ORGANIC LETTERS 2007 Vol. 9, No. 10 1871–1873

Alkyne as a Spectator Ligand for the Nickel-Catalyzed Multicomponent Connection Reaction of Diphenylzinc, 1,3-Butadiene, Aldehydes, and Amines

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Received February 9, 2007

ABSTRACT



Under nickel catalysis, in the presence of 3-hexyne, the aldimines of *aromatic amines* react with Ph_2Zn and one molecule of butadiene to provide 1 exclusively, while the aldimines of *aliphatic amines* react with Ph_2Zn and two molecules of butadiene to provide 2 exclusively, where 3-hexyne serves as a spectator ligand controlling the selective formation of 1 and 2.

Aldimines are among the least reactive carbonyl derivatives, and to successfully perform nucleophilic addition to the C= N bond, it is usually necessary to activate aldimines by using either amines or aldehydes activated by electron-withdrawing or chelating substituents. In the past decade, however, observations have indicated that this statement is not necessarily the case for transition metal-catalyzed reactions,^{1,2} where strong coordination of transition metals to the nitrogen of the aldimine greatly activates the C=N bond toward nucleophilic addition.

Recently, we³ and Jamison⁴ have demonstrated that under nickel catalysis even electronically neutral dienes and alkynes are able to undergo nucleophilic addition to aldimines.⁵ For example, aldimines composed of aldehydes (both aromatic and aliphatic) and *aromatic amines* (e.g., aniline, *o-*, *p*anisidine) react with Me₂Zn, alkynes, and 1,3-butadiene to furnish dienyl homoallylamines **3** selectively in good yields

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Scheme 1. Contrasting Reactivity of Ph₂Zn and Me₂Zn for the Ni-Catalyzed Multicomponent Connection Reaction with 1,3-Butadiene, Alkynes, Aldehydes, and Amines^a



^{*a*} Ar and Alk stand for aromatic and aliphatic substituents, respectively.

(Scheme 1). In sharp contrast to this, the aldimines of aldehydes and *aliphatic amines* (e.g., benzylamine, *n*-hexylamine) selectively furnish trienyl homoallylamines **4** in excellent yields, incorporating two molecules of 1,3-butadiene selectively.^{3d}

Here we disclose that Ph_2Zn shows entirely different reactivity from Me₂Zn; under similar conditions with Ph_2 -Zn in place of Me₂Zn, 3-hexyne is not incorporated in the product any longer and serves as a lignd. Hence, *aromatic amines* react with Ph_2Zn and 1,3-butadiene in a 1:1:1 ratio to provide homoallylamines **1** exclusively (Scheme 1). Under identical conditions, on the other hand, *aliphatic amines* react with Ph_2Zn and 1,3-butadiene in a 1:1:2 ratio to furnish (*3E*,*7E*)-dienyl homoallylamines **2** exclusively.

In these reactions 3-hexyne was not incorporated in the products. Interestingly, however, 3-hexyne was essential for the selective formation of **1** and **2**. In the absence of 3-hexyne, a complex mixture of products resulted. For example, the reaction of Ph₂Zn (3.6 mmol), 1,3-butadiene (4.0 mmol), benzaldehyde (1 mmol), *p*-anisidine (PMPNH₂, 2 mmol), and Ni(acac) ₂ (0.1 mmol) furnished the expected product **1a** only as a minor product; the major products were **5**⁶ and **2e** (Scheme 2).⁷

The multicomponent connection reaction of Ph₂Zn, 1,3butadiene, aldehydes (aromatic and aliphatic), and amines (PMPNH₂ and BnNH₂) proceeded smoothly at 30 °C and was complete within several hours (Figure 1). The selectivity,



giving either **1** for PMPNH₂ or **2** for BnNH₂, was quite general. Aromatic aldehydes bearing either electron-withdrawing (giving **1b** and **2b**) or electron-donating groups (giving **1c** and **2c**) worked similarly well. Aliphatic aldehydes showed somewhat diminished reactivity and reduced yields, yet provided the expected products **1d**, **1e**, and **2d** in acceptable yields.



Figure 1. Ni-catalyzed four-component connection reaction of Ph₂-Zn, 1,3-butadiene, aldehydes, and *p*-anisidine (giving **1**) or benzylamine (giving **2**) in the presence of 3-hexyne: an aldehyde (1 mmol) and *p*-anisidine (2 mmol, PMPNH₂) or benzylamine (2 mmol, BnNH₂) in THF (2 mL) at 30 °C overnight, and then Ni-(acac)₂ (0.1 mmol) in THF (3 mL), 3-hexyne (4 mmol), 1,3-butadiene (4 mmol), and Ph₂Zn (3.6 mmol) at 30 °C for the period of time indicated. Percent yields refer to the spectroscopically homogeneous materials isolated by means of column chromatography.

The success of the reaction with the nonactivated aldimines, particularly those composed of primary aliphatic aldehydes and aliphatic amines, e.g., yielding **2d**, and compatibility with water, which was formed during in situ preparation of an aldimine from an aldehyde and an amine, encouraged us to examine the reaction of lactols (Table 1).⁸

The lactamines of *p*-anisidine were examined in the presence and absence of 3-hexyne (entries 1-4, Table 1). Although the yields of **6a** and **6b** were almost identical under both conditions, the reactions in the presence of 3-hexyne were advantageous, since for the reactions in the absence of

⁽⁶⁾ A mixture of diastereomers (1:1.2).

⁽⁷⁾ With 1.0 and 0.2 mmol of 3-hexyne, under otherwise identical conditions, mixtures of **1a** and **2e** were obtained in 93% (11:1) and 98% (8:1) yield, respectively.

Table 1. Ni-Catalyzed Multicomponent Connection Reaction of Ph₂Zn, 1,3-Butadiene, Lactols, and Amines^{*a*}



entry	lactamine	$alkyne^b$	time (h)	% yield 6 or 7
1	n = 2, R = PMP	yes	3	6a : 71
2	n = 2, R = PMP	no	2	6a : 71 ^c
3	n = 1, R = PMP	yes	4	6b : 57
4	n = 1, R = PMP	no	4	6b : 58 ^c
5	$n = 2, \mathbf{R} = \mathbf{Bn}$	yes	4	7a : 48
6	$n = 2, \mathbf{R} = \mathbf{Bn}$	no	6	7a : 71^{c}
7	$n = 1, \mathbf{R} = \mathbf{Bn}$	yes	4	7b : 35
8	$n = 1, \mathbf{R} = \mathbf{Bn}$	no	6	7b : 58 ^c

^{*a*} Reaction conditions: a lactol (1 mmol) and an amine (2 mmol) in THF (2 mL) at 30 °C overnight, and then Ni(acac)₂ (0.1 mmol) in THF (3 mL), 3-hexyne (4 mmol, when applied), 1,3-butadiene (4 mmol), and Ph₂Zn (3.6 mmol) at 30 °C for the period of time indicated. ^{*b*} Yes and no correspond to 3-hexyne applied and not applied, respectively. ^{*c*} In addition to **6** or **7**, **8** [n = 2, R = PMP (ca. 20%, based on ¹H NMR, entry 2); n = 1, R = PMP (ca. 10%, entry 4); n = 2, R = Bn (ca. 8%, entry 6); n = 1, R = Bn (ca. 14%, entry 8)] was produced.

3-hexyne, each of **6a** and **6b** was contaminated by a considerable amount of **8** [n = 2, R = PMP (ca. 20%, based on ¹H NMR, entry 2) and n = 1, R = PMP (ca. 10%, entry 4), respectively].⁹

The lactamines of benzylamine, in the presence of 3-hexyne, provided the expected products **7a** and **7b**, albeit in modest yields (entries 5 and 7). Much better yields were recorded when the reactions were undertaken in the absence of 3-hexyne (entries 6 and 8). From a practical viewpoint, however, the former conditions are strongly recommended, since each of the byproducts **8** [n = 2, R = Bn (ca. 8%,

(9) Since 8 was hardly separable from 6 and 7, the yields of these products were estimated on the basis of ¹H NMR spectra of the mixtures.

entry 6) and n = 1, R = Bn (ca. 14%, entry 8)] formed under the latter conditions was hardly separable from **7a** and **7b**, respectively, by conventional column chromatography.⁹

The formation of 8 (and also 5) as the byproduct is quite general for all the reactions undertaken in the absence of 3-hexyne. The mechanism by which 5 and 8 is formed, especially the origin of a hydride that might be involved for the activation of 1,3-butadiene as a crotyl anion equivalent, is not clear at the moment.

The findings disclosed here clearly indicate that 3-hexyne serves as a critical spectator ligand and effects the selective formation of 1 and 6 for aromatic amines and 2 and 7 for aliphatic amines.

The contrasting reactivity between Ph_2Zn (yielding 1 and 6 or 2 and 7) and Me_2Zn (yielding 3 or 4) may be attributed to the lower activation energy of the reductive elimination process of Ni(0) from **III** or **IV** (R' = Ph) as compared with that from **III** or **IV** (R' = Me), which precludes 3-hexyne from undergoing coordination-insertion over these Ni(II) complexes.

In summary, under the catalysis of Ni(acac)₂, Ph₂Zn reacts with the aldimines of *p*-anisidine incorporating one molecule of 1,3-butadiene to provide (3E)-5-phenyl-3-pentenylamines **1** or their 1-(ω -hydroxyalkyl)-substituted derivatives **6** selectively. On the other hand, under the identical conditions, the aldimines of benzylamine selectively incorporated two molecules of 1,3-butadiene, yielding (3E,7E)-9-phenyl-3,7nonadienylamines 2 or their 1-(ω -hydroxyalkyl)-substituted derivatives 7 selectively. In these reactions, 3-hexyne serves as a spectator ligand and bestows high selectivity upon the reaction; otherwise, inseparable mixtures of 1, 2 and 5, 6and 8, or 7 and 8, result. As aldehydes, aromatic aldehydes and aliphatic aldehydes as well as ω -hydroxyaldehydes (lactols) nicely participate in the reaction. Finally, it should be noted that the reaction can be performed nearly at room temperature (30 °C) in one flask without removing the water generated during in situ preparation of aldimines and without using any phosphine ligands. The success of nucleophilic addition of electronically neutral 1,3-butadiene to the putative aldimines of low reactivity, especially those composed of aliphatic aldehydes and aliphatic amines, also should be noted.

Acknowledgment. Financial support from the Ministry of Education, Culture, Sports, Science and Technology, Japanese Government [Grant-in-Aid for Scientific Research (B) 16350058 and Priority Areas 17035065 and 18037059], is gratefully acknowledged.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0703480

⁽⁸⁾ The reaction was performed typically as follows (preparation of **2a**): Into a N₂ purged two-necked round bottom flask containing benzylamine (214 mg, 2.0 mmol) were added THF (2 mL) and benzaldehyde (106 mg, 1.0 mmol) via syringe. The mixture was stirred at 30 °C overnight (aldimine, R_f 0.57, hexane:ethyl acetate = 4:1, v/v). Into this mixture were introduced a solution of Ni(acac)₂ (25.7 mg, 0.1 mmol) in THF (3.0 mL) via cannula and 3-hexyne (457 μ L, 4.0 mmol), butadiene (400 μ L, 4.0 mmol), and Ph₂Zn (3.6 mmol). The mixture was stirred at 30 °C for 3 h, then poured into ice-water (25 mL) and extracted with ethyl acetate (25 mL). The water phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was dried (MgSO₄) and concentrated in vacuo, and the residue was subjected to column chromatography over silica gel (eluent; hexane/ethyl acetate = 200:1, v/v) to give **2a** [R_f 0.58, (hexane/ethyl acetate = 4:1, v/v)] in 94% yield.