

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

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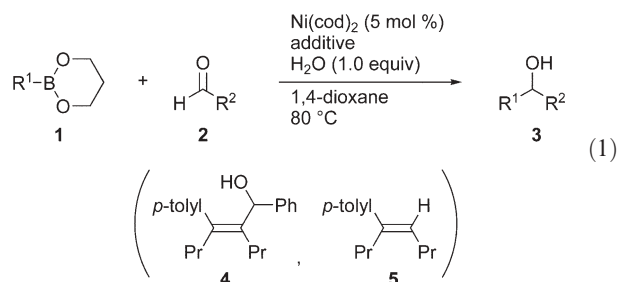
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Alkynes act not as substrates but as co-catalysts in the presence of a nickel catalyst, an organoboronate and an aldehyde to promote the addition reaction between the substrates in combination with H₂O.

Alkynes have long been representative substrates of transition metal-catalysed reactions, accepting addition of various bonds¹ 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 organotin³ or organoboron⁴ 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 H₂O (1.0 equiv) as an activator¹⁰ 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 H₂O¹¹ drastically

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

Entry	Additive	H ₂ O	Yield of 3a (%) ^b
1	None	–	0
2	None	+	0
3	Ph ₃ P (10 mol%)	–	0
4	Ph ₃ P (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 H₂O (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.

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 alkyne⁴ were generated¹⁴ 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).

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 ₆ H ₄	4-MeOC ₆ H ₄	80
2	4-MeC ₆ H ₄	4-CF ₃ C ₆ H ₄	93
3	4-MeOC ₆ H ₄	Ph	88
4	4-CF ₃ C ₆ H ₄	Ph	93
5	4-AcC ₆ H ₄	Ph	90
6	3-HOCH ₂ C ₆ H ₄	Ph	84
7 ^c	4-MeC ₆ H ₄	pentyl	96
8	4-MeOC ₆ H ₄	pentyl	80
9	4-CF ₃ C ₆ H ₄	pentyl	77
10	4-AcC ₆ H ₄	pentyl	82
11	3-HOCH ₂ C ₆ H ₄	pentyl	74
12	styryl	Ph	70
13 ^d	styryl	Ph	85

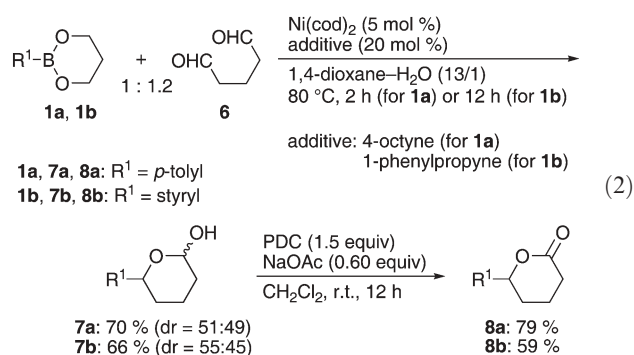
^a The reaction was carried out in 1,4-dioxane (0.45 mL) at 80 °C for 12 h using an organoboronate (0.30 mmol), an aldehyde (0.36 mmol) and Ni(cod)₂ (15 μmol) in the presence of 4-octyne (60 μmol) and H₂O (0.30 mmol). ^b Isolated yield based on the arylboronate. ^c Reaction time = 2 h. ^d 1-Phenylpropyne was used instead of 4-octyne.

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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 H₂O 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 H₂O to provide diastereoisomeric mixtures¹⁸ of lactols **7a** or **7b** (eqn. (2)). The lactols were easily oxidized to the corresponding lactones **8a** or **8b**.¹⁹



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.

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- Arylboronate **1a** was found to be relatively stable to water, not being hydrolysed on treatment of 1 equiv of H₂O in 1,4-dioxane at 80 °C for 6 h.
- p*-Tolylboronic acid did not add to **2a** at all under the conditions identical to entry 6 in Table 1.
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