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Inter- and intramolecular hydroacylation of alkenes employing a bifunctional catalyst system†

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Based on a conceptually innovative bifunctional P,N ligand, an efficient protocol for the rhodium-catalyzed inter- and intramolecular hydroacylation of alkenes has been developed.

The hydroacylation of alkenes has the potential to become an attractive atom-economic[1] synthetic method for the preparation of ketones from aldehydes *via* transition metal-catalyzed C–H bond activation.[2] However, decarbonylation of the intermediate acyl-metal hydride complex is a severe side reaction in particular for intermolecular hydroacylation reactions. Many attempts have been made to prevent the undesired decarbonylation pathway.[3] Thus, efficient methods rely on stabilization of the acyl metal hydride complex through heteroatom chelation,[4] but the request for additional donor sites in the aldehyde substrate sets limitations to the substrate scope. A more general concept to avoid decarbonylation was developed by Jun *et al.* His strategy relies on the *in situ* masking of the aldehyde function *via* the corresponding imine derived from 2-amino-3-picoline as the cocatalyst during the catalytic cycle (Fig. 1).[5] Unfortunately, in many cases high loadings (between 20 and 100 mol%) of the aminopicoline cocatalyst are necessary to get an efficient turnover.[6] We wondered whether tethering a phosphine binding site to the pyridine ring of this cocatalyst, thus generating a new bifunctional catalyst system, could be a more efficient solution (Fig. 1). Herein, we disclose the design, synthesis and application of such a bifunctional ligand **L** in the rhodium-catalyzed inter- and intramolecular hydroacylation of alkenes using a 1 : 1 Rh/**L** (5–10 mol%) ratio, thus reducing significantly the amount of aminopyridine.

The catalyst design was based on the following reflections: the aminopicoline moiety of **L** would on the one hand act as a reversibly bound directing group[7] allowing for facile C–H activation while simultaneously preventing the undesired decarbonylation through formation of an imine intermediate. Integration of the phosphine function would on the other hand, not only form an active hydroacylation catalyst, but also enhance the binding constant of the directing group to the catalytically active rhodium center and would thus increase effective molarity of the rhodium catalyst, further promoting the C–H activation step. Finally, the role of the 3-positioned methyl group would be to induce an imine conformation, which will locate the imino C–H bond in close proximity to the catalytically active metal center, again facilitating the oxidative addition of the C–H bond (Fig. 1). The use of a cocatalyst would thus become unnecessary.

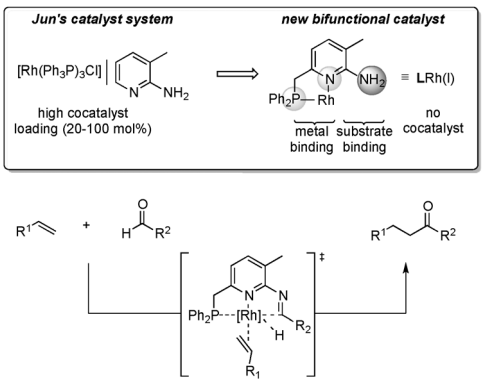
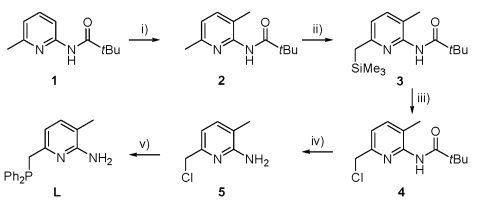


Fig. 1 Hydroacylation of alkenes: concept for a new bifunctional catalyst system **L**Rh(I) and the proposed transition state.

The synthetic approach to ligand **L** is depicted in Scheme 1. *ortho*-Lithiation of 6-methyl-2-(pivaloylamino)-pyridine (**1**) with *n*-BuLi and methylation of the resulting organo lithium species with methyl iodide gave 3,6-dimethyl-2-(pivaloylamino)-pyridine (**2**). Selective deprotonation of the methyl group in



Scheme 1 Preparation of **L**. Conditions: (i) (1) *n*-BuLi, THF, 1.5 h, −78 °C to 0 °C; (2) MeI, 16 h, 0 °C to rt (74%); (ii) (1) Schlosser's base (DIPA, *n*-BuLi and *t*BuOK), THF, −78 °C; (2) TMSCl, THF, 16 h, −78 °C to 0 °C (72%); (iii) CsF, C_2Cl_6, MeCN, 5 h, 60 °C (88%); (iv) HCl, 16 h, reflux (72%); (v) (1) Na, NH_3, 10 min, −78 °C; (2) PPh_3, 2 h, −78 °C; (3) **5**, 16 h, rt (80%).

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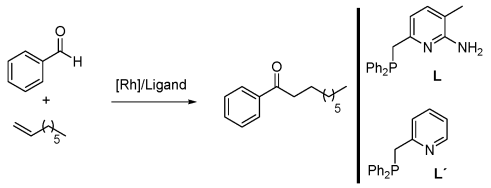
† Electronic supplementary information (ESI) available: Ligand **L**, syntheses of substrates, NMR spectra and experimental details. See DOI: 10.1039/c1cc10683j

Table 1 Optimization of intermolecular hydroacylation conditions[a]



Entry	[Rh]/Ligand (1/1) (mol%)	Isolated yield (%)
1	$[Rh(PPh_3)_3Cl]$ (5)	0
2[b]	$[Rh(PPh_3)_3Cl]$ (5)	76
3	$[Rh(COD)Cl]_2$/**L** (2.5)	45
4	**$[Rh(COD)Cl]_2$/L (5)**	**82**
5[c]	$[Rh(COD)Cl]_2$/**L** (5)	0
6[d]	$[Rh(COD)Cl]_2$/**L** (5)	51
7[e]	$[Rh(COD)Cl]_2$/**L** (5)	78
8	[Rh(COD)acac]/**L** (10)	64
9	$[Rh(CO)_2Cl]_2$/**L** (5)	31
10	$[Rh(COD)Cl]_2$/**L′** (5)	0

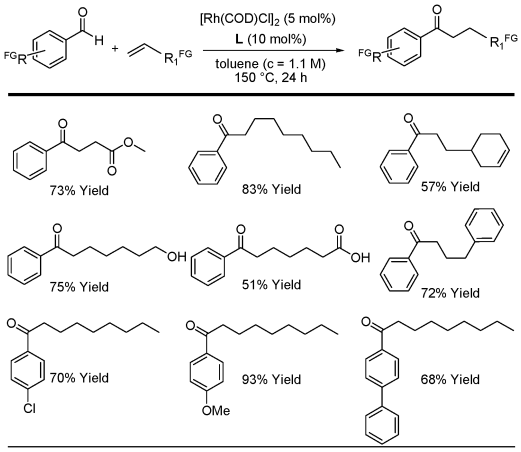
[a] Reaction conditions: 0.22 mmol of benzaldehyde and 0.55 mmol of 1-octene, the rhodium source and the ligand were heated in toluene (200 μL) in a closed Schlenk vessel at 150 °C for 24 h. [b] 2-Amino-3-picoline/$[Rh(PPh_3)_3Cl]$ = 4/1 in 200 μL of toluene. [c] [Rh]/**L** = 1/3. [d] *T* = 100 °C (conversion 52%). [e] *T* = 100 °C, 40 h (conversion 80%).

the 6-position was achieved with Schlosser's base (DIPA, *n*-BuLi and *t*BuOK); subsequent quenching with trimethylsilylchloride afforded silane **3** in 72% yield. Treatment of **3** with CsF and C_2Cl_6 yielded the chloride **4** (88%), which after deprotection and further substitution of the chlorine atom with diphenylphosphide furnished **L**.

Initial experiments focused on the reaction of benzaldehyde with 1-octene to optimize the conditions (Table 1).

Wilkinson's catalyst on its own was completely inefficient in this transformation (Table 1, entry 1). However, upon adding 2-amino-3-picoline (20 mol%) as a cocatalyst, appreciable yield of 76% of the ketone product could be obtained as already reported by Jun *et al.* (entry 2).[5] Interestingly, employing the bifunctional ligand **L**, a similar yield could be reached with 5 mol% of $[Rh(COD)Cl]_2$ (entry 4) *without the need for an additional cocatalyst*. Increasing the amount of ligand **L** to 3 : 1 shuts down the catalyst activity presumably due to irreversible blocking of free coordination sites (entry 5). Decreasing the reaction temperature to 100 °C reduced the catalyst activity; however, chemoselectivity remained high (entry 6). Extending the reaction time under these reduced temperature conditions to 40 h led to a better yield (78%, entry 7). Other rhodium precursors proved less efficient (entries 8 and 9). A control experiment with ligand **L′**, lacking the amino functionality, resulted in a complete loss of activity (entry 10), thus demonstrating the importance of the amino group within **L** for the reaction to proceed most likely through prevention of decarbonylation *via* the chelated transition state proposed in Fig. 1.

After having established optimized conditions (Table 1, entry 4), we extended the scope of this transformation to a wide range of electronically and structurally diverse alkenes and substituted benzaldehydes. The results of these studies are listed (Scheme 2). Reasonable yields ranging from 83% to



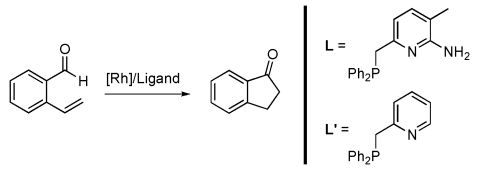
Scheme 2 Intermolecular hydroacylation of alkenes with aromatic aldehydes.

51% were obtained for the addition of various terminal alkenes to benzaldehyde. The protocol is tolerant to a variety of functional groups on the alkene moiety including ester, hydroxyl, carboxylic acid as well as an internal alkenyl group. Both electron donating as well as electron withdrawing substituents on the aryl benzaldehyde system are efficient reaction partners, thus highlighting the wide functional group tolerance of this catalyst system.

We next turned our attention toward the intramolecular hydroacylation reaction and chose *o*-vinylbenzaldehyde as a model substrate to optimize the reaction conditions, since its chemoselective hydroacylation has been found to be challenging (see Table 2). Furthermore, the resulting 1-indanone core is a structural element found in many natural products and an important building block for the development of other biologically active compounds and pharmaceutical agents.[8]

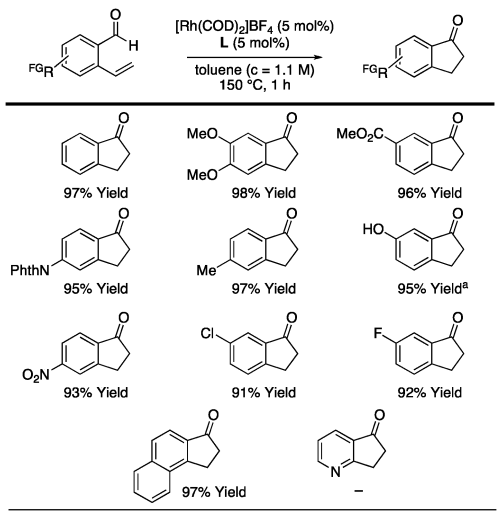
In a previous report from Fairlie and Bosnich, a maximum of 30% of 1-indanone in the rhodium-catalyzed hydroacylation of *o*-vinylbenzaldehyde was obtained.[9] Morehead and coworkers succeeded in obtaining 95% of this product; however, a slow syringe pump addition over a long period of 18 h proved necessary to suppress side reactions.[10] Also in our hands, poor results were attained with either Wilkinson's catalyst (entry 1, Table 2) or Jun's system (entry 2). Conversely, using 10 mol% of neutral $[Rh(COD)Cl]_2$ and bifunctional ligand **L** at 150 °C (entries 3 and 4), excellent yields ranging from 95% to 99% were obtained. Decreasing the loading of this neutral catalyst to 5 mol% consequently lowered the yield of the reaction ((46%) entry 5), while an excellent yield (96%) was maintained upon moving to the cationic precursor $[Rh(COD)_2]BF_4$ (entry 6). When reducing the catalyst loading from 2.5 mol% to 0.5 mol%, appreciable yields were still observed (84% to 67%, entries 7 and 8). A similar control experiment with ligand **L′**, lacking the amino functionality, furnished also here a significantly less efficient catalyst (42%, entry 9). Additionally, the formation of polystyrene was observed with this catalyst (entry 9), stemming from the polymerization of decarbonylated *o*-vinylbenzaldehyde. This observation reinforces the importance of the amino group within **L** for the prevention of decarbonylation.

Table 2 Optimization of intramolecular hydroacylation conditions[a]



Entry	[Rh]/Ligand (1/1) (mol%)	Conditions	Isolated yield (%)
1	$[Rh(PPh_3)_3Cl]$ (10)	24 h, 150 °C	22
2[b]	$[Rh(PPh_3)_3Cl]$ (10)	24 h, 150 °C	<5
3	$[Rh(COD)Cl]_2$/**L** (5)	24 h, 150 °C	99
4	$[Rh(COD)Cl]_2$/**L** (5)	2 h, 150 °C	95
5	$[Rh(COD)Cl]_2$/**L** (2.5)	2 h, 150 °C	46
6	**$[Rh(COD)_2]BF_4$/L (5)**	**1 h, 150 °C**	**96**
7	$[Rh(COD)_2]BF_4$/**L** (2.5)	2 h, 150 °C	84
8	$[Rh(COD)_2]BF_4$/**L** (0.5)	6 h, 150 °C	67
9	$[Rh(COD)_2]BF_4$/**L′** (5)	1 h, 150 °C	42

[a] Reaction conditions: 0.22 mmol of *o*-vinylbenzaldehyde, the rhodium source and the ligand were heated in 200 μL of toluene in a closed Schlenk vessel. [b] 2-Amino-3-picoline/$[Rh(PPh_3)_3Cl]$ = 4/1 in 200 μL of toluene.



Scheme 3 Intramolecular hydroacylation of *o*-vinylbenzaldehyde derivatives ([a]reaction time = 4 h).

With a highly active catalyst system in hand, (Table 2, entry 6), we investigated the scope of our protocol by diversifying the backbone of *o*-vinylbenzaldehyde (see the ESI† for the synthesis and characterization of the substrates) (Scheme 3).

The catalyst tolerates electron donating, neutral as well as electron withdrawing substituents at the aromatic nucleus. A wide range of functional groups including carboxylic esters, halogens (chlorine and fluorine), nitro groups as well as a free phenol function is compatible with the reaction conditions and excellent yields are obtained. Conversely, employing 2-vinylpyridine-3-carbaldehyde did not show any reactivity, and the starting material was recovered quantitatively: the substrate may itself act as a competitive ligand for **L** at the rhodium center thus preventing the turnover.

In summary, we have developed a new catalyst system that allows for both efficient inter- and intramolecular hydroacylation of alkenes. The efficiency of the catalyst originates from an innovative bifunctional ligand, which most likely acts through reversible substrate binding thus facilitating C–H activation, preventing decarbonylation and controlling chemoselectivity. Future studies will address the mechanism as well as further applications of bifunctional ligand **L** in homogeneous catalysis.

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