Nickel catalyzed stereoselective conjugate addition of dimethylzinc upon aldimines across 1,3-dien-8-ynes and 1,3-dien-9-ynes†

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Ni(acac)$_2$ catalyzes the five-component connection reaction of Me$_2$Zn, alkynes, diene (of 1,3-dien-8-ynes and 1,3-dien-9-ynes), aldehydes and anisidine to furnish cyclic dienyl amines *anti*-2 with high remote 1,5-diastereoselectivity.

Aldimines are among the least reactive electrophiles. Accordingly, the C–C bond formation reactions of aldimines with organometallic reagents have been achieved mostly by introduction of electron-withdrawing activating groups either on the amine[1] or on the aldehyde moiety.[2] This statement does not necessarily hold for the reactions of organic transition metals. In fact, a few precedents indicate that aldimines are more reactive than[3] or show comparable reactivity to aldehydes.[4] In transition metal catalysis, it is believed that the strong coordination of nitrogen to transition metals activate aldimines as electrophiles.

Recently, we disclosed that Ni(acac)$_2$ (acac = acetylacetonato) served as a catalyst for the conjugate addition reaction of Me$_2$Zn upon aldehydes across 1,3-dien-8-ynes and 1,3-dien-9-ynes 1 (n = 1, 2) and furnished cyclic dienyl alcohols 2′ with high 1,5-*syn* stereoselectivity and in good yields (Scheme 1).[5] Here we report that the reaction can be successfully extended to aldimines; aldimines showed comparable reactivity to aldehydes under the Ni-catalyzed conditions and provided the nitrogen analogues, cyclic dienyl amines 2. The reactions were complete at room temperature within a few hours in most cases and showed better performance than aldehydes regarding the isolated yields and stereoselectivity. Notably, aldimines and aldehydes showed an opposite stereoselectivity; aldehydes provided 2′ in ratios of *anti*/*syn* = 1 : 7 to 1 : >30, while aldimines exclusively provided 1,5-*anti*-2 as single diastereomers in all cases examined. Furthermore, the

reaction shows wider flexibility regarding the type of aldehydes (see below).

The reaction can be undertaken in one flask with great ease (run 1, Table 1): a mixture of benzaldehyde (1 mmol) and *p*-anisidine (2 mmol) in dry THF (1.5 mL) was stirred at room temperature overnight. This mixture, without removing water produced, was treated with Ni(acac)$_2$ (0.05 mmol) dissolved in THF (1.5 mL), 1a (0.5 mmol) and Me$_2$Zn (3.6 mmol, 1 M hexane) at room temperature. The reaction was complete within 1 h and provided 2a in an excellent yield (90–100%) after usual workup and purification by column chromatography over silica gel.‡ Interestingly, both an excess amount of *p*-anisidine (AN) and water produced seem to be essential, and cooperate to promote the reaction (Table 2).[6] Isolated aldimine itself did not undergo the expected addition reaction; after a long reaction, an intractable mixture of products containing unreacted 1a resulted (run 1). In the presence of either water (1 mmol) or AN (1 mmol), the reaction was complete within 1 h, and 2a was isolated in 19 or 71% yield, respectively. The yield of 2a was greatly improved in the presence of both water and AN (run 4). At the moment, the roles of these additives are not clear, but we speculate that AN might activate Me$_2$Zn by coordination to it, dissociating Me$_2$Zn-oligomers to the lower oligomers or monomer, and water produces some zinc oxide species, which might serve as a Lewis acid to activate an aldimine.

Table 1 summarizes the reactions of *in-situ* generated benzaldehyde-AN imine with a wide structural variety of 1, encompassing three- and four-carbon tethers containing oxygen and nitrogen atoms in their skeleton. As compared with the reactions with benzaldehyde, the yields of 2a–2h are either comparable or better (*e.g.*, the alcohol analogues of 2a, 2b and 2c have been isolated in 63, 70 and 61% yields, respectively).[5] A phenyl-substituted 1,3-dien-8-yne 1c was unreactive and required heating at 50 °C for an exceptionally long period of time.

The structure of 2g was determined unequivocally by X-ray crystallographic analysis.[7] The structures of other isomers were tentatively assigned by analogy.[8]

Furthermore, the reaction showed wide flexibility for a variety of aromatic aldehydes and aliphatic aldehydes. The results are summarized in Fig. 1. Aromatic aldehydes bearing either electron-donating (2i) or withdrawing group (2j), as well as a heteroaromatic aldehyde (2k) worked similarly well. Interestingly, judging from the reaction time, aliphatic aldehyde imines, 2l and 2m, seem to be more reactive than aromatic aldehyde imines.

The compatibility of the reaction with water encouraged us to examine the reaction with lactols. Curiously, 2-hydroxy-1-oxacyclohexane was unreactive under the usual conditions and no
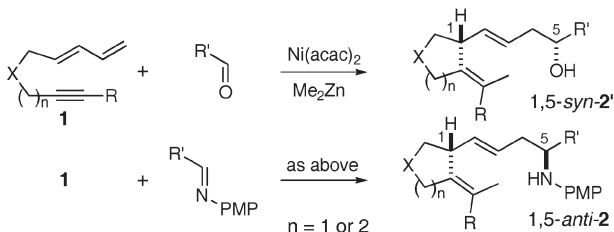
Scheme 1 Opposite 1,5-diastereoselection between aldehydes and aldimines.

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Table 1 Ni-catalyzed coupling of Me_2Zn and benzaldehyde-*p*-anisidine imine across 1,3-dien-8-ynes or 1,3-dien-9-ynes **1**[a]

Run	1	t/h	Isolated yield of product **2** (%)
1	**1a**	1	**2a**: 95
2	**1b**	1	**2b**: 79
3	**1c**	24[b]	**2c**: 62
4	**1d**	2	**2d**: 70
5	**1e**	1	**2e**: 85
6	**1f**	0.5	**2f**: 78
7	**1g**	3	**2g**: 70
8	**1h**	0.5	**2h**: 73

[a] *Reaction conditions*: benzaldehyde (1 mmol) and *p*-anisidine (2 mmol) in THF (1.5 mL) at room temperature overnight, then $Ni(acac)_2$ (0.05 mmol) dissolved in THF (1.5 mL), a 1,ω-dienyne **1** (0.5 mmol), and Me_2Zn (3.6 mmol, 1 M hexane) at room temperature under N_2 for the period of time indicated. PMP = *p*-methoxyphenyl, M = CO_2Me. [b] At 50 °C.

Table 2 Effect of additives for the reaction of **1a** (0.5 mmol), isolated aldimine (benzaldehyde-AN, 1 mmol) and Me_2Zn

Run	Additive (mmol)	Me_2Zn/mmol	t/h	Yield of **2a** (%)
1	None	1.2[a]	19	0
2	H_2O (1)	2.4	1	19
3	*p*-Anisidine (1)	2.4	0.5	71
4	*p*-Anisidine (1), H_2O (1)	3.6[b]	0.5	85

[a] The amount of Me_2Zn used is the same as that optimized for the reactions with aldehydes.[5] [b] The amount of Me_2Zn is the same as that applied to the reactions shown in Table 1.
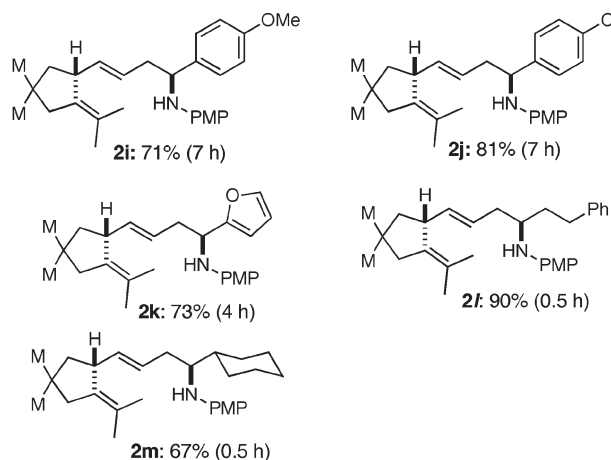

Fig. 1 Reaction of **1a** with aromatic and aliphatic aldehyde-AN imines.

2i: 71% (7 h) **2j**: 81% (7 h) **2k**: 73% (4 h) **2l**: 90% (0.5 h) **2m**: 67% (0.5 h)

expected product was obtained [eqn (1)], while pre-treatment of a lactol with AN overnight and application of the usual reaction conditions promoted the reaction as usual. The reaction was complete within 1–3 h at room temperature and furnished the expected cyclic dienyl amino alcohols **2n** and **2o** in modest to good yields as single diastereomers [eqn (2)].

2n: 61% (single isomer, n = 1, 3 h)
2o: 73% (single isomer, n = 2, 1 h)
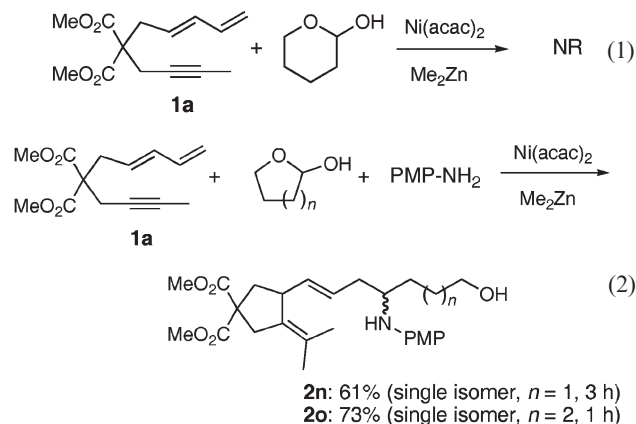
A working hypothesis that accommodates 1,5-*anti* selectivity of **2**, being opposite to that of aldehydes, is outlined in Scheme 2. The scenario is almost the same as that described for the reaction of **1** with aldehydes.[5] Although, an intermediate **I″**, favoured for the reaction with an aldehyde, exposing the substituent R^1 on an quasi-equatorial position and hence with an *anti*-conformation between R^1 and C4–C5, is not responsible any longer for the reaction with an aldimine, since in a square planer Ni^{II} geometry of **I′**, an alkyne and the PMP substituent on N might experience a severe *gauche* repulsion. In an intermediate **I**, on the other hand, a *gauche* repulsion between R^1 and C4–C5 arises, but this repulsion is expected to be much smaller than that between alkyne and PMP in **I′**. Methyl transfer from Me_2Zn to Ni^{II} might form **II**, which would undergo alkyne insertion in a *syn* fashion to give **III** and hence 1,5-*anti*-**2** via reductive elimination.

Although **2n** and **2o** were obtained as single diastereomers, their stereochemistry is not known at the moment. The similarly large steric environment (PMP and ZnMe) around N in the most probable intermediate **IV** (Scheme 2) prevents from structure determination by analogy with the mechanistic scenario. All
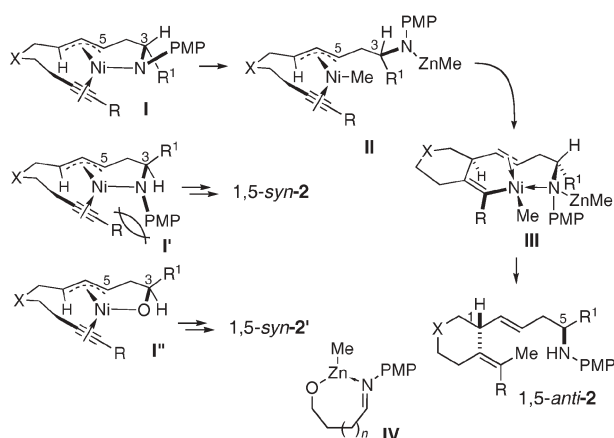
Scheme 2 Rationale for the selective formation of 1,5-*anti*-**2**.

attempts have been unsuccessful as yet to obtain crystalline solids of **2n** and **2o** and their derivatives suitable for X-ray crystallographic analysis [*e.g.*, *N*-PMP and *N*-H pyrrolidine derivatives and their HClO$_4$ salts formed by cyclization *via* intramolecular amination of **2n** (TsCl/pyridine) and PMP deprotection (CAN/CH$_3$CN–H$_2$O)].[9]

In summary, we demonstrated that Ni(acac)$_2$ catalytically promoted the five-component connection reactions of Me$_2$Zn, alkynes, diene (of 1,3-dien-8-ynes and 1,3-dien-9-ynes), aldehydes and anisidine to furnish cyclic dienyl amines **2**. Despite the low reactivity, aldimines generated *in situ* showed comparable reactivity to aldehydes under the nickel catalysis and even showed better performance than aldehydes regarding the yields (**2** *vs.* **2′**) and stereoselectivity, providing 1,5-*anti*-**2** as single diastereomers. Furthermore, although lactols failed, the corresponding lactamines successfully underwent the five-component connection reaction to give cyclic dienyl amino alcohols **2n,o** in acceptable yields.

Notes and references

‡ Reactions are typically performed as follows (see eqn (2)): A mixture of *p*-anisidine (246 mg, 2 mmol) and 2-hydroxy-1-oxacyclohexane (103 mg, 1 mmol) in dry THF (2 mL) was stirred at room temperature overnight under N$_2$. Into a flask containing Ni(acac)$_2$ (12.8 mg, 0.05 mmol) purged with N$_2$ were added successively THF (1 mL), the above-prepared solution (*via* cannula), **1a** (125 mg, 0.5 mmol) and Me$_2$Zn (3.6 mL, 1 M hexane). The homogeneous solution was stirred at room temperature for 1 h; R_f (**1a**) = 0.7, R_f (**2o**) = 0.07 (hexane–EtOAc = 2 : 1 v/v). The mixture was partitioned into EtOAc (20 mL)/H$_2$O (20 mL). The water phase was saturated with NaCl and washed with EtOAc (2 × 10 mL). The combined organic phase was dried (K$_2$CO$_3$) and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (hexane–EtOAc gradient; 2 : 1 to 1 : 1 v/v) to give 4,4-di(methoxycarbonyl)-2-[4-(*p*-anisidyl)-8-hydroxy-(1*E*)-octenyl]-1-isopropylidenecyclopentane (**2o**, 171.3 mg) in 73% yield as a colorless oil. **2o**: IR (neat) 3395 (m), 2932 (w), 1736 (s), 1512 (s), 1443 (s), 1242 (s), 1042 (s), 818 (s), 733 (w) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.41–1.60 (m, 6 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 2.06 (dd, J = 5.9,

13.2 Hz, 1 H), 2.18–2.22 (m, 2 H), 2.57 (dd, J = 8.5, 13.2 Hz, 1 H), 2.83–2.92 (m, 2 H), 3.28 (ddm, J = 5.9, 8.5 Hz, 1 H), 3.30 (m, 1 H), 3.63 (t, J = 6.3 Hz, 2 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 5.31 (dm, J = 15.1 Hz, 1 H), 5.36 (dm, J = 15.1 Hz, 1 H), 6.55 (br d, J = 8.5 Hz, 2 H), 6.75 (d, J = 8.5 Hz, 2 H); ^{1}H NMR (400 MHz, THF-d_8) δ 1.32–1.56 (m, 6 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 2.00 (dd, J = 6.2, 13.1 Hz, 1 H), 2.13 (dt, J = 13.7, 6.8 Hz, 1 H), 2.18 (dt, J = 13.7, 7.6 Hz, 1 H), 2.53 (dd, J = 8.4, 13.1 Hz, 1 H), 2.83 (br d, J = 16.6 Hz, 1 H), 2.89 (br d, J = 16.6 Hz, 1 H), 3.22 (br dd, J = 6.2, 7.6 Hz, 1 H), 3.28 (br d, J = 8.4 Hz, 1 H), 3.40–3.50 (m, 2 H), 3.61 (s, 3 H), 3.62 (s, 3 H), 3.63 (s, 3 H), 3.93 (br s, 1 H), 5.28 (dd, J = 7.6, 14.9 Hz, 1 H), 5.41 (dt, J = 14.9, 6.8 Hz, 1 H), 6.47 (d, J = 9.0 Hz, 2 H), 6.64 (d, J = 9.0 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.8, 21.6, 22.2, 32.7, 33.9, 36.7, 38.7, 41.2, 44.2, 52.6, 54.1, 55.8, 59.1, 62.7, 114.9, 125.2, 125.9, 132.9, 135.8, 152.0, 172.1, 172.2; HRMS: calc. for C$_{27}$H$_{39}$NO$_6$: 473.2777. Found *m/z* (relative intensity) 474 (M$^+$ + 1, 32), 473.2770 (M$^+$, 100), 472 (7), 456 (2), 442 (13).

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6 Similar acceleration effect of an excess amine and water has been reported in ref. 4*c*,*d*.

7 *Crystal data* for **2g**: C$_{25}$H$_{31}$NO$_2$, M = 377.53, triclinic, space group $P\bar{1}$, a = 8.8531(8), b = 10.122(2), c = 12.351(2) Å, $α$ = 85.224(5), $β$ = 85.589(3), $γ$ = 76.189(3)°, U = 1069.2(3) Å^3, T = 297.2 K, Z = 2, $μ$(Mo-Kα) = 0.7107 mm^{-1}, 4501 reflections measured, 2394 unique (R_{int} = 0.021), $wR(F_2)$ = 0.1450 (all data). This compound is a racemate with two inversion-related molecules in the $P\bar{1}$ triclinic unit cell, and the X-ray structure of **2g** determines the relative stereochemistry. CCDC 209610. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605728d.

8 The *Z* structures of **2c** and **2d** were deduced on the basis of NOE experiments. For example, irradiation of the methyl group of α-phenylethylidene of **2c** caused increments of the area intensities of C4–H (3.2%) and C2′–H (1.5%), while no increment for C2–H was observed.

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