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Further studies on Ni(0)-catalyzed cyclization of a branched 1,3-diene and tethered aldehyde via oxa-nickelacycle intermediate

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Abstract

The reactivity of oxa-nickelacycles **7**, generated by the reaction of a branched 1,3-diene and tethered carbonyl group with a Ni(0) complex, was investigated in detail. It was found that oxa-nickelacycles **7** are relatively stable and that β-hydride elimination from **7** occurred at a high temperature, producing the cyclized dienes **51** and/or **52** in good yields. This Ni(0)-catalyzed cyclization via β-hydride elimination from oxa-nickelacycles tolerated various substituents on the diene moiety and could be applied to a five- to seven-membered ring construction. Next, transmetalation of oxa-nickelacycle **7** with various organometallic reagents was investigated. It was found that the tandem reaction, i.e. cyclization of **6** followed by transmetalation of the resulting oxa-nickelacycle **7**, proceeded smoothly, giving **53** and/or **54** in good yields. In addition, the catalytic cycle in this transmetalation reaction was also established.

Keywords: Nickel; Nickelacycle; Metallacycle; Transmetalation; Diene; Aldehyde

1. Introduction

Nickel-promoted intramolecular oligomerization of 1,3-dienes and tethered multiple bonds is a useful method for stereoselective construction of cyclic compounds [1–3]. Recently, we succeeded in developing a nickel-promoted cyclization of ω-formyl-1,3-dienes [4]. The reaction of ω-formyl-1,3-diene **1** using a stoichiometric amount of a low-valent nickel complex **2**, generated by reduction of $Ni(acac)_2$ with DIBAL–H in the presence of PPh_3, afforded the cyclized products **3-I** and **3-T** in a stereoselective manner with respect to the substituents on the cycloalkane ring (Eq. (1), Scheme 1) [4a,b]. The reaction course of this cyclization can be accounted for by two possible mechanisms. The low-valent nickel complex **2**, prepared by reduction of $Ni(acac)_2$ with DIBAL–H, would contain a nickel hydride complex (i.e. H-Ni(II)–X), a zero-valent nickel complex (Ni(0)), and aluminum reagents such as $^{i}Bu_2Al(acac)$. It was thought that both nickel complexes operated in this stoichiometric reaction. These mechanistic considerations led to the discovery of two novel nickel(0)-catalyzed cyclizations of ω-formyl-1,3-dienes, which are depicted as the reactions type I and type II in Scheme 1 [4f]. In the former reaction (type I), a H–Ni(II)–SiR_3 complex is initially formed by the oxidative addition of trialkylsilane to a zero-valent nickel complex, and cyclization proceeds via π-allylnickel intermediate **4** to give the cyclized product **3′-I** having an internal olefin in the side chain. In the latter reaction (type II), a nickelacycle intermediate is initially generated by the reaction of a Ni(0) complex with substrate **1**. Then the cyclized product **3-T** having a terminal olefin in the side chain is produced via transmetalation of an oxa-nickelacycle intermediate with diisobutylaluminum acetylacetonate ($^{i}Bu_2Al(acac)$) such as intermediate **5**.

During the course of our studies on these cyclizations, we found that a branched 1,3-diene such as **6** showed considerably different reactivity from the above-mentioned ω-formyl-1,3-dienes **1**. Further studies revealed that the difference between reactivities of the branched 1,3-dienes and the ω-formyl-1,3-dienes is caused by the stability of oxa-nickelacycle **7** generated from **6** and a

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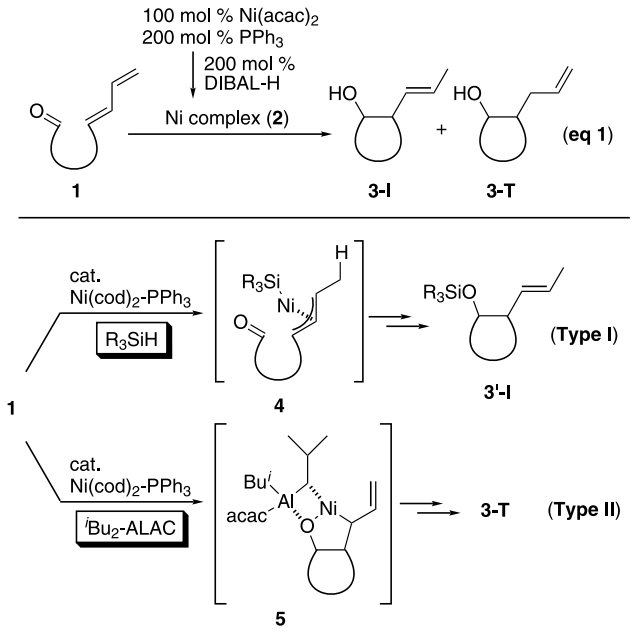


Scheme 1.

zero-valent nickel complex (Scheme 2). The unique structure and stability of oxa-nickelacycle **7** prompted us to investigate its reactivity in detail. Herein, we report Ni(0)-catalyzed cyclizations via oxa-nickelacycle **7** [5].

2. Results and discussion

2.1. Nickel(0)-catalyzed cyclization of branched 1,3-dienes via β-hydride elimination from an oxa-nickelacycle intermediate [5a]

Initially, we investigated the reaction of **6a**, which was synthesized as shown in Scheme 3. Alkylation of malonate **8** with iodide **9** using NaH gave **10** in 71% yield. Vinyl iodide **11** was synthesized in good yield by reduction of **10** with DIBAL–H followed by acetalization of resulting diol. A Pd-catalyzed Migita–Kosugi–Stille coupling [6] of **11** with tributyl(vinyl)tin followed by deprotecion gave alcohol **12a**, which was oxidized with PCC to give **6a** in 72% yield (three steps from **11**).

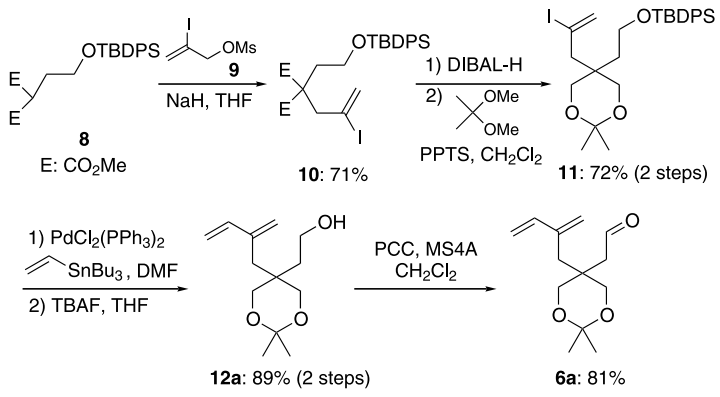
A THF solution of **6a** was added to a THF solution of a nickel complex prepared from $Ni(acac)_2$ (one equivalents), PPh_3 (two equivalent) and DIBAL–H (two equivalents) at 0 °C, and the solution was stirred at 0 °C for 1.5 h. After hydrolysis of the reaction mixture, we obtained the cyclized products **13a**, **14a**, and ***Z*-15a** in 13, 15 and 11% yields, respectively Scheme 4 [7,8]. As mentioned above, the nickel complex prepared from $Ni(acac)_2$ and DIBAL–H in the presence of PPh_3 would contain both a Ni(0) complex and a H–Ni(II)–X complex [4f]. If the H–Ni(II)–X complex reacted with a branched 1,3-diene **6a**, cyclization would proceed via π-allylnickel intermediates **16a** and/or **17a** to produce **18a** and/or **19a** (Scheme 5). On the other hand, if the Ni(0) complex reacted with **6a**, an oxa-nickelacycle **7a**, which might be in equilibrium with **20a**, would be formed. It was thought that the cyclized products **13a**, **14a**, and **15a** in the reaction shown in Scheme 4 were produced from the intermediate **7a** or **20a** by the hydrolytic work-up.

Scheme 2.

The cyclization of **6a** under type I conditions, in which a H–Ni(II)–SiR_3 complex generated from a Ni(0) complex and R_3SiH should operate as an active catalyst (see Scheme 1), was carried out. According to the usual procedures for type I cyclization [4f], **6a** was treated with $Ni(cod)_2$ (20 mol%) and PPh_3 (40 mol%) in the presence of Et_3SiH (5.0 equivalents) in THF at room temperature. The expected cyclized products **18′a** and **19′a** were not formed, but a small amount of the products **14a** and **15a** were again obtained after hydrolysis of the reaction mixture (Scheme 6). The result indicates that the oxa-nickelacycle **7a** would be formed from **6a** and a Ni(0) complex, nevertheless a H–Ni(II)–X exists in the reaction medium. Thus, we decided to investigate in detail the reactivity of **7a** generated from **6a** and a stoichiometric amount of a zero-valent nickel complex, $Ni(cod)_2$, in the presence of PPh_3.

When **6a** was treated with $Ni(cod)_2$ (one equivalent) and PPh_3 (two equivalents) in THF at 0 °C, the disappearance of **6a** was observed on TLC within 5 min. Then, hydrolysis of the reaction mixture with H_2O at 0 °C for 40 min gave the products **14a** and **15a** in 15 and 20% yields along with **21a** and **22a** in 11 and 30% yields, respectively (Scheme 7). Interestingly, when the reaction mixture, prepared from **6a**, $Ni(cod)_2$, and PPh_3 under the same conditions, was hydrolyzed with 10% HCl aqueous solution instead of H_2O, allylchloride **23a** was exclusively produced in 67% yield as a single isomer (Scheme 8) [9]. Treatment of **23a** with acetic anhydride in pyridine gave **24a** in 85% yield, the stereochemistry of which was unequivocally determined by an NOE experiment. The results shown in Schemes 7 and 8 also strongly support the formation of oxa-nickelacycle **7a** and/or **20a** from **6a** and a Ni(0) complex. However, attempts at isolation or characterization of **7a** or **20a** were unfruitful [10].

In order to examine the stability of the oxa-nickelacycles, a THF solution of **7a** was allowed to stand with stirring at 0 °C for 5 h. Interestingly, products **25a** and **26a**, which were produced by β-hydride elimination from the oxa-nickelacycle **7a**, were obtained as the main products in a total yield of 48% (ratio of 1:1.4) along

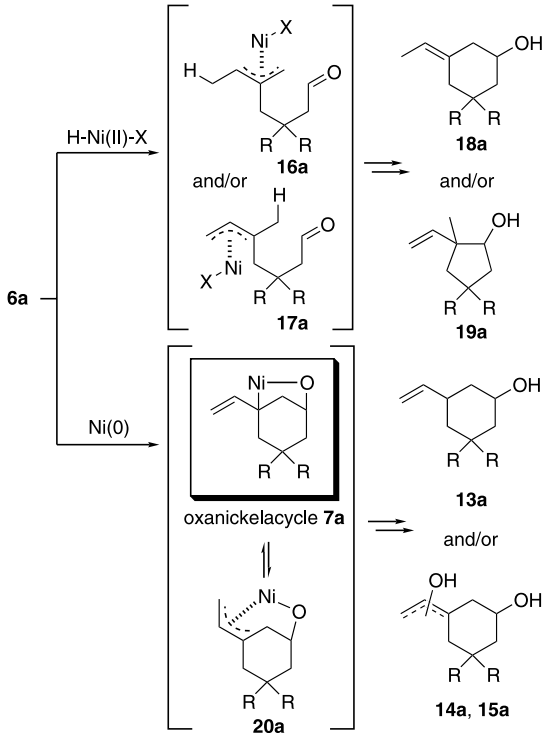


Scheme 3.

with **14a** and **15a** in a total yield of 23% after hydrolysis of the mixture (Table 1, run 1). Thus, **7a** was subjected to various conditions (Table 1). When **7a** was stirred at room temperature for 5 h, the products **25a** and **26a** were obtained in a total yield of 64% (run 2). Prolongation of the reaction time at the same temperature increased the formation of **25a** and **26a** up to 74%, whereas the yields of **14a** and **15a** decreased (run 3). A higher temperature shortened the reaction time, and **25a** and **26a** were produced within an hour in a total yield of 65% along with **14a** and **15a** in 11% yield (run 4).

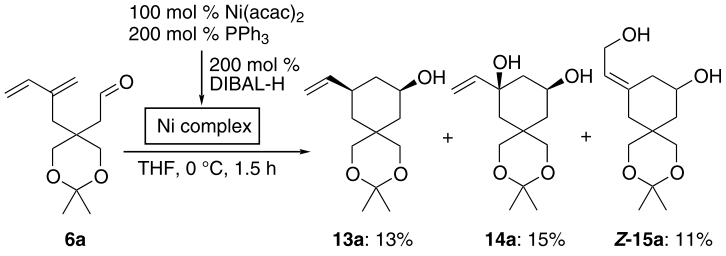
The probable mechanism of this novel cyclization is shown in Scheme 9. Oxidative cyclization of 1,3-diene and aldehyde of **6a** to a Ni(0) complex produces oxanickelacycle **7a**, which would be in a state of equilibrium with **20a** and **7'a**. Then β-hydride elimination from **7a** would occur to give oxo-nickel hydride complex **27a** or **28a**, depending on which of the hydrogen atoms, Ha or Hb, in **7a** is abstracted during this process. In the reaction using a stoichiometric amount of a Ni(0) complex, **25a** or **26a** was produced from **27a** or **28a**, while **14a** and **15a** was produced by hydrolysis of **7a**, **7′a**, or **20a**.

If reductive elimination from oxo-nickel hydride complex **27a** or **28a** proceed, the cyclized product **25a** or **26a** should be obtained in a catalytic reaction (see Scheme 9). Thus, the reaction of **6a** was carried out using a catalytic amount of $Ni(cod)_2$ in the presence of PPh_3 (Table 2). When **6a** was treated with 30 mol% of $Ni(cod)_2$ in the presence of PPh_3 (60 mol%) at 50 °C, we were pleased to find that the desired products **25a** and

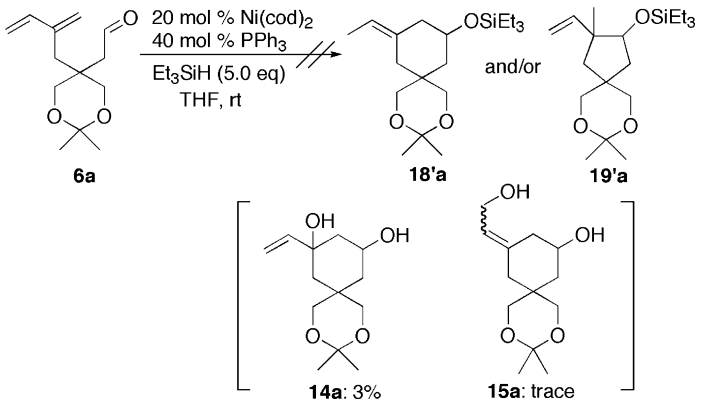


Scheme 5.

26a were obtained in 91% yield (ratio of 1:3.8) (run 1). Although the reason is not clear, reducing the amount of the catalyst did not affect the yields of **25a** and **26a** but affected the ratio of the products (runs 2 and 3), and the use of 10 mol% of the catalyst gave **25a** and **26a** in 83%



Scheme 4.

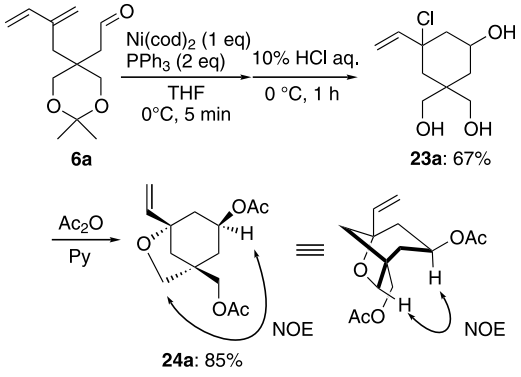


Scheme 6.

yield (ratio of 1:5.6). These results indicate that a Ni(0) complex can be regenerated via reductive elimination of **25a** or **26a** from **27a** or **28a** and that this cyclization can proceed catalytically with respect to a nickel complex.

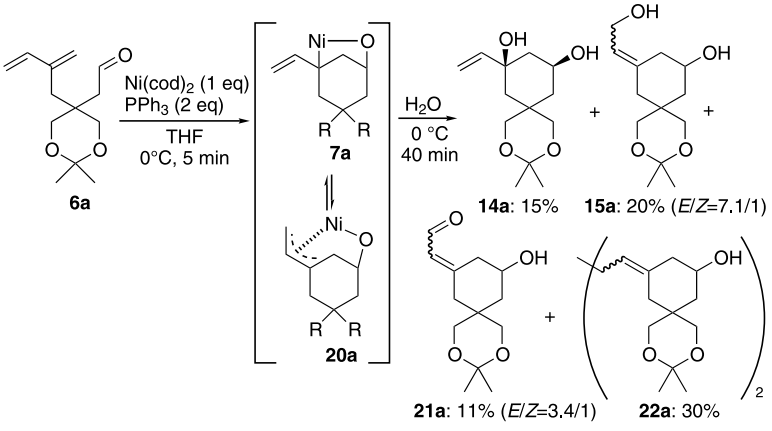
Next, catalytic reactions using various ligands were examined (Table 3). In the reaction of **6a** with 30 mol% of $Ni(cod)_2$ in the absence of a ligand, no cyclized product was obtained, and **6a** was recovered in 66% yield (run 2). Reactions using $MePPh_2$ and Me_2PPh (runs 3 and 4) also produced the products **25a** and **26a** in good yields (84 and 91% yields, respectively). However, it is noteworthy that the ratio of the products seemed to be affected by the electronic nature of ligands, and the formation of **25a** was accelerated with increase in the π-basicity of the ligands. A bidentate ligand, dppb (diphenylphosphinobutane), could be used as a ligand and afforded **25a** and **26a** in good yields (91%, ratio of 4.0:1), while the reaction using dppe (diphenylphosphinobutane) was relatively slow and gave **25a** and **26a** in 46% yields (runs 5 and 6).

In order to confirm the scope and limitation of this novel cyclization via β-elimination from oxa-nickelacycles, we decided to investigate the reactions of various substrates. The substrates **12b**, **12c** and **12d**, each having a substituent on the 1,3-diene moiety, were synthesized



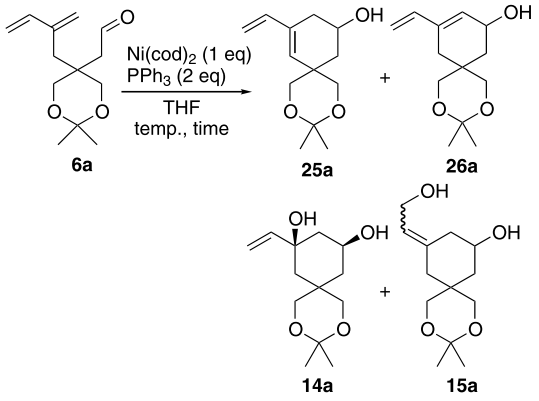
Scheme 8.

as shown in Scheme 10. Migita–Kosugi–Stille coupling reactions of vinyl iodide **11** with vinyltin reagents **29** and **30** followed by deprotection of the TBDPS group afforded alcohols **12b** and **12c** in 56% and 78% yields, respectively. On the other hand, **12d** was synthesized by a Pd-catalyzed cross-coupling reaction of **11** with a vinylaluminum reagent in the presence of $ZnCl_2$[11] followed by deprotection. Oxidation of alcohols **12b**, **12c** and **12d** gave **6b**, **6c** and **6d** in good to moderate yields.



Scheme 7.

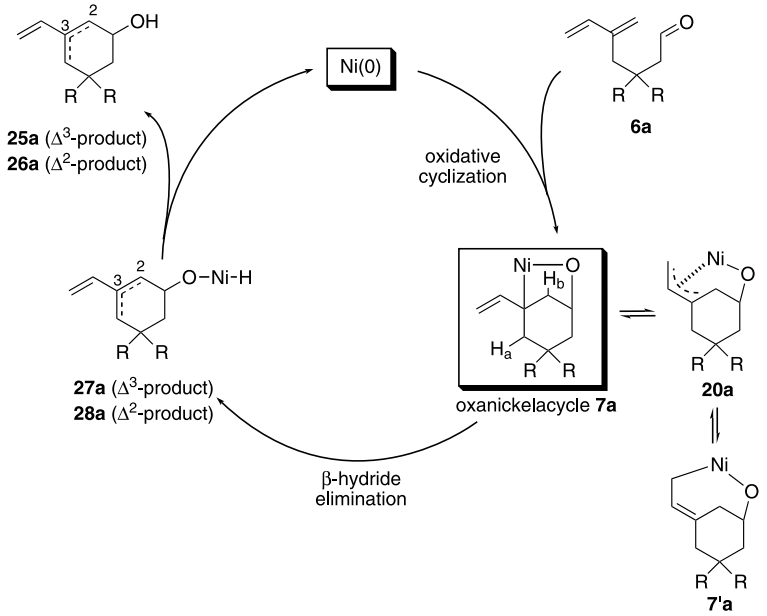
Table 1
Reaction of **6a** with a stoichiometric amount of $Ni(cod)_2$–PPh_3



Run	Temperature (°C)	Time (h)	Yield (%)	Ratio [a]	Yield (%)	Total yield (%)
			25a+**26a**	**25a**/**26a**	**14a**+**15a**	
1	0	5	48	1/1.4	23	71
2	rt	5	64	1/3.2	12	76
3	rt	18	74	1/2.7	9	83
4	50	1	65	1/1.5	11	76

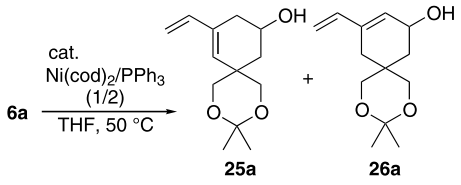
[a] The ratio was determined by ^{1}H-NMR.

The cyclization of **6b**, having a TMS group on the 1,3-diene moiety, under similar conditions was slower than that of **6a** and gave **25b**, **26b** and **29b** in 20, 6 and 39% yields, respectively (Table 4, run 1). Interestingly, ***E*-30b** was also obtained in 19% yield in this cyclization, and the total yield of the cyclized products reached 84%. The cyclization of **6c** or **6d** under similar conditions also gave the desired products **25c**, **25d**, **26c** and **26d** in good to moderate yields, and a small amount of oxidized product **29c** or **29d** was also obtained in each case (runs 2 and 3). It was thought that the oxidized products **29b**–**d** would be formed by β-hydride elimination from nickel hydride complexes **28b**–**d** along with generation of a $Ni(II)H_2$ complex, which might be able to reduce the 1,3-diene moiety of the product (Scheme 11). Compared with the cyclizations of **6c** and **6d**, a considerable amount of oxidized product **29b** was formed in the case of **6b** (Table 4, run 1), which would



Scheme 9.

Table 2
Reaction of **6a** using a catalytic amount of Ni(0) complex



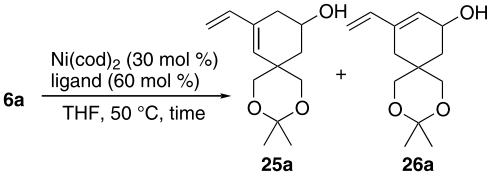
Run	Ni complex (mol%)	Time (h)	Yield (%)	Ratio [a]
			25a+26a	**25a/26a**
1	30	2.5	91	1/3.8
2	20	5	82	1/4.9
3	10	12	83	1/5.6

[a] The ratio was determined by ^{1}H-NMR.

result in the formation of ***E*-30b** from **25b** and the $Ni(II)H_2$ complex. However, the substituent effect of the TMS group **6b** is still not clear.

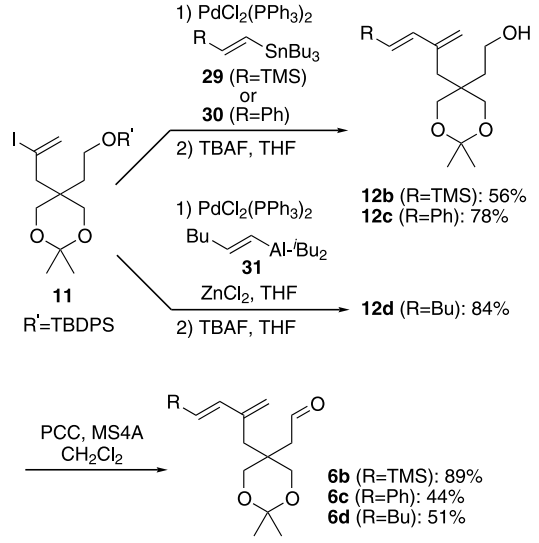
Subsequently, other substrates **31**, **33** and **36** were synthesized as shown in Scheme 12. Methyl ketone **31** was easily prepared from **6a** through the addition of MeMgBr to the aldehyde moiety of **6a** followed by oxidation with PCC (67%, 2 steps). On the other hand, mesylation of **12a** followed by reaction with KCN gave nitrile **32** in 88% yield (2 steps). Reduction of **32** with DIBAL–H followed by hydrolysis with 5% HCl gave **33** in 79% yield. For the synthesis of substrate **36**, a Migita–Kosugi–Stille coupling of bromide **34** with tributyl(vinyl)tin followed by reduction gave diol **35**.

Table 3
Reaction of **6a** using various $Ni(cod)_2$–Ln complex



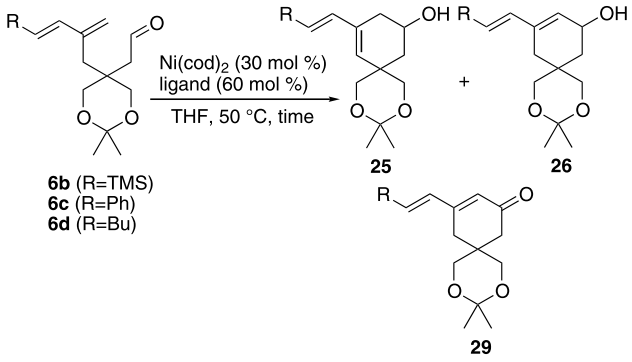
Run	Ligand	Time (h)	Yield (%)	Ratio [a]
			25a+26a	**25a/26a**
1	PPh_3	2.5	91	1/3.8
2	–	12	0 [b]	–
3	$MePPh_2$	2.5	84	1/2.0
4	Me_2PPh	2.5	91	2.1/1
5	dppb [c]	2.5	91	4.0/1
6	dppe [c]	12	46 [d]	1/1.4

[a] The ratio was determined by ^{1}H-NMR.
[b] **6a** was recovered in 66% yield.
[c] 30 mol% of ligand was used.
[d] **6a** was recovered in 27% yield.



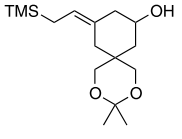
Scheme 10.

Table 4
Ni(0)-catalyzed cyclization of **6b**–**6d**



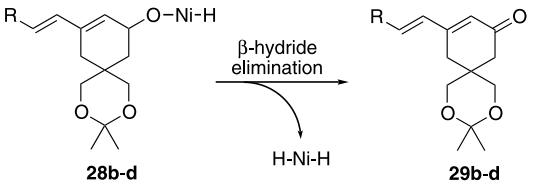
Run	Substrate	Time (h)	Yields (%)			Total yields
			25	**26**	**29**	
1	**6b**	24	20	6	39	65[a]
2	**6c**	16	22	31	2	55
3	**6d**	16	26	32	12	70

[a] E-30b was also produced in 19% yield.



Mono-benzylation of **35** and oxidation of the resulting alcohol with PCC gave **36** in 59% yield (two steps).

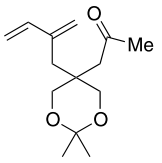
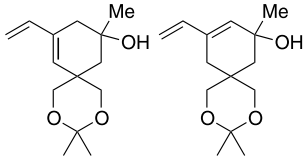
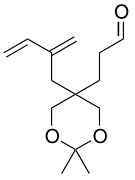
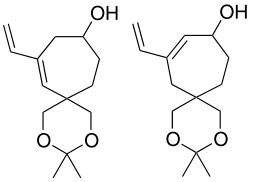
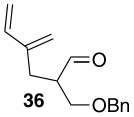
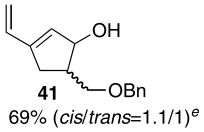
The cyclization of **31**, having a methyl ketone moiety in a tether, was investigated using 20 mol% $Ni(cod)_2$ in the presence of 40 mol% PPh_3 at 50 °C for 48 h (Table 5,



Scheme 11.

run 1). Although the cyclization of **31** was slower than that of diene-aldehyde **6a**, the cyclized products **37** and **38** were obtained in 61% yield (ratio of 1.1:1). This result indicates that not only aldehyde but also ketone can be used as a substrate in this cyclization. The cyclization of **33** under similar conditions also proceeded to give the desired products **39** and **40** in a total yield of 47% (ratio of 1.3:1), indicating that this cyclization is applicable to the construction of a seven-membered ring (run 2). It is also noteworthy that this cyclization can be applied to the construction of a five-membered ring compound. When **36** was subjected to cyclization under similar conditions, only the cyclized product **41** was obtained in 68% yield as a mixture of *cis*- and *trans*-isomers with respect to C1 and C5-positions, and another possible product **42** was not formed (Table 5, run 3). This result indicates that a regio-selective β-hydride elimination with the Hb hydrogen in oxa-nickelacycle **43** occurred in preference to the Ha hydrogen probably due to the steric factor of **43**, giving only **41** via nickel hydride complex **44** (Scheme 13).

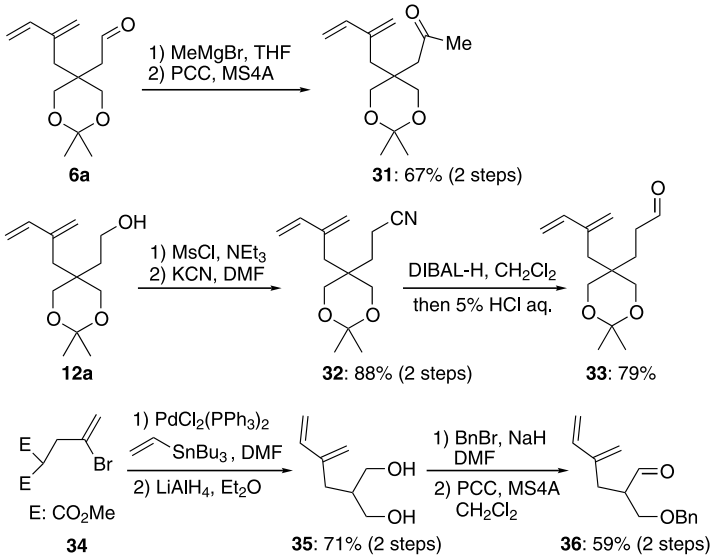
Table 5
Cyclization of various substrates

run[a]	substrate	products
1[b,c]	 **31**	 **37**: 32% **38**: 29%
2[d]	 **33**	 **39** **40** 47% (**39**/**40**=1.3/1)[e]
3[b]	 **36**	 **41** 69% (*cis*/*trans*=1.1/1)[e]

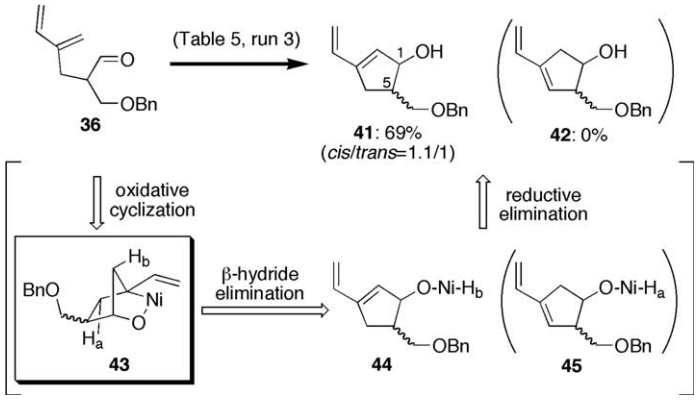
[a] All reactions were carried out in THF at 50 °C for 48 h.
[b] 20 mol % $Ni(cod)_2$ and 40 mol % PPh_3 were used. [c] SM **31** was recovered in 17% yield. [d] 30 mol % $Ni(cod)_2$ and 60 mol % PPh_3 were used. [e] The ratio was determined by ^{1}H-NMR.

2.2. Nickel(0)-catalyzed cyclization of branched 1,3-dienes via of oxa-nickelacycle with organometallic reagents [5]

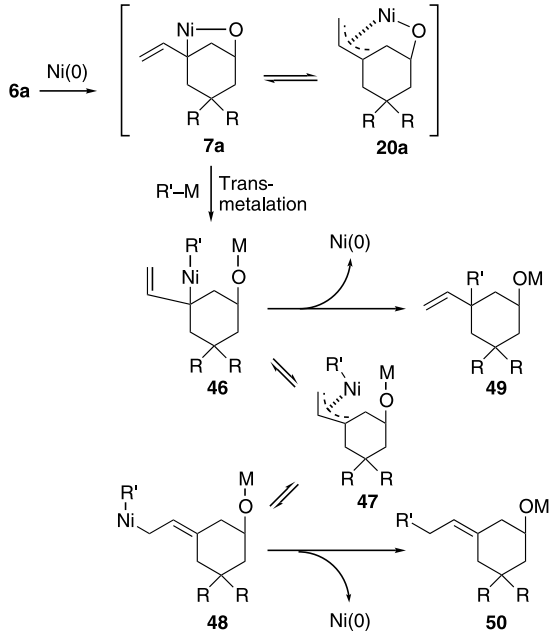
Having established a novel Ni(0)-catalyzed cyclization of **6a** via β-hydride elimination from oxa-nickelacycle **7a**, we turned our attention to a transmetalation of **6a** with various organometallic reagents (Scheme 14). If the oxa-nickelacycle **7a** can react with another organometallic reagent through transmetalation, the intermediate **46** should be formed from **7a** and the organometallic reagent (R′–M). The intermediate **46** would be in equilibration with **47** and **48**, and reductive elimination



Scheme 12.



Scheme 13.



Scheme 14.

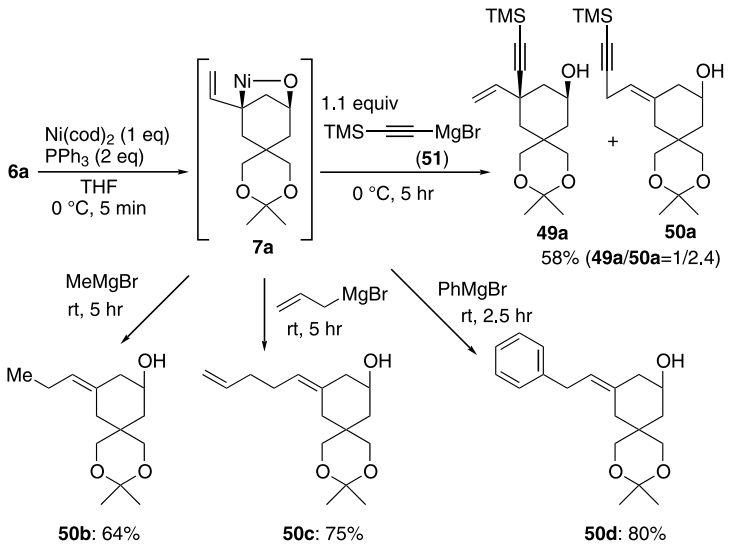
from these intermediates would afford the products **49** and/or **50**.

First, we investigated transmetalation of a stoichiometric amount of oxa-nickelacycle **7a** with various Grignard reagents (Scheme 15). When **6a** was treated with $Ni(cod)_2$ (one equivalent) and PPh_3 (two equivalents) in THF at 0 °C, the disappearance of **6a** was observed on TLC within 5 min, indicating the formation of **7a**. To a solution of **7a** was immediately added a THF solution of Grignard reagent **51** (1.1 equivalents) generated from trimethylsilylacetylene and EtMgBr in THF, and the mixture was stirred at 0 °C for 5 h. After hydrolysis of the reaction mixture, we were pleased to find that the desired products **49a** and **50a** (ratio of 1/2.4) were obtained in a total yield of 58%. It was interesting that the reactions with MeMgBr, allylmagnesium bromide and PhMgBr under similar conditions gave **50b**, **50c** and **50d** as a single isomer in 64, 75 and 80% yields, respectively. It was thought that **50a**–**50d** were produced from **48** via reductive elimination, while **49a** was produced from **46** (see Scheme 16), and that the bulkiness of an organic group (R) of Grignard reagent (RMgX) would affect the ratio of the cyclized products **49** and **50**.

Next, transmetalation of oxa-nickelacycle **7a** with various organometallic reagents having a methyl group as an organic group was examined (Table 6). Treatment of nickelacycle **7a**, generated from **6a** and a stoichiometric amount of $Ni(cod)_2$–PPh_3 as mentioned above, with MeLi (run 1) at 50 °C gave the product **50b** in 23% yield as a single isomer. The reaction of **7a** with Me_3Al, $Me_2Al(acac)$ and Me_2Zn also afforded only the product **50b** in 53, 51 and 49% yields, respectively. It is noteworthy that only **50b**, which should be produced from **48** via reductive elimination, was obtained in all cases. These results indicate that transmetalation of oxa-nickelacycle **7a** can proceed with various metal reagents (Li, Al, and Zn).

Next, transmetalation of **7a** with organometallic reagents having the β-hydrogen in its organic group was investigated (Table 7). The reaction of **7a** with DIBAL–H (run 1) gave only the hydrogenated products **49e** and **50e** in 79 and 13% yields, respectively, and no isobutylated product was obtained. In the reaction of **7a** with $^{i}Bu_2Al(acac)$, the hydrogenated product **49e** was obtained as a sole product in 62% yield. The reaction of **7a** with *t*-butyl magnesium chloride also showed the same tendency and gave only the hydrogenated products **49e** and **50e**. However, the ratio of **49e** to **50e** was reversed in this reaction, and **50e** was produced in 50% yield in preference to **49e** in 13% yield.

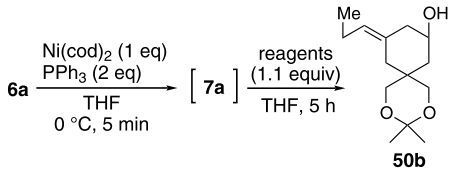
A possible mechanism for the production of the hydrogenated products **49e** and **50e** is shown in Schemes 16 and 17. In the case of runs 1 and 2 in Table 7, the intermediate **46**–^{i}**Bu** would be initially formed by transmetalation of **7a** with DIBAL–H or $^{i}Bu_2Al(acac)$, which might be in equilibration with **48**–^{i}**Bu** (Scheme 16). The β-hydride elimination from **46**–^{i}**Bu** or **48**–^{i}**Bu** produces the nickel hydride complex **46**–**H** or **48**–**H**,



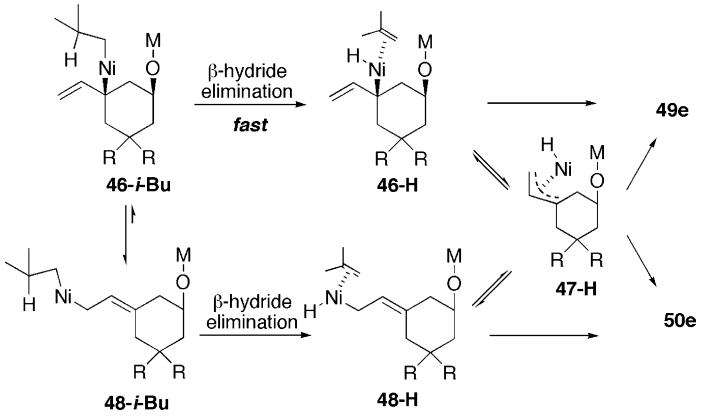
Scheme 15.

which might be also in equilibration with **47**–**H**. Reductive elimination from **46**–**H**, **47**–**H** or **48**–**H** would afford the hydrogenated product **49e** or **50e**. On the other hand, the intermediate **46**–^{t}**Bu** or **48**–^{t}**Bu** would be formed in the case of run 3 in Table 7 (Scheme 17). In this case, however, the same intermediates **46**–**H**, **47**–**H**, and **48**–**H** should be produced via β-hydride elimination from **46**–^{t}**Bu** or **48**–^{t}**Bu**. Thus, the difference in the ratios of **49e** to **50e** in these reactions (Schemes 16 and 17) indicates that reductive elimination would occur before an equilibrium state between **46**–**H**, **47**–**H** and **48**–**H** is reached. In the case of **46**–^{i}**Bu** (Scheme 16), it was thought that β-hydride elimination from **46**–^{i}**Bu** would immediately occur before an equilibrium with **48**–^{i}**Bu** is reached, producing **46**–**H**. Then, the hydrogenated product **49e** would be formed directly through reductive elimination from **46**–**H**. On the other hand, in the case of **46**–^{t}**Bu** (Scheme 17), the isomerization from **46**–^{t}**Bu** to **48**–^{t}**Bu** would occur because of the bulkiness of the *t*-butyl group, and β-hydride elimination from **48**–^{t}**Bu** would then occur to produce **48**–**H**. The hydrogenated product **50e** would be preferentially produced through reductive elimination from **48**–**H**. The fact that no alkylated product was obtained in these reactions indicates that β-hydride elimination from **46**–^{i}**Bu** or **48**–^{t}**Bu** is considerably

Table 6
Reaction of oxa–nickelacycle **7a** with various organometallic reagents

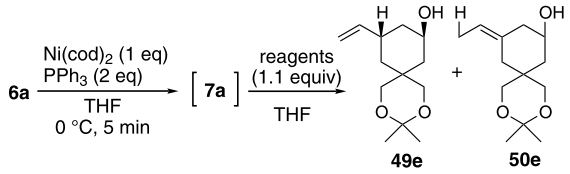


Run	Reagents	Temperature (°C)	Yield (%)
1	MeLi	50	23
2	Me_3Al	23	53
3	$Me_2AI(acac)$	23	51
4	Me_2Zn	0	49

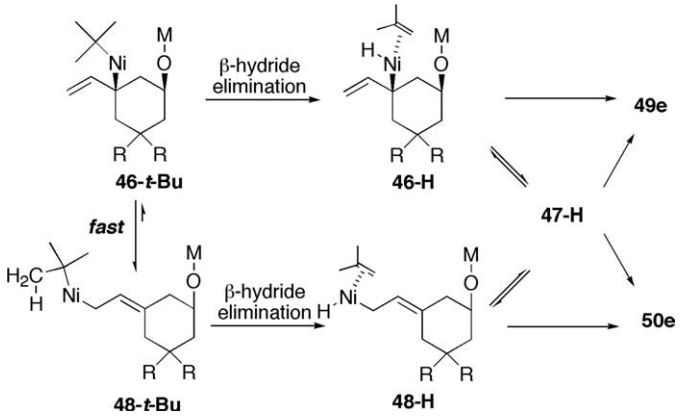


Scheme 16.

Table 7
Reaction of **7a** with various organometallic reagents having –hydrogen



Run	Reagents	Temperature (°C)	Time (h)	Yields (%)	
				49e	**50e**
1	DIBAL–H	0	1	79	13
2	$^{i}Bu_2Al(acac)$	0	1	62	–
3	$^{t}BuMgCI$	rt	14	13	50



Scheme 17.

faster than the direct reductive elimination. On the basis of these results, reductive elimination from **46**–**H** to **49e** or from **48**–**H** to **50e** would occur before an equilibrium between **46**–**H**, **47**–**H** and **48**–**H** is reached.

As shown in Scheme 14, zero-valent nickel species should be regenerated in this reaction. Thus, a tandem cyclization, i.e. formation of oxa-nickelacycle followed by transmetalation would proceed in one-pot under these conditions through two C–C bond-forming reactions. However, in order to establish the catalytic cycle in this reaction, the organometallic reagents should be intact or less reactive to the substrate (especially to an aldehyde moiety in the substrate) until the nickelacycle **7a** has formed. Many attempts using various organometallic reagents were carried out, and we finally found that the reaction of **6a** with 20 mol% $Ni(cod)_2$ and 40 mol% PPh_3 in the presence of $^{i}Bu_2Al(acac)$ (2 equiv.) gave the desired products **49e** in 53% yield and **50e** in 16% yield (Table 8, run 1). Reactions using $Me_2Al(acac)$ and Me_2Zn under similar conditions also proceeded to give only **50b** in 43% ($E/Z = 1/4.7$) and 57% ($E/Z = 1/1.1$) yields, respectively (runs 2 and 3). Thus, the catalytic cycle in this reaction was established.

2.3. Conclusions

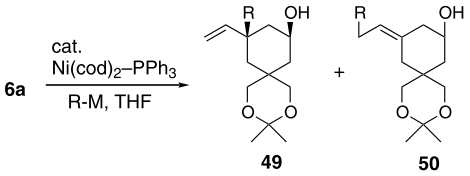
The results described in this article are summarized in Scheme 18.

The reactivity of oxa-nickelacycles **7**, generated by the reaction of a branched 1,3-diene and tethered carbonyl group with a Ni(0) complex, was investigated in detail. It was found that the oxa-nickelacycles **7** are relatively stable and that β-hydride elimination from **7** occurs at a high temperature, producing the cyclized dienes **51** and/or **52** in good yields. These findings led to the discovery of a novel Ni(0)-catalyzed cyclization of **6** via β-hydride elimination from oxa-nickelacycle **7**. In the cyclization, various substituents on the diene moiety were tolerated, and a five- to seven-membered ring could be constructed. Subsequently, transmetalation of oxa-nickelacycle **7** with various organometallic reagents was investigated. It was found that the tandem reaction, i.e. cyclization of **6** followed by transmetalation of the resulting oxa-nickelacycle **7**, proceeded smoothly, giving **53** and/or **54** in good yields [12]. In addition, the catalytic cycle in this transmetalation reaction was established.

3. Experimental

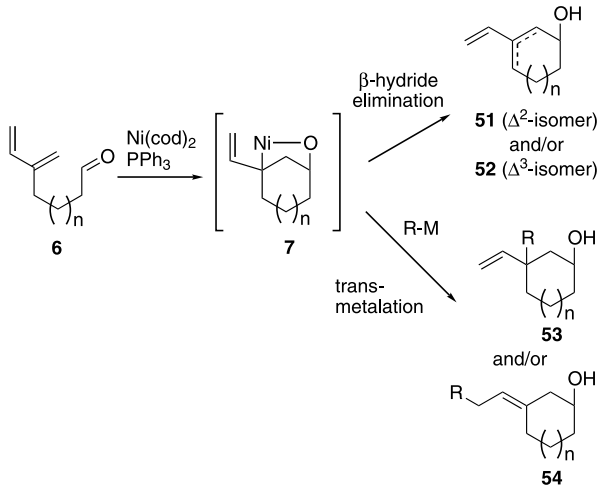
All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh), and flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) using the indicated solvent. Melting points were determined with a Ishii meilting point apparatus and are uncorrected. NMR spectra were measured on JEOL EX 270 (^{1}H at 270 MHz, ^{13}C at 67.5 MHz), JEOL AL 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), or Bruker ARX-500 (^{1}H at 500 MHz) magnetic

Table 8
Catalytic reaction of **6a** via the cyclization–transmetalation process



Run	Reagents (R–M)	$Ni(cod)_2$ (mol%)	Temperature (°C)	Time (h)	Product (R)	Yields (%)		
						49	**50**	(*E*/*Z*)
1	$^{i}Bu_2Al(acac)$ [a]	20	23	7.5	**e** (H)	53	16	(1/0)
2	$Me_2Al(acac)$ [b]	30	50	48	**b** (Me)	–	43	(1/4.7)
3	Me_2Zn [a]	20	50	68	**b** (Me)	–	57	(1/1.1)

[a] Two equivalents of R–M was used.
[b] Three equivalents of R–M was used.



Scheme 18.

resonance spectrometer. Infrared spectra were recorded on JASCO FT/IR-5300, or Perkin–Elmer FTIR 1605 spectrometer. Mass spectra were measured on JEOL DX-303 and JEOL HX-110 mass spectrometer. Elemental analysis were determined with Yanaco CHN CORDER MT-3.

3.1. Typical procedure for Ni(0)-catalyzed cyclization of *6a* via β-hydride elimination from oxa-nickelacycle intermediate (Table 2, run 1)

A solution of **6a** (56 mg, 0.25 mmol) in degassed-THF (5.0 ml) was added to a solution of $Ni(cod)_2$ (21 mg, 0.075 mmol) and PPh_3 (40 mg, 0.15 mmol) in degassed-THF (7.0 ml) at 0 °C, and the mixture was stirred at 50 °C for 2.5 h. To the mixture was added sat. NH_4Cl aqueous solution at 0 °C, and the mixture was stirred under an atmosphere of air at 0 °C for 40 min in order to decompose the catalyst. The mixture was extracted with AcOEt, and the organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane–E_2O = 1:2) to give a mixture of **25a** and **26a** (51 mg, 91%), whose ratio was determined to be 1/3.8 by ^{1}H-NMR. The mixture could be separated by carrying out preparative-TLC repeatedly, and the spectral data of each compound were recorded after the separation.

3.1.1. Spectral data of *25a*

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.35 (d, J = 14.5 Hz, 1H), 1.41 (s, 3H), 1.43 (s, 3H), 1.79 (brs, 1H), 2.03 (ddd, J = 16.5, 8.6, 1.3 Hz, 1H), 2.27 (dd, J = 14.5, 3.3 Hz, 1H), 2.62 (dd, J = 16.5, 5.3 Hz, 1H), 3.54 (dd, J = 11.9, 1.3 Hz, 1H), 3.56 (dd, J = 11.2, 1.3 Hz, 1H), 3.65 (d, J = 11.9 Hz, 1H), 3.74 (d, J = 11.2 Hz, 1H), 3.95–4.06 (m, 1H), 5.01 (d, J = 10.6 Hz, 1H), 5.16 (d, J = 17.2 Hz, 1H), 5.51 (s, 1H), 6.34 (dd, J = 17.2, 10.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6, 26.0, 33.8, 37.7, 37.9, 65.1, 67.4, 69.9, 97.9, 112.6, 129.3, 136.1, 138.6; IR (neat) 3420, 1608, 1198 cm^{-1}; LRMS (EI) *m*/*z* 209 [M^+ – Me], 194, 166, 149, 136, 131, 117, 105; HRMS (EI) *m*/*z* Calc. for $C_{13}H_{20}O_3$ 224.1413, Found 224.1420. Anal. Calc. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 68.07; H, 9.00%.

3.1.2. Spectral data of *26a*

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.31 (dd, J = 12.5, 7.9 Hz, 1H), 1.39 (s, 3H), 1.41 (s, 3H), 2.00–2.06 (m, 3H), 2.24 (d, J = 16.5 Hz, 1H), 3.50 (d, J = 9.9 Hz, 1H), 3.63 (d, J = 9.9 Hz, 1H), 3.63 (d, J = 9.6 Hz, 1H), 3.64 (d, J = 9.6 Hz, 1H), 4.33 (brs, 1H), 5.04 (d, J = 10.6 Hz, 1H), 5.23 (d, J = 17.8 Hz, 1H), 5.68 (s, 1H), 6.33 (dd, J = 17.8, 10.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.8, 24.7, 29.9, 33.0, 37.1, 64.7, 67.3, 69.7, 98.3, 113.4, 129.9, 135.4, 138.6; IR (neat) 3404, 1608, 1194 cm^{-1};

LRMS (EI) *m/z* 224 [M^+], 209, 207, 192, 166, 149, 131, 117, 105; HRMS (EI) *m/z* Calc. for $C_{13}H_{20}O_3$ 224.1413, Found 224.1425. Anal. Calc. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 68.53; H, 9.13%.

3.2. Typical procedure for a stoichiometric reaction of **7a** with organometallic reagent (transmetalation of **7a** with PhMgBr in Scheme 15)

A solution of **6a** (60 mg, 0.27 mmol) in degassed-THF (5.4 ml) was added to a cooled solution of $Ni(cod)_2$ (74 mg, 0.27 mmol) and PPh_3 (140 mg, 0.53 mmol) in degassed-THF (7.8 ml) at 0 °C, and the mixture was stirred at the same temperature for 5 min. To the mixture was added PhMgBr (1.3 M in THF, 0.25 ml, 0.32 mmol) at 0 °C, and the mixture was stirred at room temperature (r.t.) for 2.5 h. To the mixture was added saturated aqueous NH_4Cl solution at 0 °C, and the solution was stirred at the same temperature for 40 min. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane–EtOAc 3:1, 1:1) to give **50d** (64 mg, 80%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.21 (dd, $J = 13.2$, 9.9 Hz, 1H), 1.43 (s, 6H), 1.82 (d, $J = 13.9$ Hz, 1H), 1.88 (brs, 1H), 1.90 (dd, $J = 13.2$, 4.0 Hz, 1H), 2.03 (dd, $J = 12.5$, 9.9 Hz, 1H), 2.49 (dd, $J = 12.5$, 4.0 Hz, 1H), 2.81 (d, $J = 13.9$ Hz, 1H), 3.41 (d, $J = 7.3$ Hz, 2H), 3.51 (d, $J = 11.2$ Hz, 1H), 3.58 (d, $J = 11.2$ Hz, 1H), 3.58 (d, $J = 11.2$ Hz, 1H), 3.67 (d, $J = 11.2$ Hz, 1H), 3.74 (dddd, $J = 9.9$, 9.9, 4.0, 4.0 Hz, 1H), 5.52 (t, $J = 7.3$ Hz, 1H), 7.15–7.30 (m, 5H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ 22.1, 26.1, 33.4, 34.3, 35.6, 40.6, 46.3, 66.9, 67.7, 70.4, 98.5, 126.2, 126.7, 128.7, 128.8, 132.9, 141.6; IR (neat) 3420, 3026, 1736, 1602 cm^{-1}; LRMS (EI) *m/z* 287[$M^+ - Me$], 244, 226, 212, 195, 181, 167, 155, 141, 117; HRMS (EI) *m/z* Calc. for $C_{19}H_{26}O_3$ 302.1883, Found 302.1891.

3.3. Typical procedure for Ni(0)-catalyzed-tandem reaction (cyclization-transmetalation) of **6a** with organometallic reagent (reaction of **6a** with ^{i}Bu$_2$Al(acac) [Table 8, run 1])

A solution of **6a** (56 mg, 0.25 mmol) in degassed-THF (5.0 ml) and ^{i}Bu$_2$Al(acac) (1.0 M in toluene, 0.49 ml, 0.49 mmol) were added to a cooled solution of $Ni(cod)_2$ (14 mg, 0.052 mmol) and PPh_3 (27 mg, 0.10 mmol) in degassed-THF (7.2 ml) at 0 °C, and the mixture was stirred at r.t. for 7.5 h. To the mixture was added saturated aqueous NH_4Cl solution at 0 °C, and the solution was stirred at the same temperature for 40 min. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane–EtOAc 2:1, 1:1) to give **49e** (30 mg, 53%) and **50e** (8.9 mg, 16%).

3.3.1. Spectral data of **49e**

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.87 (dd, $J = 13.2$, 13.2 Hz, 1H), 1.14 (dd, $J = 14.5$, 2.6 Hz, 1H), 1.30 (ddd, $J = 13.9$, 11.9, 2.6 Hz, 1H), 1.41 (s, 3H), 1.42 (s, 3H), 1.92–1.80 (m, 2H), 1.97 (brs, 1H), 2.08 (brd, $J = 13.2$ Hz, 1H), 2.55 (m, 1H), 3.39 (d, $J = 11.2$ Hz, 1H), 3.50 (d, $J = 11.2$ Hz, 1H), 3.98 (s, 2H), 4.22 (dddd, $J = 3.3$, 3.3, 2.6, 2.6 Hz, 1H), 4.75 (d, $J = 10.6$ Hz, 1H), 5.03 (d, $J = 17.2$ Hz, 1H), 5.78 (ddd, $J = 17.2$, 10.6, 6.6 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 22.6, 25.0, 30.7, 33.0, 36.8, 37.2, 39.1, 66.7, 67.8, 71.9, 98.0, 112.6, 143.4; IR (neat) ν 3450, 1592 cm^{-1}; LRMS (EI) *m/z* 211 [$M^+ - Me$], 151, 133, 105, 91; HRMS (EI) *m/z* Calc. for $C_{12}H_{19}O_3$ [$M^+ - Me$] 211.1335, Found 211.1320.

3.3.2. Spectral data of **50e**

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.20 (dd, $J = 13.2$, 9.9 Hz, 1H), 1.42 (s, 6H), 1.45 (brd, 1H), 1.63 (d, $J = 6.6$ Hz, 3H), 1.74 (d, $J = 13.2$ Hz, 1H), 1.92 (m, 1H), 1.98 (m, 1H), 2.47 (dd, $J = 12.5$, 4.3 Hz, 1H), 2.64 (d, $J = 13.2$ Hz, 1H), 3.48 (d, $J = 11.2$ Hz, 1H), 3.57 (d, $J = 11.2$ Hz, 1H), 3.58 (d, $J = 11.2$ Hz, 1H), 3.66 (d, $J = 11.2$ Hz, 1H), 3.74 (m, 1H), 5.42 (q, $J = 6.6$ Hz, 1H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ 13.5, 22.6, 26.0, 33.1, 35.7, 40.8, 67.2, 68.1, 70.6, 98.4, 122.0, 133.0; IR (neat) ν 3406 cm^{-1}; LRMS (EI) *m/z* 226 [M^+], 211, 193, 168, 150, 133, 120; HRMS (EI) *m/z* Calc. for $C_{13}H_{22}O_3$ 226.1570, Found 226.1591.

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