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Communication

Nickel-catalysed three-component connection reaction of a phenyl group, conjugated dienes, and aldehydes: stereoselective synthesis of (*E*)-5-phenyl-3-penten-1-ols and (*E*)-3-methyl-5-phenyl-3-penten-1-ols

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This manuscript is dedicated to Professor Jean Normant on the occasion of his 65th birthday for his outstanding contribution to the development of organometallic chemistry

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Abstract

In the presence of 10 mol% of Ni(acac)$_2$, Ph$_2$Zn reacts with 1,3-butadiene and aldehydes at room temperature to give 1-alkyl and 1-aryl substituted (*E*)-5-phenyl-3-penten-1-ols (**3**) in good yields. Under similar conditions, the three components of Ph$_3$BZnEt$_2$, isoprene, and aldehydes combine with each other to furnish 1-alkyl and 1-aryl substituted (*E*)-3-methyl-5-phenyl-3-penten-1-ols (**5**) in good yields. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Dienes; Nickel; Organoboranes; Organozincs; Multi-component connection

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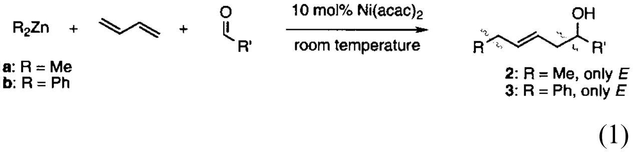
1,3-Dienes have long been utilised as one of the most versatile building blocks in organic synthesis, especially in the field of transition-metal catalysed reactions for the synthesis of complex molecules [1]. Since the isoprene C-5 unit is found abundantly in natural products, the 1,4-difunctionalisation reaction of isoprene with different kinds of reactants is particularly useful, provided the stereochemistry of the tri-substituted double bond (*E* or *Z*) as well as the regiochemistry (head or tail) of the products can be regulated appropriately.

Recently, we have developed novel nickel-catalysed three-component connection reactions of organometallic reagents, 1,3-dienes, and carbonyl compounds that furnish a variety of 4-penten-1-ols (via homoallylation of carbonyls with dienes) [2,3] and 3-penten-1-ols (via allylation of carbonyls with dienes) [4,5] with high regio- and stereoselectivity.

In the latter nickel-catalysed allylative three-component connection reactions, 1,3-butadiene underwent facile reaction with Me$_2$Zn and aldehydes at room temperature to furnish (*E*)-3-hexen-1-ols (**2**) in excellent yields (Eq. (1)). Isoprene also reacted regioselectively with Me$_2$Zn at the C-4-position and with aldehydes at the C-1 position to give 3-methyl-3-hexen-1-ols (**4**) in good yields (Eq. (2)) [4]. The reaction, however, displayed poor stereoselectivity, giving rise to mixtures of (*E*)- and (*Z*)-**4** in the ratios of ca. 3:1. The stereoselectivity was improved greatly by the use of Me$_3$B in place of Me$_2$Zn, where the (*E*)-**4** isomers were produced either exclusively (for alkyl aldehydes) or highly selectively (> 13:1, for aromatic aldehydes) (Eq. (3)) [5].



(1)

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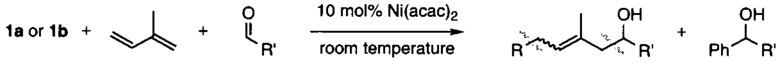
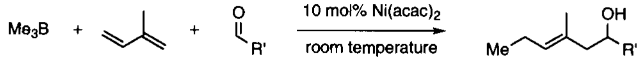


(*E*)- and (*Z*)-**4**: R = Me
(*E*)- and (*Z*)-**5**: R = Ph
6

(2)



(*E*)-**4** (*E*:*Z* = >13:1)

(3)

Here we would like to report that the three-component connection reactions of Ph–1,3-butadiene–aldehydes and Ph–isoprene–aldehydes proceed nicely and furnish (*E*)-5-phenyl-3-penten-1-ols (**3**) and (*E*)-3-methyl-5-phenyl-3-penten-1-ols (**5**), respectively, in high yields and with excellent stereoselectivity under the catalysis of a nickel complex.

We expected that the three-component connection reaction of Ph_2Zn–dienes–aldehydes would be rather problematic, since, as compared with Me_2Zn, Ph_2Zn is so reactive that it might possibly react with aldehydes without incorporating dienes as the reaction partner [6]. Accordingly, we undertook preliminary experiments for the reaction of Ph_2Zn with benzaldehyde in the absence and in the presence of a nickel catalyst (Table 1). In fact, Ph_2Zn reacted rather slowly with benzaldehyde at room temperature (runs 1 and 2). However, in the presence of 10 mol% of $Ni(acac)_2$ [acac = acetylacetonate], it underwent facile reaction. The reaction was complete within 20 min at room temperature and provided benzhydrol in a quantitative yield (run 3).

Despite these somewhat discouraging preliminary results, to our pleasant surprise, the three-component connection reaction did proceed nicely for the reaction with 1,3-butadiene and aldehydes (runs 1–4, Table 2). Except for the reaction with dihydrocinnamaldehyde (run 2, Table 2), the direct phenylation of aldehydes presented little difficulty and the expected products **3** were obtained in reasonable yields and with excellent *E*-selectivity. No (*Z*)-**3** isomers were detected. Furthermore, 1-substituted 9-phenylnona-3,7-dien-1-ols, the type of compounds obtained as the major side products in the reaction of Me_2Zn–1,3-butadiene–aldehydes [4], were not formed.

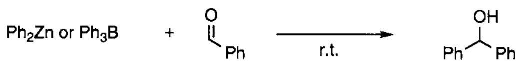
For the reaction with isoprene, on the other hand, the phenylation of aldehydes turned out to be a very serious problem, especially for the reactions with reactive aldehydes (benzaldehyde and alkyl aldehydes that do not possess substituents at the α-position) (runs 5 and 6, Table 2). In these cases, the expected products **5a** and **5b** were produced only as the minor products. An attempt to minimise **6a** by adding slowly the Ph_2Zn solution into the solution of benzaldehyde, isoprene, and $Ni(acac)_2$ over 1 h was unsuccessful, and **5a** and **6a** were obtained in 38 and 39% yields, respectively. For the reaction with less reactive secondary and tertiary alkyl aldehydes, the expected products **5c** and **5d** were obtained in moderate yields (runs 7 and 8).

In order to circumvent the competitive phenylation of aldehydes, we next examined Ph_3B as the phenylating agent, since our preliminary study indicated that Ph_3B was unreactive toward benzaldehyde even in the presence of nickel catalysts (runs 4–6, Table 1).

Although $Ni(acac)_2$ served nicely as the catalyst for the connection reaction of Me_3B–isoprene–aldehydes (Eq. (3)) [5], it turned out to be completely ineffective for the version of Ph_3B–isoprene–aldehydes and no **5** formed at all. In sharp contrast to this, $Ni(cod)_2$ [cod = cyclooctadiene] promoted the reaction effectively (Table 3). In the presence of 10 mol% of $Ni(cod)_2$, the reaction proceeded smoothly at room temperature and furnished

Table 1

Reaction of Ph_2Zn and Ph_3B with benzaldehyde in the presence and in the absence of nickel catalysts [a]



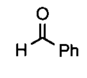
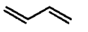
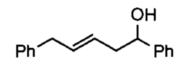
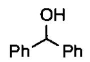
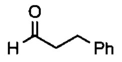
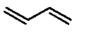
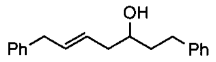
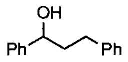
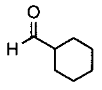
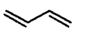
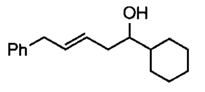
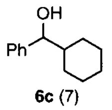
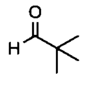
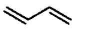
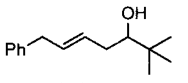
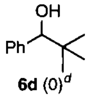
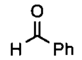
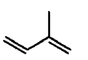
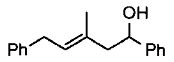
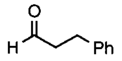
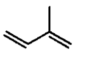
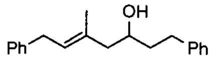
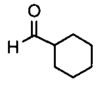
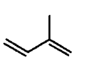
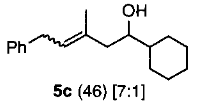
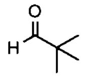
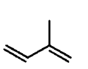
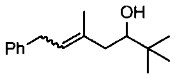
Run	Phenylating agent	Nickel catalyst	Reaction time (h)	Benzhydrol (% yield) [b]
1	Ph_2Zn	None	5	81
2	Ph_2Zn	None	0.3	65
3	Ph_2Zn	$Ni(acac)_2$	0.3	96
4	Ph_3B	None	36	0 [c]
5	Ph_3B	$Ni(acac)_2$	10	0 [c]
6	Ph_3B	$Ni(cod)_2$	10	0 [c]

[a] A mixture of benzaldehyde (1 mmol), Ph_2Zn (1.2 mmol), and a nickel catalyst (0.1 mmol, if indicated) in dry THF (5 ml) was stirred at room temperature under N_2.

[b] Yields refer to the isolated yields of benzhydrol by means of column chromatography over silica gel.

[c] No formation of benzhydrol was confirmed by means of TLC and GPLC.

Table 2
Synthesis of 5-phenyl-3-penten-1-ols (**3**) and 3-methyl-5-phenyl-3-penten-1-ols (**5**) via the three component reaction of Ph_2Zn, 1,3-dienes, and aldehydes in the presence of $Ni(acac)_2$[a]

Run	Aldehyde	Diene	Reaction time (h)	Product **5** (% yield)[b] [*E*:*Z*][c]	Product **6** (% yield)[b]
1			0.3	 **3a** (61) [onyl *E*]	 **6a** (23)
2			0.3	 **3b** (34) [onyl *E*]	 **6b** (39)
3			0.3	 **3c** (68) [onyl *E*]	 **6c** (7)
4			3	 **3d** (70) [onyl *E*]	 **6d** (0)[d]
5			0.3	 **5a** (27) [onyl *E*]	**6a** (59)
6			0.3	 **5b** (16) [onyl *E*]	**6b** (57)
7			0.3	 **5c** (46) [7:1]	**6c** (21)
8			3	 **5d** (46) [20:1]	**6d** (0)[d]

[a] A mixture of an aldehyde (1 mmol),1,3-buadiene (4 mmol) or isoprene (4 mmol), Ph_2Zn [1.2 mmol, prepared from PhMgBr (2.4 mmol) and $ZnCl_2$ (1.2 mmol)], and $Ni(acac)_2$ (0.1 mmol) in dry THF was stirred at ambient temperature under N_2. [b] Yields refer to the isolated spectroscopically homonegeous materials. [c] The *E*,*Z*-ratios were determined by means of ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz). [d] The alcohol could not be detected.

5 in reasonable yields, irrespective of the kinds of aldehydes. The stereoselectivity, however, was not satisfactory: In most cases, (*E*)- and (*Z*)-**5** were produced in the ratios of ca. 10:1.

The ratios of (*E*)- and (*Z*)-**5** could be determined with high accuracy on the basis of the base-line separated resonances of one of the diastereotopic C-2 methylene protons in their ^1H-NMR spectra (400 MHz, $CDCl_3$) [7]. The stereochemistry of (*E*)- and (*Z*)-**5** was determined unequivocally on the basis of their ^{13}C-NMR spectra (100 MHz) [7].

The product was accompanied with **6** in substantial quantities (Table 3). In the light of the results shown in runs 4–6 (Table 1), the origin of **6** is not clear at present. However, this is, to the best of our knowledge, the first example that indicates that Ph_3B is capable of undergoing the Grignard-like addition to aldehydes [8–10] under certain conditions in the presence of a nickel complex.

Encouraged by the favourable reaction features of Ph_3B as the phenylating agent, we next examined the reaction with the ate complexes of Ph_3B. The organoborate complexes were generated in situ by the reaction of Ph_3B with an equal amount of an organometallic reagent.

The results obtained for the reaction with benzaldehyde and a variety of organoborates are summarised in runs 1–6 in Table 4. As is apparent from these results, the reactivity markedly depended on the kinds of the organic substituents as well as the metal counter ions of these borate complexes. The most striking feature regarding the dependence of reactivity on the metal counter ions was observed for the pair of reactions with Ph_4BNa (run 4) and Ph_4BMgBr (run 3). Ph_4BNa was ineffective, and neither **5a** nor **6a** was produced in any detectable amount after heating at 35°C for 23 h. On the other hand, Ph_4BMgBr displayed modest reactivity at room temperature. Both the starting aldehyde and the product **5a** were detected in comparable amounts on the TLC monitored after 24 h at room temperature. The reaction completed after prolonged heating at 50°C for 10 h; however, **5a** was isolated in only modest yield.

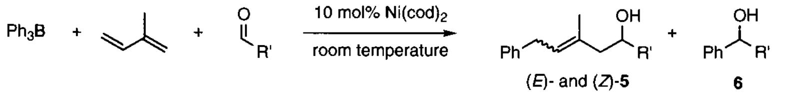
Of all the mixed organoborates, Ph_3BMR (MR = MeLi, MeMgBr, Me_2Zn, Et_2Zn), was transferred selectively the phenyl group to yield **5a** in remarkably high yields and with excellent stereoselectivity (runs 1, 2, 5, and 6, Table 4). Among these, Ph_3BZnEt_2 was the most reactive and with this mixed borate the reaction was complete in less than 2 h at room temperature (run 6, Table 4).

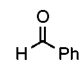
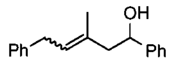
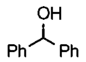
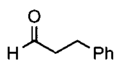
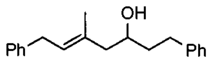
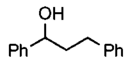
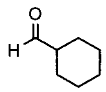
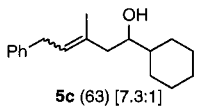
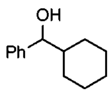
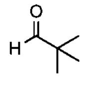
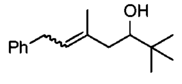
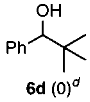
The results obtained for the reactions of aliphatic aldehydes with Ph_3BZnEt_2 are summarised in runs 7–9 (Table 4). In all cases, the (*E*)-**5** isomers were obtained in acceptable yields and with excellent (*E*)-stereoselectivity.

The reaction was performed typically as follows (run 6, Table 4): Into a solution of Ph_3B (2.4 mmol, 0.25 M in THF, Aldrich) kept at 0°C was added a solution of Et_2Zn (2.4 mmol, 1 M in hexane, Aldrich) under N_2 via a syringe. The mixture was stirred at room temperature for 1 h and then transferred through a cannula into a flask containing a solution of $Ni(acac)_2$ (25.7 mg, 0.1 mmol), isoprene (400 μl, 4 mmol), and benzaldehyde (106 mg, 1 mmol) in dry THF (5 ml) at room temperature. The resultant solution was stirred at the same temperature for 1.5 h and then poured onto an ice–2 M HCl mixture. The mixture was extracted with EtOAc (2 × 25 ml), and the combined organic phase was washed with sat. $NaHCO_3$ (2 × 20 ml) and then with brine (2 × 20 ml), dried over $MgSO_4$, and concentrated in vacuo. The colourless residue was subjected to flash column chromatography over silica gel (hexane–ethyl acetate 64:1) to give (*E*)-3-methyl-1,5-diphenyl-3-penten-1-ol ((*E*)-**5a**) in 80% yield (202 mg) [7].

In conclusion, we have developed the nickel-catalysed three-component connection reaction of a phenyl group, 1,3-dienes, and aldehydes. For the reaction with 1,3-butadiene, Ph_2Zn serves as an efficient phenylating reagent and 1-alkyl and 1-aryl substituted 5-phenyl-3-penten-1-ols (**3**) are obtained in good yields. For the reaction with isoprene, 1-alkyl and 1-aryl substituted 3-methyl-5-phenyl-3-penten-1-ols (**5**) are obtained in

Table 3
Synthesis of 3-methyl-5-phenyl-3-penten-1-ols (**5**) via the three component reaction of Ph_3B, isoprene, and aldehydes in the presence of $Ni(cod)_2$[a]

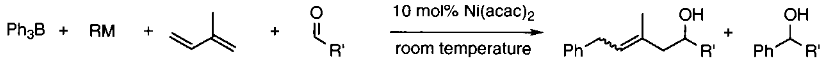


Run	Aldehyde	Reaction time (h)	Product **5** (% yield)[b] [*E*:*Z*][c]	Product **6** (% yield)[b]
1		10	 **5a** (62) [10:1]	 **6a** (8)
2		27	 **5b** (38) [only *E*]	 **6b** (22)
3		24	 **5c** (63) [7.3:1]	 **6c** (20)
4		28	 **5d** (71) [10:1]	 **6d** (0)[d]

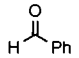
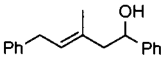
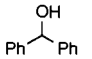
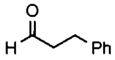
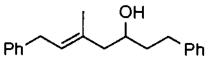
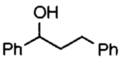
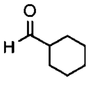
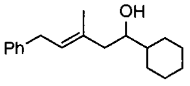
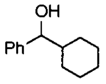
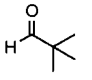
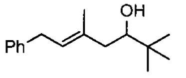
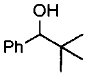
[a] A mixture of an aldehyde (1 mmol), isoprene (4 mmol), Ph_3B (2.4 mmol), and $Ni(cod)_2$ (0.1 mmol) in dry THF was stirred at ambient temperature under N_2. [b] Yields refer to the isolated spectroscopically homonegeous materials. [c] The *E*,*Z*-ratios were determined by means of ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz). [d] The alcohol could not be detected.

Table 4

Synthesis of 3-methyl-5-phenyl-3-penten-1-ols (**5**) via the three component reaction of Ph_3B, isoprene, and aldehydes in the presence of $Ni(acac)_2$ and organometallic reagents (RM)[a]



(*E*)- and (*Z*)-**5** **6**

Run	Aldehyde	RM	Time (h)/Temp (°C)	Product **5** (% yield)[b] [*E*:*Z*][c]	Product **6** (% yield)[b]
1		MeLi	24/25	 **5a** (86) [only *E*]	 **6a** (8)
2		MeMgBr	20/25 then 12/50	**5a** (91) [10:1]	**6a** (0)
3		PhMgBr	24/25 then 10/50	**5a** (49) [10:1]	**6a** (0)
4		Ph_4BNa[d]	23/35	no reaction	
5		Me_2Zn	15/25	**5a** (80) [only *E*]	**6a** (17)
6		Et_2Zn	1.5/25	**5a** (80) [only *E*]	**6a** (0)
7		Et_2Zn	2/25	 **5b** (60) [only *E*]	 **6b** (20)
8		Et_2Zn	2/25	 **5c** (60) [only *E*]	 **6c** (10)
9		Et_2Zn	10/25	 **5d** (63) [20:1]	 **6d** (0)[e]

[a] A mixture of an aldehyde (1 mmol), isoprene (4 mmol), Ph_3B (2.4 mmol), RM (2.4 mmol), and $Ni(acac)_2$ (0.1 mmol) in dry THF was stirred under N_2 at the temperature indicated. [b] Yields refer to the isolated spectroscopically homonegeous materials. [c] The *E*,*Z*-ratios were determined by means of ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz). [d] Ph_4B Na (2.4 mmol) was used as received (Aldrich). [e] The alcohol could not be detected.

good yields when isoprene is subjected to the reaction with Ph_3BZnEt_2 and aldehydes at room temperature in the presence of 10 mol% of $Ni(acac)_2$. In both reactions, the (*E*)-isomers, (*E*)-**3** and (*E*)-**5**, are obtained with excellent stereoselectivity.

Acknowledgements

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[7] (*E*)-3-Methyl-1,5-diphenyl-3-penten-1-ol ((*E*)-**5a**): IR (neat) 3400 (s), 1495 (s), 1450 (s), 1030 (s) cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.80 (brs, 3 H), 2.07 (d, $J = 2.4$ Hz, 1 H), 2.41 (dd, $J = 13.5, 9.0$ Hz, 1 H), 2.48 (dd, $J = 13.5, 4.7$ Hz, 1 H), 3.40 (d, $J = 7.3$ Hz, 2 H), 4.81 (ddd, $J = 9.0, 4.7, 2.4$ Hz, 1 H), 5.50 (brt, $J = 7.3$ Hz, 1 H), 7.11–7.38 (m, 10 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.3, 34.4, 50.2, 71.8, 125.9, 127.4, 127.7, 128.4, 128.5, 132.8, 141.1, 144.2. Anal. Calc. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.32; H, 8.18. (*Z*)-3-Methyl-1,5-diphenyl-3-penten-1-ol ((*Z*)-**5a**): ^1H-NMR (400 MHz, $CDCl_3$) δ 1.81 (brs, 3 H), 1.98 (d, $J = 2.2$ Hz, 1 H), 2.42 (dd, $J = 13.5, 5.1$ Hz, 1 H), 2.76 (dd,

$J = 13.5$, 9.0 Hz, 1 H), 3.33 (d, $J = 7.3$ Hz, 2 H), 4.86 (ddd, $J = 9.0$, 5.1, 2.2 Hz, 1 H), 5.54 (brt, $J = 7.3$ Hz, 1 H), 7.20–7.41 (m, 10 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.8, 34.2, 42.4, 72.4, 125.8, 125.9, 127.6, 127.9, 128.5, 128.9, 132.3, 141.3, 144.4.

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