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Nickel-Catalyzed 1,4-Addition of Trialkylboranes to α,*β*-Unsaturated Esters: Dramatic Enhancement by Addition of Methanol

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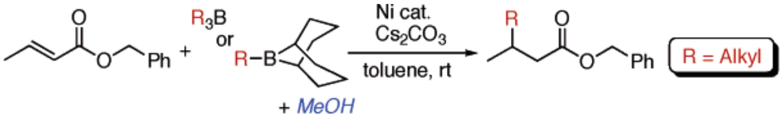
ABSTRACT



Nickel catalyst systems for 1,4-addition of trialkylboranes to α,*β*-unsaturated esters have been developed. Addition of methanol was found to be essential for the alkylation reaction with 9-alkyl-9-BBNs.

Transition metal-catalyzed 1,4-addition of alkylmetal reagents to α,*β*-unsaturated carbonyl compounds is one of the most powerful and promising carbon−carbon bond formations in organic synthesis. In particular, 1,4-addition of alkylmagnesium halides, dialkylzincs, and trialkylaluminums in the presence of copper catalysts has been developed and achieved alkylation of various unsaturated molecules involving the asymmetric version.[1] On the other hand, 1,4-addition of trialkylboranes to α,*β*-unsaturated carbonyl compounds has been much less explored. 1,4-Addition of trialkylboranes to α,*β*-unsaturated aldehydes and ketones is a well-established process under radical conditions initiated by molecular oxygen.[2] However, the radical conditions mentioned above could not be applicable to the reactions of α,*β*-unsaturated esters due to rapid radical polymerization.[3] Only photo-[4] and electrochemical[5] conditions achieved these transformations while 1,4-addition of aryl- and alkenylboronic acid derivatives to various unsaturated compounds including α,*β*-unsaturated esters became available in the presence of transition metal catalysts such as rhodium,[6] palladium,[7] and nickel.[8]

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(1) (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (b) Perlmutter, P. *Conjugate Addition Reaction in Organic Synthesis*; Tetrahedron Organic Chemistry, Ser. 9; Pergamon: Oxford, UK, 1992. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771−806. (d) Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5560−5562. Recent advances in this field: (e) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376−1378. (f) Lee, K.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182−7184. (g) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416−8417. (h) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103−9118. (i) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276−277.

(2) Brown, H. C.; Kabalka, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 714−716.

(3) Miyaura and Suzuki reported the conjugate additions of cuprous tetraalkylborates prepared from trialkylboranes, methyllithium, and copper bromide to acrylonitrile. However, the reaction with ethyl acrylate gave the desired adduct in only 44% yield with contamination by the dimerization product. See: Miyaura, N.; Itoh, M.; Suzuki, A. *Tetrahedron Lett.* **1976**, *17*, 255−258.

(4) Polykarpov, A. Y.; Neckers, D. C. *Tetrahedron Lett.* **1995**, *36*, 5483−5486.

(5) Takahashi, Y.; Yuasa, K.; Tokuda, M.; Itoh, M.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 339−340.

(6) Reviews: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844.

(7) (a) Cho, C.-S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 883−888. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768−2770. (c) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317−4324. (d) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651−9653. (e) Gini, F.; Hessen, B.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 5309−5312. (f) Yamamoto, T.; Iizuka, M.; Ohta, T.; Itoh, Y. *Chem. Lett.* **2006**, *35*, 198−199. (g) He, P.; Lu, Y.; Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 343−346.

(8) Shirakawa, E.; Yasuhara, Y.; Hayashi, T. *Chem. Lett.* **2006**, *35*, 768−769.

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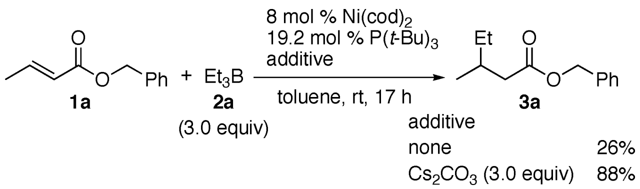
During our recent studies on the reactivity of trialkylboranes with carbonyl compounds, we found the nickel-catalyzed 1,2-addition of trialkylboranes to aldehydes.[9] Herein, we wish to report effective nickel catalyst systems for 1,4-addition of trialkylboranes to α,β-unsaturated esters. Moreover, the dramatic effect of addition of methanol in the nickel-catalyzed 1,4-addition is also described.[10]

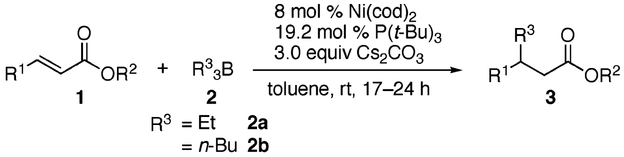
Treatment of benzyl (*E*)-crotonate (**1a**) with triethylborane (**2a**) in the presence of 8 mol % of Ni(cod)$_2$ and 19.2 mol % of P(*t*-Bu)$_3$ in toluene at room temperature, which are the optimized conditions in our previous work,[9] for 17 h afforded the 1,4-adduct, benzyl 3-methylpentanoate (**3a**), in 26% yield (Scheme 1).[11] Half of the **1a** remained untouched. According to our previous observation,[9] a stoichiometric (to triethylborane) amount of cesium carbonate was added to the reaction mixture as an activator for triethylborane. To our delight, the reaction was completed in 17 h and the desired product was obtained in 88% yield.

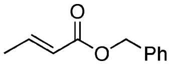
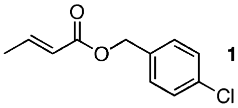
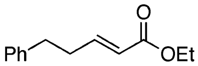
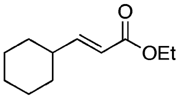
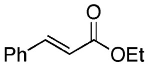
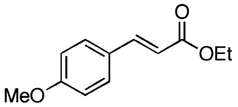
Scheme 1



With the optimized conditions in hand, we examined 1,4-addition of triethylborane to a variety of α,β-unsaturated esters (Table 1). Triethylborane reacted with **1b** smoothly to furnish **3b** in 94% yield. The conceivable Suzuki–Miyaura cross-coupling product was not obtained (entry 2). Not only crotonic acid esters but unsaturated esters having a larger alkyl group at the β position participated in the reaction. Phenylethyl- and cyclohexyl-substituted esters **1c** and **1d** were converted to **3c** and **3d** in 74% and 81% yields, respectively (entries 3 and 4). In contrast, the reaction of cinnamic acid ester **1e** resulted in low conversion and yielded a trace amount of the desired product (entry 5). Interestingly, the substitution of an electron-donating methoxy group on the aromatic ring improved the yield to 57% (entry 6). Tributylborane (**2b**) as well as triethylborane was a suitable alkylation agent. Crotonate ester **1a** underwent the butylation to provide **3g** in 87% yield while the reaction of **1b** afforded **3h** in 35% yield (entries 7 and 8). The butylations of **1c** and **1d** led to moderate conversions and yields probably due to the steric factors (entries 9 and 10).

Table 1. Nickel-Catalyzed 1,4-Addition of Triethylborane (**2a**) and Tributylborane (**2b**) to α,β-Unsaturated Esters **1**[a]

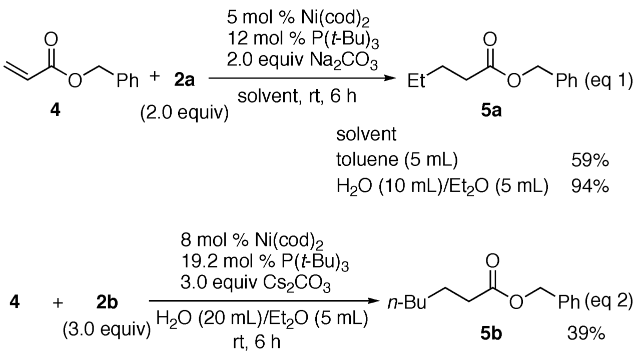


entry	1	2	3, yield (%)[b]
1	 **1a**	**2a**	**3a**, 88
2	 **1b**	**2a**	**3b**, 94
3	 **1c**	**2a**	**3c**, 74
4	 **1d**	**2a**	**3d**, 81[c]
5	 **1e**	**2a**	**3e**, trace
6	 **1f**	**2a**	**3f**, 57[d]
7	**1a**	**2b**	**3g**, 87
8	**1b**	**2b**	**3h**, 35
9	**1c**	**2b**	**3i**, 45
10	**1d**	**2b**	**3j**, 52[c, e]

[a] A mixture of **1** (0.5 mmol), **2** (3.0 equiv), Ni(cod)$_2$ (8 mol %), P(*t*-Bu)$_3$ (19.2 mol %), and Cs$_2$CO$_3$ (3.0 equiv) was stirred in toluene (5 mL) for 17–24 h at room temperature. [b] Isolated yield. [c] ^{1}H NMR yield. [d] Reduced product, ethyl 3-(4-methoxyphenyl)propanoate was also obtained in 10% yield. [e] Reduced product, ethyl 3-cyclohexylpropanoate was also obtained in 5% yield.

Next, we performed 1,4-addition of triethylborane (**2a**) to benzyl acrylate (**4**) (Scheme 2, eq 1), which is a challenging substrate since **4** can undergo polymerization much more readily. Under similar conditions for the reaction of β-sub-

Scheme 2



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(9) (a) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2005**, *7*, 4689–4691. (b) Hirano, K.; Yorimitsu, H.; Oshima, K. *Adv. Synth. Catal.* **2006**, *348*, 1543–1546.

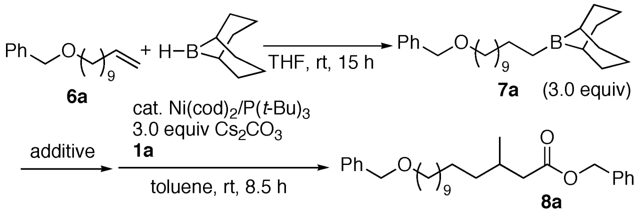
(10) Nickel-catalyzed 1,4-additions of dialkylzincs and trialkylindiums were reported. For zinc: (a) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516–517. (b) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011–5012. (c) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron*: *Asymmetry* **1992**, *3*, 581–582. (d) Corma, A.; Iglesias, M.; Martín, M. V.; Rubio, J.; Sánchez, F. *Tetrahedron*: *Asymmetry* **1992**, *3*, 845–848. (e) Yin, Y.; Li, X.; Lee, D.-S.; Yang, T.-K. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3329–3333. (f) Wakimoto, I.; Tomioka, Y.; Kawanami, Y. *Tetrahedron* **2002**, *58*, 8095–8097. For indium: (g) Pérez, I.; Sestelo, J. P.; Maestro, M. A.; Mouriño, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074–10076.

(11) NiCl$_2$ and Ni(acac)$_2$ did not catalyze the reaction. Other ligands such as PPh$_3$, P(*n*-Bu)$_3$, and P(*c*-C$_6$H$_{11}$)$_3$ were ineffective.

stituted α,β-unsaturated esters **1**, 1,4-adduct **5a** was obtained in 59% yield.[12] About half of **4** underwent the undesired polymerization. The addition of the initially formed boryl enolate to **4** would cause the side reaction. Given that the smooth protonolysis of the intermediate was essential, we conducted the reaction in an aqueous/organic biphasic system.[13] Gratifyingly, the desired product **5a** was obtained in 94% yield under water/Et_2O biphasic conditions. Unfortunately, in 1,4-addition of tributylborane (**2b**) to **4**, the polymerization was not completely suppressed (eq 2).

Alkylboranes are easily prepared from hydroboranes and alkenes via hydroboration. Taking advantage of the facile access to alkylboranes, we tested one-pot hydroboration/1,4-addition. Terminal olefin having a benzyl ether moiety **6a**, 9-borabicyclo[3.3.1]nonane (9-BBN), and benzyl (*E*)-crotonate (**1a**) were chosen as model substrates. Alkylborane **7a** was prepared from **6a** and 9-BBN in advance and transferred to a mixture of the nickel catalyst and cesium carbonate in toluene. Finally, **1a** was added dropwise. However, to our surprise, 1,4-adduct **8a** was not detected (Table 2, entry 1). The starting material was completely recovered. Thus, further optimization studies were performed to achieve the reaction with 9-alkyl-9-BBN. An addition of water was found to improve the yield of the desired product to 24% (entry 2). Interestingly, a large excess of water completely suppressed the reaction (entry 3). The oxygen atom of water seemed to coordinate to the boron center as a Lewis base and to activate alkylborane **7a**. Hence, various Lewis bases were screened.

Table 2. Nickel-Catalyzed One-Pot Hydroboration/1,4-Addition: The Effect of an Additive[a]



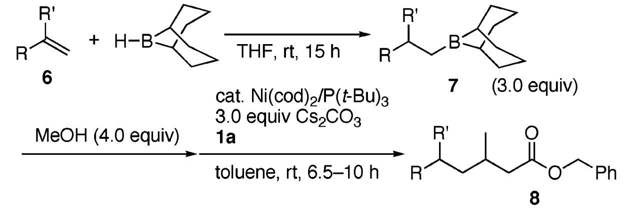
entry	additive	**8a**, yield (%)[b]
1	none	0
2	H_2O (4.0 equiv)	24
3	H_2O (1.0 mL)	0
4	MeOH (4.0 equiv)	96
5	MeOH (1.0 mL)	0
6	*t*-BuOH (4.0 equiv)	0
7	phenol (4.0 equiv)	0
8	DMA (4.0 equiv)	65
9	pyridine (4.0 equiv)	0

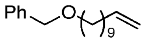
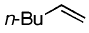
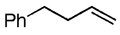
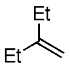
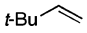
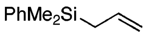
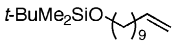
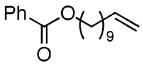
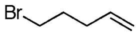
[a] A mixture of **1a** (0.5 mmol), **7a** (3.0 equiv) prepared in advance from **6a** and 9-BBN, additive, $Ni(cod)_2$ (8 mol %), $P(t\text{-}Bu)_3$ (19.2 mol %), and Cs_2CO_3 (3.0 equiv) was stirred in toluene (5 mL) for 8.5 h at room temperature. [b] Isolated yield.

Fortunately, an addition of 4.0 equiv of methanol dramatically enhanced the reaction to provide **8a** in 96% yield (entry 4). As observed in the case of the addition of water, a large amount of methanol prevented the reaction (entry 5). Other alcohols such as *tert*-butyl alcohol and phenol gave no effect on yield (entries 6 and 7). The use of *N*,*N*-dimethylacetamide (DMA), which is known to catalyze hydroboration of alkenes with catecholborane,[14] also led to the improvement of the yield, although the yield was lower than that in the presence of methanol (entry 8 vs entry 4). A much stronger Lewis base, pyridine, did not work to promote the reaction (entry 9).

By using the optimal methanol-promoted conditions, we conducted 1,4-addition of an array of 9-alkyl-9-BBN to benzyl (*E*)-crotonate (**1a**) (Table 3). The 1,4-addition of 9-hexyl-9-BBN (**7b**) and 9-(4-phenylbutyl)-9-BBN (**7c**) to **1a** proceeded to produce **8b** and **8c** in 90% and 85% yields, respectively. Alkylborane **7d** prepared from β,β-disubstituted olefin **6d** took part in the reaction without any difficulties (entry 4) while bulky substitution at the β position on alkylborane decreased the yield (entry 5). The reaction of

Table 3. Nickel-Catalyzed One-Pot Hydroboration/1,4-Addition[a]



entry	**6**		**7**	**8**, yield (%)[b]
1		**6a**	**7a**	96
2[c]		**6b**	**7b**	90
3		**6c**	**7c**	85
4		**6d**	**7d**	79
5		**6e**	**7e**	31
6		**6f**	**7f**	59
7[d]		**6g**	**7g**	58
8		**6h**	**7h**	73
9		**6i**	**7i**	61

[a] A mixture of **1** (0.5 mmol), **7** (3.0 equiv) prepared in advance from **6** and 9-BBN, MeOH (4.0 equiv), $Ni(cod)_2$ (8 mol %), $P(t\text{-}Bu)_3$ (19.2 mol %), and Cs_2CO_3 (3.0 equiv) was stirred in toluene (5 mL) for 6.5−10 h at room temperature. [b] Isolated yield. [c] Reaction time was 15 h. [d] Reaction time was 17 h.

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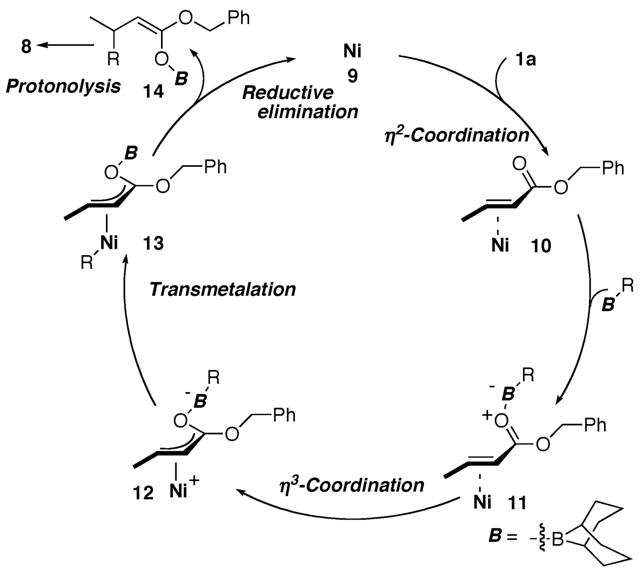
[12] In these cases, the use of Na_2CO_3 instead of Cs_2CO_3 gave better results.

[13] Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 7784−7785.

[14] Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 3224−3225.

6f provided **8f** in good yield, leaving the silyl moiety untouched (entry 6). Silyl ether and ester functionalities were tolerated under the reaction conditions (entries 7 and 8). It should be noted that alkylborane **7i** having an sp^3 C−Br bond, which the corresponding alkylmagnesium halide and dialkylzinc are difficult to prepare, underwent 1,4-addition in spite of conceivable oxidative addition of the sp^3 C−Br bond to the zerovalent nickel (entry 9).

Scheme 3



We are tempted to assume the mechanism of the reaction with 9-alkyl-9-BBN as follows (Scheme 3). A nickel(0) species **9** initially reacts with **1a** to generate η^2-coordinated complex **10**. The coordination of the carbonyl moiety of **10** to the alkylborane gives the intermediate **11**.[15] The Lewis acidity of the alkylborane promotes the formation of η^3-coordinated complex **12** followed by transmetalation to furnish the alkylnickel species **13**.[16,17] Finally, reductive elimination from **13** affords **14** and regenerates **9**. Protonolysis of **14** would provide **8**. The exact roles of cesium carbonate and methanol are not clear at this stage. They can enhance the transmetalation step through their coordination to the boron center of **12**. Moreover, methanol can be a good proton source for the intermediate **14**.

In conclusion, we have developed 1,4-addition of trialkylboranes to α,β-unsaturated esters under nickel catalysis. Moreover, addition of methanol was found to dramatically enhance the nickel-catalyzed reactions of α,β-unsaturated esters with 9-alkyl-9-BBNs. The catalyst system allows trialkylboranes to serve as the promising alkyl sources to α,β-unsaturated esters.

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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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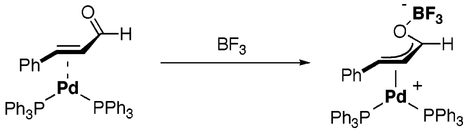
(15) The fact that the electron-rich substrate **1f** was more reactive than **1e** is highly suggestive of the existence and importance of the coordination (Table 1, entry 5 vs. entry 6). Namely, the more electron-rich carbonyl group of nickel-coordinated **1f** would have stronger interaction with alkylborane, which efficiently activates the carbonyl group of **1f**.

(16) Ogoshi and Kurosawa reported that the η^2-coordinated palladium complexes with cinnamaldehyde were converted to η^3-coordinated ones in the presence of BF$_3$ with the aid of the Lewis acidity of boron (see the following equation)



and proposed the palladium-catalyzed 1,4-addition of trimethylaluminum to benzalacetone would proceed through a similar intermediate. (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944−1950. Also see: (b) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505−5508.

(17) Chlorotrialkylsilane was known to promote transformation of η^2-coordinated nickel complexes with α,β-unsaturated aldehydes and ketones to the corresponding η^3-fashion. (a) Grisso, B. A.; Johson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160−5165. (b) Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975−5976.