Nickel-catalyzed four-component connection of oraganoaluminium (organozinc), isoprene, aldehydes and amines: stereo- and regioselective synthesis of trisubstituted (*E*)-homoallylamines[†]

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Ni(acac)₂ catalyzes the four-component connection reaction of trimethylaluminium (or diphenylzinc), isoprene, aromatic aldehydes and *p*-anisidine in this order and provides (*E*)-1- aryl-1-(*p*-methoxyphenyl)amino-3-methyl-3-hexenes (or (*E*)-1- aryl-1-(*p*-methoxyphenyl)amino-3-methyl-5-phenyl-3-pentenes) selectively in good yield.

Multi-component connection reactions of simple molecules provide very versatile and efficient methods to construct desired molecules, which have been achieved mostly by making the best use of transition-metal catalysis.¹ Isoprene is among the most important constituents of the frameworks of natural products, and the regio- and stereoselective incorporation of an isoprene unit into desired molecules has long been a subject of strong concern for synthetic organic chemists.

We recently demonstrated that a nickel salt, without applying any phosphane or nitrogen ligands, nicely catalyzed the threecomponent connection reaction of organozincs, dienes and aldehydes.² For the regio- and stereoselective incorporation of isoprene, organoboranes have proved to work much better than organozincs; the former gives rise to (*E*)-isomers almost exclusively.³ Here, we would like to disclose that the same method, with slight modification, is successfully applicable to the reaction with aldimines. This might be a great achievement, since aldimines are generally by far less reactive electrophiles than aldehydes,⁴ and through this method a variety of structurally defined homoallylamines of synthetic importance can be prepared (eqn (1)).

For the reaction with aldimine, generated *in situ* from benzaldehyde and *p*-anisidine, in addition to the expected product **1a** ($\mathbf{R} = \mathbf{H}$) (E : Z = 2 : 1), **2a** ($\mathbf{R} = \mathbf{H}$) was formed in a considerable amount, a type of product having never been observed for the reactions with aldehydes (run 1, Table 1).^{2,3} The ¹H NMR spectrum indicates that **2a** is a mixture of 4 stereoisomers arising from C3 and C8 stereocenters. The tail-to-tail connection of two molecules of isoprene was verified by ozonolysis experiments.⁵

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In order to improve the stereoselectivity and the chemical yield of **1a**, we thoroughly examined the reaction conditions and found that trimethylaluminium was the best choice of methylation reagents. With this reagent, not only the yield of **1a**, but also the stereoselectivity could be improved greatly (runs 3–5, Table 1). The stereoselectivity was temperature dependent; curiously, the higher the temperature, the better the (*E*)-selectivity. At the moment, it may be premature to give a rationale behind this unusual reactivity; however, we postulate that the monomer content, which increases with temperature in the monomer–dimer equilibrium of trimethylaluminium, is one of the important factors affecting the stereoselectivity in favor of the (*E*)-isomer.‡

The reaction could be performed very easily as follows (run 4, Table 1). A mixture of benzaldehyde (1 mmol) and *p*-anisidine (2 mmol) in dry THF (2 mL) was stirred overnight at 30 $^{\circ}$ C. The temperature was allowed to rise to 50 $^{\circ}$ C, and into this mixture,

Table 1 Optimization of reaction conditions for the reaction of
organomethyls, isoprene and benzaldehyde-p-anisidine imine^a

				Yield (%)	
Run	Me_nM	Temp./°C	Time/h	$1a (E:Z)^b$	2a
1	Me ₂ Zn	30	3	28 (2 : 1)	14
2	Me ₂ Zn	50	3	36(2:1)	10
3	Me ₃ Al	30	1	81(2:1)	10
4	Me ₃ Al	50	1	80 (9 : 1)	18
5	Me ₃ Al	60	1	74 (10 : 1)	21

^{*a*} Reaction conditions: benzaldehyde (1 mmol) and *p*-anisidine (2 mmol) in THF (2 mL) at 30 °C overnight, and then Ni(acac)₂ (0.1 mmol in 3 mL of THF), isoprene (4 mmol), Me_nM (3.6 mmol, 1 M in hexane) at the temperature indicated. ^{*b*} Isolated yield of spectroscopically homogeneous materials. In parentheses are shown the ratio of stereoisomers determined by ¹H NMR spectra (400 MHz).

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[†] Electronic supplementary information (ESI) available: A typical reaction procedure and spectral and analytical data of products (1a-j and 3a-e). See http://dx.doi.org/10.1039/b507229h

without removing water, were successively added isoprene (4 mmol), Ni(acac)₂ (27.0 mg, 0.1 mmol) [acac = acetylacetonato] dissolved in THF (3 mL), and Me₃Al (3.6 mmol, 1 M hexane). The resultant homogeneous mixture was stirred at the same temperature for 1 h. Usual work up followed by purification by means of column chromatography over silica gel provided **1a** in 80% yield as a mixture of E-Z in a ratio of 9 : 1 along with **2a** in 18% yield.

Under the conditions, thus optimized, was uniformly undertaken the four-component connection reaction of a variety of aldimines of aromatic aldehydes/*p*-anisidine (Table 2).⁶ The yields and stereoselectivities of **1** are generally acceptable, irrespective of the kind of substituents and their substitution patterns on the aromatic ring (*o*- and *p*-). Interestingly, while the C–Cl bond of the *p*-chloro isomer **1i** remained intact, the *o*-chloro isomer underwent cross-coupling reaction with Me₃Al and provided an identical product **1c** obtained for the reaction with *o*-methylbenzaldehyde (runs 2 and 8, Table 2). Although furan-2-carbaldehyde recorded a good yield (run 10, Table 2), neither pyridine-2carbaldehyde nor pyridine-3-carbaldehyde provided the expected products at all.

The present reaction seems to be only successful for aldimines composed of aromatic aldehydes and aromatic amines. Run 1, Table 2 shows the results for the reaction of the aldimine of benzaldehyde and aniline. None of the aldimines composed of

Table 2 Ni-catalyzed four-component connection reaction of Me₃Al,isoprene, a variety of aromatic aldehydes and p-anisidine^a

			Yield (%)		
Run	Aldehyde		Time/h	1 (E : Z)	2
1	СНО		4	1b : 80 (20 : 1) ^b	2b : 8 ^b
2	Me ^{-rs} —CHO	о-	1	1c : 46 (5 : 1)	2c : 37
3		р-	1	1d : 91 (10 : 1)	2d : 8
4	МеО СНО	о-	3	1e : 66 (3 : 1)	2e : 33
5		р-	1	1f : 67 (6 : 1)	2f : 30
6	сно	о-	1	1g : 76 (5 : 1)	2g : 22
7	Г	р-	1	1h : 65 (6 : 1)	2h : 28
8	СІ	о-	1	1c : 36 (1.3 : 1)	2c : 48
9		р-	1	1i : 75 (6 : 1)	2i : 13
10	СНО		0.5	1j : 89 (4 : 1)	2j : 9

^{*a*} Reaction conditions: an aromatic aldehyde (1 mmol) and *p*-anisidine (2 mmol) in THF (2 mL) at 30 °C overnight, and then Ni(acac)₂ (0.1 mmol in 3 mL of THF), isoprene (4 mmol), Me₃Al (3.6 mmol, 1 M in toluene) at 50 °C. ^{*b*} Aniline in place of *p*-anisidine.

aliphatic aldehydes and aromatic amines and aromatic aldehydes and aliphatic amines, so far, have provided the expected products **1** in the yields in the levels of synthetic use.

In sharp contrast to the reactions of Me₂Zn (runs 1 and 2, Table 1), phenylative four-component connection reaction with Ph₂Zn proceeded smoothly at room temperature and provided (*E*)-3 in good yields with excellent stereoselectivity (eqn (2)). Results examined with substituted benzaldehydes and furan-2-carbaldehyde are summarized in Table 3. All the reactions are very clean and complete within a few hours. No side products like **2** were detected at all. The reaction tolerates electron-donating and electron-withdrawing substituents on the aromatic ring.



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Table 3 Ni-catalyzed four component connection reaction of Ph_2Zn ,isoprene, a variety of aromatic aldehydes and *p*-anisidine^a

Run	Aldehyde	Temp./°C	Time/h	Yield (%) (<i>E</i>)- 3
1	СНО	30	2	3a : 80
2	СІ—	25	1	3b : 61
3	Ме-СНО	25	3	3c : 83
4	МеО-СНО	25	3	3d : 44
5	СНО	25	1	3e : 83

^{*a*} Reaction conditions: an aromatic aldehyde (1 mmol) and *p*-anisidine (2 mmol) in THF (2 mL) at 30 °C overnight, and then Ni(acac)₂ (0.1 mmol in 3 mL of THF), isoprene (4 mmol) and Ph₂Zn (3.6 mmol) at the temperature indicated. Diphenylzinc was prepared *in situ* from ZnCl₂ (3.6 mmol, 1 M ether, Aldrich) and PhMgBr (7.2 mmol, 1 M THF, Kanto Kagaku).

Notes and references

[‡] We postulate an intermediate composed of aldimine–isoprene–nickel– Me_3Al , a possible structure of which has been proposed elsewhere for the reaction of aldehydes, in place of aldimines.^{3a}

- (a) Y. Tamaru, Modern Organonickel Chemistry, Wiley-VCH, Weinheim, 2005; (b) H. Kurosawa and A. Yamamoto, Fundamentals of Molecular Catalysis, Elsevier, Amsterdam, 2003; (c) J. Tsuji, Transition Metal Reagents and Catalysis, Wiley, Chichester, 2000.
- 2 M. Kimura, S. Matsuo, K. Shibata and Y. Tamaru, Angew. Chem., Int. Ed., 1999, 38, 3386.
- 3 (a) M. Kimura, K. Shibata, Y. Koudahashi and Y. Tamaru, *Tetrahedron Lett.*, 2000, 41, 6789; (b) K. Shibata, M. Kimura, K. Kojima, S. Tanaka and Y. Tamaru, *J. Organomet. Chem.*, 2001, 624, 348.
- 4 Nickel-catalyzed nucleophilic addition of alkynes and dienes upon aldimines: (a) M. Kimura, A. Miyachi, K. Kojima, S. Tanaka and

Y. Tamaru, J. Am. Chem. Soc., 2004, **126**, 14360; (b) S. J. Patel and T. F. Jamison, Angew. Chem., Int. Ed., 2004, **43**, 3941; (c) S. J. Pater and T. F. Jamison, Angew. Chem., Int. Ed., 2003, **42**, 1364; (d) P. Heimbach, B. Hugelin, H. Peter, A. Roloff and E. Troxler, Angew. Chem., 1976, **88**, 29.

- 5 The Me substitution at C3 was deduced from the coupling pattern of the methylene protons C2 observed in the ¹H NMR spectrum of **2a** (400 MHz, CDCl₃, TMS); δ 2.27 ppm (dd, J = 13.8, 10.5 Hz, 1H) and 2.46 ppm (dd, J = 13.8, 4.1 Hz, 1H). The Me substitution at C8 was verified on the basis of the selective formation of 2-butanol, rather than 1-propanol, obtained by ozonolysis of **2a**, followed by reduction with NaBH₄.
- 6 It is crucial to perform the reactions according to the procedure indicated. As mentioned in ref. 4*a*, isolated imines and imines generated *in situ* behaved differently. For example, isolated benzaldehyde–aniline imine reacted with Me₃Al (2.4 mmol, at 50 °C for 6 h, *cf.*, run 1, Table 2) to yield a complex mixture containing **1b** as a minor product (*ca.* 25%, ¹H NMR).