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Nickel(0)-catalyzed diastereoselective three-component coupling of 1,3-dienes, aldehydes, and organometallic reagents: influence of organometallic reagents on diastereoselectivity

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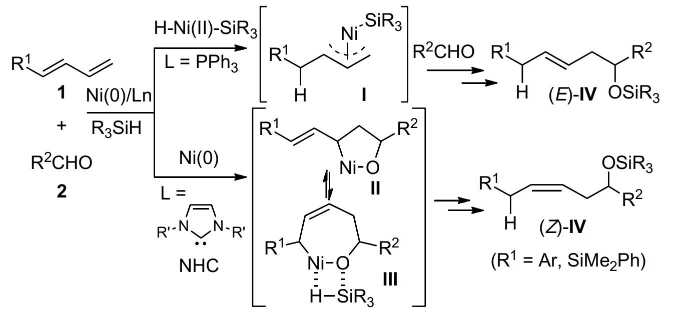
ABSTRACT

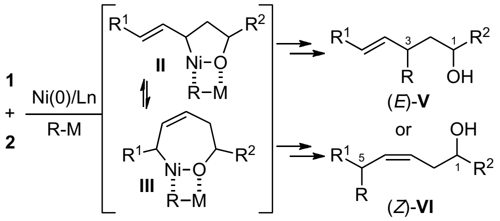
A nickel-catalyzed diastereoselective alkylative three-component coupling of 1,3-diene and aldehyde with organoboron or organosilicon reagents has been realized. The diastereoselectivity was dramatically changed depending on the class of organometallic reagents. The reaction using $ArB(OH)_2$ in the presence of PPh_3 afforded 1,3-*syn*-substituted 4-penten-1-ol derivative as a single diastereomer. On the other hand, the coupling reaction with tetraorganosilicon reagent using NHC as a ligand under similar conditions exclusively produced the corresponding 1,3-*anti* isomer.

Multicomponent coupling of more than three compounds in one pot has been a powerful and useful methodology for the construction of complex molecules in recent synthetic organic chemistry.[1] We have reported nickel-catalyzed stereoselective three-component coupling of 1,3-diene, aldehyde, and silanes (Scheme 1).[2–4] The reaction course and the stereochemistry of coupling products are controlled by the properties of ligands. In the presence of PPh_3 as a ligand, the reaction proceeds via π-allylnickel intermediate **I** to give the (*E*)-homoallylic alcohol derivative (*E*)-**IV**. On the other hand, the reaction using N-heterocyclic carbene (NHC) as a ligand affords the coupling product (*Z*)-**IV** exclusively through σ-bond metathesis between nickelacycle **III** and silane.



Scheme 1. Nickel-catalyzed stereoselective three-component coupling of 1,3-diene, aldehyde, and silane.

If the organometallic reagent (R–M) could be used for the latter 1,3-diene-aldehyde coupling using NHC ligand instead of silane, the reaction would proceed via a transmetallation process (Scheme 2).[5] That is, nickelacycle **II** or **III**, which was formed by oxidative cycloaddition of diene **1** and aldehyde **2** to zero-valent nickel, should react with an organometallic reagent to afford the corresponding coupling product (*E*)-**V** or (*Z*)-**VI** along with the introduction of an R group through further carbon–carbon bond formation.[6] Here, we report a regio- and stereoselective alkylative three-component coupling of 1,3-diene, aldehyde, and organometallic reagent catalyzed by nickel(0) complex.



Scheme 2. Plan for the alkylative three-component coupling of 1,3-diene, aldehyde, and organometallic reagent.

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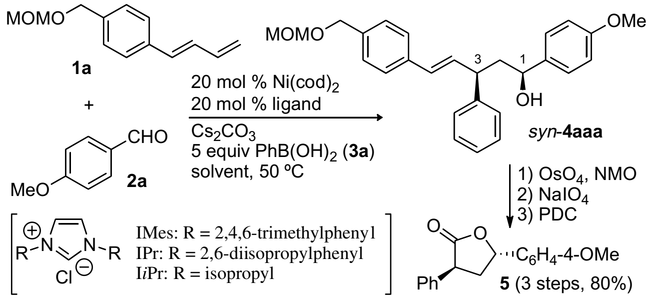
Table 1

Optimization of the reaction conditions using phenylboronic acid (**3a**)

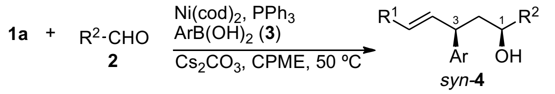


Run	Ligand	Solvent	Cs_2CO_3 (mol %)	Time (h)	Yield (%, *syn*:*anti*)
1	IMes·HCl	THF	40	60	43 (6:1)
2	IMes·HCl	CPME	40	60	40 (>50:1)
3	IMes·HCl	CPME	300	36	62 (>50:1)
4	IPr·HCl	CPME	300	27	27 (3:1)
5	IiPr·HCl	CPME	300	17	50 (>50:1)
6	PPh_3	CPME	300	15	75 (>50:1)
7[a]	PPh_3	CPME	300	15	80 (>50:1)

[a] Catalyst loading: $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %).

Table 2

Three-component coupling of various substrates in the presence of $ArB(OH)_2$ (**3**)[a]



Run	Aldehyde (**2**) (R^2=)	Ar-B(OH)$_2$ (**3**) (Ar=)	yield of *syn*-**4**[b] (reaction time)
1	**2a**: 4-$MeOC_6H_4$	**3b**: 4-$MeOC_6H_4$	**4aab**: quant (8 h)
2	**2b**: Ph	**3a**	**4aba**: 80% (10 h)
3[c]	**2c**: 4-MeC_6H_4	**3a**	**4aca**: 72% (12 h)
4	**2d**: 4-$CF_3C_6H_4$	**3a**	**4ada**: 33% (12 h)
5	**2d**	**3b**	**4adb**: 57% (17 h)
6	**2e**: 2-Naphthyl	**3a**	**4aea**: 82% (13 h)
7	**2f**: 2-Furyl	**3a**	**4afa**: 65% (16 h)
8[c]	**2g**: Me_2CHCH_2	**3a**	**4aga**: 63% (1 h)
9[c]	**2h**: Me_2CH	**3a**	**4aha**: 86% (2 h)

[a] Reaction conditions: diene (1 equiv), aldehyde (2 equiv), $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %), $ArB(OH)_2$ (5 equiv), Cs_2CO_3 (3 equiv), CPME, 50 °C.

[b] In all cases, the ratio of *syn*-isomer to *anti*-isomer was >50 to 1.

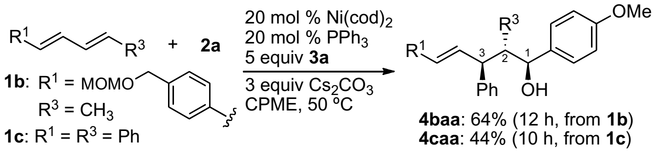
[c] Catalyst loading: $Ni(cod)_2$ (20 mol %), PPh_3 (20 mol %).

To examine the feasibility of the alkylative multicomponent reaction, we set out to investigate the coupling of 1,3-diene **1a** and *p*-anisaldehyde (**2a**) using readily available phenylboronic acid (**3a**) as a coupling partner (Table 1). First, according to our previously reported procedure,[2b–d] a mixture of **1a**, **2a**, and **3a** with 20 mol % of a Ni(0)-IMes catalyst, which was prepared from Ni-(cod)$_2$, IMes·HCl, and Cs_2CO_3, in THF was stirred at 50 °C for 60 h (run 1). As a result, the coupling product 4-penten-1-ol derivative **4aaa** was obtained as an inseparable mixture of diastereomers with respect to C1 and C3 positions in a total yield of 43% at a ratio of 6 to 1. After the derivation of **4aaa** into **5**, NOESY experiments of **5** were conducted, and the relative configurations of the hydroxy group at the C1 position and the phenyl group at the C3 position of the major diastereomer were determined to be 1,3-*syn* orientation.[7] Encouraged by this result, we continued to examine the coupling reaction using **3a** to improve the yield of *syn*-**4aaa**. Investigation of the impact of an organoboron reagent and solvent on the diastereoselectivity revealed that the reaction using **3a** in CPME (cyclopentyl methyl ether) improved the selectivity, and only *syn*-**4aaa** isomer was obtained as a single diastereomer (run 2).[8] When the amount of Cs_2CO_3 used in this reaction was increased to 300 mol %, the yield of *syn*-**4aaa** was increased to 62% (run 3).[9] After ligand screening under the same conditions (runs 4–6), we found that the use of PPh_3 as a ligand accelerated the reaction rate and improved the yield of *syn*-**4aaa** to 75% (run 6). Furthermore, the coupling reaction with lower catalyst loading (10 mol %) also proceeded to give the desired *syn*-**4aaa** in 80% yield (run 7).

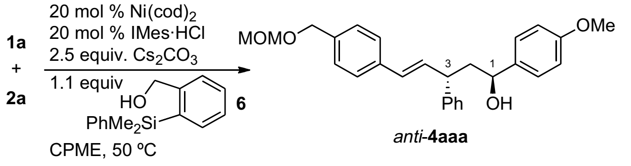
Using the optimal reaction conditions, coupling reactions of **1a** and various aldehydes with arylboronic acid **3** were investigated (Table 2). When *p*-anisylboronic acid (**3b**) was used instead of **3a**, the reaction of **1a** and **2a** was completed within 8 h to afford *syn*-**4aab** in quantitative yield (run 1). The reaction of **1a** with benzaldehyde (**2b**) and the reaction with *p*-tolualdehyde (**2c**) in the presence of **3a** also proceeded smoothly to give the corresponding *syn*-**4aba** in 80% yield and *syn*-**4aca** in 72% yield, respectively (runs 2 and 3). Although the coupling of **1a** and aldehyde **2d** with **3a** provided the product *syn*-**4ada** in low yield (33%), the use of **3b** instead of **3a** for the same reaction improved the yield of *syn*-**4ada** to 57% (runs 4 and 5). In the case of 2-naphthaldehyde (**2e**), the coupling with **1a** and **3a** afforded *syn*-**4aea** in 82% yield (run 6). On the other hand, when the heteroaromatic aldehyde **2f** was used for the coupling, the desired product *syn*-**4afa** was obtained in 65% yield (run 7). Aliphatic aldehydes were also applicable to the three-component coupling with **1a** and **3a**, and the products *syn*-**4aga** from **2g** and *syn*-**4aha** from **2h** were obtained in 63% yield and 86% yield, respectively (runs 8 and 9).

It is noteworthy that the reaction of unsymmetrical diene **1b**, *p*-anisaldehyde (**2a**), and **3a** proceeded in a regio- and diastereoselective manner, giving **4baa**, whose consecutive three-stereogenic centers were entirely controlled to be a 1,2-*anti*- and 1,3-*syn*-substitution pattern, in 64% yield as a sole product (Scheme 3). Furthermore, when (1*E*,3*E*)-1,4-diphenyl-1,3-butadiene (**1c**) was used as a substrate for the coupling with **2a** and **3a** under the same conditions, the 1,2-*anti*- and 1,3-*syn*-substituted coupling product **4caa** was obtained in 44% yield as a single diastereomer.

During the course of further screening of other organometallic reagents suitable for the three-component coupling, we found that the use of tetraorganosilicon reagent **6**, which was reported by Nakao and Hiyama,[10] dramatically changed the stereoselectivity of the alkylation. When a mixture of **1a**, **2a**, and **6** with a Ni(0)-IMes catalyst in CPME was stirred at 50 °C for 15 h, *anti*-**4aaa**, whose relative configuration was determined in the same way as that of *syn*-**4aaa**,[7] was obtained as a single diastereomer (Scheme 4, Condition A). This intriguing phenomenon prompted us to investi-



Scheme 3. Coupling reaction of internal diene and aldehyde using phenylboronic acid (**3a**).



Condition A: Addition of **6** via a cannula: 60%
Condition B: Addition of **6** over a period of 36 h by a syringe pump: 77%

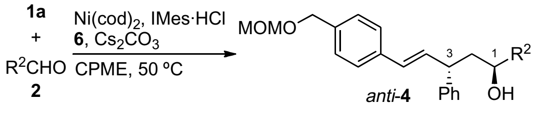
Scheme 4. Three-component coupling of 1,3-diene and aldehyde using tetraorganosilicon reagent **6**.

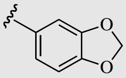
gate the *anti*-selective three-component coupling of 1,3-diene and aldehyde. However, under the above reaction conditions, some by-products, which would be formed by the addition of the phenyl group of **6** to **2a**, were obtained (data not shown). Therefore, it was necessary to suppress the formation of the by-product in order to improve the yield of *anti*-**4aaa**. Examination of the impact of conditions such as the ligand, solvent and also the reaction procedure on the *anti*-selective coupling revealed that the slow addition of organosilicon **6** was quite effective. That is, the addition of a solution of **6** in CPME to a mixture of **1a**, **2a**, Cs_2CO_3, and Ni-IMes catalyst in CPME for over a period of 36 h by a syringe pump afforded the desired product *anti*-**4aaa** in 77% yield as a sole product (Condition B).

Next, the *anti*-selective coupling reactions of various substrates in the presence of organosilicon reagent **6** were investigated under the optimized conditions (Table 3). When a diene **1a** and benzaldehyde (**2b**) were treated with **6** in the presence of a Ni-IMes catalyst under the slow addition conditions, *anti*-**4aba** was obtained in 56% yield as a single isomer (run 1). In the case of the coupling of **1a** and **2c**, additional stirring for 12 h after completion of the addition of **6** was required for the consumption of **1a**, and the yield of the desired *anti*-**4aca** was 44% (run 2). On the other hand, the reaction of **1a** and piperonal (**2i**) afforded the coupling product *anti*-**4aia** in 70% yield as a single diastereomer (run 3). Although the yield of the coupling product was lower than that in the case of the aromatic aldehyde, aliphatic aldehydes (**2g** or **2h**) were also applicable to the *anti*-selective coupling reaction, and *anti*-**4aga** (32% yield) and *anti*-**4aha** (36% yield) were obtained (runs 4 and 5).

The plausible reaction mechanism including an origin of the diastereoselectivity of the three-component coupling using organoboron or organosilicon reagent is shown in Scheme 5. First, oxidative cycloaddition of diene **1** and aldehyde **2** to a zero-valent nickel complex would give the η^3-allylalkoxynickel intermediate **7** through the five-membered oxanickelacycle **II′**.[11] The coupling of **1** and **2** with arylboronic acid **3** would proceed via transmetallation between **7** and **3** to afford the aryl-nickel intermediate **8**, which includes a styryl moiety. Then subsequent reductive elimination from **8** would occur to give the 1,3-*syn* coupling product and a zero-valent nickel complex would be regenerated (path A). In the case of the reaction using internal dienes (**1c** or **1d**), the intermediate **II′**, in which the orientation of substituents R^2 and R^3 are *anti*-relationships, could be formed to prevent the steric repulsion between R^2 and R^3.[2d] Therefore, 1,2-*anti*- and 1,3-*syn*-substituted coupling products would be obtained. On the other hand, in the reaction using a tetraorganosilicon reagent, pentacoordinate silicate **6′** would be initially formed from **6** and Cs_2CO_3.[10] It is known that a pentacoordinate silicate such as **6′** generally has a nucleophilicity, and the alkyl group on the silicon atom attacks electrophiles such as carbonyl compounds or ally halides to give the corresponding alkyl adducts.[12] From the property of **6′** as a nucleophile and the observation that only *anti*-substituted products (*anti*-**4**) were obtained in the presence of **6**, the nucleophilic backside attack of the phenyl group of **6′** to the allylalkoxynickel **7** would proceed to afford **9** having a styryl part. Consequently, the 1,3-*anti* coupling product would be obtained in a diastereoselective manner (path B).

Table 3
Three-component coupling of various substrates using tetraorganosilicon reagent **6**[a]

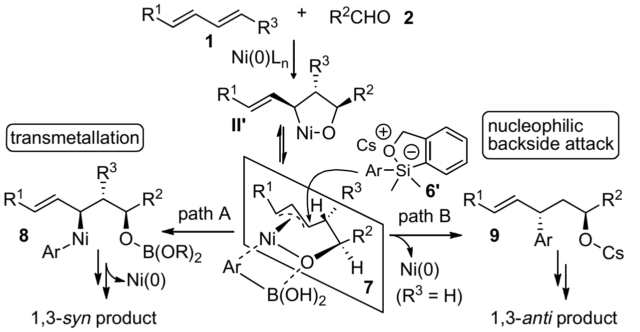


Run	Aldehyde **2** (R^2=)	Additional stirring time (h)	*anti*-**4**[b] (%)
1	**2b**: Ph	–	**4aba**: 56
2[c]	**2c**: 4-MeC_6H_4	12	**4aca**: 44
3	**2i**: 	–	**4aia**: 70
4[c]	**2g**: Me_2CHCH_2	12	**4aga**: 32
5	**2h**: Me_2CH	–	**4aha**: 36

[a] Reaction procedure: To a mixture of **1a** (1 equiv), **2** (1 equiv), $Ni(cod)_2$ (20 mol %), IMes·HCl (20 mol %), and Cs_2CO_3 (2.5 equiv) in CPME was added a solution of **6** (1.1 equiv) in CPME for over a period of 36 h by a syringe pump at 50 °C.

[b] In all cases, the ratio of *anti*-isomer to *syn*-isomer was >50 to 1.

[c] After addition of **6**, the reaction mixture was stirred at 50 °C for an additional 12 h (runs 2 and 4).



Scheme 5. Plausible reaction course: origin of the stereoselectivity.

In summary, a nickel-catalyzed diastereoselective alkylative three-component coupling of 1,3-diene, aldehyde, and organometallic reagent was realized. The diastereoselectivity was dramatically changed depending on the class of organometallic reagents. The reaction using organoboronic acid in the presence of a Ni(0)-PPh_3 catalyst proceeded via a transmetallation process with an allylalkoxynickel intermediate to give 1,3-*syn* products exclusively. On the other hand, the use of a tetraorganosilicon reagent as a coupling partner provided 1,3-*anti* products through a nucleophilic backside attack of silicate to the same allylnickel complex under similar conditions. Further investigation along these lines is now in progress.

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Supplementary data

Experimental details, determination of the relative configuration of the coupling products are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.033.

References and notes

1. (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH Gmbh and Co. KGaA: Weinheim, Germany, 2005; (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634.
2. (a) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543–4546; (b) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510–5512; (c) Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* **2004**, *6*, 1131–1133; (d) Sato, Y.;

Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. *Org. Lett.* **2007**, *9*, 5597–5599. For three-component coupling using trimethylsilyltributylstannane instead of silane, see: (e) Sato, Y.; Saito, N.; Mori, M. *Chem. Lett.* **2002**, 18–19; (f) Saito, N.; Mori, M.; Sato, Y. *J. Organomet. Chem.* **2007**, *692*, 460–471.

3. For reviews on Ni(0)-catalyzed multicomponent coupling, see: (a) Ikeda, S.-i. *Acc. Chem. Res.* **2000**, *33*, 511–519; (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473; (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. and references cited therein.
4. For recent examples of Ni(0)-catalyzed multicomponent coupling, see: (a) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699; (b) Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. *Adv. Synth. Catal.* **2004**, *346*, 905–908; (c) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360–14361; (d) Shirakawa, E.; Yamamoto, Y.; Nakao, Y.; Oda, S.; Tsuchimoto, T.; Hiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 3448–3451; (e) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201–209; (f) Kimura, M.; Kojima, K.; Tatsuyama, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 6332–6333; (g) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600–3603; (h) Ng, S.-S.; Ho, C.-Y.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 11513–11528; (i) Ho, C.-Y.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 782–785; (j) Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537–540; (k) Jayanth, T. T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5921–5924; (l) Kimura, M.; Tatsuyama, Y.; Kojima, K.; Tamaru, Y. *Org. Lett.* **2007**, *9*, 1871–1873; (m) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469–471.
5. For Ni-catalyzed reductive coupling of 1,3-diene and aldehyde using organometallic reagent in the absence or in the presence of phosphine ligand, see: (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033–4034; (b) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397–400; (c) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 656–662.
6. For a pioneering work on Ni-catalyzed alkylative coupling of 1,3-dienes and aldehydes, see: (a) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386–3388. For an intramolecular alkylative cyclization of 1,3-diene and aldehyde using Ni catalyst, see: (b) Sato, Y.; Takanashi, T.; Mori, M. *Organometallics* **1999**, *18*, 4891–4893.
7. For details of the determination of the relative configuration of the coupling products, see Supplementary data.
8. The reaction using other organoboron reagents (BPh_3 or PhB(pin)) or that in other solvents (1,4-dioxane, toluene, DMF, DMSO, or MeCN) gave poor results.
9. When the reaction was carried out in the absence of Cs_2CO_3, no coupling product was obtained. Furthermore, the reaction using other bases, such as Na_2CO_3, K_2CO_3, and K_3PO_4, gave the coupling product in low yield. Although the reason why Cs_2CO_3 is indispensable for the Ni-catalyzed three-component coupling is not clear yet, the base would activate organoboronic acids as in the case of Miyaura–Suzuki reaction. For reviews on the Miyaura–Suzuki reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (c) Suzuki, A. In *Handbook of Organopalladium Chemistry of Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley-Interscience, A John Wiley & Sons: New York, 2002; Vol. I, pp 249–262; For recent review on Ni-catalyzed cross-coupling including Miyaura–Suzuki type reaction, see: (d) Takahashi, T.; Kanno, K.-i. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH GmbH & Co. KGaA: Weinheim, 2005; pp 41–55.
10. (a) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952–6953; (b) Nakao, Y.; Sahoo, A. K.; Imanaka, H.; Yada, A.; Hiyama, T. *Pure Appl. Chem.* **2006**, *78*, 435–440.
11. Recently, the η^3-allylalkoxynickel complex from 1,3-diene and aldehyde in the presence of tricyclohexylphosphine ligand was isolated and the structure was elucidated by X-ray analysis: Ogoshi, S.; Tonomori, K.-i.; Oka, M.-a.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 7077–7086.
12. (a) Hudrlik, P. F.; Abdallah, Y. M.; Hudrlik, A. M. *Tetrahedron Lett.* **1992**, *33*, 6747–6750; (b) Hudrlik, P. F.; Arango, J. O.; Hijji, Y. M.; Okoro, C. O.; Hudrlik, A. M. *Can. J. Chem.* **2000**, *78*, 1421–1427.