

Suzuki–Miyaura Coupling of Alkynylboronic Esters Generated in Situ from Acetylenic Derivatives

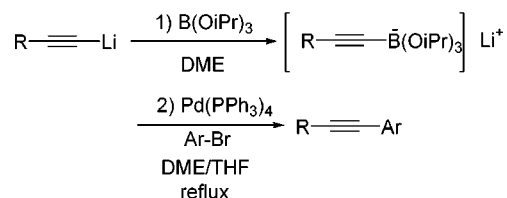
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Received August 10, 2000

ABSTRACT



A new effective Suzuki–Miyaura coupling reaction between alkynylboronic esters (generated in situ from acetylenic derivatives) and arylbromides or vinylbromides is reported.

Suzuki cross-coupling reactions of organoboron compounds and organic halides or triflates represent a versatile, pragmatic, and intensively used method for the formation of carbon–carbon bonds.¹

Among such organoboron compounds, alkynylboronic derivatives were never used in the Suzuki coupling, although alkynyl boranes were known for a long time to be useful synthetic intermediates.² They readily undergo addition to aldehydes and ketones, giving the propargylic alcohols.³ More recently an enantioselective synthesis of propargylic alcohols has been developed by using alkynylboranes.⁴ Diels–Alder cycloadditions have also been reported with these derivatives.⁵

Compared to other organoboranes, alkynylboronic esters are stronger Lewis acids and are easily hydrolyzed. There-

fore, their use in the Suzuki–Miyaura coupling, which requires a base (commonly aqueous Na₂CO₃, Ba(OH)₂, etc.) could be problematic.⁶

This difficulty has been overcome with *B*-methoxy-9-borabicyclo[3.3.1]nonane. J. A. Soderquist et al. have found that the addition of *B*-methoxy-9-borabicyclo[3.3.1]nonane to alkynyllithium reagents gave stable methoxy(alkynyl)-borate complexes which undergo efficient Suzuki coupling to produce a variety of alkynyl derivatives.⁷ At the same time, A. Fürstner and G. Seidel have reported that the borate complex can be prepared from *B*-methoxy-9-borabicyclo[3.3.1]nonane and a polar organometallic reagent RM. This approach allowed cross-couplings of aryl halides with alkynyl, methyl, and TMSCH₂ groups.⁸

In this paper we report a Suzuki–Miyaura coupling between alkynylboronic esters and aryl halides in quantitative yields.

We first studied the coupling reaction between 1-octynylboronic ester (prepared as described by H. C. Brown)⁹ and

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p-bromotoluene in the presence of 3% Pd(PPh₃)₄ and different fluorides (2 equiv) at reflux of various solvents (Table 1). The best fluoride was a solution of tetrabutyl-

Table 1. Effect of Fluoride in the Suzuki–Miyaura Cross-Coupling Reaction^a

entry	F [−]	time (h)	solvent	GC ^b	yield (%) ^c
1	CsF	4	DME	20/65	50
2	CsF	16	DMF	48/42	
3	KF	16	DME	no coupling	
4	TBAF ^d	2.5	DME	0/80	60
5	TBAF ^d	16	THF	41/44	

^a Reaction conditions: *p*-bromotoluene (1 equiv), 1-octynylboronic ester (1.3 equiv). ^b GC analysis: (% starting material)/(% coupling product). ^c Isolated yield. ^d TBAF 1 M in THF.

ammonium fluoride (1 M in THF) in refluxing DME (entry 4). The use of THF as solvent for the coupling reaction decreased the yield (entry 5).

We then tried the coupling reaction without isolating the alkynylboronic ester, which is very sensitive to atmospheric oxygen. Treatment of octynyllithium with triisopropoxyborane in DME at −78 °C afforded the “ate-complex”. In situ addition of Bu₄NF (1 M in THF) and *p*-bromotoluene in the presence of Pd(PPh₃)₄ (3 mol %) afforded after reflux the coupling product in 70% isolated yield (entry 1, Table 2).

Table 2. Optimization of the One-Pot Cross-Coupling Reaction

entry	solvent	F [−]	yield (%)
1	DME	TBAF 1 M in THF	70
2	DME	without	0
3	DME	KF + Me ₄ NCl	0
4	DME/THF, 10/1	without	98
5	THF	without	30

To demonstrate that the “ate-complex” (formed by addition of alkynyllithium with triisopropoxyborane) was the active species in the coupling reaction, we tried several experiments:

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(1) Influence of fluoride anions: the reaction in DME without TBAF in THF (entry 2) did not work as well as the reaction in DME with KF–Me₄NCl (entry 3).

(2) Influence of the solvent: the reaction in a mixture of DME/THF (10/1) without fluoride anion (entry 4) gave the coupling product in quantitative yield. The use of pure THF as solvent (entry 5) lowered the yield to 30%.

These results led to the conclusion that THF was essential to solubilize the “ate-complex”, which is not soluble in pure DME, and DME was necessary for the Suzuki coupling. In this one-pot Suzuki coupling the use of a base is not necessary. The “ate-complex” obtained by formation of alkynylboronic ester can directly transfer its organic ligand to the aryl–PdBr species to give the desired coupling product after reductive elimination.

The conditions established above were applied to the palladium-catalyzed arylation or vinylation of alkynylboronic esters starting from the alkynyllithium reagents. Table 3

Table 3. Palladium-Catalyzed Arylation or Vinylation of Alkynyllithium Reagents Mediated by B(OiPr)₃^c

entry	substrate	product	yield(%)
1			98
2			96 ^b
3			55 ^a
4			79
5			75
6			74
7			60

^a Formation of ditolylacetylene(40%). ^b DME/THF: 2.5/1 ^c Reaction conditions: alkyne (1.3 equiv), BuLi (1.4 equiv), B(OiPr)₃ (1.3 equiv), bromide (1 equiv), Pd(PPh₃)₄ (0.03 equiv), DME/THF 10/1, reflux.

summarizes the preparative results obtained. High yields were also obtained with orthosubstituted and unactivated aryl-bromides (entries 5 and 6). Uncharacterized decomposition products were observed for the Suzuki coupling between bromostyrene and 1-octyne (entry 7).

In conclusion, these results demonstrated that all kinds of boronic acids or esters including alkyl-, aryl-, and now alkynyl-boronic esters can be successfully employed as cross-coupling partners in the Suzuki–Miyaura coupling reactions.

Numerous examples of organometallic acetylide derivatives with metals such as copper (Sonogashira), tin (Stille),

zinc (Negishi), and magnesium have been reported.¹⁰ All have been shown to couple efficiently with organic electrophiles in the presence of palladium. Our Suzuki-type methodology presents also the ability to generate nucleophilic acetylides in situ, avoiding the necessity of preparing and storing large quantities of potentially unstable reagents.

Unactivated arylbromides are not often employed in Sonogashira coupling because of lower yields and homocoupling of terminal alkynes, a side reaction with such organic halides.¹¹ Therefore this Suzuki aryl–alkynyl coupling could be an alternative to the Sonogashira coupling especially in the case of orthosubstituted and unactivated

aryl bromides; yields of 75% were obtained in the Suzuki coupling of *o*-bromotoluene and *o*-bromoanisole with 1-octyne. Further studies to optimize the reaction conditions are now in progress.

All of these methodologies can indeed complement each other in the synthetic chemistry of enyne derivatives.

Acknowledgment. Financial support from Rhodia Recherches is gratefully acknowledged as well as J. R. Desmurs (Rhodia). We would like also to thank Prof. Guy Solladié for stimulating discussions.

Supporting Information Available: General experimental procedure for the coupling reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL006439D

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