Letter

Cobalt-Catalyzed Intermolecular Hydroacylation of Olefins through Chelation-Assisted Imidoyl C-H Activation

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Cobalt-Catalyzed Intermolecular Hydroacylation of Olefins through Chelation-Assisted Imidoyl C–H Activation

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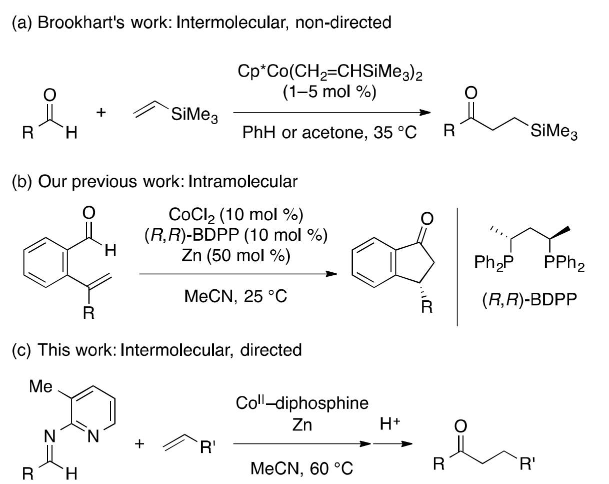
KEYWORDS: cobalt, C–H activation, hydroacylation, aldimines, alkenes.

ABSTRACT: A low-valent cobalt catalyst generated from cobalt(II) bromide, a diphosphine ligand, and zinc powder promotes intermolecular hydroacylation of olefins using *N*-3-picolin-2-yl aldimines as aldehyde equivalents, which affords, upon acidic hydrolysis, ketone products in moderate to good yields with high linear selectivity. The reaction is applicable to styrenes, vinylsilanes, and aliphatic olefins as well as to various aryl and heteroaryl aldimines. The cobalt catalysis features a distinctively lower reaction temperature (60 °C) compared with those required for the same type of transformations catalyzed by rhodium complexes (typically 130–150 °C).

The catalytic hydroacylation of unsaturated hydrocarbons offers an atom- and step-economical route to ketones from readily available aldehyde substrates.[1] While such transformations may be achieved with various catalytic systems through different mechanistic manifolds, the most extensively studied is the rhodium(I)-catalyzed hydroacylation that goes through oxidative addition of the aldehydic C–H bond to Rh, migratory insertion of the unsaturated substrate into Rh–H, and C–C bond-forming reductive elimination. In light of analogous reactivities of rhodium and its group 9 congener, cobalt,[2] and much lower cost of the latter, the use of low-valent cobalt catalysts in the same hydroacylation manifold appears feasible and attractive. Nevertheless, reports on cobalt-catalyzed hydroacylation have been sporadic.[3,4,5] In the late 1990s, Brookhart demonstrated the catalytic activity of a Cp*Co(I) complex toward intermolecular olefin hydroacylation (Scheme 1a).[4] Although the reaction is notable in that it does not require any chelation assistance, only vinylsilanes can be used as olefins. Dong and coworkers recently disclosed an intermolecular hydroacylation reaction of 1,3-dienes using an in situ-generated cobalt(I)–diphosphine catalyst,[5] while the reaction is proposed to go through aldehyde/diene oxidative cyclization rather than aldehydic C–H activation.

Recently, we reported enantioselective intramolecular hydroacylation reactions of olefins (Scheme 1b) and ketones using low-valent cobalt catalysts generated from cobalt(II) salts, chiral diphosphine ligands, and metal reductants,[6] which display efficiencies and selectivities comparable to those of the rhodium-catalyzed variants.[7,8] With the modularity of the cobalt–diphosphine catalytic system as well as the limitation of the Cp*Co(I) catalytic system with respect to the scope of olefins, we became interested in the feasibility of intermolecular olefin hydroacylation under cobalt–diphosphine catalysis. While our attempts on hydroacylation using simple aldehydes have not been successful, we have established a new cobalt–diphosphine catalytic system for the formal intermolecular hydroacylation using an *N*-3-picolin-2-yl aldimine,[9,10] which is reported herein (Scheme 1c).

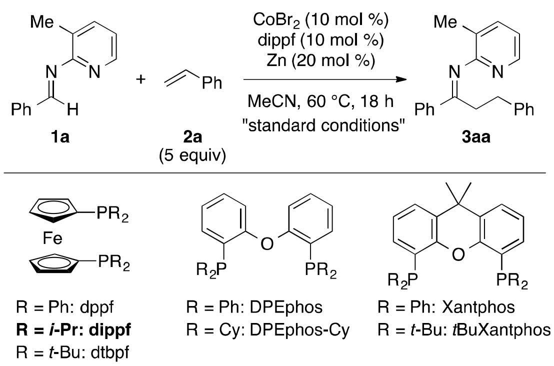
Scheme 1. Cobalt-Catalyzed Olefin Hydroacylation via C–H Activation



The seminal work of Suggs and the following extensive studies of Jun and others have shown the utility of *N*-3-picolin-2-yl and related aldimines, either preformed or in situ-generated, as aldehyde equivalents in Rh-catalyzed hydroacylation, which allow one to avoid undesirable decarbonylation by the formation of five-membered chelate intermediates upon C–H oxidative addition.[9-10] After futile attempts on cobalt–diphosphine-catalyzed hydroacylation using parent benzaldehyde and simple olefins (e.g., styrene, 1-octene), we turned our focus on this class of substrates. Extensive screening of reaction conditions using benzaldimine **1a** and styrene **2a** as model substrates led us to achieve the desired transformation using a cobalt catalyst generated from $CoBr_2$ (10 mol %), 1,1'-bis(diisopropylphosphino)ferrocene (dippf; 10 mol %), and Zn powder (20 mol %) in acetonitrile at 60 °C, affording the ketimine product **3aa** in 85% GC yield after 18 h (Table 1, entry 1). The GC analysis indicated the presence of a trace amount of a branched isomer of **3aa**, which was later confirmed by the analysis of hydrolyzed products (vide infra). Reactions of aldimines prepared from other 2-aminopyridine derivatives with **2a** under identical conditions afforded the corresponding adducts in much lower yields (see the Supporting Information). Note also that, unlike the case of rhodium(I) catalysis,[9-10] the reaction of benzaldehyde and **2a** in the presence of either catalytic or stoichiometric amounts of 2-amino-3-picoline failed to give the desired hydroacylation product.

The reaction efficiency is substantially influenced by the backbone and the phosphorus substituents of the diphosphine ligand, as evident from the lower catalytic activities obtained with other ferrocenyldiphosphines, diphenyl ether- or xanthene-based diphosphines (entries 2–7). The use of Mn powder as the reductant resulted in a significantly lower yield (entry 8), while In powder was entirely ineffective (entry 9). The cobalt precatalyst also had a significant impact on the reaction efficiency. No desired product was obtained using $CoCl_2$ (entry 10), while CoI_2 promoted the reaction to only a moderate extent (entry 11). Replacement of acetonitrile with other solvents such as toluene and THF completely shut down the hydroacylation (entries 12 and 13). Attempts to lower the catalyst loading or the equivalence of **2a** resulted in significant decrease in the product yield (entries 14 and 15).

Table 1. Effect of Reaction Conditions on Co-Catalyzed Addition of Aldimine 1a to Styrene[a]

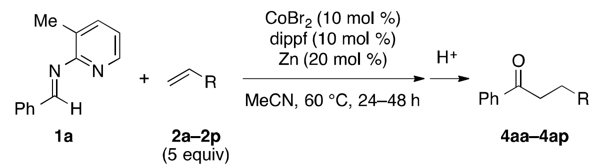


entry	deviation from "standard conditions"	yield (%)[b]
1	none	85
2	dppf instead of dippf	20
3	dtbpf instead of dippf	0
4	DPEphos instead of dippf	16
5	DPEphos-Cy instead of dippf	68
6	Xantphos instead of dippf	17
7	*t*BuXantphos instead of dippf	0
8	Mn instead of Zn	18
9	In instead of Zn	0
10	$CoCl_2$ instead of $CoBr_2$	0
11	CoI_2 instead of $CoBr_2$	32
12	Toluene instead of MeCN	0
13	THF instead of MeCN	0
14	5 mol % of $CoBr_2$ and dippf	29
15	2 equiv of **2a**	45

[a]The reaction was performed on a 0.1 mmol scale. [b]Determined by GC using *n*-tridecane as an internal standard.

With the Co–dippf catalytic system in hand, we explored the scope of the present hydroacylation reaction. First, aldimine **1a** was subjected to the reaction with various olefins (Table 2). A variety of styrene derivatives **2a**–**2k** participated in the hydroacylation reaction to afford, upon acidic hydrolysis, the linear ketone products **4aa**–**4ka** in moderate to good yields (entries 1–11). The reaction was typically accompanied by the formation of a minor amount of branched isomer with the linear-to-branched ratio ranging from 11:1 to > 20:1. The reaction of **2a** could be performed on a 5 mmol scale without decrease in the yield and the regioselectivity (entry 1). Like the styrene derivatives, 3-vinylthiophene also afforded the desired hydroacylation product **4al** in 56% yield (entry 12). Vinylsilane, allylsilane, and alkyl olefins are also amenable to the hydroacylation reaction, affording the linear adducts **4am**–**4ap** as the exclusive regioisomeric products (entries 13–16).

Table 2. Scope of Olefins

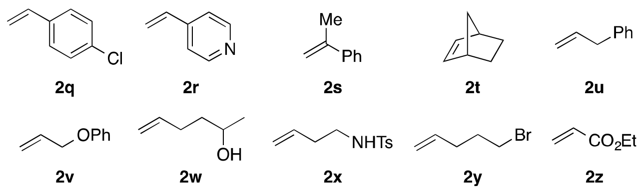


entry	R	product	yield (%)[b]	l:b[c]
1	Ph	**4aa**	78 (79)[d]	17:1
2	4-MeC_6H_4	**4ab**	70	>20:1
3	4-*t*-BuC_6H_4	**4ac**	71	>20:1
4	4-$MeOC_6H_4$	**4ad**	80	–[e]
5	4-$Me_3SiC_6H_4$	**4ae**	70	11:1
6	4-FC_6H_4	**4af**	69	>20:1
7	3-MeC_6H_4	**4ag**	63	15:1
8	3-$MeOC_6H_4$	**4ah**	63	13:1
9	3-FC_6H_4	**4ai**	85	>20:1
10	2-$MeOC_6H_4$	**4aj**	77	>20:1
11	2-FC_6H_4	**4ak**	73	19:1
12	3-thienyl	**4al**	56	19:1
13	$SiMe_3$	**4am**	61	–[e]
14	CH_2SiMe_3	**4an**	38	–[e]
15	*n*-C_6H_{13}	**4ao**	71	–[e]
16	$(CH_2)_2CO_2Et$	**4ap**	33	–[e]

[a]The reaction was performed on a 0.3 mmol scale. [b]Isolated yield. [c]The ratio of linear and branched isomers determined by ^1H NMR analysis. [d]5 mmol scale. [e]No branched isomer was detected.

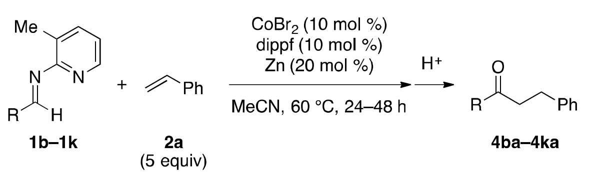
Chart 1 summarizes examples of alkenes that failed to participate in the reaction with **1a**, thus illustrating the limitation of the present hydroacylation. Among vinylarenes, 4-chlorostyrene (**2q**) and 4-vinylpyridine (**2r**) did not give the desired products at all, with near complete recovery of **1a**. The latter alkene may have interfered with the reaction by the coordination of the pyridyl group to the catalyst. On the other hand, the failure of the former alkene is not clearly rationalized at this moment, in light of the fact that an aryl chloride moiety in the aldimine reactant can be tolerated (vide infra). Other unsuccessful alkenes include sterically hindered α-methylstyrene (**2s**) and norbornene (**2t**), readily isomerizable allylbenzene (**2u**) and allyl phenyl ether (**2v**), alkyl olefins containing hydroxy (**2w**), sulfonamide (**2x**), and alkyl bromide (**2y**) moieties, and electron-deficient ethyl acrylate (**2z**).

Chart 1. Unsuccessful Alkene Substrates



Next, reactions of various aldimines with styrene (**2a**) were examined (Table 3). A variety of aldimines **1b**–**1i** derived from para- and meta-substituted benzaldehydes underwent addition to **2a** to afford the desired hydroacylation products **4ba**–**4ia** in 70% or higher yields with l:b ratios of 15:1 or higher (entries 1–8), except for the one derived from 4-cyanobenzaldehyde, which exhibited modest reactivity and slightly lower regioselectivity (entry 5). The catalytic system is sensitive to substitution at the ortho-position of the aldimine substrate, as aldimines derived from ortho-substituted benzaldehydes such as ortho-tolualdehyde failed to afford the hydroacylation products (data not shown). While aldimines derived from 2-thiophene- and 3-thiophene carboxyaldehydes smoothly participated in the hydroacylation to **2a**, curiously, they exhibited lower regioselectivities, affording the products **4ja** and **4ka** with l:b ratios of 3:1 and 5:1, respectively (entries 9 and 10). Note that alkyl aldimines were not examined, because attempts to prepare such aldimines in a pure form from the corresponding aldehydes were unsuccessful.

Table 3. Scope of Aldimines



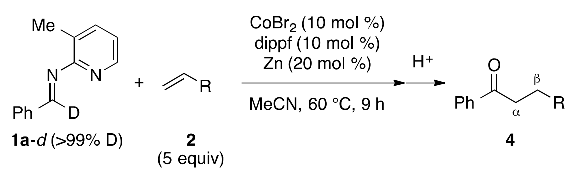
entry	R	product	yield (%)[b]	l:b[c]
1	4-*t*-BuC_6H_4	**4ba**	73	>20:1
2	4-MeOC_6H_4	**4ca**	82	16:1
3	4-FC_6H_4	**4da**	72	>20:1
4	4-ClC_6H_4	**4ea**	72	>20:1
5	4-NCC_6H_4	**4fa**	39	9:1
6	3-MeC_6H_4	**4ga**	73	15:1
7	3-MeOC_6H_4	**4ha**	74	>20:1
8	3-FC_6H_4	**4ia**	70	>20:1
9	2-thienyl	**4ja**	83	3:1
10[d]	3-thienyl	**4ka**	70	5:1

[a]The reaction was performed on a 0.3 mmol scale. [b]Isolated yield. [c]The ratio of linear and branched isomers determined by ^{1}H NMR analysis. [d]Linear (59%) and branched (11%) isomers were separated by silica gel chromatography.

During the reaction optimization and the exploration of the substrate scope, we noted the presence of a substantial induction period in the $CoBr_2$/dippf/Zn catalytic system. Thus, no hydroacylation product was observed for the initial several hours (typically 4–8 h). This observation appeared to be correlated with the change of the appearance of the reaction mixture. Thus, the characteristic blue color of Co(II) turned dark brown only gradually over several hours. Thus, the induction period may be associated with slow reduction of the Co(II) precatalyst to a catalytically active Co(I) species under the heterogeneous conditions.[11]

To gain insight into the hydroacylation pathway, we performed experiments using a deuterium-labeled aldimine **1a**-*d* (Scheme 2). The reaction of **1a**-*d* with styrene or vinyltrimethylsilane was performed under the standard conditions for a shorter reaction time of 9 h to achieve a moderate conversion, in order to analyze deuterium contents in both the recovered aldimine and the hydroacylation product. With either of the olefin substrates, we observed a decreased deuterium content in the recovered aldimine (45% D and 83% D for the reactions with styrene and vinyltrimethylsilane, respectively). The ^{1}H NMR analysis of the hydroacylation product of styrene showed a partial deuteration of the β-position (1.69H) as well as a slight deuteration of the α-position (1.90H). By contrast, the hydroacylation product of vinyltrimethylsilane featured substantial deuteration of the β-position (1.55H) with no apparent deuteration of the α-position (2.00H). Note that, as expected from the substantial H/D scrambling, we did not observe qualitatively significant difference between the reactivities of **1a**-*d* and **1a**.

Scheme 2. Deuterium-Labeling Experiment

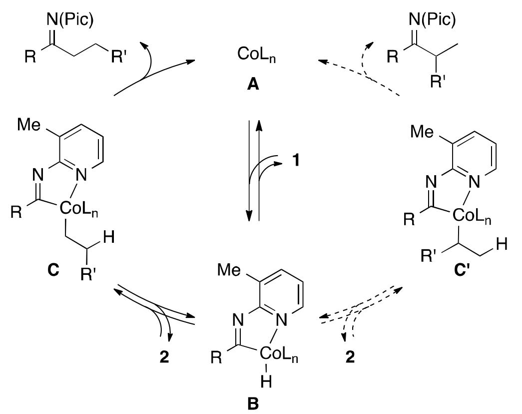


R	recovery of **1a** (%)[a]	D-content of recovered **1a** (%)[a]	yield of **4** (%)[b]	^{1}H integration[c] α	^{1}H integration[c] β
Ph	38	45	42	1.90	1.69
$SiMe_3$	46	83	33	2.00	1.55

[a]Determined by ^{1}H NMR analysis of the crude product. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis.

On the basis of the above observations as well as the analogy with the common mechanism of the rhodium-catalyzed hydroacylation,[1,9-10] we propose a catalytic cycle outlined in Scheme 3. First, reduction of $CoBr_2$ with zinc in the presence of dippf would give rise to a low-valent cobalt species **A**, which is presumably in the Co(I) oxidation state.[11] The species **A** then undergoes pyridine-assisted oxidative addition of the imidoyl C–H bond to give a cobaltacycle intermediate **B**.[12] Migratory insertion of the olefin into the Co–H bond of **B** would occur in linear or branched fashion, leading to diorganocobalt intermediates **C** or **C'**, respectively. Reductive elimination of **C** gives the major linear isomer of the hydroacylation product, while the minor branched isomer, which is formed with styrene derivatives, should arise from **C'**. The erosion of the deuterium content of the recovered aldimine (Scheme 2) can be rationalized by H/D exchange between the aldimine and the olefin through reversible C–H oxidative addition/migratory insertion processes. Because of the use of a large excess (5 equiv) of the olefin, the proportion of the deuterated olefin molecules to the total olefin molecules should be low regardless of the extent of H/D exchange, which accounts for the low deuterium incorporation into the hydroacylation product. Note that the branched insertion pathway appears to operate to some extent with styrene but does not with vinyltrimethylsilane. The propensity of the styrene derivatives to give the minor branched products may be ascribed to increased stability of the putative benzylcobalt intermediate (**C'**, R' = aryl).[12b,13,14]

Scheme 3. Proposed Catalytic Cycle (Pic = 3-picolin-2-yl)



In summary, we have demonstrated that a cobalt–diphosphine complex serves as a viable alternative catalyst for the intermolecular formal hydroacylation reaction of olefins using *N*-3-picolin-2-yl aldimines as aldehyde equivalents. The cobalt catalysis proceeds at a distinctively lower reaction temperature (60 °C) than typically required in the rhodium catalysis of the same type of hydroacylation (130–150 °C).[9-10] In light of the tremendous success of rhodium-catalyzed hydroacylation using chelating aldehydes,[1,8c,9-10,15] the present results may hold promise for further development of cobalt catalysts for chelation-assisted hydroacylation. Further studies toward the extension of the scope of cobalt-catalyzed hydroacylation and related C–H functionalization reactions are currently underway.

ASSOCIATED CONTENT

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/csXXXX.

Experimental details and compound characterization data (pdf)

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Notes

The authors declare no competing financial interest.

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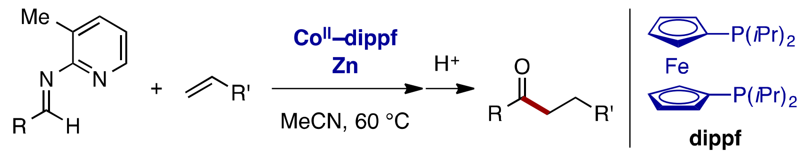
Me
N
N
R
H
+
R'
Co^{II}–dippf
Zn
H+
MeCN, 60 °C
O
R
R'
P(iPr)2
Fe
P(iPr)2
dippf