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Remarkable Regio-Controlled Effect of 1,3-Diene as a Ligand on Nickel-Promoted Cyclization

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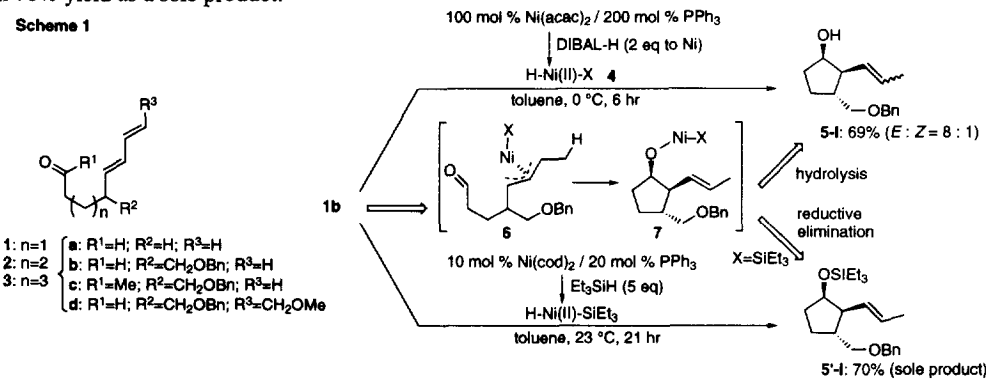
Abstract: In a nickel-promoted cyclization, 1,3-diene can serve as a ligand and it affects the reaction course. A *s-cis* conformation of 1,3-diene is necessary for coordination to the metal, and the highest selectivity (**5-T/5-I**=98/2) was obtained in the reaction of **1b** with hydride nickel complex **4** using cyclopentadiene **22** as a ligand.

A nickel-promoted intramolecular oligomerization of 1,3-diene and multiple bonds is valuable in modern synthetic organic chemistry because regio- and stereospecific ring construction is achieved.[1,2] Recently, we have reported a novel nickel-promoted stereoselective cyclization of 1,3-diene having a carbonyl group in a chain.[3] In this cyclization, a hydride nickel complex **4**, genarated from $Ni(acac)_2$ and PPh_3 by treatment with DIBAL-H, played an important role, and a possible reaction mechanism is outlined in Scheme 1. The reaction of **1b** with a stoichiometric amount of **4** produced π-allylnickel complex **6**, which reacted with the aldehyde in the side chain giving nickel complex **7**. After hydrolysis of the reaction mixture, the cyclized product **5-I** was obtained stereoselectively with respect to three carbon centers of the cyclopentane ring. When Et_3SiH was used as a hydride source, the cyclization proceeded catalytically on a nickel complex affording the cyclized product **5'-I** in 70% yield as a sole product.

Scheme 1



Here, we report that 1,3-diene affects the stereochemistry of the product in this cyclization. During the course of our investigation of the cyclization of **1b**, we found that the cyclized product **5-T** having a terminal olefin on the side chain was obtained in preference to **5-I** having an internal one when a catalytic amount of hydride nickel complex **4** was used (Table 1). The formation of product **5-T** could not be explained in the

above-mentioned mechanism *via* π-allylnickel complex **6**, and it was speculated that an excess of **1b** would coordinate to nickel complex **4** acting as a ligand, and it affected the regiochemistry of the cyclized product. That is, the nickel complex **8** coordinated by 1,3-diene possesses a different reactivity from **4**.

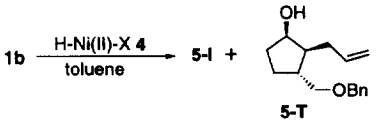
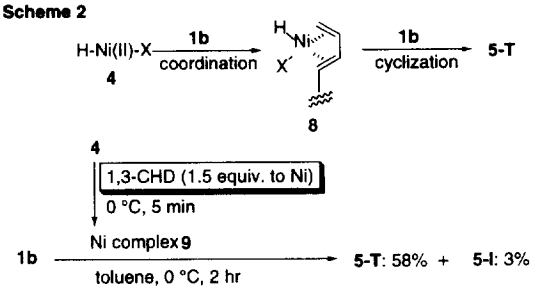


Table 1. Cyclization Using Various Amounts of Ni Complex **4**

run	Ni (mol %)	temp	time (hr)	yield (%) 5-I + 5-T	5-I	5-T
1	100	0 °C	6	69	69 [a]	—
2	50	0 °C	6	65	6 [b]	59
3	30	0 °C	20	36	—	36
4	10	rt	20	10	—	10

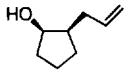
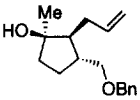
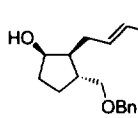
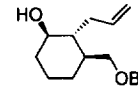
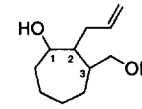
[a] *E*/*Z* = 8/1 [b] The ratio was not determined.

Scheme 2



On the basis of these assumptions, we examined the effect of 1,3-diene on the cyclization of **1b** using the hydride nickel complex **4**. To a stirred toluene solution of hydride nickel complex **4**, generated *in situ* by treatment of $Ni(acac)_2$ (100 mol %) and PPh_3 (200 mol %) with DIBAL-H (200 mol %), was added 150 mol % of 1,3-cyclohexadiene (1,3-CHD) at 0 ℃, and the solution was stirred for a few minutes. A toluene solution of substrate **1b** was then added to the resultant mixture and the solution was stirred at 0 ℃ for 2 hours. It was very surprising to find that hydrolysis of the reaction mixture with 10% HCl at 0 ℃ afforded the cyclopentane derivative **5-T** having a *terminal olefin* at the side chain in 58% yield as a main product along with **5-I** in 3% yield, while in the absence of 1,3-CHD, only **5-I** was obtained in 69% yield. This reaction proceeded in a stereoselective manner at the C1, C2 and C3 carbon centers of the cyclopentane ring.

Table 2. Cyclization of various substrates in the presence of 1,3-cyclohexadiene (1,3-CHD)

run [a]	substrate	temp (°C)	time (hr)	product
1	**1a**	0	1	 **10-T**: 70%
2	**1c**	25	7	 **11-T**: 60%[b]
3	**1d**	0	2	 **12**: 73%
4	**2b**	0	2	 **13-T**: 80%[c]
5	**3b**	25	2	 **14-T**: 47%[d]

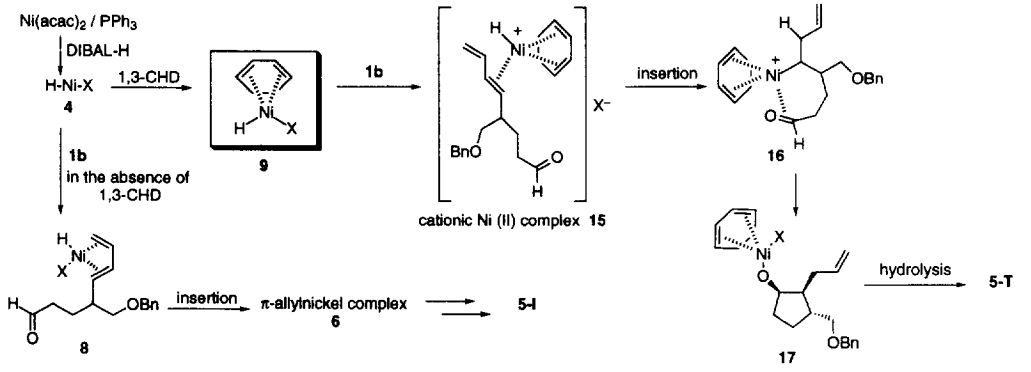
[a] All reactions were carried out in toluene using a stoichiometric amount of nickel complex **9** (for preparation of **9**, see text). [b] Cyclized product **11-I**, having an internal olefin at the side chain, was also obtained in 10% yield. [c] Cyclized product **13-I**, having an internal olefin at the side chain, was also obtained in 6% yield. [d] **14-T** was obtained as two isomers with respect to C1, C2 or C3 of the cycloheptane ring

Encouraged by these results, we investigated the cyclization of various substrates under similar conditions in the presence of 1,3-CHD. In the reaction of **1a**,[4] the cyclopentane derivative **10-T** was produced as a sole product. The reaction of **1c**, having a ketone moiety as a carbonyl group, proceeded smoothly at 25 ℃ preferentially giving **11-T** in 60% yield. The cyclization of **1d**, having an internal 1,3-diene moiety, gave the cyclized product **12** as a sole product. In the formation of a six-

membered ring, the cyclohexane derivative **13-T** was obtained in 80% yield stereoselectively. It is notable that this cyclization is applicable to the construction of a seven-membered ring, and the reaction of **3b** afforded the cycloheptane derivative **14-T** in 47% yield. In all cases, cyclized products having internal olefin on the side chain were predominantly produced in the absence of 1,3-CHD.[3]

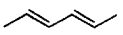
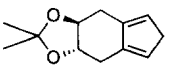
A possible mechanism of this cyclization is shown in Scheme 3. Coordination of 1,3-CHD to the nickel metal of **4** would form nickel complex **9**. Then, cationic Ni(II) complex **15** would be produced by coordination of the olefin in **1b** followed by dissociation of X^- (*e.g.* acetylacetonate anion) from the metal. Insertion of the olefin into the hydride–nickel bond would afford complex **16** followed by insertion of the

Scheme 3



carbonyl group in a chain into the nickel-carbon bond providing **17**. After hydrolysis of **17**, the cyclized product **5-T** is obtained stereoselectively.[5] On the other hand, in the absence of 1,3-CHD, coordination of 1,3-diene moiety of **1b** to the nickel metal of **4** would form complex **8**, followed by simultaneous formation of π-allylnickel complex **6** giving the cyclized product **5-I** having an internal olefin on the side chain stereoselectively.[6] In order to find the best ligand, the reactions of **1b** with hydride nickel complex **4** in the presence of various alkenes were carried out, and the results are summarized in Table 3.

Table 3. Cyclization of **1b** in the presence of various alkenes

run [a]	alkene [b]	yield 5-T+5-I (%)	ratio [c] 5-T/5-I	run	alkene	yield 5-T+5-I (%)	ratio 5-T/5-I
1	 (1,3-CHD)	61	95/5	4	 **20**	72	46/54
2	 **18**	57	80/20	5	 **21**	71	25/75
3	 **19**	80	58/42	6	 **22**	70	98/2

[a] All reactions were carried out in toluene at 0 °C. [b] 150 mol % of alkenes were used. [c] The ratio was determined by ^{1}H-NMR.

1,4-Diene (run 4) and mono-olefin (run 5) were less effective for the formation of **5-T** than 1,3-dienes (runs 1, 2, 3 and 6). 1,3-CHD (run 1) showed higher selectivity than a linear 1,3-diene **18** or **19**. These results indicated that *s-cis* conformation of 1,3-diene is necessary for coordination to the metal to form complex **9**. It

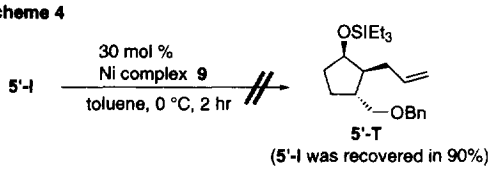
was very interesting that **5-T** was obtained in 70% yield with the highest selectivity (**5-T/5-I**=98/2) when cyclopentadiene **22**[7] was used as a ligand.[8]

In conclusion, we succeeded in demonstrating that 1,3-diene can serve as a ligand and affects the reaction course in nickel-promoted cyclization. We also found that a *s-cis* conformation of 1,3-diene is necessary for coordination to the metal in this cyclization. This is the first study using 1,3-diene as a ligand in nickel-mediated intramolecular cyclizations. Further studies, including the application to catalytic asymmetric synthesis using this methodology, are in progress.

References and Notes

1. For reviews, see: (a) Jolly, P. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G A.; Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8, p 613. (b) Keim, W.; Behr, A.; Roper, M. *ibid.* p 371. (c) Heimback, P. *Angew Chem., Int. Ed. Engl.* **1973**, *12*, 975. (d) Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185.
2. (a) For [4+4] cycloadditions, see: Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089 and references cited therein. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Syn. Lett.* **1992**, 539. Tamao, K.; Kobayashi, K.; Ito, Y. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 381. (c) For [4+2] cycloadditions, see: Wender, P. A.; Smith, T E. *J. Org. Chem.* **1995**, *60*, 2962 and refereneces cited therein. (d) For nickel-promoted intermolecular reactions of 1,3-diene and carbonyl compound, see: Baker, R.; Cook, A. H.; Crimmin, M. J. *J. Chem. Soc. Chem. Commun.* **1975**, 727. Baker, R.; Crimmin, M. J. *J. Chem. Soc. Perkin I* **1979**, 1264.
3. Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771.
4. For the synthesis of **1a**, see: Müller, G.; Jas, G. *Tetrahedron Lett.* **1992**, *33*, 4417.
5. Hydrolysis of the reaction mixture with DCl-D_2O provided no product containing deuterium. This result indicates that no C–Ni bond is formed at the last stage of this cyclization.
6. When **5'-I** was treated with the hydride nickel complex **9** (30 mol %), no **5'-T** was obtained and **5'-I** was recovered in 90%. This indicates that olefin isomerization of **5'-I** into **5'-T** by nickel complex **9** does not occur.

Scheme 4



7. Halterman, R. L.; Vollhardt, K. P. C. *Tetrahedron Lett.* **1986**, *27*, 1461.
8. In this reaction, unchanged **22** was recovered in 69%, which indicates that diene **22** does not react with hydride nickel complex **4** under the conditions of this cyclization, and that **22** plays a role as a ligand to affect the reaction course.

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