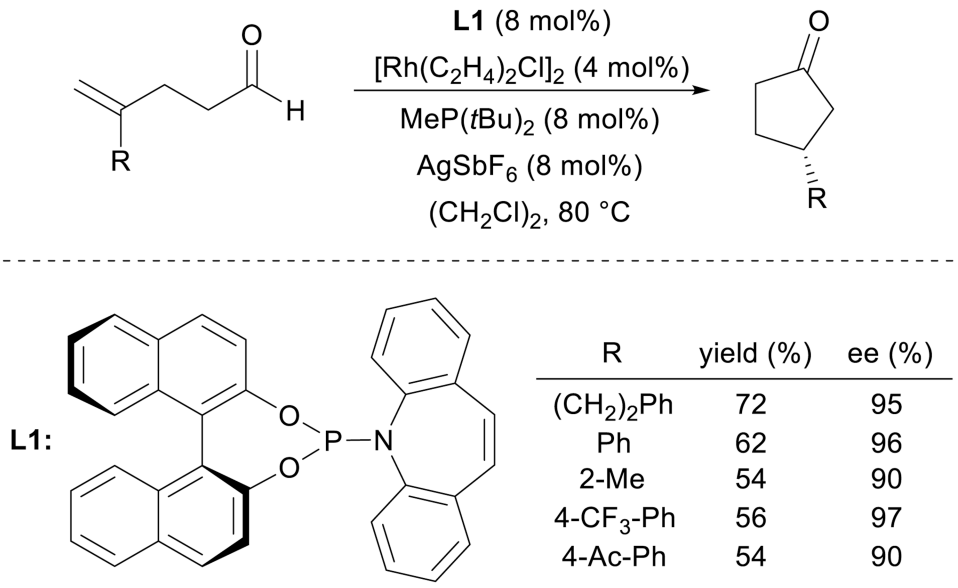


Scheme 1.
Kinetic resolution of racemic 4-pentenals by hydroacylation.

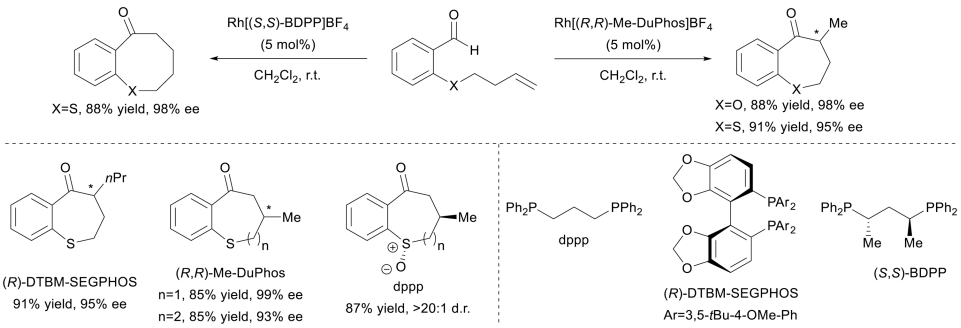


Scheme 2.
Asymmetric cyclisation of 4-pentenals with cationic rhodium.



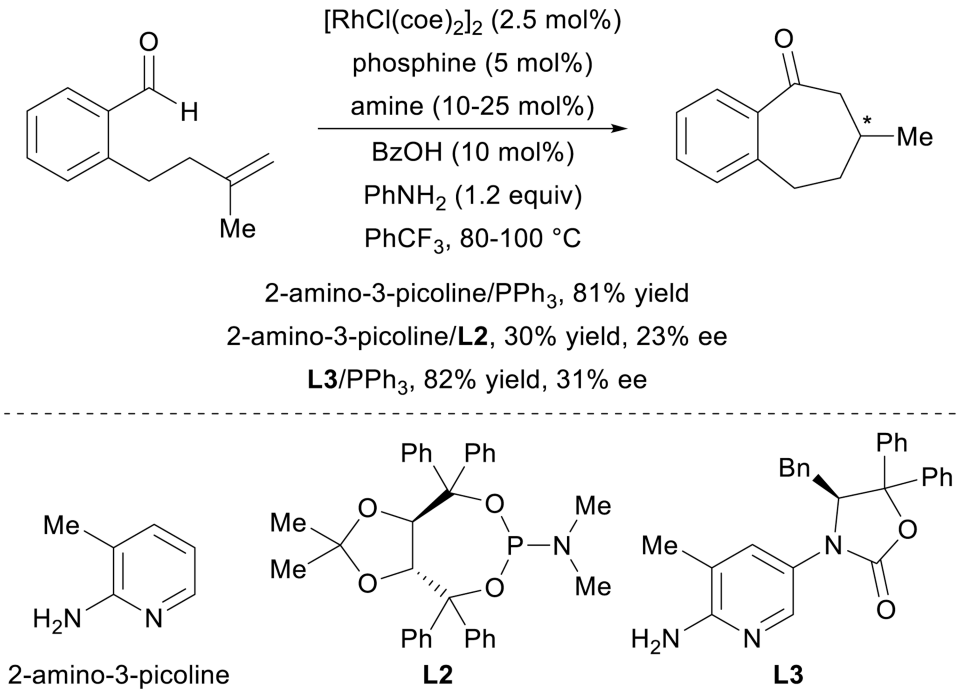
R	yield (%)	ee (%)
$(CH_2)_2Ph$	72	95
Ph	62	96
2-Me	54	90
4-CF_3-Ph	56	97
4-Ac-Ph	54	90

Scheme 3.
Asymmetric cyclisation of 4-pentenals with a P-olefin ligand.

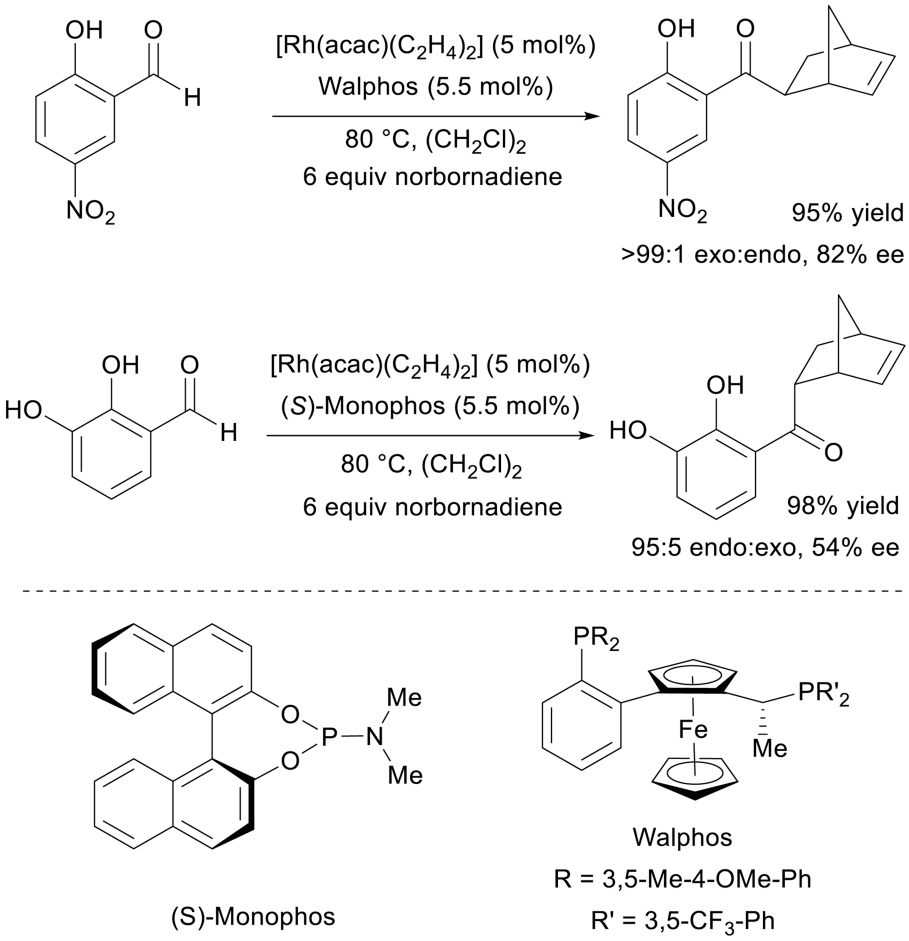


Scheme 4.

Medium-ring formation using asymmetric hydroacylation.

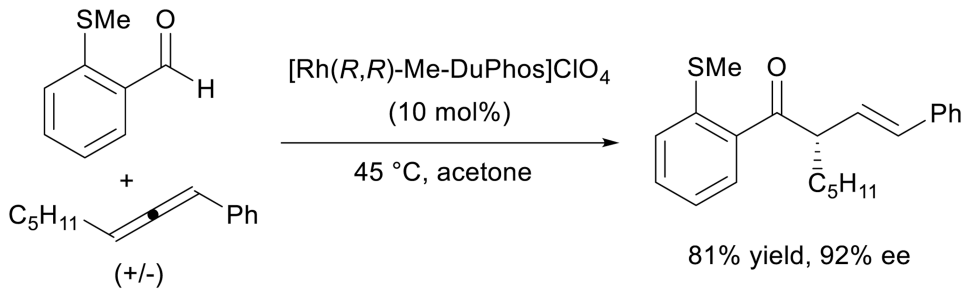


Scheme 5.
Metal-organic cooperative catalysis for medium-ring synthesis.

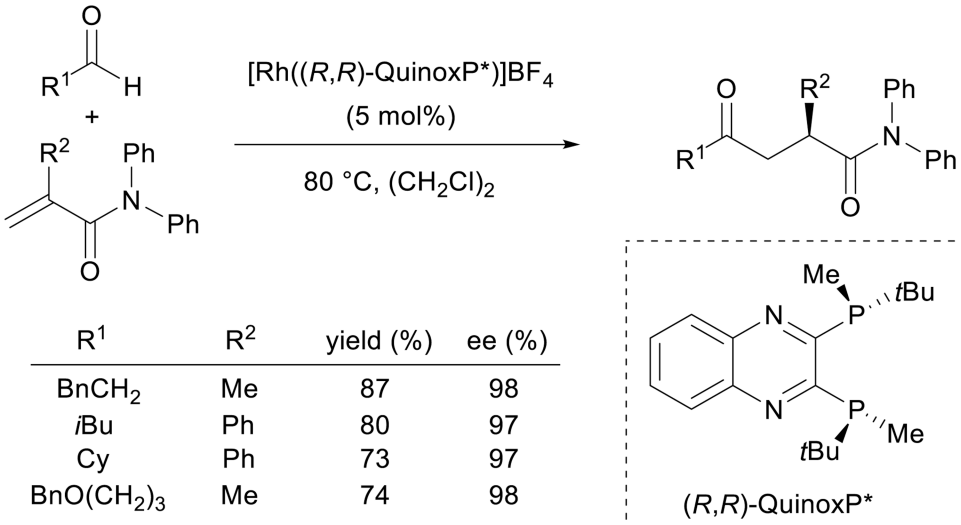


Scheme 6.

Asymmetric hydroacylation of norbornadienes with salicylaldehydes.

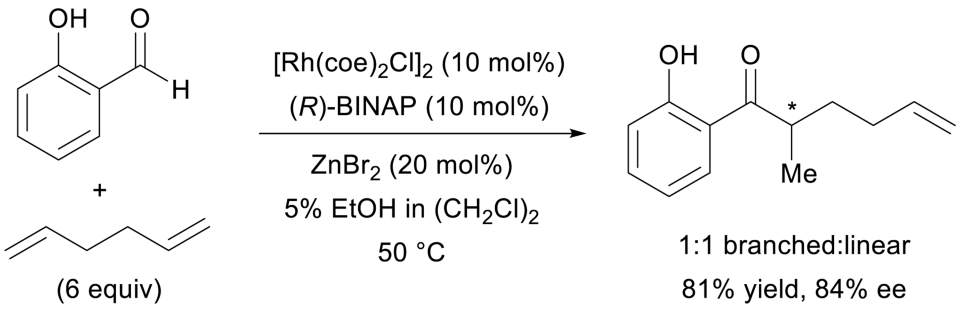


Scheme 7.
Asymmetric hydroacylation of allenes.

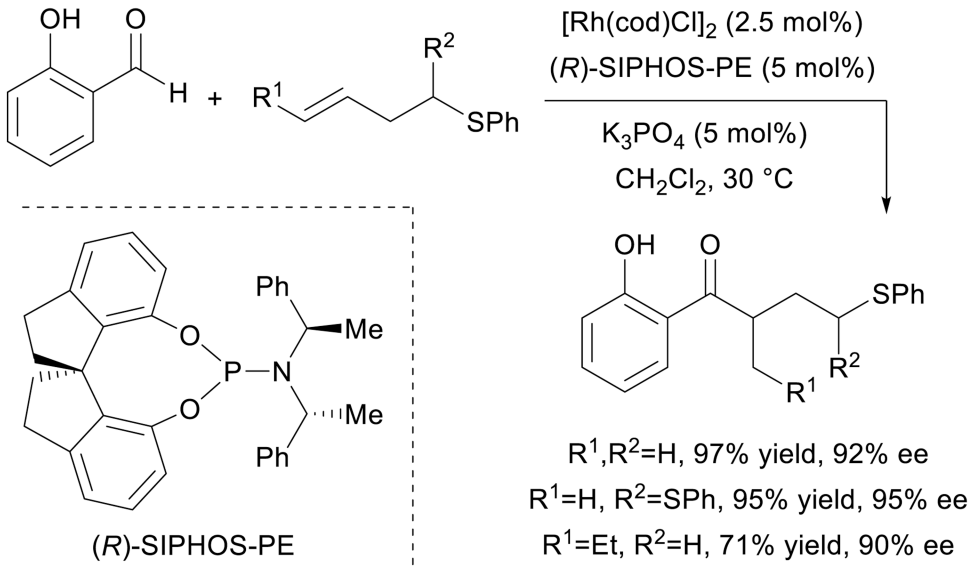


R^1	R^2	yield (%)	ee (%)
$BnCH_2$	Me	87	98
*i*Bu	Ph	80	97
Cy	Ph	73	97
$BnO(CH_2)_3$	Me	74	98

Scheme 8.
Asymmetric hydroacylation of acrylamides.

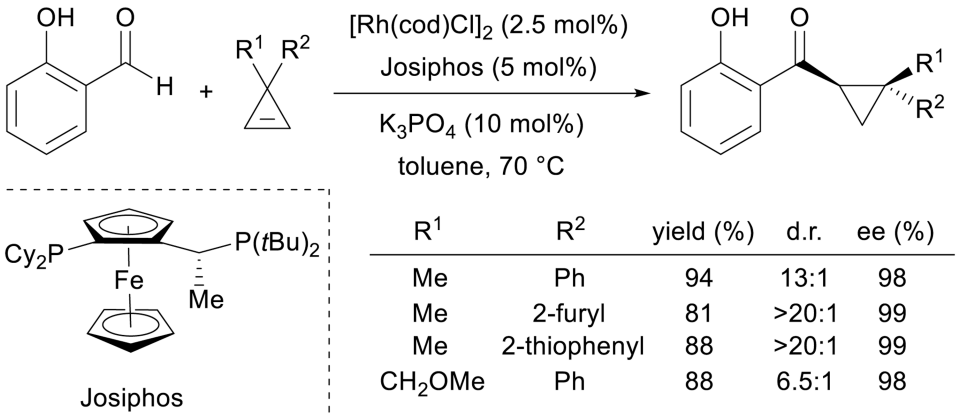


Scheme 9.
Asymmetric hydroacylation of 1,5-hexadienes with salicylaldehydes.



Scheme 10.

Asymmetric hydroacylation of homoallylic sulphides with salicylaldehydes.



R^1	R^2	yield (%)	d.r.	ee (%)
Me	Ph	94	13:1	98
Me	2-furyl	81	>20:1	99
Me	2-thiophenyl	88	>20:1	99
CH_2OMe	Ph	88	6.5:1	98

Scheme 11.
Asymmetric hydroacylation of cyclopropenes with salicylaldehydes.