# Nickel-Catalyzed Ring-Opening Hydroacylation of Methylenecyclopropanes: Synthesis of γ,δ-Unsaturated Ketones from Aldehydes

Hiroki Taniguchi, Toshimichi Ohmura,* and Michinori Suginome*

*Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Kyoto 615-8510, Japan*

Received June 9, 2009; E-mail: ohmura@sbchem.kyoto-u.ac.jp; suginome@sbchem.kyoto-u.ac.jp
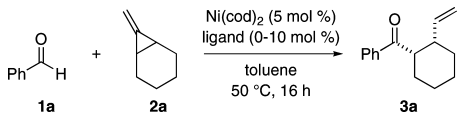
Transition-metal-catalyzed hydroacylation of unsaturated hydrocarbons has become increasingly important in recent organic synthesis because of growing demands for efficient, atom-economical processes.[1] Hydroacylation has allowed efficient construction of useful organic structures via C−C bond formation at aldehyde C−H bonds: α,β-unsaturated ketones from alkynes,[2] β,γ-unsaturated ketones from 1,2- and 1,3-dienes,[3] and cyclopentanes by intramolecular reaction of 4-pentenal derivatives.[4] To expand the scope of hydroacylation, it would be highly desirable to exploit new reaction partners with efficient catalyst systems that would produce ketones that are difficult to synthesize by other methods.

Methylenecyclopropanes (MCPs) are interesting candidates for hydroacylation because of their unique, multifarious reactivities.[5] However, no attempt at MCP hydroacylation has been reported,[6] except for rhodium-catalyzed intramolecular hydroacylation to form seven-membered-ring γ,δ-unsaturated ketones.[7] Herein, we describe the nickel-catalyzed intermolecular hydroacylation of MCPs.[8] We found that the reaction proceeds via stereospecific opening of the cyclopropane ring to give γ,δ-unsaturated ketones.

We found the new hydroacylation in a reaction of benzaldehyde (**1a**) with 7-methylenebicyclo[4.1.0]heptane (**2a**, 1.5 equiv) in toluene at 50 °C in the presence of Ni(cod)$_2$ (5 mol %) and PPh$_3$ (5 mol %) (Table 1, entry 1). The reaction gave *cis*-1-benzoyl-2-vinylcyclohexane (**3a**) in 31% yield after 16 h, indicating that hydroacylation took place via stereospecific cleavage of the proximal C−C bond of the MCP. The major side reaction was oligomerization of **2a**,[9] whereas neither decarbonylative products[2a] such as 1-phenyl-2-vinylcyclohexane nor simple addition products that retained the cyclopropane ring[8c] were formed under these conditions. The yield of **3a** was improved to 46−60% using cyclohexyl-substituted phosphorus ligands (entries 2−4), while P(*t*-Bu)$_3$ was ineffective for the reaction (entry 5). We finally found that the hydroacylation was effectively catalyzed by a nickel complex bearing less sterically demanding P(*n*-Bu)$_3$, affording **3a** in 90% yield (entry 6). It should be noted that the ratio of ligand to nickel (P/Ni = 1:1) is critical for the catalyst efficiency: slower hydroacylation with faster oligomerization was encountered with a P/Ni ratio of 2:1 (entry 7), while phosphine-free nickel gave a complex mixture (entry 8). The hydroacylation proceeded smoothly at 60 °C to give **3a** in high yield, although a small amount of the trans isomer was formed (cis/trans = 97:3; entry 6).

Various aldehydes were subjected to the reaction with **2a** in the presence of Ni(cod)$_2$ (5 mol %) with P(*n*-Bu)$_3$ (5 mol %) (Table 2, entries 1−11). Reaction of aryl aldehydes **1b−d** took place at 60 °C to give the corresponding ketones **3b−d** in high yields (entries 1−3). Although the slow reaction of benzaldehydes having 4-dimethylamino, 4-methoxycarbonyl, and 2-methyl groups resulted in the major formation of oligomers of **2a** at 60 °C, ketones **3e−g** were obtained in high yield when the reactions were carried out at 80 °C (entries 4−6). The nickel catalyst was also effective for the reactions with 2-furfural (**1h**) and 2-thiophenecarboxaldehyde (**1i**), giving the corre-

**Table 1.** Optimization of Reaction Conditions[a]



| entry | ligand (P/Ni) | yield (%)[b] |
|---|---|---|
| 1 | PPh$_3$ (1:1) | 31 |
| 2 | PCyPh$_2$ (1:1) | 60 |
| 3 | PCy$_2$Ph (1:1) | 46 |
| 4 | PCy$_3$ (1:1) | 46 |
| 5 | P(*t*-Bu)$_3$ (1:1) | trace |
| 6 | P(*n*-Bu)$_3$ (1:1) | 90 (87)[c] |
| 7 | P(*n*-Bu)$_3$ (2:1) | 29 |
| 8 | − | <3[d] |

[a] **1a** (0.20 mmol), **2a** (0.30 mmol), Ni(cod)$_2$ (10 μmol), and ligand (0−20 μmol) were stirred in toluene (0.1 mL) for 16 h at 50 °C, unless otherwise noted. [b] GC yield based on **1a**. [c] Isolated yield when the reaction was carried out for 4 h at 60 °C using **2a** (0.40 mml). The reaction gave the product with a cis/trans ratio of 97:3. [d] Complex mixture.
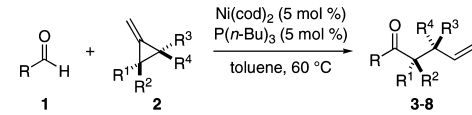
sponding ketones **3h** and **3i** in high yields (entries 7 and 8). The hydroacylation was also applicable to aliphatic aldehydes **1j** and **1k**, although a higher reaction temperature (80−100 °C) was required (entries 9 and 10). However, the reaction of pivalaldehyde (**1l**) suffered from sluggish hydroacylation with major formation of the dimer of **2a** (entry 11). Although the reactions of **2a** generally gave the corresponding cis ketones stereospecifically (cis/trans > 99:1), a small amount of the trans isomers were formed in the reactions with some aldehydes having electron-deficient or sterically demanding aryl groups (entries 1, 2, 5, and 6).[10]

Various MCPs were then reacted with aldehyde **1a** (Table 2, entries 12−18). Diastereomeric *cis*-**2b** and *trans*-**2b** reacted with **1a** in a highly stereospecific manner, giving (S*,S*)-**4** and (S*,R*)-**4**, respectively, with high diastereomeric purities (entries 12 and 13). Reaction of **2c** bearing silyloxy groups took place slowly at 80 °C to give **5** in good yield (entry 14). Sterically hindered **2d** also underwent reaction with **1a** to give highly methylated ketone **6** in 83% yield (entry 15). Reactions of MCPs **2e−g**, which have two nonequivalent C−C bonds to be cleaved, proceeded with selective cleavage of the less hindered C−C bond to give ketones **7−9** in good yields (entry 16−18).[11]

Reaction of 2-vinylbenzaldehyde (**1m**) with *trans*-**2b** gave ketone **10** (42%) with the unexpected cyclopropane-retaining adduct **11** in 34% yield (eq 1):
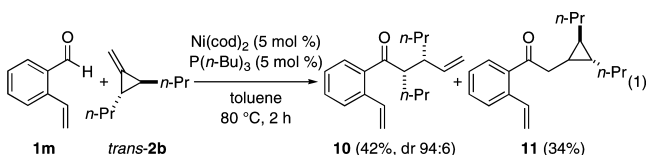


This result suggests a mechanism involving a cyclopropylmethylnickel

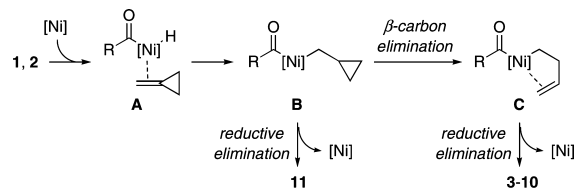**Table 2.** Nickel-Catalyzed Reaction of Aldehyde **1** with MCP **2**[a]

| entry | RCHO | MCP | time (h) | product | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1b** (R = 2-naphthyl) | **2a** | 4 | **3b** | 88[c] |
| 2 | **1c** (R = 4-FC$_6$H$_4$) | **2a** | 4 | **3c** | 96[d] |
| 3 | **1d** (R = 4-MeOC$_6$H$_4$) | **2a** | 5 | **3d** | 94 |
| 4 | **1e** (R = 4-Me$_2$NC$_6$H$_4$) | **2a** | 2[e] | **3e** | 95 |
| 5 | **1f** (R = 4-MeO$_2$CC$_6$H$_4$) | **2a** | 6[e] | **3f** | 70[f] |
| 6 | **1g** (R = 2-MeC$_6$H$_4$) | **2a** | 2[e] | **3g** | 84[g] |
| 7 | **1h** (R = 2-furyl) | **2a** | 4 | **3h** | 75 |
| 8 | **1i** (R = 2-thienyl) | **2a** | 8 | **3i** | 84 |
| 9 | **1j** (R = n-C$_6$H$_{13}$) | **2a** | 1[h] | **3j** | 64 |
| 10 | **1k** (R = Cy) | **2a** | 2[e] | **3k** | 65 |
| 11 | **1l** (R = t-Bu) | **2a** | 2[e] | **3l** | 18 |
| 12[i] | **1a** (R = Ph) | cis-**2b** | 4 | (S*,S*)-**4** | 74[j] |
| 13 | **1a** | trans-**2b** | 4 | (S*,R*)-**4** | 88 |
| 14[k] | **1a** | **2c** | 24[e] | **5** | 63 |
| 15 | **1a** | **2d** | 4 | **6** | 83 |
| 16 | **1a** | **2e** | 6 | **7** + **7'** (7:7' = 91:9) | 59[l] |
| 17 | **1a** | **2f** | 6 | **8** + **8'** (8:8' = 87:13) | 72[l] |
| 18 | **1a** | **2g** | 4 | **9** + **9'** (9:9' = 96:4) | 77[l] |

[a] **1** (0.20 mmol), **2** (0.40 mmol), Ni(cod)$_2$ (10 μmol), and P(n-Bu)$_3$ (10 μmol) were stirred in toluene (0.1 mL) at 60 °C, unless otherwise noted. [b] Isolated yield based on **1**. [c] cis/trans = 98:2. [d] cis/trans = 98:2. [e] At 80 °C. [f] cis/trans = 91:9. [g] cis/trans = 58:42. [h] At 100 °C. [i] **2b** (cis/trans = 92:8) was used. [j] dr = 94:6. [k] **2c** (0.30 mmol) was used. [l] Yield of major isomer.

intermediate **B**, as shown in Scheme 1. Oxidative addition of the C−H bond of the formyl group in **1** followed by coordination of **2** gives complex **A**, which affords acyl(cyclopropylmethyl)nickel complex **B** by insertion of the C≡C bond into the Ni−H bond. Intermediate **B** undergoes β-carbon elimination to form acyl(homoallyl)nickel **C**, which gives ketones **3**−**10** via reductive elimination.[12] Cyclopropane **11** may be formed via direct reductive elimination from **B**, probably because intramolecular coordination of the vinyl group in the aldehyde partially suppresses the β-carbon elimination.

**Scheme 1.** Possible Mechanism



In conclusion, we have established an efficient method for conversion of aldehydes to γ,δ-unsaturated ketones via nickel-catalyzed ring-opening hydroacylation of MCPs. The reaction is applicable to a wide array of aldehydes and proceeds with high stereospecificity and regioselectivity for the cleavage of the cyclopropane ring.

**Supporting Information Available:** Experimental details and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) GC/MS analysis indicated the formation of the dimer of **2a** as a major byproduct. For the structure of the dimer, see the Supporting Information.
(10) Isomerization of initially formed cis-**3g** to the trans isomer was observed in the reaction of **1g** with **2a** under these conditions.
(11) Substituted MCPs such as benzylidenecyclopropane and (3-phenylpropylidene)cyclopropane did not give clean reactions. See the Supporting Information.
(12) Reaction of naphthaldehyde-a-d$_1$ with **2a** gave deuterated **3b** having a 1-deuterioethenyl group (99% D). For details, see the Supporting Information.

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