

Nickel-catalyzed Conjugate Addition of Arylboron Reagents to α,β -Unsaturated Carbonyl Compounds with the Aid of a Catalytic Amount of an Alkyne

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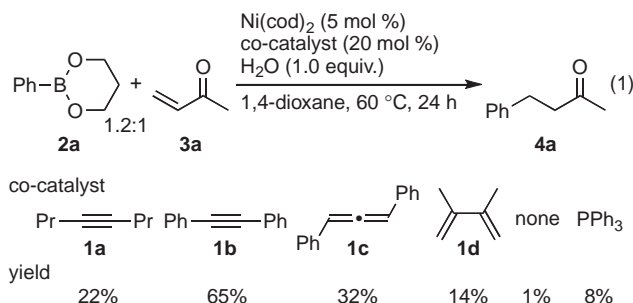
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Alkynes in combination with a catalytic amount of a nickel complex were found to catalyze the conjugate addition of arylboron reagents to α,β -unsaturated carbonyl compounds, where use of an optically active alkyne induces the asymmetric addition.

Transition metal-catalyzed addition of organoboron reagents to electron-deficient olefins has recently attracted much attention due mainly to high chemoselectivity and low toxicity of organoboron reagents. In particular, a vast number of reports on the rhodium-catalyzed asymmetric reaction have been published for a decade.¹ Although palladium complexes also are found to be effective as catalysts,² there has been no report on the reaction catalyzed by nickel, a group 10 metal as same as palladium. On the other hand, we have previously reported a nickel-alkyne catalyst system for the addition of arylboronates to aldehydes, where the addition does not take place at all in the absence of an alkyne.³ Here, we report that the nickel-alkyne catalyst system is applicable also to the conjugate addition of arylboronates to α,β -unsaturated carbonyl compounds. To the best of our knowledge, this is the first example of the nickel-catalyzed conjugate addition of organoboron reagents.

We first examined 4-octyne (**1a**), the most effective co-catalyst tested for the addition of a *p*-tolylboronate to benzaldehyde,³ as a co-catalyst in the nickel-catalyzed reaction of 2-phenyl-1,3,2-dioxaborinane (**2a**) with 3-buten-2-one (**3a**) (eq 1). Thus, the treatment of **2a** (1.2 equiv.) and **3a** (1.0 equiv.) with bis(1,5-cyclooctadiene)nickel (Ni(cod)₂; 5 mol %) and H₂O (1.0 equiv.) in 1,4-dioxane at 60 °C for 24 h gave 4-phenyl-2-butanone (**4a**) in 22% yield. Use of diphenylacetylene (**1b**) instead of **1a** as an additive was much more effective to increase the yield to 65%. Besides alkynes, 1,2- and 1,3-dienes such as 1,3-diphenyl-1,2-propadiene (**1c**) and 2,3-dimethyl-1,3-butadiene (**1d**) also showed some catalytic activity.⁴⁻⁶ In contrast, the reaction without any additive or with a conventional phosphine ligand like PPh₃ gave **4a** only in 1 or 8% yield, respectively. Use of Ni(acac)₂ as a catalyst precursor was totally ineffective.



The Ni-PhC≡CPh catalyst was applied to other combinations of substrates (Table 1).⁷ In addition to phenylboronate **2a** (Entry 1), those having an electron-withdrawing or -donating

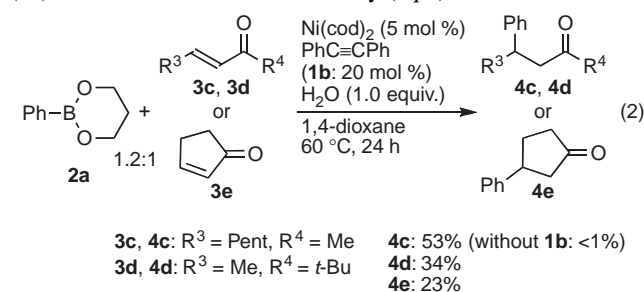
Table 1. Addition of arylboron reagents to α,β -unsaturated carbonyl compounds^a

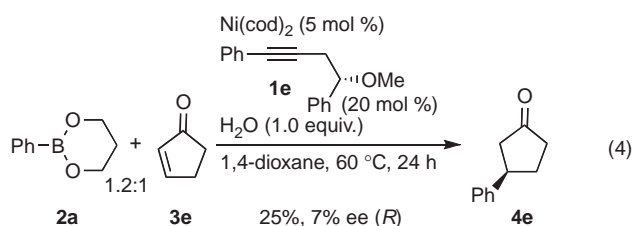
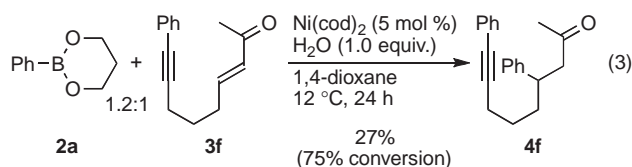
Entry	2	R ² in 3	Yield/% ^b
1	PhB[O(CH ₂) ₃ O] (2a)	Me (3a)	65
2	4-CF ₃ C ₆ H ₄ B[O(CH ₂) ₃ O] (2b)	Me (3a)	51
3	4-MeOC ₆ H ₄ B[O(CH ₂) ₃ O] (2c)	Me (3a)	41
4	Ph ₃ B (2d)	Me (3a)	65
5	<i>B</i> -Ph-9BBN (2e)	Me (3a)	41
6 ^c	PhB[O(CH ₂) ₃ O] (2a)	OEt (3b)	67

^aThe reaction was carried out in 1,4-dioxane (0.45 mL) at 60 °C for 24 h under a nitrogen atmosphere using an arylboron reagent (0.36 mmol) and an α,β -unsaturated carbonyl compound (0.30 mmol) in the presence of Ni(cod)₂ (15 μ mol), diphenylacetylene (60 μ mol), and H₂O (0.30 mmol). ^bIsolated yield based on the α,β -unsaturated carbonyl compound. ^cTemperature = 80 °C.

group underwent the reaction with **3a** (Entries 2 and 3). Other arylboron reagents such as triphenylborane (**2d**) and 9-phenyl-9-borabicyclo[3.3.1]nonane (**2e**) also added to **3a** (Entries 4 and 5), whereas the reaction did not take place at all with phenylboronic acid. Ethyl acrylate (**3b**) also accepted the addition of **2a** (Entry 6).

β -Substituted enones including a cyclic one also reacted with phenylboronate **2a** in the presence of the Ni-**1b** catalyst (eq 2).⁸ Here again, the reaction of 3-nonen-2-one (**3c**) in the absence of an alkyne resulted in a poor yield (<1%). Necessity of an alkyne functionality was confirmed also by the result that enone **3f** having an alkyne moiety at an appropriate position underwent the conjugate addition with **2a** in the absence of an extra alkyne such as **1b** to give β -phenylated ketone **4f** (eq 3).^{9,10} If alkynes play a critical role in the carbon-carbon bond-forming step, namely the enantioface-differentiating step, use of an optically active alkyne should induce the asymmetric addition. Actually, the reaction of **2a** with 2-cyclopentenone (**3e**) in the presence of (*S*)-4-methoxy-1,4-diphenyl-1-butyne (**1e**)¹¹ gave (*R*)-3-phenylcyclopentanone (**4e**) albeit in a low enantioselectivity (eq 4).





In conclusion, the nickel-catalyzed conjugate addition of arylboron reagents to α,β -unsaturated carbonyl compounds was accomplished for the first time by use of alkynes as co-catalysts. The catalyst system features the first asymmetric synthesis induced by a catalytic amount of an optically active alkyne, showing the promising possibility of optically active alkynes as chiral sources.

References and Notes

- For the first non-asymmetric reaction, see: M. Sakai, H. Hayashi, N. Miyaoura, *Organometallics* **1997**, *16*, 4229; For the asymmetric version, see: Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaoura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052; For a review, see: T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829.
- C.-S. Cho, S. Motofusa, K. Ohe, S. Uemura, *J. Org. Chem.* **1995**, *60*, 883; T. Nishikata, Y. Yamamoto, N. Miyaoura, *Angew. Chem., Int. Ed.* **2003**, *42*, 2768; T. Nishikata, Y. Yamamoto, N. Miyaoura, *Organometallics* **2004**, *23*, 4317; X. Lu, S. Lin, *J. Org. Chem.* **2005**, *70*, 9651; F. Gini, B. Hessen, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 5309; T. Yamamoto, M. Iizuka, T. Ohta, Y. Ito, *Chem. Lett.* **2006**, *35*, 198.
- G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Chem. Commun.* **2005**, 1459.
- Dienes **1c** and **1d** in combination with a catalytic amount of a nickel complex were found to catalyze the addition of 2-(*p*-tolyl)-1,3,2-dioxaborinane to hexanal in comparable efficiencies (97 and 80% yields, respectively) to 4-octyne (96% yield) under the identical conditions described in Ref. 3.
- Rhodium complexes coordinated with a C_2 -symmetric chelating diene show high enantioselectivities and high catalytic activities in the conjugate addition of arylboronic acids to enones. T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508.
- Alkynes as well as 1,3- and 1,2-dienes accept addition of arylboron reagents in the presence of a nickel catalyst.

For alkynes: E. Shirakawa, G. Takahashi, T. Tsuchimoto, Y. Kawakami, *Chem. Commun.* **2001**, 2688; For 1,3-dienes: E. Shirakawa, G. Takahashi, T. Tsuchimoto, Y. Kawakami, *Chem. Commun.* **2002**, 2210; For 1,2-dienes: G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Adv. Synth. Catal.* **2006**, *348*, 837.

- General procedure: A solution (0.45 mL) of diphenylacetylene (10.7 mg, 60.0 μmol) in 1,4-dioxane was degassed by three freeze-thaw cycles. After Ni(cod)_2 (4.1 mg, 15 μmol) was dissolved in the solution, an enone (0.30 mmol), water (5.4 mg, 0.30 mmol), and an arylboronate (0.36 mmol) were added successively to the resulting solution. After the mixture was stirred at 60 $^\circ\text{C}$ for 24 h, the resulting mixture was treated with a saturated NH_4Cl aqueous solution (10 mL) and extracted with diethyl ether (15 mL \times 3). The combined organic layer was washed with a saturated NaHCO_3 aqueous solution (10 mL) and brine (10 mL), and then dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent followed by PTLC on silica gel (hexane-ethyl acetate) gave the corresponding ketone. The results are summarized in Table 1.
- Unfortunately, the addition to enals does not proceed regioselectively. The reaction of 2-hexenal with **2a** under the same conditions as Table 1 and eq 2 gave a 59:13:28 mixture of the 1,2-adduct (1-phenyl-2-hexen-1-ol), the 1,4-adduct (3-phenylhexanal), and diarylation products (diastereomers of 1,3-diphenyl-1-hexanol) in 71% yield (determined by $^1\text{H NMR}$ using nitromethane as an internal standard).
- GC and $^1\text{H NMR}$ analyses show that the yields of other products derived from enone **3f** should be less than 3% and most of **3f** seems to undergo oligomerization and/or polymerization. The reaction at a higher temperature resulted in a complex mixture.
- Although we do not have any evidence to clarify the reaction mechanism, the results that alkynes in addition to 1,3- and 1,2-dienes were much more effective than triphenylphosphine may imply that these hydrocarbons do not behave merely as conventional ligands. As these hydrocarbons in combination with aldehydes or conjugated enones are considered to readily undergo oxidative cyclization to nickel(0) complexes, there may be some possibility that the present reaction involves thus formed nickelacycles, which react with arylboronates with cleavage of the proximately-formed carbon-carbon bond. For an example of nickelacycle formation, see: S. Ogoshi, M. Oka, H. Kurosawa, *J. Am. Chem. Soc.* **2004**, *126*, 11802, and references cited therein.
- Optically pure alkyne **1e** was prepared as follows. The reaction of (*R*)-styrene oxide with phenylethyneyllithium (2.8 equiv.) in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.8 equiv.) in THF at -78°C for 10 min gave (*R*)-1,4-diphenylbut-3-yn-1-ol (45% yield) and 2,4-diphenylbut-3-yn-1-ol (24% yield). The former was treated with sodium hydride (1.5 equiv.) and iodomethane (4.0 equiv.) in THF at room temperature for 2 h to give **1e** in 88% yield.