cyclohexanedione), involving a transfer of chirality from (*S*)-1-phenylethylamine to generate an enantiopure 3a-(2-nitrophenyl)hexahydroindol-4-one, from which the additional rings of the target molecule are assembled with high stereocontrol. Taking into account our previous work,[6d] the strategy developed here provides a general synthetic route for the enantioselective synthesis of *Strychnos* alkaloids.

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[14] The chemical shifts of our synthetic sample were coincident with those reported for a natural sample of the Wieland – Gumlich aldehyde: G. Massiot, B. Massoussa, M.-J. Jacquier, P. Thépénier, L. Le Men-Olivier, C. Delaude, R. Verpoorte, *Phytochemistry* **1988**, *27*, 3293 – 3304.

[15] Starting from *rac*-**4**, which is prepared from the N-methyl analogue of **2**,[6d] we have also completed the synthesis of the racemic Wieland – Gumlich aldehyde.

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[17] This *ee* value is in agreement with the optical purity of **2**, which was prepared from an (*S*)-1-phenylethylamine with about 96 % *ee* and used as a 97:3 mixture (according to HPLC analysis) of *cis* diastereomers.

Nickel-Catalyzed Homoallylation of Aldehydes and Ketones with 1,3-Dienes and Complementary Promotion by Diethylzinc or Triethylborane**

Masanari Kimura, Hidetaka Fujimatsu, Akihiro Ezoe, Kazufumi Shibata, Masamichi Shimizu, Satoru Matsumoto, and Yoshinao Tamaru*

Allylation of carbonyl compounds is a fundamental process in organic syntheses, and many efficient methodologies have been developed.[1] Besides the allyl derivatives of alkali and alkaline earth metals, those of transition metals[2] and metalloids (e.g., allylstannanes, -silanes, -boranes, etc.)[1] have been utilized for the regio- and stereoselective allylation of carbonyl compounds. Homoallylation could have similar importance in organic transformations; however, this process has received little attention, probably owing to the limited variety of homoallylating agents $CH_2{=}CHCH_2CH_2M$, which are restricted to metals of high electropositivity such as Li and Mg, since the polarity of homoallylic C–M bonds is considerably lower than that of allylic C–M bonds.

By analogy with the stoichiometric homoallylation of carbonyl compounds with $[ZrCp_2(1,3\text{-diene})]$ (Cp = cyclo-

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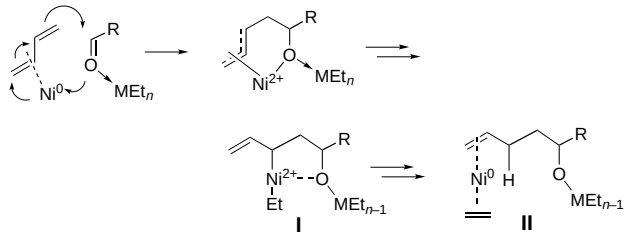
pentadienyl) complexes,[3] we envisaged that a catalytic homoallylation of carbonyl compounds with 1,3-dienes[4] might be realized by an appropriate combination of nickel(0) complexes of 1,3-dienes and ethylmetal compounds Et_nM (Scheme 1). These two might constitute an electron relay,[5]



Scheme 1.

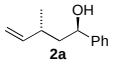
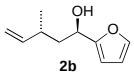
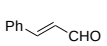
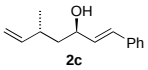
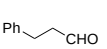
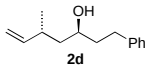
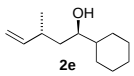
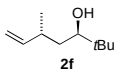
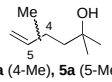
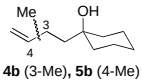
and through a sequence of reactions furnish the σ-allylethylnickel(II) complex **I**, in which the σ-allyl structure is stabilized by coordination with the oxygen atom of the metal alkoxide. By virtue of this σ-allyl nature of complex **I**, the ethyl group would deliver hydrogen to the allylic position that is bound to nickel to produce the nickel(0) bishomoallyl alcohol complex **II**. The nickel(0) center of **II** can be used to repeat the reaction.

As we previously reported,[6] triethylborane, in accordance with the scenario outlined above, acts as a Lewis acid to activate carbonyl compounds and as a reducing agent to promote the homoallylation (reductive coupling) of benzaldehyde with a variety of 1,3-dienes in the presence of a catalytic amount of [Ni(acac)$_2$] [1–10 mol%, acac = acetylacetonato, Eq. (a)]. The reaction proceeds at room temperature and provides bishomoallyl alcohols **1** in good yields and with high regio- and stereoselectivities. 2-Substituted 1,3-dienes react at the C1 position to provide 1,3-*anti*-**1**, and 1-substituted 1,3-dienes furnish either 1,2-*syn*-**1** (from *Z* dienes) or 1,2-*anti*-**1** (from *E* dienes) selectively.

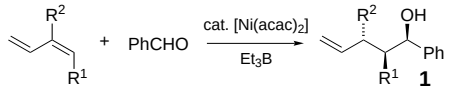
Here we disclose that diethylzinc also promotes the nickel-catalyzed homoallylation regio- and stereoselectively. This Et_2Zn/Ni combination is particularly effective for the homoallylation of saturated aldehydes and ketones, which is either reluctant or entirely unsuccessful with the previously reported Et_3B/Ni combination; hence, these two methods complement each other.

To clarify the scope of the Et_3B/Ni catalytic system, we examined the reaction of carbonyl compounds other than benzaldehyde with isoprene as the 1,3-diene (Table 1). The reaction was successful for aromatic and unsaturated aldehydes and provided 1,3-*anti*-**2** with excellent regio- and stereoselectivities [Table 1, entries 2 and 3; Eq. (b)]; however, it was only moderately successful for saturated aldehydes (entries 4–6). The yields of isolated **2d**–**f** decreased with increasing steric hindrance at the carbonyl group. Ketones were entirely unreactive with the Et_3B/Ni catalyst system, and the expected products were not obtained (entries 7 and 8).

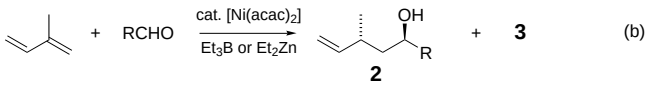
Table 1. Nickel-catalyzed homoallylation of aldehydes and ketones with isoprene with promotion by diethylzinc or triethylborane.[a]

Entry	Substrate	Product	Et_2Zn time [h]	Et_2Zn yield [%] (*syn*:*anti*)[b]	Et_3B time [h]	Et_3B yield [%] (*syn*:*anti*)[b]
1	PhCHO	 **2a**	4	**2a**: 63 (1:15); **3a**: 16[c]	35	**2a**: 90 (1:15); **3a**: 0[c]
2		 **2b**	1	**2b**: 66 (1:3); **3b**: 3[c]	22	**2b**: 77 (1:>20); **3b**: 0[c]
3		 **2c**	0.5	**2c**: 0; **3c**: 28[c]	70	**2c**: 81 (1:>20); **3c**: 0[c]
4		 **2d**	1[d]	**2d**: 73 (1:15)	28	**2d**: 48
5		 **2e**	0.5	**2e**: 83 (1:>20)	10	**2e**: 28
6	*t*BuCHO	 **2f**	1	**2f**: 66 (1:15)	48	**2f**: 16
7		 **4a** (4-Me), **5a** (5-Me)	1	**4a**, **5a**: 69 (5.3:1)	25	**4a**, **5a**: 0
8		 **4b** (3-Me), **5b** (4-Me)	1	**4b**: 61; **5b**: 11	46	**4b**: 0; **5b**: 0

[a] A mixture of [Ni(acac)$_2$] (0.1 mmol), isoprene (4 mmol), aldehyde or ketone (1 mmol), and Et_2Zn (2.4 mmol, 1M in hexane) or Et_3B (2.4 mmol, 1M in hexane) in dry THF (5 mL) was stirred at room temperature under N_2. [b] Yields refer to isolated, spectroscopically homogeneous materials. All products were characterized by ^1H (400 MHz), ^{13}C NMR (100 MHz), and IR spectroscopy, high-resolution mass spectrometry, and/or elemental analyses. The *syn* and *anti* isomers were not separated; the ratios were determined by GLC and ^1H and/or ^{13}C NMR spectroscopy. [c] **3a**: 1-Phenylpropan-1-ol; **3b**: 1-(2-furyl)propan-1-ol; **3c**: 3-phenylpentanal. [d] After addition of Et_2Zn to a mixture of [Ni(acac)$_2$], isoprene, and dihydrocinnamaldehyde at 0 °C, the mixture was stirred at room temperature for 1 h.



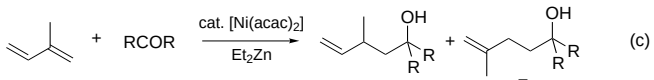
(a)



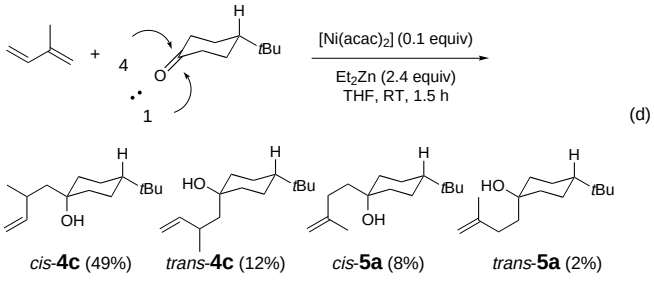
(b)

As shown in entries 1 and 2 of Table 1, the homoallylation of aromatic aldehydes with the Et_2Zn/Ni system is plagued with the ethylation of the aldehydes, which leads to diminished yields of the desired products **2**. Apparently, the nickel catalyst takes part in the ethylation reaction; in the absence of the catalyst, neither ethylation nor homoallylation takes place. The reaction of cinnamaldehyde gave a complex mixture of products, of which only the conjugate addition product 3-phenylpentanal (**3c**) was identified (entry 3).

In contrast to these results, the Et_2Zn/Ni system proved to be advantageous for reactions with saturated aldehydes and ketones. These reactions are completed within 1 h at room temperature and provide the homoallylation products in reasonable yields (entries 4–8). Interestingly, in these reactions no ethylation products are formed. For the reactions with alkyl-substituted aldehydes, 1,3-*anti* isomers **2d–f** were obtained with excellent selectivities (entries 4–6). In the reaction with ketones [entries 7 and 8; Eq. (c)], partial loss of regioselectivity is observed and mixtures of **4** (the C1 addition product) and **5** (the C4 addition product) were obtained in a



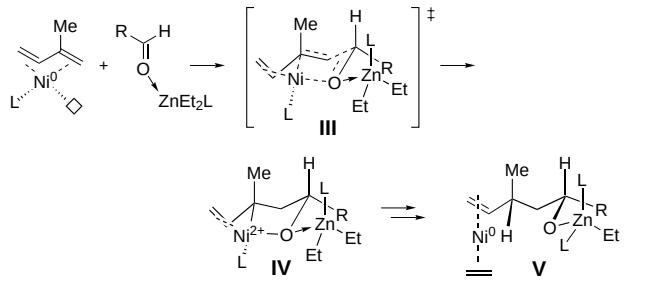
(c)



(d)

ratio of 5:1 to 6:1. Strong preference for equatorial attack over axial attack (ca. 4:1), as was observed for 4-*tert*-butylcyclohexanone [Eq. (d)], suggests that a bulky species participates in nucleophilic addition to the carbonyl group.[7]

Scheme 2 presents our proposed mechanism for the homoallylation of aldehydes with the Et_2Zn/Ni catalyst system. The s-*trans*-isoprenenickel(0) complex[8] selectively reacts at the



Scheme 2.

C1 position, which bears the highest electron density, and the aldehyde carbonyl group is activated by coordination to Et_2Zn. In the cyclic transition state **III**, the aldehyde may be arranged in such a way that the oxygen atom is placed in the vacant site of the nickel(0) complex (symbolized as ◇) and the substituent R in a quasiequatorial position so as to avoid a quasi-1,3-diaxial repulsion that might result from an alternative orientation of the aldehyde. An ethyl group of the resulting 5-vinyl-2-oxa-1-nickelacyclopentane intermediate **IV** migrates from the zinc(II) to the nickel(II) center. β-Hydrogen elimination then delivers the hydrogen atom to the allylic position that is bound to the nickel center with retention of configuration. Reductive elimination of nickel(0) finally produces the Ni^0 complex of ethylene and 1,3-*anti*-**2** (**V**).[9]

In the reactions with ketones, a 1,3-diaxial repulsion is inevitable in a transition state of type **III**. Accordingly, a sterically less demanding C4 addition of isoprene may compete with C1 addition and give a mixture of **4** and **5**.

In conclusion, we have demonstrated that both the Et_2Zn/$[Ni(acac)_2]$ and Et_3B/$[Ni(acac)_2]$ catalysts promote the homoallylation of carbonyl compounds. The former is particularly effective for reactions of saturated aldehydes and ketones, while the latter is advantageous for the homoallylation of aromatic and unsaturated aldehydes. Hence, these two systems complement each other and enable the successful homoallylation of a wide variety of aldehydes and ketones. With both catalytic systems, isoprene reacts with aldehydes to provide 1,3-*anti*-isomers **2** with excellent selectivity.

Experimental Section

2e: To a homogeneous solution of $[Ni(acac)_2]$ (25.6 mg, 0.1 mmol) in dry THF (5 mL) were successively added isoprene (400 μL, 4 mmol), cyclohexanecarbaldehyde (112.2 mg, 1 mmol), and Et_2Zn (2.4 mL, 2.4 mmol in hexane). The mixture was stirred at room temperature for 30 min under N_2 and then quenched by addition of 2 M HCl (3 mL). The mixture was extracted with ethyl acetate (2×20 mL), and the organic extracts were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (16/1) to give **2e** (151 mg, 83%). $R_f = 0.58$ (hexane/ethyl acetate 2/1); GLC retention time: 21.6 min (1,3-*syn*-**2e**: 22.1 min), Thermon-1000 (Shimadzu), initial $T = 80\,^\circ C$ (8 min), heating rate $8\,^\circ C\,min^{-1}$, final $T = 240\,^\circ C$, flow rate 1 mL s^{-1}, He); IR (neat): $\tilde{\nu} = 3340$ (s), 1060 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (d, $J =$ 6.6 Hz, 3H), 1.03–1.36 (m, 7H), 1.42 (m, 1H, coalesces to dd, $J = 7.7$, 14.1 Hz on irradiation at $\delta = 3.47$), 1.46 (m, 1H, coalesces to dd, $J = 6.6$, 14.1 Hz on irradiation at $\delta = 3.47$), 1.57 (br s, 1H), 1.61–1.69 (m, 2H), 1.70–1.81 (m, 2H), 2.34 (m, 1H, coalesces to dt, $J = 6.6$, 7.7 Hz on irradiation at $\delta = 1.01$), 3.47 (m, 1H), 4.94 (br d, $J = 10.3$ Hz, 1H), 5.04 (br d, $J = 17.4$ Hz, 1H), 5.81 (ddd, $J = 7.7$, 10.3, 17.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.9$, 26.3, 26.4, 26.6, 27.6, 29.3, 35.4, 41.3, 44.0, 74.5, 112.6, 145.5 (1,3-*syn*-**2e**: $\delta = 21.5$, 26.3, 26.4, 26.6, 27.9, 29.1, 34.9, 41.2, 44.2, 73.8, 113.5, 144.2). Satisfactory elemental analysis.

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[5] A similar electron relay was suggested for the nickel(0)-catalyzed reductive coupling of aldehydes and alkynes to give allylic alcohols: E. Oblinger, J. Montgomery, *J. Am. Chem. Soc.* **1997**, *119*, 9065 – 9066.
[6] M. Kimura, A. Ezoe, K. Shibata, Y. Tamaru, *J. Am. Chem. Soc.* **1998**, *120*, 4033 – 4034.
[7] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 735.
[8] Since the cyclic dienes 1,3-cyclohexadiene and 1,3-cyclooctadiene give intractable mixtures of products, the s-*trans*-dienenickel(0) complex is assumed to be a reactive species.
[9] 5-Vinyl-2-oxa-1-palladacyclopentanes, the palladium analogues of **IV**, undergo ring opening to give mixtures of dienes and carbonyl compounds, the formal reverse of the present reaction: H. Harayama, T. Kuroki, M. Kimura, S. Tanaka, Y. Tamaru, *Angew. Chem.* **1997**, *109*, 2449 – 2451; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2352 – 2354.

Biosynthesis of Psoralen: Mechanism of a Cytochrome P450 Catalyzed Oxidative Bond Cleavage

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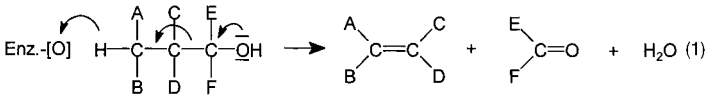
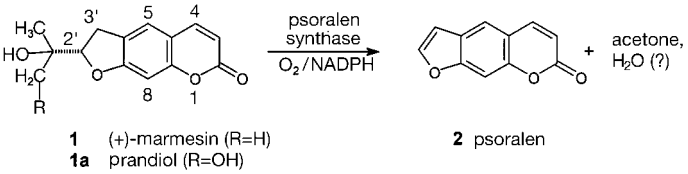
The oxidative cleavage of C–C bonds that leads to olefins and a carbonyl fragment is a common transformation in secondary metabolism and is generally catalyzed by enzymes requiring molecular oxygen as a cofactor. Typical examples are given by the formation of homo- and norterpenes from isoprenoid precursors or by the biosynthesis of 1-alkenes from fatty acids. In general, the resulting unsaturated products are metabolites of precursors that already carry an oxygen atom [Eq. (1); Enz. = enzyme].[1] Such transformations have been



well studied for steroids, where angular methyl groups are oxidatively removed with concomitant introduction of a double bond into the carbon skeleton.[2] The reactions are catalyzed by enzymes belonging to the large family of cytochrome P450. Specific enzymes endowed with multiple catalytic activities catalyze all required transformations, namely, 1) the functionalization of the unactivated methyl group to an alcohol, 2) the subsequent oxidation to an aldehyde, and 3) the actual oxidative bond cleavage generating the unsaturated nor-steroid and formic acid.[3–6]

It is as yet unknown, whether or not this sequential degradation is representative for other oxidative bond cleavage reactions that lead to unsaturated natural products. For example, the dealkylation of (+)-marmesin (**1**) to the phototoxic furocoumarin psoralen (**2**) is achieved by the psoralen synthase (Scheme 1), an enzyme that also belongs to



1 (+)-marmesin (R=H)
1a prandiol (R=OH)
2 psoralen

Scheme 1. Cytochrome P450 catalyzed dealkylation of **1**.

the large family of cytochrome P450 catalysts.[7] This dealkylation is of central importance for the biosynthesis of all other linear furocoumarins, since the resulting psoralen (**2**) serves as an intermediate en route to the other members of this family.[8] Linear and angular furocoumarins are widespread in the plant kingdom, especially in the order of the Apiaceae, where they are produced in response to insect injury and infection.[9] The existence of a natural product such as the diol **1a** (prandiol)[10, 11] could indeed suggest a stepwise degradation of marmesin to psoralen that is analogous to the dealkylation of steroids. Here we disclose that the dealkylation of marmesin indeed does not involve a sequential oxidative degradation of the 2-hydroxy-2-propyl substituent, but proceeds in a single step to yield equimolar amounts of psoralen and acetone. The previously postulated, but now for the first time proven, one-step degradation[12] may be representative for other oxidative transformations that lead to unsaturated nor- and seco-compounds in nature.

Unambiguous evidence for the one-step dealkylation and details of the stereochemical course of the reaction follow from transformations of the specifically deuterated precursors **3** – **7**[13] by microsomes from elicited cell cultures of *Ammi majus* and subsequent analysis of the resulting products.[14] Thus, if the microsomes are treated with [$^2H_7$]marmesin (**7**) in the presence of NADPH and oxygen,[7] equimolar amounts of [8-$^2H_1$]psoralen (**8**) and [$^2H_6$]acetone are formed (Scheme 2). Both products can be identified and quantified by GC-MS. Product **8** is readily distinguished from traces of natural [8-^{1}H]psoralen because of a remaining deuterium label at C8. About 20 – 40 % of the resulting psoralen are further oxidized to bergaptol (5-hydroxypsoralen).[7] [$^2H_6$]Acetone is unambiguously identified and quantified after derivatization to the corresponding imine with pentafluorobenzylhydroxylamine.[15] With respect to the conservation of all six hydrogen isotopes in the C_3 fragment, an intermediate functionalization of the 2-hydroxy-2-propyl substituent is excluded (see **1a**).

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