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Rh-catalyzed π-facial selective intermolecular hydroacylation of norbornenes

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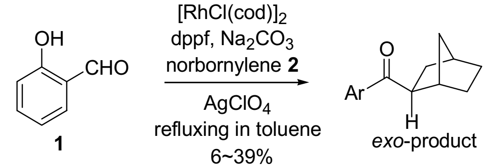
Abstract—Rh-catalyzed π-facial selective intermolecular hydroacylations of norbornenes with salicylaldehyde have been attained. In the reaction with norbornylene, the *exo*-hydroacylated product was produced because of steric hindrance. In the case of norbornadiene, the *endo*-product was obtained because of chelation effect. Lastly, because of chelation and remote substituent effects, the product formed in the reaction of 7-*tert*-butoxynorbornadiene was the *endo*,*syn*-product. Deuterium-labeling experiments revealed that the hydroacylation stereoselectively proceeded via *endo*- and *exo*-intermediates.

Transition-metal catalyzed C–C or C–X bond forming reactions have attracted much attention from many organic, and organometallic chemists.[1] Recently, quite a bit of attention has been focused on transition-metal catalyzed modifications of norbornene skeletons, such as, metal-catalyzed cycloaddition, hydroamination, hydroesterification, and arylation of norbornenes. However, stereo- or site-selective modification of norbornenes have been limited, those reactions almost always afford *exo*- and *anti*-substituted norbornanes.[2] Here, we describe the Rh-catalyzed stereo (*exo* vs *endo*)- and site (*syn* vs *anti*)-selective hydroacylation[3] of norbornene derivatives, based on steric, chelation,[4,5] and remote substituent effects.

An intermolecular hydroacylation of norbornylene (NB) **2** with salicylaldehyde **1** using Rh-complex $[RhCl(cod)]_2$, was reported by the Miura group.[6] Unfortunately, the isolated yield of *exo*-hydroacylated norbornane was merely 6–39% (Scheme 1).



Scheme 1. Reported Rh-catalyzed intermolecular hydroacylation of norbornylene.[6]

Thus, we envisaged that the stereoselective hydroacylations would occur under mild reaction conditions by using a Wilkinson-complex $RhCl(PPh_3)_3$,[7] based on our 'chelation' and 'double-chelation' concepts.[5] The results are summarized in Table 1.

The intermolecular hydroacylation of **2** with **1** by the $RhCl(PPh_3)_3$ could not proceed at room temperature, but fortunately the hydroacylation proceeded at 80 °C to give the *exo*-hydroacylated product **5** in quantitative yield (entry 1). Addition of $AgClO_4$, which may produce a cationic Rh-complex, promoted the hydroacylation to give the *exo*-**5** even at room temperature (entry 3). The hydroacylation of *exo*-5,6-(isopropylidenedioxy)norbornene (IDN) **3**, bearing an acetonide function by using $RhCl(PPh_3)_3$ and K_2CO_3 afforded *exo*-**6** in 55% yield (entry 5). The addition of $AgClO_4$ was advantageous to promote the hydroacylation at room temperature, albeit the isolated yield was not satisfactory (entry 6). The stereochemistry of **5** and **6** were determined to be *exo* on the basis of the NOESY ^1H NMR spectra. Moreover, the stereochemistry of **6** was unambiguously

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Keywords: Rh-complex; Hydroacylation; Norbornene; π-Facial selection; C–C forming reaction; C–H activation.

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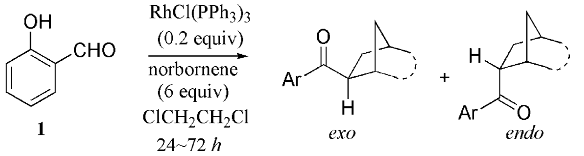
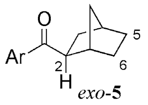
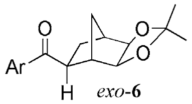
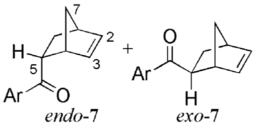
Table 1. Rh-catalyzed intermolecular hydroacylation of norbornenes and NBD with salicylaldehyde



Entry[a]	Norbornene	Additive	Temp (°C)	Product: % yield (ratio: *endo*/*exo*)	
1	NB **2**	—	80	 *exo*-**5**	>99[b]
2	NB **2**	K_2CO_3	rt		—
3	NB **2**	$AgClO_4$	rt		90[b]
4	IDN **3**[c]	—	80	 *exo*-**6**	36[b]
5	IDN **3**	K_2CO_3	80		55[b]
6	IDN **3**	$AgClO_4$	rt		21[b]
7	NBD **4**	—	80	 *endo*-**7** *exo*-**7**	16 (5/1)
8	NBD **4**	K_2CO_3	rt		81 (15/1)
9	NBD **4**	K_2CO_3	80		>99 (20/1)[d]
10	NBD **4**	K_2CO_3	80		91 (2/1)[e]
11	NBD **4**	K_3PO_4	80		>99 (>25/1)[d]

[a] Hydroacylation using benzaldehyde could not proceed.

[b] *endo*-Product was not detected.

[c] *exo*-5,6-(Isopropylidenedioxy)norbornene.

[d] The reaction was completed within 5 h.

[e] 0.05 equiv of Rh-catalyst was used.

confirmed to be *exo* by the X-ray crystallographic analysis.[8]

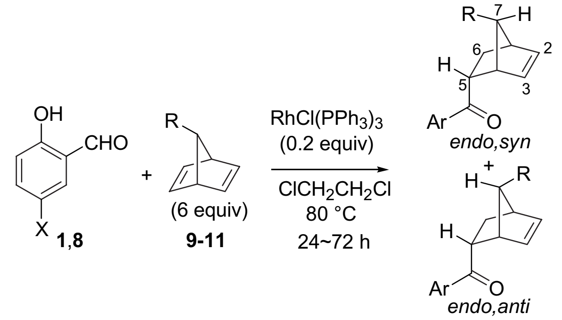
The hydroacylation of norbornadiene (NBD) **4** with **1** by $RhCl(PPh_3)_3$ proceeded in the presence of either K_2CO_3 or K_3PO_4, to give a mixture of *endo*- and *exo*-hydroacylated products **7**. The yield was 81% at room temperature (entry 8), and in quantitative at 80 °C (entries 9–11). The *endo*-**7** was predominantly formed in the reaction of **4**. It is noteworthy that the Rh-catalyzed hydroacylation of NBD **4** preferentially afforded *endo*-**7**, whereas that of norbornenes **2** and **3** gave *exo*-**5** and *exo*-**6** but no *endo*-products were produced. In entry 10, even though the $RhCl(PPh_3)_3$ was reduced to 0.05 equiv, the hydroacylation proceeded smoothly, but the *endo*/*exo*-stereoselectivity decreased. This low *endo*/*exo*-selectivity would be attributed to the fact that the *endo*-**7** could be converted into the thermodynamically stable *exo*-**7**.[9] The best *endo*/*exo*-selectivity (>25:1) of **7** was accomplished when K_3PO_4 was added and the reaction was completed in the shortened reaction time (entry 11).[10]

Next, we examined the Rh-catalyzed hydroacylation of 7-substituted NBDs (Table 2).[11] By treatment with the $RhCl(PPh_3)_3$ at 80 °C, salicylaldehyde **1** and 7-*tert*-butoxynorbornadiene **9** reacted to produce an *endo*,*syn*-hydroacylated product **12** in 11% yield (entry 1).[2b,12] The reaction of **9** with 5-nitrosalicylaldehyde **8**, instead of **1**, afforded two diastereomeric isomers *endo*,*syn*-**13** (63%) and *endo*,*anti*-**13** (20%) (entry 2). The NOESY ^1H NMR spectra suggested that the stereochemistry of the major product was *endo*,*syn* and that of the minor product was *endo*,*anti*.[12] Finally, the stereochemistry of *endo*,*syn*- and *endo*,*anti*-**13** was confirmed by the X-ray crystallographic analyses.[8] Addition of bases promoted the hydroacylation, probably by deprotonation of salicylaldehyde, and thus, the *endo*,*syn*-**12** was exclusively isolated in quantitative yield in the presence of K_3PO_4 (entries 3 and 4). However, the use of a reduced amount of $RhCl(PPh_3)_3$ (0.05 equiv) was detrimental for the site-selectivity.

The Rh-catalyzed hydroacylation of **10** bearing a 7-phenyl substituent afforded an inseparable 1 to 1 mixture of *endo*,*syn*- and *endo*,*anti*-**14**, along with a small amount of *exo*-product (entries 6–8). In the case of Rh-catalyzed hydroacylation of **11** bearing a 7-acetoxy substituent, the *endo*,*syn*-hydroacylated product was preferred to the *endo*,*anti*-product, but the selectivity was moderate (entries 10–12). The substituent at the C(7)-position strongly affected the reactivity and the site-selectivity of hydroacylation.[13,14a]

The Rh-catalyzed intermolecular hydroacylation might proceed via a catalytic cycle of oxidative addition and reductive elimination.[1c] The *endo*/*exo*-stereoselection could plausibly be explained on the basis of intermediates (*a*) and (*b*), as shown in Figure 1. Norbornylene cannot chelate to the Rh-metal because there is only one olefin. Thus, the steric hindrance affects the Rh–substrate intermediate, which produces *exo*-complex (*a*) as a favorable intermediate. In this case, only salicylaldehyde chelates to the Rh-metal. On the other hand, the NBD can chelate to the Rh-metal because there are two olefins. As a result, *endo*-complex (*b*) may be the preferred intermediate for the chelation of NBD. In the intermediate (*b*), both salicylaldehyde and NBD chelate to the Rh-metal (double-chelation). It is notable that the *syn*-positional olefin of the two olefins in 7-*tert*-butoxynor-

Table 2. Rh-catalyzed intermolecular hydroacylation of 7-substituted NBDs with salicylaldehyde



Entry	NBD (R =)	Aldehyde (X =)	Additive (0.2 equiv)	Products: % yield (ratio: *endo*: *syn*/*anti*)
1	**9**: O-*t*Bu	H	—	**12**: 11 (11/0)
2	**9**: O-*t*Bu[a]	NO_2	—	**13**: 83 (63/20)[b]
3	**9**: O-*t*Bu	H	K_2CO_3	**12**: 51 (51/0)
4	**9**: O-*t*Bu	H	K_3PO_4	**12**: >99 (>99/0)[c]
5	**10**: Ph	H	—	**14**: 0
6	**10**: Ph	NO_2	—	**15**: 68 (1/1)
7	**10**: Ph	H	K_2CO_3	**14**: 43[d]
8	**10**: Ph	H	K_3PO_4	**14**: 75[d]
9	**11**: OAc	H	—	**16**: 0
10	**11**: OAc[a]	NO_2	—	**17**: 72 (42/30)[b]
11	**11**: OAc	H	K_2CO_3	**16**: 84 (61/23)[b,e]
12	**11**: OAc	H	K_3PO_4	**16**: 87 (66/21)[b,e]

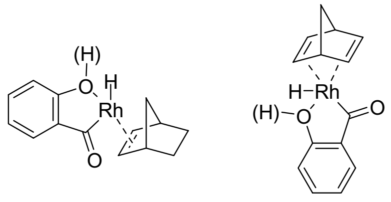
[a] 1.2 equiv of NBD was used.

[b] Separated.

[c] The use of 0.05 equiv of Rh-complex afforded *endo,syn*-**12** (60%) and *endo,anti*-**12** (8%).

[d] Inseparable mixture of stereoisomers.

[e] Trace amount of *exo*-products were detected.

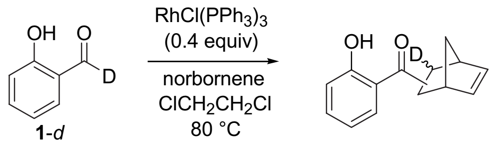


intermediate (*a*) intermediate (*b*)

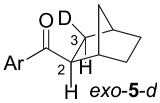
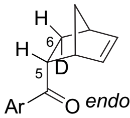
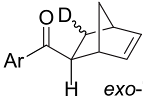
Figure 1. Plausible intermediates. In the intermediate (*a*) chelation of salicylaldehyde is formed, whereas in the intermediate (*b*) both chelations of salicylaldehyde and NBD are formed (double-chelation).

bornadiene was discriminated by the Rh-catalyzed reaction, and exclusively hydroacylated to produce the *endo,syn*-**12**. This site-selectivity may be attributed to the fact that the π orbital on the *endo,syn*-side of the olefin would be distorted by the opposite-side bulky and electronegative 7-*tert*-butoxy substituent, and the *endo,syn* π orbital may become more reactive.[13] That is to say, the discrimination of olefinic π faces can be attained not only by conventional stereochemical effect, but also by the π orbital distortion induced by a remote substituent effect.[14]

Table 3. Experiments by using deuterated salicylaldehyde **1**-*d*



1-*d*

Entry	Norbornene (6 equiv)	Product: % yield		
		(Ratio: *endo*/*exo*)		*d*-content %
1	NB **2**	 *exo*-**5**-*d*	52	35
2[a]	NBD **4**	 *endo*-**7**-*d* +  *exo*-**7**-*d*	37 (3/1)	80 Not determined

[a] K_3PO_4 (0.2 equiv) was used.

To obtain mechanistic information, the hydroacylation using deuterated salicylaldehyde **1**-*d* was examined (Table 3). The reaction between **1**-*d* (1.0 equiv) and NB **2** (6.0 equiv) with the $RhCl(PPh_3)_3$ afforded the hydroacylated product.[6] The molecular ion peak m/z 217 (M^+) in the EI-MS spectrum indicated the existence of deuterium in **5**-*d*. This result is in contrast with the case of 1,5-hexadiene, in which the use of 6.0 equiv of 1,5-hexadiene afforded a non-deuterated product.[5b] The ^1H NMR spectrum of **5**-*d* showed the methylene H_{exo} signal of the C(3)-position at δ 2.04 (m, 0.65H) and the H_{endo} signal of the C(3)-position at δ 1.51 (m, 1H), indicating that 35% of *exo*-H at the C(3)-position was deuterated. These results suggested that the reaction proceeded via *exo*-Rh-coordinated norbornylene intermediate (a) in Figure 1.

The hydroacylation between **1**-*d* and NBD **4** (6.0 equiv) with the $RhCl(PPh_3)_3$ and K_3PO_4 afforded a mixture of *endo*-**7**-*d* and *exo*-**7**-*d* (3:1). The ^1H NMR spectrum of *endo*-**7**-*d* showed the methine H_{exo} signal of the C(5)-position at δ 3.90 (dd, $J = 3.4, 9.3$ Hz, 0.75H), the methylene H_{exo} signal of the C(6)-position at δ 1.97 (dm, $J = 9.3$ Hz, 0.75H), and the H_{endo} signal of the C(6)-position at δ 1.63 (m, 0.15H), suggesting the *d*-content in *endo*-**7**-*d* was 80% at the H_{endo} of C(6)-position.[15] The *d*-content of *exo*-**7**-*d* could not be determined due to the signal overlap. These results support the hypothesis that the hydroacylation of **4** mainly proceeded via *endo*-intermediate (*b*) to produce *endo*-**7** by *syn*-addition of hydride and acyl groups.

We developed *endo*, *exo*, and site selective Rh-catalyzed intermolecular hydroacylations. It is noteworthy that *endo* versus *exo*-selectivity drastically changed between NBs and NBD, and the stereoselective mechanisms could be explained on the basis of the 'chelation' and 'double-chelation' intermediates. Furthermore, the hydroacylation of 7-*tert*-butoxynorbornadiene exclusively afforded the *endo,syn*-hydroacylated product by the remote substituent effect. So far, no such transition-metal catalyzed π-facial selective modifications of norbornenes have been reported.

These results show that the concepts 'chelation' and 'double-chelation' are useful not only for the enhancement of reactivity,[5] but also for the control of stereoselectivity.

Acknowledgments

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8. CCDC-260662, 260663, and 260664 contain the supplementary crystallographic data for this letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
9. In the case that the isolated *endo*-**7** and K_2CO_3 in $ClCH_2CH_2Cl$ was heated at 80 °C, *endo*-**7** was partly converted into *exo*-**7**.
10. General procedure for the Rh-catalyzed reactions: A solution of salicylaldehyde **1** (61 mg, 0.50 mmol), norbornene (3.0 mmol), additive (0.10 mmol), and $RhCl(PPh_3)_3$ (92 mg, 0.10 mmol) in $ClCH_2CH_2Cl$ (10 mL) was stirred at 80 °C under Ar atomosphere. After being cooled to room temperature, the solution was evaporated in vacuo, and the residue was purified by column chromatography on silica gel to give the hydroacylated product. In the case that some impurities were contaminated, the product was purified by gel permeation chromatography (GPC; column, JAIGEL 1H and JAIGEL 2H; eluent, $CHCl_3$; flow rate, 3.8 mL/min).
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15. The stability and reactivity of Rh-substrate intermediates would affect the *d*-content % of products.