Alkynes as activators in the nickel-catalysed addition of organoboronates to aldehydes†

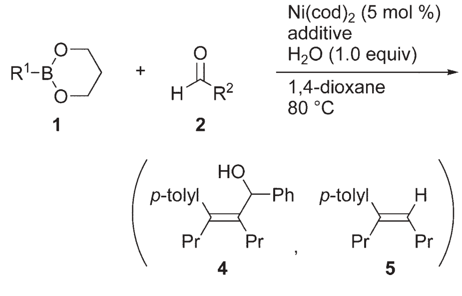
Go Takahashi,[a] Eiji Shirakawa,*[b] Teruhisa Tsuchimoto[a] and Yusuke Kawakami[a]

Received (in Cambridge, UK) 17th November 2004, Accepted 23rd December 2004
First published as an Advance Article on the web 25th January 2005
DOI: 10.1039/b417353h

Alkynes act not as substrates but as co-catalysts in the presence of a nickel catalyst, an organoboronate and an aldehyde to promote the addition reaction between the substrates in combination with H_2O.

Alkynes have long been representative substrates of transition metal-catalysed reactions, accepting addition of various bonds[1] or undergoing diverse types of cyclization reactions.[2] In particular, late transition metals such as palladium and nickel, having a strong affinity for alkynes, readily catalyse the transformation of alkynes. In this context, we have been developing the palladium- or nickel-catalysed addition of organotin[3] or organoboron[4] compounds to alkynes, where alkynes are good reaction partners of the organometallic compounds. Furthermore, alkynes are known to undergo three-component coupling with aldehydes and organometallics including organoboron compounds in the presence of a nickel catalyst to give allylic alcohols.[5,6] Here we report the unusual behavior of alkynes in the presence of a transition metal catalyst and an organometallic compound, where alkynes act not as substrates but as activators. Thus, a catalytic amount of alkynes assists a nickel catalyst to promote the addition of organoboron compounds to aldehydes.[7–9]

We first examined the nickel-catalysed addition of 2-(*p*-tolyl)-1,3,2-dioxaborinane (**1a**) to benzaldehyde (**2a**). Treatment of **1a** and **2a** with bis(1,5-cyclooctadiene)nickel (5 mol%) in 1,4-dioxane at 80 °C for 2 h did not afford even a trace amount of the desired phenyl(*p*-tolyl)methanol (**3a**) (eqn. (1) and entry 1 of Table 1). Addition of H_2O (1.0 equiv) as an activator[10] of **1a** and/or triphenylphosphine (10 mol%) as a ligand did not promote the reaction at all (entries 2–4). Other ligands such as tributylphosphine, 1,3-bis(diphenylphosphino)propane and 2,2′-bipyridyl were equally ineffective. In sharp contrast, use of a catalytic amount of 4-octyne in conjunction with H_2O[11] drastically changed the result to give **3a** in 99% yield (entries 5 and 6),[12,13] where three-component coupling product **4** between **1a**, **2a** and 4-octyne was not observed (entry 6). With an increased amount (1.2 equiv) of 4-octyne, **4** (5% yield) and hydroarylation product **5** (4% yield) of the alkyne[4] were generated[14] but **3a** still predominated (entry 7). More electron-deficient alkynes also mediated the addition but sluggishly (entries 8 and 9). A nickel(II) complex did not catalyse the addition (entry 10).



(1)

Table 1 Effect of additives in the nickel-catalysed addition of 2-(*p*-tolyl)-1,3,2-dioxaborinane to benzaldehyde[a]

Entry	Additive	H_2O	Yield of **3a** (%)[b]
1	None	−	0
2	None	+	0
3	Ph_3P (10 mol%)	−	0
4	Ph_3P (10 mol%)	+	0
5	Pr–C≡C–Pr (20 mol%)	−	28
6	Pr–C≡C–Pr (20 mol%)	+	99
7	Pr–C≡C–Pr (1.2 equiv)	+	79
8	Ph–C≡C–Me (20 mol%)	+	52 (85)[c]
9	Ph–C≡C–Ph (20 mol%)	+	48 (72)[d]
10[e]	Pr–C≡C–Pr (20 mol%)	+	0

[a] The reaction was carried out in 1,4-dioxane (0.45 mL) at 80 °C for 2 h using 2-(*p*-tolyl)-1,3,2-dioxaborinane (**1a**: 0.30 mmol), benzaldehyde (**2a**: 0.36 mmol) and $Ni(cod)_2$ (15 μmol) in the presence or absence of H_2O (0.30 mmol). [b] Isolated yield based on arylboronate **1a**. [c] The isolated yield after 12 h. [d] The isolated yield after 24 h. [e] $Ni(acac)_2$ was used instead of $Ni(cod)_2$.

The $Ni(cod)_2$–4-octyne catalyst was found to be applicable to various combinations of organoboronates and aldehydes (Table 2).

Table 2 Nickel-catalysed addition of organoboronates to aldehydes[a]

Entry	R^1	R^2	Yield of **3** (%)[b]
1	4-MeC_6H_4	4-$MeOC_6H_4$	80
2	4-MeC_6H_4	4-$CF_3C_6H_4$	93
3	4-$MeOC_6H_4$	Ph	88
4	4-$CF_3C_6H_4$	Ph	93
5	4-AcC_6H_4	Ph	90
6	3-$HOCH_2C_6H_4$	Ph	84
7[c]	4-MeC_6H_4	pentyl	96
8	4-$MeOC_6H_4$	pentyl	80
9	4-$CF_3C_6H_4$	pentyl	77
10	4-AcC_6H_4	pentyl	82
11	3-$HOCH_2C_6H_4$	pentyl	74
12	styryl	Ph	70
13[d]	styryl	Ph	85

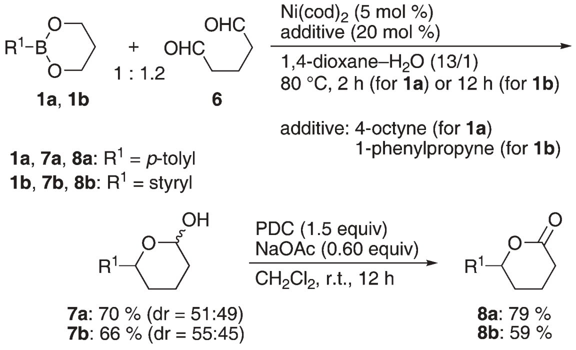
[a] The reaction was carried out in 1,4-dioxane (0.45 mL) at 80 °C for 12 h using an organoboronate (0.30 mmol), an aldehyde (0.36 mmol) and $Ni(cod)_2$ (15 μmol) in the presence of 4-octyne (60 μmol) and H_2O (0.30 mmol). [b] Isolated yield based on the arylboronate. [c] Reaction time = 2 h. [d] 1-Phenylpropyne was used instead of 4-octyne.

---

† Electronic supplementary information (ESI) available: Experimental details. See http://www.rsc.org/suppdata/cc/b4/b417353h/
*shirakawa@kuchem.kyoto-u.ac.jp

p-Tolylboronate **1a** added to both electron-rich and -poor aromatic aldehydes (entries 1 and 2). Benzaldehyde (**2a**) accepted the addition of phenylboronates having a methoxy, trifluoromethyl, acetyl or hydroxymethyl group (entries 3–6). In contrast to more nucleophilic arylmetals such as arylmagnesium halides and aryllithiums, organoboronates are compatible with electrophilic functional groups such as ketone and hydroxy. Hexanal, an aliphatic aldehyde, also underwent the reaction with diverse types of arylboronates to give α-pentylbenzyl alcohols with an electron-donating or -withdrawing group at their *para* or *meta* position (entries 7–11). Ketone moieties were unaffected, showing a strong preference for aldehydes (entries 5 and 10). For the addition of an alkenylboronate, 1-phenylpropyne was found to be more effective than 4-octyne as an additive, affording an increased yield of the corresponding allylic alcohol (entries 12 and 13).

Use of water as a solvent should be favorable for environmental and safety reasons.[15] Because H_2O was found to be a crucial activator in the addition (entries 5 and 6 of Table 1), we expected that the reaction should be accelerated in the presence of a substantial excess of the activator. Actually, the addition of **1a** to **2a** in water proceeded at a much lower temperature (40 °C, 2 h) to afford **3a** in 97% yield, though it required an excess amount (1.5 equiv with respect to **2a**) of **1a** because of competitive hydrolysis of **1a** to toluene.[16] Furthermore, glutaraldehyde (**6**),[17] which is usually available only as an aqueous solution, successfully reacted with organoboronates in a mixed solvent consisting of 1,4-dioxane and H_2O to provide diastereoisomeric mixtures[18] of lactols **7a** or **7b** (eqn. (2)).The lactols were easily oxidized to the corresponding lactones **8a** or **8b**.[19]



(2)

In conclusion, we have disclosed that a catalytic amount of alkynes in combination with a nickel catalyst promotes the addition of organoboronates to aldehydes. Alkynes, one of the most representative substrates in transition metal catalysis, do not react with organoboron compounds or aldehydes but activate them. Although the reaction mechanism including the role of the alkynes is not clear at present, the complete inability of usual ligands such as triphenylphosphine and 2,2′-bipyridyl might imply that the alkynes do not behave as conventional ligands.[20,21] Studies on the mechanistic details as well as application of the system to other substrates are in progress.

We thank Professor Tamio Hayashi (Kyoto University) for helpful discussions. This work was supported in part by Daicel Chemical Industries, Ltd.

Go Takahashi,[a] Eiji Shirakawa,*[b] Teruhisa Tsuchimoto[a] and Yusuke Kawakami[a]
[a]Graduate School of Materials Science, Japan Advanced Institute of Science and Technology, Tatsunokuchi, Ishikawa, 923-1292, Japan
[b]Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto, 606-8502, Japan.
E-mail: shirakawa@kuchem.kyoto-u.ac.jp; Fax: 81 75 753 3988

Notes and references

1 For recent reviews, see: F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079–3159; M. Beller, J. Seayad, A. Tillack and H. Jiao, *Angew. Chem. Int. Ed.*, 2004, **43**, 3368–3398.

2 For recent reviews, see: S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901–2915; M. Rubin, A. W. Sromek and V. Gevorgyan, *Synlett*, 2003, 2265–2291.

3 For the palladium- or nickel-catalysed carbostannylation of alkynes, see: E. Shirakawa, H. Yoshida, T. Kurahashi, Y. Nakao and T. Hiyama, *J. Am. Chem. Soc.*, 1998, **120**, 2975–2976; E. Shirakawa, H. Yoshida, Y. Nakao and T. Hiyama, *J. Am. Chem. Soc.*, 1999, **121**, 4290–4291; E. Shirakawa, K. Yamasaki, H. Yoshida and T. Hiyama, *J. Am. Chem. Soc.*, 1999, **121**, 10221–10222; E. Shirakawa, H. Yoshida, Y. Nakao and T. Hiyama, *Org. Lett.*, 2000, **2**, 2209–2211; H. Yoshida, E. Shirakawa, T. Kurahashi, Y. Nakao and T. Hiyama, *Organometallics*, 2000, **19**, 5671–5678; E. Shirakawa, Y. Yamamoto, Y. Nakao, T. Tsuchimoto and T. Hiyama, *Chem. Commun.*, 2001, 1926–1927; H. Yoshida, E. Shirakawa, Y. Nakao, Y. Honda and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 637–647.

4 For the nickel-catalysed addition of arylboron compounds to alkynes, see: E. Shirakawa, G. Takahashi, T. Tsuchimoto and Y. Kawakami, *Chem. Commun.*, 2001, 2688–2689.

5 E. Oblinger and J. Montgomery, *J. Am. Chem. Soc.*, 1997, **119**, 9065–9066; X.-Q. Tang and J. Montgomery, *J. Am. Chem. Soc.*, 1999, **121**, 6098–6099; X.-Q. Tang and J. Montgomery, *J. Am. Chem. Soc.*, 2000, **122**, 6950–6954; W.-S. Huang, J. Chan and T. F. Jamison, *Org. Lett.*, 2000, **2**, 4221–4223; E. A. Colby and T. F. Jamison, *J. Org. Chem.*, 2003, **68**, 156–166; K. M. Miller, W.-S. Huang and T. F. Jamison, *J. Am. Chem. Soc.*, 2003, **125**, 3442–3443; K. M. Miller, T. Luanphaisarnnont, C. Molinaro and T. F. Jamison, *J. Am. Chem. Soc.*, 2004, **126**, 4130–4131.

6 The three-component coupling between phenylboronic acid, 1-phenylpropyne and an imine derived from benzaldehyde has been reported. S. J. Patel and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2003, **42**, 1364–1367.

7 To the best of our knowledge, there has been no report on the transition metal-catalysed addition of organoboron compounds to aldehydes except for the rhodium-catalysed reaction. M. Sakai, M. Ueda and N. Miyaura, *Angew. Chem. Int. Ed.*, 1998, **37**, 3279–3281; M. Ueda and N. Miyaura, *J. Org. Chem.*, 2000, **65**, 4450–4452; A. Fürstner and H. Krause, *Adv. Synth. Catal.*, 2001, **343**, 343–350; C. Moreau, C. Hague, A. S. Weller and C. G. Frost, *Tetrahedron Lett.*, 2001, **42**, 6957–6960. See also ref. 9.

8 Asymmetric addition of arylboronates to aromatic aldehydes mediated by an excess amount of diethylzinc in the presence of a chiral oxazolylalcohol has been reported. C. Bolm and J. Rudolph, *J. Am. Chem. Soc.*, 2002, **124**, 14850–14851.

9 Addition products of triphenylborane to aldehydes were produced as by-products (yield ⩽ 22%) in the nickel-catalysed three-component coupling between triphenylborane, isoprene and aldehydes. K. Shibata, M. Kimura, K. Kojima, S. Tanaka and Y. Tamaru, *J. Organomet. Chem.*, 2001, **624**, 348–353.

10 H_2O has played a crucial role in the nickel-catalysed hydroarylation of alkynes or 1,3-dienes using arylboronates. For alkynes, see ref. 4. For 1,3-dienes, see: E. Shirakawa, G. Takahashi, T. Tsuchimoto and Y. Kawakami, *Chem. Commun.*, 2002, 2210–2211.

11 Although the role of water is not clear at present, it may act as a Lewis base that coordinates to the boron atom and promotes the attack of the aryl groups on the aldehyde carbons.

12 Arylboronate **1a** was found to be relatively stable to water, not being hydrolysed on treatment of 1 equiv of H_2O in 1,4-dioxane at 80 °C for 6 h.

13 *p*-Tolylboronic acid did not add to **2a** at all under the conditions identical to entry 6 in Table 1.

14 Yields of **4** and **5** were determined by isolation with SiO_2 chromatography and ^1H NMR, respectively.

15 For reviews of transition metal-catalysed reactions in aqueous media, see: C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley, New York, 1997, pp. 115–160; B. Cornils and W. A. Herrmann, *Aqueous-Phase Organometallic Chemistry*, Wiley-VCH, Weinheim, 1998; D. Sinou, in *Modern Solvents in Organic Synthesis*, ed. P. Knochel, Springer, Berlin, 1999, pp. 41–59.

16 The reaction of **1a** with **2a** in water in a ratio of 1 to 1.2 gave **3a** only in *ca*. 60% yield (determined by ^{1}H NMR).

17 The triethylborane-promoted, nickel-catalysed homoallylation of glutaraldehyde in an aqueous media has been reported. M. Kimura, A. Ezoe, S. Tanaka and Y. Tamaru, *Angew. Chem. Int. Ed.*, 2001, **40**, 3600–3602.

18 Although we have not determined the stereochemistry of each compound, the observation that the isomers were transformed to a single lactone after oxidation should show that they are diastereomers.

19 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **31**, 2647–2650.

20 Grigg and co-workers proposed the potentiality of alkynes as activators in the rhodium-catalysed cyclization of unconjugated enynes, where the enynes act both as substrates and co-catalysts adding oxidatively to a rhodium(I) catalyst at their terminal acetylenic C–H bond. R. Grigg, P. Stevenson and T. Worakun, *Tetrahedron*, 1988, **44**, 4967–4972. Furthermore, in the rhodium–bisphosphine-catalysed successive cleavage of carbon–carbon and carbon–oxygen bonds of 2-(alkoxymethyl)-cyclobutanones, diphenylacetylene was used as an effective co-ligand, which is thought to coordinate to a rhodium–bisphosphine complex inhibiting unfavorable coordination of the olefinic moiety of the substrates. M. Murakami, T. Itahashi, A. Amii, K. Takahashi and Y. Ito, *J. Am. Chem. Soc.*, 1998, **120**, 9949–9950.

21 Considering the significant number of examples of an alkyne and an aldehyde undergoing oxidative cyclization with a nickel(0) complex to give a 2-oxanickellacyclopent-4-ene, there might be some possibility that the reaction proceeds through the nickellacycles, which react with organoboronates with cleavage of the C(3)–C(4) bond to afford addition product **3**, the nickel(0) complex and 4-octyne. See ref. 5. Oxidative cyclization of enals to nickel(0) complexes to afford 2-oxanickellacyclopentanes also has recently been reported. S. Ogoshi, M. Oka and H. Kurosawa, *J. Am. Chem. Soc.*, 2004, **126**, 11802–11803.