Doctoral Dissertation

Studies on Catalytic Transformation of Aldehydes via η^2-Coordination to Nickel(0)

Yoichi Hoshimoto

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Graduate School of Engineering
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Preface and Acknowledgements

The study in this thesis has been carried out under the direction of Professor Sensuke Ogoshi at the Department of Applied Chemistry, Faculty of Engineering, Osaka University from April 2008 to March 2013. The thesis describes the catalytic transformation of aldehydes via η^2-coordination to nickel(0).

For accomplishment of my works, there were really lots of helps, advices, and supports. I owe all of them a great debt of gratitude; however, I regret to say that I cannot all of them here.

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Yoichi Hoshimoto

Contents

Abbreviations

The following abbreviations are used in the thesis.

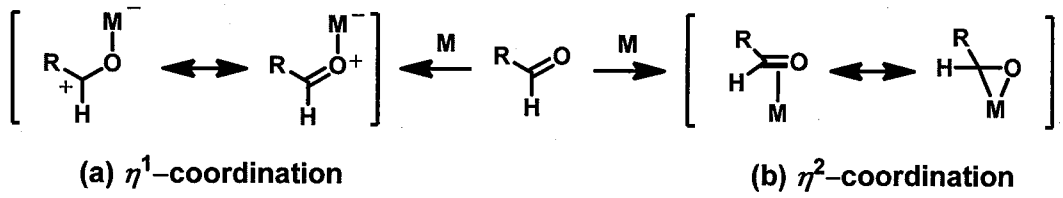
anal.	Elemental anaylsys
Ac	acetyl
aq.	aqueous
Ar	aryl
br	broad
Bn	benzyl
Bu	butyl
cat.	catalyst
cf.	confer
CI	chemical ionization
cod	1,5-cyclooctadiene
Cy	cyclohexyl
C	temperature in degrees centigrade
d	doublet
δ	chemical shift of NMR signal in ppm
EI	electron ionization
eq.	equation
equiv	equivalent
Et	ethyl
Et_2O	diethylether
GC	gas chromatography
h	hour(s)
Hex	hexyl
HMBC	hetero-nuclear multiple-bond connectivity
HMQC	hetero-nuclear multiple quantum coherence
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass specra
Hz	hertz
i	iso
IR	infrared spectroscopy
J	coupling constant in NMR
KIE	kinetic isotope effect
L	ligand
M	metal
m	meta
Me	methyl
min	minute(s)
mL	milliliter
µL	microliter
MS	mass spectral
n	normal
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance

o	ortho
ORTEP	Oak Ridge thermal ellipsoid plot
p	para
Ph	phenyl
Pr	propyl
PR_3	trialkyl- or triaryl-phosphine
q	quartet
quant	quantitative
ref.	reference
RT	room temperature
s	singlet
sept	septet
sext	sextet
t	triplet
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
t	triplet

Chapter 1

General Introduction

Aldehydes are one of the most important carbonyl compounds, and often need to be activated for their use in organic synthesis. Thus, a number of methods to activate aldehydes have been developed to date.[1a] The coordination of an aldehyde to typical and transition metals has been accepted as an especially important method. For example, an η^1-coodination of carbonyl oxygen to Lewis acidic metals has been well-known (Scheme 1.1a).[1] Such η^1-coordination results in an enhancement of electrophilicity at the carbonyl carbon, which allows aldehyde to react with nucleophiles. An η^2-coordination of aldehydes to the low-valent transition metals has been also well-studied.[2,3] The η^2-aldehyde complex has a contribution of an oxametallacyclopropane structure as a resonance structure due to the back bonding from the metals (Scheme 1.1b). Since Roper's first report on the isolation of η^2-formaldehyde Os(0) complex in 1979,[2m,4] a variety of η^2-aldehyde transition metal complexes have been reported. Nevertheless, only a few numbers of catalytic reactions via η^2-aldehyde complexes have been developed except nickel(0) catalysis (*vide infra*).

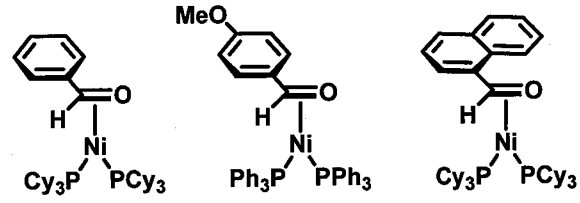


Scheme 1.1. Activation of aldehydes via (a) η^1-coodination to Lewis acidic metals and (b) η^2-coordination to low-valent transition metals.

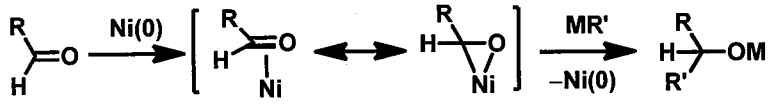
In order to generate an η^2-aldehyde intermediate in transition-metal catalysis, a catalyst should donates electrons strongly to the aldehyde by back bonding. The combination of electron-rich nickel(0) and strong electron-donating ligands, such as PR_3 or NHCs, is a potential candidate for such a catalyst. Especially, NHCs are promising candidates since they have an electron lone pair in a higher energy σ orbital than even basic phosphines, such as PCy_3.[5] Thus, the strong back bonding from nickel(0)/NHC catalyst to substrates would be expected.

Several reports on the isolation of (η^2-aldehyde)$Ni(PR_3)_2$ complexes have been known to date (Scheme 1.2).[3] In addition, nickel(0)-catalyzed intermolecular addition of organometallic reagents to aldehydes via η^2-aldehyde nickel(0) intermediates has been reported (Scheme 1.3).[6] In these reports, the contribution of oxanickelacyclopropane structure was proposed. For early examples, Shirakawa and Oshima independently reported the nickel(0)/PR_3-catalyzed arylation and alkylation of aldehydes with organoboron reagents, respectively.[6a,b] As another example, Woodward reported the

asymmetric addition of organoaluminum reagents to aldehydes catalyzed by nickel(0).[6f] These reports are rare examples of metal-catalyzed transformation of aldehydes to which the contribution of oxametallacyclopropane structure was applied.[7]

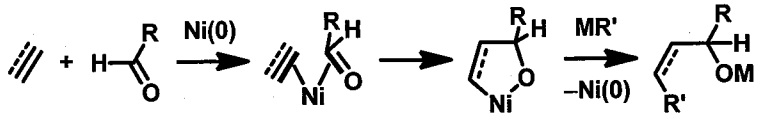


Scheme 1.2. Examples for isolated (η^2-aldehyde)Ni(PR_3)$_2$ complexes.



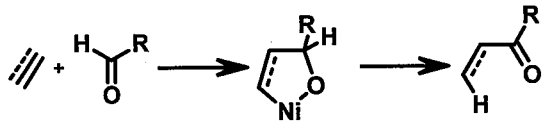
Scheme 1.3. Nickel(0)-catalyzed addition of organometallic reagents to aldehydes via η^2-aldehyde nickel(0) complex and oxanickelacyclopropane as a key intermediate.

It has been also known that aldehydes and unsaturated compounds such as alkene, alkyne, diene, and allene coordinate to nickel(0) simultaneously (Scheme 1.4).[8] Then, the oxidative cyclization takes place to give an oxanickelacycle with the formation of C–C, C–Ni, and O–Ni bonds. The oxanickelacycles have been often found as key intermediates in the nickel(0)-catalyzed multi-component coupling reactions, which have been extensively studied by our group, Montgomery, Jamison and Sato.



Scheme 1.4. Nickel(0)-catalyzed multi-component coupling reaction.

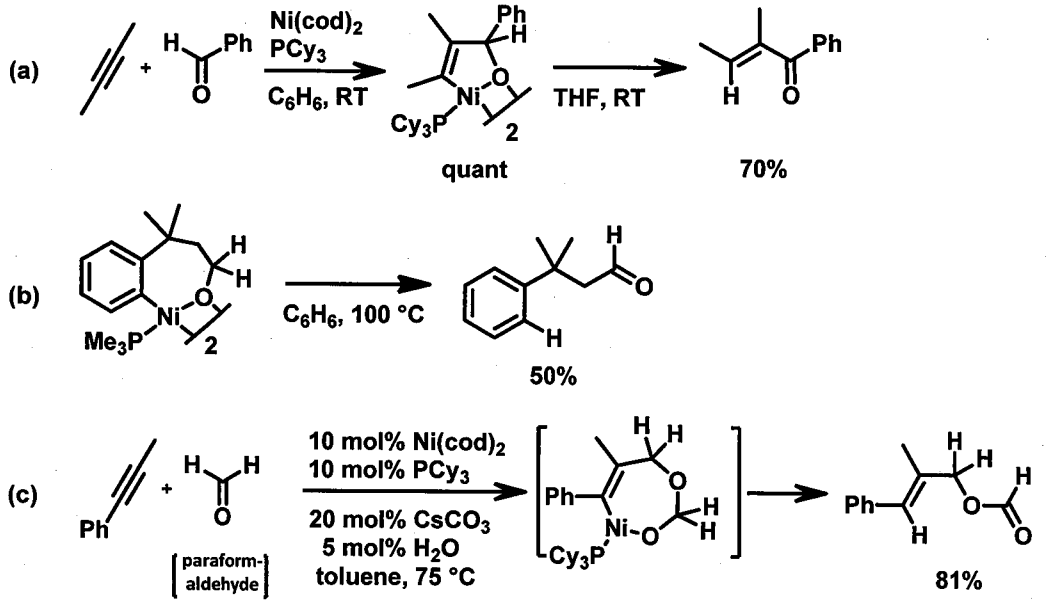
The oxanickelacycle has a β-hydrogen derived from the aldehyde. Thus, the transformation via the elimination of this β-hydrogen can be designed (Scheme 1.5).



Scheme 1.5. β-Hydrogen elimination from oxanickelacycles giving acyl compounds.

In fact, synthesis of an enone was reported via β-hydrogen elimination from an oxanickelacycle prepared by the stoichiometric reaction of an alkyne, an aldehyde, and

nickel(0)/PCy_3 (Scheme 1.6a).[3e] Hillhouse also demonstrated β-hydrogen elimination from seven-membered oxanickelacycle as shown in Scheme 1.6b.[9] As an example on catalytic reaction, Breit and Krische reported the nickel(0)/PCy_3-catalyzed synthesis of a formate via β-hydrogen elimination from a seven-membered dioxanickelacycle intermediate generated by the oxidative cyclization of an alkyne and two equimolar amount of formaldehyde (generated from paraformaldehyde) on nickel(0) (Scheme 1.6c).[10] These reactions are an ideal method to prepare acyl compounds because of their high atom-efficiency; however only three reports mentioned above have been reported.



Scheme 1.6. For examples on β-hydrogen elimination from (a, b) oxa- and (c) dioxa-nickelacycle complexes.

The purpose of this study is the development of catalytic transformation via η^2-coordination of aldehydes to nickel(0), which has remained relatively unexplored in organic synthesis. Especially, this study focuses on the development of the reactions proceeding via β-hydrogen elimination from oxanickelacycle intermediates. This thesis consists of the general introduction in this chapter and the following four chapters.

In chapter 2, the nickel(0)-catalyzed intramolecular alkene hydroacylation is reported. The key to achieve the reaction is the formation of (η^2-alkene)(η^2-aldehyde)Ni(0) and oxanickelacycle intermediates, both of which were isolated.

Chapter 3 describes the nickel(0)-catalyzed homo-dimerization of aldehydes. The reaction would proceed via bis(η^2-aldehyde)Ni(0) intermediate, which was directly observed by means of NMR spectroscopy.

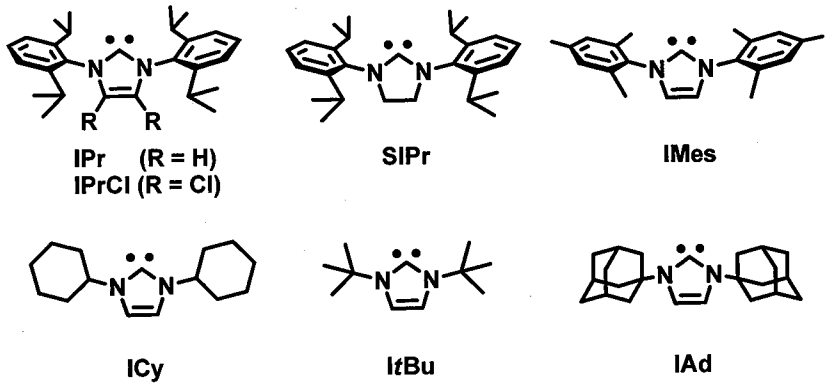
Furthermore, an application of the nickel(0) catalyst developed in chapter 3 to

crossed dimerization of aliphatic and aromatic aldehydes is discussed in chapter 4. Experimental results supported that reaction would take place via β-hydrogen elimination from dioxanickelacycle intermediate.

Demonstrated in chapter 5 is the nickel(0)-catalyzed electrophilic addition of arysilanes to (η^2-aldehyde)Ni(0) complex.

Finally, this thesis is summarized in the conclusion.

In order to achieve the works in chapters 2–5, an activation of substrates coordinated to nickel(0) through back bonding has been crucial. Thus, as strong σ-electron-donating ligand to activate nickel(0), NHCs depicted in Scheme 1.7 have been employed.[11]



Scheme 1.7. NHCs employed in this thesis.

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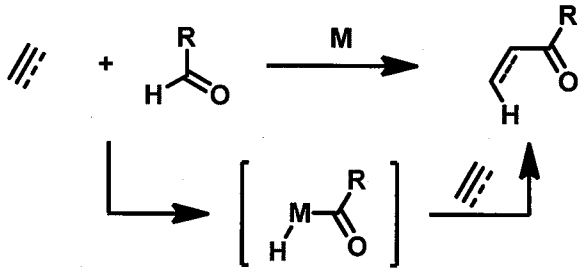
Chapter 2

Ni(0)-Catalyzed Intramolecular Hydroacylation via (η^2-Aldehyde)(η^2-Alkene)Nickel(0) Intermediate

Abstract: Ni(0)/NHC catalyst system was found to be highly effective for intramolecular alkene hydroacylation to afford a variety of five-membered benzocyclic ketones, of which structural motifs have been found in the synthetic intermediates of numerous biologically active natural products and medicinal agents. Furthermore, the method can be applied to the synthesis of six-membered benzocyclic ketones, which were difficult to prepare by the reported hydroacylation systems without chelation assistance by heteroatoms. This reaction represents 100% atom-efficiency and generates no waste. The results of mechanistic studies including the isolation of an oxanickelacycle, a key reaction intermediate, the structure of which was unambiguously identified by X-ray crystallography, were discussed.

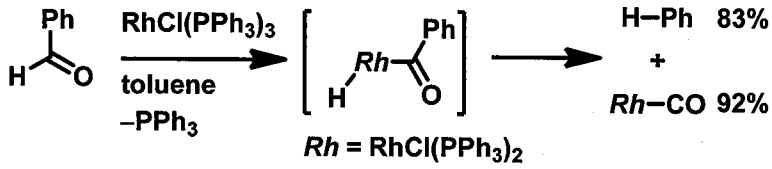
2.1. Introduction

Transition-metal-catalyzed hydroacylation has been accepted as a promising synthetic method to form C–C bonds between an aldehyde and unsaturated compounds, such as alkenes and alkynes (Scheme 2.1).[1] The most accepted mechanism for



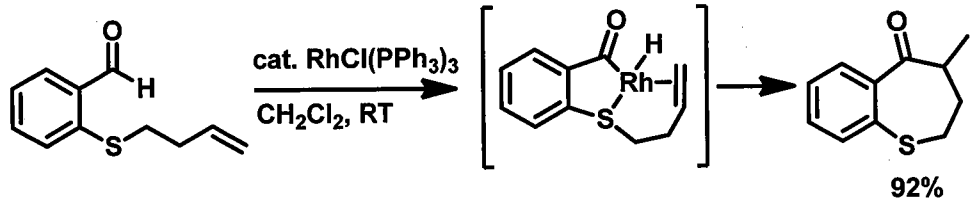
Scheme 2.1. Transition-metal-catalyzed hydroacylation.

transition-metal-catalyzed hydroacylation includes an acyl metal intermediate generated by the oxidative addition of the aldehyde to the metal center. This acyl metal complex was also proposed as a key intermediate in transition-metal-catalyzed decarbonylation of aldehydes. For example, Tsuji reported that the decarbonylation of benzaldehyde took place in the presence of $RhCl(PPh_3)_3$ to give benzene and rhodium carbonyl complex $(CO)RhCl(PPh_3)_2$ (Scheme 2.2).[2] Many strategies have been developed for the



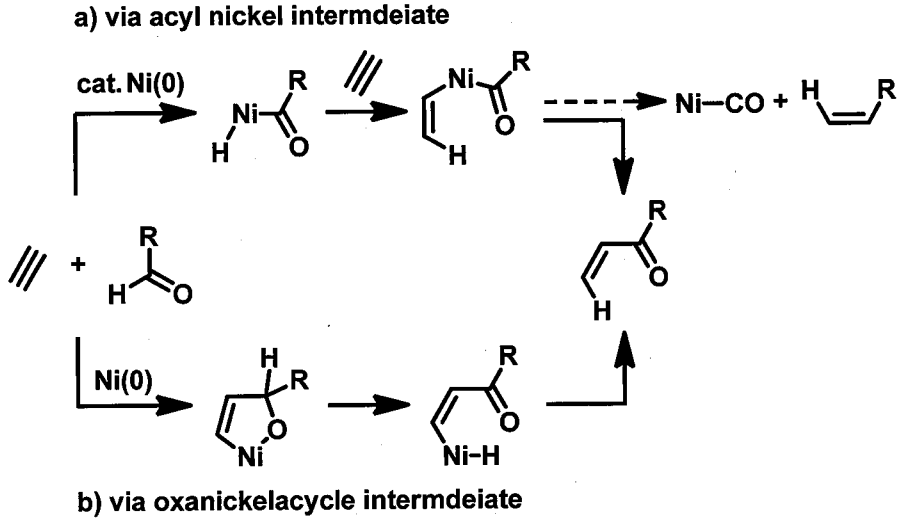
Scheme 2.2. Decarbonylation of benzaldehyde with $RhCl(PPh_3)_3$.

hydroacylation reaction to suppress decarbonylation from the acyl metal intermediate since the decarbonylation decreases a yield of the target compound and deactivates the catalyst through the coordination of carbon monoxide. Chelation-assisted procedures are one of the most important methods.[3,4] For an example on an intramolecular alkene hydroacylation, Bendorf reported the formation of seven-membered cyclic ketones catalyzed by $RhCl(PPh_3)_3$ (Scheme 2.3).[3b] In this reaction, an introduction of suitable chelation assistance by the sulfur was essential to suppress the decarbonylation through coordination to a vacant site of the acyl rhodium intermediate. These developments of strategies and catalysts have contributed to achieve the high enatio-, regio-, and chemo-selectivity.[1] In the interest of promoting further progress, it is worthwhile to provide an alternative strategy to avoid decarbonylation.



Scheme 2.3. Rh-catalyzed chelation-assisted alkene hydroacylation.

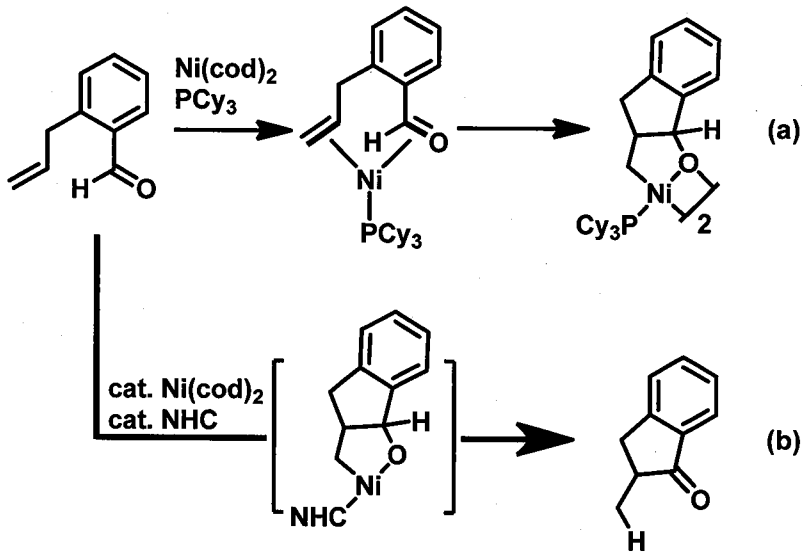
Tsuda and Saegusa reported Ni(0)/PR_3-catalyzed intermolecular alkyne hydroacylation to give α,β-enones.[5,6] They proposed two possible reaction pathways: a) proceeds through an acyl nickel intermediate, and b) proceeds through an oxanickelacycle intermediate (Scheme 2.4). They concluded that the former was more plausible because of the formation of decarbonylated olefinic product in the reaction with benzaldehyde. On the other hand, during the course of the research on heteronickelacycles,[7] our group demonstrated that an oxanickelacycle prepared by oxidative cyclization of an alkyne and an aldehyde with Ni(0) slowly decomposed to furnish an α,β-enone and no decarbonylated product.[7b] This result indicated that the oxanickelacycle can act as a potential intermediate in Ni(0)-catalyzed hydroacylation (Scheme 2.4b).



Scheme 2.4. Ni(0)-catalyzed alkyne hydroacylation through (a) an acyl nickel intermediate or (b) a nickelacycle intermediate.

The formation of dimeric oxanickelacycles in the stoichiometric reaction of *o*-allylbenzaldehyde (**1a**), $Ni(cod)_2$, and tertiary phosphines has been reported as well (Scheme 2.5a).[7a] Thus, the construction of a catalytic alkene hydroacylation through an oxanickelacycle seems quite effective for the generation of a benzocyclic ketone without decarbonylation (Scheme 2.5b). Given the importance of benzocyclic ketones,

the structural motifs of which have been found in the synthetic intermediates of numerous biologically active natural products and medicinal agents,[8,9] this new approach is an attractive method. Reported in this chapter is an intramolecular alkene hydroacylation catalyzed by a Ni(0)/NHC complex that yields a variety of five- and six-membered benzocyclic ketones. Mechanistic studies that include stoichiometric reactions and the isolation of (η^2-aldehyde)(η^2-alkene)nickel(0) and oxanickelacycle intermediate are also discussed.

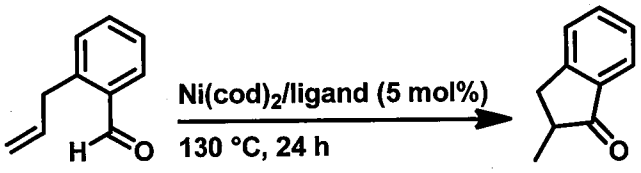


Scheme 2.5. (a) Formation of an oxanickelacycle complex with PCy_3. (b) Catalytic generation of a benzocyclic ketone without decarbonylation.

2.2 Optimization of Reaction Conditions

The results of the optimization of the reaction conditions are summarized in Table 2.1. The reaction of **1a** in toluene at 130 °C in the presence of $Ni(cod)_2/PPh_3$ (10 mol%) did not proceed at all (entry 1). In the case of PCy_3, **1a** was fully consumed. However was obtained a complicated mixture including a little amount of the hydroacylated ketone (**2a**) (9%) (entry 2). NHCs were examined instead of phosphines, and IAd and I^{t}Bu were found to be the best ligand to give **2a** in 93% yield (entries 8 and 9). Next, the effect of solvent on the reaction was surveyed by employing a combination of $Ni(cod)_2$/I^{t}Bu (5 mol%). As a result, mesitylene was found to be the best solvent giving **2a** in > 99% yield (entry 10). Although the use of THF, DME, and cyclohexane allowed the reaction to give **2a** in moderate to good yields (61–82%), ethyl acetate was ineffective probably due to the poor solubility of $Ni(cod)_2$.

Table 2.1. Ni(0)-catalyzed hydroacylation of **1a**.[a]



1a **2a**

entry	ligand	solvent	conversion of 1a (%)	yield (%)
1[b]	PPh_3	toluene	–	–
2[b]	PCy_3	toluene	> 99	9
3[b]	IPr	toluene	> 99	25
4[b]	IPrCl	toluene	95	30
5[b]	SIPr	toluene	98	24
6[b]	IMes	toluene	> 99	33
7[b]	ICy	toluene	> 99	39
8[b]	IAd	toluene	> 99	93
9	I^{t}Bu	toluene	>99	93 (93)[b]
10	I^{t}Bu	mesitylene	> 99	> 99
11	I^{t}Bu	THF	> 99	82
12	I^{t}Bu	DME	> 99	61
13	I^{t}Bu	cyc-hexane	> 99	77
14	I^{t}Bu	EtOAc	90	7

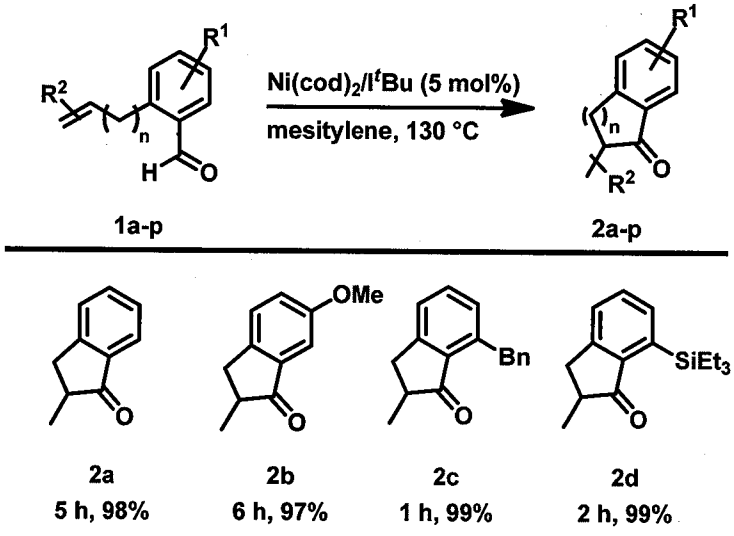
[a] Conversion of **1a** and yield of **2a** were determined by GC. [b] $Ni(cod)_2$/ligand (10 mol%) was used.

2.3 Ni(0)-Catalyzed Intramolecular Alkene Hydroacylation

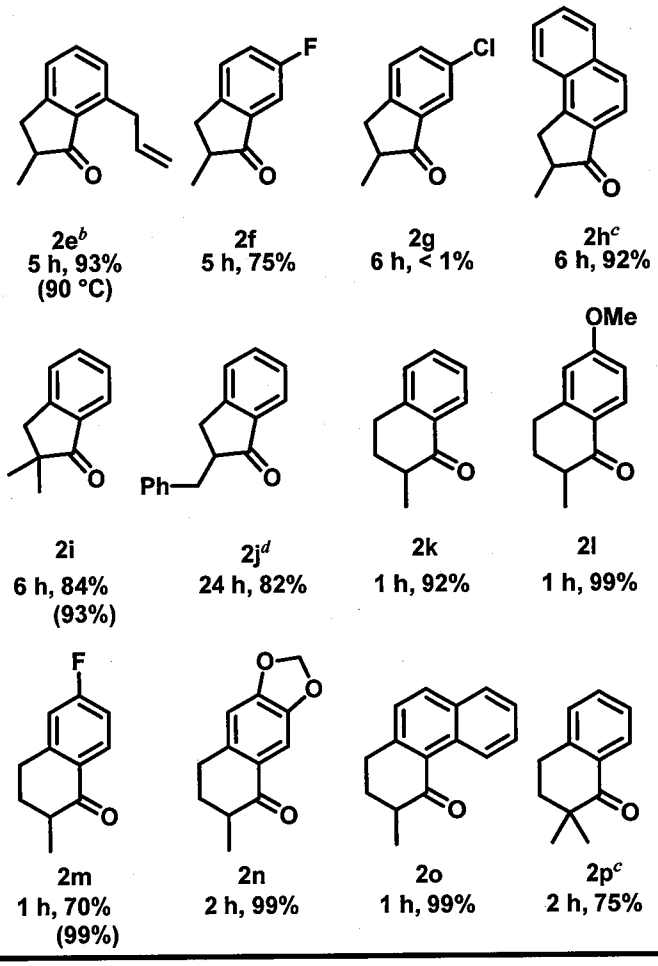
The scope of the reaction was investigated with respect to *o*-allylbenzaldehyde derivatives (**1a–j**) (Table 2.2). When an electron-donating group was bonded to the benzene ring (**1b–d**), the hydroacylation proceeded to give the corresponding indanones

(**2b–d**), which were isolated in > 97% yield. An optimization of the amount of catalysts and reaction temperature was required for the hydroacylation of 2,6-diallylbenzaldehyde (**1e**) because an isomerization of allyl group catalyzed by I^{t}Bu took place under the standard conditions. Fluorine-substituted product (**2f**) was obtained in moderate yield. Chlorine-substituted substrate (**1g**) did not afford the corresponding ketone (**2g**) and 95% of **1g** was recovered after isolation. In this case, *o*-allylbenzaldehyde was detected by GC-MS, thus the oxidative addition of an Ar–Cl bond to Ni(0) might deactivate the catalyst. Although Ni(cod)$_2$/I^{t}Bu (10 mol%) was required, **1h** was successfully converted into **2h** in 92% yield. This method can also be applied to substituted allyl groups (**1i** and **1j**) to give the corresponding ketones (**2i** and **2j**) in moderate to good yields. Furthermore, we applied the method to the hydroacylation of *o*-homoallylbenzaldehyde derivatives (**1k–p**). As mentioned above, the formation of six-membered (or larger) ring systems is difficult for reported transition-metal-catalyzed alkene hydroacylations,[3,10–12] as the rate of the ring closing step is much slower than that of the decarbonylation from the acyl metal intermediate.[1a] In the Ni(0)/I^{t}Bu-catalyst system, the formation of 1-tetralone derivatives was successfully achieved in excellent yields (**2k–o**, up to 99% yield) without the need for chelation assistance. A decrease in yield was observed in the case of **2p**, and the decarbonylated olefinic product, 2-methyl-4-phenylbutene was also detected in 2% yield by GC analysis (*vide infra*).

Table 2.2. Ni(0)-catalyzed intramolecular alkene hydroacylation.[a]



2a	2b	2c	2d
5 h, 98%	6 h, 97%	1 h, 99%	2 h, 99%

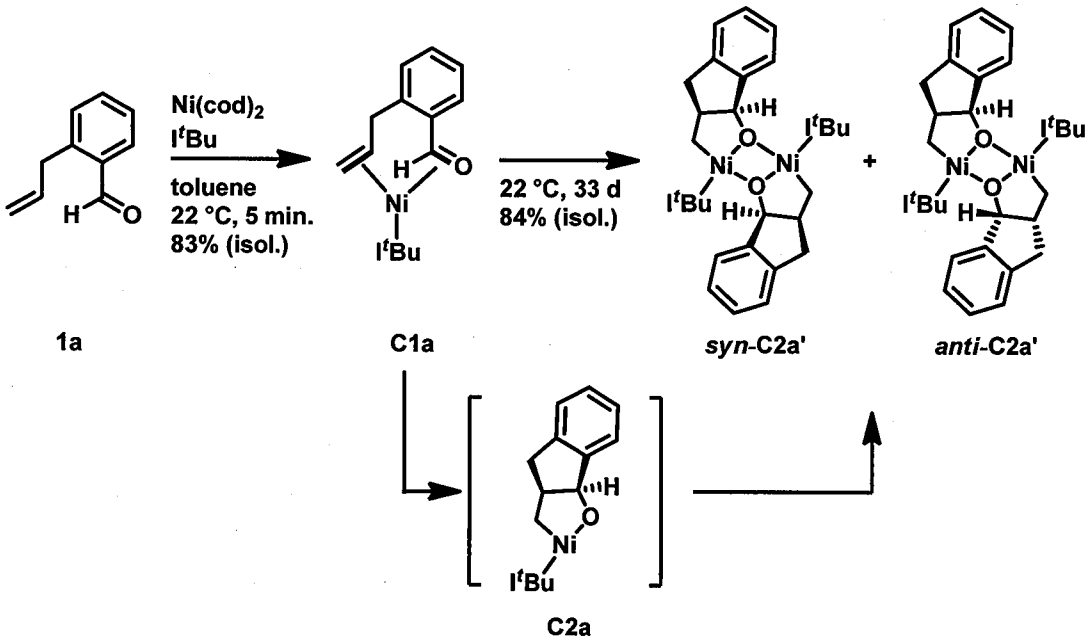


[a] General conditions; Enal **1a–p** (0.80 mmol), $Ni(cod)_2$/I^{t}Bu (0.040 mmol) and mesitylene (2 mL) were reacted at 130 °C. Yields of isolated product are presented. GC yields using *n*-pentadecane as an internal standard are given in parenthesis. [b] 7 mol% $Ni(cod)_2$ and 5 mol% I^{t}Bu were used in toluene. [c] $Ni(cod)_2$/I^{t}Bu (10 mol%) was used. [d] $Ni(cod)_2$/IMes (10 mol%) was used.

The presented Ni(0)-catalyzed hydroacylation is 100% atom-efficient and generates no waste. Thus, it is a highly environmentally favorable route to 1-indanone and 1-tetralone derivatives.[8, 9, 13] The most common approach to these compounds has been the intramolecular Friedel–Crafts acylation with conventional conditions that require excess amounts of acid promoters and high temperatures, particularly for the formation of 1-indanone.[14] Thus, the approach for the preparation of five- and six-membered benzocyclic ketones demonstrated here has synthetic utility.

2.4. Mechanistic Studies

To gain insight into the reaction mechanism, some stoichiometric reactions were conducted (Scheme 2.6). The treatment of **1a** with $Ni(cod)_2$ and I^tBu in C_6D_6 (or toluene) at 22 °C resulted in the quantitative formation of (η^2:η^2-CH_2=$CHCH_2C_6H_4CHO$)Ni(I^tBu) (**C1a**) within 5 min, which was isolated in 83% yield. Complex **C1a** was converted into dimeric oxanickelacycle (**C2a'**), which was isolated in 84% yield (22 °C, 33 days). The monomeric complex (**C2a**) was not observed by NMR spectroscopy measured at 22 °C; however, it is logical that **C2a'** was formed through the dimerization of **C2a**. The structure of **C2a'** in solution was identified by NMR as a mixture of two isomers, *syn*-**C2a'** and *anti*-**C2a'** (*syn*/*anti* = 3/2) (Figure 2.1). Moreover, the molecular structure of *anti*-**C2a'** was confirmed by X-ray crystallography (Figure 2.2).[15]



Scheme 2.6. Stoichiometric reaction of **1a** with $Ni(cod)_2$/I^tBu.

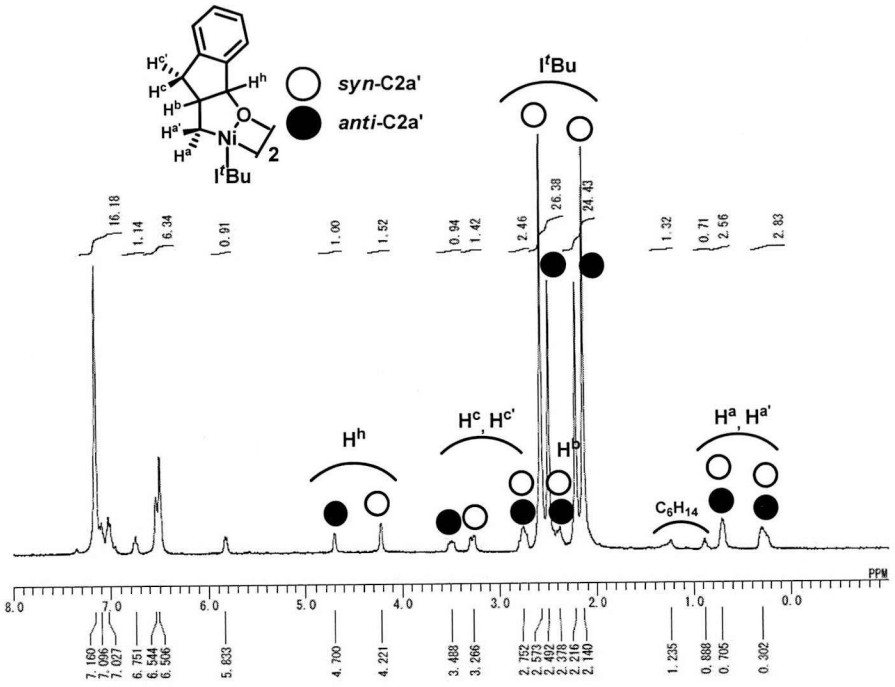


Figure 2.1. ^{1}H NMR (400 MHz, C_6D_6) for **C2a'** (*syn*/*anti*-mixture).

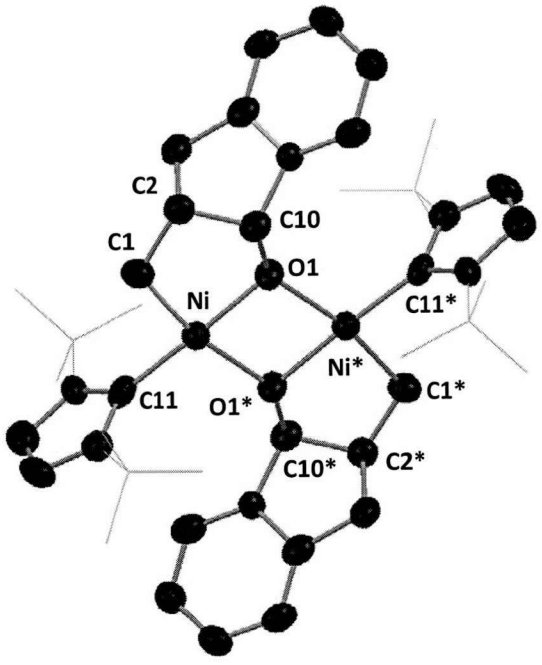
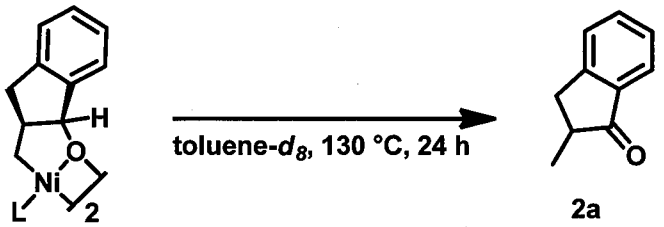


Figure 2.2. Molecular structure of *anti*-**C2a'** with thermal ellipsoids set at 50% probability. Calculated hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Ni–O1 1.883(6), Ni–C1 1.918(6), C2–C10 1.883(6); selected angles (°): C1–Ni–O1 87.6(3), O1*–Ni–C11 103.1(3), C1–Ni–C11 89.6 (4), O1–Ni–O1* 79.7(2).

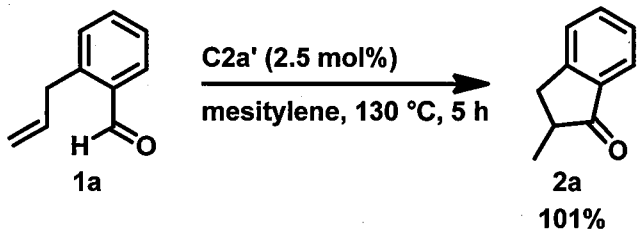
The conversion of **C2a'** into the hydroacylated ketone **2a** was observed in 32% yield when **C2a'** was heated at 130 °C for 24 h (Scheme 2.7). On the other hand, thermolysis of the PCy_3 complex at 130 °C for 24 h proceeded to completion, giving a complicated mixture of **2a** (35%) and unidentified products. This result rationalized the inefficiency of the formation of **2a** under the catalytic condition with PCy_3 (entry 2, Table 2.1).



L	conv.	
I^tBu (C2a')	32%	32%
PCy_3	100%	35%

Scheme 2.7. Thermolysis of the oxanickelacycles.

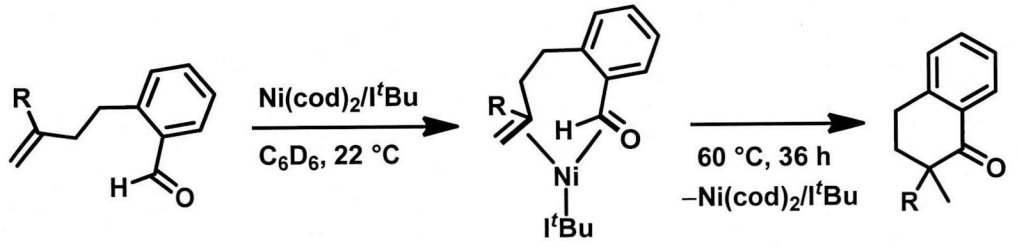
In the presence of 2.5 mol% **C2a'**, **2a** was obtained in 101% from both **1a** and **C2a'** (maximal yield of **2a** is 105%) within 5 h (Scheme 2.8). The results shown in schemes 2.7 and 2.8 would support the participation of the oxanickelacycle in the presented hydroacylation. In addition, equilibrium between **C2a** and **C2a'** would be existed under the catalytic conditions.



Scheme 2.8. Hydroacylation of **1a** in the presence of **C2a'**.

The stoichiometric reaction of **1k** or **1p** with $Ni(cod)_2/I^tBu$ was also examined to confirm whether the decarbonylation occurs through (η^2:η^2-enal)Ni(I^tBu) complex (**C1**) or not. Both **1k** and **1p** quantitatively reacted with $Ni(cod)_2/I^tBu$ to give **C1k** and **C1p**, respectively (Scheme 2.9). The structure of **C1k** was confirmed by X-ray analysis (Figure 2.3). Thermolysis of **C1k** or **C1p** in C_6D_6 at 60 °C for 36 h resulted in the quantitative formation of the corresponding tetralone derivatives (**2k** or **2p**) with the regeneration of $Ni(cod)_2/I^tBu$.[16] Although a small amount of the decarbonylated olefinic product was observed in the catalytic reaction of **1p**, no decarbonylated product was observed by ^1H NMR or GC-MS analysis during the formation of **2p** from **C1p**. Based

on these results, **C1p** afforded **2p** exclusively, and the lower yield of **2p** than that of **2k** in the catalytic reaction could be rationalized by the slower formation of **C1p** (24 h) than that of **C1k** (30 min).[17] Thus, the simultaneous coordination of alkene and aldehyde moieties would be crucial to avoid the decarbonylation, and to form the oxanickelacycle by oxidative cyclization on nickel(0).[7a]



Scheme 2.9. Stoichiometric reactions with **1k** and **1p**.

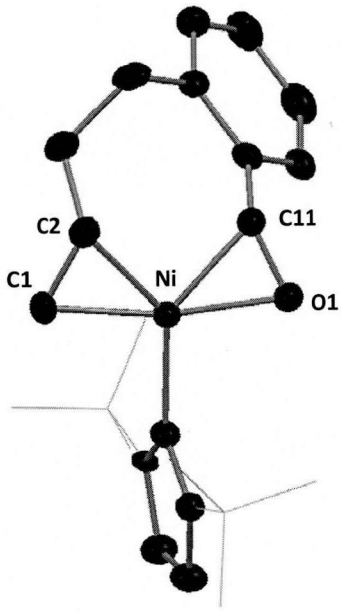
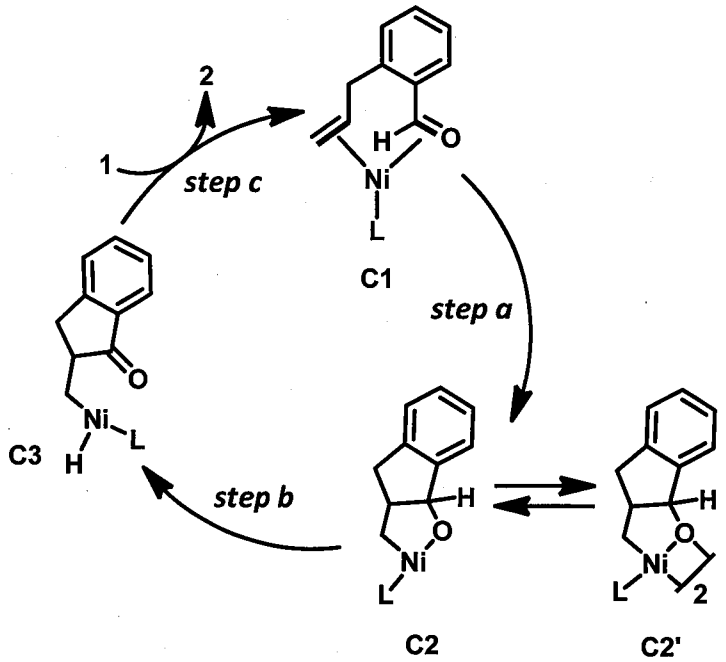


Figure 2.3. Molecular structure of **C1k** with thermal ellipsoids set at 50% probability. Calculated hydrogen atoms are omitted for clarity.

2.5. Plausible Reaction Mechanism

This intramolecular hydroacylation might proceed through the steps shown in Scheme 2.10. The coordination of **1** to Ni(0)/L gives rise to **C1** and the oxidative cyclization then occur to give a monomeric nickelacycle intermediate **C2** (step a). Then,

β-hydrogen elimination yields **C3** (step b) followed by the reductive elimination giving **2** (step c), along with regeneration of the catalyst. The dimeric oxanickelacycle (**C2'**) might influence the observed rate constant, but it would not be included in the catalytic cycle to afford **2**.



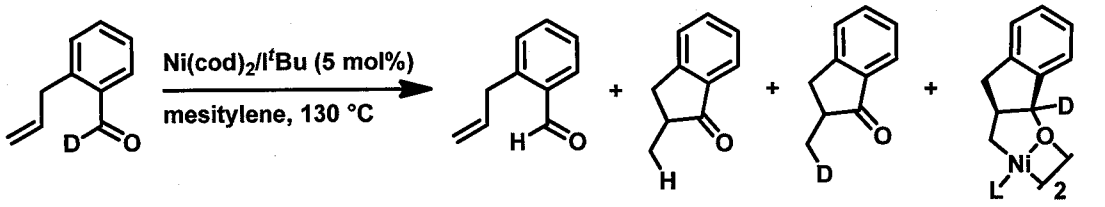
Scheme 2.10. A plausible reaction mechanism for Ni(0)-catalyzed intramolecular hydroacylation.

2.6. Kinetic studies

In order to explore the change in the concentration of **1a**, the hydroacylation of **1a** was monitored by GC analysis. The rate constant for disappearance of **1a** (k_s = 1.88(8)×10^{-3} mol m^{-3} min^{-1}) is zeroth-order with respect to the concentration of **1a**. This result indicates that the coordination of **1a** to nickel(0) is not the rate-limiting step in the reaction. The rate constant for the production of **2a** was a rather small value, which was estimated as k_P = 1.47(8)×10^{-3} mol m^{-3} min^{-1} (*vide infra*). In addition, the reaction exhibits first-order dependence on [Ni(cod)$_2$/I^{t}Bu].

To gain further insight into the reaction mechanism, a deuterium labeling experiment was carried out. In the presence of Ni(cod)$_2$/I^{t}Bu (5 mol%), the reaction of **1a-*d*$_1$** was monitored by ^{2}D NMR (measured at 22 °C) and GC analysis (Scheme 2.11). Through the reaction, H/D scrambling in **1a-*d*$_1$** was not observed at all; however a significant H/D scrambling in hydroacylated ketone was observed. When the reaction was conducted for 1.5 h, **2a** was formed, which was confirmed by ^{1}H NMR after isolation, with the concomitant formation of mesitylene-d_n in which methyl groups were partially

deuterated. Dimeric oxanickelacycle (**C2a'-d$_n$**) with the deuterium derived from **1a-d_1** and I^{t}Bu-d_n having partially deuterated methyl groups were also observed. Deuterated ketone (**2a-d_1**) was yielded at the end of the reaction.[18] These results indicated that the H/D scrambling would occur between nickel deuteride intermediate (**C3**, Scheme 2.10) and methyl groups in mesitylene and/or I^{t}Bu bound to nickel. Since no H/D scrambling in **1a-d_1** was observed under these conditions, the oxidative cyclization (step a, Scheme 2.10) and/or β-hydrogen elimination (step b, Scheme 2.10) would be irreversible. Moreover, no H/D scrambling in **C2a'-d_n** was observed, which implies that reinsertion of C=O into Ni–H in **C3** might not be involved in the reaction. Thus, β-hydrogen elimination might be irreversible. From the results shown in schemes 2.6–2.8 and 2.11, the author supposes that β-hydrogen elimination might contribute to k_S significantly. As the rational explanation for the small value of k_P compared to k_S, the rate for the production of **2a** would be influenced by the H/D scrambling reaction which compete with the reductive elimination.



1a-d_1 **1a** **2a** **2a-d_1** **C2a'-d_n (L = I^{t}Bu-d_n)**

time (h)	conv. (%)				
1.5	57	–	detected	–	detected
4	79	–	detected	detected	–

Scheme 2.11. Ni(0)-catalyzed hydroacylation of **1a-d_1**.

2.7. Conclusion for Chapter 2

In chapter 2, the first Ni(0)/NHC-catalyzed intramolecular hydroacylation was developed. A variety of indanone derivatives were prepared in good to excellent yields. Notably, the synthesis of tetralone derivatives, which were difficult to prepare by the reported hydroacylation systems without chelation assistance, was also achieved. The enal-coordinated complex **C1** and the dimeric oxanickelacycle **C2'** were isolated. The transformation of **C2'** into the corresponding ketone under both stoichiometric and catalytic conditions was also observed, which indicated the participation of the oxanickelacycle complex in the presented hydroacylation. This work provides a novel design for alkene hydroacylation that proceeds without the decarbonylation, that is, the

simultaneous coordination of both alkene and aldehyde moieties to Ni(0) followed by oxidative cyclization to give the oxanickelacycle.

2.7. Experimental Section

General remarks compatible to all the experimental part in this thesis

All manipulations were conducted under a nitrogen atmosphere using standard Schlenk or dry box techniques. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on JEOL AL–400, Bruker DPX 400 and Bruker AVANCE III 400 spectrometers at 25 °C unless otherwise stated. The chemical shifts in ^{1}H nuclear magnetic resonance spectra were recorded relative to Me_4Si or residual protonated solvent (C_6D_5H (δ 7.16), C_7D_7H (δ 2.09) or $CHCl_3$ (δ 7.26)). The chemical shifts in the ^{13}C spectra were recorded relative to Me_4Si or deutrated solvent (C_6D_6 (δ 128.06) or $CDCl_3$ (δ 77.16)). Assignment of the resonances in ^{1}H and ^{13}C NMR spectra was based on ^{1}H-^{1}H COSY, HMQC and HMBC experiments. Mass spectra were obtained using a Shimadzu GCMS-QP 2010 instrument with an ionization voltage of 70 eV. Medium-pressure column chromatography was carried out on a Biotage Flash Purification System Isolera, equipped with a 254 nm UV detector. Analytical gas chromatography (GC) was carried out on a Shimadzu GC-2014 gas chromatograph, equipped with a flame ionization detector. High resolution mass spectrometry (HRMS) and elementary analyses were performed at Instrumental Analysis Center, Faculty of Engineering, Osaka University. X-ray crystal data were collected by a Rigaku RAXIS-RAPID Imaging Plate diffractometer.

Materials

Mesitylene, toluene, benzene-d_6, and toluene-d_8 were distilled from sodium benzophenone ketyl and other solvents were distilled and degassed prior to use. All commercially available reagents were distilled over CaH_2 under reduced pressure prior to use. *N*-Heterocyclic carbenes (NHCs) were furnished by the known procedures (please, see Ref. 11 in chapter 1). Preparation procedures for substrates are found in the Supporting Information for *Angew. Chem. Int. Ed.* **2012**, *51*, 10812.

Optimization of reaction conditions (Table 2.1)

General procedures for the evaluation of ligands (entries 1–9): A reaction tube was charged with **1a** (58.5 mg, 0.40 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and ligand (0.040 mmol) in toluene (2 mL). The reaction mixture was heated at

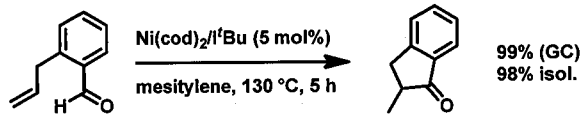
130 °C for 24 h. The reaction was monitored by gas chromatography. GC yield of **2a** was determined using *n*-pentadecane as an internal standard.

General procedures for the evaluation of solvents (entries 10–14): A reaction tube was charged with **1a** (117.0 mg, 0.80 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and I^{t}Bu (7.2 mg, 0.040 mmol) in solvent (2 mL). The reaction mixture was heated at 130 °C for 24 h. The reaction was monitored by gas chromatography. GC yield of **2a** was determined using *n*-pentadecane as an internal standard.

Scope of substrates (Table 2.2)

General procedures: A reaction tube was charged with **1** (0.80 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and I^{t}Bu (7.2 mg, 0.040 mmol) in mesitylene (2 mL). The reaction mixture was heated at 130 °C. The reaction was monitored by gas chromatography. GC yields of **2** were determined using *n*-pentadecane as an internal standard. The products were isolated by silica gel column chromatography. Further purification, distillation or recrystallization, was carried out as needed.

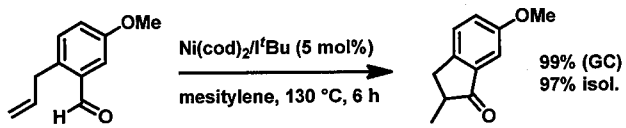
Reaction of 1a giving 2a:



1a **2a**

The general procedure was followed with **1a** (116.4 mg, 0.80 mmol) and reaction was conducted at 130 °C for 5 h. Yield of 2-metyl-1-indanone (**2a**) was 99% determined by GC analysis. Purification by silica gel column chromatography gave **2a** (113.8 mg, 0.78 mmol, 98%) as pale yellow oil. Spectroscopic data of **2a** was identified to that previously reported.[19a]

Reaction of 1b giving 2b:

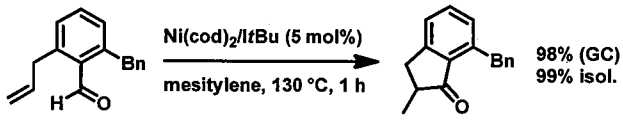


1b **2b**

The general procedure was followed with **1b** (140.6 mg, 0.80 mmol) and reaction was conducted at 130 °C for 6 h. Yield of 6-methoxy-2-metyl-1-indanone (**2b**) was 99% determined by GC analysis. Purification by silica gel column chromatography gave **2b**

(136.4 mg, 0.78 mmol, 97%) as pale yellow oil. Spectroscopic data of **2b** was identified to that previously reported.[19b]

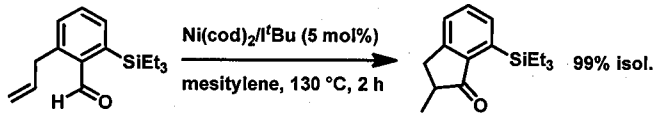
Reaction of 1c giving 2c:



1c 2c

The general procedure was followed with **1c** (188.3 mg, 0.80 mmol) and reaction was conducted at 130 °C for 1 h. Yield of 7-benzyl-2-metyl-1-indanone (**2c**) was 98% determined by GC analysis. Purification by silica gel column chromatography gave **2c** (188.9 mg, 0.80 mmol, 99%) as pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (dd, J = 7.6, 7.6 Hz, 1H, Ar–*H*), 7.18 (m, 1H, Ar–*H*), 7.07 (d, J = 7.6 Hz, 1H, Ar–*H*), 4.54 (d, J = 15.2 Hz, 1H, ArC*H*$_2$Ph), 4.43 (d, J = 15.2 Hz, 1H, ArC*H*$_2$Ph), 3.35 (dd, J = 8.8, 18.0 Hz, 1H, ArC*H*$_2$CH), 2.73–2.66 (m, 2H, ArC*H*$_2$CH and CH_2CHCH_3), 1.31 (d, J = 7.2 Hz, 3H, Me). Five Ar–*H*s are obscured by $CHCl_3$. **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 210.2, 154.5, 142.1, 140.6, 134.3, 133.3, 129.4, 128.8, 128.5, 126.2, 124.5, 42.5, 36.8, 34.7, 16.4. **HRMS** (EI): *m/z* Calcd for $C_{17}H_{16}O$: (M^+) 236.1201, found 236.1204.

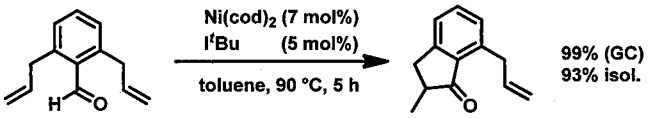
Reaction of 1d giving 2d:



1d 2d

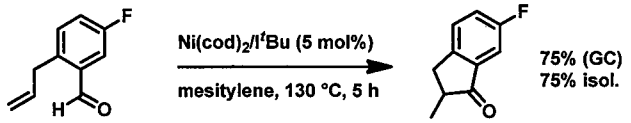
The general procedure was followed with **1d** (207.8 mg, 0.80 mmol) and reaction was conducted at 130 °C for 2 h. Purification by silica gel column chromatography gave **2d** (206.6 mg, 0.79 mmol, 99%) as pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53–7.50 (m, 2H, Ar–*H*), 7.43–7.41 (m, 1H, Ar–*H*), 3.39 (dd, J = 7.6, 16.8 Hz, 1H, ArC*H*$_2$CH), 2.71–2.63 (m, 2H, ArC*H*$_2$CH and CH_2CHCH_3), 1.30 (d. J = 7.2 Hz, 3H, Me), 0.98–0.87 (m, 15H, $SiEt_3$). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 210.7, 153.9, 141.5, 137.9, 135.1, 133.2, 127.2, 41.7, 35.2, 16.3, 7.9, 3.2. **HRMS** (CI): *m/z* Calcd for $C_{16}H_{24}OSi$: $[M+H]^+$ 261.1675, found 261.1676.

Reaction of 1e giving 2e:



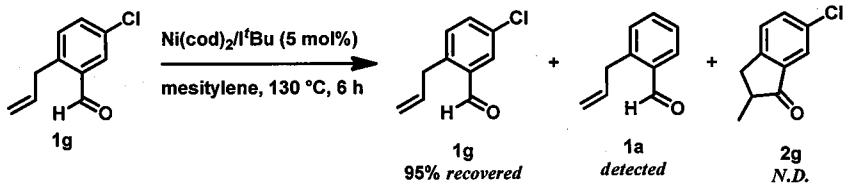
The general procedure was followed with **1e** (148.6 mg, 0.80 mmol), $Ni(cod)_2$ (15.5 mg, 0.056 mmol) and I^{t}Bu (7.2 mg, 0.040 mmol) and reaction was conducted in toluene (2 mL) at 90 °C for 5 h. Yield of 7-allyl-2-metyl-1-indanone (**2e**) was 99% determined by GC analysis. Purification by silica gel column chromatography gave **2e** (138.3 mg, 0.74 mmol, 93%) as pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (dd, J = 7.6, 7.6 Hz, 1H, Ar–*H*), 7.28 (d, J = 7.6 Hz, 1H, Ar–*H*), 7.15 (d, J = 7.6 Hz, 1H, Ar–*H*), 6.06–5.96 (m, 1H, CH_2CH=CH_2), 5.10–5.04 (m, 2H, CH_2CH=CH_2), 3.92–3.81 (m, 2H, CH_2CH=CH_2), 3.35 (dd, J = 7.6, 17.6 Hz, 1H, CH_2CHCH_3), 2.72–2.65 (m, 2H, $ArCH_2CH$ and CH_2CHCH_3), 1.30 (d, J = 7.2 Hz, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 210.1, 154.5, 141.1, 136.8, 134.4, 133.3, 128.3, 124.5, 116.1, 42.5, 35.6, 34.7, 16.5. **HRMS**: (EI): *m/z* Calcd for $C_{13}H_{14}O$: (M^+) 186.1045, found 186.1039.

Reaction of 1f giving 2f:



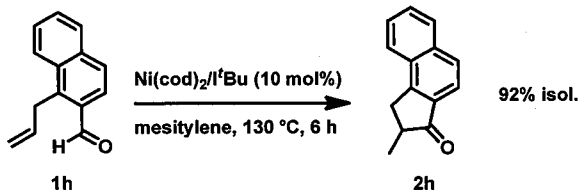
The general procedure was followed with **1f** (131.2 mg, 0.80 mmol) and reaction was conducted at 130 °C for 5 h. Yield of 6-fluoro-2-metyl-1-indanone (**2f**) was 75% determined by GC analysis. Purification by silica gel column chromatography gave **2f** (98.7 mg, 0.60 mmol, 75%) as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43–7.37 (m, 2H, Ar–*H*), 7.32–7.27 (m, 1H, Ar–*H*), 3.37 (dd, J = 7.6, 16.8 Hz, 1H, $ArCH_2CH$), 2.81–2.74 (m, 1H, CH_2CHCH_3), 2.69 (dd, J = 4.0, 16.8 Hz, 1H, $ArCH_2CH$), 1.31 (d, J = 7.2 Hz, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 208.9, 162.8 (d, J_{CF} = 246.4 Hz), 149.2 (d, J_{CF} = 2.2 Hz), 138.5, 128.3 (d, J_{CF} = 8.0 Hz), 122.8 (d, J_{CF} = 23.4 Hz), 110.2 (d, J_{CF} = 21.2 Hz), 43.4, 34.8, 16.7. **HRMS** (EI): *m/z* Calcd for $C_{10}H_9FO$: (M^+) 164.0637, found 164.0639.

Reaction of 1g:



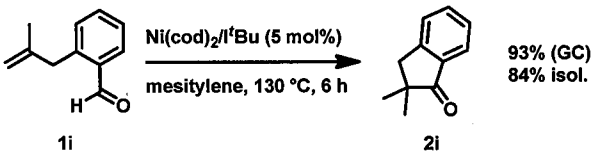
The general procedure was followed with **1g** (144.5 mg, 0.80 mmol) and reaction was conducted at 130 °C for 6 h. The reaction was monitored by GC.

Reaction of 1h giving 2h:



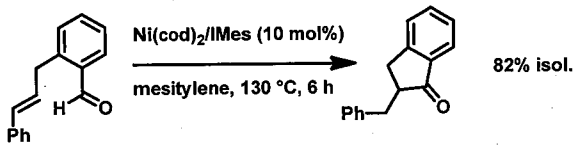
The general procedure was followed with **1h** (78.3 mg, 0.40 mmol), $Ni(cod)_2$ (11.5 mg, 0.042 mmol) and I^tBu (7.1 mg, 0.040 mmol), and reaction was conducted at 130 °C for 6 h. Purification by silica gel column chromatography gave 2-metyl-4,5-benzoindanone (**2h**) (72.2 mg, 0.37 mmol, 92%) as orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H, Ar–*H*), 7.96 (d, J = 7.2 Hz, 1H, Ar–*H*), 7.82 (d, J = 8.4 Hz, 1H, Ar–*H*), 7.75 (d, J = 8.4 Hz, 1H, Ar–*H*), 7.71–7.62 (m, 2H, Ar–*H*), 3.75 (dd, J = 7.2, 17.4 Hz, 1H, $ArCH_2CH$), 3.02 (dd, J = 3.2, 17.4 Hz, 1H, $ArCH_2CH$), 2.93–2.85 (m, 1H, CH_2CHCH_3), 1.41 (d, J = 7.6 Hz, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 209.2, 154.6, 136.5, 133.6, 130.3, 129.0, 128.8, 128.4, 126.9, 124.3, 119.6, 41.7, 33.2, 16.5. **HRMS** (EI): *m/z* Calcd for $C_{14}H_{12}O$: (M^+) 196.0888, found 196.0889.

Reaction of 1i giving 2i:



The general procedure was followed with **1i** (128.1 mg, 0.80 mmol) and reaction was conducted at 130 °C for 6 h. Yield of 2,2-dimetyl-1-indanone (**2i**) was 93% determined by GC analysis. Purification by silica gel column chromatography gave **2i** (107.8 mg, 0.67 mmol, 84%) as pale yellow oil. Spectroscopic data of **2i** was identified to that previously reported.[19c]

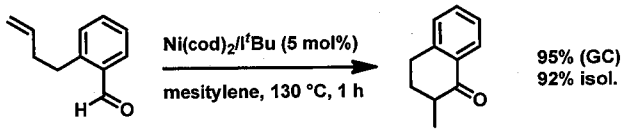
Reaction of 1j giving 2j:



1j 2j

The general procedure was followed with **1j** (88.0 mg, 0.40 mmol), $Ni(cod)_2$ (11.4 mg, 0.040 mmol) and IMes (12.1 mg, 0.040 mmol), and reaction was conducted at 130 °C for 6 h. Purification by silica gel column chromatography gave **2j** (71.8 mg, 0.32 mmol, 82%) as pale yellow oil. Spectroscopic data of **2j** was identified to that previously reported.[19d]

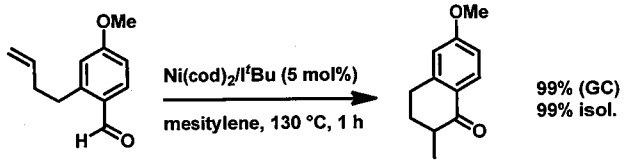
Reaction of 1k giving 2k:



1k 2k

The general procedure was followed with **1k** (128.7 mg, 0.80 mmol) and reaction was conducted at 130 °C for 1 h. Yield of 2-metyl-1-tetralone (**2k**) was 95% determined by GC analysis. Purification by silica gel column chromatography gave **2k** (118.0 mg, 0.74 mmol, 92%) as pale yellow oil. Spectroscopic data of **2k** was identified to that previously reported.[19e]

Reaction of 1l giving 2l:

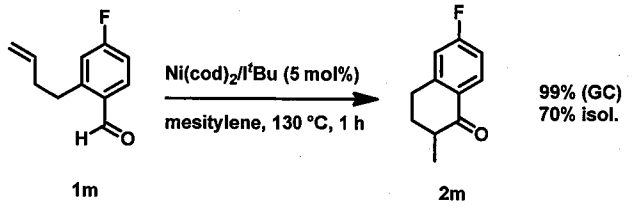


1l 2l

The general procedure was followed with **1l** (152.4 mg, 0.80 mmol) and reaction was conducted at 130 °C for 1 h. Yield of 6-methoxy-2-metyl-1-tetralone (**2l**) was 99% determined by GC analysis. Purification by silica gel column chromatography gave **2l** (150.2 mg, 0.79 mmol, 99%) as pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.8 Hz, 1H, Ar–*H*), 6.82 (dd, J = 2.4, 8.8 Hz, 1H, Ar–*H*), 6.68 (d, J = 2.4 Hz, 1H, Ar–*H*), 3.85 (s, 3H, OCH_3), 3.04–2.89 (m, 2H, $ArCH_2CH_2$ and CH_2CHCH_3), 2.58–2.51 (m, 1H, $ArCH_2CH_2$), 2.21–2.14 (m, 1H, CH_2CH_2CH), 1.91–1.81 (m, 1H, CH_2CH_2CH), 1.26 (d, J = 6.8 Hz, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.8, 163.5, 146.8,

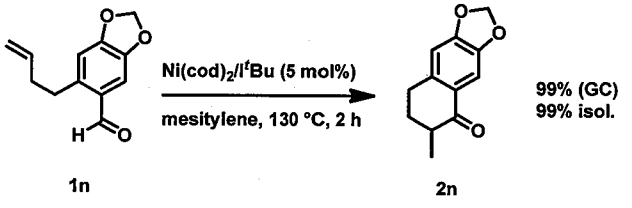
130.0, 126.2, 113.2, 112.6, 55.5, 42.4, 31.6, 29.3, 15.7. **HRMS** (EI): *m/z* Calcd for $C_{12}H_{14}O_2$: (M^+) 190.0994, found 190.0993.

Reaction of 1m giving 2m:



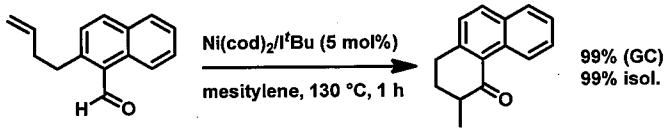
The general procedure was followed with **1m** (96.5 mg, 0.54 mmol), $Ni(cod)_2$ (8.2 mg, 0.030 mmol) and I^{t}Bu (5.4 mg, 0.030 mmol), and reaction was conducted at 130 °C for 1 h. Yield of 6-fluoro-2-metyl-1-tetralone (**2m**) was 99% yield determined by GC analysis. Purification by silica gel column chromatography gave **2m** (67.6 mg, 0.38 mmol, 70%) as a white solid. **2m** was found to be easily sublimated under the reduced pressure. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08–8.03 (m, 1H, Ar–*H*), 6.98 (ddd, *J* = 2.4, 8.4, 8.4 Hz, 1H, Ar–*H*), 6.91 (dd, *J* = 2.4, 9.6 Hz, 1H, Ar–*H*), 3.05-2.91 (m, 2H, Ar$CH_2$$CH_2$ and $CH_2$$CH$$CH_3$ are overlapped), 2.62–2.53 (m, 1H, Ar$CH_2$$CH_2$), 2.22–2.16 (m, 1H, $CH_2$$CH_2$CH), 1.93–1.83 (m, 1H, $CH_2$$CH_2$CH), 1.27 (d, *J* = 7.6 Hz, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 199.4, 165.7 (d, J_{CF} = 253.3 Hz), 147.3 (d, J_{CF} = 9.1 Hz), 130.6 (d, J_{CF} = 9.1 Hz), 129.2, 115.0 (d, J_{CF} = 21.2 Hz), 114.3 (d, J_{CF} = 21.2 Hz), 42.5, 31.3, 29.1, 15.5. **HRMS** (EI): *m/z* Calcd for $C_{11}H_{11}FO$: (M^+) 178.0794, found 178.0795.

Reaction of 1n giving 2n:



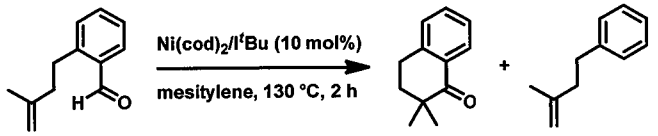
The general procedure was followed with **1n** (162.9 mg, 0.80 mmol) and reaction was conducted at 130 °C for 2 h. Yield of 6,7-methoxylendioxy-2-metyl-1-tetralone (**2n**) was 99% determined by GC analysis. Purification by silica gel column chromatography gave **2n** (162.3 mg, 0.79 mmol, 99%) as a white solid. Spectroscopic data of **2n** was identified to that previously reported.[18f]

Reaction of 1o giving 2o:



The general procedure was followed with **1o** (168.3 mg, 0.80 mmol) and reaction was conducted at 130 °C for 1 h. Yield of 2-metyl-7,8-benzotetralone (**2o**) was 99% determined by GC analysis. Purification by silica gel column chromatography gave **2o** (165.9 mg, 0.79 mmol, 99%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.35 (d, J = 8.8 Hz, 1H, Ar–*H*), 7.90 (d, J = 8.4 Hz, 1H, Ar–*H*), 7.80 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.63–7.59 (m, 1H, Ar–*H*), 7.50–7.46 (m, 1H, Ar–*H*), 7.29 (d, J = 8.4 Hz, 1H, Ar–*H*), 3.26–3.10 (m, 2H, ArCH_2CH_2 and CH_2CHCH_3), 2.81–2.72 (m, 1H, ArCH_2CH_2), 2.30–2.24 (m, 1H, CH_2CH_2CH), 2.05–1.93 (m, 1H, CH_2CH_2CH), 1.32 (d, J = 6.8 Hz, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 203.6, 146.0, 133.9, 132.9, 131.5, 128.7, 128.4, 127.4, 127.0, 126.7, 125.9, 44.0, 31.3, 30.5, 16.1. **HRMS** (EI): *m/z* Calcd for $C_{15}H_{14}O$: (M^+) 210.1045, found 210.1044.

Reaction of 1p giving 2p:



The general procedure was followed with **1p** (69.7 mg, 0.40 mmol), $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and I^{t}Bu (7.57 mg, 0.040 mmol), and reaction was conducted at 130 °C for 2 h. GC yields of 2,2-dimetyl-1-tetralone (**2p**) and 2-methyl-4-phenylbutene were 79% and 2%, respectively. Purification by silica gel column chromatography gave **2p** (51.5 mg, 0.30 mmol, 75%) as pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (dd, J = 1.2, 7.6 Hz, 1H, Ar–*H*), 7.47-7.43 (m, 1H, Ar–*H*), 7.32-7.28 (m, 1H, Ar–*H*), 7.22 (d, J = 7.6 Hz, 1H, Ar–*H*), 2.99 (t, J = 6.4 Hz, 2H, ArCH_2CH_2), 1.99 (t, J = 6.4 Hz, 2H, $CH_2CH_2C(Me)_2$), 1.22 (s, 6H, Me). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 203.4, 143.9, 133.4, 131.9, 129.1, 128.4, 127.0, 42.1, 37.1, 26.2, 24.8. **HRMS** (EI): *m/z* Calcd for $C_{12}H_{14}O$: (M^+) 174.1045, found 174.1049.

Mechanistic studies

Stoichiometric reaction of 1a with Ni(cod)$_2$/I^{t}Bu (Scheme 2.6): To a solution of

$Ni(cod)_2$ (11.0 mg, 0.040 mmol) and I^{t}Bu (7.2 mg, 0.040 mmol) in C_6D_6 (0.5 mL) was added **1a** (5.8 mg, 0.040 mmol) at room temperature. The resulting yellow mixture was transferred into a J-Young NMR tube and the reaction was monitored by ^{1}H NMR. A full consumption of **1a** and the quantitative formation of **C1a** were observed within 5 minutes. The reaction mixture gradually turned into brown as the transformation of **C1a** into **C2a'**, which was partially participated as yellow crystal, proceeded. **C2a'** was formed in almost quantitatively for 33 days as a *syn*/*anti* mixture.

Isolation of C1a: To a solution of $Ni(cod)_2$ (110.6 mg, 0.40 mmol) and I^{t}Bu (72.0 mg, 0.40 mmol) in toluene (10.0 mL) was added **1a** (59.4 mg, 0.41 mmol) at room temperature. After the reaction mixture was stirred for 5 minutes, all volatiles were removed under the reduced pressure. The residue was washed with hexane to give **C1a** as a yellow solid (127.2 mg, 0.33 mmol, 83%). **^{1}H NMR** (400 MHz, C_6D_6): δ 7.90 (d, J = 7.2 Hz, 1H, Ar–*H*), 7.12–7.08 (m, 3 H, Ar–*H*), 6.97 (s, 1H, C*H*O), 6.68 (s, 1H, NC*H*CHN), 6.63 (s, 1H, NCHC*H*N), 3.79–3.72 (m, 2H, CH_2CH=CH_2 and CH_2CH=CH_2), 2.56–2.45 (m, 2H, CH_2CH=CH_2 and CH_2CH=CH_2), 2.09 (d, J = 12.4 Hz, 1H, CH_2CHCH_2), 1.47 (s, 9H, ^{t}Bu), 1.20 (s, 9H, ^{t}Bu). **^{13}C{^{1}H} NMR** (100 MHz, C_6D_6): δ 191.6, 147.0, 143.6, 125.8, 117.9, 117.8, 101.2, 67.3, 57.8, 57.6, 50.6, 37.3, 31.5, 31.2. Some Ar–*C*s are obscured by C_6D_6. **Anal. Calcd for $C_{21}H_{30}N_2NiO$**: C, 65.48; H, 7.85; N, 7.27. Found: C, 65.48; H, 8.28; N, 7.04.

Isolation of C2a': To a solution of $Ni(cod)_2$ (110.6 mg, 0.40 mmol) and I^{t}Bu (72.0 mg, 0.40 mmol) in toluene (5.0 mL) was added **1a** (58.7 mg, 0.40 mmol) at room temperature. The reaction mixture was stirred for 33 days and then was heated at 130 °C for 5 minutes in order to dissolve the participates. The resultant brown solution was quickly filtered, and the obtained solution was concentrated in vacuo to give **C2a'** (142.0 mg, 36.8 mmol as monomer, 84%) as a yellow solid. The ratio of *syn*/*anti* was estimated as *syn*:*anti* = 3:2 by ^{1}H NMR (Figure 2.1). Single crystals of *anti*-**C2a'** suitable for X-ray diffraction analysis were obtained by recrystallization from toluene/hexane at –30 °C (Figure 2.2). **^{1}H NMR of *syn*-C2a'** (400 MHz, C_6D_6): δ 7.10 (t, J = 7.2 Hz, 2H, Ar–*H*), 7.03 (t, 7.2 Hz, 2H, Ar–*H*), 6.55 (s, 2H, NC*H*CHN), 6.51 (s, 4H, NCHC*H*N and Ar–*H*), 4.22 (d, J = 4.8 Hz, 2H, H^b), 3.27 (dd, J = 6.0, 14.4 Hz, 2H, H^c), 2.74 (dd, J = 6.0, 14.4 Hz, 2H, $H^{c'}$), 2.57 (s, 18H, ^{t}Bu), 2.41–2.39 (m, 2H, H^b), 2.16 (s, 18H, ^{t}Bu), 0.72–0.68 (m, 2H, H^a), 0.33–0.26 (m, 2H, $H^{a'}$). An Ar–*H* is obscured by C_6D_5H. **^{1}H NMR of *anti*-C2a'** (400 MHz, C_6D_6): δ 7.01 (t, J = 7.2 Hz, 2H, Ar–*H*), 6.75 (t, 7.6 Hz, 2H, Ar–*H*), 6.54 (s, 2H, NC*H*CHN), 6.49 (s, 2H, NCHC*H*N), 5.83 (d, J = 7.6

Hz, 2H, Ar–*H*), 4.70 (d, J = 5.2 Hz, 2H, H^h), 3.50 (dd, J = 7.6, 14.8 Hz, 2H, H^c), 2.77 (dd, J = 7.6, 14.8 Hz, 2H, $H^{c'}$), 2.49 (s, 18H, ^{t}Bu), 2.44–2.38 (m, 2H, H^b), 2.22 (s, 18H, ^{t}Bu), 0.71 (dd, J = 6.4, 10.8 Hz, 2H, H^a), 0.25 (dd, J = 4.8, 10.4 Hz, 2H, $H^{a'}$). An Ar–*H* is obscured by C_6D_5H. $^{13}C\{^1H\}$ NMR spectra of **C2a'** (*syn*/*anti* mixture) were not fully assigned due to its complexity, especially for the aromatic regions. **$^{13}C\{^1H\}$ NMR of *syn*-C2a'** (100 MHz, C_6D_6): δ 178.2 (NCN), 118.7 (NCHCHN), 118.0 (NCHCHN), 86.9 (*C*–H^h), 56.8 (*C*–$H^{b,b'}$), 38.5 (*C*–$H^{c,c'}$), 11.9 (*C*–$H^{a,a'}$). **$^{13}C\{^1H\}$ NMR of *anti*-C2a'** (100 MHz, C_6D_6): δ 178.5 (NCN), 118.5 (NCHCHN), 117.8 (NCHCHN), 86.1 (*C*–H^h), 56.3 (*C*–$H^{b,b'}$), 39.1 (*C*–$H^{c,c'}$), 10.8 (*C*–$H^{a,a'}$). **Anal. Calcd for $C_{42}H_{60}N_4Ni_2O_2$**: C, 65.48; H, 7.85; N, 7.27. Found: C, 65.02; H, 8.17; N, 7.33.

Thermolysis of C2a' (Scheme 2.7): The mixture of **C2a'** (14.1 mg, 0.020 mmol as a dimer) and ethyl acetate (2.4 mg, 0.027 mmol) as an internal standard in toluene-d_8 (1 mL) was transferred into a J-Young tube. The reaction mixture was heated at 130 °C for 24 h, and then cooled to room temperature. The conversion of **C2a'** and the yield of **2a** were 32% determined by ^{1}H NMR.

The reaction of 1a in the presence of a catalytic amount of C2a' (Scheme 2.8): A reaction tube was charged with **1a** (116.8 mg, 0.80 mmol) in the presence of **C2a'** (15.2 mg, 0.40 mmol for Ni) in mesitylene (2 mL). The reaction mixture was heated at 130 °C for 5 h. **2a** was formed in 101% yield (maximum yield of **2a** is expected as 105%) determined by GC analysis using *n*-pentadecane as an internal standard.

Stoichiometric reaction of 1k with Ni(cod)$_2$/I^{t}Bu (Scheme 2.9): To a solution of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and I^{t}Bu (7.2 mg, 0.040 mmol) in C_6D_6 (0.5 mL) was added **1k** (5.8 mg, 0.036 mmol) and hexamethyldisiloxane (1.6 mg, 0.010 mmol) as an internal standard at room temperature. The resulting orange mixture was transferred into a J-Young NMR tube and the reaction was monitored by ^{1}H NMR. A full consumption of **1k** and the quantitative formation of **C1k** were observed within 30 minutes. Then, the reaction mixture was heated at 60 °C for 36 h to give **2k** quantitatively with the regeneration of $Ni(cod)_2$ and I^{t}Bu.[16]

Isolation of C1k: To a solution of $Ni(cod)_2$ (220.0 mg, 0.80 mmol) and I^{t}Bu (144.0 mg, 0.80 mmol) in toluene (10.0 mL) was added **1k** (140.9 mg, 0.88 mmol, 1.1 eq.) at room temperature. After the reaction mixture was stirred for 30 minutes, all volatiles were removed under the reduced pressure. The residue was washed with hexane to give **C1k**

as a reddish-brown solid (322.2 mg, 0.80 mmol, 100%). Single crystals of **C1k** suitable for X-ray diffraction analysis were obtained by recrystallization from toluene/hexane at −30 °C (Figure 2.3). **^{1}H NMR** (400 MHz, C_6D_6): δ 8.09 (d, J = 6.0 Hz, 1H, Ar–*H*), 7.22–7.16 (m, 2H, Ar–*H*), 7.07 (d, J = 6.0 Hz, 1H, Ar–*H*), 6.70 (s, 2H, NC*H*C*H*N), 6.69 (s, 1H, C*H*O), 3.16–3.06 (m, 2H, CH_2CH=CH_2 and CH_2CH_2CH), 2.98-2.92 (m, 1H, $ArCH_2CH_2$), 2.89–2.79 (m, 1H, $ArCH_2CH_2$), 2.46 (d, J = 8.4 Hz, 1H, CH_2CH=CH_2), 1.62 (d, J = 13.6 Hz, 1H, CH_2CH=CH_2), 1.49 (s, 9H, ^{t}Bu), 1.26 (s, 9H, ^{t}Bu), 0.60–0.54 (m, 1H, CH_2CH_2CH). **^{13}C{^{1}H} NMR** (100 MHz, C_6D_6): δ 192.2, 145.0, 138.1, 128.9, 127.8, 126.4, 125.3, 125.0, 118.3, 118.0, 88.7, 62.8, 58.0, 57.4, 51.2, 33.5, 31.4.

Stoichiometric reaction of 1p with Ni(cod)$_2$/I^{t}Bu (Scheme 2.9): To a solution of $Ni(cod)_2$ (11.1 mg, 0.040 mmol) and I^{t}Bu (7.3 mg, 0.040 mmol) in C_6D_6 (0.5 mL) was added **1p** (7.2 mg, 0.040 mmol) at room temperature. The resulting orange mixture was transferred into a J-Young NMR tube and the reaction was monitored by ^{1}H NMR. A full consumption of **1p** and the quantitative formation of **C1p** were observed after 24 h. Then, the reaction mixture was heated at 60 °C for 36 h to give **2p** quantitatively with the regeneration of $Ni(cod)_2$ and I^{t}Bu. Identification of **C1p**: **^{1}H NMR** (400 MHz, C_6D_6): δ 8.01 (d, J = 8.8 Hz, 1H, Ar–*H*), 7.14–7.13 (m, 1H, Ar–*H* overlapped with C_6D_5H), 7.02 (d, J = 8.8 Hz, 1H, Ar–*H*), 6.64 (s, 1H, NC*H*CHN), 6.63 (s, 1H, NCHC*H*N), 6.17 (s, 1H, C*H*O), 3.11 (t, J = 13.0 Hz, 1H, CH_2CH_2C(Me)), 2.80–2.75 (m, 1H, $ArCH_2CH_2$), 2.66–2.61 (m, 1H, CH_2CH_2C(Me)), 2.28 (s, 1H, $CH_2C(Me)CH_2$), 1.84 (s, 1H, $CH_2C(Me)CH_2$), 1.58 (s, 9H, ^{t}Bu), 1.50 (s, 9H, ^{t}Bu), 0.76 (t, J = 13.0 Hz, 1H, CH_2CH_2C(Me)). **^{13}C{^{1}H} NMR** (100 MHz, C_6D_6): δ 191.9, 145.5, 137.8, 128.8, 126.1, 125.3, 124.7, 118.0, 117.8, 95.0, 68.1, 57.6, 57.5, 55.5, 38.0, 31.5, 30.2, 23.9. An Ar–*C* is obscured by C_6D_6.

Determination of the reaction rate constant of the hydroacylation of 1a (First Run): To a solution of $Ni(cod)_2$ (22.0 mg, 0.080 mmol) and I^{t}Bu (14.4 mg, 0.080 mmol) in mesitylene (4 mL) was added **1a** (235.6 mg, 1.61 mmol) and pentadecane (207.7 mg) as an internal standard. Initially the reaction mixture was heated at 128–130 °C for 15 minutes, and then the monitoring of the reaction by GC started at the temperature. The results were summarized in Figure 2.4. The rate constants of disappearance of **1a** (k_S) and production of **2a** (k_P) were evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equations (Eqs. 2.1 and 2.2).

$$-d[\mathbf{1a}]/dt = k_S = 2.03(6) \times 10^{-3}\ [\text{mol m}^{-3}\ \text{min}^{-1}] \qquad (2.1)$$

$$d[\mathbf{2a}]/dt = k_P = 1.66(5) \times 10^{-3} \text{ [mol m}^{-3} \text{ min}^{-1}\text{]} \quad (2.2)$$

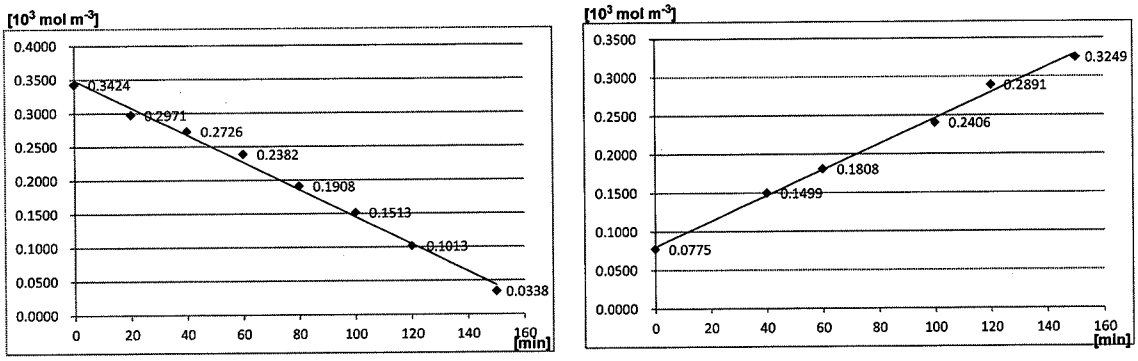


Figure 2.4. Concentration vs. time profiles of the disappearance of **1a** (left) and production of **2a** (right)

Determination of the reaction rate constant of the hydroacylation of 1a (Second Run): To a solution of $Ni(cod)_2$ (22.0 mg, 0.080 mmol) and I^{t}Bu (14.4 mg, 0.080 mmol) in mesitylene (4 mL) was added **1a** (233.1 mg, 1.59 mmol) and pentadecane (187.8 mg) as an internal standard. Initially the reaction mixture was heated at 130 °C for 15 minutes and then the monitoring of the reaction by GC started at the temperature. The rate constants of disappearance of **1a** (k_S) and production of **2a** (k_P) were evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equations (Eqs. 2.3 and 2.4).

$$-d[\mathbf{1a}]/dt = k_S = 1.72(6) \times 10^{-3} \text{ [mol m}^{-3} \text{ min}^{-1}\text{]} \quad (2.3)$$

$$d[\mathbf{2a}]/dt = k_P = 1.27(6) \times 10^{-3} \text{ [mol m}^{-3} \text{ min}^{-1}\text{]} \quad (2.4)$$

Determination of order in substrate: The rate constants of the reaction of **1a** was estimated as

$$k_H = 1.88(8) \times 10^{-3} \text{ [mol m}^{-3} \text{ min}^{-1}\text{]}$$

based on the average value of Eqs. 2.1 and 2.3.

Determination of the order of the reaction in catalyst

[Ni(cod)$_2$/I^{t}Bu] = 0.080 M: To a solution of $Ni(cod)_2$ (88.0 mg, 0.32 mmol) and I^{t}Bu (57.6 mg, 0.32 mmol) in mesitylene (4 mL) was added **1a** (234.0 mg, 1.60 mmol) and pentadecane (177.4 mg) as an internal standard. Initially the reaction mixture was heated at 130 °C for 15 minutes and then the monitoring of the reaction by GC started at the temperature. The results were summarized in Figure 2.5. The rate constants of the production of **2a** (k_1) was evaluated by least-squares fitting of time-concentration

profiles to zeroth-order rate equation (Eq. 2.5).

$$k_1 = d[\mathbf{2a}]/dt = 4.3(3) \times 10^{-3} \text{ [mol m}^{-3} \text{ min}^{-1}\text{]} \quad (2.5)$$

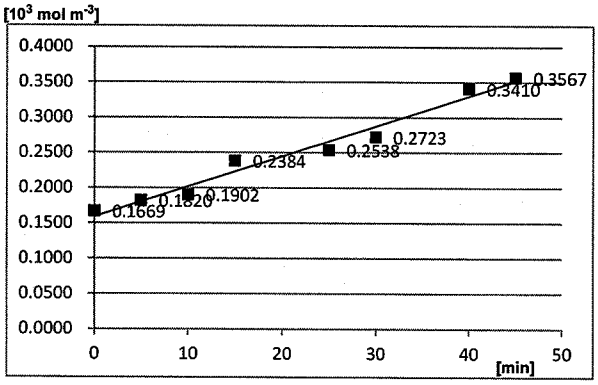


Figure 2.5. Concentration vs. time profiles of the production of **2a** in the case of **[Ni(cod)$_2$/I^{t}Bu]** is 0.080 M.

[Ni(cod)$_2$/I^{t}Bu] = 0.060 M: To a solution of Ni(cod)$_2$ (33.0 mg, 0.12 mmol) and I^{t}Bu (21.6 mg, 0.12 mmol) in mesitylene (2 mL) was added **1a** (116.5 mg, 0.80 mmol) and pentadecane (99.9 mg) as an internal standard. Initially the reaction mixture was heated at 130 °C for 15 minutes and then the monitoring of the reaction by GC started at the temperature. The results were summarized in Figure 2.6. The rate constants of the production of **2a** (k_2) was evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equation (Eq. 2.6).

$$k_2 = d[\mathbf{2a}]/dt = 3.3(1) \times 10^{-3} \text{ [mol m}^{-3} \text{ min}^{-1}\text{]} \quad (2.6)$$

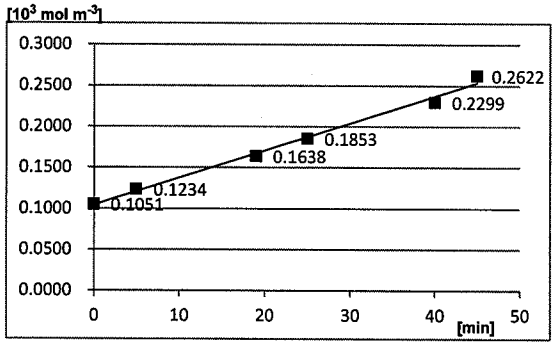


Figure 2.6. Concentration vs. time profiles of the production of **2a** in the case of **[Ni(cod)$_2$/I^{t}Bu]** is 0.060 M.

[Ni(cod)$_2$/I^{t}Bu] = 0.040 M: To a solution of Ni(cod)$_2$ (22.0 mg, 0.080 mmol) and I^{t}Bu

(14.4 mg, 0.080 mmol) in mesitylene (2 mL) was added **1a** (118.6 mg, 0.81 mmol) and pentadecane (103.7 mg) as an internal standard. Initially the reaction mixture was heated at 130 °C for 15 minutes, and then the monitoring of the reaction by GC started at the temperature. The results were summarized in Figure 2.7. The rate constants of the production of **2a** (k_3) was evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equation (Eq. 2.7).

$$k_3 = \mathrm{d}[\mathbf{2a}]/\mathrm{dt} = 2.44(9) \times 10^{-3}\ [\mathrm{mol\ m^{-3}\ min^{-1}}] \qquad (2.7)$$

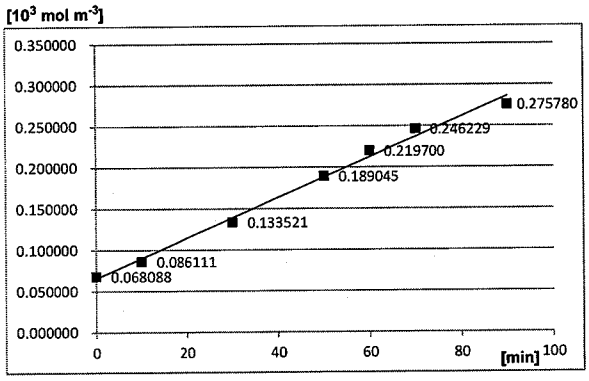


Figure 2.7. Concentration vs. time profiles of the production of **2a** in the case of **[Ni(cod)$_2$/I^{t}Bu]** is 0.040 M.

Order in catalyst (Ni(cod)$_2$/I^{t}Bu): From these results, a plot of k vs. [Ni(cod)$_2$/I^{t}Bu] gave a straight line ($R^2 = 0.98$), suggesting a first order dependence on catalyst (figure 2.8).

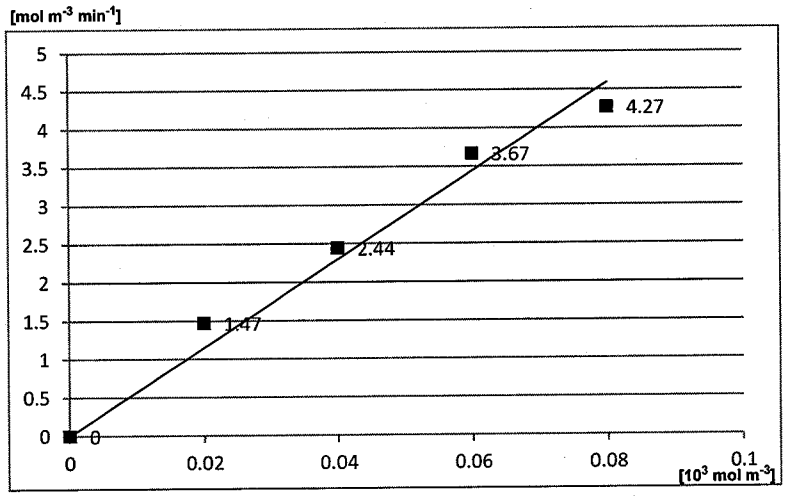


Figure 2.8. k vs. [cat] profiles.

Deuterium labeling experiment (Scheme 2.11): To a solution of Ni(cod)$_2$ (11.3 mg, 0.080 mmol) and I^{t}Bu (7.3 mg, 0.080 mmol) in mesitylene (2 mL) was added **1a-*d*$_1$** (117.0 mg, 0.80 mmol) and pentadecane (108.2 mg) as an internal standard. The

reaction mixture was heated at 130 °C, and then the reaction was monitored by ^{2}D NMR and GC analysis. Note that ^{2}D NMR was measured at 22 °C.

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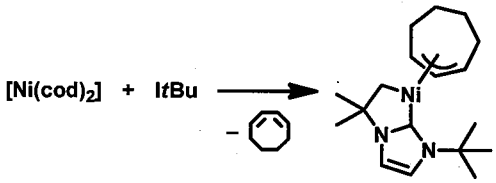

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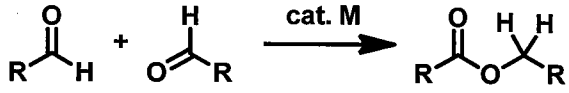
Chapter 3

Ni(0)-Catalyzed Homo-Dimerization of Aldehydes via Bis(η^2-Aldehyde)Nickel(0) Intermediate

Abstract: A Ni(0)/NHC-catalyzed Tishchenko reaction was developed for the first time which can be applied to a variety of aliphatic aldehydes (1°, 2°, 3°) and aromatic aldehydes. The key reaction intermediate, bis(η^2-aldehyde)Ni(0) complex, was observed at –60 °C by NMR. Neither decarbonylation nor H/D scrambling in both substrate and product were observed in this reaction.

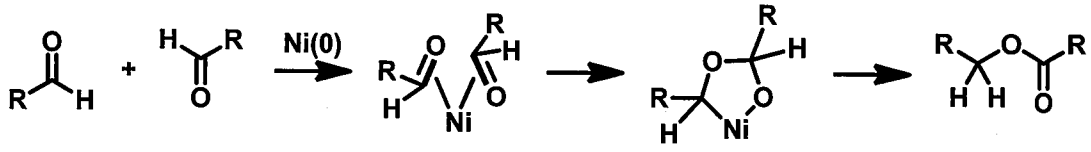
3.1. Introduction

Ester compounds are one of the most important compounds in our daily life, and the need for them will never lessen. Thus it is worthwhile to provide an environmentally benign method to synthesize esters.[1] One of the most promising methods is the Tishchenko reaction, which is a direct catalytic conversion of simple aldehydes to esters (Eq. 3.1).[2] Since its discovery in 1887, a variety of catalysts, such as Lewis acid catalysts and transition-metal catalysts, have been elaborated to develop the reaction. Despite much developments and industrial applications, however, the Tishchenko reaction has not been accepted as a common method for ester synthesis because of the following limitations: (a) there are few catalysts applicable to the Tishchenko reaction of both aliphatic and aromatic aldehydes and (b) there is no selective crossed Tishchenko reaction that can prepare a single cross-coupled ester selectively from among the four possible esters that could be formed from two different aldehydes (see chapter 4). In order to overcome these limitations, development of a novel catalyst for the Tishchenko reaction would be required.



(3.1)

Stone reported that the formation of a dioxanickelacycle by oxidative cyclization of $(CF_3)_2C{=}O$ on nickel(0).[3] The generation of the corresponding dioxanickelacycle from aldehdyes might allow us to design the Tishchenko reaction involving the β-hydrogen elimination from the dioxanickelacycle (Scheme 3.1). Based on this assumption, the author envisioned the development of the Ni(0)-catalyzed Tishchenko reaction.



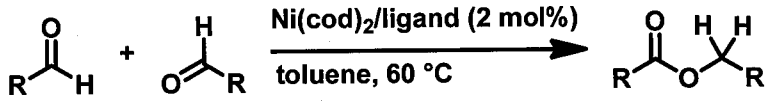
Scheme 3.1. Ni(0)-catalyzed homo-coupling reaction of aldehydes via dioxanickelacycle.

3.2. Optimization of the reaction conditions

In the presence of $Ni(cod)_2$/IPr (2 mol%), the Tishchenko reaction of CyCHO ($\mathbf{A^1}$) proceeded efficiently at 60 °C to give $CyCOOCH_2Cy$ ($\mathbf{A^1A^1}$) in > 99% yield (entry 1, Table 3.1). While both IPr and IPrCl were very effective for the Tishchenko reaction of

$\mathbf{A^1}$ (entries 1 and 2), a siginificant difference in the reaction rate was observed in the homo-dimerization of PhCHO ($\mathbf{B^1}$) (entries 3 and 4). In addition, in contrast to IPr, IPrCl was found to be ineffective as organocatalyst for aldol or benzoin condensation of aldehydes. Thus, IPrCl was employed as the optimized ligand for the following experiments.

Table 3.1. Ni(0)-catalyzed Tishchenko reaction of CyCHO and PhCHO.[a]



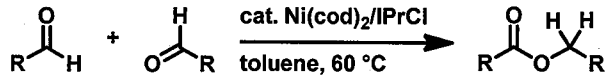
entry	R	ligand	time (h)	yield (%)
1	Cy (A^1)	IPr	0.25	> 99
2	Cy (A^1)	IPrCl	0.25	> 99
3	Ph (B^1)	IPr	6	> 99
4	Ph (B^1)	IPrCl	1.5	98

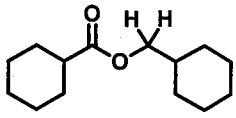
[a] GC yields are presented.

3.3 Ni(0)/IPrCl-catalyzed Tishchenko reaction

Ni(0)/IPrCl catalyst was applied to the Tishchenko reaction of various aliphatic and aromatic aldehydes to give the corresponding esters in excellent yields (Table 3.2). Primary, secondary, and tertiary aliphatic aldehydes were available for this reaction ($\mathbf{A^1}$–$\mathbf{A^4}$).[4] Even in the presence of 0.5 mol% catalyst, $\mathbf{B^1B^1}$ was yielded quantitatively. Aromatic aldehydes having either a sterically hindered group or an electron-withdrawing group required a higher reaction temperature or a larger amount of catalyst ($\mathbf{B^4B^4}$, $\mathbf{B^5B^5}$, $\mathbf{B^7B^7}$ and $\mathbf{B^8B^8}$). Both 2-naphthaldehyde ($\mathbf{B^9}$) and 2-furaldehyde ($\mathbf{B^{10}}$) also underwent the Tishchenko reaction to give the expected esters. From these results, it was found that the Ni(0)/IPrCl-catalyst can be applied to the Tishchenko reaction of both aromatic and aliphatic aldehydes, including enolizable aldehydes that readily undergo aldol reaction under the reported Tishchenko reaction conditions.[5] In addition, the decarbonylation was not observed at all in the presented reactions while the reported transition-metal-catalyzed Tishchenko reactions, which took place via acyl metal intermediates, often suffered from the decarbonylation.[6]

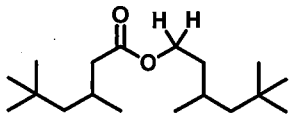
Table 3.2. Ni(0)/IPrCl-catalyzed Tishchenko reaction.[a]





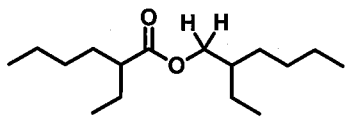
A^1A^1

1 mol%
1h, 99%



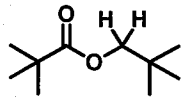
A^2A^2

1 mol%
1h, 96%



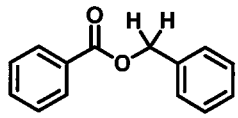
A^3A^3

2 mol%
1h, 94%



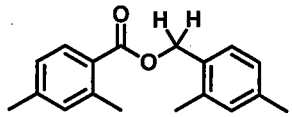
A^4A^4

1 mol%
1h, > 99%[b]



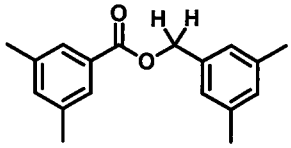
B^1B^1

0.5 mol%
4 h, 99%[c]



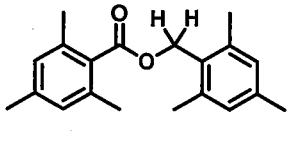
B^2B^2

1 mol%
3 h, 99%



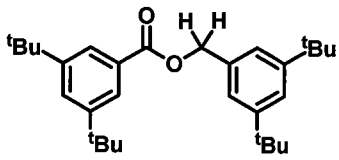
B^3B^3

1 mol%
3 h, 99%



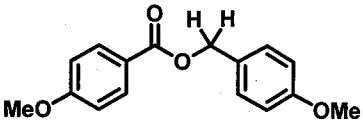
B^4B^4

3 mol%
24 h, 84%



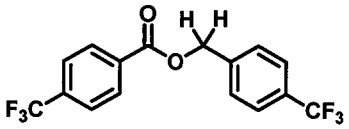
B^5B^5

2 mol%
2 h, 99%[c]



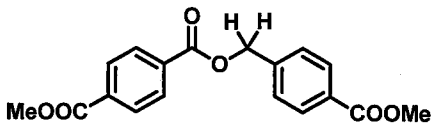
B^6B^6

2 mol%
2 h, 95%



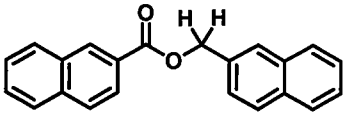
B^7B^7

10 mol%
4 h, 82%



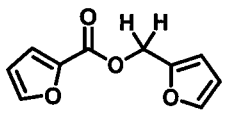
B^8B^8

2 mol%
3 h, 99%[c]



B^9B^9

3 mol%
2 h, 82%



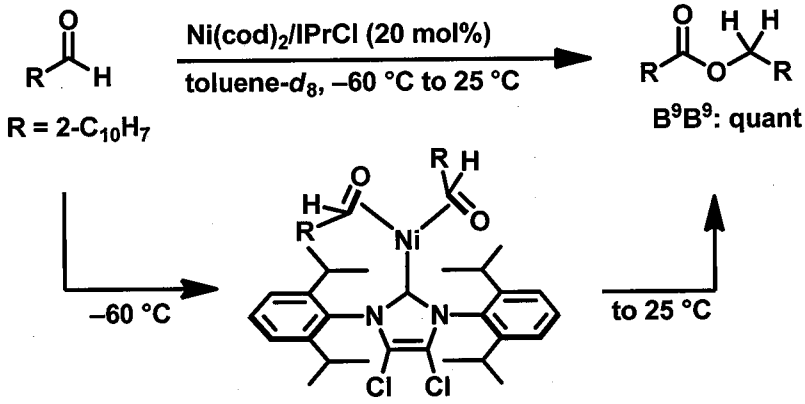
$B^{10}B^{10}$

2 mol%
4 h, 62%

[a] General conditions; aldehydes A^1–A^4 and B^1–B^{10} (0.40–8.00 mmol), $Ni(cod)_2$/IPrCl (0.040 mmol) and toluene (2 mL) were reacted. Yields of isolated product are presented. [b] GC yield. [c] 80 °C.

3.4. NMR Experiments

In the presence of $Ni(cod)_2$/IPrCl (20 mol%), the Tishchenko reaction of 2-naphthaldehyde ($\mathbf{B^9}$) was monitored by NMR (Scheme 3.2). At –60 °C, the resonances of the carbonyl hydrogen and the carbon of the aldehyde ligated to nickel(0) were observed at δ 4.7 in ^{1}H NMR and δ 109.3 in ^{13}C NMR, which indicates that $\mathbf{B^9}$ coordinates to the nickel(0) center in η^2-mode.[7,8] Moreover, the resonance at δ 4.7 disappeared in ^{1}H NMR spectra of the reaction with $\mathbf{B^9}$-d_1 at –60 °C. The ratio of the integration of the aldehyde hydrogen toward the isopropyl group of IPrCl indicates that two aldehyde molecules coordinate to nickel(0). The reaction mixture was allowed to warm to 25 °C to give $\mathbf{B^9B^9}$ quantitatively.



Scheme 3.2. NMR monitoring of the Tishchenko reaction of $\mathbf{B^9}$.

3.5. Kinetic Studies

The reaction exhibits zeroth-order dependence on [$\mathbf{B^9}$]. Thus, coordination of aldehydes to nickel(0) might not be the rate-limiting step in the reaction. In order to gain more information about the rate-limiting step, the labeling experimental of $\mathbf{B^9}$ and $\mathbf{B^9}$-d_1 was conducted. In the presence of 3 mol% of $Ni(cod)_2$/IPrCl, the reaction of $\mathbf{B^9}$ (or $\mathbf{B^9}$-d_1) was monitered at 60 °C by means of ^{1}H NMR spectroscopy. The rate constants of disappearance of $\mathbf{B^9}$ (k_H) and $\mathbf{B^9}$-d_1 (k_D) are $3.55(3)\times10^{-4}$ and $1.87(1)\times10^{-4}$ mol m^{-3} sec^{-1}, respectively, showing a primary kinetic isotope effect (k_H/k_D = 1.9). This indicates that the cleavage of $C_{carbonyl}$–H bond or Ni–H bond contributes to the reaction rate. In addition, no H/D scrambling in both substrate and product was not observed at all. The detailed disscusions about the reaction mechanism are found in the following chapter.

3.6. Conclusion for Chapter 3

The Tishchenko reaction catalyzed by Ni(0)/NHC complex was developed for the first time, in which the simultaneous coordination of two aldehydes to nickel(0) is an important key reaction step. The reaction can be applied to a variety of aliphatic aldehydes (1°, 2°, 3°) and aromatic aldehydes. Thus, this reaction shows the high potential of the nickel catalyst for the Tishchenko reaction.

3.7. Experimental Section

Materials

Toluene and toluene-d_8 were distilled from sodium benzophenone ketyl. All commercially available reagents were distilled over CaH_2 under reduced pressure prior to use. *N*-Heterocyclic carbenes (NHCs) were furnished by the known procedures (please, see Ref. 11 in chapter 1). 2-Naphthaldehyde-d_1 was furnished by known procedures.[9]

Optimization of reaction conditions (Table 3.1)

General procedures: A reaction tube was charged with $\mathbf{A^1}$ or $\mathbf{B^1}$ (2.00 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and ligand (0.040 mmol) in toluene (2 mL). The reaction mixture was heated at 60 °C for 24 h. The reaction was monitored by gas chromatography. GC yield of $\mathbf{A^1A^1}$ or $\mathbf{B^1B^1}$ was determined using *n*-pentadecane as an internal standard.

Scope of substrates (Table 3.2)

General procedures: To a solution of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and IPrCl (18.3 mg, 0.040 mmol) in 2 mL of toluene was added the aldehyde under inert atmosphere at 23 °C. The reaction mixture was heated at 60 °C or 80 °C for 1–24 h. The reaction was monitored by GC analysis. GC yields were determined using pentadecane as an internal standard. The product was isolated by a silica gel chromatography.

Cyclohexylmethyl cyclohexanecarboxylate ($\mathbf{A^1A^1}$): The general procedure was followed with cyclohexanecarbaldehyde $\mathbf{A^1}$ (450.2 mg, 4.01 mmol) and reaction mixture was stirred at 60 °C for 1 h. Purification by column chromatography gave $\mathbf{A^1A^1}$ (451.5 mg, 2.01 mmol, 99%) as colorless oil.[10]

3,5,5-Trimethylhexyl 3,5,5-trimethylhexanoate (A^2A^2): The general procedure was followed with 3,5,5-trimethylhexanal A^2 (569.9 mg, 4.01 mmol) and reaction mixture was stirred at 60 °C for 1 h. Purification by column chromatography gave A^2A^2 (543.3 mg, 1.91 mmol, 96%) as colorless oil. This product was obtained as a diasteremer mixture (**P/P'** = 60/40, estimated by ^{1}H NMR). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.09–4.05 (m, 2H of **P** and **P'**, OCH_2CH_2), 2.31–2.29 (m, 1H of **P'** ^{t}BuCH$_2$C*H*(Me)CH_2), 2.28–2.26 (m, 1H of **P**, ^{t}BuCH$_2$C*H*(Me)CH_2), 2.13–2.03 (m, 2H), 1.63–1.59 (m, 2H), 1.44–1.42 (m, 1H), 1.25 (t, J = 4.0 Hz, 2H of **P'**, ^{t}BuCH_2CH(Me)CH$_2$), 1.21 (t, J = 4.0 Hz, 2H of **P**, ^{t}BuCH_2CH(Me)CH$_2$), 1.13–1.01 (ddd, 2H), 0.97 (d, J = 4.0 Hz, 3H of **P'**, Me), 0.95 (d, J = 4.0 Hz, 3H of **P'**, Me), 0.89 (s, 9H of **P** and **P'**, ^{t}Bu), 0.87 (s, 9H of **P** and **P'**, ^{t}Bu). **^{13}C NMR** ($CDCl_3$, 67 MHz): δ 173.4, 62.8, 51.1 (**P'**), 51.1 (**P**), 50.7, 44.3, 38.0, 31.2, 30.2 (**P'**), 30.1 (**P**), 27.1 (**P**), 26.9 (**P'**), 26.3, 22.8 (**P'**), 22.8 (**P**), 22.7 (**P**), 22.6(**P'**). **HRMS**: Calcd. for $C_{18}H_{36}O_2$ 284.2715, Found 284.2713.

2-Ethylhexyl 2-ethylhexanoate (A^3A^3): The general procedure was followed with 2-ethylhexanal A^3 (519.3 mg, 4.05 mmol) and reaction mixture was stirred at 60 °C for 1 h. Purification by column chromatography gave A^3A^3 (483.3 mg, 1.88 mmol, 94%) as colorless oil.[10]

Neopentyl pivalate (A^4A^4): The general procedure was followed with pivalaldehyde A^4 (442 uL, 344.8 mg, 4.00 mmol) and reaction mixture was stirred at 60 °C for 1 h. Neopentyl pivalate (A^4A^4) is difficult to isolate because of its low boiling point. Therefore, product yield was determined by GC.[10]

Benzyl benzoate (B^1B^1): The general procedure was followed with benzaldehyde B^1 (847.8 mg, 7.99 mmol) and reaction mixture was stirred at 80 °C for 4 h. Purification by column chromatography gave B^1B^1 (848.5 mg, 8.00 mmol, > 99%) as pale yellow oil.[10]

2,4-Dimethylbenzyl 2,4-dimethylbenzoate (B^2B^2): The general procedure was followed with 2,4-dimethylbenzaldehyde B^2 (536.4 mg, 4.00 mmol) and reaction mixture was stirred at 60 °C for 3 h. Purification by column chromatography gave B^2B^2 (532.8 mg, 1.99 mmol, > 99%) as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.31 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.04 (m, 4H, Ar–*H*), 5.31 (s, 2H, OCH_2Ar), 2.59 (s, 3H, Me), 2.39 (s, 3H, Me), 2.35 (s, 3H, Me), 2.34 (s, 3H, Me). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.5, 142.7, 140.7, 138.4, 137.1, 132.7, 131.4, 131.3,

131.1, 129.7, 126.8, 126.7, 126.6, 64.8, 22.0, 21.5, 21.2, 19.1. **HRMS**: Calcd. for $C_{18}H_{20}O_2$ 268.1463, Found 268.1465.

3,5-Dimethylbenzyl 3,5-dimethylbenzoate (B^3B^3): The general procedure was followed with 3,5-dimethylbenzaldehyde B^3 (542.8 mg, 4.05 mmol) and reaction mixture was stirred at 60 °C for 3 h. Purification by column chromatography gave B^3B^3 (531.5 mg, 1.98 mmol, > 99%) as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (s, 2H, Ar–*H*), 7.22 (s, 1H, Ar–*H*), 7.11 (s, 2H, Ar–*H*), 7.02 (s, 1H, Ar–*H*), 5.33 (s, 2H, OC*H*$_2$Ar), 2.39 (s, 6H, Me), 2.38 (s, 6H, Me). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.9, 138.2, 138.0, 136.1, 134.7, 130.2, 130.0, 127.5, 126.2, 66.8, 21.3, 21.2. **HRMS**: Calcd. for $C_{18}H_{20}O_2$ 268.1463, Found 268.1458.

2,4,6-Trimethylbenzyl 2,4,6-trimethylbenzoate (B^4B^4): The general procedure was followed with 2,4,6-trimethylbenzaldehyde B^4 (202.1 mg, 1.36 mmol) and reaction mixture was stirred at 60 °C for 24 h. Purification by column chromatography gave B^4B^4 (170.3 mg, 0.57 mmol, 84%) as yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.88 (s, 2H, Ar–*H*), 6.82 (s, 2H, Ar–*H*), 5.40 (s, 2H, OC*H*$_2$Ar), 2.40 (s, 6H, Me), 2.27 (s, 6H, Me), 2.26 (s, 6H, Me). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.4, 139.1, 138.5, 138.2, 134.9, 131.3, 129.1, 128.8, 128.3, 61.4, 21.1, 21.0, 19.7, 19.6. **HRMS**: Calcd. for $C_{20}H_{24}O_2$ 296.1776, Found 296.1774.

3,5-Di-*tert*-butylbenzyl 3,5-di-*tert*-butylbenzoate (B^5B^5): The general procedure was followed with 3,5-di-*tert*-butylbenzaldehyde B^5 (439.1 mg, 2.01 mmol) and reaction mixture was stirred at 80 °C for 2 h. Purification by column chromatography gave B^5B^5 (441.2 mg, 2.01 mmol, > 99%) as yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.22 (s, 2H, Ar–*H*), 7.85 (s, 1H, Ar–*H*), 7.62 (s, 1H, Ar–*H*), 7.55 (s, 2H, Ar–*H*), 5.63 (s, 2H, OC*H*$_2$Ar), 1.55 (s, 36H, Me). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.0, 151.0, 150.9, 135.7, 129.9, 127.1, 124.0, 122.0, 121.9, 67.0, 34.9, 34.8, 31.6, 31.5. **HRMS**: Calcd. for $C_{30}H_{44}O_2$ 436.3341, Found 436.3344.

4-Methoxybenzyl 4-methoxybenzoate (B^6B^6): The general procedure was followed with 4-methoxybenzaldehyde B^6 (274.3 mg, 2.01 mmol) and reaction mixture was stirred at 60 °C for 2 h. Purification by column chromatography gave B^6B^6 (260.8 mg, 1.92 mmol, 95%) as yellow oil.[10]

4-(Trifluoromethyl)benzyl 4-(trifluoromethyl)benzoate (B^7B^7): The general

procedure was followed with 4-trifuluoromethylbenzaldehyde $\mathbf{B^7}$ (69.8 mg, 0.40 mmol) and reaction mixture was stirred at 60 °C for 4 h. Purification by column chromatography gave $\mathbf{B^7B^7}$ (61.4 mg, 0.18 mmol, 88% as crude yield). Further purification by recrystallization gave $\mathbf{B^7B^7}$ (57.2 mg, 0.17 mmol, 82%) as a colorless solid.[10]

4-(Methoxycarbonyl)benzyl methyl terephthalate ($\mathbf{B^8B^8}$): The general procedure was followed with 4-methoxycarbonylbenzaldehyde $\mathbf{B^8}$ (329.6 mg, 2.01 mmol) and reaction mixture was stirred at 80 °C for 4 h. Purification by column chromatography gave $\mathbf{B^8B^8}$ (324.7 mg, 0.99 mmol, 99%). Further purification by recrystallization gave $\mathbf{B^8B^8}$ as a colorless solid.[10]

Naphthalen-2-ylmethyl 2-naphthoate ($\mathbf{B^9B^9}$): The general procedure was followed with 2-naphthadehyde $\mathbf{B^9}$ (208.6 mg, 1.34 mmol) and reaction mixture was stirred at 60 °C for 3 h. Purification by column chromatography gave $\mathbf{B^9B^9}$ (195.8 mg, 0.63 mmol, 94% as crude yield). Further purification by recrystallization gave $\mathbf{B^9B^9}$ (170.8 mg, 0.55 mmol, 82%) as a colorless solid.[10]

Furfuryl furoate ($\mathbf{B^{10}B^{10}}$): The general procedure was followed with furfral $\mathbf{B^{10}}$ (192.2 mg, 2.00 mmol) and reaction mixture was stirred at 60 °C for 3 h. Purification by column chromatography gave $\mathbf{B^{10}B^{10}}$ (118.6 mg, 0.62 mmol, 62%) as yellow oil.[10]

NMR Monitoring of the Tishchenko reaction of $\mathbf{B^9}$ (Scheme 3.2): To a solution of $Ni(cod)_2$ (110.0 mg, 0.40 mmol) and IPrCl (183.2 mg, 0.40 mmol) in 2 mL of toluene-d_8 was added $\mathbf{B^9}$ (312.4 mg, 2.00 mmol) at 23 °C and the sample was transferred to an NMR tube equipped with a sealable teflon cap. The tube was sealed and inserted in a NMR spectrometer. The ^{1}H NMR analysis was conducted at 25 °C and then the sample was cooled to −60 °C. After the measurement of ^{1}H NMR, ^{13}C NMR and HMBC at −60 °C (Figure 3.1), the sample was allowed to warm to 25 °C. $\mathbf{B^9}$ was fully consumed to the give $\mathbf{B^9B^9}$ quantitatively (1 d). Selected spectrum data for **bis(η^2-$\mathbf{B^9}$)Ni(IPrCl)**: **^{1}H NMR** (600 MHz, toluene-d_8, −60 °C): δ 4.70 (brs, 2H, ArC*H*O), 3.12 (br, 2H, ^{i}Pr), 2.97 (br, 2H, ^{i}Pr), 1.61 (br, 6H, ^{i}Pr), 1.17 (br, 6H, ^{i}Pr), 1.07 (br, 6H, ^{i}Pr), 1.02 (br, 6H, ^{i}Pr). **^{13}C NMR** (150 MHz, toluene-d_8, −60 °C): δ 196.0, 109.3, 29.6, 28.8, 24.8, 24.3, 24.0, 23.6.

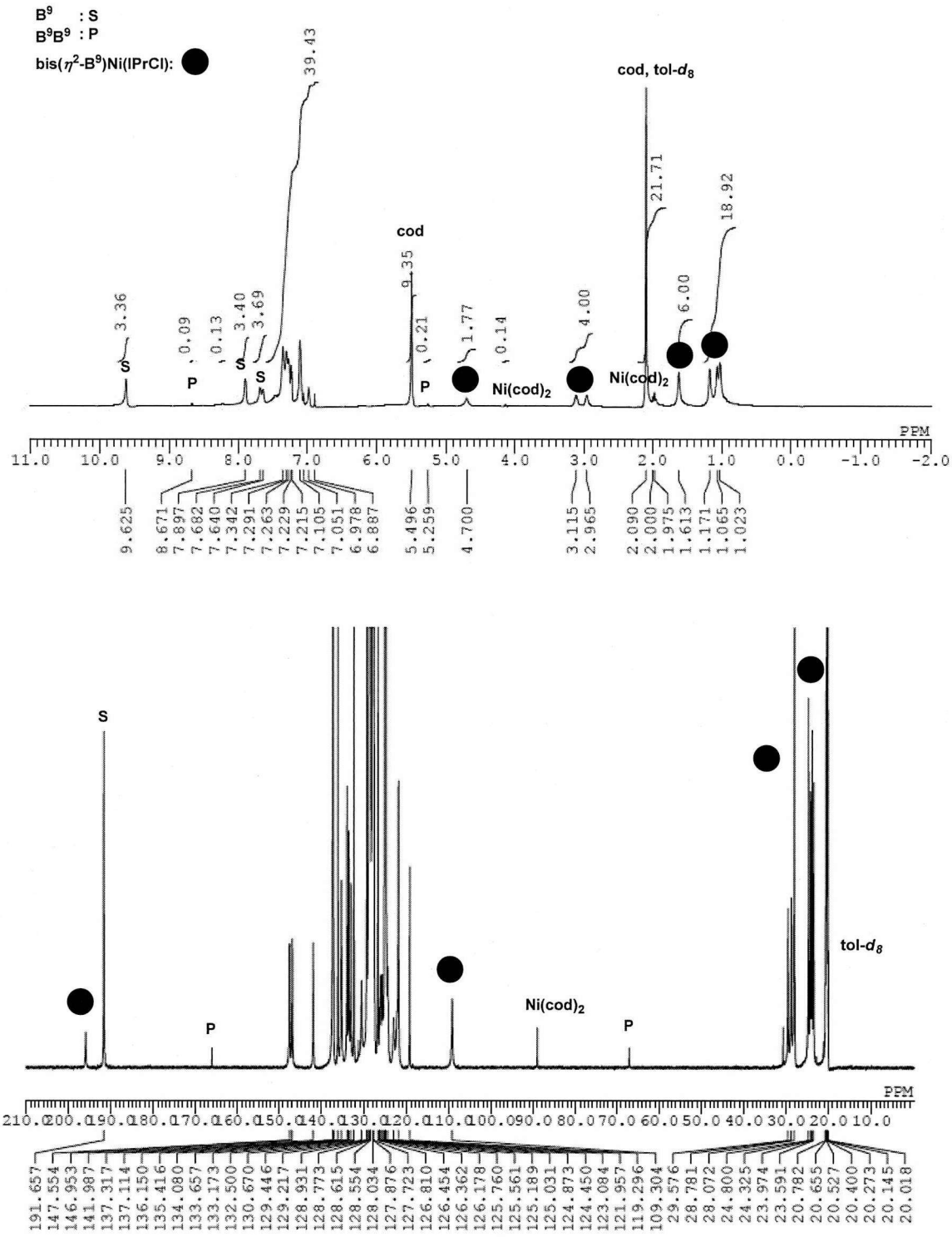


Figure 3.1. ^{1}H NMR (top) and ^{13}C NMR (bottom) in toluene-d_8 at−60 °C.

NMR Monitoring of the Tishchenko reaction of B^9-d_1: To a solution of $Ni(cod)_2$ (110.0 mg, 0.40 mmol) and IPrCl (183.2 mg, 0.40 mmol) in 2 mL of toluene-d_8 was added $\mathbf{B^9}$-d_1 (314.4 mg, 2.00 mmol) at 23 °C and the sample was transferred to an NMR tube equipped with a sealable teflon cap. The ^1H NMR analysis was conducted at –60 °C and disappearance of the resonance of the coordinated carbonyl hydrogen (δ 4.70 in Figure 3.1) was observed.

Kinetic Studies

Reaction rate constant of the Tishchenko reaction of B^9, k_H:

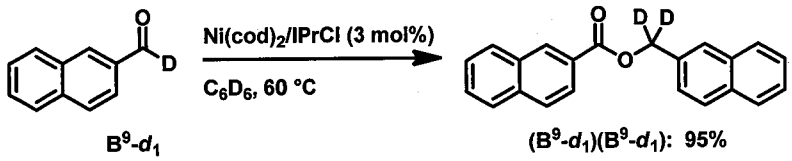
$d[B^9]/dt = k_H = 3.55(3)\times10^{-4}$ [mol m^{-3} sec^{-1}]

To a solution of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and IPrCl (18.3 mg, 0.040 mmol) in 0.5 mL of C_6D_6 was added $\mathbf{B^9}$ (206.2 mg, 1.32 mmol) and 1,4-dioxane (39.5 mg, 0. 45 mmol) as an internal standard at 25 °C. The reaction mixture was heated at 60 °C, and then the integral values at δ_H 8.12 ppm and 3.32 ppm, the resonances attributable to the aromatic proton in $\mathbf{B^9B^9}$ and to 1,4-dioxane, respectively, were monitored periodically (every 5 minutes) by means of ^1H NMR spectroscopy (Figure 3.2). The rate constant of disappearance of $\mathbf{B^9}$ (k_H) was evaluated by least-squares fitting of the conversion-time profiles to a zeroth-order rate equation (Eq. 3.2).

$$-d[\mathbf{B^9}]/dt = k_H = 3.55(3)\times10^{-4} \text{ [mol m}^{-3}\text{ sec}^{-1}\text{]} \quad (3.2)$$

$$\text{where } [\mathbf{B^9}] = [\mathbf{B^9}]_0 - 2[\mathbf{B^9B^9}],\ [\mathbf{B^9}]_0 = 1.169(5) \text{ [mol m}^{-3}\text{]}$$

Reaction rate constant of the Tishchenko reaction of B^9-d_1, k_D:



$d[B^9\text{-}d_1]/dt = k_D = 1.87(1)\times10^{-4}$ [mol m^{-3} sec^{-1}]

To a solution of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and IPrCl (18.3 mg, 0.040 mmol) in 0.5 mL of C_6D_6 was added $\mathbf{B^9}$-d_1 (207.5 mg, 1.32 mmol) and 1,4-dioxane (40.5 mg, 0. 46 mmol) as an internal standard at 25 °C. The reaction mixture was heated at 60 °C, and then the integral values at δ_H 8.12 ppm and 3.32 ppm, the resonances attributable to

the aromatic proton in $(\mathbf{B}^9\text{-}d_1)(\mathbf{B}^9\text{-}d_1)$ and to 1,4-dioxane, respectively, were monitored periodically (every 5 minutes) by means of ^{1}H NMR spectroscopy (Figure 3.3). The rate constant of disappearance of $\mathbf{B}^9\text{-}d_1$ (k_D) was evaluated by least-squares fitting of the conversion-time profiles to a zeroth-order rate equation (Eq. 3.3).

$$-\mathrm{d}[\mathbf{B}^9\text{-}d_1]/\mathrm{dt} = k_D = 1.87(1)\times10^{-4}\ [\mathrm{mol\ m^{-3}\ sec^{-1}}] \qquad (3.3)$$

where $[\mathbf{B}^9\text{-}d_1] = [\mathbf{B}^9\text{-}d_1]_0 - 2[(\mathbf{B}^9\text{-}d_1)(\mathbf{B}^9\text{-}d_1)]$, $[\mathbf{B}^9\text{-}d_1]_0 = 1.180(4)$ [mol m^{-3}]

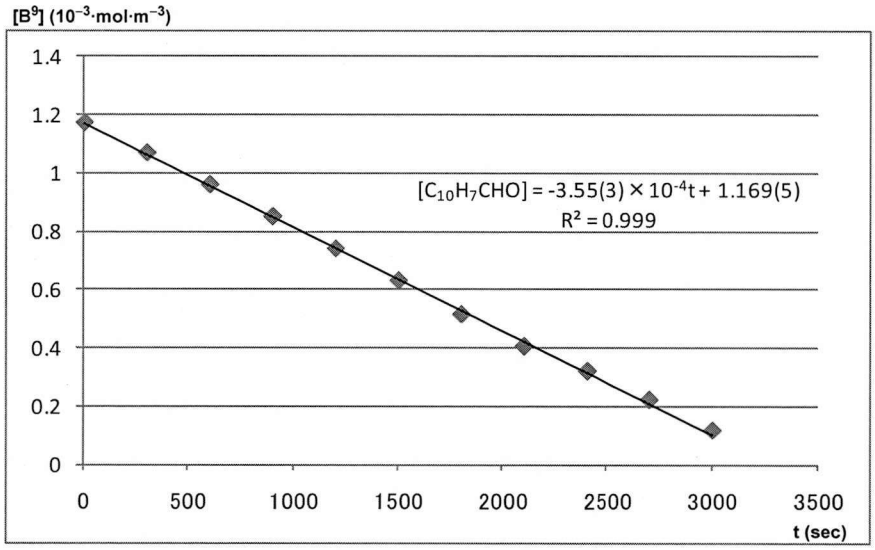


Figure 3.2. Concentration vs. time profiles of the consumption of $\mathbf{B}^9$.

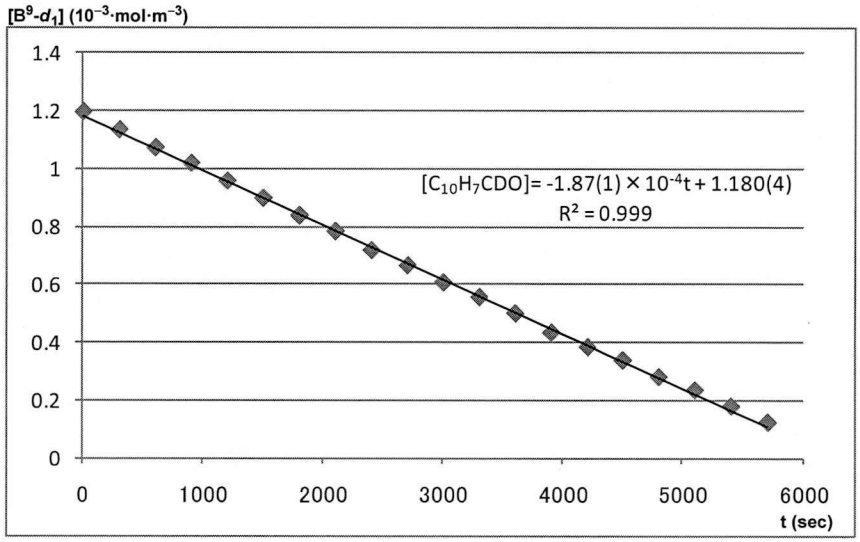


Figure 3.3. Concentration vs. time profiles of the consumption of $\mathbf{B}^9\text{-}d_1$.

These two experiments show a KIE value of reaction rate ($k_H/ k_D = 1.9$).

3.7. References and Notes

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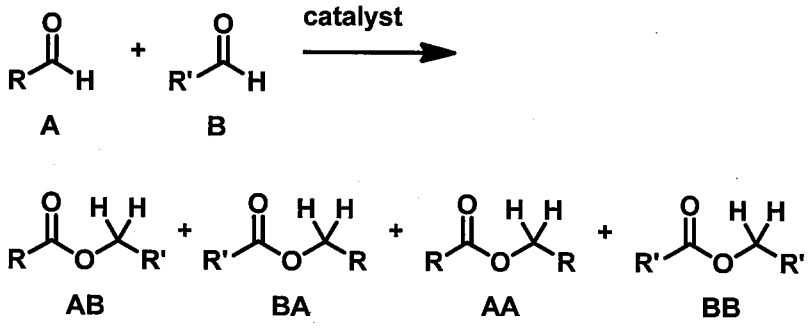
Chapter 4

Ni(0)-Catalyzed Crossed Tishchenko Reaction of Aliphatic Aldehydes with Aromatic Aldehydes

Abstract: Despite its long and successful history, the Tishchenko reaction has not been accepted as a common method for ester synthesis because of a crucial limitation: there is no selective crossed Tishchenko reaction. A new strategy for the crossed Tishchenko reaction has been sought for more than 120 years. Discussed in this chapter is the first example on the selective crossed Tishchenko reaction. In the presence of a nickel(0) catalyst, the crossed Tishchenko reaction of an aliphatic aldehyde with an equimolar amount of an aromatic aldehyde proceeded in a highly selective manner to yield a cross-coupled ester as an almost single product. This reaction can be applied to a variety of aliphatic aldehyde (1°, 2°, *cyc*-2° and 3°) and aromatic aldehyde combinations. This reaction represents 100% atom efficiency because no decarbonylation occurred. Mechanistic studies have revealed that the striking features of the reaction is the simultaneous coordination of two aldehydes to nickel(0) and the following oxidative cyclization to give a dioxanickelacycle intermediate.

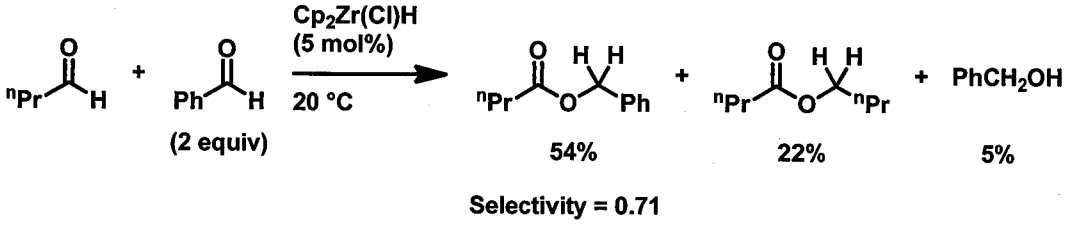
4.1. Introduction

The crossed Tishchenko reaction of two different aldehydes (**A** and **B**) gives four possible esters: two cross-coupled (**AB** and **BA**) and two homo-coupled products (**AA** and **BB**) as shown in the following equation (4.1):



(4.1)

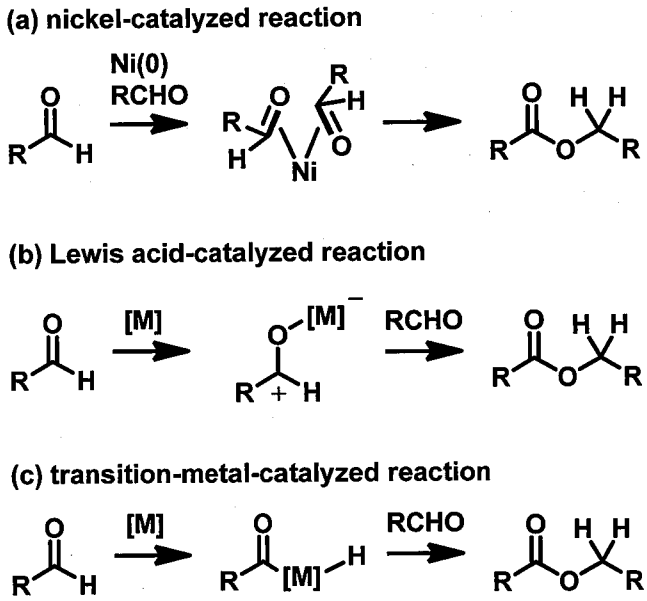
So far, some groups have attempted to prepare a single cross-coupled ester from among these four esters, but it has never been accomplished except the very special substrate combinations.[1-3] The highest selectivity before this work started has been 0.71 reported by Ishii,[1i] where the selectivity is defined as **AB**/(**AB**+**BA**+**AA**+**BB**) using the labels in Eq. 4.1. They carried out the cross-dimerization of butanal (^{n}PrCHO) with two equimolar amount of benzaldehyde (PhCHO) in the presence of a zirconium-hydride catalyst, which does not catalyze the homo-dimerization of aromatic aldehydes, and obtained a cross-coupled ester (^{n}PrCOOCH$_2$Ph) in 54% yield with concomitant formation of ^{n}PrCOOCH$_2{}^n$Pr and PhCH$_2$OH in 22 and 5% yield, respectively (Scheme 4.1). For the development of a selective crossed Tishchenko reaction, a new catalyst that can discriminate between two different aldehydes should be discovered and developed.



Scheme 4.1. Zirconium-catalyzed cross-dimerization of ^{n}PrCHO with PhCHO.

In chapter 3, the Ni(0)/NHC-catalyzed Tishchenko reaction which can dimerize both aliphatic and aromatic aldehydes was reported (Scheme 4.2a). A striking feature of the reaction mechanism for the Ni(0)-catalyzed reaction is that two aldehyde molecules react with the catalyst simultaneously, while two aldehydes react with the catalysts in a step by step manner in the reported Lewis acid- or transition-metal-catalyzed

Tishchenko reactions (Scheme 4.2b and c).[4] This distinctive feature prompted the author to apply the Ni(0)/NHC-catalyst to the crossed Tishchenko reaction.



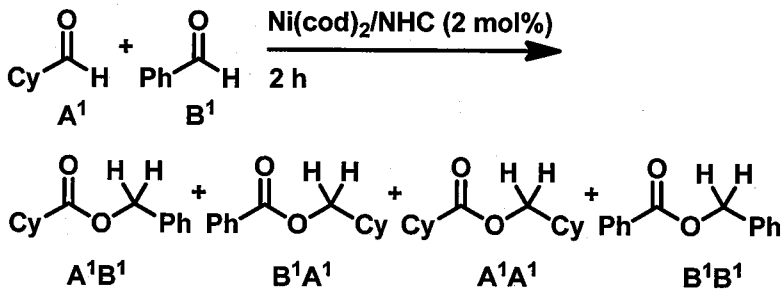
Scheme 4.2. Proposed mechanisms for the Tishchenko reaction.

4.2. Optimization of the reaction conditions

Initially, the optimized conditions for the homo-dimerization reaction were applied (entry 1, Table 4.1). The reaction of CyCHO ($\mathbf{A^1}$) with an equimolar amount of PhCHO ($\mathbf{B^1}$) in benzene at 60 °C in the presence of $Ni(cod)_2$/IPrCl (2 mol%) gave a cross-coupled ester, $CyCOOCH_2Ph$ ($\mathbf{A^1B^1}$), predominantly in 58% yield, with concomitant formation of $PhCOOCH_2Cy$ ($\mathbf{B^1A^1}$), $CyCOOCH_2Cy$ ($\mathbf{A^1A^1}$) and $PhCOOCH_2Ph$ ($\mathbf{B^1B^1}$) in 4, 12 and 18% yield, respectively, and the selectivity was moderate (0.63). It should be emphasized that two aldehydes were employed in a 1:1 ratio. Encouraged by this result, the optimization of NHC ligand was conducted (entries 1–5). When SIPr and IPr were employed as a ligand, $\mathbf{A^1B^1}$ was obtained in 87 and 86% yield, respectively (entries 2 and 3). IMes was less effective than SIPr and IPr (entry 4). In stark contrast to these results, *N*-alkyl substituted ICy gave complicated mixtures which contained a trace amount of target compounds (entry 5). Based on these results, SIPr was employed for the optimizations of temperature and solvents. Among temperature examined at 25 to 80 °C, the highest result (94% yield, 0.94 selectivity) was obtained at 40 °C in the reaction of $\mathbf{A^1}$ with $\mathbf{B^1}$ (entries 6–9). Altering the solvent from toluene to THF, $\mathbf{A^1B^1}$ was also obtained in high yield and selectivity (entry 10).

However, in the case of 1,4-dioxane, ethyl acetate and hexane, a considerable decrease in yield of $\mathbf{A^1B^1}$ was observed (entries 11–13). In these reactions, benzoin condensation of $\mathbf{B^1}$ proceeded, and the crossed Tishchenko reaction was suppressed. Thus, the conditions in entry 7 were determined as the optimized conditions.

Table 4.1. Ni(0)/NHC-catalyzed crossed Tishchenko reaction of CyCHO ($\mathbf{A^1}$) with PhCHO ($\mathbf{B^1}$).[a]



entry	NHC	solvent	temp. (°C)	$\mathbf{A^1B^1}$ (%)	$\mathbf{B^1A^1}$ (%)	$\mathbf{A^1A^1}$ (%)	$\mathbf{B^1B^1}$ (%)	selectivity
1	IPrCl	benzene	60	58	4	12	18	0.63
2	SIPr	benzene	60	87	< 1	6	7	0.87
3	IPr	toluene	60	86	< 1	6	7	0.86
4	IMes	benzene	60	79	2	9	9	0.79
5	ICy	benzene	60	complicated mixture				–
6	SIPr	toluene	23[b]	80	< 1	6	8	0.85
7	SIPr	toluene	40[c]	94	< 1	2	4	0.94
8	SIPr	toluene	50	90	< 1	3	7	0.90
9	SIPr	toluene	80	78	< 1	6	11	0.82
10	SIPr	THF	50	88	< 1	6	6	0.88
11	SIPr	1,4-dioxane	50	37	< 1	1	4	0.88
12	SIPr	EtOAc	50	8	–	< 1	2	0.80
13	SIPr	hexane	50	23	–	1	3	0.85

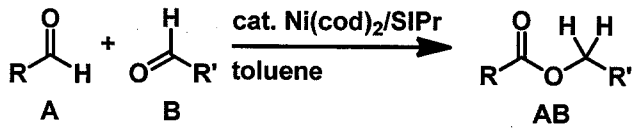
[a] General conditions: $\mathbf{A^1}$, $\mathbf{B^1}$ (both 2.00 mmol), $Ni(cod)_2$/NHC (0.040 mmol) and solvent (2 mL) were reacted at the indicated temperature. Yields of each ester were determined by GC analysis. Selectivity for **AB** was calculated as following: **AB**/(**AB**+**BA**+**AA**+**BB**). [b] 28 h. [c] 4 h.

4.3. Ni(0)/NHC-catalyzed crossed Tishchenko reaction

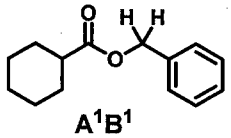
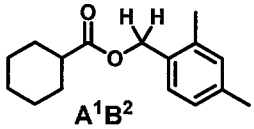
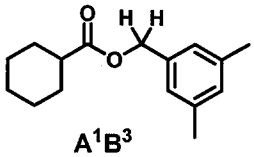
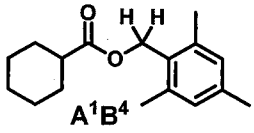
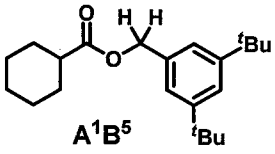
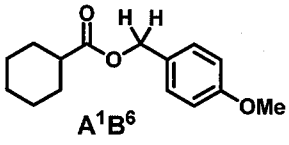
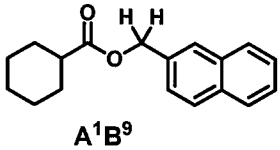
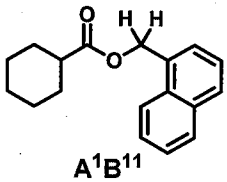
A wide variety of the combinations of substrates were examined, and the results are summarized in Table 4.2. Treatment of $\mathbf{A^1}$ with an equimolar amount of $\mathbf{B^1}$ or 2,4- or 3,5-xylylaldehyde ($\mathbf{B^2}$ and $\mathbf{B^3}$) resulted in the formation of the corresponding cross-coupled esters ($\mathbf{A^1B^1}$–$\mathbf{A^1B^3}$) in excellent yields with excellent selectivity (92–94% yield, 0.92–0.94 selectivity; entries 1–3). Although a decrease in selectivity was observed in the reaction of $\mathbf{A^1}$ with 2,4,6-trimethyl benzaldehyde ($\mathbf{B^4}$) (57 % yield, 0.64 selectivity; entry 4), $\mathbf{B^5}$ having bulky substitutes at the 3 and 5 positions gave excellent results (89% yield, 0.89 selectivity; entry 5). *p*-Anisaldehyde ($\mathbf{B^6}$) and naphthaldehyde derivatives ($\mathbf{B^9}$ and $\mathbf{B^{11}}$) afforded the cross-coupled esters in excellent selectivity (0.87–0.98; entries 6–8). In the course of evaluating the scope of electron-deficient aromatic aldehydes, the crossed Tishchenko reaction of *p*-Cl- or *p*-NO_2-substituted benzaldehydes with $\mathbf{A^1}$ was carried out. However, the cross-coupled esters were not obtained at all; unidentified precipitations were observed instead. Next, the cross-coupling reaction of various aliphatic aldehydes (1°, 2° and 3°) with $\mathbf{B^{11}}$ was examined (entries 9–11), as $\mathbf{B^{11}}$ afforded the excellent selectivity in the reaction with $\mathbf{A^1}$ (entry 8). As expected, the corresponding cross-coupled esters ($\mathbf{A^2B^{11}}$, $\mathbf{A^5B^{11}}$ and $\mathbf{A^4B^{11}}$) were obtained as almost single products (0.93–0.99 selectivity). Recent attention to 1-naphthylmethyl esters has focused on their utility, for example, as an identification group to pursue the production of dendrimers[5] and anti-diabetic drugs.[6] Although $\mathbf{A^2}$ and $\mathbf{A^5}$ can be employed in the reaction with other aromatic aldehydes with no loss of selectivity (entries 12 and 13), a significant decrease in selectivity was observed in the case of $\mathbf{A^4}$. It is noted that the aliphatic aldehyde (**A**) tends to become the carboxylic acid part and the aromatic aldehyde (**B**) the alcohol part. This tendency was also observed in previous reports.[1h,i] One of the advantages of this catalyst system is its simplicity in the isolation of the products. In most cases, simple distillation can be used to isolate the products from the reaction mixture using a Kugelrohr distillation oven.

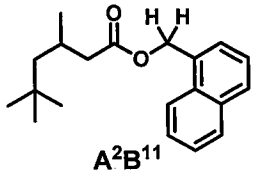
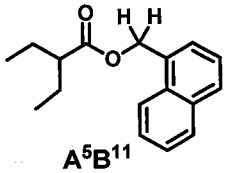
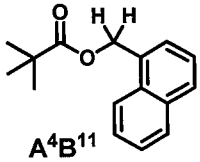
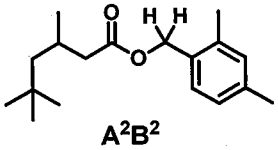
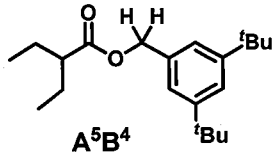
Combinations of two different aliphatic or aromatic aldehydes were examined, but it was difficult to prepare a single cross-coupled ester selectively under the presented reaction conditions. For example, the reaction of $\mathbf{A^1}$ with an equimolar amount of $\mathbf{A^4}$ in the presence of $Ni(cod)_2$/IPr (10 mol%) gave $\mathbf{A^1A^4}$, $\mathbf{A^4A^1}$, $\mathbf{A^1A^1}$ and $\mathbf{A^4A^4}$ in 9, 34, 24 and 31% yield, respectively. The reaction of two different aromatic aldehydes was rather selective. The reaction of $\mathbf{B^6}$ with an equimolar amount of $\mathbf{B^{11}}$ in the presence of $Ni(cod)_2$/IMes (10 mol%) gave $\mathbf{B^6B^{11}}$, $\mathbf{B^{11}B^6}$, $\mathbf{B^6B^6}$ and $\mathbf{B^{11}B^{11}}$ in 53, 1, 2 and 17% yield, respectively, and 0.73 selectivity for $\mathbf{B^6B^{11}}$.

Table 4.2. Ni(0)/NHC-catalyzed crossed Tishchenko reaction of aliphatic aldehydes (**A**) with aromatic aldehydes (**B**).[a]



A B AB

entry	AB	condition[b]	conv. of B[c] (%)	yield[d] (%)	selectivity[c]
1	 A^1B^1	2/40/4	> 99	94(84)	0.94
2	 A^1B^2	4/40/4	> 99	92(88)	0.92
3	 A^1B^3	2/40/4	> 99	94(85)	0.94
4	 A^1B^4	4/40/4	89	57	0.64
5	 A^1B^5	2/40/4	> 99	89(81)	0.89
6	 A^1B^6	2/40/4	> 99	87(82)	0.87
7	 A^1B^9	4/50/2	98	92(83)	0.94
8	 A^1B^{11}	2/50/2	66	64(47)	0.98

9	 A^2B^{11}	4/50/2	61	61(66)	> 0.99
10[e]	 A^5B^{11}	10/23/12	81	75(65)	0.93
11[f]	 A^4B^{11}	10/23/12	83	73(65)	0.94
12	 A^2B^2	4/40/4	90	82(66)	0.94
13	 A^5B^4	4/40/4	> 99	88(83)	0.88

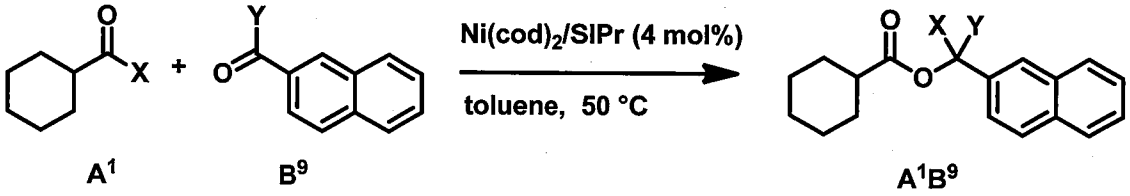
[a] Aldehydes (0.40, 1.00 or 2.00 mmol), $Ni(cod)_2$/SIPr (0.040 mmol) and toluene (2 mL) were reacted at the indicated temperature. [b] Catalyst loading (mol%) / temperature (°C) / time (h). [c] Conversions (%) of **B** and selectivity were determined by GC analysis. [d] Yields (%) of **AB** were determined by GC analysis; isolated yields are given in parentheses. [e] IPr was employed. [f] IMes was employed.

4.4. Kinetic Studies

To gain insight into the reaction mechanism, kinetic studies were conducted utilizing the combination of $\mathbf{A^1}$ and $\mathbf{B^9}$. In order to explore the change in the concentration of each component, the crossed Tishchenko reaction of $\mathbf{A^1}$ with $\mathbf{B^9}$ (entry 7, Table 4.2) was monitored by GC analysis. The rate constants for disappearance of $\mathbf{A^1}$ ($k_{\text{A-cross}}$) and $\mathbf{B^9}$ ($k_{\text{B-cross}}$) are zeroth-order with respect to the concentration of $\mathbf{A^1}$ and $\mathbf{B^9}$, respectively. Moreover, the rate constant for production of $\mathbf{A^1B^9}$ (k_{I}) was almost equal to $k_{\text{A-cross}}$ and $k_{\text{B-cross}}$, i.e., $k_{\text{A-cross}} \approx k_{\text{B-cross}} \approx k_{\text{I}} \approx 13\times10^{-5}$ mol m^{-3} sec^{-1}. These results indicate that the coordination of the aldehydes to nickel(0) is not the rate-limiting step in the reaction. In addition, the reaction exhibits first-order dependence on the Ni(0)/SIPr catalyst.

Deuterium labeling experiments were conducted to estimate the kinetic isotope effects (KIEs). The measured KIEs are as follows; KIE(II) = 1.2, KIE(III) = 2.0 and KIE(IV) = 1.9 (Table 4.3). In these experiments, deuterium was exactly incorporated

Table 4.3. Labeling experiments for the crossed Tishchenko reaction of $\mathbf{A^1}$ with $\mathbf{B^9}$.

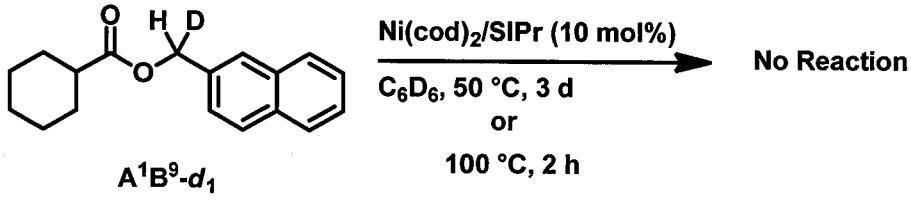


$\mathbf{A^1}$ $\mathbf{B^9}$ $\mathbf{A^1B^9}$

experiment	X	Y	k_N[a]	KIE (N)[b]	selectivity
I	H	H	12.9(1)	–	0.94
II	H	D	10.9(1)	1.2	0.93
III	D	H	6.4(3)	2.0	0.83[c]
IV	D	D	6.7(1)	1.9	0.85[d]

[a] Rate constant (10^{-5} mol m^{-3} s^{-1}) for the production of the ester in experiment N, where N is the roman numeral label for the experiment. [b] Kinetic isotope effect, estimated as KIE(N) = k_I/k_N. [c] The yields of **AB**, **BA**, **AA**, and **BB** were 71, < 1, 2, and 13% yield, respectively. [d] The yields of **AB**, **BA**, **AA**, and **BB** were 77, < 1, 3, and 10% yield, respectively.

into the X and/or Y positions without loss of its enrichment ratio. In addition, scrambling of the deuterium in $\mathbf{A^1B^9}$-d_1 was not observed at all when $\mathbf{A^1B^9}$-d_1 was subjected either to the catalytic conditions (50 °C, 3 d) or more harsh conditions (100 °C, 2 h) (Scheme 4. 3).

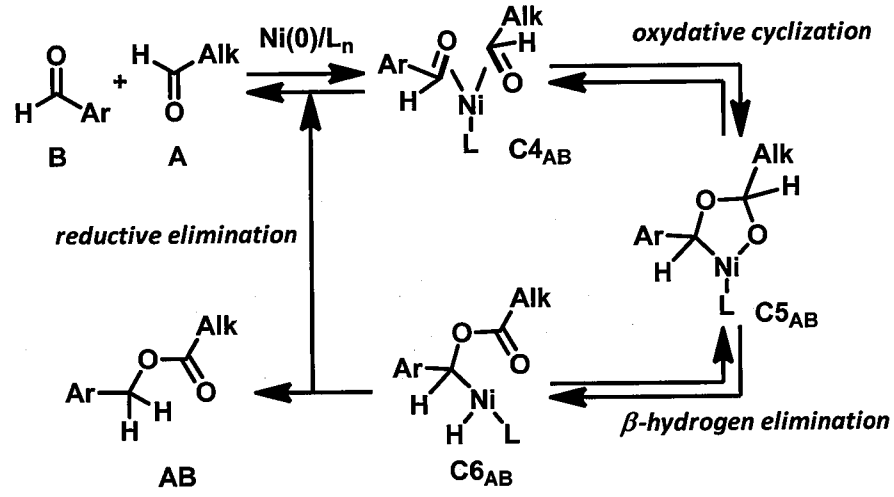


$\mathbf{A^1B^9}$-d_1

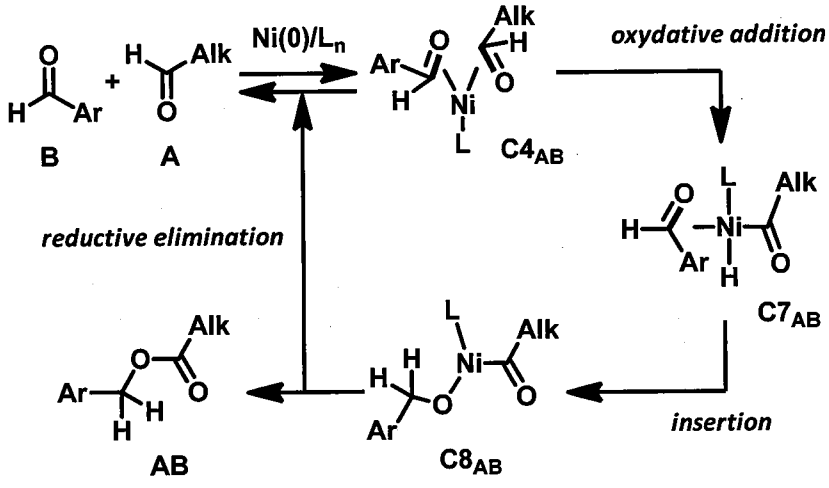
Scheme 4.3. H/D scrambling test by using $\mathbf{A^1B^9}$-d_1.

4.5. Plausible reaction mechanisms

Plausible reaction mechanisms for the formation of **AB** are described in Schemes 4.4 and 4.5. The coordination of **A** and **B** to the catalyst gives rise to (η^2-**A**)(η^2-**B**)NiL complex (**C4**$_{AB}$). After the formation of **C4**$_{AB}$, there might be two possible paths for the nickel(0)-catalyzed crossed Tishchenko reaction: via a dioxanickelacycle intermediate (path (a), Scheme 4.4) or an acyl nickel intermediate (path (b), Scheme 4.5).[7,8]



Scheme 4.4. Plausible reaction path (a) via a dioxanickelacycle intermediate.



Scheme 4.5. Plausible reaction path (b) via an acyl nickel intermediate.

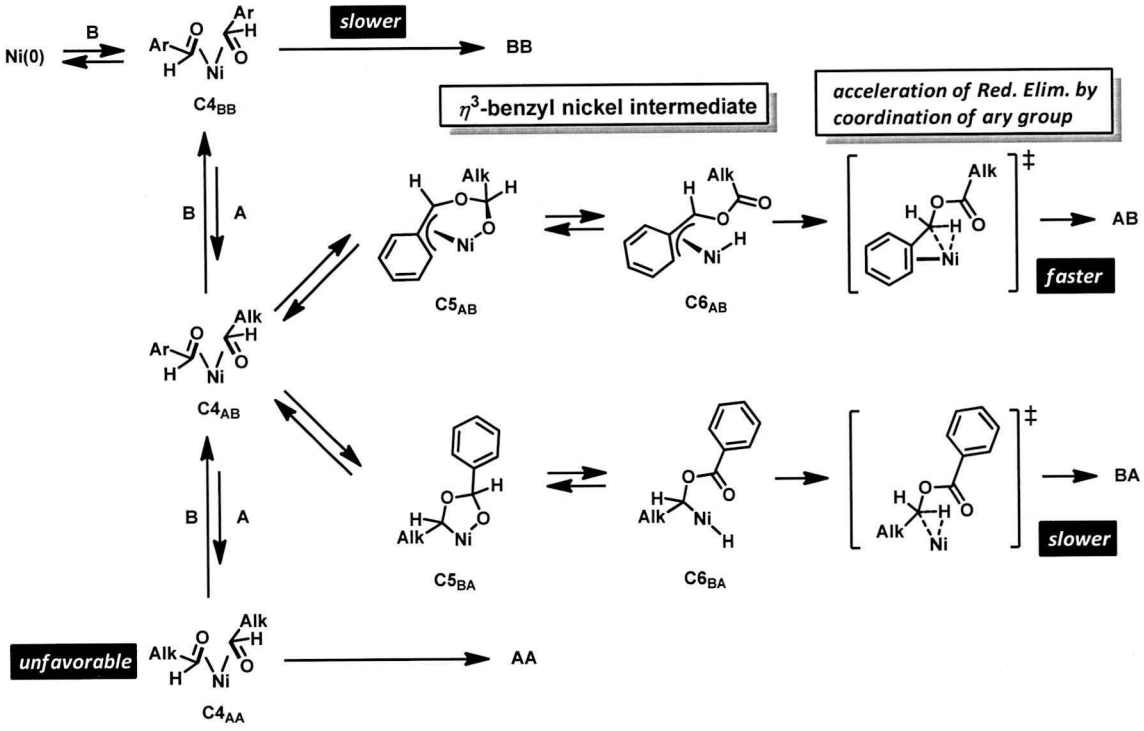
In path (a), the oxidative cyclization of aldehyde moieties in $\mathbf{C4_{AB}}$ would give dioxanickelacycle $\mathbf{C5_{AB}}$, after which β-hydrogen elimination and reductive elimination would yield the cross-coupled ester **AB**.[9,10] On the other hand, in path (b), oxidative addition of the C–H bond of **A** in $\mathbf{C4_{AB}}$ to Ni(0) would generate a Ni–H complex $\mathbf{C7_{AB}}$. Insertion of the C=O bond of **B** into Ni–H would then give rise to $\mathbf{C8_{AB}}$, after which reductive elimination would result in the formation of **AB**.

The observed KIE(III) is in the range of a primary KIE, clearly suggesting that the cleavage of C–H bond in $\mathbf{A^1}$ or the Ni–H bond significantly contributes to the reaction rate.[11] Thus, the rate-limiting step might be either β-hydrogen elimination or reductive elimination. However, the value of KIE(II), which is in the range of a normal secondary KIE, should not be observed in the β-hydrogen elimination step. Therefore, in path (a), the rate-limiting step might be the reductive elimination. In path (b), the oxidative addition or the insertion could be the rate-limiting step. However, KIE(II) is consistent with neither of these possibilities. In the oxidative addition step, a KIE should not be observed for aryl aldehyde. In the insertion step, an inverse secondary KIE should be observed because of the hybridization change of the carbonyl carbon of aryl aldehyde from sp^2 to sp^3.[11,12] Thus, the path (a) is more likely, and a very rapid pre-equilibrium process involving $\mathbf{C4_{AB}}$ and $\mathbf{C6_{AB}}$ might exist.[13] Furthermore, no decarbonylation was observed in this work, although it was reported that decarbonylation occurred in the transition-metal-catalyzed hydroacylation of aldehydes via an acyl metal intermediate such as $\mathbf{C7_{AB}}$.[14]

The observed KIE(III) and KIE(IV) were almost the same value, which suggests that the rate of the cross-coupling reaction relies mainly on the reactivity of the aliphatic aldehydes $\mathbf{A^1}$. This rationalization is also consistent with the decrease in selectivity observed when the deuterium was incorporated into $\mathbf{A^1}$ (entries 3 and 4, Table 4.3). Because cleavage of a Ni–D bonds (from $\mathbf{C6_{AB}}$ to **AB** in path (a)) generally requires a higher energy than for the corresponding Ni–H bond, the formation of **AB** is retarded and the ratio of **BB** increased.

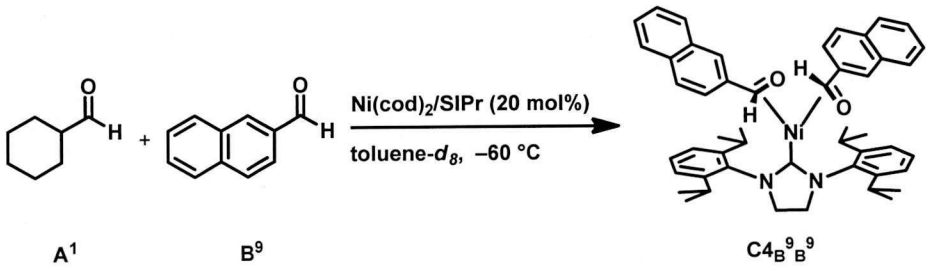
4.5. Origin of selectivity among the four esters

All reaction paths are proposed in Scheme 4.6. The formation of $\mathbf{C4_{BB}}$ would occur prior to the formation of $\mathbf{C4_{AB}}$. Some theoretical studies have demonstrated that a more electron-deficient π component can coordinate to nickel(0) in the η^2 mode more efficiently because of a strong back bonding interaction.[15] Aromatic aldehydes, which generally are more electron-deficient than aliphatic aldehydes, coordinate to nickel(0) to



Scheme 4.6. All reaction paths for the Ni(0)-catalyzed crossed Tishchenko reaction.

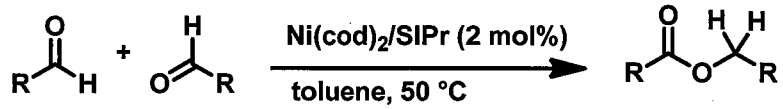
give $\mathbf{C4_{BB}}$. In fact, at –60 °C, the exclusive formation of $\mathbf{C1_B{}^9{}_B{}^9}$ was observed in the reaction of $\mathbf{A^1}$ (5 equiv) and $\mathbf{B^9}$ (5 equiv) with $Ni(cod)_2$ and SIPr in toluene-d_8 by NMR spectroscopy (Scheme 4.7). However, even at 25 °C, broadening of the resonances of the carbonyl hydrogen of $\mathbf{A^1}$ and $\mathbf{B^9}$ was observed. Thus, under the reaction conditions, the exchange of **B** with **A** generating $\mathbf{C4_{AB}}$ would occur much faster than the formation of homo-coupled ester **BB** from $\mathbf{C4_{BB}}$.



Scheme 4.7. Formation of $\mathbf{C4_B{}^9{}_B{}^9}$ under the cross-coupling conditions at –60 °C.

The reaction rate for the homo-dimerization of $\mathbf{A^1}$ ($k_{\mathbf{A}\text{-homo}} = 8.9(2)\times10^{-4}$ mol m^{-3} sec^{-1}) is much faster than that of $\mathbf{B^9}$ ($k_{\mathbf{B}\text{-homo}} = 5.2(2)\times10^{-5}$ mol m^{-3} sec^{-1}) (Scheme 4.8). However, the formation of **AA** was suppressed under the crossed dimerization

conditions since $\mathbf{C4_{AA}}$ would be thermodynamically and kinetically unfavorable intermediate compared to $\mathbf{C4_{BB}}$ and $\mathbf{C4_{AB}}$.



R	k_{homo} (mol m^{-3} sec^{-1})
Cy (A^1)	$8.9(2)\times 10^{-4}$
2-Np (B^9)	$5.2(2)\times 10^{-5}$

Scheme 4.8. Ni(0)/SIPr-catalyzed Tishchenko reaction of $\mathbf{A^1}$ and $\mathbf{B^9}$.

For the predominant formation of **AB** over **BA**, the coordination of aryl group to nickel might play a key role (Scheme 4.6): stabilizing $\mathbf{C5_{AB}}$ and $\mathbf{C6_{AB}}$ compared to $\mathbf{C5_{BA}}$ and $\mathbf{C6_{BA}}$ by forming an η^3-benzyl nickel complex,[16] and accelerating the reductive elimination ($\mathbf{C6_{AB}}$ to **AB**).[17] It has been reported that the formation of η^3-benzyl nickel complex effectively occurred from 1-naphthaldehyde, rationalizing that the crossed Tishchenko reaction with 1-naphthaldehyde especially gave high selectivity (entries 8–11, Table 4.2).[16]

Based on these discussions, the formation of **AB** might occur prior to the formation of other esters under the presented reaction conditions.

4.6. Conclusion for chapter 4

Demonstrated in this chapter is the first example of a selective crossed Tishchenko reaction of two different aldehydes by employing nickel(0) as a catalyst. This reaction can be applied to various combinations of aliphatic aldehydes with equimolar amounts of aromatic aldehydes, and cross-coupled esters are obtained in a highly selective manner. Mechanistic studies revealed that all of the key intermediates might include two aldehyde molecules and that the reaction rate is controlled by the aliphatic aldehyde. Experimental results discussed in this chapter would be consistent with the participation of the dioxanickelacycle in this reaction. The author convinces that the presented study would contribute to further development of the environmentally benign synthesis of esters.

4.7. Experimental Section

Materials

Toluene, benzene, THF, benzene-d_6 and toluene-d_8 were distilled from sodium benzophenone ketyl. Other solvents were used prior to degassed and distilled. All commercially available reagents were distilled over CaH_2 under reduced pressure prior to use. *N*-Heterocyclic carbenes (NHCs) were furnished by the known procedures (please, see Ref. 11 in chapter 1). Cyclohexanecarbaldehyde-d_1 were furnished by known procedures.[18]

Optimization of reaction conditions (Table 4.1)

Evaluation of ligands (entries 1–5): A reaction tube was charged with cyclohexanecarbaldehyde ($\mathbf{A^1}$; 224.4 mg, 2.00 mmol) and benzaldehyde ($\mathbf{B^1}$; 212.2 mg, 2.00 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and NHC (0.040 mmol) in benzene (entries 1, 2, 4 and 5) or toluene (entry 3) (2 mL). The reaction mixture was heated at 60 °C. The reaction was monitored by gas chromatography. GC yields of each ester were determined using pentadecane as an internal standard.

Evaluation of reaction temperature (entries 6–9): A reaction tube was charged with $\mathbf{A^1}$ (224.4 mg, 2.00 mmol) and $\mathbf{B^1}$ (212.2 mg, 2.00 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and SIPr (15.6 mg, 0.040 mmol) in toluene (2 mL). The reaction mixture was heated at indicated temperature. The reaction was monitored by gas chromatography. GC yields of each ester were determined using pentadecane as an internal standard.

Evaluation of solvents (entries 10–13):A reaction tube was charged with $\mathbf{A^1}$ (224.4 mg, 2.00 mmol) and $\mathbf{B^1}$ (212.2 mg, 2.00 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and SIPr (15.6 mg, 0.040 mmol) in THF, 1,4-dioxane, ethyl acetate, or hexane (2 mL). The reaction mixture was heated at 50 °C. The reaction was monitored by gas chromatography. GC yields of each ester were determined using pentadecane as an internal standard.

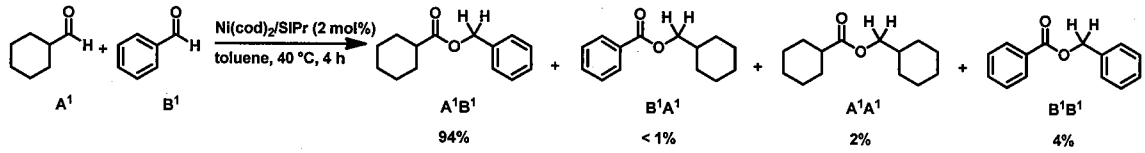
Scope of substrates (Table 4.2 and entry S14)

Note: in some cases, sum of the GC yield and/or conversions of each aldehyde may be slightly over 100% because of measurement division.

General Experimental Procedure: A reaction tube was charged with **A** (2.00 mmol) and **B** (2.00 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and SIPr (15.6 mg, 0.040 mmol) in toluene (2 mL). The reaction mixture was heated at 40 °C with

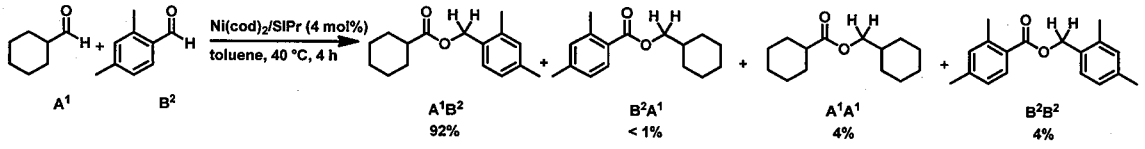
stirring. The reaction was monitored by gas chromatography. GC yields of each ester were determined using pentadecane as an internal standard. The product was isolated by Kugelrohr distillation. Further purification, a silica gel chromatography or distillation, was carried out as needed. The homo-coupled products (**AA** and **BB**) are identical to those reported in chapter 3.

Benzyl cyclohexanecarboxylate (A^1B^1):



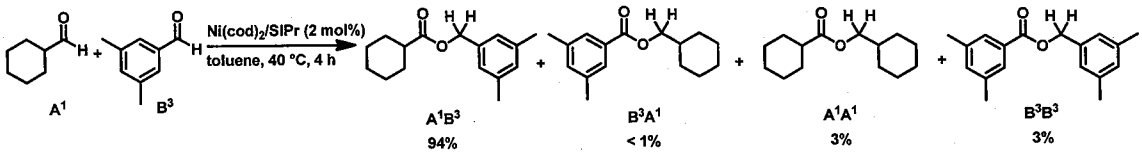
The general procedure was followed with $\mathbf{A^1}$ (225.2 mg, 2.01 mmol) and $\mathbf{B^1}$ (213.0 mg, 2.01 mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^1}$ (94%), $\mathbf{B^1A^1}$ (< 1%), $\mathbf{A^1A^1}$ (2%) and $\mathbf{B^1B^1}$ (4%). Purification by Kugelrohr distillation gave $\mathbf{A^1B^1}$ (368.5 mg, 1.69 mmol, 84%) as a colorless oil. Spectroscopic data of $\mathbf{A^1B^1}$ was identified to that previously reported.[19]

2,4-Dimethylbenzyl cyclohexanecarboxylate (A^1B^2):



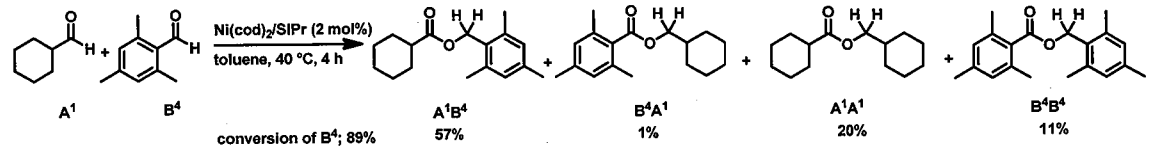
The general procedure was followed with $\mathbf{A^1}$ (113.1 mg, 1.01 mmol) and $\mathbf{B^2}$ (134.8 mg, 1.00 mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^2}$ (92%), $\mathbf{B^2A^1}$ (< 1%), $\mathbf{A^1A^1}$ (4%) and $\mathbf{B^2B^2}$ (4%). Purification by silica gel chromatography followed by Kugelrohr distillation gave $\mathbf{A^1B^2}$ (214.3 mg, 0.88 mmol, 88%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.01 (d, J = 8.0 Hz, 1H, Ar–*H*), 5.07 (s, 2H, OCH_2Ar), 2.34 (m, 1H, $CHC(O)CH_2$), 2.32 (s, 3H, Me), 2.31 (s, 3H, Me),1.93–1.22 (m, 10H, Cy–*H*). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.2, 138.4, 137.1, 131.3, 129.5, 126.7, 64.6, 43.4, 29.2, 25.9, 25.6, 21.2, 19.0. An Ar–*C* is obscured by other Ar–*C*s. **HRMS**: $C_{16}H_{22}O_2$: 246.1620, Found 246.1616. **IR** (neat, cm^{-1}): 1731.

3,5-Dimethylbenzyl cyclohexanecarboxylate (A^1B^3):



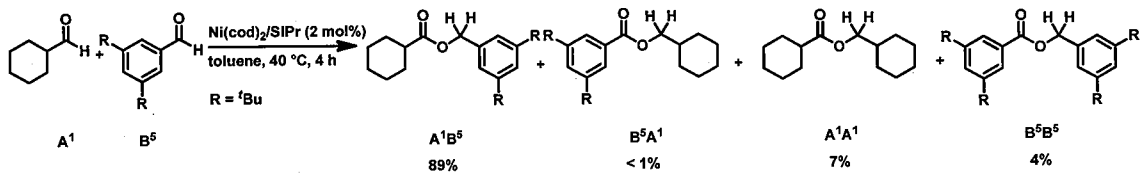
The general procedure was followed with $\mathbf{A^1}$ (224.7 mg, 2.00 mmol) and $\mathbf{B^3}$ (268.7 mg, 2.00 mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^3}$ (94%), $\mathbf{B^3A^1}$ (< 1%), $\mathbf{A^1A^1}$ (3%) and $\mathbf{B^3B^3}$ (3%). Purification by Kugelrohr distillation gave $\mathbf{A^1B^3}$ (417.1 mg, 1.69 mmol, 85%) as a colorless oil. **<u>^{1}H NMR</u>**(400 MHz, $CDCl_3$): δ 6.97 (s, 3H, Ar–*H*), 5.04 (s, 2H, OCH_2Ar), 2.35 (m, 1H, $CHC(O)CH_2$), 2.33 (s, 6H, $ArCH_3$), 2.33–1.25 (m, 10H, Cy–*H*). **<u>^{13}C NMR</u>** (100 MHz, $CDCl_3$): δ 176.1, 138.2, 136.3, 129.9, 126.0, 66.1, 43.3, 29.1, 25.9, 25.6, 21.4. **<u>HRMS</u>**: Calcd. for $C_{16}H_{22}O_2$: 246.1620, Found 246.1615. **<u>IR</u>** (neat, cm^{-1}): 1734.

2,4,6-Trimethylbenzyl cyclohexanecarboxylate (A^1B^4):



The general procedure was followed with $\mathbf{A^1}$ (112.8 mg, 1.00 mmol) and $\mathbf{B^4}$ (149.5 mg, 1.00 mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^4}$ (57%), $\mathbf{B^4A^1}$ (1%), $\mathbf{A^1A^1}$ (20%) and $\mathbf{B^4B^4}$ (11%). **<u>^{1}H NMR</u>** (400 MHz, $CDCl_3$): δ 6.86 (s, 2H, Ar–*H*), 5.13 (s, 2H, OCH_2Ar), 2.33 (s, 6H, Me), 2.29 (s, 3H, Me), 1.93–1.22 (m, 10H, Cy–*H*). **<u>^{13}C NMR</u>** (100 MHz, $CDCl_3$): δ 176.5, 138.4, 138.3, 129.4, 129.2, 61.0, 43.4, 29.2, 25.9, 25.6, 21.1, 19.6. **<u>HRMS</u>**: Calcd. for $C_{17}H_{24}O_2$: 260.1776, Found 260.1777. **<u>IR</u>** (neat, cm^{-1}): 1730.

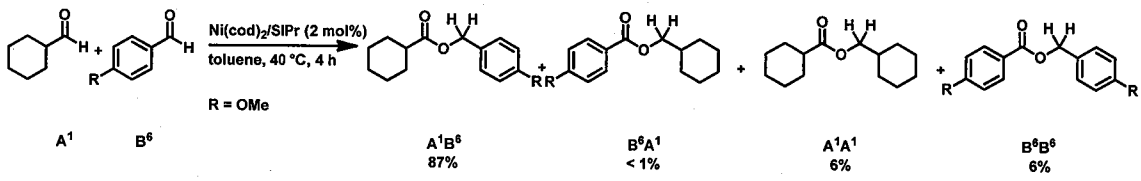
3,5-Di-tert-butylbenzyl cyclohexanecarboxylate (A^1B^5):



The general procedure was followed with $\mathbf{A^1}$ (224.2 mg, 2.00 mmol) and $\mathbf{B^5}$ (436.4 mg,

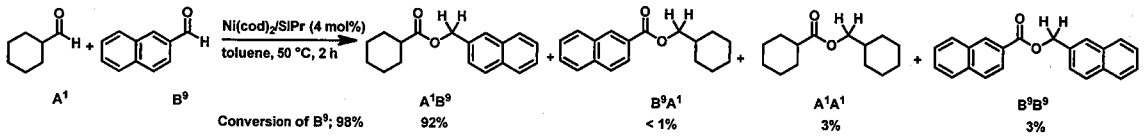
2.00 mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^5}$ (89%), $\mathbf{B^5A^1}$ (< 1%), $\mathbf{A^1A^1}$ (7%) and $\mathbf{B^5B^5}$ (4%). Purification by Kugelrohr distillation gave $\mathbf{A^1B^5}$ (536.1 mg, 1.62 mmol, 81%) as a colorless oil. At room temperature, $\mathbf{A^1B^5}$ exists in the solid state. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (s, 1H, Ar–*H*), 7.18 (s, 2H, Ar–*H*), 5.11 (s, 2H, OCH_2Ar), 2.38 (m, 1H, $CHC(O)CH_2$), 1.93–1.22 (m, 10H, Cy–*H*), 1.34 (s, 18H, ^{t}Bu). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.1, 151.1, 135.5, 122.3, 122.2, 66.7, 43.4, 35.0, 31.6, 29.2, 25.9, 25.6. **HRMS**: Calcd. for $C_{22}H_{34}O_2$: 330.2559, Found 330.2556. **IR** (KBr, cm^{-1}): 1734.

4-Methoxybenzyl cyclohexanecarboxylate ($\mathbf{A^1B^6}$):



The general procedure was followed with $\mathbf{A^1}$ (224.0 mg, 2.00 mmol) and $\mathbf{B^6}$ (271.6 mg, 1.99 mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^6}$ (87%), $\mathbf{B^6A^1}$ (< 1%), $\mathbf{A^1A^1}$ (6%) and $\mathbf{B^6B^6}$ (6%). Purification by Kugelrohr distillation gave $\mathbf{A^1B^6}$ (404.7 mg, 1.63 mmol, 82%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.4 Hz, 2H, Ar–*H*), 6.88 (d, J = 8.4 Hz, 2H, Ar–*H*), 5.08 (s, 2H, OCH_2Ar), 3.87 (s, 3H, OCH_3), 2.42(m, 1H, $CHC(O)CH_2$), 2.02–1.31(m, 10H, Cy–*H*). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.0, 160.0, 130.0, 128.5, 114.0, 65.7, 55.3, 43.2, 29.0, 25.8, 25.5. **HRMS**: Calcd. for $C_{15}H_{20}O_3$: 248.1412, Found 248.1409. **IR** (neat, cm^{-1}): 1730.

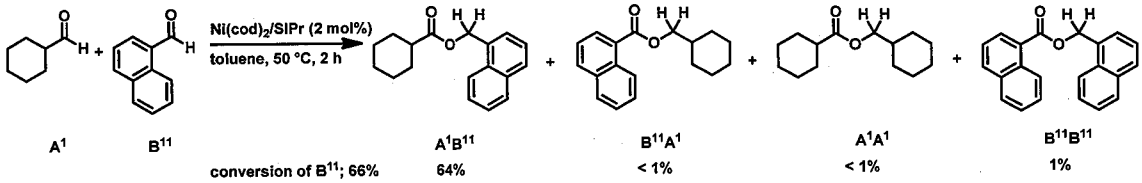
Naphthalen-2-ylmethyl cyclohexanecarboxylate ($\mathbf{A^1B^9}$):



The general procedure was followed with $\mathbf{A^1}$ (112.0 mg, 1.01 mmol) and $\mathbf{B^9}$ (156.2 mg, 1.00 mmol) and reaction mixture was stirred at 50 °C for 2 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^9}$ (92%), $\mathbf{B^9A^1}$ (< 1%), $\mathbf{A^1A^1}$ (3%) and $\mathbf{B^9B^9}$ (3%). Purification by Kugelrohr distillation gave $\mathbf{A^1B^9}$ (222.3 mg, 0.83 mmol, 83%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (m, 4H, Ar–*H*), 7.51 (m, 3H, Ar–*H*),

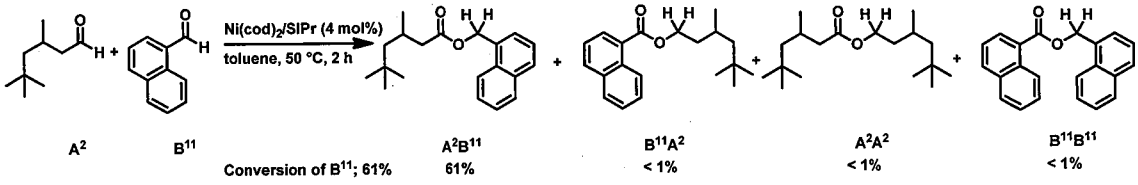
5.31 (s, 2H, OCH_2Ar), 2.43 (m, 1H, CHC(O)CH$_2$), 2.02–1.29 (m, 10H, Cy–H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.9, 133.8, 133.3, 133.1, 128.4, 128.0, 127.7, 127.1, 126.3, 126.2, 125.8, 66.1, 43.3, 29.1, 25.8, 25.5. **HRMS**: Calcd. for $C_{18}H_{20}O_2$: 268.1463, Found 268.1465. **IR** (neat, cm^{-1}): 1732.

Naphthalen-1-ylmethyl cyclohexanecarboxylate (A^1B^{11}):



The general procedure was followed with $\mathbf{A^1}$ (224.4 mg, 2.00 mmol) and $\mathbf{B^{11}}$ (312.4 mg, 2.00 mmol) and reaction mixture was stirred at 50 °C for 2 h. Yields of each product were determined by GC analysis: $\mathbf{A^1B^{11}}$ (64%), $\mathbf{B^{11}A^1}$ (< 1%), $\mathbf{A^1A^1}$ (< 1%) and $\mathbf{B^{11}B^{11}}$ (1%). Purification by Kugelrohr distillation gave $\mathbf{A^1B^{11}}$ (251.6 mg, 0.94 mmol, 47%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H, Ar–H), 7.90 (m, 2H, Ar–H), 7.42 (m, 4H, Ar–H), 5.61 (s, 2H, OCH_2Ar), 2.45 (m, 1H, CHC(O)CH$_2$), 2.03–1.24 (m, 10H, Cy–H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.1, 133.8, 131.9, 131.7, 129.3, 128.8, 127.3, 126.6, 126.0, 125.4, 123.7, 64.5, 43.4, 29.1, 25.8, 25.5. **HRMS**: Calcd. for $C_{18}H_{20}O_2$: 268.1463, Found 268.1465. **IR** (neat, cm^{-1}): 1730.

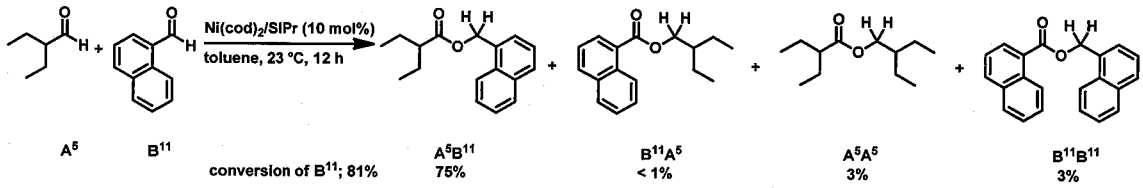
Naphthalen-1-ylmethyl 3,5,5-trimethylhexanoate (A^2B^{11}):



The general procedure was followed with $\mathbf{A^2}$ (142.9 mg, 1.00mmol) and $\mathbf{B^{11}}$ (156.2 mg, 1.00mmol) and reaction mixture was stirred at 50 °C for 2 h. Yields of each product were determined by GC analysis: $\mathbf{A^2B^{11}}$ (61%), $\mathbf{B^{11}A^2}$ (< 1%), $\mathbf{A^2A^2}$ (< 1%) and$\mathbf{B^{11}B^{11}}$ (< 1%). Purification by Kugelrohr distillation gave $\mathbf{A^2B^{11}}$ (196.9 mg, 0.66mmol, 66%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.0 Hz, 1H, Ar–H), 7.88 (m, 2H, Ar–H), 7.58–7.44 (m, 4H, Ar–H), 5.66 (d, J = 12.6 Hz, 1H, OCHHAr), 5.57 (d, J = 12.6 Hz, 1H, OCHHAr), 2.42–2.38 (dd, J = 6.0 and 16.0 Hz, 1H, CHHC(O)), 2.27–2.21 (dd, J = 8.0 and 16.0 Hz, 1H, CHHC(O)), 2.16–2.07 (m, 1H, CH(Me)CH$_2$), 1.30–1.25 (dd, J = 4.0 and 14.0 Hz, 1H, ^{t}BuCHHCH),1.16–1.11 (dd, J = 6.4 and 14.0

Hz, 1H, ^{t}BuC*H*HCH), 1.01 (d, J = 6.4 Hz, 3H,Me), 0.91 (s, 9H, ^{t}Bu). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.1, 133.7, 131.6, 129.2, 128.7, 127.5, 126.5, 125.9, 125.3, 123.6, 64.3, 50.4, 44.0, 31.0, 30.0, 27.1, 22.7. An Ar–*C* is obscured by other Ar–*C*s. **HRMS**: Calcd. for $C_{20}H_{26}O_2$: 298.1933, Found 298.1920. **IR** (neat, cm^{-1}): 1736.

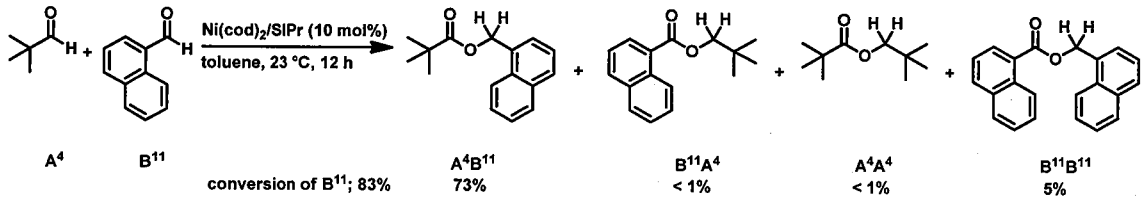
Naphthalen-1-ylmethyl 2-ethylbutanoate (A^5B^{11}):



GC experiment: The general procedure was followed with IPr (14.7 mg, 0.038 mmol), $\mathbf{A^5}$ (40.6 mg, 0.40 mmol) and $\mathbf{B^{11}}$ (62.5 mg, 0.40 mmol) and reaction mixture was stirred at 23 °C for 12 h. Yields of each product were determined by GC analysis: $\mathbf{A^5B^{11}}$ (75%), $\mathbf{B^{11}A^5}$ (< 1%), $\mathbf{A^5A^5}$ (3%) and $\mathbf{B^{11}B^{11}}$ (3%).

Isolation experiment: The general procedure was followed with $Ni(cod)_2$ (27.5 mg, 0.10 mmol), IPr (38.8 mg, 0.10 mmol), $\mathbf{A^5}$ (100.2 mg, 1.00mmol), $\mathbf{B^{11}}$ (157.2 mg, 1.01mmol) and toluene (5 mL) and reaction mixture was stirred at 23 °C for 12 h. Purification by Kugelrohr distillation gave $\mathbf{A^5B^{11}}$ (167.2 mg, 0.65mmol, 65%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.92 (m, 2H, Ar–*H*), 7.57–7.44 (m, 4H, Ar–*H*), 5.59 (s, 2H, O*C*H_2Ar), 2.25 (m, 1H, Et_2*C*H*C*(O)), 1.68 (m, 2H, CH_3C*H*HCH), 1.53 (m, 2H, CH_3CH*H*CH), 0.87 (dd, J = 7.2 Hz, 6H, C*H*$_3$$CH_2$CH). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.4, 133.9, 131.9, 131.8, 129.3, 128.8, 127.5, 126.6, 126.0, 125.4, 123.8, 64.4, 49.1, 25.1, 11.9. **HRMS**: Calcd. for $C_{17}H_{20}O_2$: 256.1463, Found 256.1465. **IR** (neat, cm^{-1}): 1730.

Naphthalen-1-ylmethyl pivalate (A^4B^{11}):

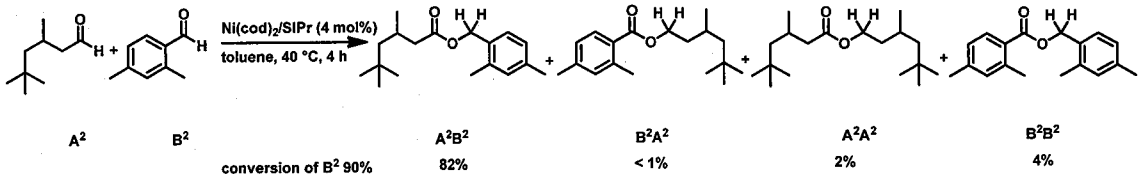


GC experiment: The general procedure was followed with IMes (12.2 mg, 0.040 mmol), $\mathbf{A^4}$ (45 μL, 0.40 mmol) and $\mathbf{B^{11}}$ (63.3 mg, 0.41 mmol) and reaction mixture was stirred at 23 °C for 12 h. Yields of each product were determined by GC analysis: $\mathbf{A^4B^{11}}$

(73%), $\mathbf{B^{11}A^4}$ (< 1%), $\mathbf{A^4A^4}$ (< 1%) and $\mathbf{B^{11}B^{11}}$ (5%).

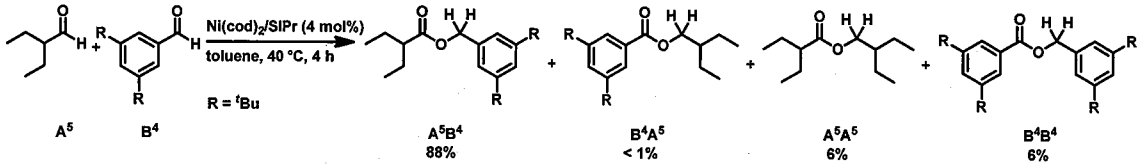
Isolation experiment: The general procedure was followed with $Ni(cod)_2$ (27.5 mg, 0.10 mmol), IPr (30.4 mg, 0.10 mmol), $\mathbf{A^4}$ (110.4 μL, 1.00mmol), $\mathbf{B^{11}}$ (156.7 mg, 1.00mmol) and toluene (5 mL) and reaction mixture was stirred at 23 °C for 12 h. Purification by Kugelrohr distillation gave $\mathbf{A^4B^{11}}$ (157.8 mg, 0.65mmol, 65%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.87 (m, 2H, Ar–*H*), 7.57–7.44 (m, 4H, Ar–*H*), 5.60 (s, 2H, OC*H*$_2$Ar), 1.35 (s, 9H, ^{t}Bu). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 178.6, 133.9, 132.0, 131.8, 129.2, 128.8, 127.1, 126.5, 126.0, 125.4, 123.8, 64.8, 39.1, 27.4. **HRMS**: Calcd. for $C_{16}H_{18}O_2$: 242.1307, Found242.1305. **IR** (neat, cm^{-1}): 1728.

2,4-Dimethylbenzyl 3,5,5-trimethylhexanoate ($\mathbf{A^2B^2}$):



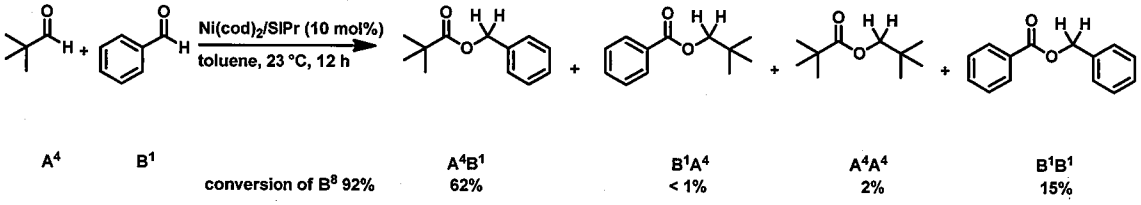
The general procedure was followed $\mathbf{A^2}$ (142.4 mg, 1.00mmol) and $\mathbf{B^2}$ (135.0 mg, 1.01mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^2B^2}$ (82%), $\mathbf{B^2A^2}$ (< 1%), $\mathbf{A^2A^2}$ (2%) and $\mathbf{B^2B^2}$ (4%). Purification by silica gel chromatography followed by Kugelrohr distillation gave $\mathbf{A^2B^2}$ (182.0 mg, 0.66mmol, 66%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (d, J = 7.6 Hz, 1H, Ar–*H*), 7.01 (m, 2H, Ar–*H*), 7.58–7.44 (m, 4H, Ar–*H*), 5.10 (d, J = 16.0 Hz, 1H, OCH*H*Ar), 5.06 (d, J = 16.0 Hz, 1H, OCH*H*Ar), 2.36–2.30 (7H, CH(Me)C*H*HC(O) and two Ar–C*H*$_3$s are overlapping), 2.19–2.13 (dd, J = 8.0 and 14.4 Hz, 1H, CH(Me)CH*H*C(O)), 2.09–2.01 (m, 1H, CH_2CH(Me)CH_2), 1.26–1.21 (dd, J = 4.0 and 14.0 Hz, 1H, ^{t}BuCH*H*CH), 1.13–1.08 (dd, J = 6.4 and 10.8 Hz, 1H, ^{t}BuC*H*HCH), 0.97 (d, J = 6.4 Hz, 3H, Me), 0.89 (s, 9H, ^{t}Bu). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.3, 138.5, 137.1, 131.3, 131.2, 129.7, 126.8, 64.5, 50.6, 44.2, 31.2, 30.1, 27.3, 22.8, 21.2, 19.0. **HRMS**: Calcd. for $C_{18}H_{28}O_2$: 276.2089, Found 276.2081. **IR** (neat, cm^{-1}): 1736.

3,5-Di-tert-butylbenzyl 2-ethylbutanoate (A^5B^4):



The general procedure was followed $\mathbf{A^5}$ (100.2 mg, 1.00mmol) and $\mathbf{B^4}$ (218.3 mg, 1.00 mmol) and reaction mixture was stirred at 40 °C for 4 h. Yields of each product were determined by GC analysis: $\mathbf{A^5B^4}$ (88%), $\mathbf{B^4A^5}$ (< 1%), $\mathbf{A^5A^5}$ (6%) and $\mathbf{B^4B^4}$ (6%). Purification by Kugelrohr distillation gave $\mathbf{A^5B^4}$ (264.0 mg, 0.83mmol, 83%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (s, 1H, Ar–*H*), 7.19 (s, 2H, Ar–*H*), 5.19 (s, 2H, OCH_2Ar), 2.38 (m, 1H, $Et_2CHC(O)$), 1.76 (m, 2H, CH_3CHHCH), 1.64 (m, 2H, CH_3CHHCH), 1.43 (s, 18H, ^{t}Bu), 1.02 (dd, J = 7.2 Hz, 6H, CH_3CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.2, 151.0, 135.5, 122.2, 122.1, 66.5, 49.0, 34.9, 31.5, 25.2, 11.9. **HRMS**: Calcd. for $C_{21}H_{34}O_2$: 318.2559, Found 318.2560. **IR** (neat, cm^{-1}): 1736.

Benzyl pivalate (A^4B^1) (entry S14):



The general procedure was followed with IPr (15.0 mg, 0.039mmol), $\mathbf{A^4}$ (45 μL, 0.40 mmol) and $\mathbf{B^1}$ (42.7 mg, 0.41 mmol) and reaction mixture was stirred at 23 °C for 12 h. Yields of each product were determined by GC analysis: $\mathbf{A^4B^1}$ (62%), $\mathbf{B^1A^4}$ (< 1%), $\mathbf{A^4A^4}$ (2%) and $\mathbf{B^1B^1}$ (15%). Selectivity for $\mathbf{A^4B^1}$ is calculated as 0.78.

Kinetic studies

Determination of reaction rate constant of the crossed Tishchenko reaction of $\mathbf{A^1}$ with $\mathbf{B^9}$: To a solution of $Ni(cod)_2$ (33.0 mg, 0.12 mmol) and SIPr (46.8 mg, 0.12 mmol) in 6.0 mL of toluene was added $\mathbf{A^1}$ (336.6 mg, 3.00 mmol), $\mathbf{B^9}$ (468.4 mg, 3.00mmol) and pentadecane (112.2 mg) as an internal standard at 25 °C. The reaction mixture was heated at 50 °C, and then the reaction was monitored by GC. The results were summarized in Figure 4.1. The rate constants of disappearance of $\mathbf{A^1}$ ($k_{\text{A-cross}}$) and $\mathbf{B^9}$ ($k_{\text{B-cross}}$) and production of $\mathbf{A^1B^9}$ (k_{I}) were evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equations (Eqs. 4.2–4.4).

$$-d[\mathbf{A}^1]/dt = k_{\text{A-cross}} = 13.6(4)\times 10^{-5}\ [\text{mol m}^{-3}\ \text{sec}^{-1}] \quad (4.2)$$

$$-d[\mathbf{B}^9]/dt = k_{\text{B-cross}} = 13.5(3)\times 10^{-5}\ [\text{mol m}^{-3}\ \text{sec}^{-1}] \quad (4.3)$$

$$d[\mathbf{A}^1\mathbf{B}^9]/dt = k_{\text{I}} = 12.9(1)\times 10^{-5}\ [\text{mol m}^{-3}\ \text{sec}^{-1}] \quad (4.4)$$

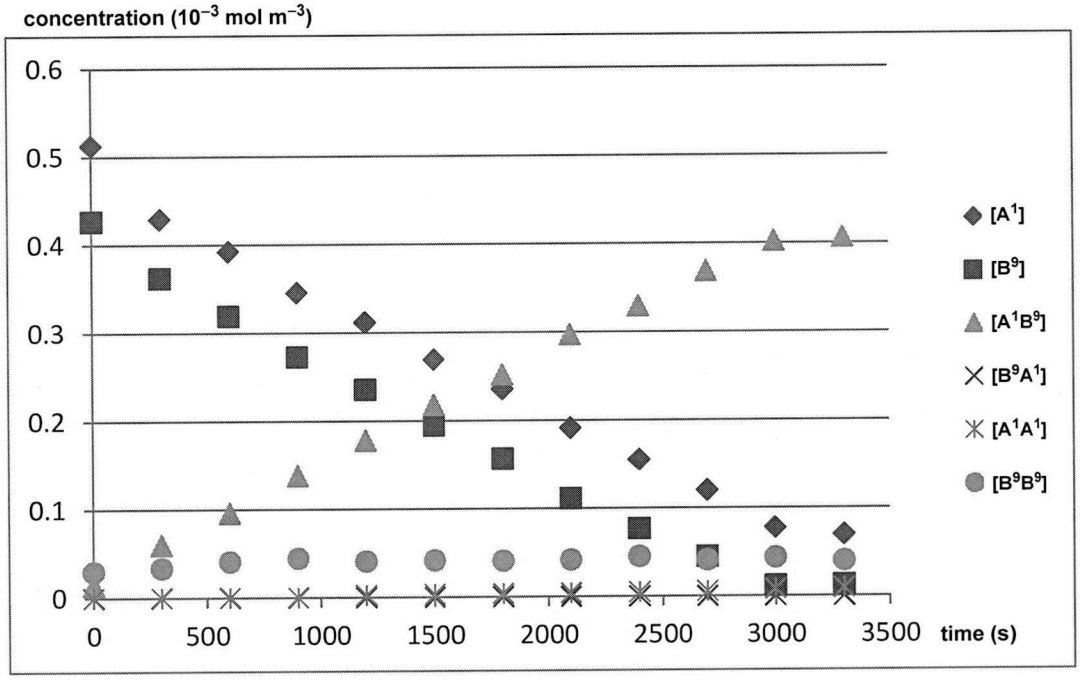


Figure 4.1. Concentration vs. time profiles of the reaction of $\mathbf{A}^1$ with $\mathbf{B}^9$

Determination of reaction rate constant of the crossed Tishchenko reaction of $\mathbf{A}^1$ with $\mathbf{B}^9$-d_1: To a solution of $Ni(cod)_2$ (22.0 mg, 0.080mmol) and SIPr (31.2 mg, 0.080mmol) in 4.0 mL of toluene was added $\mathbf{A}^1$ (225.2 mg, 2.01mmol), $\mathbf{B}^9$-d_1 (314.1 mg, 2.00mmol) and pentadecane (74.2 mg) as an internal standard at 25 °C. The reaction mixture was heated at 50 °C, and then the reaction was monitored by GC. The results were summarized in Figure 4.2. The rate constant of the production of $\mathbf{A}^1(\mathbf{B}^9$-$d_1)$ (k_{II}) was evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equations (Eq. 4.5).

$$d[\mathbf{A}^1(\mathbf{B}^9\text{-}d_1)]/dt = k_{\text{II}} = 10.9(1)\times 10^{-5}\ [\text{mol m}^{-3}\ \text{sec}^{-1}] \quad (4.5)$$

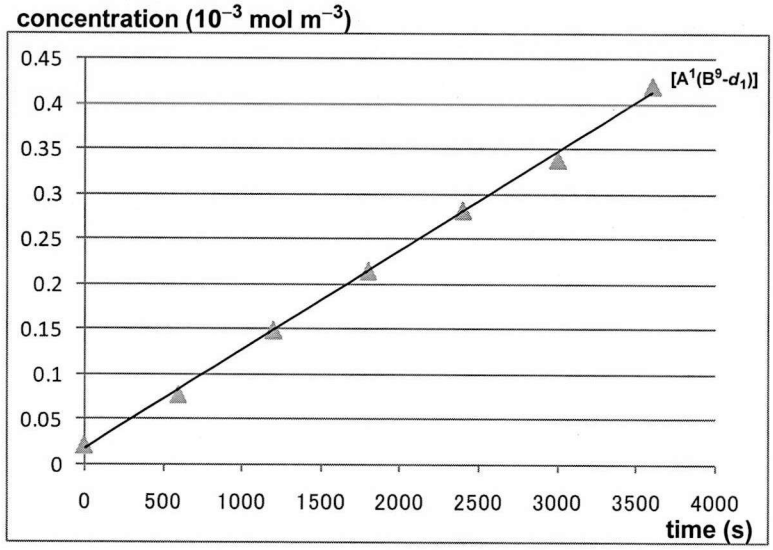


Figure 4.2. Concentration vs. time profiles of the production of $\mathbf{A^1(B^9}$-$d_1)$

Determination of reaction rate constant of the crossed Tishchenko reaction of $\mathbf{A^1}$-d_1 with $\mathbf{B^9}$: To a solution of $Ni(cod)_2$ (33.0 mg, 0.12 mmol) and SIPr (46.8 mg, 0.12 mmol) in 6.0 mL of toluene was added $\mathbf{A^1}$-d_1(339.7 mg, 3.00 mmol), $\mathbf{B^9}$ (468.4 mg, 3.00mmol) and pentadecane (97.2 mg) as an internal standard at 25 °C. The reaction mixture was heated at 50 °C, and then the reaction was monitored by GC. The results were summarized in Figure 4.3. The rate constant of the production of $(\mathbf{A^1}$-$d_1)\mathbf{B^9}$ (k_{III}) was evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equations (Eq. 4.6).

$$d[(\mathbf{A^1}\text{-}d_1)\mathbf{B^9}]/dt = k_{III} = 6.4(3)\times 10^{-5}\ [\text{mol m}^{-3}\ \text{sec}^{-1}] \qquad (4.6)$$

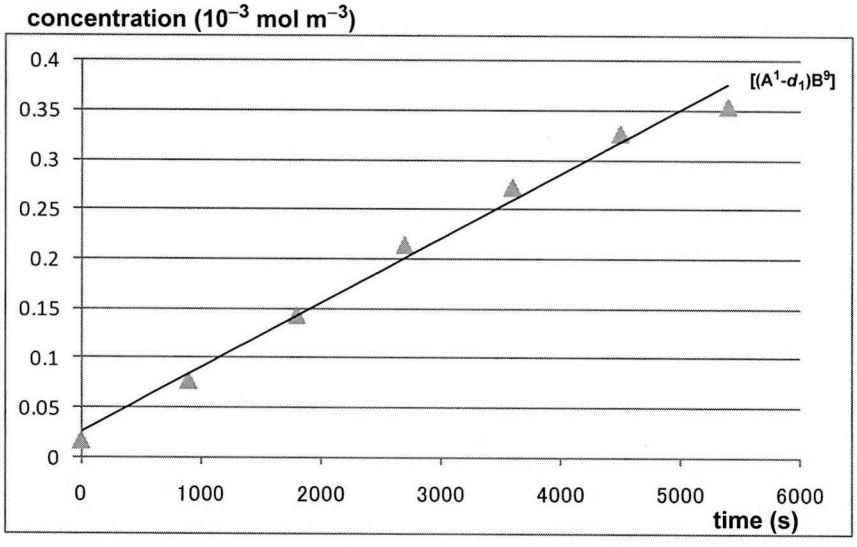


Figure 4.3. Concentration vs. time profiles of the production of $(\mathbf{A^1}$-$d_1)\mathbf{B^9}$

Determination of reaction rate constant of the crossed Tishchenko reaction of $\mathbf{A^1}$-d_1 with $\mathbf{B^9}$-d_1: To a solution of $Ni(cod)_2$ (22.0 mg, 0.080mmol) and SIPr (31.2 mg, 0.080mmol) in 4.0 mL of toluene was added $\mathbf{A^1}$-d_1(226.4 mg, 2.00mmol), $\mathbf{B^9}$-d_1 (314.3 mg, 2.00mmol) and pentadecane (96.0 mg) as an internal standard at 25 °C. The reaction mixture was heated at 50 °C, and then the reaction was monitored by GC. The results were summarized in Figure 4.4. The rate constant of the production of $(\mathbf{A^1}$-$d_1)(\mathbf{B^9}$-$d_1)$ (k_{1V}) was evaluated by least-squares fitting of time-concentration profiles to zeroth-order rate equations (Eq. 4.7).

$$d[(\mathbf{A^1}\text{-}d_1)(\mathbf{B^9}\text{-}d_1)]/dt = k_{1V} = 6.7(1)\times 10^{-5}\ [\text{mol m}^{-3}\ \text{sec}^{-1}] \quad (4.7)$$

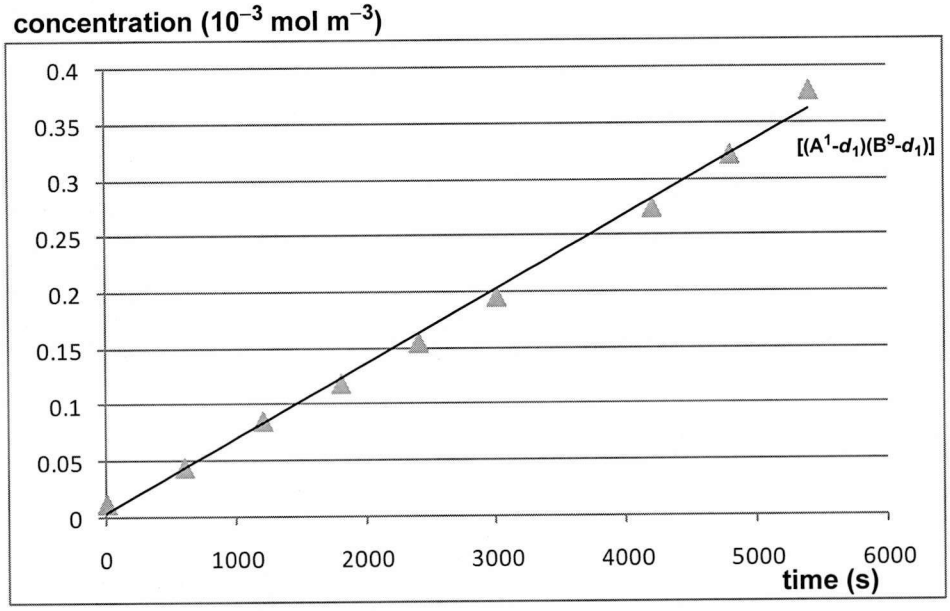


Figure 4.4. Concentration vs. time profiles of the production of $(\mathbf{A^1}$-$d_1)(\mathbf{B^9}$-$d_1)$

Determination of the order of the reaction in catalyst

[$Ni(cod)_2$/SIPr] = 0.010 M: To a solution of $Ni(cod)_2$ (16.5 mg, 0.060 mmol) and SIPr (23.4 mg, 0.060 mmol) in 6.0 mL of toluene were added $\mathbf{A^1}$ (335.7 mg, 2.99 mmol), $\mathbf{B^9}$ (468.7 mg, 3.00 mmol) and pentadecane (100.5 mg) as an internal standard. The reaction mixture was heated at 50 °C, and then the reaction was monitored by GC (Figure 4.5). The rate constant of production of $\mathbf{A^1B^9}$ was evaluated by time-concentration profiles to zeroth-order rate equation (Eq. 4.8).

$$k_V = 4.4(1)\times 10^{-5}\ [\text{mol m}^{-3}\ \text{sec}^{-1}] \quad (4.8)$$

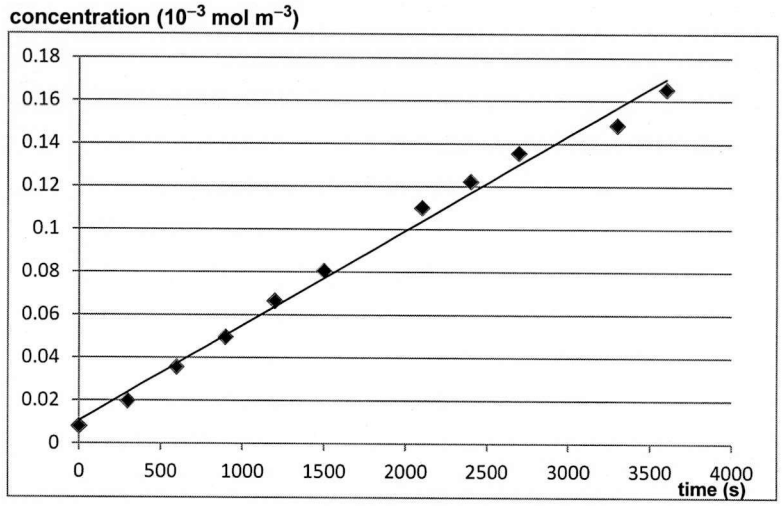


Figure 4.5. Concentration vs. time profiles of the production of $\mathbf{A^1B^9}$ ([cat] = 0.010 M)

[Ni(cod)$_2$/SIPr] = 0.030 M: To a solution of Ni(cod)$_2$ (49.5 mg, 0.18 mmol) and SIPr (70.2 mg, 0.18 mmol) in 6.0 mL of toluene were added $\mathbf{A^1}$ (336.2 mg, 3.00 mmol), $\mathbf{B^9}$ (468.8 mg, 3.00 mmol) and pentadecane (114.0 mg) as an internal standard. The reaction mixture was heated at 50 °C, and then the reaction was monitored by GC (Figure 4.6). The rate constant of production of $\mathbf{A^1B^9}$ was evaluated by time-concentration profiles to zeroth-order rate equation (Eq. 4.9).

$$k_{VI} = 2.3(0) \times 10^{-4} \text{ [mol m}^{-3} \text{ sec}^{-1}\text{]} \tag{4.9}$$

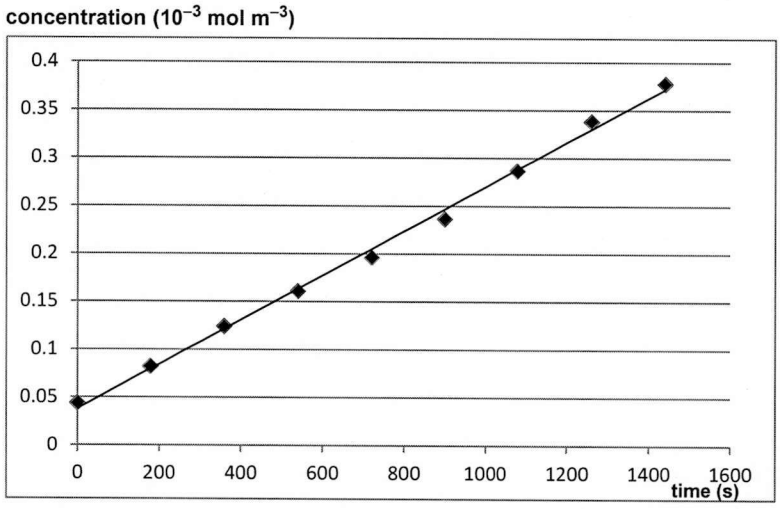


Figure 4.6. Concentration vs. time profiles of the production of $\mathbf{A^1B^9}$ ([cat] = 0.030 M)

Ni(cod)$_2$/SIPr = 0.050 M: To a solution of Ni(cod)$_2$ (82.5 mg, 0.30 mmol) and SIPr

(117.2 mg, 0.30 mmol) in 6.0 mL of toluene were added $\mathbf{A^1}$ (337.4 mg, 3.01 mmol), $\mathbf{B^9}$ (469.2 mg, 3.00 mmol) and pentadecane (149.6 mg) as an internal standard. The reaction mixture was heated at 50 °C, and then the reaction was monitored by GC (Figure 4.7). The rate constant of production of $\mathbf{A^1B^9}$ was evaluated by time-concentration profiles to zeroth-order rate equation (Eq. 4.10)

$$k_{VII} = 3.8(2)\times 10^{-4} \text{ [mol m}^{-3} \text{ sec}^{-1}\text{]} \quad (4.10)$$

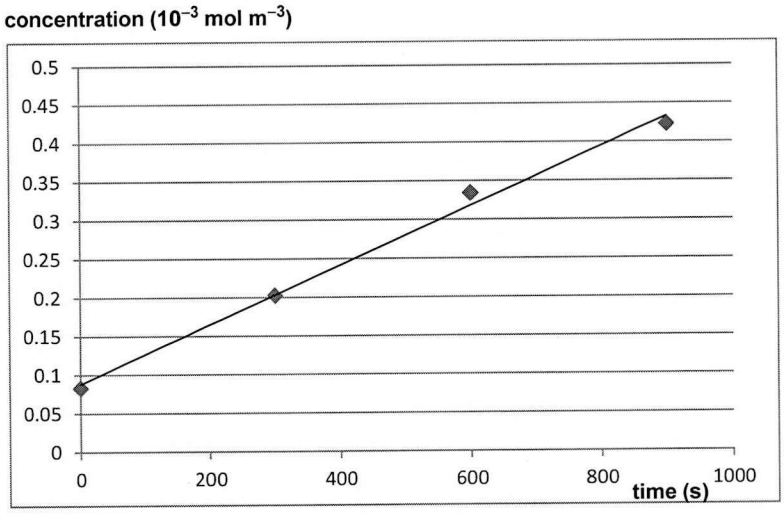


Figure 4.7. Concentration vs. time profiles of the production of $\mathbf{A^1B^9}$ ([cat] = 0.050 M)

Order in catalyst (Ni(0)/SIPr): From these results, a plot of d[**AB**]/dt (k) vs. [Ni(cod)$_2$/SIPr] gave a straight line (R^2 = 0.98), suggesting a first-order order dependence on catalyst (Figure 4.8).

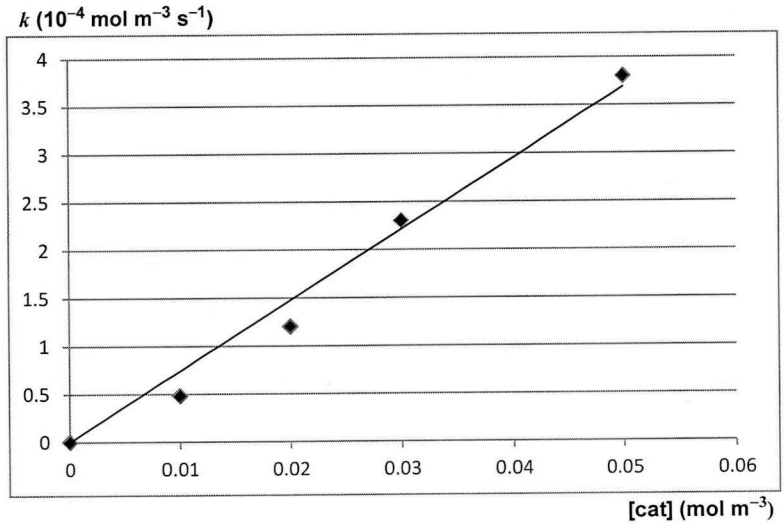


Figure 4.8. k vs. [cat] profiles.

NMR experiments

NMR monitoring of the crossed Tishchenko reaction of A^1 with B^9 (Scheme 4.7): To a solution of $Ni(cod)_2$ (12.2 mg, 0.044 mmol) and SIPr (16.2 mg, 0.041 mmol) in 0.5 mL of toluene-d_8 was added $\mathbf{A^1}$ (21.9 mg, 0.20 mmol) and $\mathbf{B^9}$ (31.1 mg, 0.20 mmol) at 23 °C and the reaction mixture was transferred to an NMR tube. The tube was sealed and inserted in a NMR spectrometer. The ^1H NMR analysis was conducted at 25 °C and then the reaction mixture was cooled to –60 °C as soon as possible to prevent the progress of the reaction. After the measurement of ^1H, ^{13}C NMR and HMQC at –60 °C, the reaction mixture was allowed to warm to 25 °C. The reaction did not proceed at –60 °C. Spectral data for $\mathbf{C1_B{}^9{}_B{}^9}$: ^1H NMR (600 MHz, toluene-d_8, –60 °C): δ 4.73 (brs, ca. 2H, ArC*H*O), 3.71–3.65 (br, 8H, ^{i}Pr–*H*), 1.73 (br, 6H, ^{i}Pr–*H*), 1.39 (br, 6H, ^{i}Pr–*H*), 1.25 (br, 6H, ^{i}Pr–*H*), 1.12 (br, 6H, ^{i}Pr–*H*). **^{13}C NMR** (150 MHz, toluene-d_8, –60 °C): δ 221.0, 147.8, 107.8, 54.3. Other peaks cannot be identified because of overlapping.

NMR monitoring of the crossed Tishchenko reaction of A^1 with B^9-d_1: To a solution of $Ni(cod)_2$ (33.0 mg, 0.12mmol) and SIPr (46.8 mg, 0.12mmol) in 1.0 mL of toluene-d_8 was added $\mathbf{A^1}$ (67.1 mg, 0.60 mmol) and $\mathbf{B^9}$-d_1 (93.1 mg, 0.59mmol) at 23 °C and the reaction mixture was transferred to an NMR tube. The tube was sealed and inserted in a NMR spectrometer. At –60 °C, the measurement of ^1H and ^{13}C NMR were conducted to find a disappearance of the resonance at δ 4.73 in ^1H NMR.

Isolation of A^1B^9-d_1: To a solution of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and SIPr (15.6 mg, 0.040 mmol) in 2.00 mL of toluene were added $\mathbf{A^1}$ (112.2 mg, 1.01 mmol) and $\mathbf{B^9}$-d_1 (117.9 mg, 0.75mmol, 99% *d* incorporated) and reaction mixture was stirred at 50 °C for 1 h. Purification by Kugelrohr distillation gave $\mathbf{A^1B^9}$-d_1 (171.1 mg, 0.64mmol, 85% as a R/S mixture, 99% *d* incorporated) as a colorless oil. The ratio of deuterium incorporated was determined as 99% by ^1H NMR.

NMR monitoring of the reaction of A^1B^9-d_1 (Scheme 4.3): To a solution of $Ni(cod)_2$ (5.5 mg, 0.020 mmol) and SIPr (7.8 mg, 0.020 mmol) in 0.50 mL of C_6D_6 were added $\mathbf{A^1B^9}$-d_1 (53.4 mg, 0.20 mmol, 99% *d* incorporated) and 1,4-dioxane (8.2 mg, 0.10 mmol) as an internal standard, and the reaction mixture was transferred to an NMR tube. The reaction mixture was heated at 50 °C (or 100 °C), and then the reaction was monitored by ^1H NMR for 3 days (or 2 h). In both cases, no H/D scrambling was observed.

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Chapter 5

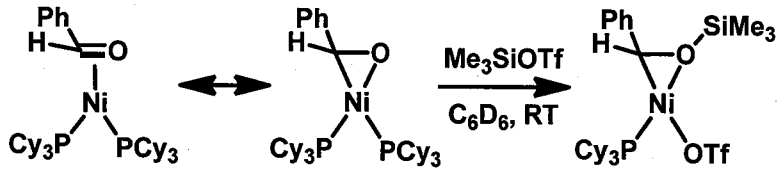
Intramolecular Electrophilic Addition of Arylsilanes to (η^2-Aldehyde)Ni(0) Complex

Abstract: A nickel(0)-catalyzed synthesis of benzoxasiloles was developed for the first time. Aryl- and vinylbenzoxasiloles were prepared in excellent yields at room temperature with 100% atom-efficiency. The reaction mechanism would involve the formation of an oxanickelacyclopropane intermediate and intramolecular electrophilic addition of aryl silane moiety to the oxanickelacyclopropane intermediate.

5.1. Introduction

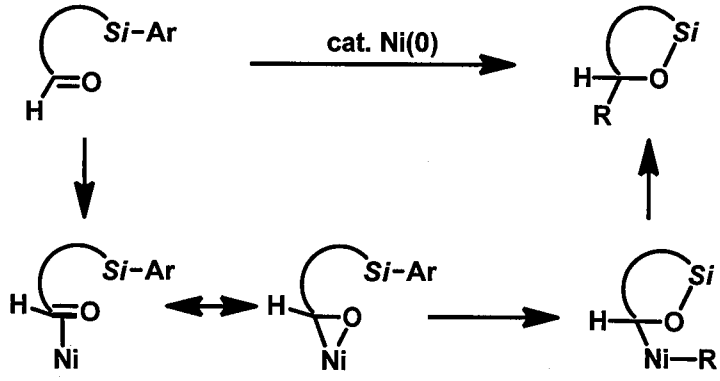
As mentioned in chapter 1, catalytic transformation of aldehydes via η^2-aldehyde complex has been limited to the nickel-catalyzed 1,2-addition reactions of organometallic reagents.[1] These reaction proceeded through the formation of an oxanickelacyclopropane complex, which is a resonance structure of an η^2-aldehyde complex, followed by transmetalation with organometallic reagents. As organometallic reagents, activated borate compounds generated in situ or alkyl aluminum reagents were employed. So far, 1,2-addition reaction of organosilicon compounds via η^2-aldehyde intermediate has not been developed.

Organosilicon compounds are generally unreactive toward aldehyde without the activation by additional bases.[2] However these activators would become wastes at the end of the reaction. Thus, it would be favorable to avoid using activators. Our group reported the electrophilic addition of Me_3SiOTf to (η^2-PhCHO)Ni(PCy_3)$_2$ (Scheme 5.1).[3] Inspired by this result, the author designed an intramolecular electrophilic



Scheme 5.1. Electrophilic addition of Me_3SiOTf to (η^2-PhCHO)Ni(PCy_3)$_2$.

addition of arylsilane to (η^2-aldehyde)Ni(0) complex (Scheme 5.2). In this reaction, a carbonyl oxygen activated by the back bonding from Ni(0) might play a role to activate an arylsilane moiety as a nucleophile. The expected product is cyclic silyl ether



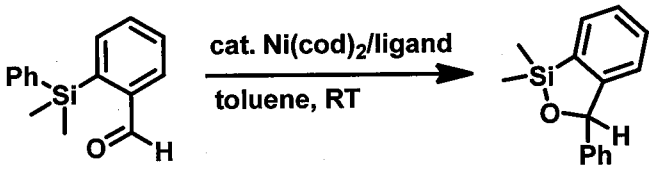
Scheme 5.2. Ni(0)-catalyzed synthesis of cyclic silyl ether via intramolecular electrophilic addition of Si-Ar to η^2-aldehyde nickel(0) complex.

compounds, which are interesting compounds since they have chemically labile O–Si and C–Si bonds.[4] Thus, this reaction would be environmentally favorable route to prepare these compounds.[5] In this chapter, the results of the synthesis of 3-aryl- or vinyl-benzoxasiloles via (η^2-aldehyde)Ni(NHC)$_n$ complexes are reported.

5.2. Synthesis of 3-phenylbenzoxasiloles

The reaction of *o*-dimethylphenylsilylbenzaldehyde (**3a**) was examined with 10 mol% of Ni(cod)$_2$ and PCy$_3$ at 60 °C (entry 1, Table 5.1). After 18 h, 3-phenyl-2,1-benzoxasilole (**4a**) was obtained in 47% GC yield with the formation of Si–O and C_{Ph}–$C_{carbonyl}$ bonds. The reaction took place more efficiently even at RT in the presence of IPrCl or IPr (entries 2 and 3). With 1 mol% Ni(cod)$_2$ and IPr, the reaction was completed within 0.5 h to furnish **4a** in 99% isolated yield (entry 4). The reaction conditions in entry 4 are very similar to that of the nickel-catalyzed Tishchenko reaction (chapter 3); however the formation of ester was not observed at all by GCMS analysis. Thus, the formation of benzoxasilole would take place much faster than the Tishchenko reaction.

Table 5.1. Ni(0)-catalyzed synthesis of 3-phenyl-2,1-benzoxasilole.[a]



3a 4a

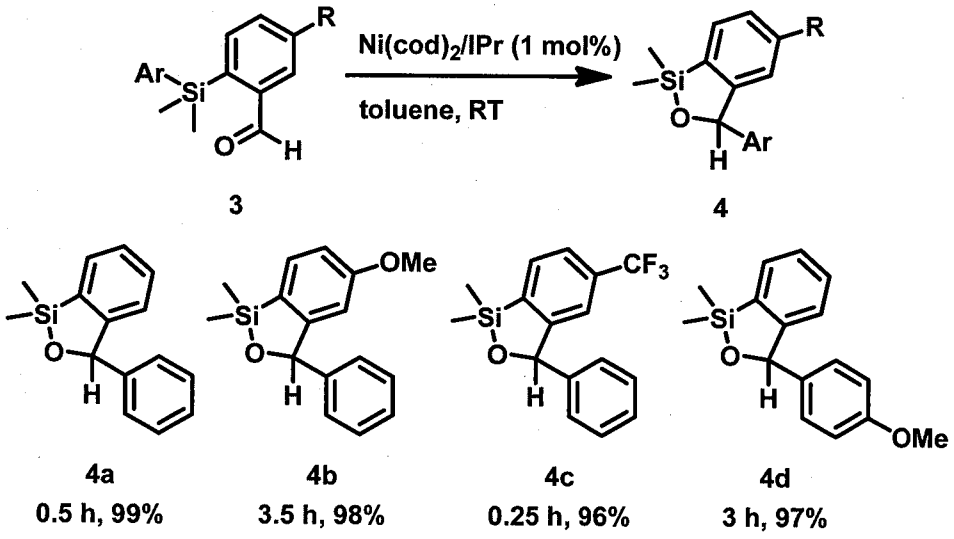
entry	ligand	cat. (mol%)	time (h)	GC yield (%)
1	PCy$_3$	10	18[a]	47
2	IPrCl	10	1	89
3	IPr	10	0.25	89[b]
4	IPr	1	0.5	99[b]

[a] 80 °C. [b] Isolated yield.

The substrate scope of *o*-dimethylarylsilylbenzaldehydes (**3a–3d**) is shown in Table 5.2. Introducing an electron-donating methoxy group into the para position with respect to the SiMe$_2$Ph group retarded the transformation to afford **4b** in 98% yield for 3.5 h.

By contrast, **4c** was formed in 96% yield within 0.25 h when an electron withdrawing trifluoromethyl group was bonded to the benzene ring. The formation of benzoxasilole **4d** also required longer reaction time compared to that of **4a**.

Table 5.2. Ni(0)-catalyzed synthesis of 3-aryl-2,1-benzoxasilole.[a]



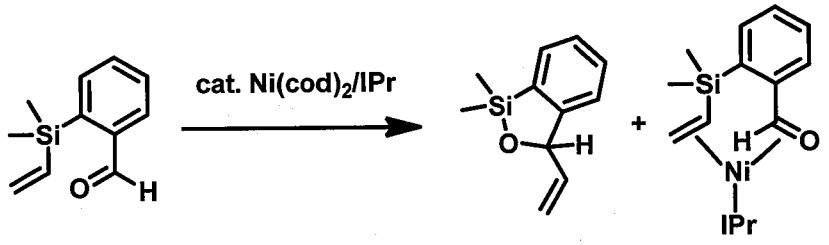
[a] General conditions: **3** (2.00 mmol), $Ni(cod)_2$ (0.020 mmol) and IPr (0.020 mmol) were reacted in toluene (5 mL) at RT. Yields of isolated products are given. [b] THF was used as a solvent. [c] GC yield.

5.3. Synthesis of 3-vinylbenzoxasilole

Next, application of corresponding vinylsilane was examined. In the presence of $Ni(cod)_2$/IPr (10 mol%) in THF-d_8, the reaction of *o*-dimethylvinylsilylbenzaldehyde (**5**) for 0.25 h at RT gave 3-vinyl-2,1-benzoxasilole (**6**) in 74% yield (conv. of **5** was 83%) with the concomitant formation of (η^2:η^2-CH_2=$CHSi(Me)_2C_6H_4CHO$)Ni(IPr) (**C10**) in 10% yield, which was confirmed by ^{1}H NMR analysis (entry 1, Table 5.3). Employing 20 mol% IPr was found to improve the yield of **6** (90% yield, entry 2). Louie reported that $Ni(cod)_2$ and IPr (2 equiv) exist in equilibrium with $Ni(IPr)_2$ and COD (K_{eq} = 1) in THF.[6] Thus, it would be considered that an effective generation of $Ni(IPr)_2$ promoted the reaction. Although a slight decrease in yields was observed in the reaction with 2 mol% $Ni(cod)_2$ and 4 mol% IPr, **6** was isolated in 79% yield (entry 3). **5** was obtained in 52% yield when the reaction was conducted in CD_3CN (entry 5); however C_6D_6 was ineffective even at 80 °C (entry 4). The reaction did not proceed in the absence of $Ni(cod)_2$ (entry 6).[7] As Ni(II) precursors, $Ni(acac)_2$ and $NiCl_2$ were used and found to be

ineffective under the conditions. Based on these results, transformation of **5** into **6** required nickel(0) catalyst.

Table 5.3. Ni(0)-catalyzed synthesis of 3-vinyl-2,1-benzoxasilole.[a]



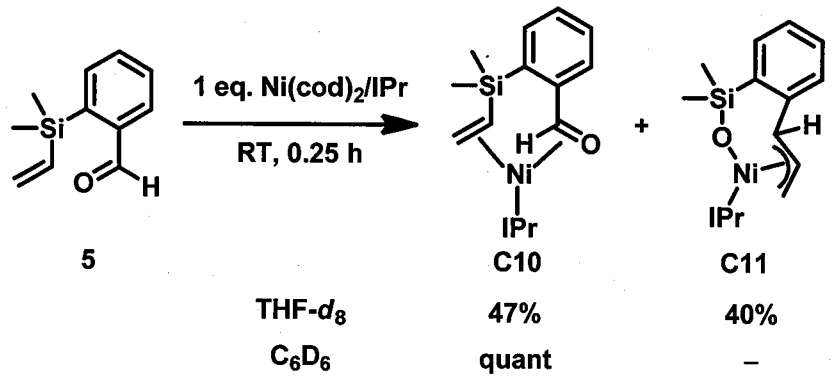
5 **6** **C10**

entry	Ni/IPr (mol%)	solv	temp (°C)	time (h)	yield of 6 (%)
1	10/10	THF-d_8	RT	0.25	74[b]
2	10/20	THF-d_8	RT	0.25	90[b]
3	2/4	THF	RT	1	(79)
4	10/10	C_6D_6	80	2	–[b]
5	10/10	CD_3CN	RT	0.25	52
6	0/10	THF-d_8	60	3	–[e]
7[c]	10/20	THF-d_8	RT	24	–[e]
8[d]	10/20	THF-d_8	RT	24	–[e]

[a] General conditions: **5** (0.40–2.00 mmol), $Ni(cod)_2$ (0.040 mmol) and IPr (0.040–0.080 mmol) were reacted in solvent (1 mL) at indicated temperature. Yields of **6** were determined by ^1H NMR. Isolated yield is given in parenthesis. [b] **C10** was formed in 10% yield. [c] $Ni(acac)_2$ was used as a nickel source. [d] $NiCl_2$ was used as a nickel source. [e] **5** was recovered quantitatively.

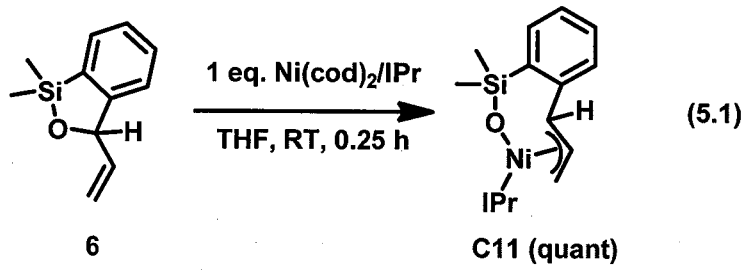
The stoichiometric reaction of **5** with $Ni(cod)_2$/IPr in THF-d_8 resulted in the formation of **C10** in 47% yield with the concomitant formation of an η^3-allylnickel complex (**C11**) in 40% yield (Scheme 5.3). Another equivalent of IPr was added to the resultant mixture; however the result remained unchanged. Furthermore, the reaction of **5** using 10 mol% of **C10** did not proceed at all. From these results, **C10** would be excluded in the catalytic cycle giving **6**. When the reaction was conducted in C_6D_6, a quantitative formation of **C10** was observed as a sole product. This result indicates that the catalytic

reaction did not proceed in C_6D_6 (entry 4, Table 5.3).



Scheme 5.3. Stoichiometric reactions of **5** with $Ni(cod)_2$ and IPr.

An oxidative addition of nickel(0)/IPr to the C_{benzyl}–O bond in **6** gave **C11** quantitatively, which was confirmed by the stoichiometric reaction shown in the following equation (5.1):



(5.1)

Molecular structure of **C11** was unambiguously identified by X-ray crystallography (Figure 5.1). At the end of the catalytic reaction in THF, **C10** was generated in the quantitative yield to nickel(0), and the formation of **C11** was not observed at all (entries 1 and 2, Table 5.3).

5.4. A plausible reaction mechanism

A plausible reaction mechanism is described in Scheme 5.4. The coordination of substrate (**S**) to the catalyst in η^2-fashion gives rise to **A** and an oxanickelacyclopropane intermediate **B** as its resonance structure. Intramolecular electrophilic addition of Si-Ar furnishes a pentavalent silicon intermediate **C**, followed by intra- or inter-molecular aryl migration and reductive elimination to give benzoxasilole (**P**) with the regeneration of **A**.

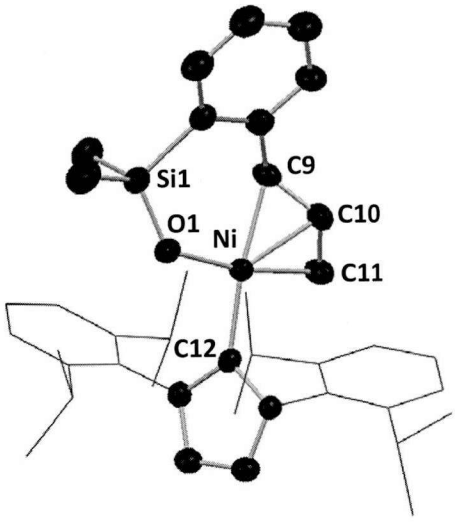
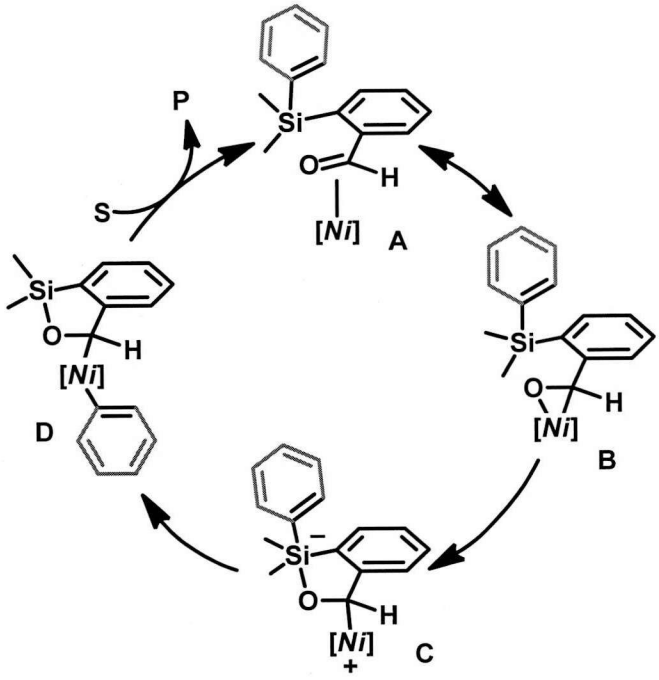


Figure 1. Molecular structure of **C11** with thermal ellipsoids at 50% level. Calculated hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): Ni–O1 1.869(3); Ni–C9 2.065(5); Ni–C10 1.980(5); Ni–C11 2.001(5); Ni–C12 1.903(4); O1–Ni1–C9 95.8(1); C9–Ni1–C11 73.3(2); C11–Ni1–C12 93.2(1); C12–Ni1–O1 97.2(1).



Scheme 5.4. A plausible reaction mechanism. [*Ni*] = Ni(IPr)$_n$ (n = 1–2).

In the case of **5**, the formation of **6** was promoted by using two equivalent of IPr

based on nickel(0) in THF since the formation of **C10** would be suppressed under these conditions. This is rationalized by the following fact: the reaction of *o*-allylbenzaldehyde, $Ni(cod)_2$ and two equivalent of PPh_3 quantitatively furnished (η^2-aldehyde)$Ni(PPh_3)_2$ while (η^2:η^2-enal)$Ni(PPh_3)$ was formed in the presence of $Ni(cod)_2$ and an equimolar amount of PPh_3.[8] On the other hand, in the case of **3**, an excess amount of IPr was not required since the formation of η^2-phenyl:η^2-formyl coordination complex such as **C10** would be negligible under the reaction conditions.

5.5. Conclusion for chapter 5

In chapter 5, the novel synthetic method of benzoxasiloles catalyzed by nickel(0) was demonstrated. The reaction can be conducted with 1–2 mol% catalyst at RT to give 3-vinyl- and 3-aryl-2,1-benzoxasiloles in excellent yields. The reaction would proceed via η^2-aldehyde nickel(0) complex and the following electrophilic addition of organosilicon compounds.

5.6. Experimental section

Materials

Toluene, benzene, THF, and benzene-d_6 were distilled from sodium benzophenone ketyl. Other solvents were used prior to degassed and distilled. All commercially available reagents were distilled over CaH_2 under reduced pressure prior to use. *N*-Heterocyclic carbenes (NHCs) were furnished by the known procedures (please, see Ref. 11 in chapter 1).

Nickel-catalyzed reaction of *o*-dimethylaryllsilylbenzaldehyde 3a–d (Table 5.2)

General procedure: To a solution of $Ni(cod)_2$ (5.5 mg, 0.020 mmol) and IPr (7.8 mmol, 0.020 mmol) in toluene (2 mL) was added *o*-dimethylarylsilylbenzaldehydes (2.00 mmol) at RT. The resultant mixture was stirred for each time. Then, all volatiles were removed under the reduced pressure to give crude products. The crude products were purified by silica gel chromatography.

Reaction of 3a giving 1,1-dimethyl-2-oxa-3-phenyl-1-silaindane (4a): The general procedure was followed with **3a** (477.0 mg, 1.98 mmol) and the reaction mixture was stirring for 0.5 h. After purification, **4a** (478.7 mg, 1.99 mmol, > 99%) was obtained as pale yellow oil. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.65 (m, 1H, Ar–*H*), 7.39–7.29 (m, 7H,

Ar–*H*), 7.06 (m, 1H, Ar–*H*), 6.21 (s, 1H, ArC*H*(Ph)O), 0.57 (s, 3H, Me), 0.49 (s, 3H, Me). **$^{13}C\{^1H\}$ NMR** (100 MHz, C_6D_6): δ 152.6, 143.9, 135.2, 130.8, 129.9, 128.6, 127.9, 127.3, 127.3, 123.9, 84.2, 1.4, 0.6. **HRMS** (EI): *m/z* Calcd for $C_{15}H_{16}OSi$: (M^+) 240.0970, found 240.0965.

Reaction of 3b giving 1,1-dimethyl-5-methoxy-2-oxa-3-phenyl-1-silaindane (4b): The general procedure was followed with **3b** (539.7 mg, 2.00 mmol) and the reaction mixture was stirring for 3 h. After purification, **4b** (526.3 mg, 1.95 mmol, 98%) was obtained as a white solid. **^1H NMR** (400 MHz, C_6D_6): δ 7.52 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.34–7.27 (m, 5H, Ar–*H*), 6.89 (dd, J = 2.0, 8.0 Hz, 1H, Ar–*H*), 6.53 (d, J = 2.0 Hz, 1H, Ar–*H*), 6.11 (s, 1H, ArC*H*(Ph)O), 3.72 (s, 3H, OMe), 0.51 (s, 3H, Me), 0.43 (s, 3H, Me). **$^{13}C\{^1H\}$ NMR** (100 MHz, C_6D_6): δ 161.5, 154.9, 143.8, 131.9, 128.7, 128.0, 127.3, 126.3, 114.4, 108.8, 84.0, 55.3, 1.6, 0.9. **HRMS** (EI): *m/z* Calcd for $C_{16}H_{18}OSi$: (M^+) 270.1076, found 270.1078.

Reaction of 3c giving 1,1-dimethyl-5-trifluoromethyl-2-oxa-3-phenyl-1-silaindane (4c): The general procedure was followed with **3c** (617.6 mg, 2.00 mmol) and the reaction mixture was stirring for 0.25 h. After purification, **4c** (589.5 mg, 1.91 mmol, 96%) was obtained as a pale yellow solid. **^1H NMR** (400 MHz, C_6D_6): δ 7.73 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.56 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.39–7.28 (m, 6H, Ar–*H*), 6.19 (s, 1H, ArC*H*(Ph)O), 0.56 (s, 3H, Me), 0.48 (s, 3H, Me). **$^{13}C\{^1H\}$ NMR** (100 MHz, C_6D_6): δ 153.3, 149.2, 140.0, 132.3 (q, J_{CF} = 32 Hz), 131.4, 128.9, 128.4, 127.3, 124.3 (q, J_{CF} = 270 Hz), 124.1 (q, J_{CF} = 4 Hz), 120.5 (q, J_{CF} = 4 Hz), 84.1, 1.2, 0.5. **HRMS** (EI): *m/z* Calcd for $C_{16}H_{15}F_3OSi$: (M^+) 308.0844, found 308.0842.

Reaction of 3d giving 1,1-dimethyl-2-oxa-3-(4-methoxyphenyl)-1-silaindane (4d): The general procedure was followed with **3d** (541.0 mg, 2.00 mmol) and the reaction mixture was stirring for 3 h. After purification, **4d** (525.0 mg, 1.94 mmol, 97%) was obtained as a white solid. **^1H NMR** (400 MHz, C_6D_6): δ 7.64–7.62 (m, 1H, Ar–*H*), 7.34–7.32 (m, 2H, Ar–*H*), 7.21–7.19 (m, 2H, Ar–*H*), 7.04–7.01 (m, 1H, Ar–*H*), 6.89–6.87 (m, 2H, Ar–*H*), 6.15 (s, 1H, ArC*H*(Ph)O), 3.80 (s, 3H, OMe), 0.52 (s, 3H, Me), 0.46 (s, 3H, Me). **$^{13}C\{^1H\}$ NMR** (100 MHz, C_6D_6): δ 159.4, 152.8, 136.3, 135.3, 130.7, 129.9, 128.6, 127.2, 123.9, 114.0, 83.8, 55.4, 1.4, 0.6. **HRMS** (EI): *m/z* Calcd for $C_{16}H_{18}O_2Si$: (M^+) 270.1076, found 270.1078.

Nickel-catalyzed reaction of *o*-dimethylvinylsilylbenzaldehyde 5 (Table 5.3).

Entry 1: A J-Young NMR tube was charged with **5** (77.9 mg, 0.41 mmol) in the presence of $Ni(cod)_2$ (11.0 mg, 0.040 mmol) and IPr (15.4 mg, 0.040 mmol) in THF-d_8 (0.5 mL). The reaction was monitored by ^1H NMR.

Entry 2: A J-Young NMR tube was charged with **5** (76.1 mg, 0.40 mmol) in the presence of $Ni(cod)_2$ (10.8 mg, 0.039 mmol) and IPr (30.8 mg, 0.079 mmol) in THF-d_8 (0.5 mL). The reaction was monitored by ^1H NMR.

Entry 3: A reaction tube was charged with **5** (192.8 mg, 1.01 mmol) in the presence of $Ni(cod)_2$ (5.6 mg, 0.020 mmol) and IPr (15.5 mg, 0.040 mmol) in THF (2 mL). The reaction mixture was stirred at RT for 1 h. Purification by Kugelrohr distillation gave 1,1-dimethyl-2-oxa-3-vinyl-1-silaindane (**6**) (152.6 mg, 0.80 mmol, 79%) as colorless oil. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.50–7.00 (m, 4H, Ar–*H*), 6.95 (m, 1H, CHC*H*=CH_2), 5.61 (d, J = 6.4 Hz, 1H, ArC*H*(CH_2)O), 5.36 (d, J = 17.2 Hz, 1H, CH=CH_2), 5.15 (d, J = 10.0 Hz, 1H, CH=CH_2), 0.31 (s, 3H, Me), 0.31 (s, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, C_6D_6): δ 152.1, 141.1, 135.4, 131.1, 129.9, 127.4, 123.4, 114.1, 83.0, 1.3, 0.5. **HRMS** (EI): *m/z* Calcd for $C_{11}H_{14}OSi$: (M^+) 190.0814, found 190.0813.

Entry 4: A J-Young NMR tube was charged with **5** (76.2 mg, 0.40 mmol) in the presence of $Ni(cod)_2$ (10.8 mg, 0.039 mmol) and IPr (15.5 mg, 0.040 mmol) in C_6D_6 (0.5 mL). The reaction mixture was heated at 80 °C. The reaction was monitored by ^1H NMR.

Entry 5: A J-Young NMR tube was charged with **5** (76.6 mg, 0.40 mmol) in the presence of $Ni(cod)_2$ (10.4 mg, 0.038 mmol) and IPr (15.4 mg, 0.040 mmol) in CD_3CN (0.5 mL). The reaction was monitored by ^1H NMR.

Entry 6: A J-Young NMR tube was charged with **5** (78.2 mg, 0.41 mmol) in the presence of IPr (15.3 mg, 0.039 mmol) in THF-d_8 (0.5 mL). The reaction mixture was heated at 60 °C. The reaction was monitored by ^1H NMR.

Entry 7: A J-Young NMR tube was charged with **5** (38.1 mg, 0.40 mmol) in the presence of $Ni(acac)_2$ (5.1 mg, 0.020 mmol) and IPr (15.5 mg, 0.040 mmol) in THF-d_8 (0.5 mL). The reaction was monitored by ^1H NMR.

Entry 8: A J-Young NMR tube was charged with **5** (38.1 mg, 0.40 mmol) in the presence of $NiCl_2$ (2.6 mg, 0.020 mmol) and IPr (15.5 mg, 0.040 mmol) in THF-d_8 (1.0 mL). The reaction was monitored by ^{1}H NMR.

Stoichiometric reaction of 5 with Ni(cod)$_2$/IPr in THF-d_8 (Scheme 5.3): To a solution of $Ni(cod)_2$ (22.0 mg, 0.080 mmol) and IPr (31.4 mg, 0.080 mmol) in THF-d_8 (1.0 mL) was added **5** (15.3 mg, 0.080 mmol) at RT. The resulting orange mixture was transferred into a J-Young NMR tube and the reaction was monitored by ^{1}H NMR. The formation of **C10** and **C11** was confirmed by ^{1}H NMR spectra of each isolated compounds (*vide infra*).

Stoichiometric reaction of 5 with Ni(cod)$_2$/IPr in C_6D_6: To a solution of $Ni(cod)_2$ (11.0 mg, 0.04 mmol) and IPr (15.5 mg, 0.040 mmol) in C_6D_6 (1.0 mL) was added **1** (7.6 mg, 0.040 mmol) at RT. The resulting orange mixture was transferred into a J-Young NMR tube and the reaction was monitored by ^{1}H NMR. **C10** was found to be formed quantitatively. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.28–6.92 (m, 11H, Ar–*H,* IPr and C*H*O), 6.63 (s, 2H, IPr), 3.10 (m, 4H, IPr), 2.60 (d, J = 12.8 Hz, 1H, SiCH=CH_2), 2.42 (dd, J = 12.8, 16.2 Hz, 1H, SiC*H*=CH$_2$), 1.82 (d, J = 16.2 Hz, 1H, SiCH=CH_2), 1.27 (d, J = 6.6 Hz, 6H, IPr), 1.22 (d, J = 6.6 Hz, 6H, IPr), 1.09–1.06 (m, 12H, IPr), 0.37 (s, 3H, Me), –0.19 (s, 3H, Me). **^{13}C{^{1}H} NMR** (100 MHz, C_6D_6): δ 197.8, 152.0, 146.4, 146.3, 144.5, 137.3, 133.2, 129.8, 126.8, 124.6, 124.3, 124.0, 101.8, 56.3, 52.1, 29.4, 25.9, 23.1, 0.0, –1.9.

Stoichiometric reaction of 6 with Ni(cod)$_2$/IPr: To a solution of $Ni(cod)_2$ (76.7 mg, 0.28 mmol) and IPr (108.0 mg, 0.28 mmol) in THF (5.0 mL) was added **6** (52.9 mg, 0.28 mmol) at RT. The resulting mixture was stirring at RT for 0.25 h and **C11** was found to be formed quantitatively confirmed by ^{1}H NMR (in C_6D_6). Then, all volatiles were removed under the reduced pressure and the residue was washed with hexane to give **C11** as a reddish brown solid (186.7 mg, 0.29 mmol, > 99%). Single crystals of **C11** suitable for X-ray diffraction analysis were obtained by recrystallization from toluene/hexane at –30 °C (121.3 mg, 0.190 mmol, 68%). **^{1}H NMR** (400 MHz, C_6D_6): δ 7.56 (d, J = 6.8 Hz, 1H, Ar–*H*), 7.24–7.10 (m, 9H, Ar–*H* and IPr), 6.53 (s, 2H, IPr), 4.75 (m, 1H, NiC*H*CH$_2$), 4.02 (d, J = 12.8 Hz, 1H, NiC*H*Ar), 3.30 (m, 2H, IPr), 2.98 (m, 2H, IPr), 1.85 (d, J = 6.4 Hz, 1H, NiCHCH_2), 1.42 (d, J = 6.6 Hz, 6H, IPr), 1.28 (d, J = 6.6 Hz, 6H, IPr), 1.19 (d, J = 10.8 Hz, 1H, NiCHCH_2), 1.06 (d, J = 6.6 Hz, 6H, IPr), 0.99 (d, J = 6.6 Hz, 6H, IPr), 0.43 (s, 3H, Me), 0.14 (s, 3H, Me). **^{13}C{^{1}H}**

NMR (100 MHz, C_6D_6): δ 189.1, 146.4, 146.2, 145.8, 136.8, 132.8, 130.0, 129.0, 126.7, 125.9, 124.3, 124.2, 124.1, 106.9, 78.3, 39.6, 28.9, 28.7, 26.3, 26.0, 23.7, 23.1, 4.4, 3.1. **Anal. Calcd for $C_{21}H_{30}N_2NiO$**: C, 65.48; H, 7.85; N, 7.27. Found: C, 65.48; H, 8.28; N, 7.04.

5.7. References and Notes

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Conclusion

Described in this thesis are studies on catalytic transformation of aldehydes via η^2-coordination to nickel(0). Since catalytic transformation of aldehydes via η^2-coordination to late transition-metals has been rather limited, the results found in this thesis would have a significant importance. The key to achieve these works was a choice of a catalyst. The combination of electron-rich nickel(0) and strong electron-donating NHC ligands were found to be adequate because aldehydes could be highly activated by strong back bonding from the Ni(0)/NHC catalyst.

By employing the Ni(0)/NHC catalyst, the intramolecular hydroacylation of alkenes (chapter 2), and homo/crossed dimerization of aldehydes (chapters 3 and 4) were developed for the first time. These reactions were found to proceed via (η^2-aldehyde)(η^2-alkene)nickel(0) or bis(η^2-aldehyde)nickel(0) complexes, respectively, which were unambiguously confirmed by some stoichiometric and kinetic experiments. Furthermore, the mechanistic studies would support the reaction paths involving β-hydrogen elimination from oxa- or dioxa-nickelacycle intermediates generated by oxidative cyclization. In chapter 5, nickel(0)/NHC catalyzed synthesis of benzoxasiloles was demonstrated, which would took place via intramolecular electrophilic addition of an aryl- or a vinyl-silane to oxanickelacyclopropane intermediate. All of the reactions developed in this thesis represents 100% atom-efficiency, generates no wastes, and can be conducted in neutral conditions. Thus, these reactions would be regarded as environmentally favorable methods to transform aldehydes into ketones, esters, and silyl ethers.

The author envisions that the presented reactions would open up new strategies for catalytic transformation of aldehydes, and will contribute to further progress on this chemistry.

List of Publications

Nickel-catalyzed Tishchenko reaction *via* hetero-nickelacycles by oxidative cyclization of aldehydes with nickel(0) complex
Sensuke Ogoshi, Yoichi Hoshimoto, Masato Ohashi
Chem. Commun. **2010**, *46*, 3354–3356.

Nickel-Catalyzed Selective Conversion of Two Different Aldehydes to Cross-Coupled Esters
Yoichi Hoshimoto, Masato Ohashi, Sensuke Ogoshi
J. Am. Chem. Soc. **2011**, *133*, 4668–4671.

Synthesis of Five- and Six-Membered Benzocyclic Ketones through Intramolecular Alkene Hydroacylation Catalyzed by Nickel(0)/*N*-Heterocyclic Carbenes
Yoichi Hoshimoto, Yukari Hayashi, Haruka Suzuki, Masato Ohashi, Sensuke Ogoshi
Angew. Chem. Int. Ed. **2012**, *51*, 10812–10815.

Nickel-Catalyzed Synthesis of 3-Vinyl- and 3-Arylbenzoxasiloles from Benzaldehyde Derivatives with *o*-Vinyl- or *o*-Aryl-Me_2Si Group
Yoichi Hoshimoto, Hayato Yabuki, Haruka Suzuki, Masato Ohashi, Sensuke Ogoshi
Manuscript in preparation