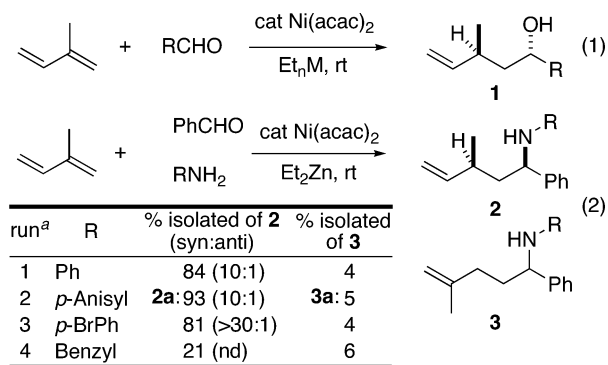# Highly Stereo- and Regioselective Ni-Catalyzed Homoallylation of Aldimines with Conjugated Dienes Promoted by Diethylzinc

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For the construction of desired molecules, the C−C bond formation via nucleophilic allylation of carbonyl compounds is among the most widely used methods. This is due to the high nucleophilicity and easy availability of allylic nucleophilic species: allylmetals and metalloids (M = Li, Mg, Zn, B, Si, Sn, etc.), metal enolates, and enol ethers of esters, ketones, and aldehydes.[1] Compared with allylation, homoallylation has been by far less utilized probably due to the low nucleophilicity and difficult availability of homoallylmetal species.

run[a]	R	% isolated of 2 (syn:anti)	% isolated of 3
1	Ph	84 (10:1)	4
2	p-Anisyl	2a: 93 (10:1)	3a: 5
3	p-BrPh	81 (>30:1)	4
4	Benzyl	21 (nd)	6

[a]For the reaction conditions, see footnote a in Table 1 and text.

Recently, we have demonstrated that under nickel catalysis, 1,3-dienes serve as a homoallyl anion equivalent and undergo nucleophilic addition to aldehydes to furnish bishomoallyl alcohols (eq 1), where a formal hydride anion is derived from the methyl of the ethyl group of triethylborane (Et3B)[2] or diethylzinc (Et2Zn).[3] The reaction is highly regio- and stereoselective. For example, isoprene reacts at the C1 position with benzaldehyde and provides 1,3-anti-1 (R = Ph, eq 1) with 95% diastereomeric selectivity.

Here we would like to disclose that the same combination of reagents, Ni(acac)2 and Et2Zn, works for the homoallylation of aldimines (eq 2).[4] The reaction is remarkable in many respects. First, the reaction proceeds with an opposite sense of stereoselectivity to that of aldehydes, providing 1,3-syn-2 selectivity. Regioselectivity with respect to dienes (C1 or C4) is slightly lower than that observed for aldehydes, and isomers 3 are produced as minor products. Second, despite the diminished electrophilicity of aldimines,[5] the homoallylation is completed at room temperature within 1 h. Third, aniline and its para-substituted derivatives (both with electron-donating OMe and electron-withdrawing Br) give satisfactory results (runs 1−3, eq 2), while aliphatic amines do not (run 4). Fourth, the reaction can be undertaken in one flask with great operational ease: a mixture of an aldehyde (1 mmol) and an aromatic amine (1.1~2.0 mmol) was stirred in THF for 5−10 h at

Table 1. Ni-Catalyzed Stereoselective Homoallylation of Anisidine Imine, Generated in Situ, with Isoprene

run[a]	Aldehyde	time (h)	2: % isolated [syn:anti][c]	3: % isolated
1[b]	(p-tolyl)CHO	1	2b: 89 [8:1]	3b: 6
2	(p-Cl-C6H4)CHO	1	2c: 89 [7:1]	3c: 7
3[b]	(2-furyl)CHO	0.5	2d: 82 [20:1]	3d: 4
4	(CH2O)n	21	2e: 78	3e: 1
5[d]	iPrCHO	0.5	2f: 62 [>30:1]	3f: 20

[a] Reaction procedure: An aldehyde (1 mmol) and anisidine (2 mmol) in THF (2 mL) were reacted at 50 °C for 10 h under N2, and then Ni(acac)2 (0.1 mmol) was dissolved in THF (3 mL), isoprene (4 mmol), and Et2Zn (3.6 mmol, 1 M in hexane) at room temperature for the period of time indicated. [b] An aldehyde (1.0 mmol) and anisidine (1.1 mmol). [c] Diastereomeric ratios were determined by 400 MHz ^{1}H and 100 MHz ^{13}C NMR. p-An = p-methoxyphenyl. [d] Imine formation: Isobutyraldehyde (1 mmol) and anisidine (2 mmol) were reacted at room temperature for 20 h.

rt−50 °C, and then, without removing water produced, Ni(acac)2 (10 mol %), isoprene (4 mmol), and Et2Zn (360 mol %) were added in this order at room temperature.

We utilized p-anisidine, because the p-methoxyphenyl group can be easily removed oxidatively, giving primary amines in good yields.[6] Table 1 demonstrates the scope of the reaction regarding the kinds of aldehydes that encompasses not only aromatic aldehydes (runs 1−3) but also aliphatic aldehydes, including paraformaldehyde (runs 4 and 5).

It may be important to note that the isolated imines and the imines generated in situ behave differently. Thus, isolated formaldehyde-anisidine imine does not react under usual conditions and is recovered almost completely after 24 h at room temperature (cf. run 4, Table 1). On the other hand, isolated benzaldehyde-anisidine imine reacts under usual conditions (with 2.4 mmol of Et2Zn instead of 3.6 mmol, 0.5 h at room temperature in THF); however, 2a and 3a are isolated in 34% (syn:anti = 4:1) and 14% yields, respectively (cf. run 2, eq 2), along with a double-bond positional isomer of 2a, 5-(p-anisidyl)-3-methyl-5-phenyl-2-pentene (4) in 42% isolated

Table 2. Ni-Catalyzed Stereoselective Homoallylation of Aldimine Generated in Situ from Furfural and Anisidine with Various 1,3-Dienes

run[a]	Diene	time (h)	2: % isolated [syn:anti][b]
1		0.5	**2g**: 81 [>30:1]
2		0.5	**2h**: 98 [>30:1]
3		0.5	**2i**: 94 [15:1]
4		0.5	**2j**: 98 [15:1]
5		5	**2k**: 67 [>30:1]

[a] See footnote a in Table 1. [b] See footnote c in Table 1. Fur = 2-furyl.

Scheme 1. Possible Intermediates **III** and **VI** for the Stereo- and Regiocontrolled Formation of 1,3-syn-**2**.
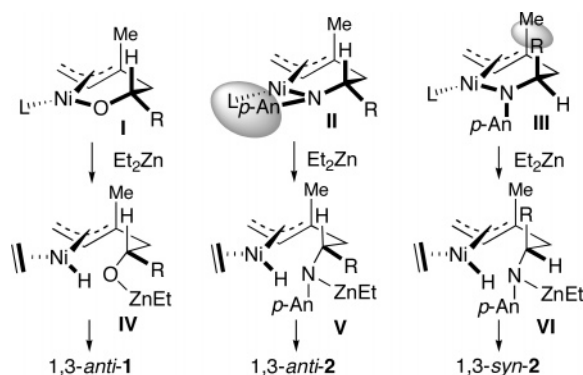
yield. It turned out that water produced in situ had nothing to do with the reaction,[7] while *p*-anisidine played a pivotal role in determining the course of reaction; thus, in the presence of 1 equiv of *p*-anisidine (with 2.4 mmol of Et₂Zn), **2a** and **3a** were obtained in 89 (syn:anti = 7:1) and 9% yields, respectively. Almost the same results were obtained in the presence of *p*-anisidine and water (1 mmol each, with 3.6 equiv of Et₂Zn).

The reaction is applicable to a wide structural variety of 1,3-dienes (Table 2). These reactions were examined using an aldimine generated in situ from furfural and anisidine (at room temperature for 5 h). Furfural was selected as an aldehyde, since furan can be utilized as C4 or C1 building blocks for many purposes ([4 + 2]- and [4 + 3]cycloadditions, oxidation to 1,4-dioxo-2-butenes, carboxylic acid).[8] All dienes reacted regioselectively at the diene termini bearing the highest electron density and provided 1,3-syn-**2** with more than 94% diastereoselectivity.[2a,3a] Cyclohexadiene showed apparently low reactivity,[9] and the reaction took 5 h for completion (run 5, Table 2). The product **2k** was obtained as a single stereoisomer. The relative configuration has not been determined yet. Interestingly, the reactions with unsymmetrical dienes listed in Table 2 did not yield regioisomers **3** in any detectable amounts (runs 1, 2, and 4).

The structures of 1,3-syn-**2a**, -**2d**, -**2f**, and -**2i** were determined by means of X-ray crystallographic analyses.[10] Scheme 1 outlines a rationale for opposite stereoselectivity between aldehydes and imines using isoprene as a diene. As has been discussed pre-

viously,[3a,11] the 1,3-anti selectivity for aldehydes stems from an equatorial orientation of an aldehyde in intermediate **I**. For the case of aldimines, on the other hand, placing an aldimine in the same equatorial position causes severe steric repulsion between *p*-anisyl and a ligand on nickel(II) with a square planar configuration in intermediate **II**. Hence, as a second choice, an aldimine would take on a diaxial configuration (intermediate **III**),[12,13] which leads to 1,3-syn-**2**[14] via β-H elimination and cis-reductive elimination of an Ni−H intermediate **VI**. In intermediate **III**, there still arises 1,3-diaxial repulsion between methyl and R. This may be the reason sterically demanding aldimines, typified by run 5 in Table 1, tend to give **3** in considerable amounts.

In conclusion, aldimines formed in situ from aralkyl aldehydes and aromatic amines undergo homoallylation regio- and stereoselectively by reductive coupling with dienes by the catalysis of nickel and provide 1,3-syn-**2** in good yields and with high stereoselectivity, where Et₂Zn serves as a reducing agent (an H donor).

Supporting Information Available: Typical experimental procedures, spectral data for all new compounds, and ChemBats3D presentation of X-ray structures of **2a**, **2d**, **2f**, and **2i** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org

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(7) In the presence of 1 equiv of water (with 3.6 mmol of Et₂Zn), **2a**, **3a**, and **4** were isolated in 54 (syn:anti = 4: 1), 10, and 29% yields, respectively.

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(10) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-199890 (**2a**), CCDC-199891 (**2d**), CCDC-244542 (**2f**), and CCDC-219226 (**2i**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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(12) Molecular models show that a dihedral angle between L and *p*-anisyl for **II** is ca. 10−20°, while that for **III** is 90°.

(13) Intermediate models **I**−**III** with *s*-trans conformation do not apply to the reaction of cyclohexadiene. Homoallylation of benzaldehyde with cyclohexadiene, promoted by Et₃B, does not proceed,[2a] while the reaction promoted with Et₂Zn provides the expected bishomoallyl alcohol with poor selectivity (4:1 in 64% yield, unpublished results).[9b] In this context, the selective formation of **2k** is unusual and remarkable, and some other mechanistic frameworks might be operating for *s-cis*-dienes, which will be proposed in due course when the structure of **2k** is determined.

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