DOI: 10.1002/adsc.200606136

Alkylation of Aldehydes with Trialkylboranes in Water

Koji Hirano,[a] Hideki Yorimitsu,[a,]* and Koichiro Oshima[a,]*

[a] Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan
Fax: +81-75-383-2438; e-mail: yori@orgrxn.mbox.media.kyoto-u.ac.jp or oshima@orgrxn.mbox.media.kyoto-u.ac.jp

Received: March 24, 2006; Accepted: May 15, 2006

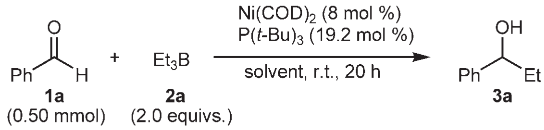
Abstract: Water enables the alkylation of aldehydes with trialkylboranes under nickel catalysis without the addition of a base. Trialkylboranes prepared from borane-dimethyl sulfide and terminal olefins *via* hydroboration as well as commercially available trialkylboranes could be employed for the reaction. The reaction would proceed *via* η^2-coordinated nickel complexes with aldehydes as the key intermediates.

Keywords: aldehydes; alkylation; cyclodextrin; nickel; trialkylboranes; water

Water is an interesting solvent in organic synthesis due to its cheap, non-toxic, and non-flammable properties. Therefore, the use of water instead of an organic solvent has attracted significant attention in the view points of economy and green chemistry. In addition, synthetic reactions that are unique in water have been developed[1] since the extraordinary effect of water as a solvent was observed in the pericyclic processes of Diels–Alder reactions[2] and Claisen rearrangements.[3] The additions of organometallic reagents to aldehydes in water have also been widely explored. Allylation with allylmetals[4] and arylation or alkenylation with organoboronic acid derivatives in the presence of transition metal catalysts[5] have been established in aqueous media. However, the alkylation of aldehydes in water is not a trivial reaction.[6] This is probably because organometallic reagents having alkyl groups, which are effective in the alkylation of carbonyl compounds, are generally highly reactive and very sensitive to water.[7] With the aid of transition metal catalysis, water-tolerant organoboranes seem to be good reagents for the alkylation in water. However, alkyl group transfer from boron to transition metals is usually difficult.

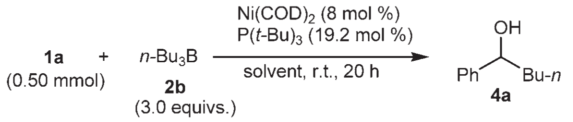
Recently, we have reported the nickel-catalyzed addition of trialkylboranes to aldehydes in an organic solvent with cesium carbonate as an activator.[8] By this reaction, alkyl group transfer from boron to nickel has become available. This advantage promoted us to develop the alkylation of aldehydes with trialkylboranes by nickel catalysis in water. Here we report the results of the alkylation in water and the unique effect of water as a solvent in the alkylation reaction.

We first examined the ethylation and butylation of benzaldehyde (**1a**) (Scheme 1 and Scheme 2). Treatment of **1a** (0.50 mmol) with triethylborane (**2a**, 1.0 mmol) in the presence of 8 mol% of $Ni(COD)_2$[9] and 19.2 mol% of $P(t\text{-}Bu)_3$ in degassed water (20 mL) at room temperature for 20 h provided the corresponding secondary alcohol **3a** in 81% yield. It is worth noting that **1a**, **2a**, and the nickel catalyst were completely insoluble in water, and the reaction proceeded in a biphasic system, organic particles in water. On the other hand, **1a** was converted to **3a** in moderate yield in degassed toluene. The addition of



Solvent	Additive	Yield of **3a**
toluene (10 mL)	none	45%
toluene (10 mL)	Cs_2CO_3 (2.0 equivs.)	87%
H_2O (20 mL)	none	81%

Scheme 1.



Solvent	Additive	Yield of **4a**
toluene (10 mL)	none	<2%
toluene (10 mL)	Cs_2CO_3 (3.0 equivs.)	88%
toluene (10 mL)	H_2O (3.0 equivs.)	<2%
H_2O (5 mL)	none	33%
H_2O (10 mL)	none	63%
H_2O (20 mL)	none	90%

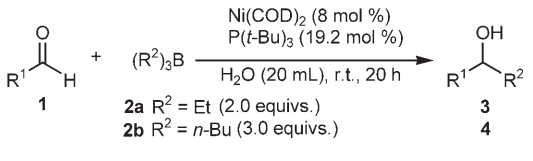
Scheme 2.

an excess amount of cesium carbonate was essential for a satisfactory yield. In the butylation of **1a** with tributylborane (**2b**), the effect of water as a solvent was much more remarkable. The reaction of **1a** in toluene without cesium carbonate resulted in no conversion. Other organic solvents such as THF, DMF, and AcOEt led to the same result. Gratifyingly, use of water (20 mL) as a solvent improved the yield of the desired product **4a** to 90%. The amount of water also dramatically influenced the yield. Addition of 3.0 equivs. of water in toluene had no effect. In 5 mL and 10 mL of water, benzaldehyde (**1a**) underwent butylation to give the corresponding alcohol **4a** in 33% and 63% yield, respectively. These results strongly suggest that use of water as a solvent would play an important role in the reaction.

By using optimal conditions, we performed the ethylation and butylation of an array of various aldehydes in water (Table 1). The reaction of sterically demanding aldehyde **1b** proceeded smoothly to furnish the corresponding alcohol **3b** in 81% yield. Electron-rich aldehyde **1c** was converted to **3c** and **4c** in moderate yields. However, use of the electron-deficient aldehyde **1d** resulted in a low conversion.[10] Aliphatic aldehydes as well as aromatic ones participated in the reaction. Dihydrocinnamaldehyde (**1e**) and cyclohexanecarbaldehyde (**1f**) underwent ethylation without difficulties to afford the alkylated products in good yields.

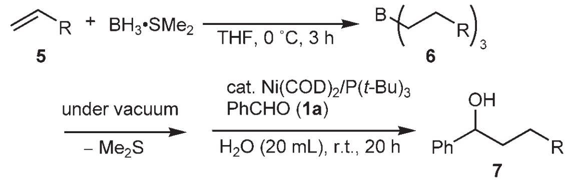
Trialkylboranes prepared from alkenes *via* hydroboration can be also employed for the reaction (Table 2). 1-Hexene (**5a**) was added to a solution of borane-dimethyl sulfide in THF and the mixture was stirred for 3 h at 0 °C. Dimethyl sulfide was then removed under vacuum (30 torr) at 0 °C for 1 h. The trihexylborane (**6a**) obtained was transferred under argon to a dispersion of benzaldehyde (**1a**) and the nickel catalyst in water at 0 °C. The mixture was allowed to warm to room temperature and rigorously stirred for 20 h to furnish 1-phenyl-1-heptanol (**7a**) in 74% yield (entry 1). Bulky substitution on the trialkylborane at the β position did not prevent the reaction (entry 2). However, the reaction with tri(4-phenylbutyl)borane (**6c**) resulted in a moderate yield (entry 3). An ester function was compatible under the reaction conditions albeit the yield was low (entry 4). The reaction with a trialkylborane having a silyl ether moiety proceeded smoothly to produce the corresponding alcohol **7e** (entry 5) while a benzyl ether moiety in **6f** decreased the yield (entry 6).

Table 1. Nickel-catalyzed alkylation of aldehydes with trialkylboranes in water.



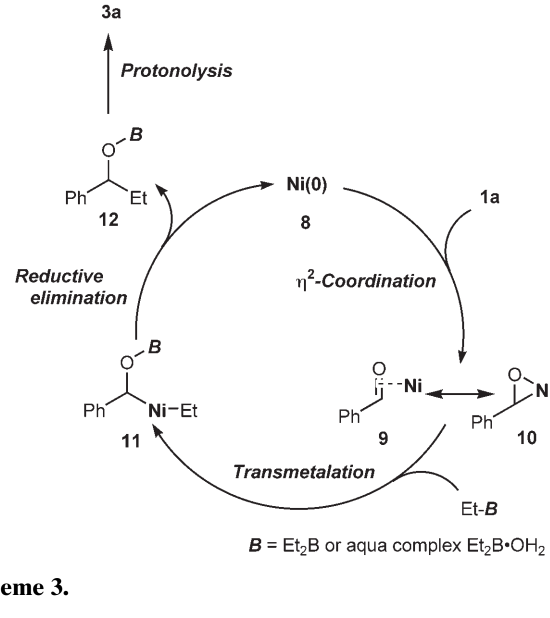
Entry	R^{1}CHO	(R^2)$_3$B	Product	Yield
1	2-MeC$_6$H$_4$CHO (**1b**)	**2a**	**3b**	81%
2	4-MeOC$_6$H$_4$CHO (**1c**)	**2a**	**3c**	59%
3	**1c**	**2b**	**4c**	27%
4	4-CF$_3$C$_6$H$_4$CHO (**1d**)	**2a**	**3d**	5%
5	Ph(CH$_2$)$_2$CHO (**1e**)	**2a**	**3e**	69%
6	c-C$_6$H$_{11}$CHO (**1f**)	**2a**	**3f**	60%

Table 2. One-pot hydroboration/alkylation.

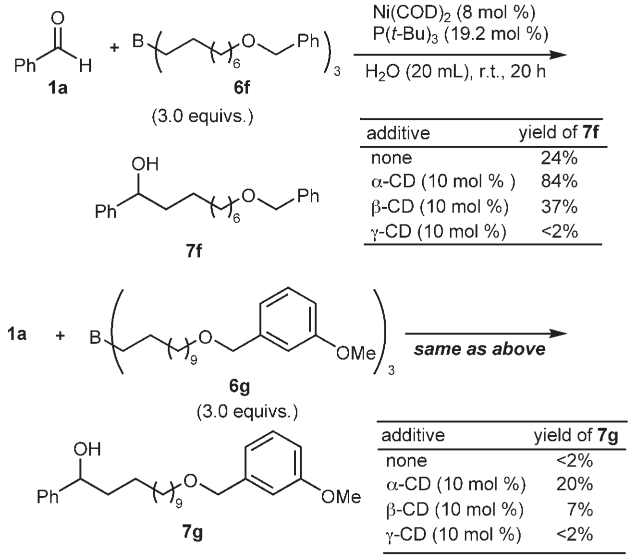


Entry	R	Trialkylborane	Product	Yield
1	n-Bu (**5a**)	**6a**	**7a**	74%
2	t-Bu (**5b**)	**6b**	**7b**	71%
3	(CH$_2$)$_2$Ph (**5c**)	**6c**	**7c**	36%
4	(CH$_2$)$_6$OCO-t-Bu (**5d**)	**6d**	**7d**	17%
5	(CH$_2$)$_6$OSiMe$_2$-t-Bu (**5e**)	**6e**	**7e**	69%
6	(CH$_2$)$_6$OCH$_2$Ph (**5f**)	**6f**	**7f**	24%

We are tempted to assume the mechanism for the alkylation of aldehyde to be as follows (Scheme 3). A nickel(0) species **8** initially reacts with **1a** to generate the η^2-coordinated complex **9** or its resonance form **10**.[11] Subsequent transmetalation of **10** with Et$_3$B or its aqua complex Et$_3$B·OH$_2$ gives intermediate **11** followed by reductive elimination to furnish **12** and to



Scheme 3.



additive	yield of **7f**
none	24%
α-CD (10 mol %)	84%
β-CD (10 mol %)	37%
γ-CD (10 mol %)	<2%

additive	yield of **7g**
none	<2%
α-CD (10 mol %)	20%
β-CD (10 mol %)	7%
γ-CD (10 mol %)	<2%

Scheme 4.

regenerate **8**. Finally, protonolysis of **12** upon work-up affords alcohol **3a**. The effect of water as a reaction medium is not clear at this stage. Water can enhance the η^2-coordination step and/or the transmetalation step. These steps cause a reduction of the total volume of the organic components, which water would enhance by taking advantage of hydrophobic interactions. Moreover, the aqua complex $Et_3B{\cdot}OH_2$ can more readily undergo the transmetalation.

To our delight, the addition of 10 mol% of α-cyclodextrin (α-CD) improved the yield of **7f** to 84% compared to Table 2, entry 6 (Scheme 4). Interestingly, additions of β-cyclodextrin (β-CD) and γ-cyclodextrin (γ-CD) showed less efficiency.[12] The effect was also examined in the reaction of benzaldehyde (**1a**) with the trialkylborane **6g** having a *meta*-substituted benzyl ether moiety. In the absence of α-CD, the reaction completely failed to afford the desired product. The addition of 10 mol% of α-CD enabled the conversion of **1a** to the corresponding alcohol **7g** albeit the yield was low.[13] Unfortunately, additions of β-CD or γ-CD could not improve the yield. The exact role of α-CD is not clear at this stage.[14,15]

In conclusion, we have found an example of the alkylation of aldehydes in water and the unique effect of water as a solvent in the reaction. In addition, an interesting effect of cyclodextrins was observed.

Experimental Section

Synthesis of 3a

In a glovebox filled with argon, $Ni(COD)_2$ (11 mg, 0.04 mmol) was placed in a reaction flask. THF (0.5 mL) and $P(t\text{-}Bu)_3$ (purchased from Wako and diluted to prepare a degassed hexane solution, 1.0M, 0.096 mL, 0.096 mmol) were added dropwise. The solution was stirred for 10 min at 0 °C. Degassed water (20 mL), benzaldehyde (**1a**, 53 mg, 0.5 mmol), and Et_3B (1.0M hexane solution, 1.0 mL, 1.0 mmol) were then added. The mixture was allowed to warm to room temperature and stirred for 20 h. The resulting mixture was poured into 3.0M hydrochloric acid (10 mL). Extraction with hexane/ethyl acetate (5:1) followed by silica gel column purification afforded 1-phenyl-1-propanol (**3a**); yield: 55 mg (0.41 mmol, 81%).

Synthesis of 4a

In a glovebox filled with argon, $Ni(COD)_2$ (11 mg, 0.04 mmol) was placed in a reaction flask. THF (0.5 mL) and $P(t\text{-}Bu)_3$ (1.0M hexane solution, 0.096 mL, 0.096 mmol) were added dropwise. The solution was stirred for 10 min at 0 °C. Degassed water (20 mL), benzaldehyde (**1a**, 53 mg, 0.5 mmol), and $n\text{-}Bu_3B$ (1.0M THF solution, 1.5 mL, 1.5 mmol) were then added. The mixture was allowed to warm to room temperature and stirred for 20 h. Extraction with hexane/ethyl acetate (5:1) followed by concentration afforded the crude product. The crude product obtained was oxidized with aqueous H_2O_2 (30%, 0.8 mL) and aqueous NaOH (6.0M, 0.5 mL) in EtOH/THF (1.2 mL and 2 mL) at reflux for 1 h. After aqueous sodium thiosulfate was added, extraction and purification provided 1-phenyl-1-pentanol (**4a**); yield: 74 mg (0.45 mmol, 90%).

Synthesis of 7a

1-Hexene (**5a**, 379 mg, 4.5 mmol) was added to a solution of borane-dimethyl sulfide (commercially available from Aldrich, 10M, 0.15 mL, 1.5 mmol) in THF (2 mL) and the solution was stirred for 3 h at 0 °C. Dimethyl sulfide was then removed under vacuum (30 torr) at 0 °C for 1 h to prepare trihexylborane (**6a**). At the same time, in a glovebox filled with argon, $Ni(COD)_2$ (11 mg, 0.04 mmol) was placed in another reaction flask. THF (0.5 mL) and $P(t\text{-}Bu)_3$ (1.0M hexane solution, 0.096 mL, 0.096 mmol) were added dropwise. The solution was stirred for 10 min at 0 °C. Degassed water (20 mL) and benzaldehyde (**1a**, 53 mg, 0.5 mmol) were then added. Finally, the trihexylborane (**6a**) prepared in advance was transferred to the mixture *via* a syringe under argon. The resulting mixture was allowed to warm to room temperature and stirred for 20 h. Extraction with hexane/ethyl acetate (5:1) followed by concentration afforded the crude product. After the crude product obtained had been oxidized under the same conditions for the synthesis of **4a**, extraction and purification provided 1-phenyl-1-heptanol (**7a**); yield: 71 mg (0.37 mmol, 74%).

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research and COE Research from the Ministry of Education, *Culture, Sports, Science, and Technology, Japan. K.H. acknowledges JSPS for financial support.*

References

[1] a) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, **1997**; b) P. A. Grieco, *Organic Synthesis in Water*, Blackie Academic & Professional, London, **1998**; c) A. Lubineau, J. Auge, in: *Modern Solvents in Organic Synthesis* (Ed.: P. Knochel), Springer-Verlag, Berlin, Heidelberg, **1999**; d) C.-J. Li, *Chem. Rev.* **1993**, *93*, 2023–2035; e) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751–2772; f) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3166.

[2] D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816–7818.

[3] a) A. A. Ponaras, *J. Org. Chem.* **1983**, *48*, 3866–3868; b) R. M. Coates, B. D. Roger, S. J. Hobbs, D. R. Peck, D. P. Curran, *J. Am. Chem. Soc.* **1987**, *109*, 1160–1170; c) J. J. Gajewski, J. Jurayj, D. R. Kimbrough, M. E. Gande, B. Ganem, B. K. Carpenter, *J. Am. Chem. Soc.* **1987**, *109*, 1170–1186; d) S. D. Copley, J. Knowles, *J. Am. Chem. Soc.* **1987**, *109*, 5008–5013; e) E. Brandes, P. A. Grieco, J. J. Gajewski, *J. Org. Chem.* **1989**, *54*, 515–516.

[4] For tin: a) J. Nokami, J. Otera, T. Sudo, R. Okawara, *Organometallics* **1983**, *2*, 191–193; for zinc: b) C. Petrier, J. L. Luche, *J. Org. Chem.* **1985**, *50*, 910–912; c) C. Einhorn, J. L. Luche, *J. Organomet. Chem.* **1987**, *322*, 177–183; for indium: d) C.-J. Li, T.-H. Chan, *Tetrahedron Lett.* **1991**, *32*, 7017–7020; e) T.-H. Chan, C.-J. Li, *J. Chem. Soc., Chem. Commun.* **1992**, 747–748; for gallium: f) T. Tsuji, S. Usugi, H. Yorimitsu, H. Shinokubo, S. Matsubara, K. Oshima, *Chem. Lett.* **2002**, 2–3; for boron: g) M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 7182–7183.

[5] For rhodium: a) M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450–4452; b) A. Fürstner, H. Krause, *Adv. Synth. Catal.* **2001**, *4*, 343–350; c) A. Takezawa, K. Yamaguchi, T. Ohmura, Y. Yamamoto, N. Miyaura, *Synlett* **2002**, *10*, 17733–11735; for nickel: d) G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Chem. Commun.* **2005**, 1459–1460.

[6] The only precedent: C. C. K. Keh, C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 4062–4063.

[7] Recently, Woodward has reported alkylation of aldehydes with air-stable trialkylaluminum reagents in organic solvent under nickel catalysis: K. Biswas, O. Prieto, P. J. Goldsmith, S. Woodward, *Angew. Chem. Int. Ed.* **2005**, *44*, 2232–2234.

[8] K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2005**, *7*, 4689–4691.

[9] $NiCl_2$ and $Ni(acac)_2$ did not catalyze the reaction. Other ligands such as Ph_3P, n-Bu_3P, and $(c\text{-}C_6H_{11})_3P$ were ineffective.

[10] Similar trends were observed in organic solvents, see ref.[8]

[11] η^2-Coordinated nickel complexes with aldehydes have been reported, see: a) S. Ogoshi, M. Oka, H. Kurosawa, *J. Am. Chem. Soc.* **2004**, *126*, 11802–11803. The intermediate **9** or **10** was suggested in other nickel-catalyzed reactions, see: refs.[7, 8] and b) K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 483–485.

[12] The cavity volumes of α-CD, β-CD, and γ-CD are 174, 262, and 472 mL mol^{-1}, respectively. α-CD is known to accommodate a phenyl ring most tightly, see: F. Hapiot, S. Tilloy, E. Monflier, *Chem. Rev.* **2006**, *106*, 767–781.

[13] We assumed that the substitution at the *meta*-position in **6g** would allow α-CD to dissociate easily from the phenyl ring of **6g** due to the steric factors.

[14] In the catalytic cycle, transmetalation of the nickel complex **10** with trialkylborane would be a key step. Therefore, we suppose that in the reaction with trialkylborane **6f**, interactions between the oxygen atom of **6f** and the nickel or boron center would suppress the step to result in the low yield (Table 2, entry 6). On the basis of the assumption, we thus tested the addition of cyclodextrins to the reaction media. Namely, we expected that the internal cavity of cyclodextrins would accommodate the aromatic ring of **6f** to block out the unfavorable interaction as described above.

[15] Cyclodextrin can interact with phosphine or nickel-(phosphine)complex to improve the catalytic activity: a) E. Monflier, H. Bricout, F. Hapiot, S. Tilloy, A. Aghmiz, A. M. Masdeu-Bultó, *Adv. Synth. Catal.* **2004**, *346*, 425–431; b) C. Binkowski, J. Cabou, H. Bricout, F. Hapiot, E. Monflier, *J. Mol. Catal. A* **2004**, *215*, 23–32.