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Ni^0-catalyzed regio- and stereoselective coupling reaction of Me_3B, isoprene, and aldehydes

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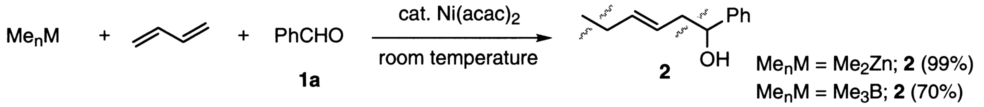
Abstract

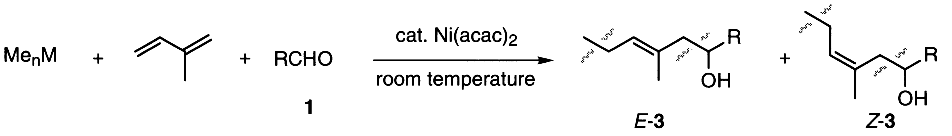
In the presence of $Ni(acac)_2$ (0.1 equiv.), the three components of trimethylborane, isoprene, and aromatic and aliphatic aldehydes combine to produce 1-substituted 3-methyl-3-hexenols (**3**) in good yield and with high regio- and stereoselectivity (E:Z > 13:1).

Keywords: aldehydes; boron and compounds; dienes; nickel and compounds.

Transition metal-catalyzed processes that allow the coupling of two different components at the 1,2- or 1,4-positions of 1,3-dienes in one pot are particularly useful in the synthesis of highly functionalized molecules, especially when they utilize simple, readily available starting materials and provide products with high regio- and stereoselectivity.[1]



(1)



(2)

Me$_n$M = Me$_2$Zn, R = Ph; **3a**: 92%; (E)-**3a**:(Z)-**3a** = 2.2:1
Me$_n$M = Me$_3$B, R = Ph; **3a**: 56%; (E)-**3a**:(Z)-**3a** = 20:1

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Recently, we have demonstrated that, in the presence of a catalytic amount of Ni(acac)$_2$ (acac = acetylacetonate), 1,3-butadiene reacts at the C1 and C4 positions with Me$_2$Zn and benzaldehyde to provide (*E*)-1-phenyl-3-hexenol (**2**) in good yield and with excellent stereoselectivity (Eq. (1)).[2] Isoprene undergoes a similar three-component connection reaction, combining regioselectively with benzaldehyde at the C1 position and with Me$_2$Zn at the C4 position (Eq. (2)). The yield is quite satisfactory. Unfortunately, however, the stereoselectivity is rather poor, and a mixture of (*E*)- and (*Z*)-1-phenyl-3-methyl-3-hexenols (**3a**) is produced in a ratio of 2.2:1.

Here we would like to disclose that Me$_3$B is able to take the place of Me$_2$Zn for the above mentioned nickel-catalyzed three-component connection reaction and affords **2** and **3a** in reasonable yield (Eq. (1) and Eq. (2)). Especially rewarding here is the excellent stereoselectivity that is attained in the reaction with isoprene; a mixture of (*E*)- and (*Z*)-**3a** was produced in a ratio of as high as 20:1. Furthermore, to the best of our knowledge, this is the first example demonstrating that the methyl group of trimethylborane is capable of being accommodated in the products **2** and **3a**, most likely through intermediary transmetallation of the methyl group from B to Ni^{2+} of π-allylnickel intermediates (vide infra).

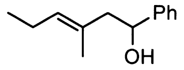
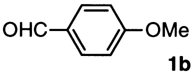
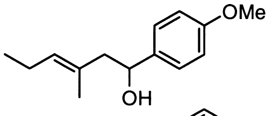
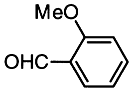
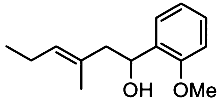
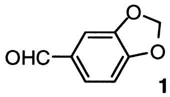
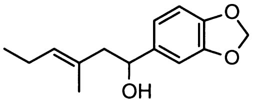
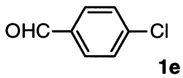
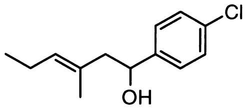
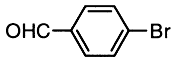
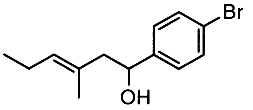
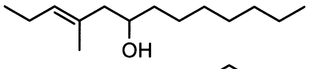
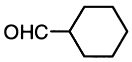
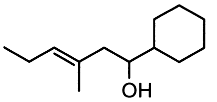
From a practical point of view, there seemed to be no advantages to using Me$_3$B in place of Me$_2$Zn for the reaction with butadiene; Me$_2$Zn exclusively provides (*E*)-**2** in much better yield than Me$_3$B (Eq. (1)). Accordingly, we focused our attention on the reaction of Me$_3$B with isoprene toward aldehydes. Trimethylborane (4 mmol) was generated by adding either MeLi (12 mmol, ether solution) or MeMgBr (12 mmol, ether solution) into BCl$_3$ (4 mmol, *n*-heptane solution) at 0°C. After stirring for 2 h at 0°C, the Me$_3$B solution was transferred into a THF (10 ml) solution of isoprene (8 mmol), benzaldehyde (2 mmol), and Ni(acac)$_2$ (0.2 mmol) through a cannula, and this mixture was stirred under N$_2$ for several hours at room temperature. After usual extractive workup (ethyl acetate) and purification by flash column chromatography over silica gel (hexane:ethyl acetate 64:1, v/v), **3a** was isolated.[3] Results for the reactions with Me$_3$B generated from MeLi and with that generated from MeMgBr are summarized in runs 1 and 2, respectively, in Table 1. In both cases, the yields are moderate; however, the stereoselectivity is remarkably good. The ratio of (*E*)- and (*Z*)-**3a** was determined accurately on the basis of the base-line separated resonances of the C-6 methyl protons and of one of the C-2 methylene protons in their ^{1}H NMR spectra (400 MHz, CDCl$_3$): δ 0.97 (t, J = 7.2 Hz, 3H) and 2.41 (dd, J = 3.8, 13.8 Hz, 1H) for (*E*)-**3a**; δ 0.90 (t, J = 7.3 Hz, 3H) and 2.63 (dd, J = 9.0, 13.4 Hz, 1H) for (*Z*)-**3a**. The structures of (*E*)- and (*Z*)-**3a** were determined unequivocally on the basis of their ^{13}C NMR spectra.

Results obtained for the reactions of aromatic aldehydes bearing electron-donating or electron-withdrawing substituents with Me$_3$B, generated from BCl$_3$ and MeLi, are summarized in runs 3–7 in Table 1. Generally, the stereoselectivity is quite satisfactory, providing (*E*)-**3** in high preference over (*Z*)-**3** [(*E*)-**3**:(*Z*)-**3** > 13:1]. The yield is also excellent, except that in run 7. The reason for the fall in the yield for the reaction of *p*-bromobenzaldehyde (**1f**) is not clear at present; no trace amount of 3-methyl-1-*p*-tolyl-3-hexenol, the product being expected to be produced from **3f** through substitution of Me for Br (the Kumada-Tamao coupling reaction), was detected in the reaction mixture.

Aliphatic aldehydes underwent the three-component connection reaction with the similar ease and efficiency (runs 8 and 9, Table 1). In these cases, the *E*-selectivity turned out to be almost perfect and neither (*Z*)-**3g** nor (*Z*)-**3h** was detected in the ^{1}H and ^{13}C NMR spectra of the products isolated by flash column chromatography.

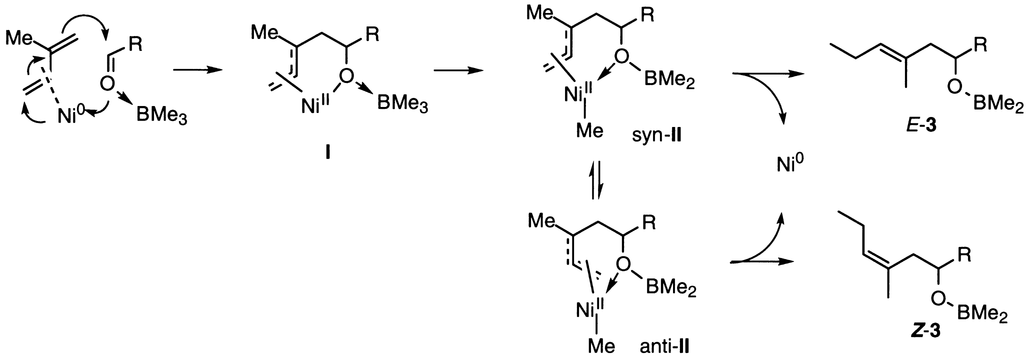
Table 1

Ni^0-catalyzed (*E*)-selective three-component connection reaction of Me_3B, isoprene, and aldehydes **1**[a]

run	aldehyde **1**	reaction time (h)	product **2** (isolated yield) [b] [*E*:*Z*] [c]
1	OHC–Ph **1a**	2	 **3a** (56) [20:1]
2	**1a**	4	**3a** (63) [20:1] [d]
3	 **1b**	5	 **3b** (85) [13:1]
4	 **1c**	22	 **3c** (87) [13:1]
5	 **1d**	24	 **3d** (97) [15:1]
6	 **1e**	20	 **3e** (93) [17:1]
7	 **1f**	3	 **3f** (50) [16:1]
8	OHC-C_7H_{15} **1g**	17	 only *E*-**3g** (54)
9	 **1h**	12	 only *E*-**3h** (80)

a) General reaction conditions: Me_3B [4 mmol, prepared from BCl_3 (4 mmol in *n*-heptane) and MeLi (12 mmol in ether)] was added into a homogeneous solution of isoprene (8 mmol), an aldehyde **1** (2 mmol), and $Ni(acac)_2$ (0.2 mmol) in dry THF (10 ml), and the mixture was stirred at ambient temperature for the period indicated under N_2. b) Yield refers to the combined isolated yield of (*E*)- and (*Z*)-**3**, which contain an unidentified by-product (< 8%) common to all runs. All the products were properly characterized by IR, ^1H, ^{13}C NMR, and HRMS or elemental analysis. Only the (*E*)-isomers could be obtained in a stereochemically homogeneous state by means of recycle GPLC ($CHCl_3$ as an eluent). c) The ratio was determined on the basis of ^1H and/or ^{13}C NMR spectra (see text). d) Me_3B [4 mmol, prepared from BCl_3 (4 mmol in *n*-heptane) and MeMgBr (12 mmol in ether)] was used.

The reaction may proceed via a similar mechanism to that proposed for the three-component connection reaction of Me_2Zn, isoprene and benzaldehyde, as depicted in Scheme 1.[2] Among the steps, the particular step involving the methyl group transfer from B to Ni^{2+}, i.e. leading oxy-π-allylnickel(II) intermediate **I** to methyl-π-allylnickel(II) intermediate **II**, remains speculative at present. Many precedents indicate that a methyl (or alkyl) group is a typical substituent of organometalloids and their ate complexes (B,[4] Si,[5] Sn[6]) that can be transmetallated only with great difficulty. In fact, Kobayashi et al.[7] have shown that only the aryl and vinyl groups of such ate complexes as aryl(Me)B$(OR)_2$ and vinyl(Me)B$(OR)_2$ are selectively transferred onto π-allylnickel(II)



Scheme 1.

intermediates. Furthermore, our attempts to use Ph_3B (THF solution, Aldrich) as a phenylating agent and $Me_4B^-M^+$ as a methylating agent for the present three-component connection reaction all met with failure. The former reaction did not furnish the expected product at all, and the latter reaction provided **3a** in low yield: 18% with $Me_4B^-Li^+$ (room temperature for 21 h); 18% with $Me_4B^-Mg^{2+}Br^-$ (room temperature for 24 h) under otherwise identical conditions, shown in footnote a, Table 1. Nevertheless, we still favor the mechanism involving **I** and **II** as intermediates (Scheme 1).[8] In an intermediate **I**, electron donation from oxygen to B, an efficient orbital overlap between the B–Me bond, and an empty orbital on Ni^{2+} that lie in close proximity to each other might well cooperate to promote the methyl group migration from B to Ni^{2+}.[9,10] Reductive elimination through *syn*-**II** and *anti*-**II** that equilibrate to each other via a π–σ mechanism might provide (*E*)-**3** and (*Z*)-**3**, respectively, and at the same time regenerate Ni^0 as well. The selective formation of (*E*)-**3** might owe its origin to the higher thermodynamic stability of *syn*-**II** over *anti*-**II**, which is suggested by molecular modeling studies.

Acknowledgements

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$C_{13}H_{18}O$: 190.1358; found *m*/*z* (relative intensity): 190.1359 (M^+, 6), 107 (100). (*Z*)-3-Methyl-1-phenyl-3-hexen-1-ol [(*Z*)-**3a**]: ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.74 (br s, 3H), 1.91–2.10 (m, 2H, coalescing to dq, J = 6.8, 7.3 Hz, by irradiation at 1.74), 2.29 (dd, J = 4.8, 13.4 Hz, 1H), 2.63 (dd, J = 9.0, 13.4 Hz, 1H), 4.79 (dd, J = 4.8, 9.0 Hz, 1H), 5.36 (t, J = 6.8 Hz, 1H), 7.25–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.3, 23.7, 42.3, 72.2, 125.8, 127.5, 128.3, 131.4, 131.5, 144.3.

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