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Nickel-Catalyzed Homoallylation Reaction of Aldehydes with 1,3-Dienes: Stereochemical and Mechanistic Studies

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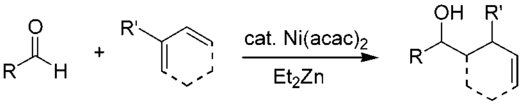
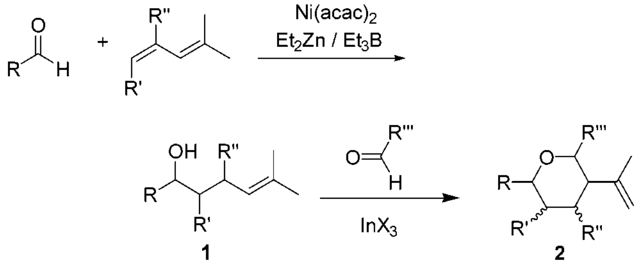
ABSTRACT



Contrary to what was reported, the coupling reaction of nickel-catalyzed cyclic diene such as cyclohexadiene with carbonyl compounds in the presence of diethyl zinc afforded γ,δ-alkenyl alcohols in good yields.

Most recently, our group has developed a new method for the synthesis of substituted tetrahydropyrans via a novel In(OTf)$_3$-catalyzed (3,5)-oxonium ene type cyclization (Scheme 1).[1] During the course of these studies, we are required to prepare the requisite alkenyl alcohol (**1**) in optically pure form. An attractive strategy is to apply the nickel(0)-catalyzed coupling of 1,3-dienes to a chiral aldehyde elegantly developed by Tamaru[2] and Mori.[3] This homoallylation of carbonyl compounds has been demonstrated to be a useful process because it produces synthetically useful γ,δ-alkenyl alcohols.[4,5]

Scheme 1



However, the major limitations of this reaction are the difficulty of obtaining the product when cyclic dienes were employed in the reaction and the lack of stereochemical studies. For example, Tamaru and co-workers had found that styrene and 2,5-dimethyl-2,4-hexadiene were unreactive, and cyclic dienes reacted slowly to provide intractable mixtures of addition products in low yields.[2a] On the basis of this information, they proposed the involvement of a trans nickel oxametallacycle intermediate in the reaction pathway (Figure 1).[6] Interestingly, in the course of our studies, we discovered

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(1) (a) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (b) Loh T.-P.; Hu, Q. Y.; Tan, K. T.; Cheng, H. S. *Org. Lett.* **2001**, *3*, 2669. For examples on the synthetic application of In(OTf)$_3$, see (c) Loh, T. P.; Chua, G. L.; Vittal, J. J.; Wong, M. W. *Chem. Commun.* **1998**, 861. (d) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743. (e) Gadhwal, S.; Sandhu, J. S.; *J. Chem. Soc., Perkin Trans. 1* **2000**, 2827.

(2) (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (b) Kimura, M.; Shibata, K.; Koudahashi, Y.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 6789. (c) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3600. (d) Shibata, K.; Kimura, M.; Kojima, K. Tamaru, Y. *J. Organomet. Chem.* **2001**, *624*, 348. (e) Shibata K.; Kimura M.; Shimizu M.; Tamaru Y. *Org. Lett.* **2001**, *3*, 2181.

(3) (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato Y.; Takimoto M.; Mori M. *Tetrahedron Lett.* **1996**, *37*, 887. (c) Sato Y.; Takimoto M.; Mori M. *Synlett* **1997**, 734. (d) Sato Y.; Saito N.; Mori M. *Tetrahedron* **1998**, *54*, 1153. (e) Sato Y.; Takanashi T.; Mori M**.** *Organometallics* **1999**, *18*, 4891. (f) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (g) Sato, Y.; Saito, N.; Mori, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2371. (h) Sato, Y.; Takimoto, M.; Mori, M. *Chem. Pharm. Bull.* **2000**, *48*, 1753.

(4) For NiH-mediated stoichiometric homoallylation of carbonyl compounds with 1,3-dienes, see (a) Sato, Y.; Takimoto, M.; Mori, M. *Synlett* **1998**, 734. For transition metal catalyzed allylation with 1,3-dienes, see (b) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543. (c) Kitayama, K.; Tsuji, H.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 4169.

(5) For reviews, see: (a) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576* (1−2), 215. (b) Ikeda, S. I. *Acc. Chem. Res.* **2000**, *33*, 511. (c) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467.

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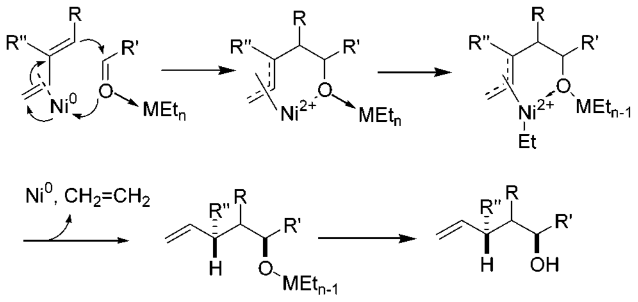


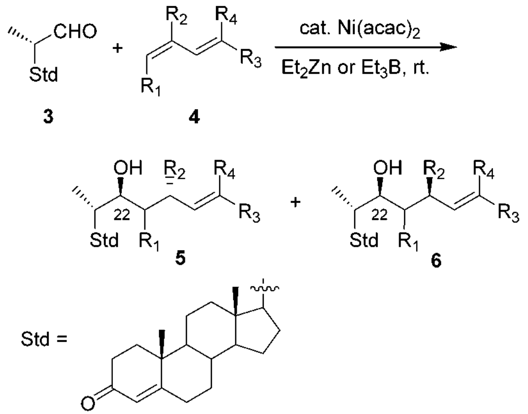
Figure 1.

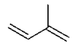
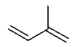
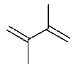
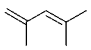
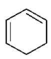
that this nickel-catalyzed reaction also proceeded with cyclohexadiene which greatly expanded the synthetic utility of the reaction. In this paper, we report that Ni(acac)$_2$-catalyzed reaction of cyclohexadiene with a wide variety of aldehydes in the presence of Et$_2$Zn as the reducing reagent.

Initially, we carried out the reaction of various 1,3-dienes with chiral steroidal aldehyde **3** catalyzed by Ni(acac)$_2$ in the presence of diethylzinc (Et$_2$Zn) or triethyl borane (Et$_3$B). The results are shown in Table 1. It was found that the reaction with Et$_2$Zn was much faster than the reaction with Et$_3$B (entry 1 vs entry 2). Therefore, Et$_2$Zn was used for all the subsequent reactions. In all these cases, the reaction proceeded smoothly to afford the desired products in good yields with moderate to good selectivities. For the nickel-catalyzed reaction of chiral steroidal aldehyde **3** with isoprene under the treatment of Et$_2$Zn, this reaction offered the corresponding homoallylation product in good yield (82%) and moderate stereoselectivity with 1,3-anti product as the major product (**5a**/**6a**: 70/30). These reactions are highly chemoselective, reacting only with the aldehyde functional group without affecting the enone functionality. Furthermore, all these reactions proceeded in very high facial selectivity in which only the Felkin−Ahn's product (22β)[7] was observed.

The stereochemistry of the homoallylation product **5a** was confirmed by a single-crystal X-ray crystallography (Figure 2).[8] The stereochemical assignment of the minor product **6a** was assigned after comparing the spectroscopic data of the corresponding ketone **8a** with the ketone **7a** obtained from **5a** (Figure 2).[9] The difference in the ^{13}C NMR suggested that it is most probably the Felkin−Ahn's product of the syn isomer. The stereochemical assignments of products of entry 3 to 4 were based on comparison (^{1}H NMR and ^{13}C NMR) with **5a** and **6a**.

Table 1. Nickel-Catalyzed Homoallylation of Chiral Steroidal Aldehyde 3 with Various Dienes[a]



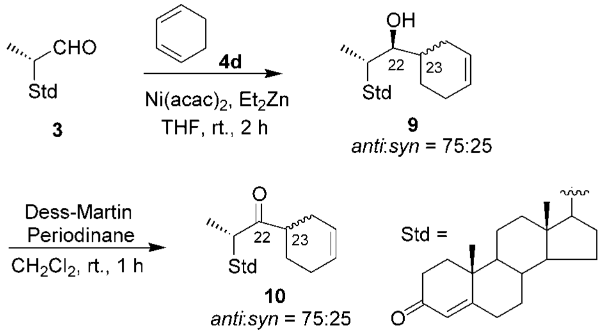
entry	diene		reducing reagent / *t* [h]	yield[b] (%)	selectivity[c] (**5**:**6**)
1	a		Et$_3$B / 12	72	85:15
2	a		Et$_2$Zn / 2	82	70:30
3	b		Et$_2$Zn / 2	84	90:10
4	c		Et$_2$Zn / 2	60[d]	62:38
5	d		Et$_2$Zn / 2	61[e]	75:25

[a] Reaction conditions: Ni(acac)$_2$ (0.1 mmol), aldehyde (1 mmol), dry THF (5 mL), diene (4 mmol), and Et$_2$Zn or Et$_3$B (2.4 mmol). [b] Based on isolated product. [c] Determined by the ^{1}H NMR or weight of diastereomers separated. [d] The diene reacts only at the least substituted position. [e] Product was obtained in 45% yield when Et$_3$B was used instead of Et$_2$Zn.

Similarly, the product **9** obtained from cyclohexadiene (entry 5) was oxidized to the corresponding ketone **10** (Scheme 2). The ratio of the two isomers (75:25) of ketone **10** observed in the ^{1}H NMR, and ^{13}C NMR was consistent with the diastereomeric ratio of alcohol **9**, which indicated the difference in the configuration of C-23.

Interestingly, cyclohexadiene reacted with steroidal aldehyde **3** to afford the desired product in moderate yield and

Scheme 2



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(6) (a) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem.* **1999**, *111*, 410−413; *Angew. Chem., Int. Ed.* **1999**, *38*, 397−400. (b) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386-3388.

(7) (a) Hein, S. J.; Keszler, D. A. *Acta Crystallogr. C.* **1987**, *43*, 2457−2459. (b) Mulzer, J.; Schulze, T.; Strecker, A.; Denzer, W. *J. Org. Chem.* **1988**, *53*, 4098−4103. (c) Mulzer, J.; Kattner, L.; Strecker, A. R.; Schroder, C.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 4218−4229. (d) Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 5, 441−443.

(8) X-ray data for **5a**: C$_{27}$H$_{42}$O$_2$; Fw = 398.61; Orthorhombic; space group *P*2(1)2(1)2; a = 11.9828(8), b = 24.1612(16), c = 8.1881(5) Å; V = 2370.6(3) Å^3; Z = 4; R_1 = 0.0405, wR_2 = 0.0550; GOF = 0.756 for 6678 observations with $I > 2\sigma(I)$.

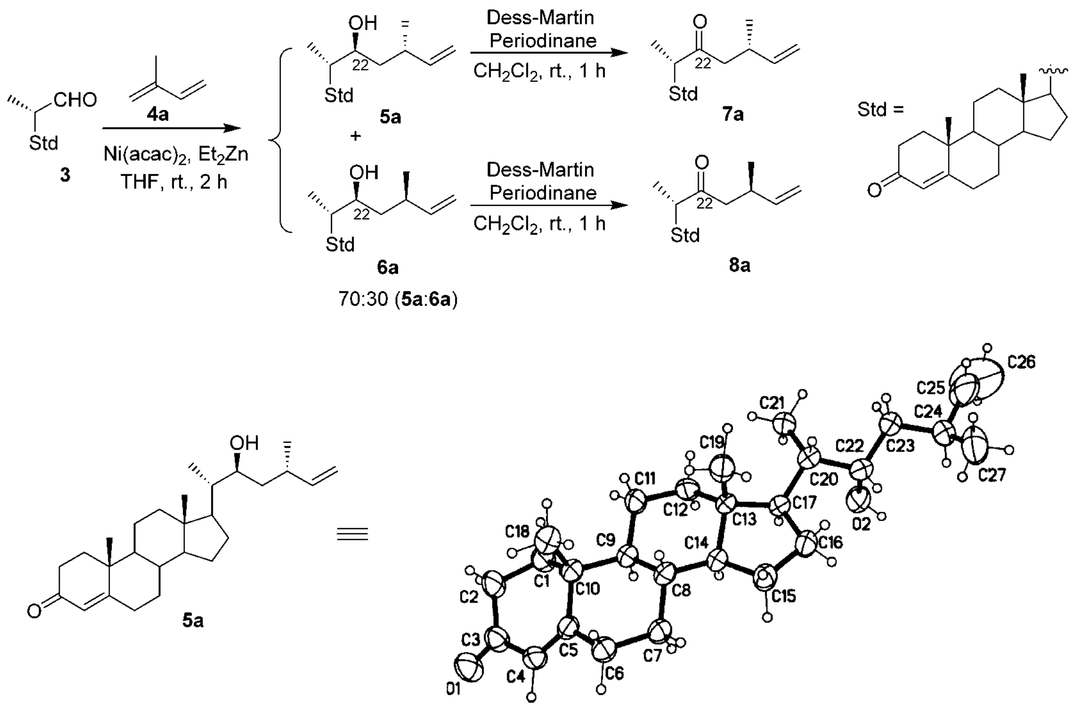
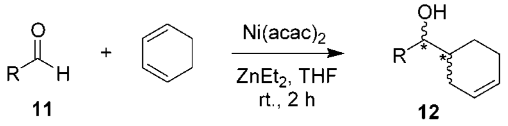


Figure 2. Single-crystal X-ray diffraction analysis of **5a** and clarification of the structure of **6a**.

selectivity. Since the cyclohexane moiety is featured in a large number of biologically important natural products, and the development of synthetic methods other than Diels–Alder and olefin metathesis reactions is needed, the reaction was studied in detail. Accordingly, we focused our attention on the $Et_2Zn/Ni(acac)_2$ condition and expanded this condition to other aldehydes. The results are listed in Table 2.

As shown in Table 2, most of the aldehydes reacted with 1,3-cyclohexadiene smoothly and gave the products in moderate to good yields. It is interesting to note that this cis diene afforded the product in low (1,2)-diastereoselectivity.

Table 2. Nickel-catalyzed Homoallylation of Aldehydes with 1,3-Cyclohexadiene[a]



entry		R	yield (%)[b]	selectivity[c] (anti:syn)
1	**a**	$PhCH_2CH_2$	92	58:42
2	**b**	n-C_5H_{11}	60	60:40
3	**c**	n-C_8H_{17}	55	61:39
4	**d**	c-C_6H_{11}	65	68:32
5	**e**	Ph	62	72:28

[a] Reaction conditions: $Ni(acac)_2$ (0.1 mmol), aldehyde (1 mmol), dry THF (5 mL), 1,3-cyclohexadiene (4 mmol), and Et_2Zn (2.2 mL, 1.1 M solution in toluene, 2.4 mmol). The reaction mixture was stirred for 2 h at room temperature. [b]Based on separated yield. [c]Determined by the ^{1}H NMR. *Interconvertible (relative stereochemistry not determined).

In conclusion, this work has demonstrated the utility of nickel-catalyzed homoallylation strategy as an efficient method for the synthesis of γ,δ-alkenyl alcohols. Excellent Felkin–Ahn's product was obtained for all the dienes when chiral steroidal aldehyde was used. Moderate 1,3-diastereoselectivity was observed. Furthermore, we have found that contrary to what was reported, nickel-catalyzed cyclic diene such as cyclohexadiene afforded the products in good yields. The ability to work with cyclic dienes indicates that a cis nickel oxametallacycle does play a role in the reaction pathway. Furthermore, to account for the low 1,2-diastereoselectivity observed even with this cis diene, we proposed that a less rigid, open-chain transition state may be involved. Efforts to further understand the mechanism and increase the selectivity are currently in progress.

Acknowledgment. We thank the national university of Singapore for generous financial support. We also thank Dr. Jagadese J. Vittal and Ms. Tan Geok Kheng for determining the crystal structure of **5a**.

Supporting Information Available: Complete experiment details, including characterization data for all new compounds and X-ray crystal data for **5a**. This material is available free of charge via the Internet http://pubs.acs.org.

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[9] Products **5a** (white solid) and **6a** (oil) were isolated by flash column chromatography. The structure of **5a** was confirmed by single-crystal X-ray diffraction analysis; treatment of **5a** and **6a**, respectively, with Dess–Martin periodinane gave the corresponding ketone **7a** and **8a** as diastereomers, by which the stereochemistry of **6a** was determined to be 1,3-syn configuration.