Novel and Highly Regio- and Stereoselective Nickel-Catalyzed Homoallylation of Benzaldehyde with 1,3-Dienes
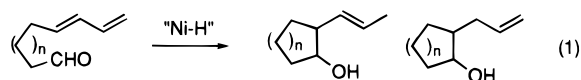
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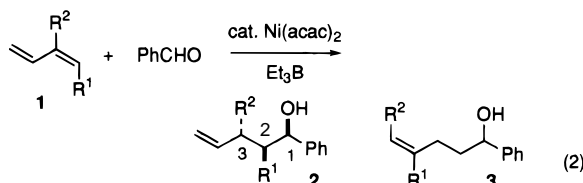*1-14 Bunnkyo, Nagasaki 852-8521, Japan*

Organonickel complexes are distinctive in their nucleophilic reactivity from organometal complexes of the other group 10 elements.[1] By virtue of this characteristic, many efficient nickel-catalyzed or -promoted C−C bond formation reactions have been developed.[2,3] Among these, allylation of carbonyls and alkyl and allyl halides with π-allylnickels has proved to be particularly useful and has been utilized widely for the synthesis of natural and unnatural products.[4,5] Unfortunately, however, this methodology requires a stoichiometric amount of nickel.

Recently, a useful version of catalytic addition of π-allylnickel to aldehyde has been developed, which promotes the cyclization of ω-dienyl aldehydes to 2-[(*E*)-1-propenyl]cycloalkanols (eq 1).[6] 2-Allylcycloalkanols may be obtained selectively by employing a stoichiometric amount of "Ni−H" complexes generated under sophisticated conditions (eq 1).[7]

Here, we disclose that Ni(acac)$_2$ (acac = acetylacetonato) in combination with triethylborane nicely catalyzes the homoallylation of benzaldehyde with 1,3-dienes to provide 1-phenyl-4-pentenols **2** in excellent yields and with pronounced regio- and stereoselectivities (eq 2). For example, as exemplified in run 2,

Table 1, when a mixture of isoprene (**1b**, 4 mmol), benzaldehyde (1 mmol), Ni(acac)$_2$ (0.1 mmol), and Et$_3$B (2.4 mmol) in dry THF (5 mL) was stirred at room temperature under nitrogen for 35 h, 3-methyl-1-phenyl-4-pentenol (**2b**) was obtained in a 90% isolated yield.[8] The use of 2.4 mmol of Et$_3$B seems to be essential; with 1.2 mmol, the reaction is not completed (80% isolated yield of **2b** based on 70% conversion after 71 h). In the absence of Et$_3$B, the reaction provides neither **2b** nor the oligomers of **1b** as monitored by GLC and TLC.

The reaction is remarkable in many respects. First, **1b** reacts with benzaldehyde exclusively at the C1 position of the diene moiety with an exclusive delivery of hydrogen at C2. No other products that might stem from the C−C bond formation at C4 and the hydrogen delivery to the other allylically related positions were detected.[9] Thus, the reaction formally corresponds to a reductive coupling of the C1−C2 double bond of **1b** and the C=O double bond of benzaldehyde, whereby Et$_3$B serves as a reducing agent. Second, the reaction exhibits high 1,3-diastereoselectivity, providing 1,3-*anti*-**2b** in preference to 1,3-*syn*-**2b** (15:1) (see Figure 1 for selected NMR data).[10,11] 1,3-Dienes with a similar substitution pattern, e.g., **1c** and **1f** (runs 3 and 7), show higher 1,3-asymmetric induction than **1b**, giving rise to 1,3-*anti*-**2c** and 1,3-*anti*-**2f** as single diastereomers, respectively. Third, the selective and high yield formation of a 1:1 adduct of diene and aldehyde is surprising in light of the propensity of nickel complexes to promote oligomerization of simple dienes.[1,4] In fact, it has been reported that nickel catalyzes or promotes the coupling reaction of isoprene and aldehyde (or ketone) to furnish homoallyl alcohols as a mixture of 1:1, 2:1, and 3:1 adducts, each of which consists of many possible regio- and stereoisomers.[12]

1,3-Pentadiene (**1d**) exhibited a different reaction feature (run 4), where both termini of the diene moiety took part in the reaction, providing **3a** (C1 addition product) as a major product together with **2d** (C4 addition product, as a 5.2:1 diastereomeric mixture). Judging from the exclusive formation of 1,3-*anti*-**2e** (C4 addition product) from 3-methyl-1,3-pentadiene (**1e**, run 5), however, the C3 methyl group is apparently more influential than the C4 methyl group in controlling the regioselectivity. In this regard, both methyl groups of **1g** are properly arranged to cooperatively promote the C1 addition reaction (run 8). Indeed, the expected isomer, 1,3-*anti*-**2g**, was obtained exclusively. Together with these, the selective reaction of **1h** at the terminus carrying an electron-withdrawing group (run 9) suggests that the butadiene terminus bearing higher electron density undergoes an addition reaction to aldehyde in a nucleophilic fashion. Under the usual reaction conditions, styrene and 2,5-dimethyl-2,4-hexadiene were unreactive and cyclic dienes (1,3-cyclohexadiene and 1,3-cyclooctadiene) reacted slowly to provide intractable mixtures of addition products in low yields.

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(3) Ni-catalyzed 1,4-addition to enones: Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779−4780. Montgomery, J.; Oblinger, E.; Savchenko, A. V. *Ibid.* **1997**, *119*, 4911−4920. Montgomery, J.; Savchenko, A. V. *Ibid.* **1996**, *118*, 2099−2100. Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248−8255. Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015−5016. Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975−5976. Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *Ibid.* **1992**, *114*, 5160−5165. Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *Ibid.* **1991**, *113*, 6172−6177.

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(7) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887−890.

(8) The same reaction, using Ni(cod)$_2$ (cod = cyclooctadiene) (0.1 mmol) in place of Ni(acac)$_2$ (0.1 mmol), proceeded much faster and provided **2b** in a 88% isolated yield within 3 h at room temperature.

(9) ZrCp$_2$(isoprene) reacts with ketones to provide C1 homoallylation products of isoprene: Yasuda, H.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120−126. Erker, G.; Engel, K.; Atwood, J. L.; Hunter, W. E. *Angew., Int. Ed. Engl.* **1983**, *22*, 494−495. Erker, G.; Dorf, U. *Ibid.* **1983**, *22*, 777−778.

(10) The ratio of diastereomers was determined by combination of GLC, ^{1}H NMR (400 MHz), and/or ^{13}C NMR (100 MHz).

(11) The stereochemistry of **2** was determined unequivocally on the basis of ^{1}H and ^{13}C NMR spectra of cyclic compounds **5**−**7** (Figure 1), derived from **2** by chemical transformations: **5** (cis:trans = 5:1) in 30% overall yield from **2b** (1,3-*anti*:*syn* = 15:1) via (1) BH$_3$ in THF, (2) H$_2$O$_2$/NaOH, and (3) TsCl/pyridine; **6** (*syn*:*anti* = 5.3:1) in a 58% overall yield from **2e** (1,2-*syn*: *anti* = 13:1) and *syn*-**6** in 42% overall yield from **2i** via (1) O$_3$ in CH$_2$CH$_2$ and (2) H$_2$O$_2$/H$_2$SO$_4$ in AcOH; **7a** in 70% overall yield from **2h** via (1) LiAlH$_4$ in THF and (2) Me$_2$C(OMe)$_2$/TsOH; **7b** in 70% overall yield from **2j** via (1) Bu$_4$NF in THF and (2) Me$_2$C(OMe)$_2$/TsOH. The stereochemistry of **2c**, **2f**, and **2g** was tentatively assigned by analogy with that of **2b** and **2j**.

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Table 1. Nickel-Catalyzed Homoallylation of Benzaldehyde with Acyclic 1,3-Dienes

run	diene	time (h)[a]	products (% isolated yield)[b]
1	**1a**	21	**2a:** 77 **4:** 13
2	**1b**	35	**2b:** 90 (*syn:anti* = 1:15)
3	**1c**	43	**2c:** 89
4	**1d**	50	**2d:** 23 (*syn:anti* = 1:5.2) **3a:** 55
5	**1e**[c]	41	**2e:** 94 (1,2-*syn:anti* = 8:1)
6	**1e**[c,d]	22	**2e:** 79 (1,2-*syn:anti* = 3.7:1)
7	**1f**	23	**2f:** 86
8	**1g**	46	**2g:** 82
9	**1h**	47	**2h:** 79
10	**1i**[e]	28	**2i:** 95 (1,2-*syn:anti* = 15:1)

[a] Reaction conditions: diene (4.0 mmol), benzaldehyde (1.0 mmol), Ni(acac)$_2$ (0.1 mmol), and Et$_3$B (2.4 mmol, 1 M in hexane) in dry THF (5 mL) at room temperature under N$_2$. [b] All products were properly characterized by ^{1}H (400 MHz), ^{13}C NMR (100 MHz), IR, HRMS, and/or elemental analyses. The *syn−anti* mixture was not separated, and their structures were assigned on the basis of mixtures (see ref 11 and Figure 1). [c] A mixture of *Z:E* = 1.9:1 was used. [d] A reduced amount of **1e** (1.0 mmol) was used. [e] A mixture of *Z:E* = 6.9:1 was used.
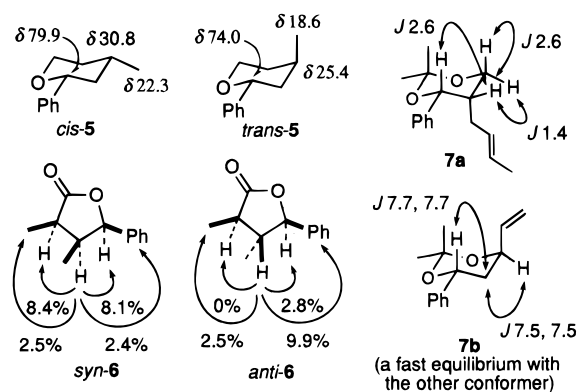

Figure 1. Selected NMR data diagnostic for structure determination: δ in ppm [^{13}C NMR (100 MHz, CDCl$_3$)], *J* in Hz [^{1}H NMR (400 MHz, CDCl$_3$)], and percent (%) increment in NOE.

Interestingly, the ratio of 1,2-*syn*-**2e** to 1,2-*anti*-**2e** decreases with a decrease in the initial molar ratio of **1e** (a mixture of *Z:E* = 1.9:1) to benzaldehyde (runs 5 and 6). This may be rationalized by assuming that (1) (*Z*)-**1e** reacts faster than (*E*)-**1e** and (2) (*Z*)-**1e** and (*E*)-**1e** selectively furnish 1,2-*syn*-**2e** and 1,2-*anti*-**2e**, respectively. On this assumption, it may be explained that **1i**

Table 2. Nickel-Catalyzed Homoallylation of Benzaldehyde with Dienes with Reduced Amounts of Ni(acac)$_2$ and Dienes[a]

run	diene (equiv)	Ni cat (mol%)	time (h)	major products (% isolated yield) [isomer ratio]
	1b			**2b** [1,3-*syn:anti* = 1:15]
1	4.0	10.0	35	90
2	4.0	2.5	35	94
3	4.0	1.0	48	82
	1h			**2h** [1,2-*syn:anti* = 1:>25]
4	4.0	10.0	47	79
5	4.0	2.5	50	80
6	4.0	1.0	66	91
7	1.1	2.5	75	75
	1j			**2j** [1,3-*syn:anti* = 1:>25]
8	2.0	5.0	65	65
9	1.1	5.0	65	62

[a] A mixture of diene (indicated amount), benzaldehyde (1.0 mmol for runs 1 and 4; 2 mmol for runs 2, 5, and 7−9; 5 mmol for runs 3 and 6), Ni(acac)$_2$ (indicated amount), and Et$_3$B (2.4 equiv) in dry THF (5 mL for runs except for runs 3 and 6; 3 mL for runs 3 and 6) at room temperature under N$_2$.

(*Z:E* = 6.9:1) provides 1,2-*syn*-**2i** with remarkably high stereoselectivity (run 10).

For convenience of experimental procedure, we routinely applied 4 equiv of diene and 0.1 equiv of Ni(acac)$_2$ relative to benzaldehyde. The homoallylation, however, turned out to be successful with reduced amounts of dienes and the catalyst (Table 2). The initial molar ratio of diene to benzaldehyde could be minimized virtually to unity without serious deterioration of the yields (runs 7 and 9, Table 2; see also run 6, Table 1). This aspect is beneficial especially when dienes are expensive or prepared with difficulty. Furthermore, the amount of the catalyst could be reduced to as small as 1 mol % (runs 3 and 6, Table 2), under which neither the yields nor the reaction rates discernibly decreased.

In conclusion, the Ni(acac)$_2$−Et$_3$B system allows us to obtain the reductive coupling products **2** of benzaldehyde and acyclic 1,3-dienes of a wide structural variety. The utility of the reaction may be apparent from (1) the usefulness of **2**, which is obtained in excellent yields and with high 1,2-, 1,3-, and 1,2,3-diastereoselectivities, (2) the mildness of the reaction conditions (room temperature), (3) the ease of the experimental procedure, and (4) the high catalytic turnover number over 80 (runs 3 and 6, Table 2). The low cost of the reagents [Ni(acac)$_2$ and Et$_3$B] and a 1:1 stoichiometry of the reaction partners (diene and benzaldehyde) are important aspects from an economic point of view. This paper demonstrates, for the first time, that Et$_3$B plays an important role as a reducing agent in maintaining the catalytic cycle for transition-metal-catalyzed reductive coupling reactions. We are now undertaking extensive study aimed at a catalytic asymmetric synthesis of **2** and reactions with other electrophiles, such as imines and allylic halides.

Supporting Information Available: Physical and spectral data of **2a−j**, **3a**, and **4** (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.