C–H Activation

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A Second-Generation Catalyst for Intermolecular Hydroacylation of Alkenes and Alkynes Using β-S-Substituted Aldehydes: The Role of a Hemilabile P-O-P Ligand**

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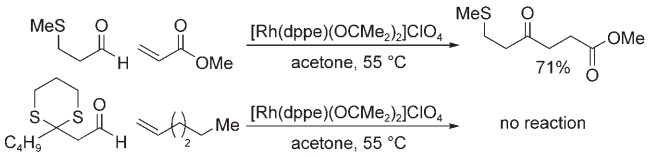
Hydroacylation reactions of alkenes and alkynes catalyzed by transition metals are examples of the growing number of transformations which form carbon–carbon bonds based on C–H-bond activation.[1] In particular, hydroacylation reactions offer an atom-economic entry to a variety of ketone-containing products.[2,3] Although intramolecular reactions that afford cyclopentanones are well established,[4] access to larger ring systems[5] and intermolecular reactions remain a considerable challenge.[6] We recently described a intermolecular rhodium-catalyzed reaction based on the use of β-S-substituted aldehydes.[7] Although this method had advantages over previous protocols, in that the use of alkyl aldehydes under mild reaction conditions (55–65 °C) is permitted, several limitations remained. Paramount among these were the need to use electron-poor alkenes to achieve good reactivity (Scheme 1) and the use of [Rh(dppe)-(acetone)$_2$]ClO$_4$[4a] as the catalyst. Although this catalyst performs relatively well in intermolecular reactions, the need to generate it immediately before use from the hydrogenation of [Rh(dppe)(nbd)]ClO$_4$ (nbd = norbornadiene) considerably detracts from its utility.[8] We document herein the development of a highly active hydroacylation catalyst that can be



Scheme 1. Intermolecular hydroacylation. dppe = 1,2-bis(diphenylphosphanyl)ethane.

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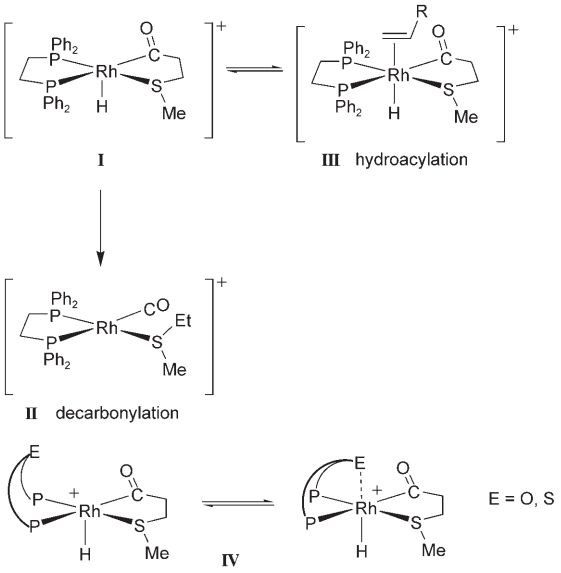
generated using commercial components without recourse to hydrogenation. In addition, we provide a structural study accounting for the enhanced reactivity of our new system, including the characterization of a rare acyl–rhodium hydride intermediate.

To achieve successful metal-catalyzed hydroacylation reactions, the intermediate acyl–metal species must be stabilized. Although the β-S-substituents on S-substituted aldehydes perform this function well with activated compounds,[9] the system fails with less reactive substrates such as unfunctionalized alkenes; in these cases decarbonylation of the putative five-coordinate acyl hydride intermediate and catalyst decomposition results (**I**→**II**, Scheme 2). We reasoned that use of a ligand capable of providing additional

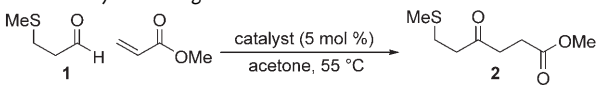


Scheme 2. Intermediate cationic rhodium species.

coordinative stabilization to the acyl–metal intermediate should deliver a more robust system, and speculated that incorporation of a hemilabile[10] substitutent on the ligand would provide extra stabilization to the cationic rhodium center while still allowing the necessary latent-vacant coordination site for the reaction to proceed (**IV**, Scheme 2). Related arguments have been used to account for the higher turnover numbers that have been observed when excess alkene was employed.[11] In our system, the use of additional alkene provided no benefit.

To explore this idea, we studied the union of the thioether-substituted aldehyde **1** and methyl acrylate, and employed a variety of catalysts (Table 1). The reaction using the standard catalyst $[Rh(dppe)(acetone)_2]ClO_4$ takes 90 minutes (entry 1, Table 1). Replacing dppe with the rigid P-O-P ligand xantphos (Figure 1) resulted in complete loss of reactivity. However, by using the more flexible variant, dpephos, complete conversion was achieved in only 60 minutes (entries 2 and 3, Table 1). The analogous thio- and methylene-bridged versions of dpephos (ligands **3** and **4**) failed to generate active catalysts (entries 4 and 5, Table 1).

Table 1: Catalyst investigation.[a]



Entry	Catalyst	Conv. [%][c]	*t*
1	$[Rh(dppe)(nbd)]ClO_4$	100[b]	90 min
2	$[Rh(xantphos)(nbd)]ClO_4$	0	48 h
3	$[Rh(dpephos)(nbd)]ClO_4$	100	60 min
4	[Rh(**3**)(nbd)]ClO_4	0	48 h
5	[Rh(**4**)(nbd)]ClO_4	0	48 h
6	$[Rh(dpephos)(nbd)]PF_6$	100	4 h
7	$[Rh(dpephos)[nbd)]BAr^F{}_4$	100	75 min
8	$[Rh(dpephos)(nbd)]CB_{11}H_6Cl_6$	100	30 min
9	$[Rh(dpephos)(nbd)]CB_{11}H_6Br_6$	100	45 min
10[d]	$[\{Rh(cod)Cl\}_2]$/dpephos/$Ag(CB_{11}H_6Cl_6)$	100	45 min
11[d]	$[\{Rh(cod)Cl\}_2]$/dpephos/$Ag(ClO_4)$	100	90 min

[a] Conditions: aldehyde (1.0 equiv), methyl acrylate (2.0 equiv), catalyst (5 mol%), acetone, 55 °C. The catalyst was generated by addition of H_2 (1 atm, 5 min, acetone), except for entries 10 and 11, for structures of the ligands tested, see Figure 1. [b] Product obtained as a 4:1 mixture of linear and branched regioisomers. Exclusive formation of the linear isomer was observed for all other entries. [c] Determined by ^1H NMR spectroscopy. [d] Catalyst generated from the simple combination of the three components.

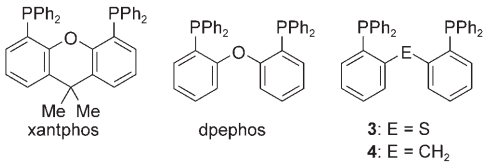


Figure 1. Ligands tested in Table 1

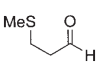
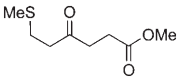
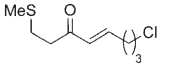
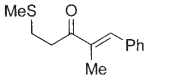
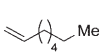
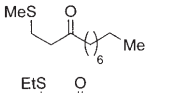
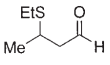
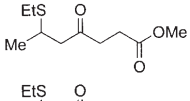
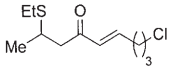
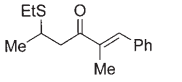
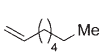
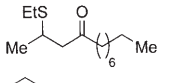
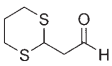
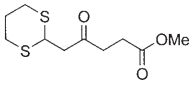
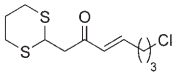
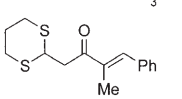
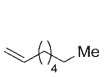
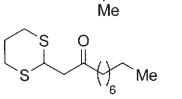
In an attempt to further increase the catalyst activity, we explored the use of alternative counterions. A screening of possible anion combinations showed that the weakly coordinating carborane anions $(CB_{11}H_6X_6)^-$ (X = Cl, Br)[12] gave the best turnovers, with reaction completion in only 30 and 45 minutes respectively, while use of $(BAr^F{}_4)^-$, $(ClO_4)^-$ and $(PF_6)^-$ gave no advantage (entries 6–9, Table 1). Monitoring the reactions by GC demonstrated that the relative rates showed the same variation on changing the anion. The rate enhancement for reactions catalyzed by cationic transition-metal centers partnered with weakly coordinating anions such as monoanionic carboranes is now well established,[13] and arises from a combination of the availability of reactive vacant sites and the stabilization of the active catalyst by the anion. At this stage, the active catalysts were being generated by hydrogenation of the [Rh(nbd)(phosphine)](anion) precursors, and, although we had identified several highly reactive systems, we still considered the need to activate with hydrogen gas a practical limitation. The use of the chelating aldehyde **1** now proved to be a real advantage, as simply combining $[\{Rh(cod)Cl\}_2]$ (cod = cycloocta-1,5-diene), dpephos, and $Ag(CB_{11}H_6Cl_6)$ generated an active catalyst that achieved complete conversion in only 45 minutes (entry 10, Table 1). A catalyst incorporating the $(ClO_4)^-$ counterion could be generated in a similar way, and 100% conversion was reached in 90 minutes (entry 11, Table 1).[14] Using the ligand

dpephos provides an additional advantage, in that the reactions with methyl acrylate were now completely selective for the linear regioisomer; use of the original dppe-derived catalyst resulted in a 4:1 mixture of linear and branched isomers.[7a]

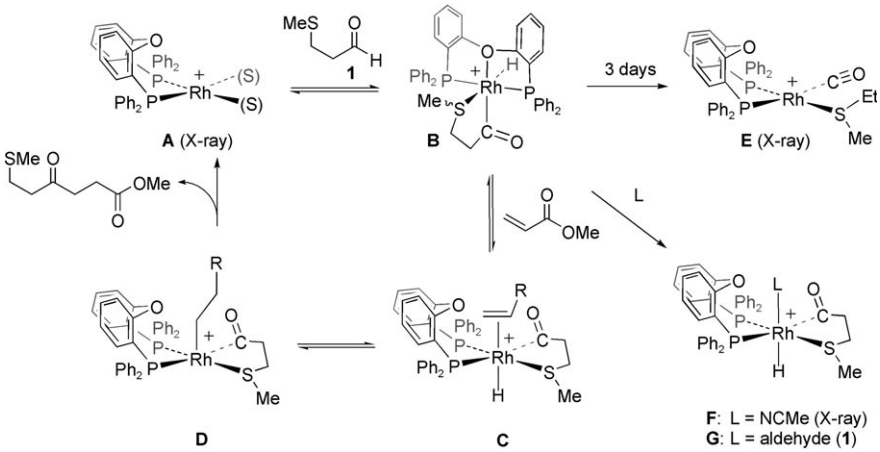
As we could generate a highly active catalyst without the need for hydrogen activation, we briefly evaluated the scope of the reactions promoted by these systems. From a practical standpoint, we elected to use the catalyst featuring the perchlorate anion as opposed to the more expensive carborane systems, even though use of the latter gave the best rates. Table 2 demonstrates that a catalyst generated from $[\{Rh(cod)Cl\}_2]$, dpephos, and $Ag(ClO_4)$ is effective at promoting the union of a variety of aldehyde, alkene, and alkyne components. In all cases, the efficiency of the reactions matches or surpasses that achieved previously. Of particular note are the reactions employing octene (entries 4, 8 and 12, Table 1); the products from these reactions were either inaccessible or only available in low yield[15] using the original catalyst system.

Encouraged by the fact that use of dpephos resulted in the best catalytic performance, we looked in more detail at the catalytic cycle. The active catalyst species $[Rh(dpephos)(OCMe_2)_2]CB_{11}H_6Cl_6$ (**A**, Scheme 3) was generated by hydrogenation of $[Rh(dpephos)(nbd)]CB_{11}H_6Cl_6$ in acetone. The solid-state structure of **A** (Figure 2) shows a square-planar Rh^I motif, with no close Rh···O interactions from the P-O-P ligand (O(3)–Rh 3.562(2) Å). The NMR spectroscopic data of a solution of the complex are in full accord with this structure. Addition of one equivalent of aldehyde **1** to catalyst **A** immediately generates a complex which was identified by spectroscopic methods as the acyl hydride $[Rh(dpephos)(H)(MeSCH_2CH_2CO)]CB_{11}H_6Cl_6$ (**B**). The room-temperature ^1H NMR spectrum shows a broadened hydride signal at $\delta = -8.75$ ppm as a doublet of triplets ($J(RhH) = 23$ Hz, $J(PH) \approx 1$ Hz) and a doublet in the $^{31}P\{^1H\}$ NMR spectrum, suggesting a fluxional process that renders the phosphine atoms equivalent. On cooling (−93 °C), the $^{31}P\{^1H\}$ NMR spectrum displays tightly coupled AB systems that show *trans* PP coupling, at $\delta = 26.8$, 25.9 ppm ($J(RhP) = 125$ Hz, $J(PP) = 303$ Hz), while the ^1H NMR spectrum reveals a single hydride resonance at $\delta = -8.62$ ppm that shows *cis* coupling to phosphorus. On the basis of this data, we assign the structure at low-temperature to be **B**, in which the dpephos coordinates *mer* with the metal, possibly with a coordinated oxygen atom. Complexes containing *trans*-spanning dpephos with a coordinated oxygen are known.[16] We assign the hydride as being opposite to the sulfur, as it is unlikely to reside opposite to the highly *trans*-influencing acyl ligand. The relatively large $J(RhH)$ coupling constant (23 Hz) is consistent with this. The fluxional processes at room temperature could possibly proceed via a five-coordinate intermediate with either the oxygen or sulfur atoms not

Table 2: Intermolecular hydroacylation using the new catalyst system.[a]

Entry	Aldehyde	Alkene/ alkyne	Product	*t* [h]	Yield [%][b]
1				1	74
2				1	82
3				16	80
4				24	70
5				16	81
6				16	97
7				24	73
8				48	61
9				4	75
10				4	87
11				24	82
12				48	89

[a] Conditions: aldehyde (1.0 equiv), alkene, or alkyne (2.0 equiv), $[\{Rh(cod)Cl\}_2]$ (2.5 mol%), dpephos (5 mol%), $Ag(ClO_4)$ (5 mol%), acetone, 55 °C. [b] Yields of isolated single isomers.



Scheme 3. Proposed mechanism for the hydroacylation reaction. Compound structures confirmed by X-ray analysis are indicated.

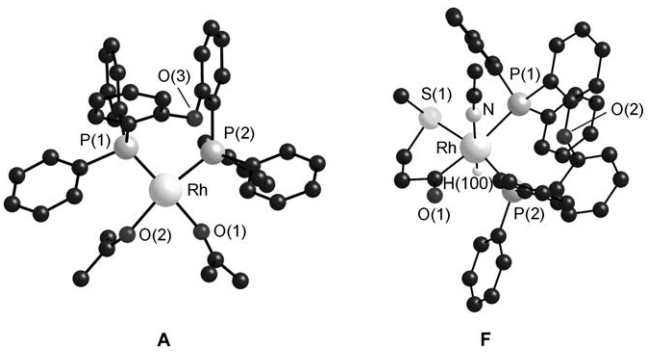


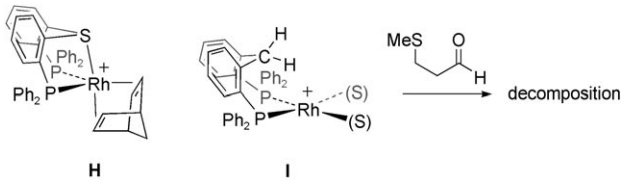
Figure 2. Solid-state structures of **A** and **F**. Selected bond distances [Å] and angles [°]: **A** Rh–O(1) 2.154(2), Rh–O(2) 2.126(4), Rh–O(3) 3.562(1), Rh–P(1) 2.202(5), Rh–P(2) 2.198(1), P(1)-Rh-P(2) 96.23(2); **F** Rh–C(41) 2.039(4) Rh–P(1) 2.508(1), Rh–P(2) 2.305(1), Rh–S(1) 2.372(1), Rh–O(2) 4.271(1), P(1)-Rh-P(2) 100.37(3).

bound, although we favor the former because of the isolation of complex **F** (described below). Complex **B** is stable to decarbonylation in solution at room temperature for an appreciable time ($t_{1/2} = 24$ h), although after three days smooth conversion of **B** into the decarbonylated product **E** is observed, and attempts to recrystallize **B** also led to the decarbonylated product **E** (see the Supporting Information for the solid-state structure).

Support for the facile decoordination of the oxygen atom in the dpephos ligand comes from addition of a slight excess of aldehyde **1** or acetonitrile to **B** which results in the instant formation of $[Rh(dpephos)(L)(H)(MeSCH_2CH_2CO)]CB_{11}H_6Cl_6$ **F** (L = MeCN) or **G** (L = **1**), in which the oxygen atom is no longer bound. The solid-state structure of **F** (Figure 2) confirms the acyl–hydride motif, with the acetonitrile ligand *trans* to the (located) hydride ligand. The strong *trans* influence of the acyl ligand is clearly demonstrated in the two Rh−P bond lengths that differ by 0.2 Å. NMR data suggest two isomers in solution. Given that in the $^{31}P\{^1H\}$ NMR spectrum there is a large difference in the J(RhP) coupling constants for the two inequivalent phosphines (that is: 150 and 65 Hz), this suggests that the acyl ligand lies *trans* to a phosphine, and therefore we assign structures to these isomers in which either the hydride and ligand (L), or the sulfur and L have swapped places.

Compound **F** is a model for the putative alkene adduct **C** in the hydroacylation cycle (Scheme 3). Moreover, **B** and **F** can enter directly into the catalytic cycle, as addition of alkene immediately results in catalytic turnover. Acyl–hydridorhodium complexes resulting from the addition of simple aldehydes are rare[17] as they generally suffer from decarbonylation,[18] and as far as we are aware **B** and **F** represent true examples (rather than model systems) of such species, which are also competent in the catalytic hydroacylation of useful substrates.[19] Such complexes have often been suggested but not experimentally observed. Presumably the dpephos ligand temporarily blocks a vacant site on **B** necessary for decarbonylation[17d,18] but it is able to move aside to allow the coordination of substrate, whereas in **F** the acetonitrile fulfils this role.

Support for this hypothesis comes from varying the ligand set to change the coordinating properties of the ligand. Use of ligand **3**, in which the thioether would be expected to bind strongly, results in the complex, $[Rh(\mathbf{3})(nbd)]CB_{11}H_6Cl_6$ (**H**, Scheme 4), in which the sulfur binds so effectively that the



Scheme 4. Additional complexes evaluated as hydroacylation catalysts. (S) = acetone solvent.

resulting 18-electron complex does not react with H_2 (see the Supporting Information for the X-ray structure). Conversely, the methylene-bridged ligand **4**, which can provide no additional stabilization, can be used to form $[Rh(\mathbf{4})(acetone)_2]CB_{11}H_6Cl_6$ (**I**, Scheme 4), but on addition of aldehyde **1**, very rapid (5 min) decomposition results and we observe no acyl hydride intermediate. Finally, $[Rh(dppe)(acetone)_2]CB_{11}H_6Cl_6$ reacts with **1** to form an acyl hydride intermediate that decomposes within one hour to afford a mixture of products—one of which we have identified as the product of decarbonylation, $[Rh(dppe)(CO)(SMeEt)]CB_{11}H_6Cl_6$.

In conclusion, we have reported a new, more efficient catalyst for intermolecular hydroacylation reactions of alkenes and alkynes employing β-S-substituted aldehydes. The catalyst can be generated from the simple combination of Rh^I salt, counterion, and ligand, and hydrogenation is unnecessary. The catalyst so formed allows previously unreactive substrates to participate in efficient coupling processes. Mechanistic studies have established the intermediacy of a key acyl–hydridorhodium species, and have also demonstrated that a hemilabile[10] oxygen atom of the P-O-P ligand is responsible for the increased stability of the active catalyst. Application of this catalyst-stabilization/activation concept to alternative processes is underway and will be reported in due course.

Experimental Section

Representative procedure using the catalyst generated from $[\{Rh(cod)Cl\}_2]$, dpephos, and $Ag(ClO_4)$ to prepare ketone **2** (Table 2, entry 1): Acetone (1.5 mL) was added under argon to $[\{Rh(cod)Cl\}_2]$ (3.7 mg, 0.0075 mmol) followed by silver perchlorate (3.1 mg, 0.015 mmol). The resulting mixture was stirred at room temperature for 10 min. After this time dpephos (8 mg, 0.015 mmol) was added and the mixture was stirred for a further 15 min. Subsequently 3-(methylthio)propionaldehyde (**1**, 30 μL, 0.3 mmol) was added, immediately followed by methyl acrylate (54 μL, 0.6 mmol). The resulting solution was heated and stirred at 55 °C for 90 min. The solution was then cooled to room temperature, concentrated in vacuo, and purified by flash chromatography (4:1 Hexane/EtOAc) giving **2** as a colorless oil (42 mg, 74 % yield); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.68$ (3H, s), 2.71–2.81 (6H, m), 2.61 (2H t, $J = 6.3$ Hz), 2.11 ppm (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$):

δ = 207.1, 173.2, 51.9, 42.5, 37.3, 27.9, 27.7, 15.79 ppm. The data was consistent to those reported in the literature.[7a]

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Keywords: C–H activation · hemilabile ligands · homogeneous catalysis · intermolecular hydroacylation · rhodium

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