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Rh(I)-Catalyzed Intermolecular Hydroacylation: Enantioselective Cross-Coupling of Aldehydes and Ketoamides

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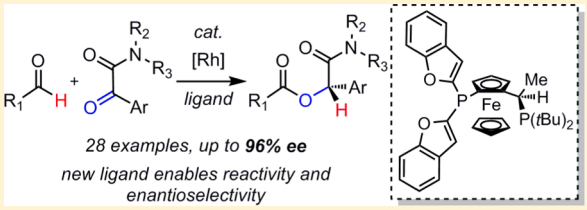
Supporting Information

ABSTRACT: Under Rh(I) catalysis, α-ketoamides undergo intermolecular hydroacylation with aliphatic aldehydes. A newly designed Josiphos ligand enables access to α-acyloxyamides with high atom-economy and enantioselectivity. On the basis of mechanistic and kinetic studies, we propose a pathway in which rhodium plays a dual role in activating the aldehyde for cross-coupling. A stereochemical model is provided to rationalize the sense of enantioinduction observed.

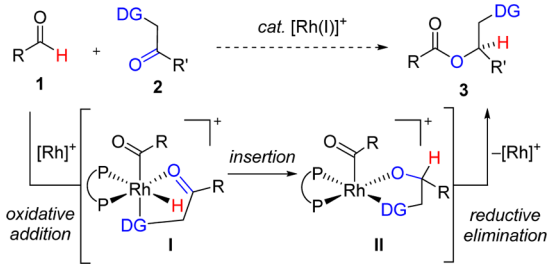


INTRODUCTION

The catalytic functionalization of aldehyde C−H bonds represents a mild and atom-economical approach to prepare esters.[1] While there has been much progress in developing hydroacylation of aldehydes,[2−6] the hydroacylation of ketones is relatively unexplored and warrants attention due to its potential for constructing chiral esters.[4] Our laboratory has demonstrated intramolecular ketone hydroacylations, including the first examples of enantioselective lactonizations.[7] Due to the propensity of nonchelating aldehydes to engage in decarbonylation,[8−10] Tishchenko dimerizations,[5] and aldol condensations, *inter*molecular hydroacylations are considerably more challenging.[11−13] Herein, we report the design and development of the first enantioselective intermolecular ketone hydroacylation.

We imagined a novel cross-coupling between a broad range of aldehydes **1** and ketones bearing a directing group (DG) **2** (Scheme 1). On the basis of previous studies, we proposed that this functional group would promote preferential ketone binding to the Rh(I) center and favor chemoselective cross-coupling over aldehyde dimerization or decarbonylation.[9d,e,14] In the presence of a suitable bidentate phosphine ligand, coordination of ketone **2** to Rh, followed by oxidative addition of aldehyde **1**, would generate coordinatively saturated Rh(III)-hydride **I**. Octahedral complex **I** has a lower propensity to undergo carbonyl deinsertion, a process that deactivates the rhodium catalyst.[8] Ketone insertion into acyl-Rh(III)-hydride **I** would lead to Rh(III)-alkoxide **II**, followed by reductive elimination to give ester **3** with concomitant regeneration of the Rh(I) catalyst. In comparison to conventional approaches to ester synthesis, this catalytic method obviates the need for prefunctionalization of the acyl component and is amenable to enantioselective synthesis of esters.

Scheme 1. Proposed Rh(I)-Catalyzed Cross-Coupling of Aldehydes and Ketones



RESULTS AND DISCUSSION

Method Development. To test our hypothesis, we chose hydrocinnamaldehyde (**1a**) and α-ketoamide **2a** as model substrates (Chart 1). A number of Rh-bis(phosphine) catalysts were examined because previous studies in our lab had demonstrated that these complexes promote intramolecular ketone hydroacylation.[7,15] After studying various ligands, we found Rh(I)-Josiphos catalysts most promising. Commercially available ligand **L1** provides modest yield and 13% ee. Changing to ligand **L2**, which contains a diphenylphosphine and a dialkylphosphine, results in a small improvement in enantioselectivity (21% ee). Josiphos **L3** containing a more π-accepting difurylphosphine and a σ-donating di-*tert*-butylphosphine affords the desired α-acyloxyamide **3a** in 46% yield and 73% ee. We reason that this C_1-symmetric ligand may facilitate the product-determining hydride delivery via the *trans* effect; the hydride *trans* to the electron-rich dialkylphosphine becomes more hydridic, while the ketone *trans* to the π-acceptor becomes more prone to insertion (Scheme 2).[16,17]

Inspired by **L3**, we created new Josiphos ligands to study the steric influence of the phosphine substituents. In comparison to

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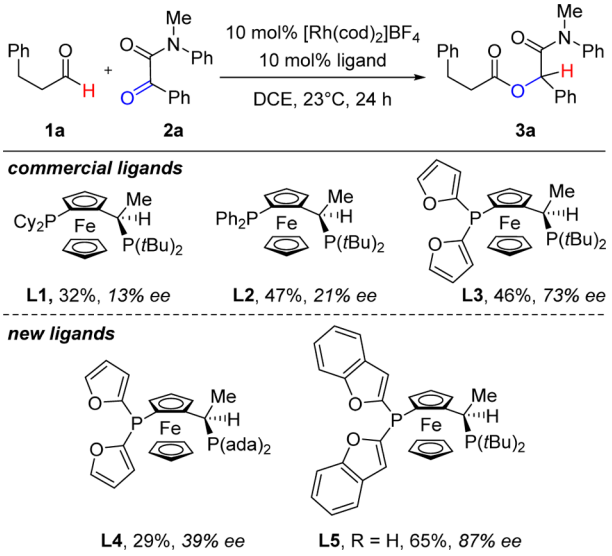
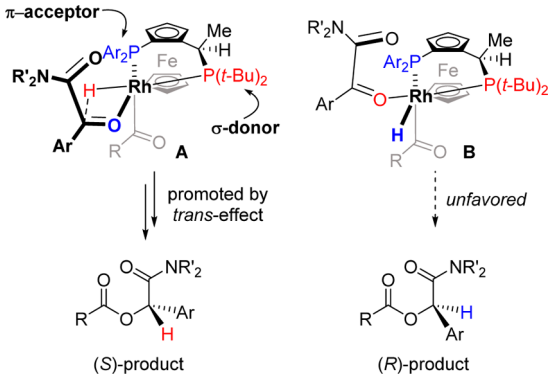
Chart 1. Evaluation of Ligands for Enantioselective Ketone Hydroacylation[a]



[a]Conditions: **1a** (1.2 equiv), **2a** (1 equiv), $[Rh(cod)_2]BF_4$ (0.1 equiv), ligand (0.1 equiv), DCE, rt (23 °C), 24 h.

Scheme 2. Proposed Model for Enantioinduction



commercial **L3**, ligand **L4** bears bulkier adamantyl groups and shows inferior performance. In contrast, **L5** with bulkier π-accepting dibenzofurylphosphines affords better results than **L3** (65% yield, 87% ee). The Rh-**L5** catalyst shows excellent chemoselectivity with no observable aldehyde dimerization.[4,5]

Scope of Intermolecular Ketone Hydroacylation. This mild Rh(I)-catalyzed method offers an attractive approach to enantioenriched esters that are structurally related to those obtained via the multicomponent Passerini reaction.[19−21] A conventional route to these motifs would involve enantioselective ketone reduction followed by an additional acylation step (which generally requires stoichiometric activating agents) to obtain the α-acyloxyamides. Moreover, the asymmetric reduction of α-ketoamides has not been well-studied and remains limited in scope and/or selectivity. A method featuring Rh catalysis with bidentate amidophosphine−phosphinite ligands appears most promising and has been applied to reduce α-ketoamides with good enantioselectivity for a few aryl-substituted ketones.[22] There is one example of ruthenium-catalyzed α-ketoamide hydrogenation where excellent ee was achieved following recrystallization for a bulky *tert*-butyl-substituted ketone.[23] Biocatalytic methods have also been reported for reducing α-ketoamides, although with low efficiency.[24]

Thus, with Rh-**L5** in hand, we studied the coupling of α-ketoamides **2** with nonchelating aliphatic aldehydes **1** (Table 1). Aryl ketones containing various substituents and substitution patterns undergo hydroacylation with hydrocinnamaldehyde (**1a**) (entries 1−7) and hexanal (**1b**) (entries 8−14) in good to high yields (53−98%) and high enantioselectivities (84−96%). Sterically demanding 2-methylphenyl (entries 2 and 9), mesityl (entries 4 and 11), and 1-naphthyl ketones (entries 5 and 12) tend to give higher conversions and selectivities even with lower (5 mol %) catalyst loadings, resulting in 73−98% yields of the α-acyloxyamides with 94−96% ee. α-Ketoamides bearing smaller aryl groups, such as 3-methylphenyl (entries 3 and 10), 4-chlorophenyl (entries 6 and 13), and 3,5-difluorophenyl groups (entries 7 and 14), require a higher catalyst loading to provide the corresponding α-acyloxyamides in 53−81% yields and 84−90% ee.

Sterically encumbered primary aldehydes (R = *i*-Bu and neopentyl, entries 15−17) are effective coupling partners, providing the desired products in high yields and ee. Using aldehyde **1d** and ketone **2e**, we show that the reaction can also be performed on a larger scale (1.0 mmol, 353 mg product isolated, 91% yield, 93% ee) at 5 mol % catalyst loading (entry 16). The rhodium loading can be further reduced to 3.5 mol % at elevated temperature conditions (60 °C), providing hydroacylation product **3p** in 92% yield and 87% ee (entry 17). Transforming α-branched cyclohexanecarboxaldehyde (entry 18) requires elevated temperatures (50 °C) to proceed and furnishes the desired α-acyloxyamide **3q** in 57% yield and 90% ee. Aryl aldehydes do not participate in hydroacylation to any appreciable extent under the current reaction conditions (<5% conversion), perhaps due to a higher barrier to C−H activation.[25] Compared to the *N*,*N*′-alkylarylamide, ketones containing *N*,*N*′-diaryl- or dialkylamides are also less effective (entries 19 and 20) and provide α-acyloxyamides **3r** and **3s** with modest yields and enantioselectivities. A cyclic ketoamide is converted to 3-acyloxyindolinone **3t** (entry 21) in 54% yield and 58% ee. The efficacy of this reaction is improved by employing **L3**, which provides heterocycle **3t** in 88% yield and 69% ee. The amide motif impacts both reactivity and enantioselectivity, presumably due to a directing group role.

The absolute configuration of the products was assigned based on X-ray analysis of α-acyloxyamide **3c** (see Supporting Information).[26] The observed *S*-enantiomer is consistent with a proposed model that invokes the *trans*-effect in promoting the product-determining ketone insertion step (Scheme 2). In this model, the C_1-symmetric ligand cooperatively renders the hydride more nucleophilic and the ketone more electrophilic (complex **A**), and thus substantially favors formation of the *S*-stereoisomer in the case of (S_P,*R*)-**L5**. Conversely, the alternative complex **B** is stabilized by the *trans*-effect which would result in an increased barrier to migratory insertion.[16,17] We propose the acyl group to be situated on the "bottom" apical position, with the less hindering *N*,*N*′-disubstituted amide carbonyl bound to the "top" apical position. This ligand arrangement minimizes unfavorable steric interactions between the acyl group and the substituents on the phosphines and is supported by DFT calculations.[27]

We find that morpholine amides direct hydroacylation effectively to yield cross-coupled products in good yields and enantioselectivities (Table 2). A similar trend is observed in which ketones bearing larger aryl groups perform better, both

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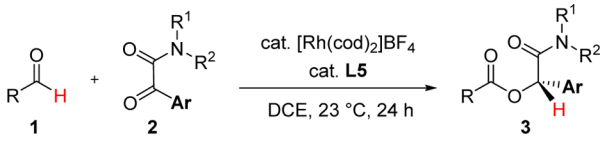
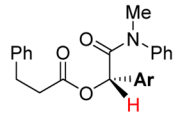
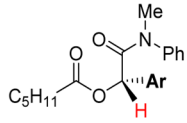
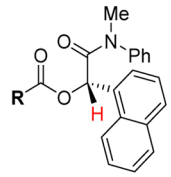
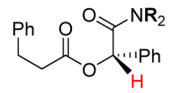
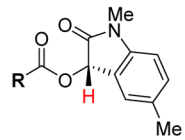
Table 1. Coupling Aldehydes with α-Ketoamides[a,b]



Entry	Product	Variable		mol % cat.	Yield (%)[c]	ee (%)[d,e]
1		Ar = Ph	**3a**	10	65	87
2		Ar = 2-MeC$_6$H$_4$	**3b**	5	88	95
3		Ar = 3-MeC$_6$H$_4$	**3c**	10	62	86
4		Ar = Mes	**3d**	5	82	96
5		Ar = 1-naphthyl	**3e**	5	86	95
6		Ar = 4-Cl-C$_6$H$_4$	**3f**	10	71	84
7		Ar = 3,5-F$_2$-C$_6$H$_3$	**3g**	10	67	88
8		Ar = Ph	**3h**	10	86	89
9		Ar = 2-MeC$_6$H$_4$	**3i**	10	98	95
10		Ar = 3-MeC$_6$H$_4$	**3j**	10	78	86
11		Ar = Mes	**3k**	5	76 (84)[f]	96 (94)[f]
12		Ar = 1-naphthyl	**3l**	5	73	96
13		Ar = 4-Cl-C$_6$H$_4$	**3m**	10	53	87
14		Ar = 3,5-F$_2$-C$_6$H$_3$	**3n**	10	81	90
15		R = *i*-Bu	**3o**	5	91	94
16[g]		R = Neopentyl	**3p**	5	91	93
17[f,g]				3.5	92	87
18[h]		R = Cy	**3q**	10	57	90
19[i]		R = Ph	**3r**	10	47	78
20[i]		R = Bn	**3s**	10	46	81
21		R = Ph(CH$_2$)$_2$	**3t**	10	54 (88)[j]	58 (69)[j]

[a]Conditions: 0.12 mmol of **1**, 0.1 mmol of **2**. [b]The catalyst was activated by hydrogenation (see Supporting Information). [c]Isolated yields. [d]Enantiomeric excess determined by chiral SFC analysis. [e]See ref 18. [f]At 60 °C. [g]With 1.2 mmol of **1**, 1.0 mmol of **2**. [h]At 50 °C, 4 days. [i]For 3 days. [j]**L3**, 7.5 h.

in terms of isolated yields and enantioselectivities. Phenyl ketone **4a** is hydroacylated with 3,3-dimethylbutanal (**1d**) to furnish ester **5a** in 67% yield and 80% ee, whereas larger mesityl and 1-naphthyl ketones give **5b** and **5d** in 94 and 75% yields, respectively (95 and 92% ee). Other aldehydes including cyclohexanecarboxaldehyde, hexanal, and hydrocinnamaldehyde are also good coupling partners. The use of the morpholine amide as a directing group provides a handle for further chemical manipulations.[28]

The Rh-**L5** catalyst described in this study, however, is not effective with α-keto-Weinreb amide **2k** (Scheme 3). To this end, we have identified an alternative rhodium catalyst derived from methoxy-BIPHEP **L6**, which provides good reactivity and modest enantioselectivity for this transformation to yield ester **6** (93%, 51% ee).

Investigation of the Kinetics of Intermolecular Hydroacylation. We initiated mechanistic studies by examining the kinetics for the cross-coupling of aldehyde **1d** and α-ketoamide **2e** by ^{1}H NMR. These particular substrates were chosen because their ^{1}H NMR signals are distinct and no products of decomposition were observed over the course of reaction progress, thus simplifying data analysis. Initial rates for the hydroacylation of **2e** were then measured by varying the concentrations of **1d**, **2e**, and rhodium catalyst. These experiments revealed a first-order dependence of the rate on both aldehyde **1d** (Figure 1) and ketone **2e** concentrations (Figure 2). More intriguing is the observed second-order rate dependence on catalyst concentration (Figure 3), which suggests the involvement of two rhodium species in the turnover-limiting step. A study on the correlation between the enantiomeric excess of the catalyst and that of the product

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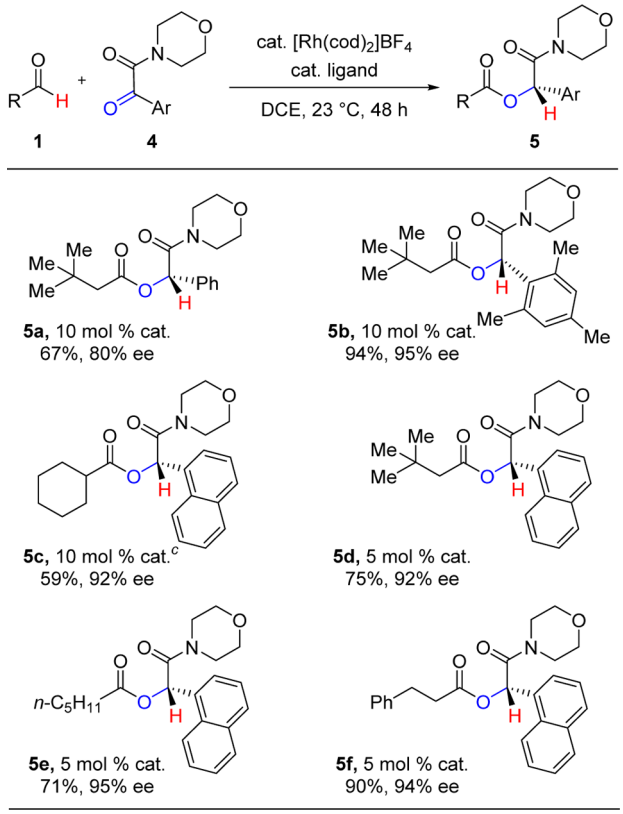
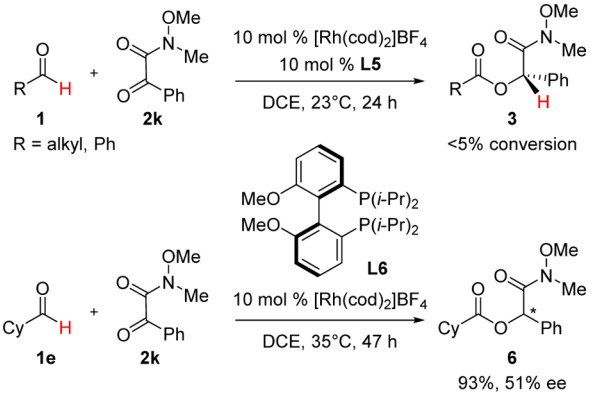
Table 2. Ketone Hydroacylation Using Morpholine Amide Directing Group[a,b]



[a]Conditions: 0.12 mmol of **1**, 0.1 mmol of **2**. [b]The catalyst was hydrogenated at rt for 45 min prior to adding substrates (see Supporting Information). [c]At 50 °C, 72 h.

Scheme 3. Ketone Hydroacylation with Weinreb Amide Directing Group[a]



[a]Conditions: 0.12 mmol of **1**, 0.1 mmol of **2**. The catalyst was hydrogenated at rt for 45 min prior to adding substrates (see Supporting Information).

yielded a small, positive nonlinear relationship (Figure 4).[29] Such a phenomenon is consistent with the added degree of complexity in the reaction mechanism as indicated by the kinetic profile.

The rate data obtained from the kinetics experiments allowed us to calculate initial turnover frequencies. Under standard catalytic conditions using 5 mol % catalyst, 1.0 equiv of ketone, and 1.2 equiv of aldehyde at 25 °C, the initial turnover frequency is determined to be 4.8×10^{-4} s^{-1}.

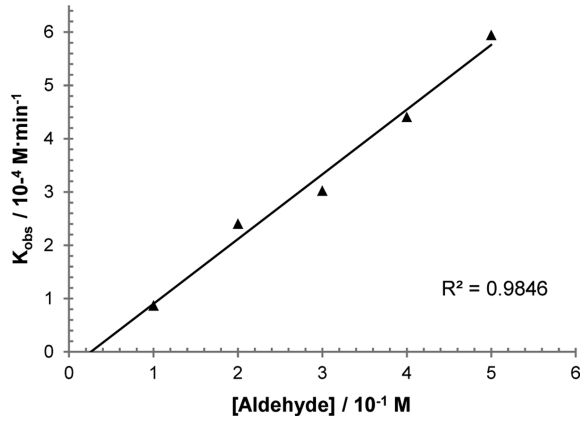


Figure 1. Plot of initial rates (k_{obs}) with respect to [aldehyde **1d**] showing first-order dependence; [**2e**] = 0.17 M, [catalyst] = 0.0083 M.

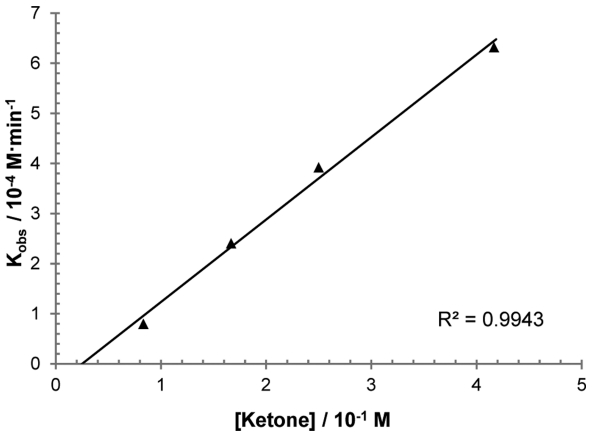


Figure 2. Plot of initial rates (k_{obs}) with respect to [α-ketoamide **2e**] showing first-order dependence; [**1d**] = 0.20 M, [catalyst] = 0.0083 M.

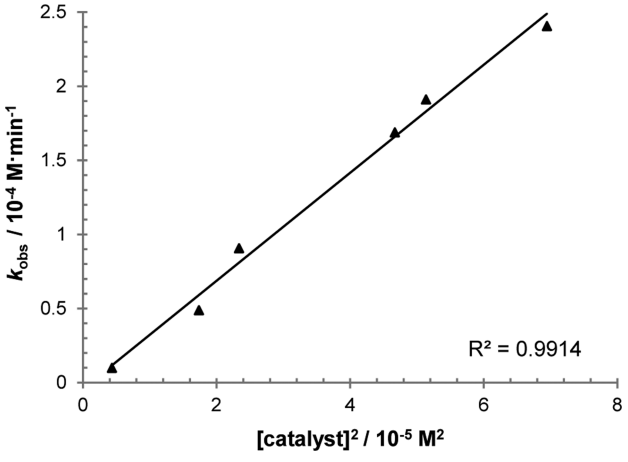


Figure 3. Plot of initial rates (k_{obs}) with respect to [catalyst]^2 showing second-order dependence; [**1d**] = 0.20 M, [**2e**] = 0.17 M.

Isotope Labeling Study. To gain further insight into the mechanism, we measured the kinetic isotope effect (KIE) by running two independent, side-by-side experiments using protio-**1a** and deuterated **1a-D** (Scheme 4).[30] Aldehyde **1a-D** was chosen (over **1d** and others) for this study due to ease of isolation. Examination of the initial rates resulted in a KIE of

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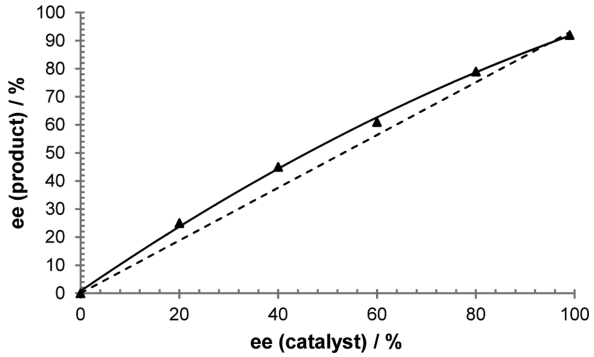
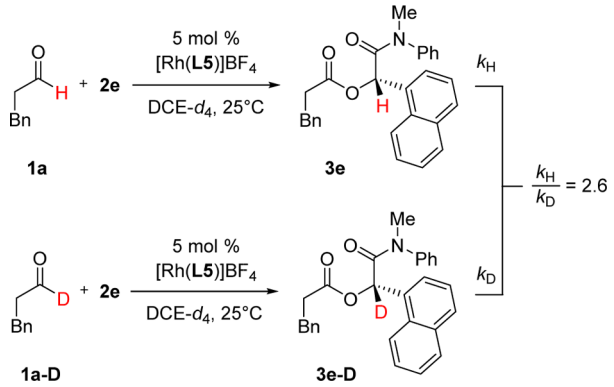


Figure 4. Relationship between the enantioselectivity of the reaction and the ee of the chiral catalyst. Each data point was run in duplicate.

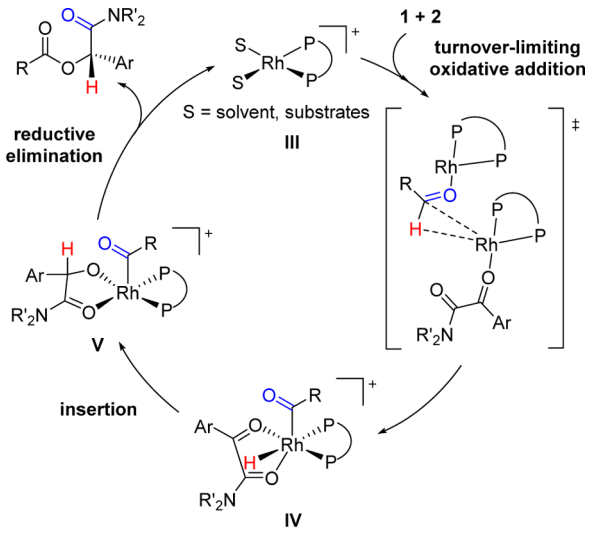
Scheme 4. KIE Measurement from Two Parallel Reactions Using Method of Initial Rates



2.6 and supports C−H bond activation to be turnover-limiting. This value is larger than that previously observed for an *intramolecular* ketone hydroacylation where insertion was implicated as the turnover-limiting step (KIE = 1.79 ± 0.06).[7b,31] The absence of a directing group on the aldehyde in the present system likely increases the barrier to oxidative addition significantly.[32,33]

On the basis of the kinetic analysis and KIE, we propose a mechanism invoking homobimetallic activation[34] of the aldehyde where one rhodium catalyst acts as a Lewis acid by coordinating the oxygen atom of the aldehyde and a second rhodium catalyst participates in the oxidative addition of the formyl C−H bond to produce acyl-Rh(III)-hydride **IV** (Scheme 5).[35] A report of cationic rhodium complexes behaving as Lewis acid catalysts supports this proposal.[36] In addition, Lewis acid additives (i.e., $ZnCl_2$, $ZnBr_2$, ZnI_2, etc.) have been found to be beneficial in a study on intermolecular alkene hydroacylation, although their role is unclear.[37] The mechanism proceeds with insertion to generate acyl-Rh(III)-alkoxide **V**, followed by reductive elimination to furnish the product and turnover the Rh(I) catalyst. It is possible for the reaction to occur through bimetallic intermediates following oxidative addition; however, reactive intermediates were not observed spectroscopically.[38] We believe that rapid coordination and dissociation of solvent and substrate leads to broadening of the ^{31}P NMR resonance signals and is thus consistent with [Rh(diphosphine)(solvent)$_2$]$^+$ **III** being a resting state.

Scheme 5. Proposed Mechanism via Rate-Limiting Oxidative Addition Catalyzed by Two Rhodium Centers



CONCLUSIONS

By developing a new Rh-Josiphos catalyst, we achieved the first enantioselective intermolecular ketone hydroacylation, which features the rare use of nonchelating aldehydes. Kinetic analysis reveals a second-order rate dependence on the rhodium catalyst and, together with a study on nonlinear relationship and the KIE, points to a unique mechanism involving homobimetallic oxidative addition as the turnover-limiting step. This work provides a foundation for understanding C−H activation and hydroacylation using nonactivated aldehydes which will guide future studies and applications.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic data, characterization data for new compounds, and chiral chromatographic analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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