JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

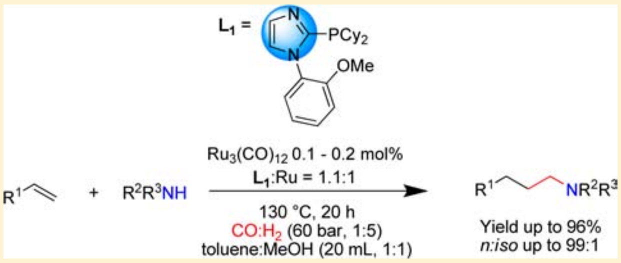
Efficient and Regioselective Ruthenium-catalyzed Hydroaminomethylation of Olefins

Lipeng Wu, Ivana Fleischer, Ralf Jackstell, and Matthias Beller*

Leibniz-Institut für Katalyse e.V., an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

Ⓢ *Supporting Information*

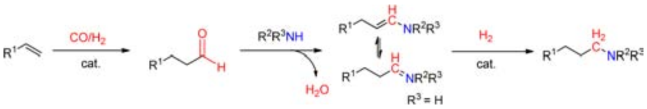
ABSTRACT: An efficient and regioselective ruthenium-catalyzed hydroaminomethlyation of olefins is reported. Key to success is the use of specific 2-phosphino-substituted imidazole ligands and triruthenium dodecacarbonyl as catalyst. Both industrially important aliphatic as well as various functionalized olefins react with primary and secondary amines to give the corresponding secondary and tertiary amines generally in high yields (up to 96%) and excellent regioselectivities (*n*/*iso* up to 99:1).



INTRODUCTION

Amines constitute essential pharmaceutically and biologically active compounds, dyes and agrochemicals, which are produced on significant industrial scale.[1] A plethora of methods is available for the synthesis of these compounds. Most commonly, reductive amination of carbonyl compounds[2] and stoichiometric waste-generating nucleophilic substitutions of alkyl halides are performed. In addition, hydrocyanation of alkenes[3] followed by reduction,[4] and modern catalytic technologies such as "borrowing hydrogen" reaction[5] and hydroaminations[6] are known. Unfortunately, in the latter case selective transformation to the linear amines from readily available aliphatic olefins is still not possible. However, applying hydroformylation conditions in the presence of amines, the so-called hydroaminomethylation reaction takes place.[7] This three step domino process[8] is of particular interest in terms of atom-efficiency, selectivity, and applicability (Scheme 1). First, the olefin is hydroformylated to the corresponding aldehyde, which then reacts with the amine to form the enamine or imine. Subsequent reduction provides the desired amine. Clearly, the metal used in hydroaminomethylation must be active and selective in both the hydroformylation and the hydrogenation step. Aldol-type side reactions may take place under the basic conditions if the reduction is slow. Moreover, the amine can act as σ-donor ligand and thus compete with the original ligand.

Scheme 1. Hydroaminomethylation of Alkenes

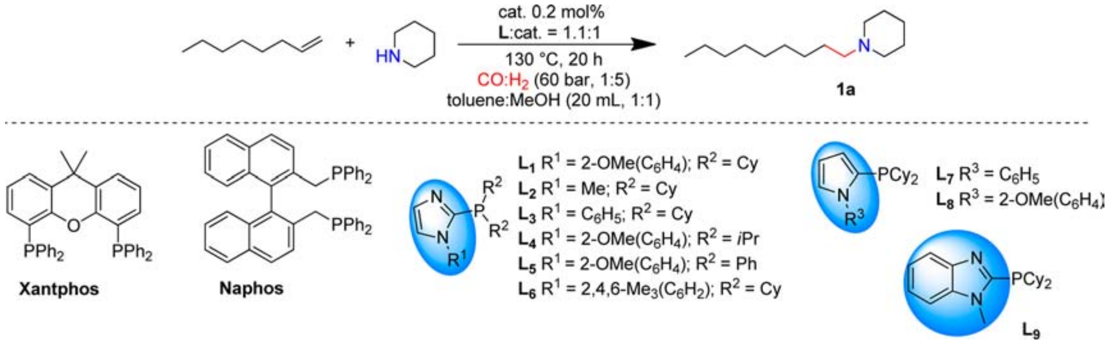


Although the first hydroaminomethylation reaction was discovered by Reppe already more than 60 years ago,[9] it was not until the 1990's when more efficient and versatile applications were reported especially by Eilbracht and co-workers.[10] Since then, our group has developed rhodium catalysts based on modified Naphos- and Xantphos-ligands for *n*-selective hydroaminomethylation of terminal and internal olefins as well as other rhodium complexes for the preparation of bioactive compounds.[11] More recently, notable catalyst improvements based on rhodium and novel synthetic applications were reported by the groups of Zhang,[12] Vogt,[13] Alper,[14] Kalck,[15] and others.[16] In addition, methodology development on biphasic systems,[17] and microwave-assisted hydroaminomethylations were reported.[18]

In contrast to all these efforts, the application of alternative metals apart from expensive rhodium was rarely reported. The reason for the underrepresentation of other metals in this reaction is mainly their lower activity in the hydroformylation step.[19] In this regard it is interesting that Nozaki and co-workers reported recently the application of [Cp*Ru] complexes for hydroformylation of propene and 1-decene using bisphosphite and bisphosphine ligands.[20] Parallel to this work we applied 2-phosphino-substituted imidazole ligands[21] for ruthenium(0)-catalyzed hydroxymethylation reactions.[22] Based on these results and our continuous interest on hydroformylation and related reactions we investigated the possibility of ruthenium-catalyzed hydroaminomethylations. Surprisingly, there exists only one study on the ruthenium-catalyzed hydroaminomethylation reaction of propene by Keim and Schaffrath using carbon monoxide.[23] To the best of our knowledge, no other olefins were explored and no general methodology has been developed. In addition, Eilbracht and co-workers reported on $Ru_3(CO)_{12}$-catalyzed hydroaminomethylation under reverse water-gas-shift-reaction conditions.[24] However, high catalyst loading and harsh reaction conditions were applied. Herein, we present a general and practical ruthenium-catalyzed hydroaminomethylation reaction of in-

Received: December 16, 2012
Published: February 18, 2013

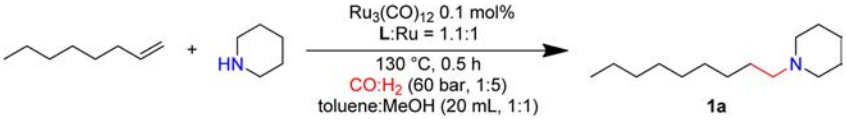
Table 1. Ruthenium-Catalyzed Hydroaminomethylation of 1-Octene with Piperidine: Ligand Effect[a]



entry	catalyst	ligand	conversion[b] [%]	selectivity[b] [%] amine	selectivity[b] [%] linear amine	selectivity[b] [%] N-formyl piperidine	n/iso[b]
1	$Ru_3(CO)_{12}$	PPh_3	97	72	52	2	72:28
2	$Ru_3(CO)_{12}$	Xantphos	47	74	72	<1	97:3
3	$Ru_3(CO)_{12}$	Naphos	80	31	26	6	84:16
4	$Ru_3(CO)_{12}$	$\mathbf{L_1}$	>99	93	88	<1	95:5
5	$Ru_3(CO)_{12}$	$\mathbf{L_2}$	>99	90	85	<1	94:6
6	$Ru_3(CO)_{12}$	$\mathbf{L_3}$	>99	90	86	1	95:5
7	$Ru_3(CO)_{12}$	$\mathbf{L_4}$	99	91	86	<1	94:6
8	$Ru_3(CO)_{12}$	$\mathbf{L_5}$	98	69	65	<1	94:6
9	$Ru_3(CO)_{12}$	$\mathbf{L_6}$	>99	74	71	1	96:4
10	$Ru_3(CO)_{12}$	$\mathbf{L_7}$	83	35	29	2	83:17
11	$Ru_3(CO)_{12}$	$\mathbf{L_8}$	80	34	29	2	85:15
12	$Ru_3(CO)_{12}$	$\mathbf{L_9}$	98	64	61	1	94:6
13[c]	$[Rh(cod)_2]BF_4$	$\mathbf{L_1}$	>99	91	52	<1	57:43

[a] Reaction conditions: 20 mmol 1-octene, 24 mmol piperidine, 0.2 mol% $Ru_3(CO)_{12}$, 0.66 mol% ligand, 10 mL of MeOH, 10 mL of toluene, 10 bar CO, 50 bar H_2, 130 °C, 20 h. [b] Determined by GC analysis using isooctane as internal standard. [c] 0.6 mol% $[Rh(cod)_2]BF_4$, 2 h.

Table 2. Activities of 2-Phosphino-substituted Imidazole Ligands L_1–L_5[a]



entry	ligand	conversion[b] [%]	selectivity[b] [%] amine	selectivity[b] [%] linear amine	n/iso[b]	TOF [h^{-1}]
1	$\mathbf{L_1}$	78	85	82	97:3	440
2	$\mathbf{L_2}$	56	86	83	96:4	320
3	$\mathbf{L_3}$	75	76	73	96:4	380
4	$\mathbf{L_4}$	72	83	81	97:3	400
5	$\mathbf{L_5}$	81	70	67	95:5	380

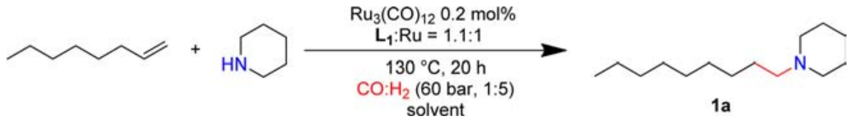
[a] Reaction conditions: 20 mmol 1-octene, 24 mmol piperidine, 0.1 mol% $Ru_3(CO)_{12}$, 0.33 mol% Ligand, 10 mL of MeOH, 10 mL of toluene, 10 bar CO, 50 bar H_2, 130 °C, 0.5 h. [b] Determined by GC analysis using isooctane as internal standard.

dustrially important and functionalized olefins with various amines using $Ru_3(CO)_{12}$/2-(dicyclohexylphosphino)-1-(2-methoxyphenyl)-1*H*-imidazole as catalyst system. This work extends the scope of Ru-catalyzed C–C bond forming reactions.[25,26]

■ RESULTS AND DISCUSSION

Initially, the ruthenium-catalyzed hydroaminomethylation of 1-octene with piperidine was systematically investigated. Based on our previous experience in hydroaminomethylations, a 1:1 mixture of MeOH and toluene was chosen as solvent for the variation of the ligand. In general, the reaction was performed at 130 °C with 0.2 mol% of $Ru_3(CO)_{12}$ under 60 bar pressure of CO and H_2 (CO/H_2 = 1:5). Using standard monodentate PPh_3 as ligand, only moderate amine selectivity (72%) was achieved due to the high extent of isomerization of the substrate (Table 1, entry 1). Besides, the regioselectivity (*n/iso* = 72:28) was also at moderate level. The bidentate *P*-ligands Xantphos and Naphos showed different activity in ruthenium-catalyzed hydroaminomethylation: low conversion (47%), moderate amine selectivity (74%), although high regioslectivity (*n/iso* = 97:3) were obtained with Xantphos (Table 1, entry 2), while Naphos gave 80% conversion with only 31% amine selectivity and somewhat lower regioselectivity (*n/iso* = 84:16) (Table 1, entry 3). To our delight, full conversion (>99%), high amine selectivity (93%) and regioselectivity (*n/iso* = 95:5) were obtained with the imidazole-substituted monophosphine ligand $\mathbf{L_1}$ (Table 1, entry 4). Therefore, the structural influence of the

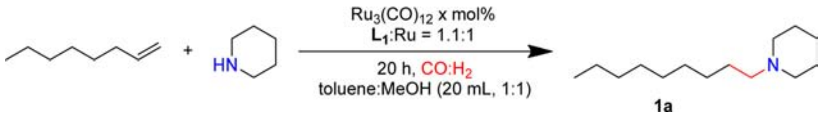
Table 3. Ruthenium-catalyzed Hydroaminomethylation of 1-Octene with Piperidine: Solvent Effect[a]



entry	solvent	conversion[b] [%]	selectivity[b] [%] amine	selectivity[b] [%] linear amine	selectivity[b] [%] *N*-formyl piperidine	*n/iso*[b]
1[c]	MeOH/Tol	>99	93	88	<1	95:5
2	Tol	99	85	80	<1	94:6
3	MeOH	99	84	79	1	94:6
4	EtOH	99	83	77	<1	93:7
5	THF	99	84	78	1	93:7
6	PC	90	44	42	1	96:4
7	NMP	98	61	57	<1	94:6

[a] Reaction conditions: 20 mmol 1-octene, 24 mmol piperidine, 0.2 mol% $Ru_3(CO)_{12}$, 0.66 mol% $\mathbf{L_1}$, 20 mL solvent, 10 bar CO, 50 bar H_2, 130 °C, 20 h. [b] Determined by GC analysis using isooctane as internal standard. [c] 10 mL MeOH and 10 mL toluene.

Table 4. Ruthenium-catalyzed Hydroaminomethylation of 1-Octene with Piperidine: Variation of Reaction Parameters[a]



entry	*x*	CO/H_2 [bar]	conversion [%][b]	selectivity [%][b] amine	selectivity [%][b] linear amine	selectivity [%][b] *N*-formyl piperidine	*n/iso*[b]
1	0.2	10:50	>99	93	88	<1	95:5
2	0.1	10:50	99	89	85	<1	95:5
3	0.05	10:50	99	85	81	2	95:5
4[c]	0.1	10:50	99	79	76	<1	96:4
5	0.1	10:40	99	84	79	1	94:6
6	0.1	7:35	99	87	83	1	95:5
7	0.1	5:25	99	76	71	<1	94:6
8	0.1	2:10	98	38	35	<1	94:6
9	0.1	20:40	99	81	77	2	95:5

[a] Reaction conditions: 20 mmol 1-octene, 24 mmol piperidine, *x* mol% $Ru_3(CO)_{12}$, 3.3*x* mol% $\mathbf{L_1}$, 10 mL of MeOH, 10 mL of toluene, 130 °C, 20 h. [b] Determined by GC analysis using isooctane as internal standard. [c] 120 °C.

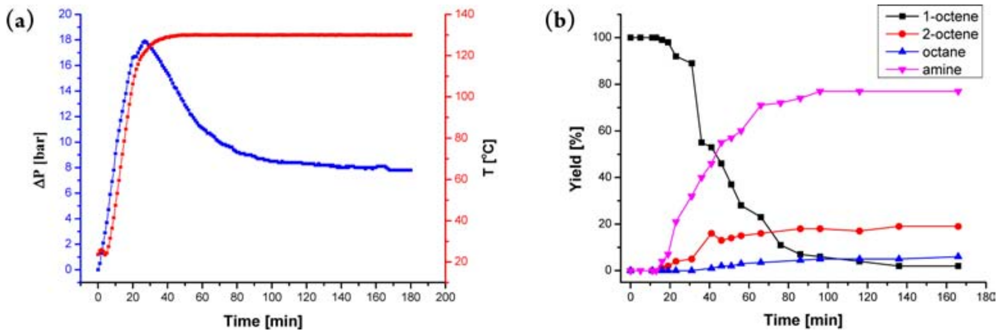
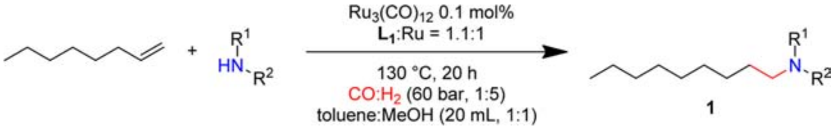
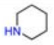
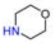
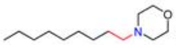
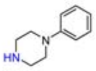
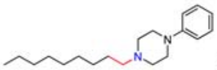
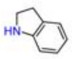
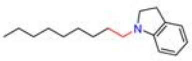
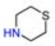
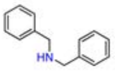
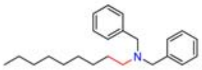
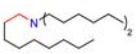
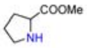
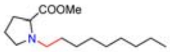
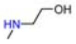
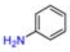
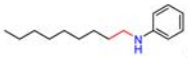
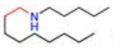
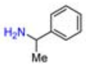
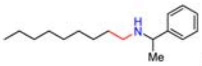
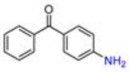
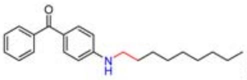
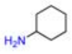
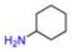
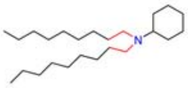


Figure 1. Ruthenium-catalyzed Hydroaminomethylation of 1-Octene and Piperidine: (a) Δp (Pressure change compared to initial pressure) curve and temperature curve. (b) Composition of the reaction mixture.

2-phosphino-substituted heterocyclic ligands $\mathbf{L_1}$−$\mathbf{L_9}$ was evaluated (Table 1, entries 4−12). Almost all these ligands tested afforded quantitative conversion with different levels of chemoselectivity. Ligands $\mathbf{L_1}$−$\mathbf{L_4}$ bearing different substituents on nitrogen or phosphorus provided high amine selectivity without significant differences (Table 1, entries 4−7). Though $\mathbf{L_5}$ and $\mathbf{L_6}$ showed high conversion, the amine selectivities were somewhat lower (Table 1, entries 8−9). Lower amine selectivity arose from the isomerization of the olefins. 2-Phosphino-substituted pyrole ligands $\mathbf{L_7}$ and $\mathbf{L_8}$ gave good conversion but only low chemo- and regioselectivity (Table 1, entries 10−11). Then, the benzimidazole derived ligand $\mathbf{L_9}$ was tested and gave quantitative conversion but moderate amine selectivity (Table 1, entry 12). Except using Naphos, negligible amounts of *N*-formyl piperidine were formed in all cases. Finally, the ligand $\mathbf{L_1}$ was tested with $[Rh(cod)_2]BF_4$. Compared with our Ru catalyst, the rhodium-based complex yielded similar amount of amine in shorter reaction time, but only 57:43 regioselectivity was achieved (Table 1, entry 13). In order to compare the activity of 2-phosphino-substituted

Table 5. Ruthenium-catalyzed Hydroaminomethylation of 1-Octene with Amines[a]



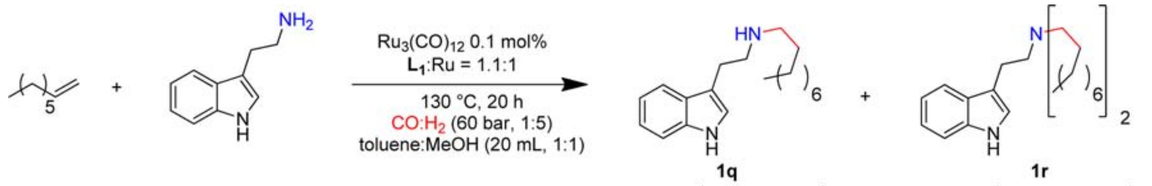
Entry	Amine	Major product **1**	GC yield [%][b]	Isolated yield [%][c]	*n/iso*[b]
1		 **1a**	88	81	95:5
2		 **1b**	90	85	94:6
3		 **1c**	89	80	93:7
4		 **1d**	84	74	94:6
5		 **1e**	90	77	93:7
6		 **1f**	10	8	92:8
7		 **1g**	89	83	93:7
8		 **1h**	87	61	96:4
9		 **1i**	84	79	95:5
10		 **1j**	91	73	94:6
11		 **1k**	76	68	94:6
12		 **1l**	71	62	93:7
13		 **1m**	82	77	93:7
14		 **1n**	47	36	96:4
15		 **1o**	83	76	94:6
16[d]		 **1p**	70	65	87:13

[a]Reaction conditions: 20 mmol 1-octene, 24 mmol amine, 0.1 mol% $Ru_3(CO)_{12}$, 0.33 mol% L_1, 10 mL of MeOH, 10 mL of toluene, 10 bar CO, 50 bar H_2, 130 °C, 20 h. [b]Determined by GC analysis using isooctane as internal standard. [c]Isolated yield after distillation or column chromatography. [d]20 mmol amine, 40 mmol olefins, 0.2 mol% $Ru_3(CO)_{12}$, 0.66 mol% L_1, 20 bar CO, 40 bar H_2 used.

imidazole ligands, the turnover frequency (TOF) values of the corresponding complexes were compared 30 min after the reaction temperature was reached. Again, ligand $\mathbf{L_1}$ performed best (Table 2, entry 1). A significant difference in reactivity was observed between ligands $\mathbf{L_2}$ and $\mathbf{L_5}$ (Table 2, entries 2 and 5). Whereas the conversion achieved with ligand $\mathbf{L_2}$ was moderate, the amine selectivity was particularly high. On the other hand, good conversion, but also higher extent of isomerization were obtained with $\mathbf{L_5}$.

Often in hydrogenation reactions the solvent has a significant influence on the reactivity and selectivity of the catalyst system. Hence, with the best ligand $\mathbf{L_1}$, the influence of different solvents was studied (Table 3). Compared with the mixture of methanol and toluene, lower chemoselectivity was achieved when the reaction was performed in pure toluene or methanol (Table 3, entries 2, 3). Similar results were obtained in ethanol and THF (Table 3, entries 4, 5). The use of propylene carbonate (PC) as a solvent led only to a moderate amine selectivity due to high extent of isomerization of 1-octene (Table 3, entry 6). The conversion and selectivity were slightly improved in NMP, but only to a moderate level (Table 3, entry 7).

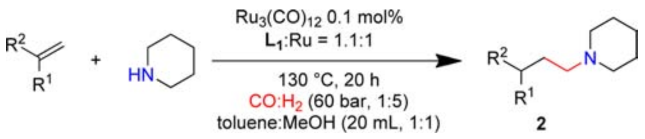
Scheme 2. Hydroaminomethylation of Tryptamine and 1-Octene[a]

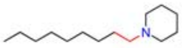
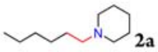
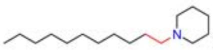
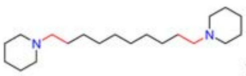
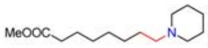
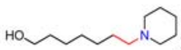
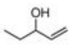
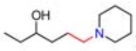
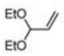
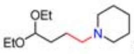
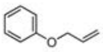
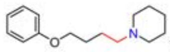
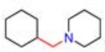
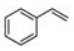
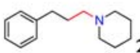
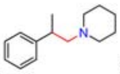
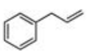
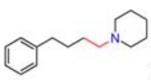
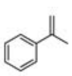
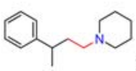


		1q GC Yield[b]	1q n/iso[b]	1r GC Yield[b]	1r n/iso[b]
10 mmol	12 mmol	55%	95:5	23%	96:4
10 mmol	20 mmol	63%	95:5	16%	94:6
24 mmol	12 mmol	33%	95:5	61%	96:4

[a]Reaction conditions as shown. [b]Determined by GC analysis using isooctane as internal standard.

Table 6. Ruthenium-catalyzed Hydroaminomethylation of Olefins with Piperidine[a]

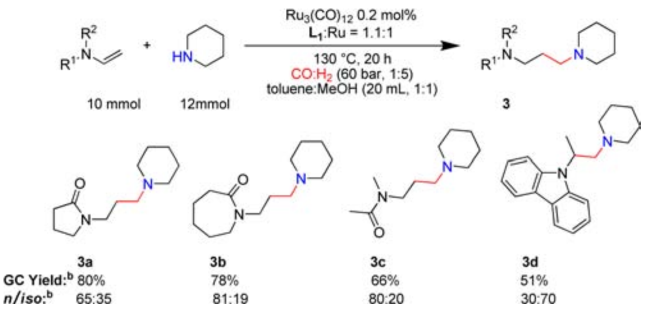


Entry	Alkene	Major product	GC yield [%][b]	Isolated yield [%][c]	n/iso[b]
1		 1a	88	81	95:5
2		 2a	82	80	93:7
3		 2b	83	80	95:5
4		 2c	85	80	93:7
5[d]		 2d	79	70	89:11
6[e]		 2e	78	67	95:5
7		 2f	91	85	95:5
8		 2g	84	76	99:1
9		 2h	75	64	86:14
10		 2i	34	30	98:2
11[f]		 2j	65	58	-
12[g]		 2k  2k'	96	80[i]	45:55
13		 2l	90	84	88:12
14[h]		 2m	64	55	>99:1

[a]Reaction conditions: 20 mmol olefin, 24 mmol piperidine, 0.1 mol% $Ru_3(CO)_{12}$, 0.33 mol% **L_1**, 10 mL of MeOH, 10 mL of toluene, 10 bar CO, 50 bar H_2, 130 °C, 20 h. [b]Selectivity was determined by GC analysis using isooctane as internal standard. [c]Isolated yield after distillation or column chromatography. [d]20 mmol olefin, 48 mmol piperidine, 0.2 mol% $Ru_3(CO)_{12}$, 0.66 mol% **L_1**, 20 bar CO, 40 bar H_2 used. [e]Performed with with 7 mmol olefin. [f]160 °C. [g]5 h. [h]40 h. [i]Combined yield.

Further efforts toward condition optimization are summarized in Table 4. The amount of $Ru_3(CO)_{12}$ can be reduced to 0.1 mol% without significant loss of activity (Table 4, entry 2). However, further lowering the catalyst loading resulted in lower amine selectivity, albeit same regioselectivity was obtained (Table 4, entry 3). Variation of the temperature showed that

Scheme 3. Hydroaminomethylation of Enamines with Piperidine[a]



[a]Reaction conditions: 10 mmol olefins, 12 mmol amine, 0.2 mol% $Ru_3(CO)_{12}$, 0.33 mol% $\mathbf{L_1}$, 10 mL of MeOH, 10 mL of toluene, 10 bar CO, 50 bar H_2, 130 °C, 20 h. [b]Determined by GC analysis using isooctane as internal standard.

130 °C was essential to achieve high amine selectivity (Table 4, entry 4). Reduction of partial hydrogen or overall pressure led to inferior results in means of chemoselectivity (Table 4, entries 5−9).

Next, the reaction progress of the ruthenium-catalyzed hydroaminomethylation of 1-octene with piperidine was examined under the optimized reaction conditions: 0.1 mol% $Ru_3(CO)_{12}$, 1.1 equiv of ligand $\mathbf{L_1}$ with 10 bar CO and 50 bar H_2 in MeOH/toluene mixture (1:1) at 130 °C. As depicted in Figure 1a the gas consumption started at 125 °C and the reaction rate decreased after 90 min. The explanation is obtained from the analysis of samples taken from the reaction mixture (Figure 1b). The conversion of 1-octene to the corresponding amine started at 125 °C. At the same time, isomerization of the double bond took place, albeit at lower rate. However, 1-octene was almost completely consumed after 90 min and 2-octene dominated in the system, which led to a slower isomerization-hydroaminomethylation pathway. To our surprise, neither aldehyde, enamine nor imine were detected during the whole reaction time, which indicates fast reactions of the aldehyde with the amine and subsequent hydrogenation.[27]

Although the mechanism of ruthenium-catalyzed hydroaminomethylation is still not clear yet, we propose a similar mechanism to Nozaki's work[20] and commonly accepted rhodium-catalyzed hydroformylations.[28] First, a monometallic Ru-hydride species should be formed from the triruthenium-dodecacarbonyl complex in the presence of ligand, CO, and H_2. Coordination and insertion of the alkene gives the respective alkyl complex. After migratory insertion of CO, the corresponding ruthenium acyl species is formed, which undergoes hydrogenolysis to release the aldehyde. Condensation of amine and the aldehyde forms the enamine or imine. Finally, reduction of the enamine or imine provides the desired amine in the last step. In contrast to most rhodium-catalyzed hydroaminomethylations, here the hydrogenation of the imine (enamine) should not constitute the rate determining step of the reaction sequence since these intermediates are not detected.

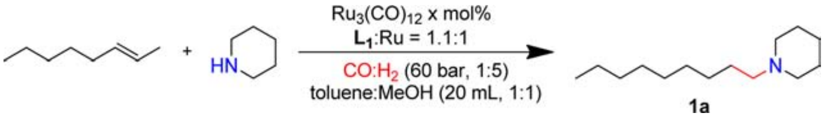
Next, the compatibility and limitations of our ruthenium-catalyzed hydroaminomethylation protocol were tested on more than 30 substrates. For example, we studied the reaction of 1-octene with different secondary, primary, and functional groups-containing amines (Table 5). Applying piperidine, morpholine, 1-phenylpiperazine, 2,3-dihydro-indole, *N,N*-dimethylamine the corresponding linear products **1a−e** were obtained in good to excellent yields and regioselectivities (Table 5, entries 1−5). Secondary amines with more bulky substituents gave the products **1g-h** similarly with excellent results (Table 5, entries 7−8). The amino acid derivative pyrrolidine-2-carboxylic acid methyl ester successfully yielded **1i**. Noteworthy, the ester group survived the hydroaminomethylation conditions without problems (Table 5, entry 9). 2-(Methylamino)ethanol reacted readily with 1-octene to provide the interesting amino alcohol **1j** in high yield and selectivity (Table 5, entry 10).

In addition to secondary amines, primary amines also reacted well with 1-octene to give **1k−m** in moderate to high yields and selectivities (up to 82% GC yield and 96:4 regioselectivity) (Table 5, entries 11−13). With (4-aminophenyl)(phenyl)-methanone, the ketone was retained in the product **1n** (Table 5, entry 14). Depending on the amine/alkene ratio, cyclohexylamine can selectively react with one or two equivalents of 1-octene to yield the mono- or dialkylated amines **1o** and **1p**, respectively (Table 5, entries 15−16).

Tryptamine and its derivatives are important alkaloids showing numerous biological activities. For example, they act as Serotonin Releasing Agents and Serotonergic Activity Enhancers.[29] Hydroaminomethylation of tryptamine with alkenes provides an effective and benign way to selectively alkylate the 9-NH_2 position. Applying standard conditions, both mono- and dialkylated tryptamine are obtained. The two compounds can be easily separated by column chromatography. However, varying the ratio of alkene and trypamine allows for a selective formation of mono- or dialkylated trypamines (Scheme 2).

Subsequently, we focused our attention on the variation of olefins using piperidine (Table 6). Both lower and higher aliphatic olefins provided the corresponding linear amines **1a**,

Table 7. Ruthenium-catalyzed Hydroaminomethylation of 2-Octene with Piperidine[a]



					selectivity[b] [%]			
entry	*x*	*T* [°C]	time [h]	conversion[b] [%]	amine	linear amine	*N*-formyl piperidine	*n/iso*[b]
1	0.1	130	20	40	70	50	2	71:29
2	0.1	160	40	89	60	49	9	81:19
3	0.2	160	30	94	71	59	10	83:17

[a]Reaction conditions: 20 mmol 2-octene, 24 mmol piperidine, x mol% $Ru_3(CO)_{12}$, 3.3x mol% $\mathbf{L_1}$, 10 mL of MeOH, 10 mL of toluene, 10 bar CO, 50 bar H_2. [b]Determined by GC analysis using isooctane as internal standard.

2a−c with excellent yields and regioselectivities (Table 6, entries 1−4). Octa-1,7-diene reacted with two equivalents of piperidine to yield the interesting 1,10-di(piperidin-1-yl)decane **2d** (Table 6, entry 5). Dihydrochlorides of this type of amine have potential radioprotective activity.[30] We were also delighted to find that the olefin bearing ester functionality underwent exclusively hydroaminomethylation reaction to produce **2e** without side reactions involving the ester group (Table 6, entry 6). Linear and branched unprotected olefinic alcohols were efficiently converted into interesting amino alcohols **2f−g** in high yield and with up to 99:1 regioselectivity (Table 6, entries 7−8). Moreover, acrolein diethylacetal underwent straightforward hydroaminomethylation to produce the protected γ-amino-aldehyde **2h** in moderate yield and regioselectivity (Table 6, entry 9). **2i** was obtained in lower yield from allyloxybenzene, because of the ether-bond cleavage (Table 6, entry 10). Higher temperature was necessary to convert the less reactive cyclohexene to the corresponding product **2j** in 65% yield (Table 6, entry 11). In case of styrene an almost 1:1 mixture of *n*- and *iso*-amine **2k**/**2k′** was obtained in high yield because of the stabilization of the benzylic metal complex (Table 6, entry 12). On the other hand, allylbenzene was converted to **2l** with high regioselectivity (Table 6, entry 13). The more sterically demanding aromatic olefin α-methylstyrene provided **2m** in inferior yield (Table 6, entry 14).

Selective hydroaminomethylation reactions of enamines and enamides are known to be difficult, because of the hampered formation of the acyl metal species.[31] Gratifyingly, with 0.2 mol% of our catalyst system 1-vinyl-2-pyrrolidinone and 1-vinyl-2-azepanone were successfully converted to **3a** and **3b** in good yields (80% and 78%) and moderate to good linear selectivity (*n*/*iso* = 65:35 and 81:19). Though the yield of **3c** was slightly lower (66%), linear selectivity (*n*/*iso* = 80:20) was retained. 9-Vinylcarbazole was also employed as a substrate and gave **3d** with preferred selectivity for the branched isomer. Noteworthy, the related *N*-(alkyl-piperidyl)carbazole derivatives are pharmacologically useful substrates (Scheme 3).[32]

Finally, the more challenging isomerization-hydroaminomethylation of 2-octene was investigated (Table 7). The transformation of internal olefins is of considerable interest for industrial applications due to their availability and advantageous price. Applying the above-described conditions to the reaction of 2-octene with piperidine, only 40% conversion and moderate selectivity were observed after 20 h (Table 7, entry 1). In order to increase the overall reaction rate, the reaction was performed at higher temperature (Table 7, entries 2, 3). To our delight, 89% conversion and higher selectivity were achieved. Finally, doubling of the amount of $Ru_3(CO)_{12}$ led to 94% conversion and 83:17 regioselectivity.

CONCLUSION

We have developed a general catalytic system for hydroaminomethylation reactions of various olefins. Key to success is the use of triruthenium dodecacarbonyl together with 2-phosphino-substituted imidazole ligands. In general, synthetically important linear amines are obtained in good to excellent yields and regioselectivities. This system also showed promising activity in the challenging hydroaminomethylation of enamides and internal olefins. The lower price of ruthenium, the lower amount of ligand compared to rhodium-based catalysts and the generality of our system render it a complementary option for the synthesis of amines.

ASSOCIATED CONTENT

Supporting Information

Synthetic details, ligand and products data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

Matthias.Beller@catalysis.de

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work has been funded by the Deutsche Forschungsgemeinschaft (Leibniz-price), Chinese Scholarship council (grants for L.W.), Swiss National Science Foundation (SNSF, grants for I.F.) and Evonik Industries AG. We thank Dr. Christine Fischer, Susann Buchholz, Susanne Schareina, Ilona Stahr, Andreas Koch and Dr. Wolfgang Baumann for their technical and analytical support. We are grateful to Dr. Min Zhang, Dr. Yang Li and MSc Jola Pospech for helpful discussions.

REFERENCES

(1) (a) Heilen, G.; Mercker, H. J.; Frank, D.; Reck, A.; Jäckh, R. *Ullmanns Encyclopedia of Industrial Chemistry*, Vol. *A2*; Wiley-VCH: Weinheim, 1985; p 1. (b) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2004.

(2) (a) Blaser, H.-U.; Spinder, F. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; p 1193. (b) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055−2058. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84−86. (d) Lee, O.-Y.; Law, K.-L.; Yang, D. *Org. Lett.* **2009**, *11*, 3302−3305. (e) Dangerfield, E. M.; Plunkett, C. H.; Win-Mason, A. L.; Stocker, B. L.; Timer, M. S. M. *J. Org. Chem.* **2010**, *75*, 5470−5477.

(3) (a) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325−6326. (b) Bini, L.; Müller, C.; Wilting, J.; von Chrzanowski, L.; Spek, A. L.; Vogt, D. *J. Am. Chem. Soc.* **2007**, *129*, 12622−12623. (c) Göthlich, A. P. V.; Tensfeldt, M.; Rothfuss, H.; Tauchert, M. E.; Haap, D.; Rominger, F.; Hofmann, P. *Organometallics* **2008**, *27*, 2189−2200.

(4) (a) Grey, R. A.; Pez, G. P.; Wallo, A. *J. Am. Chem. Soc.* **1981**, *103*, 7536−7542. (b) Li, T.; Bergner, I.; Haque, F. N.; Zimmer-De Iuliis, M.; Song, D.; Morris, R. H. *Organometallics* **2007**, *26*, 5940−5949. (c) Enthaler, S.; Junge, K.; Addis, D.; Erre, G.; Beller, M. *ChemSusChem* **2008**, *1*, 1006−1010.

(5) For selected reviews see: (a) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575. (b) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611−1641. (c) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853−1864. (d) Moran, J.; Krische, M. J. *Pure Appl. Chem.* **2012**, *84*, 1729−1739.

(6) For references on hydroamination: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704. (b) Nobis, M.; Drießen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983−3986. (c) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, *10*, 1579−1594. (d) Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−892. (e) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131* (51), 18246−18247. (f) Leitch, D. C.; Turner, C. S.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2010**, *49* (36), 6382−6386. (g) Brinkmann, C.; Barrett, A. G.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 2193−207.

(7) For reviews on hydroaminomethylation, see: (a) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329−3366. (b) Eilbracht, P.; Schmidt, A. M. *Transition*

Metals for Organic Synthesis; Beller, M., Bolm, C., Eds.; Wiley-VCH Verlag GmbH: New York, 2008; pp 57−82. (c) Eilbracht, P.; Schmidt, A. *Top. Organomet. Chem.* **2006**, *18*, 65−95. (d) Crozet, D.; Urrutigoïty, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102−1118.

(8) For reviews on domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379. (c) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020.

(9) Reppe, W.; Vetter, H. *Liebigs Ann. Chem.* **1953**, *582*, 133−161.

(10) (a) Eilbracht, P.; Kranemann, C. L.; Bärfacker, L. *Eur. J. Org. Chem.* **1999**, 1907−1914. (b) Rische, T.; Bärfacker, L.; Eilbracht, P. *Eur. J. Org. Chem.* **1999**, 653−660. (c) Koç, F.; Wyszogrodzka, M.; Eilbracht, P.; Haag, R. *J. Org. Chem.* **2005**, *70*, 2021−2025. (d) Subhani, M. A.; Mueller, K.-S.; Eilbracht, P. *Adv. Synth. Catal.* **2009**, *351*, 2113−2123. (e) Beigi, M.; Ricken, S.; Mueller, K. S.; Koc, F.; Eilbracht, P. *Eur. J. Org. Chem.* **2011**, 1482−1492.

(11) (a) Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676−1678. (b) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311−10318. (c) Ahmed, M.; Bronger, R. P. J.; Jackstell, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Beller, M. *Chem.—Eur. J.* **2006**, *12*, 8979−88. (d) Ahmed, M.; Buch, C.; Routaboul, L.; Jackstell, R.; Klein, H.; Spannenberg, A.; Beller, M. *Chem.—Eur. J.* **2007**, *13*, 1594−1601.

(12) (a) Liu, G.; Huang, K.; Cai, C.; Cao, B.; Chang, M.; Wu, W.; Zhang, X. *Chem.—Eur. J.* **2011**, *17*, 14559−14563. (b) Liu, G.; Huang, K.; Cao, B.; Chang, M.; Li, S.; Yu, S.; Zhou, L.; Wu, W.; Zhang, X. *Org. Lett.* **2012**, *14*, 102−105.

(13) (a) Hamers, B.; Bäuerlein, P. S.; Müller, C.; Vogt, D. *Adv. Synth. Catal.* **2008**, *350*, 332−342. (b) Hamers, B.; Kosciusko-Morizet, E.; Müller, C.; Vogt, D. *ChemCatChem* **2009**, *1*, 103−106.

(14) (a) Vieira, T. O.; Alper, H. *Chem. Commun.* **2007**, 2710−2711. (b) Vieira, T. O.; Alper, H. *Org. Lett.* **2008**, *10*, 485−487.

(15) Crozet, D.; Gual, A.; McKay, D.; Dinoi, C.; Godard, C.; Urrutigoïty, M.; Daran, J.-C.; Maron, L.; Claver, C.; Kalck, P. *Chem.—Eur. J.* **2012**, *18* (23), 7128−7140.

(16) (a) Briggs, J. R.; Klosin, J.; Whiteker, G. T. *Org. Lett.* **2005**, *7*, 4795−4798. (b) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2010**, *49* (14), 2626−2629. (c) Fuentes, J. A.; Wawrzyniak, P.; Roff, G. J.; Buhl, M.; Clarke, M. L. *Catal. Sci. Technol.* **2011**, *1* (3), 431−436. (d) Khan, S. R.; Khedkar, M. V.; Qureshi, Z. S.; Bagal, D. B.; Bhanage, B. M. *Catal. Commun.* **2011**, *15* (1), 141−145. (e) Melo, D. S.; Pereira-Júnior, S. S.; dos Santos, E. N. *Appl. Catal., A* **2012**, *411−412* (0), 70−76. (f) Sacher, J. R.; Weinreb, S. M. *Org. Lett.* **2012**, *14* (8), 2172−2175.

(17) (a) Zimmermann, B.; Herwig, J.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2372−2375. (b) Chen, H.; Li, Y.; Chen, J.; Cheng, P.; He, Y.-e.; Li, X. *J. Mol. Catal. A: Chem* **1999**, *149*, 1−6. (c) Wang, Y.; Chen, J.; Luo, M.; Chen, H.; Li, X. *Catal. Commun.* **2006**, *7*, 979−981. (d) Wang, Y. Y.; Luo, M. M.; Lin, Q.; Chen, H.; Li, X. J. *Green Chem.* **2006**, *8*, 545−548. (e) Behr, A.; Becker, M.; Reyer, S. *Tetrahedron Lett.* **2010**, *51*, 2438−2441.

(18) Petricci, E.; Mann, A.; Salvadori, J.; Taddei, M. *Tetrahedron Lett.* **2007**, *48*, 8501−8504.

(19) For selected examples on other metal-catalyzed hydroformylation, see: (a) Hayashi, T.; Hui, Gu, Z.; Sakakura, T.; Tanaka, M. *J. Organomet. Chem.* **1988**, *352*, 373−378. (b) Khan, M. M. T.; Halligudi, S. B.; Abdi, S. H. R. *J. Mol. Catal. A: Chem.* **1988**, *48*, 313−317. (c) Mitsudo, T.-a.; Suzuki, N.; Kondo, T.; Watanabe, Y. *J. Mol. Catal. A: Chem.* **1996**, *109*, 219−225. (d) Frediani, P.; Bianchi, M.; Salvini, A.; Carluccio, L. C.; Rosi, L. *J. Organomet. Chem.* **1997**, *547*, 35−40. (e) Jennerjahn, R.; Piras, I.; Jackstell, R.; Franke, R.; Wiese, K.-D.; Beller, M. *Chem.—Eur. J.* **2009**, *15*, 6383−6388. (f) Piras, I.; Jennerjahn, R.; Jackstell, R.; Spannenberg, A.; Franke, R.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 280−284.

(20) (a) Takahashi, K.; Yamashita, M.; Tanaka, Y.; Nozaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 4383−4387. (b) Takahashi, K.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2012**, *134*, 18764−18757.

(21) For reports on 2-phosphino-substituted heterocycle derived ligands, see: (a) Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3884−3887. (b) Díez, V.; Espino, G.; Jalón, F. A.; Manzano, B. R.; Pérez-Manrique, M. *J. Organomet. Chem.* **2007**, *692*, 1482−1492. (c) Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. *J. Am. Chem. Soc.* **2007**, *129*, 9592−9593. (d) Grotjahn, D. B. *Dalton Trans.* **2008**, 6497−6506. (e) Wong, S. M.; So, C. M.; Kwong, F. Y. *Synlett* **2012**, 1132−1153.

(22) Fleischer, I.; Dyballa, K. M.; Jennerjahn, R.; Jackstell, R.; Franke, R.; Spannenberg, A.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, DOI: 10.1002/anie.201207133.

(23) For one example of a Ru-catalyzed hydroaminomethylation under water gas shift conditions, see: (a) Jachimowicz, F.; Raksis, J. W. *J. Org. Chem.* **1982**, *47*, 445−447. For ruthenium-catalyzed hydroaminomethylation reactions of propene, see: (b) Schaffrath, H.; Keim, W. *J. Mol. Catal. A: Chem* **1999**, *140*, 107−113.

(24) Srivastava, V. K.; Eilbracht, P. *Catal. Commun.* **2009**, *10*, 1791−1795.

(25) For selected reports on Ru$_3$(CO)$_{12}$-catalyzed C-C bond forming reactions, see: (a) Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160−7161. (b) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663−12674. (c) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070−8073. (d) Leung, J. C.; Geary, L. M.; Chen, T.-Y.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 15700−15703.

(26) For a review on Ru-catalyzed hydroacylation reactions, see: For selected reports, see: (a) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1982**, *240*, 285−288. (b) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286−1291. (c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120−14122. (d) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094−14095. (e) Moran, J.; Krische, M. J. *Pure Appl. Chem.* **2012**, *84*, 1729−1739. (f) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324−327.

(27) See the Supporting Information.

(28) (a) Van Leeuwen, P. W. N. M.; Claver, C. *Rhodium Catalyzed Hydroformylation*; Springer: Berlin Heidelberg, 2008. (b) Breit, B. *Metal Catalyzed Reductive C-C Bond Formation*; Krische, M., Ed.; Springer: Berlin Heidelberg, 2007, 139−172. (c) Murzin, D. Y.; Bernas, A.; Salmi, T. *J. Mol. Catal. A: Chem.* **2010**, *315* (2), 148−154. (d) Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 10306−10317. (e) Franke, R.; Selent, D.; Börner, R. *Chem. Rev.* **2012**, *112*, 5675−5732.

(29) Offermeier, J.; Ariëns, E. J. *Arch. Int. Pharmacodyn. Ther.* **1966**, *164*, 216−245.

(30) Ermakova, M. I.; Belova, I. M.; Latosh, N. I.; Tarakhtii, É. A.; Tregubenko, I. P.; Semenov, D. I. *Pharm. Chem. J.* **1987**, *21*, 439−442.

(31) Bärfacker, L.; Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 7177−7190.

(32) Ferorelli, S.; Abate, C.; Colabufo, N. A.; Niso, M.; Inglese, C.; Berardi, F.; Perrone, R. *J. Med. Chem.* **2007**, *50*, 4648−4655.