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# Nickel-Catalyzed Alkylation of Aldehydes with Trialkylboranes

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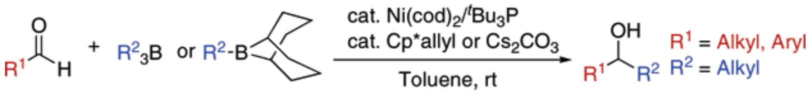
## ABSTRACT



**Nickel-catalyzed alkylation of aldehydes with trialkylboranes proceeds smoothly in the presence of a catalytic amount of 5-allyl-1,2,3,4,5-pentamethyl-1,3-cyclopentadiene or an excess of cesium carbonate to afford the corresponding secondary alcohols.**

The alkylation of aldehydes with organometallic reagents is one of the most important reactions in organic chemistry. Generally, reactive alkylmetals such as Grignard reagents are utilized to achieve this transformation. Conventional alkylborane reagents do not react with aldehydes. The few exceptional examples require highly reactive alkylborane compounds such as 1-boraadamantane[1] and dialkylhaloboranes.[2,3] On the other hand, alkylations of aldehydes with dialkylzinc[4] and trialkylaluminum[5] reagents under nickel catalysis have been reported. These reactions prompted us to develop a nickel-catalyzed alkylation reaction with alkylboranes. Herein, we report such a reaction. To the best of our knowledge, this is the first example of a transition metal-catalyzed 1,2-addition reaction of alkylboranes.[6]

Treatment of benzaldehyde (**1a**, 0.5 mmol) with triethylborane (**2a**, 1.0 mmol) in the presence of 5 mol % of $Ni(cod)_2$ and 10 mol % of $^tBu_3P$ in toluene (5 mL) at room temperature for 24 h afforded 1-phenyl-1-propanol (**3a**) in low yield (45%) (Table 1, entry 1).[7] Half of the **1a** remained unchanged. In the reaction flask, a black suspension was formed. It is assumed that bulky phosphines dissociated easily from the nickel center, which resulted in the generation of catalytically inactive nickel species. We then examined the effect of various additives (Table 1). As a result, we found that olefins were stabilizers of active zerovalent nickel. A monodentate olefin, 3,3-dimethyl-1-butene, was not effective (entry 2) while a bidentate diene, norbornadiene, slightly improved the yield (entry 3). We surveyed conjugated 1,3-dienes, which would be expected to bind nickel more tightly. Fortunately, 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene derivatives were effective stabilizers in this reaction. An addition of 0.1 equiv of 1,2,3,4,5,5-hexamethyl-1,3-cyclopentadiene (Cp*Me) improved the yield to 70% (entry 4). Moreover, 5-allyl-1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (Cp*allyl) drastically enhanced the efficiency of the ethylation (entry 5). Under the optimized conditions (5 mol % of $Ni(cod)_2$, 10 mol % of $^tBu_3P$, and 0.1 equiv of Cp*allyl in toluene (5 mL) at 0 °C for 24 h), the desired alcohol was obtained in excellent yield (entry 6).

Next, we examined butylation reaction of **1a** with tributylborane (**2b**). However, to our surprise, the desired product, 1-phenyl-1-pentanol (**3b**), was obtained in only 2% yield even with the aid of Cp*allyl (entry 7). Considering

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[1] Mikhailov, B. M.; Baryshnikova, T. K.; Shashkov, A. S. *J. Organomet. Chem.* **1981**, *219*, 301−308.

[2] Kabalka, G. W.; Wu, Z.; Trotman, S. E.; Gao, X. *Org. Lett.* **2000**, *2*, 255−256.

[3] Additions of trialkylboranes under electrochemical and free radical conditions were reported: (a) Choi, J. H.; Youm, J. S.; Cho, C.; Czae, M.; Hwang, B. K.; Kim, J. S. *Tetrahedron Lett.* **1989**, *39*, 4835−4838. (b) Miyaura, N.; Itoh, M.; Suzuki, A.; Brown, H. C.; Midland, M. M.; Jacob, P. *J. Am. Chem. Soc.* **1972**, *94*, 6549−6550.

[4] Burguete, M. I.; Collado, M.; Escorihuela, J.; Galindo, F.; García-verdugo, E.; Luis, S. V.; Vicent, M. J. *Tetrahedron Lett.* **2003**, *44*, 6891−6894.

[5] (a) Ichiyanagi, T.; Kuniyama, S.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1998**, 1033−1034. (b) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2232−2234.

[6] Nickel-catalyzed 1,2-addition reactions of aryl- and alkenylboronic ester derivatives have been reported. Takahashi, G.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2005**, 1459−1460.

[7] $NiCl_2$ and $Ni(acac)_2$ did not catalyze the reaction. Other ligands such as $Ph_3P$, $^nBu_3P$, and $(^cC_6H_{11})_3P$ were ineffective.

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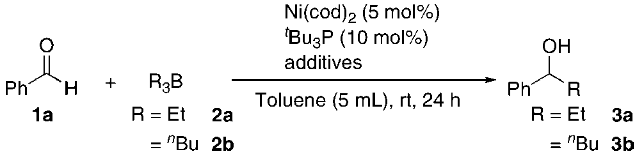
**Table 1.** Optimization for Ethylation and Butylation of Benzaldehyde (**1a**)



| entry | additives (equiv) | R$_3$B (equiv) | % yield (product) |
|---|---|---|---|
| 1 | none | **2a** (2.0) | 45 (**3a**) |
| 2 | 3,3-dimethyl-1-butene (0.3) | **2a** (2.0) | 46 (**3a**) |
| 3 | norbornadiene (0.1) | **2a** (2.0) | 58 (**3a**) |
| 4 | Cp*Me (0.1) | **2a** (2.0) | 70 (**3a**) |
| 5 | Cp*allyl (0.1) | **2a** (2.0) | 90 (**3a**) |
| 6$^a$ | Cp*allyl (0.1) | **2a** (1.2) | 93 (**3a**) |
| 7 | Cp*allyl (0.1) | **2b** (1.2) | 2 (**3b**) |
| 8 | Cp*allyl (0.1) and CsF (2.0) | **2b** (2.0) | 12 (**3b**) |
| 9 | Cp*allyl (0.1) and Cs$_2$CO$_3$ (2.0) | **2b** (2.0) | 38 (**3b**) |
| 10$^b$ | Cp*allyl (0.1) and Cs$_2$CO$_3$ (2.0) | **2b** (2.0) | 64 (**3b**) |
| 11$^b$ | Cs$_2$CO$_3$ (2.0) | **2b** (2.0) | 80 (**3b**) |
| 12$^{b,c}$ | Cs$_2$CO$_3$ (3.0) | **2b** (3.0) | 86 (**3b**) |

[a] At 0 °C. [b] 10 mL of toluene was used. [c] 8 mol % of Ni(cod)$_2$ and 19.2 mol % of $^t$Bu$_3$P were used.

tributylborane has lower reactivity than triethylborane, we screened various bases as an additive to increase the reactivity of tributylborane. Although TBAF, K$_2$CO$_3$, and Na$_2$CO$_3$ were not effective, CsF (entry 8) and Cs$_2$CO$_3$ (entry 9) improved the yield. Additionally, the concentration of nickel dramatically influenced this reaction (entry 10), and Cp*allyl was not required in this case (entry 11). Finally, with 8 mol % of Ni(cod)$_2$, 19.2 mol % of $^t$Bu$_3$P, and 3.0 equiv of Cs$_2$CO$_3$ in toluene (10 mL), butylation of benzaldehyde (**1a**) afforded **3b** in 86% yield (entry 12).

By using the optimal cesium-promoted conditions, we performed ethylation and butylation of an array of aldehydes (Table 2). Sterically hindered 2-methylbenzaldehyde (**1b**) and electron-rich 4-anisaldehyde (**1c**) underwent alkylation smoothly (entries 1, 2, and 3). Exceptionally, ethylation of electron-deficient 4-bromobenzaldehyde (**1d**) gave **3f** in moderate yield (entry 4).[8] Aliphatic aldehydes were converted to secondary alcohols without any difficulties. Alkylation of dihydrocinnamaldehyde (**1e**) furnished **3g** and **3h** in 76% and 83% yields, respectively (entries 5 and 6). The reaction of cyclohexanecarbaldehyde (**1f**) also afforded the corresponding alcohols **3i** and **3j** in good yields (entries 7 and 8). Ketone and ester functionalities were compatible under the reaction conditions (entries 9 and 10).

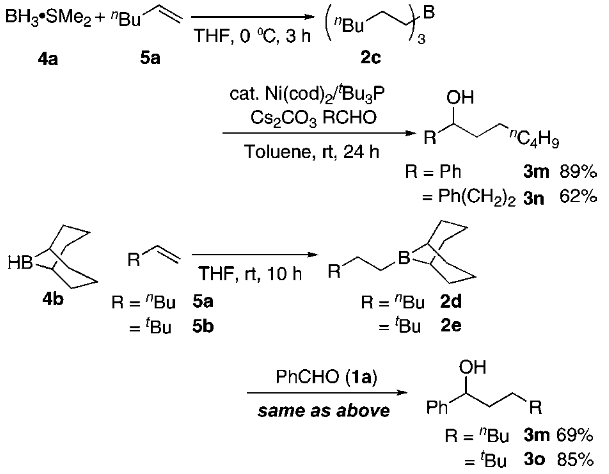
**Table 2.** Nickel-Catalyzed Alkylation of Aldehydes with Trialkylboranes$^a$

| entry | aldehyde | borane | product | yield (%)$^b$ |
|---|---|---|---|---|
| 1 | 2-MeC$_6$H$_4$CHO (**1b**) | **2a** | **3c** | 83 (100) |
| 2 | **1b** | **2b** | **3d** | 88 |
| 3 | 4-MeOC$_6$H$_4$CHO (**1c**) | **2a** | **3e** | 81 (86) |
| 4 | 4-BrC$_6$H$_4$CHO (**1d**) | **2a** | **3f** | 50 |
| 5 | Ph(CH$_2$)$_2$CHO (**1e**) | **2a** | **3g** | 76 (83) |
| 6 | **1e** | **2b** | **3h** | 83 |
| 7 | $^c$C$_6$H$_{11}$CHO (**1f**) | **2a** | **3i** | 82 (88) |
| 8 | **1f** | **2b** | **3j** | 66 |
| 9 | MeCO(CH$_2$)$_8$CHO (**1g**) | **2a** | **3k** | 84 |
| 10 | MeOCO(CH$_2$)$_4$CHO (**1h**) | **2a** | **3*l*** | 62 |

[a] For ethylation, the reaction was carried out with 2.0 equiv of Et$_3$B in the presence of 2.0 equiv of Cs$_2$CO$_3$ while for butylation, 3.0 equiv of $^n$Bu$_3$B and 3.0 equiv of Cs$_2$CO$_3$. [b] The yields in the presence of 0.1 equiv of Cp*allyl instead of Cs$_2$CO$_3$ are in parentheses.

Trialkylboranes prepared from hydroboranes and alkenes via hydroboration can be employed for this reaction (Scheme 1). Trihexylborane (**2c**) was first prepared from borane–dimethyl sulfide complex (**4a**) and 3 equiv of 1-hexene (**5a**). Treatment of benzaldehyde (**1a**) with **2c** in the presence of 8 mol % of Ni(cod)$_2$, 19.2 mol % of $^t$Bu$_3$P, and 3.0 equiv of Cs$_2$CO$_3$ afforded 1-phenyl-1-heptanol (**3m**) in 89% yield. The hexylation of **1e** also took place to give the corresponding alcohol **3n** in moderate yield. To reduce the amount of alkene used, 9-borabicyclo[3.3.1]nonane (**4b,** 9-BBN) as a hydroboration agent was preferred to **4a**. With 9-hexyl-9-BBN (**2d**), alkylation of **1a** also proceeded to furnish **3m** in 69% yield. 9-(3,3-Dimethylbutyl)-9-BBN (**2e**) prepared from **4b** and 3,3-dimethyl-1-butene (**5b**) also reacted with **1a** to provide 4,4-dimethyl-1-phenyl-1-pentanol (**3o**) in 85% yield.

**Scheme 1**



We are tempted to assume the mechanism for the alkylation of aldehyde as follows (Scheme 2). A nickel(0) species **6** initially reacts with **1a** to generate $\eta^2$-coordinated complex **7** or its resonance form **8**.[9] Subsequent transmetalation with Et$_3$B or its borate formed by the action of Cs$_2$CO$_3$ gives the intermediate **9** followed by reductive elimination to furnish **10** and to regenerate **6**. Finally, protonolysis of **10** upon

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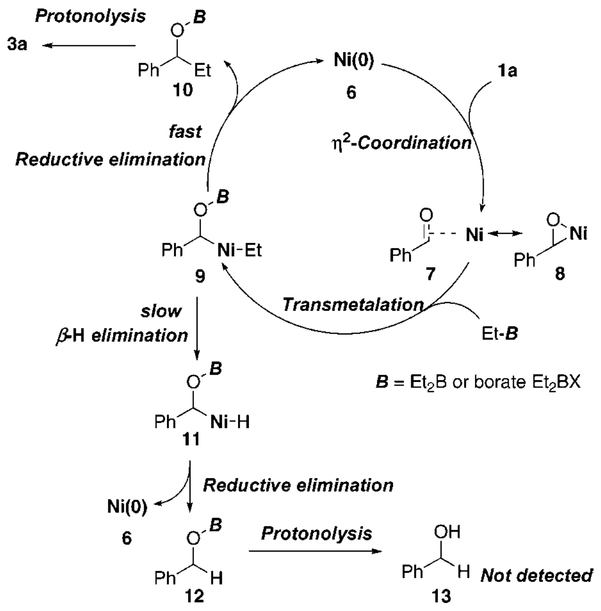
(8) The conversion of **1d** was low and about 40% of the starting material remained unchanged. The conceivable Suzuki–Miyaura coupling product was obtained in less than 2% yield. The reaction of other electron-deficient aromatic aldehydes also resulted in low conversions. For examples, ethylations of 4-trifluoromethylbenzaldehyde and 4-methoxycarbonylbenzaldehyde provided the corresponding adducts in 49% and 29% yields, respectively.

**Scheme 2**



workup afforded alcohol **3a**. If $\beta$-H elimination from the intermediate **9** occurred, subsequent reductive elimination from **11** and protonolysis of **12** would afford **13**. However, **13** was not detected. This result would indicate that reductive elimination from **9** is more rapid than $\beta$-H elimination.[10]

In conclusion, we have found the first example of 1,2-addition of trialkylboranes to aldehydes by nickel catalysis. This system allows alkylboranes to serve as promising nucleophilic alkyl sources to aldehydes.

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**Supporting Information Available:** Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) $\eta^2$-Coordinated nickel complexes with aldehydes have been reported. Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802–11803. Although the possibility of a radical pathway cannot be completely excluded, addition of a radical scavenger, TEMPO, gave no effect on yield.

(10) Unfortunately, in the case of alkylboranes having secondary alkyl groups such as $^{s}\mathrm{Bu}_3\mathrm{B}$, the reduced product **13** was mainly obtained, probably due to considerably rapid $\beta$-H elimination from the intermediate corresponding to **9**.