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Nickel-Catalyzed Hydroacylation of Styrenes with Simple Aldehydes: Reaction Development and Mechanistic Insights

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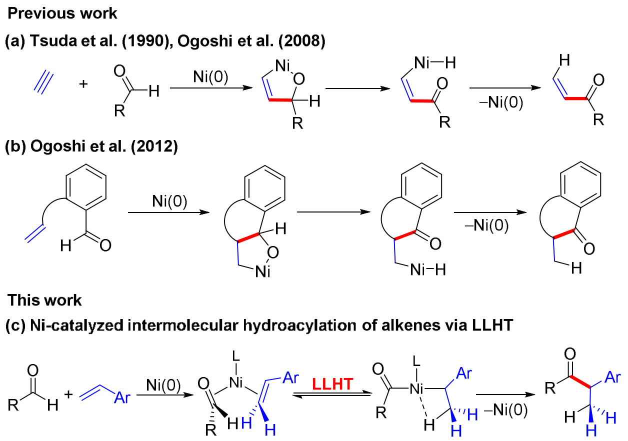
ABSTRACT: The first nickel-catalyzed intermolecular hydroacylation reaction of alkenes with simple aldehydes has been developed. This reaction offers a new approach to the selective preparation of branched ketones in high yields (up to 99%) and branched selectivities (up to 99:1). Experimental data provide evidence for reversible formation of acyl-nickel–alkyl intermediate and DFT calculations show that the aldehyde C–H bond transfer to a coordinated alkene without oxidative addition is involved. The origin of the reactivity and regioselectivity of this reaction was also investigated computationally which are consistent with experimental observations.

Transition metal–catalyzed hydroacylation of alkenes with aldehydes is a useful and atom-economical method for the synthesis of ketones.[1] This cross-coupling reaction involves metal-catalyzed activation of a C–H bond and addition of the aldehyde to the alkene to form a new C–C bond. The first example of this transformation was reported in 1972 by Sakai et al.,[2] who used a stoichiometric amount of a rhodium catalyst for intramolecular hydroacylation of alkenes to produce cyclopentanones. Since then, significant progress on rhodium-catalyzed intramolecular hydroacylation of alkenes has been made,[3] and rhodium-catalyzed intermolecular hydroacylation of alkenes with aldehydes has also been extensively studied.[4] However, because the acyl-rhodium intermediates tend to undergo undesired decarbonylation during the intermolecular reaction, substrates must usually have additional coordinating groups.[5] This drawback can be partially avoided by using cobalt,[6] ruthenium,[7] and N-heterocyclic carbene catalysts.[8]

Tsuda and Saegusa et al. reported nickel-catalyzed hydroacylation of alkynes to give α,β-enones (Scheme 1a).[9] Ogoshi and co-workers developed a nickel-catalyzed intramolecular hydroacylation of alkenes (Scheme 1b).[10] Those two reactions are proposed to proceed through an oxa-nickelacycle intermediate. However, the coupling of an alkene and an aldehyde via oxidative cyclization with nickel usually need activation of a third component such as silyl triflate or trimethylaluminum to provide allylic alcohol derivatives.[11] Thus, the nickel-catalyzed intermolecular direct hydroacylation of alkenes with simple aldehydes remains a challenge.

We have studied nickel-catalyzed asymmetric coupling of aldehydes with alkynes and 1,3-dienes for the synthesis of chiral allylic and bishomoallylic alcohols, respectively, as well as coupling of imines with alkynes for the synthesis of chiral allylic amines.[12] As part of our ongoing studies of the coupling of aldehydes with alkenes and alkynes, we herein report the first nickel-catalyzed intermolecular hydroacylation of alkenes to provide branched ketones in high yields with excellent selectivities. The experiments and density functional theory (DFT) calculations showed that the reaction involves an aldehyde C–H bond transfer to the coordinated alkene, forming an acyl-nickel–alkyl intermediate reversibly (Scheme 1c), which is different from the oxidative cyclization pathway (Scheme 1a and 1b).

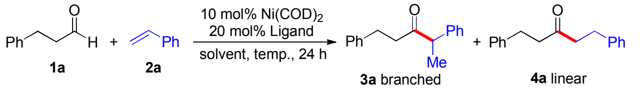
Scheme 1. Nickel-catalyzed Hydroacylation of Alkynes and Alkenes



We optimized the hydroacylation reaction conditions using 3-phenylpropionaldehyde (**1a**) and styrene (**2a**) as substrates (Table 1). The reaction was initially performed in 1,4-dioxane at 100 °C in the presence of a nickel catalyst prepared in situ from 10 mol% of Ni(COD)$_2$ (COD = 1,5-cyclooctadiene) and 20 mol% of a monophosphine ligand.

Electron-rich monophosphine ligands, such as P(*c*-pentyl)$_3$ and PCy$_3$, gave good results, providing branched ketone **3a** as the major product, along with minor amounts of linear product **4a** in a 95:5 ratio and overall yields of 74% and 81%, respectively (entries 3 and 4). The ligand P*n*Bu$_3$, which is less sterically bulky, gave a very low conversion (38%) and yield (7%) and exhibited lower selectivity for the branched product (entry 2). No reaction was observed with the very bulky electron-rich phosphine ligand P*t*Bu$_3$ (entry 5). In addition, when the N-heterocyclic carbene ligand IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) was used, the hydroacylation product was obtained in very low yield (5%) with a branched/linear ratio of 20:80 (entry 6).[13] Adding additional ligand (ca. 10 mol%), bringing the Ni/ligand ratio to 1:3, increased both the conversion (95%) and the yield (86%) of the reaction (entry 7). The reaction could also be performed at a catalyst loading of 5 mol%, but the conversion and yield decreased (entry 8).

Table 1. Optimization of Reaction Conditions[a]

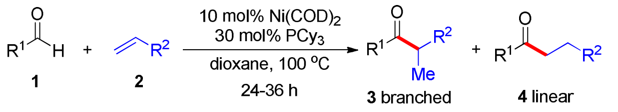


entry	ligand	conv. (%)[b]	yield (%)[b]	B/L (**3a**:**4a**)[b]
1	none	0	0	–
2	P^{n}Bu$_3$	38	7	76:24
3	PCyp$_3$	87	74	95:5
4	PCy$_3$	90	81	95:5
5	P*t*Bu$_3$	0	0	–
6[c]	IPr	95	5	20:80
7[d]	PCy$_3$	95	86(83)	96:4
8[e]	PCy$_3$	75	68	96:4

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), Ni(COD)$_2$ (0.02 mmol) and ligand (0.06 mmol) were stirred in solvents (2.0 mL) for 24 h at 100 °C unless otherwise noted. [b] Conversions, yields and B/L ratios were determined by GC analysis using *n*-dodecane as an internal standard; isolated yields are given in parentheses. [d] The Ni/ligand ratio was 1:3. [e] Using 5 mol% catalyst.

Using the optimal reaction conditions, we evaluated various aldehydes **1** and alkenes **2** (Table 2). The substituent on the phenyl ring of the styrenes had little influence on the yield and selectivity of the reaction. High yields (78–99%) and excellent branched/linear ratios (92:8–99:1) were obtained for most of the tested styrenes (entries 1–13). An exception was *p*-methoxystyrene (**1c**), which gave hydroacylation product **3c** in only 42% yield (entry 3). Hydroacylation of 2-vinylnaphthalene (**1n**) required a higher reaction temperature (120 °C) to produce desired product **3n**, which was obtained in 52% yield (entry 14). A reasonable yield of vinylpyridine (**1o**) could be obtained only when 40 mol% PCy$_3$ was used, to prevent coordination of the pyridyl ring of the substrate to the catalyst (entry 15). Various aliphatic aldehydes were examined in the hydroacylation of styrene, and all of them gave high yields and excellent branched/linear ratios (entries 16–20). The hydroacylation with an aromatic aldehyde (benzaldehyde) was sluggish, even when the catalyst loading was increased to 20 mol%, and the yield was very low (17% yield, entry 21). However, moderate or higher yields were achieved in the reaction of benzaldehyde with 4-(trifluoromethyl)styrene (**1v**) or 3,5-bis(trifluoromethyl)styrene (entries 22, 23). When *p*-methoxybenzaldehyde and *o*-methyl benzaldehyde were used, the yields increased to 80% and 75%, respectively (entries 24, 25). The N,N-dimethylacrylamide can also undergo the hydroacylation with aldehydes **1a** and **1u** in moderate yields and excellent regioselectivity (entries 26, 27).[7b] The 1-hexene was inert in the hydroacylation reaction with aldehyde **1a** (entry 28).

Table 2. Hydroacylation of Alkenes and Aldehydes[a]

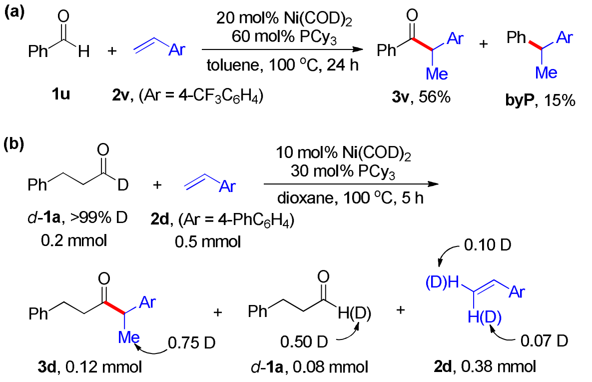


entry	R^1	R^2	3	yield (%)[b]	B/L (3:4)[c]
1	$C_6H_5(CH_2)_2$	C_6H_5	**3a**	83	96:4
2	$C_6H_5(CH_2)_2$	4-MeC_6H_4	**3b**	78	92:8
3[d]	$C_6H_5(CH_2)_2$	4-MeOC_6H_4	**3c**	42	92:8
4	$C_6H_5(CH_2)_2$	4-PhC_6H_4	**3d**	89	98:2
5	$C_6H_5(CH_2)_2$	4-FC_6H_4	**3e**	95	97:3
6	$C_6H_5(CH_2)_2$	4-$CF_3C_6H_4$	**3f**	98	98:2
7	$C_6H_5(CH_2)_2$	4-$MeO_2CC_6H_4$	**3g**	99	99:1
8	$C_6H_5(CH_2)_2$	4-TMSC_6H_4	**3h**	92	99:1
9	$C_6H_5(CH_2)_2$	3-MeC_6H_4	**3i**	90	99:1
10	$C_6H_5(CH_2)_2$	3-MeOC_6H_4	**3j**	86	99:1
11	$C_6H_5(CH_2)_2$	3-FC_6H_4	**3k**	98	98:2
12	$C_6H_5(CH_2)_2$	2-MeC_6H_4	**3l**	95	99:1
13	$C_6H_5(CH_2)_2$	2-FC_6H_4	**3m**	98	98:2
14[d]	$C_6H_5(CH_2)_2$	2-naphthyl	**3n**	52	98:2
15[e]	$C_6H_5(CH_2)_2$	2-pyrindyl	**3o**	61	99:1
16	$C_6H_5CH_2$	C_6H_5	**3p**	73	99:1
17	C_5H_{11}	C_6H_5	**3q**	92	98:2
18	2,6-dimethyl-oct-5-enyl	C_6H_5	**3r**	97	99:1
19	^{i}Pr	C_6H_5	**3s**	85	93:7
20	Cy	C_6H_5	**3t**	93	96:4
21[f]	C_6H_5	C_6H_5	**3u**	17	>99:1
22[f]	C_6H_5	4-$CF_3C_6H_4$	**3v**	56	>99:1
23[f]	C_6H_5	3,5-$(CF_3)_2C_6H_3$	**3w**	62	>99:1
24[f]	4-MeOC_6H_5	3,5-$(CF_3)_2C_6H_3$	**3x**	80	>99:1
25[f]	2-MeC_6H_5	3,5-$(CF_3)_2C_6H_3$	**3y**	75	>99:1
26[d,f]	$C_6H_5(CH_2)_2$	$CONMe_2$	**3z**	45	>99:1
27[d,f]	C_6H_5	$CONMe_2$	**3aa**	68	>99:1

28	$C_6H_5(CH_2)_2$	*n*Bu	**3ab**	0	–

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), $Ni(COD)_2$ (0.02 mmol) and PCy_3 (0.06mmol) were stirred in 1,4-dioxane (2.0 mL) for 24–36 h at 100 °C unless otherwise noted. [b] Isolated yields based on **1**. [c] Determined by GC analysis. [d] Performed in toluene for 36 h at 120 °C. [e] Performed using 40 mol% PCy_3 for 36 h at 120 °C. [f] Performed using 20 mol% catalyst in toluene.

Scheme 2. Hydroacylation of 4-(Trifluoromethyl)styrene with Benzaldehyde and Deuterium-labeling Experiment



To investigate the reaction mechanism, we identified the by-product generated in the hydroacylation reaction of benzaldehyde (**1u**) and 4-(trifluoromethyl)-styrene (**2v**). The by-product was found to be a 1,1-diarylethane (**byP**) in which one aryl group came from styrene and the other came from benzaldehyde, after decarbonylation (Scheme 2a). Moreover, the formation of catalytically unreactive nickel carbonyl complexes $Ni(PCy_3)_2(CO)_2$ was also observed by ^{31}P NMR analysis.[14] To assess whether C–H bond cleavage is reversible, we conducted the reaction with 1-*d*-3-phenylpropionaldehyde (*d*-**1a**) and *p*-phenyl-styrene (**2d**) to partial conversion (Scheme 2b). We found that deuteration rate of the new formed methyl group was not up to 33% (0.75 D), and the recovered aldehyde was decreased deuteration content to 0.50 D. Also, the residual deuterium was detected from the recovered *p*-phenyl-styrene.[15] These experimental observations showed that the reaction proceeds through a mechanism involving reversible aldehyde C–H bond cleavage and formation of acyl-nickel–benzyl intermediate.[16]

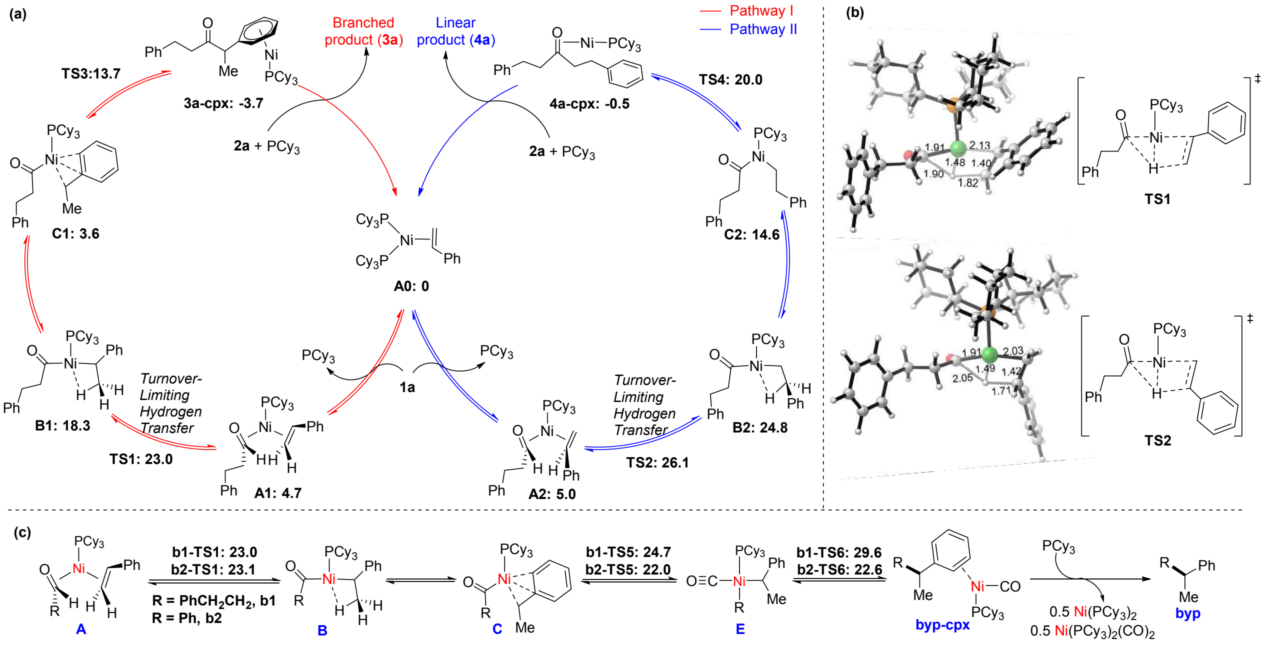


Figure 1. (a) Proposed catalytic cycle with DFT-calculated free energies (kcal mol^{-1}) in dioxane for the reaction between 3-phenylpropionaldehyde **1a** and styrene **2a** (b) Structures of transition states **TS1** and **TS2**. (c) Proposed decarbonylation processes with DFT-calculated free energies of transition states of the reaction of 3-phenylpropionaldehyde **1a** and benzaldehyde **1u**.

To deeply understand the details of the proposed mechanism, DFT studies were performed using the reactions of 3-phenylpropionaldehyde (**1a**) with styrene (**2a**) as models.[17,18] As shown in Figure 1a, the catalytic cycle initials with the Ni(0) complex **A0**, where the nickel catalyst $Ni(PCy_3)_2$ is coordinated to styrene.[19] Other possible Ni(0) complexes were also considered and their energy are found all higher than that of **A0** (see Table S2-1).[14] The coordination of **1a** to the nickel center of **A0** to replace the PCy_3 ligand forms the complexes **A1** and **A2** with two different coordinating orientations relative to **2a**. Then, the reaction can proceed along two distinct pathways, pathway **I** (in red) and pathway **II** (in blue). In the pathway **I**, **A1** undergoes the hydrogen transfer from the bound aldehyde to the bound styrene via **TS1** (Figure 1b) which is termed ligand-to-ligand hydrogen transfer (LLHT)[20] The resulting acyl-nickel–alkyl intermediate **B1** isomerizes to a more stable species **C1** by rotating styrene along the Ni-C$_{ben}$ bond to approach a η^3 binding mode. Next, **C1** undergoes the reductive elimination via a transition state **TS3** to produce the product complex **3a-cpx**. Finally, **3a-cpx** releases the branched product **3a** by binding with styrene **2a** and the PCy$_3$ ligand to form **A0** complex, which starts the next catalytic cycle. Similar steps are involved in the pathway **II**: the aldehyde hydrogen transfer via **TS2** and the subsequent reductive elimination via **TS4** to form the linear product **4a**. The hydrogen transfer processes have the highest energy barriers (**TS1** and **TS2**) in the pathways **I** and **II**, respectively. Thus, the hydrogen transfer is the turnover-limiting step of the overall process.[21] **TS1** is more stable than **TS2** by 3.1 kcal/mol, indicating that the aldehyde C–H bond prefers to transfer to the electron-deficient carbon atom of the styrene. Therefore, the branched adduct should be the main product, and the reactions involving the electron-deficient alkenes should proceed better, which are consistent with the experimental results (entries 3, 6). And the energy of species **C1** is close to **A0** in the main pathway, which means they have sufficient stability to interconvert under the reaction condition. The experiment of H/D exchange of aldehyde *d*-**1a** also showed this process is reversible.

The decarbonylation processes of 3-phenyl-propionaldehyde and benzaldehyde were also computed (Figure 1c).[14] The highest energy of transition state of reaction of benzaldehyde (**b2-TS1**, 23.1 kcal/mol) is lower than that in the reaction of 3-phenyl-propionaldehyde (**b1-TS6**, 29.6 kcal/mol), indicating that the aromatic aldehydes are easier to undergo the decarbonylation than the aliphatic aldehydes. This consequently rationalizes the low yield of aromatic aldehydes in the hydroacylation reaction.

Our computed results indicate that an alternative pathway, which involves the oxidative addition of the aldehyde C–H bond and the migratory insertion of the alkene into the nickel-hydride bond, is less favorable (Figure S2-3).[14] In addition, we also consider another possible reaction mechanism, which mainly involves the sequential steps of oxidative cyclization, hydrogen migration and reductive elimination to form the product. The computational results show that this pathway requires a very high activation energy of 56.2 kcal/mol (Figure S2-4).[14]

In summary, we have developed a highly selective nickel-catalyzed hydroacylation reaction of styrenes with aldehydes that does not require chelating groups. This reaction offers a new approach to the selective preparation of branched ketones in high yields. The experimental and computational studies show that the reaction proceeds through a LLHT pathway which involves the aldehyde hydrogen transfer to a coordinated alkene to form acyl-nickel–benzyl intermediate without oxidative addition. These results also disclosed that the origins of the reactivity and regioselectivity of the reaction, which may provide useful insights for developing new intermolecular hydroacyaltion reactions with nickel or other transition metal catalysts.

ACKNOWLEDGMENT

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SUPPORTING INFORMATION PARAGRAPH.

Experimental procedures and and analytical data of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See the Supporting Information (SI) for details.

(15) The H/D exchange between aldehydes and alkenes were confirmed by conducting the reaction with β-d_2-*p*-phenylstyrene (d_2-**2d**) and 3-phenylpropionaldehyde (**1a**). For details, see the SI-2(b). (16) For mechanistic study on the C–H activation of aldehydes catalyzed by Rh, see: (a) Shen, Z.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V. M. *J. Am. Chem. Soc*. **2009**, *131*, 1077. (b) Prades, A.; Fernández, M.; Pike, S. D.; Willis, M. C.; Weller, A. S. *Angew. Chem. Int. Ed*. **2015**, *54*, 8520, and ref. 4e.

(17) All reported free energies are in kcal/mol and calculated using M06/SDD-6-311+G(d,p)/SMD(1,4-dioxane)//B3LYP/SDD-6-31G(d) method. For details, see the SI.

(18) For recent review of DFT studies of nickel-catalyzed reactions, see: Sperger, T.; Sanhueza, I. A.; Kalvet, I.; Schoenebeck, F. *Chem. Rev.* **2015**, *115*, 9532.

(19) A similar structure of nickel complex has been confirmed by single crystal X-ray diffraction, see: (a) Cornella, J.; Gómez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997. (b) Ohashi, M.; Shibata, M.; Saijo, H.; Kambara, T.; Ogoshi, S. *Organometallics* **2013**, *32*, 3631.

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SYNOPSIS TOC.