ORGANIC LETTERS

1999
Vol. 1, No. 9
1423−1425

Solventless Suzuki Coupling Reactions on Palladium-Doped KF/Al_2O_3

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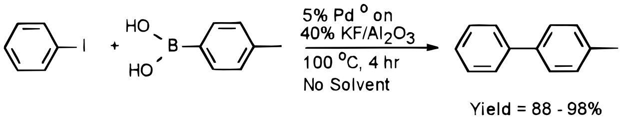
Received August 20, 1999

ABSTRACT

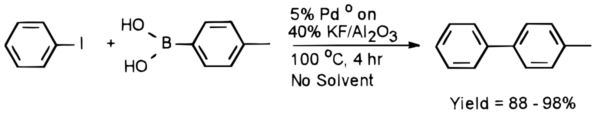


A solventless Suzuki coupling has been developed. A commercially available potassium fluoride–alumina mixture is utilized along with palladium black.

The foundation of synthetic organic chemistry rests on the ability to form and manipulate carbon−carbon bonds. In 1972, Kumada[1] and Corriu[2] independently reported that Ni(II) complexes greatly enhanced the rate of reactions of Grignard reagents with aryl and alkenyl halides. Similar results were later reported by Murahashi for palladium-catalyzed coupling reactions.[3] Negishi and co-workers then reported an alkynyl transfer from a 1-alkynyl(trialkyl)borate to iodobenzene through a palladium-catalyzed, addition−elimination sequence analogous to the Heck reaction.[4,5]

Boronic esters and acids are thermally stable, relatively unreactive to both oxygen and water, and thus easily handled without special precautions. They have been utilized in a number of carbon−carbon bond-forming reactions, the most celebrated of which is known as the Suzuki coupling reaction.[6] Due to our interest in organic reactions carried out on alumina surfaces, we decided to investigate carbon−carbon bond-forming reactions on alumina.[7] The focus of this study was the development of a novel, solventless Suzuki coupling methodology incorporating the use of a commercially available potassium fluoride/γ-alumina mixture, KF/Al_2O_3, doped with a ligandless Pd^0 catalyst, Scheme 1.

Scheme 1



A number of parameters were investigated. In general, the Suzuki reactions require the presence of a base, which is also true of the solid-state reaction (Table 1). Both potassium phosphate and potassium fluoride were effective in inducing the solid-phase coupling reactions. Because KF/Al_2O_3 was commercially available, it was used for the study.

The quantity of palladium was also found to be important; a 4−5% loading of palladium worked most efficiently. Although these levels are significantly higher than the quantities normally utilized in solution, the ability to recycle the solid catalyst should lead to more efficient use of the palladium. The reactions were generally complete in a matter

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(1) (a) Tamao, K.; Sumitani, K.; Kumada M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268. (c) Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973,** *50*, *C12*. (d) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (e) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(2) Corriu, R.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.

(3) Yamamura, M.; Moritani, I.; Murahashi, S. *J. Organomet. Chem.* **1975**, *23*, *C*39.

(4) (a) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.;. Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393. (b) Negishi, E. *Aspects of Mechanism and Organometallic Chemistry*; Plenum Press: New York, 1978.

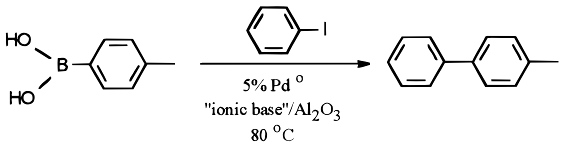
(5) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985.

(6) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Miyaura, N.; Suzuki, A. *Chem Rev.* **1995**, *95*, 2457.

(7) Kabalka, G. W.; Pagni, R. M. *Tetrahedron* **1997**, *24*, 7999.

10.1021/ol990972f CCC: $18.00

Table 1. Base Study



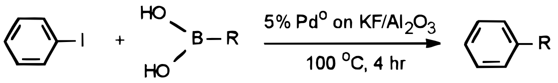
base[a]	reaction time (h)	yield (%)
NaOH	3	23
K_2CO_3	3	27
K_3PO_4	3	71
KF	3	86
NaF	4	5
Al_2O_3 (basic)	6	0

[a] Base (40%) by weight was added to the alumina prior to reactions.

of hours, but the time, as expected, was inversely proportional to the temperature. For convenience, the reactions were generally carried out at 100 °C.

Overall, the solid-phase Suzuki reactions were successful for coupling arylboronic acids to aromatic halides. Reactions involving alkyl halides (hexyl iodide, butyl iodide, isopropyl iodide, cyclohexyl iodide, and butyl bromide) or vinyl halides were unsuccessful, although allylic systems did undergo the reaction (Table 2). The reaction can also be used to couple aryl iodides to aryl, vinyl, and alkylboronic acids, but the yields are variable (Table 3).

Table 2. Halide Survey



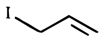
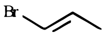
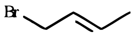
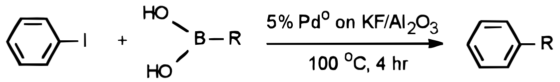
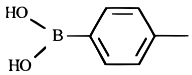
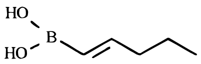
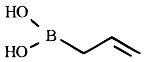
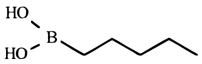
R-X	YIELD (%)	RECOVERED PhI (%)
Iodobenzene	99	<1
Bromobenzene	60	0
Chlorobenzene	5	0
Fluorobenzene	0	0
	39	0
	0	0
	66	0
Alkyl-X	0	0

Table 3. Boronic Acid Survey



BORONIC ACID	PRODUCT YIELD	RECOVERY (C_6H_5I)
	98	0
	79	0
	0	29
	29	trace

Requisite boronic acids were prepared via literature procedures.[8] KF/Al_2O_3 (Aldrich Chemical Co.) was ground to a powder and then exposed to air over a period of days to allow for hydration of the surface. Other reagents were analytical grade and used as received.

The synthesis of 4-methylbiphenyl is representative: To a mixture of KF/Al_2O_3 (0.950 g, 40 wt %) and palladium black (0.050 g, 0.470 mmol, 99.9+% as a submicron powder) was added *p*-methylphenylboronic acid (0.150 g, 1.10 mmol) contained in a clean, dry, round-bottomed flask. The solid mixture was stirred at room temperature in the open air until homogeneous. Iodobenzene (0.209 g, 1.02 mmol) was then added with stirring. The mixture was stirred at room temperature for an additional 15−20 min to ensure efficient mixing.

A condenser was put in place and the flask placed in a preheated oil bath (100 °C). Stirring was continued during the entire reaction period. After the allotted time period, the oil bath was removed and the reaction allowed to cool to room temperature. A small quantity of hexanes was then added and the slurry stirred at room temperature for an additional 20−30 min to ensure product removal from the surface. The mixture was vacuum filtered through a sintered glass funnel using Celite as a filter aid. The mixture was separated via flash chromatography to yield 4-methylbiphenyl (89%); mp 44.0−45.5 °C; ^{1}H NMR ($CDCl_3$; δ ppm) 7.40 (m, 9H) 2.37 (s, 3H).

The use of KF/alumina as a solid-phase support for solventless Suzuki reactions offers a convenient, environmentally friendly alternative to traditional reactions. It would appear that KF is the most effective base. The reactivity trends observed in solution reactions are also observed in the solid-state syntheses. That is, organic iodides react faster than the bromides and chlorides; aryl moieties are more reactive than alkenyl groups that are themselves more reactive than alkyl. In addition, the solid-phase syntheses provide one of the few successful Suzuki methodologies that can be carried out utilizing ligandless palladium reagents. Although our studies are not yet complete, the solid-state

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(8) (a) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1992**, *11*, 652. (b) Brown, H. C.; Scouten, C. G.;. Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96.

methodology offers the opportunity to recycle the reagent (via simple filtration) which has significant commercial appeal.

Acknowledgment. We thank the U.S. Department of Energy and the Robert H. Cole Foundation for their support.

OL990972F