

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

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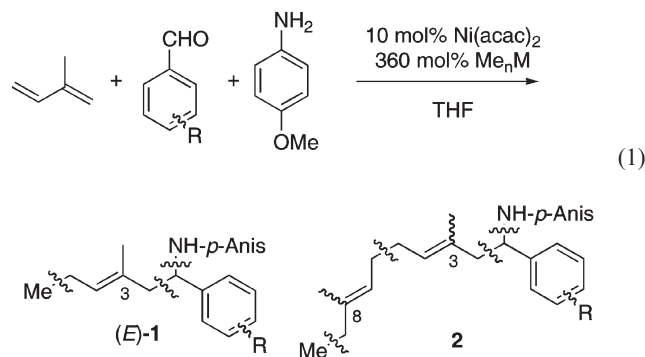
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Ni(acac)₂ catalyzes the four-component connection reaction of trimethylaluminium (or diphenylzinc), isoprene, aromatic aldehydes and *p*-anisidine in this order and provides (*E*)-1-aryl-1-(*p*-methoxyphenyl)amino-3-methyl-3-hexenes (or (*E*)-1-aryl-1-(*p*-methoxyphenyl)amino-3-methyl-5-phenyl-3-pentenes) 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 three-component 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** (R = H) (*E* : *Z* = 2 : 1), **2a** (R = 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



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 °C. The temperature was allowed to rise to 50 °C, and into this mixture,

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

Run	Me _n M	Temp./°C	Time/h	Yield (%)	
				1a (<i>E</i> : <i>Z</i>) ^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-2-carbaldehyde 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

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.

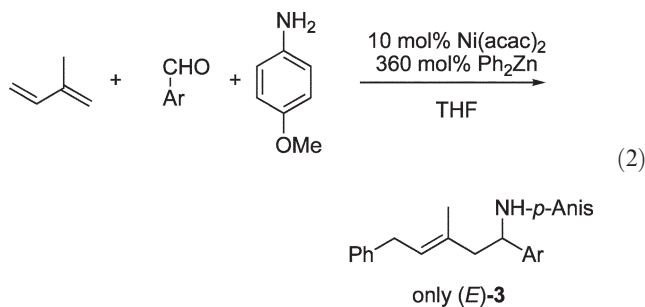


Table 2 Ni-catalyzed four-component connection reaction of Me₃Al, isoprene, a variety of aromatic aldehydes and *p*-anisidine^a

Run	Aldehyde	Time/h	Yield (%)	
			1 (<i>E</i> : <i>Z</i>)	2
1		4	1b : 80 (20 : 1) ^b	2b : 8 ^b
2		<i>o</i> - 1	1c : 46 (5 : 1)	2c : 37
3		<i>p</i> - 1	1d : 91 (10 : 1)	2d : 8
4		<i>o</i> - 3	1e : 66 (3 : 1)	2e : 33
5		<i>p</i> - 1	1f : 67 (6 : 1)	2f : 30
6		<i>o</i> - 1	1g : 76 (5 : 1)	2g : 22
7		<i>p</i> - 1	1h : 65 (6 : 1)	2h : 28
8		<i>o</i> - 1	1c : 36 (1.3 : 1)	2c : 48
9		<i>p</i> - 1	1i : 75 (6 : 1)	2i : 13
10		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.

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Table 3 Ni-catalyzed four component connection reaction of Ph₂Zn, isoprene, a variety of aromatic aldehydes and *p*-anisidine^a

Run	Aldehyde	Temp./°C	Time/h	Yield (%)
				(<i>E</i>)- 3
1		30	2	3a : 80
2		25	1	3b : 61
3		25	3	3c : 83
4		25	3	3d : 44
5		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–Me₃Al, a possible structure of which has been proposed elsewhere for the reaction of aldehydes, in place of aldimines.^{3a}

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- 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. 4a, 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).