



## Nickel-catalyzed multi-component coupling reaction of aldimine, alkyne, and dimethylzinc via dimerization of butadiene

Masanari Kimura<sup>a,\*</sup>, Mariko Togawa<sup>b</sup>, Yasushi Tatsuyama<sup>b</sup>, Kimiko Matsufuji<sup>a</sup>

<sup>a</sup> Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

<sup>b</sup> Graduate School of Science and Technology, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

### ARTICLE INFO

#### Article history:

Received 21 February 2009

Revised 12 April 2009

Accepted 23 April 2009

Available online 3 May 2009

#### Keywords:

Nickel

Diene

Alkyne

Aldimine

Dimethylzinc

### ABSTRACT

In the presence of a Ni/phosphine ligand catalyst, dimethylzinc, alkyne, butadiene, aldehyde, and primary amine were successively combined via dimerization of butadiene to provide (3*E*,7*E*,10*Z*)-dodecatrienylamine in good yields with excellent regio and stereoselectivities.

© 2009 Elsevier Ltd. All rights reserved.

Multi-component coupling reaction can be challenging, yet offers one of the most efficient and versatile synthetic strategies for C–C bond formation.<sup>1</sup> For the oligomerization and polymerization of butadiene, the use of a Ni/phosphine ligand catalyst allowed the formation of  $\eta^1, \eta^3$ -allylnickel species, which then reacted with aldehydes to provide complex mixtures of regio- and stereoisomers of dienyl and trienyl homoallyl alcohols.<sup>2</sup> Unfortunately, precise control of the nucleophilic allylation of carbonyls by butadiene, by virtue of oxidative cyclization of butadiene with Ni(0) complexes, has proved to be extremely problematic so far (Scheme 1).<sup>3</sup>

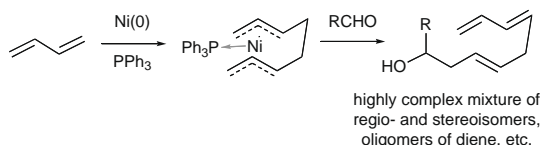
Recently, we have developed a highly regio- and stereo-controlled methodology of C–C bond formation featuring a Ni-catalyzed, five-component coupling reaction involving dimethylzinc, alkyne, butadiene, aldehydes, and primary amines.<sup>4</sup> The reaction scheme, however, was dependent on the type of amines: aromatic

amines provided 3,6-octadienylamines, whereas aliphatic amines furnished 3,7,10-dodecatrienylamines via bis-butadiene Ni(0) complex. Herein, we disclose that the Ni/phosphine ligand catalyst can readily promote the dimerization of butadiene to generate  $\eta^1, \eta^3$ -allylnickel species (as an octadienyl carbanion), followed by a multi-component coupling reaction involving alkyne, aldimines, and dimethylzinc to afford (3*E*,7*E*,10*Z*)-dodecatrienylamine in excellent yields, irrespective of the amine.

The coupling reaction was carried out as follows. A mixture of *p*-anisidine and benzaldehyde in dry THF was stirred at room temperature. Into a flask containing nickel catalyst and phosphine ligand purged with nitrogen were successively added THF, the above prepared solution via cannula, butadiene, 3-hexyne, and dimethylzinc, and the reaction mixture was stirred at room temperature.<sup>5</sup> As summarized in Table 1, the reaction course was significantly influenced by phosphine ligands. In the presence of PPh<sub>3</sub>, the reaction was predominated over the multi-component coupling involving dimerization of two molecules of butadiene providing dodecatrienylamine **2a** in excellent yield (Table 1, run 2).

Other bidentate phosphine ligands such as dppe, dppp, dpbb, and dppf displayed similar reactivities affording **2a** in good to excellent yields (Table 1, runs 2–6). In the absence of phosphine ligands, however, the Ni catalyst promoted the five-component successive coupling reactions of dimethylzinc, alkyne, butadiene, aldehyde, and amine to afford dienylamine **1a** in a high yield (Table 1, run 1).

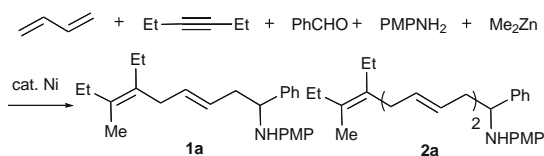
As shown in Table 2, our multi-component coupling reaction involving the Ni/phosphine ligand catalyst was applied to a wide



**Scheme 1.** Ni/PPh<sub>3</sub>-promoted C–C bond formation via bis- $\pi$  allylnickel.

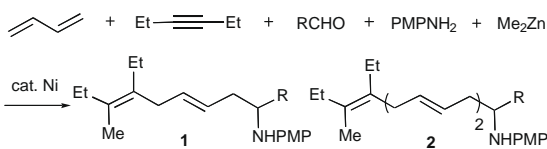
\* Corresponding author. Tel.: +81 95 819 2677; fax: +81 95 819 2684.

E-mail address: [masanari@nagasaki-u.ac.jp](mailto:masanari@nagasaki-u.ac.jp) (M. Kimura).

**Table 1**Ni-catalyzed multi-component connection reaction of aldimine, alkyne, butadiene, and Me<sub>2</sub>Zn<sup>a</sup>

Run	Ligand	Time (h)	Yield (%)	
			<b>1a</b>	<b>2a</b>
1	None	3	91	0
2	PPh <sub>3</sub>	3	0	87
3	dppe	24	0	85
4	dppp	24	0	72
5	dppb	24	0	63
6	dppf	6	0	87

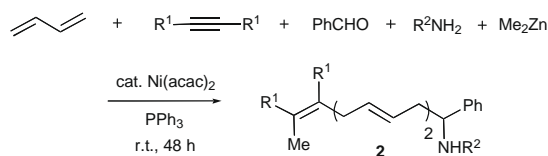
<sup>a</sup> Reaction conditions: PhCHO (1 mmol), PMPNH<sub>2</sub> (2 mmol) in THF (2 mL) at room temperature, and then Ni(acac)<sub>2</sub> (0.1 mmol), PPh<sub>3</sub> (0.2 mmol), or bidentate phosphine ligand (0.1 mmol) in THF (3 mL), 3-hexyne (4 mmol), butadiene (4 mmol), Me<sub>2</sub>Zn (3.6 mmol) at room temperature.

**Table 2**Ni-catalyzed multi-component connection reaction of various aldehydes<sup>a</sup>

Run	Aldehyde R	PPh <sub>3</sub> (mmol)	Time (h)	Yield (%)	
				<b>1</b>	<b>2</b>
1	<i>p</i> -MeOC <sub>6</sub> H <sub>5</sub>	0	2	<b>1b</b> : 88	<b>2b</b> : 0
2	<i>p</i> -MeOC <sub>6</sub> H <sub>5</sub>	0.2	3	0	68
3	<i>p</i> -ClC <sub>6</sub> H <sub>5</sub>	0	1	<b>1c</b> : 97	<b>2c</b> : 0
4	<i>p</i> -ClC <sub>6</sub> H <sub>5</sub>	0.2	3	0	77
5	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	0	1	<b>1d</b> : 87	<b>2d</b> : 0
6	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	0.2	3	0	64
7	<i>i</i> -Pr	0	1	<b>1e</b> : 84	<b>2e</b> : 0
8	<i>i</i> -Pr	0.2	3	0	74
9		0	3	<b>1f</b> : 71	<b>2f</b> : 0
10		0.2	6	0	78
11		0	2	<b>1g</b> : 86	<b>2g</b> : 0
12		0.2	6	0	86

<sup>a</sup> Reaction conditions: PhCHO (1 mmol), PMPNH<sub>2</sub> (2 mmol) in THF (2 mL) at room temperature, and then Ni(acac)<sub>2</sub> (0.1 mmol), PPh<sub>3</sub> (0.2 mmol or none) in THF (3 mL), 3-hexyne (4 mmol), butadiene (4 mmol), Me<sub>2</sub>Zn (3.6 mmol) at room temperature for 3 h.

variety of aldehydes. For aromatic aldehydes with an electron-donating group or a halogen (Table 2, runs 1–4), the multi-component coupling reaction proceeded smoothly, in which the presence of PPh<sub>3</sub> accelerated the dimerization of butadiene to exclusively afford trienyamines **2**. For aliphatic aldehydes, the presence of PPh<sub>3</sub> favored the formation of trienyamine **2**, whereas its absence favored dienyamine **1** (Table 2, runs 5–8). The stability of the present reaction in the presence of water, which is generated during the in situ formation of an aldimine between the aldehyde and primary amine, encouraged us to investigate in detail our coupling reaction using cyclic hemiacetals.<sup>6</sup> Depending on the catalytic system, 2-hydroxy-1-oxacyclopentane-*p*-anisidine imine afforded dienyamino alcohol **1f** or trienyamino alcohol **2f** (Table 2, runs 9 and 10); similarly, 2-hydroxy-1-oxacyclohexane-*p*-anisidine

**Table 3**Ni-catalyzed multi-component connection reaction of various amines<sup>a</sup>

Run	Alkyne R <sup>1</sup>	Amine R <sup>2</sup>	Yield of <b>2</b> (%)
1	Et	C <sub>6</sub> H <sub>5</sub>	<b>2h</b> : 78
2	Et	<i>p</i> -BrC <sub>6</sub> H <sub>5</sub>	<b>2i</b> : 88
3	Et	<i>p</i> -ClC <sub>6</sub> H <sub>5</sub>	<b>2j</b> : 63
4	Et	Bn	<b>2k</b> : 74 (94) <sup>b</sup>
5	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>5</sub>	<b>2l</b> : 73

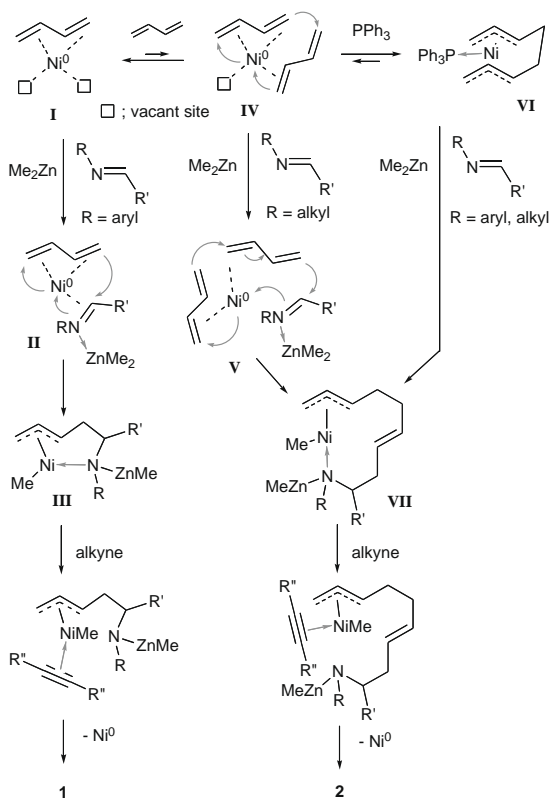
<sup>a</sup> Reaction conditions: PhCHO (1 mmol), amine (2 mmol) in THF (2 mL) at room temperature, and then Ni(acac)<sub>2</sub> (0.1 mmol), PPh<sub>3</sub> (0.2 mmol) in THF (3 mL), alkyne (4 mmol), butadiene (4 mmol), Me<sub>2</sub>Zn (3.6 mmol) at room temperature.

<sup>b</sup> **2k** was obtained in 94% in the absence of PPh<sub>3</sub>.

imine underwent the coupling reaction to afford the corresponding amino alcohols (Table 2, runs 11 and 12).

In the presence of PPh<sub>3</sub>, aldimine composed of aromatic amine tends to undergo dimerization of butadiene to provide trienyamines **2h–2j** in excellent yields (Table 3, runs 1–3). On the other hand, aliphatic amine gave trienyamine **2**, irrespective of the presence of PPh<sub>3</sub>; for example, benzylamine-imine provided trienyamine **2k** exclusively, even in the absence of PPh<sub>3</sub> (Table 3, run 4). Diphenylacetylene served as a capable carbon source in providing the desired coupling product **2**, as well as 3-hexyne (Table 3, run 5).

The proposed reaction mechanism for the multi-component coupling reaction catalyzed by Ni/phosphine ligand catalyst is



**Scheme 2.** Ni-catalyzed selective coupling reaction of 2,3-butadiene, aldimine, alkyne, and Me<sub>2</sub>Zn.

shown in Scheme 2. Aromatic amine-imines would react with mono butadiene-Ni(0) species **I**, in the presence of dimethylzinc, to form azanickelacyclo intermediate **III** providing dienylamine **1** by virtue of the insertion of alkyne. On the other hand, for less reactive aliphatic amine-imines, the potential of **I** to undergo oxidative cyclization might be insufficient to lead to **III**.<sup>7</sup> Thus, a small equilibrium concentration and the less populated bis-butadiene-nickel(0) complex **IV** are assumed to display higher reactivity than **I** owing to its greater polarizability, and would be followed by cis-insertion of an alkyne at the terminal carbon of the allylnickel moiety giving rise to trienylamine **2** through azanickelacyclo intermediate **VII**.<sup>8</sup> The reaction feature of these multi-component coupling reactions is consistent with the insertion of alkynes toward a  $\pi$ -allylnickel(II) complex to form 1,4-pentadienyl nickel intermediate.<sup>9</sup> In the presence of PPh<sub>3</sub>, the butadiene would quickly dimerize to give more nucleophilic bis- $\pi$ -allylnickel species **VI**,<sup>10</sup> which would readily participate in the reaction with aldimines to provide trienylamine **2** via insertion of an alkyne involving a similar allylnickel intermediate **VII**, irrespective of the nature of the primary amines.

In summary, we have developed a Ni-catalyzed multi-component coupling reaction with alkyne, aldimines, and dimethylzinc to afford (3*E*,7*E*,10*Z*)-dodecatrienylamine in excellent yields via  $\eta^1, \eta^3$ -allylnickel species, involving the dimerization of butadiene induced by phosphine ligands. The applicability and scope of this method for the asymmetric syntheses of terpenes and physiologically active molecules are currently under investigations.

## Acknowledgment

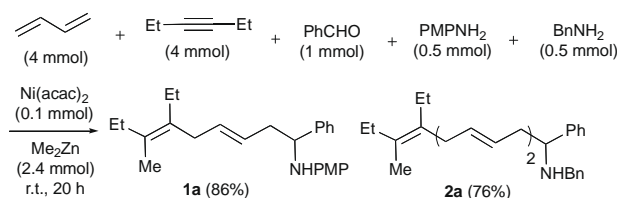
We thank financial support from the Ministry of Education, Culture, Sports, Science, and Technology, of the Japanese Government.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.086.

## References and notes

- (a) Tsuji, J. *Transition Metal Reagents and Catalysis*; Wiley: Chichester, 2000; (b) Kurosawa, H.; Yamamoto, A. *Fundamentals of Molecular Catalysis*; Elsevier: Amsterdam, 2003; (c) Tamaru, Y. *Modern Organonickel Chemistry*; Wiley-VCH: Weinheim, 2005.
- (a) Ziegler, K.; Wilms, H. *Justus Liebig's Ann. Chem.* **1950**, 567, 1; (b) Jolly, P. W.; Jonas, K.; Krüger, C.; Tsay, Y.-H. *J. Organomet. Chem.* **1971**, 33, 109; (c) Benn, R.; Büssemeier, B.; Holle, S.; Jolly, P. W.; Mynott, R.; Tkatchenko, I.; Wilke, G. *J. Organomet. Chem.* **1985**, 279, 63; (d) Heimbach, P.; Kluth, J.; Schenkluhn, H.; Weimann, B. *Angew. Chem., Int. Ed.* **1980**, 19, 569.
- (a) Baker, R. *Chem. Rev.* **1973**, 73, 487; (b) Akutagawa, S. *Bull. Chem. Soc. Jpn.* **1976**, 49, 3646; (c) Baker, R.; Crimmin, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1264; (d) Wilke, G. *Angew. Chem., Int. Ed.* **1988**, 27, 185.
- Kimura, M.; Kojima, K.; Tatsuyama, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, 128, 6332.
- See Supplementary data for details.
- (a) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, 126, 14360; (b) Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, 7, 637; (c) Kojima, K.; Kimura, M.; Tamaru, Y. *Chem. Commun.* **2005**, 4717; (d) Kimura, M.; Mori, M.; Mukai, N.; Kojima, K.; Tamaru, Y. *Chem. Commun.* **2006**, 2813; (e) Kojima, K.; Kimura, M.; Ueda, S.; Tamaru, Y. *Tetrahedron* **2006**, 62, 7512; (f) Kimura, M.; Tatsuyama, Y.; Kojima, K.; Tamaru, Y. *Org. Lett.* **2007**, 9, 1871.
- (a) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, 38, 3386; (b) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, 127, 201.
- Under similar catalytic system, exposure of same amount of *p*-anisidine (0.5 mmol) and benzylamine (0.5 mmol) to PhCHO (1 mmol) provided a mixture of dienylamine **1a** (86%) and trienylamine **2a** (76%) (Eq 1). Dienylamine **1a** was successfully formed from *p*-anisidine, whereas trienylamine **2a** was produced by benzylamine. This result implies the reaction feature depends on the electrophilicity of aldimine generated from aromatic amine or aliphatic amine as shown in Scheme 2. It seems to rule out the alternative reaction mechanism that amine or the corresponding aldimine acts as a ligand to enhance the nucleophilicity of allylnickel species.



- (a) Jolly, P. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, (b) Billington, D. C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 423; (c) Chiusoli, G. P. *Acc. Chem. Res.* **1973**, 6, 422; (d) Casser, L.; Chiusoli, G. P.; Guerrieri, F. *Synthesis* **1973**, 509; (e) Llebaria, A.; Moreto, J. *J. Organomet. Chem.* **1993**, 452, 1; (f) Ikeda, S.; Cui, D.-M.; Sato, Y. *J. Org. Chem.* **1994**, 59, 6877; (g) Cui, D.-M.; Tsuzuki, T.; Miyake, T.; Ikeda, S.; Sato, Y. *Tetrahedron* **1998**, 54, 1063.
- G. Wilke et al. have been established that a Ni(0) complex containing two molecules of butadiene and PPh<sub>3</sub> readily undergoes intramolecular rearrangement to give bis( $\pi$ -allyl)nickel species: (a) Jolly, P. W.; Wilke, G. In *The Organic Chemistry of Nickel*; Academic Press: New York, 1974; Vols. I and II, Ni-catalyzed nucleophilic allylation of carbon monoxide via bis- $\pi$ -allylnickel in the presence of PPh<sub>3</sub> ligand has been reported: (b) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2002**, 124, 10008; (c) Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* **2004**, 126, 5956; (d) Takimoto, M.; Kajima, Y.; Sato, Y.; Mori, M. *J. Org. Chem.* **2005**, 70, 8605.