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Tetrahedron Letters 45 (2004) 6239–6241

Tetrahedron Letters

New polystyrene-supported stable source of 2-pyridylboron reagent for Suzuki couplings in combinatorial chemistry

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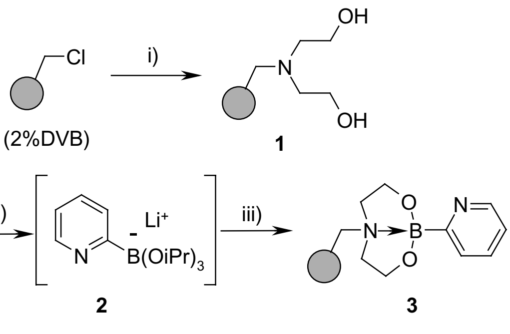
Received 8 June 2004; revised 22 June 2004; accepted 23 June 2004

Abstract—The first stable polystyrene-supported 2-pyridylboron reagent has been prepared and involved in Suzuki–Miyaura couplings. Very efficient reactions have been obtained with clean release of target coupling products providing a new tool for combinatorial chemistry.

The Suzuki–Miyaura reaction is one of the most popular processes for preparation of unsymmetrical biaryl compounds.[1] This Pd(0)-catalyzed coupling can be run under mild conditions with tolerance of a wide range of functionalities and weak sensitivity to steric effects. However, the literature essentially reports couplings between aryl boronic acids or esters and (het)aryl halides but only scarce examples of use of hetarylboronic derivatives. This is particularly obvious in pyridine series due to the strong tendency of these sensitive species to undergo protodeborylation.[2] The increasing need for these versatile reagents has drawn the chemists to develop new methodologies to obtain stabilized pyridine boron compounds. The preparation of stable unsubstituted 2-pyridylboron derivatives remains a synthetic challenge since Rault and co-workers have shown recently that the presence of halogens (bromine or chlorine) on the pyridine ring is necessary to ensure the stability of 3-pyridyl and 2-pyridyl boronic acids.[3] Other works report the introduction of boron via palladium catalyzed coupling of 2-halogeno-pyridines with the expensive bis-(pinacolato)diboron reagent but the obtained pyridylboronates were found instable and in situ homocoupled.[4] Hodgson and Salingue[5] recently described a large scale preparative procedure from 2-bromopyridine using an in situ lithiation–borylation–transesterification sequence leading to N-phenyldiethanolamine-2-pyridyboronate apparently stabilized by an excess of *i*-PrOLi. We thought that a valuable alternative could be the immobilization of 2-pyridylboron derivatives on a solid support. From our knowledge, such an approach successfully used to bind phenylboronic acids,[6] has never been developed in the far more sensitive pyridine series. Herein, we report the first stable polystyrene-supported 2-pyridylboronate and its ability to effect efficient Suzuki reactions with clean release of desired bi(het)aryl products thus providing a new tool for combinatorial synthesis of pyridyl containing libraries.



Scheme 1. Reagents and conditions: (i) $NH(CH_2CH_2OH)_2$ (20 equiv), NaI (5 equiv), DMF, rt, 48 h. (ii) BuLi (1.2 equiv), $B(Oi\text{-}Pr)_3$ (1.2 equiv), THF, −78 °C then rt, 4 h. (iii) **1** (0.3 equiv), THF, reflux, 12 h.

Keywords: Suzuki–Miyaura; Pyridine; Polystyrene.

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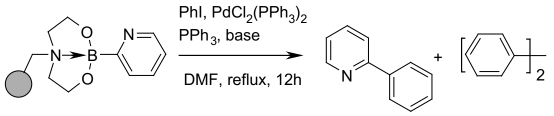
doi:10.1016/j.tetlet.2004.06.098

Table 1. Conditions screening for cross coupling of **3** with PhI[a]



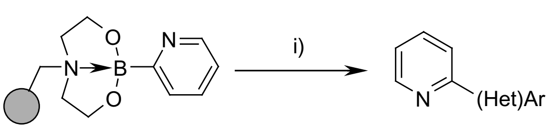
3 **4a** **5**

Run	PhI (equiv)	Base (equiv)	Additive (%)	Co-solvent	**4a**%[b]	**5**%[b]
1	1.2	Et_3N (2)	—	—	Tr	30
2	2	Et_3N (3)	—	—	Tr	40
3	5	Et_3N (5)	—	—	Tr	35
4	2	K_2CO_3 (3)	—	H_2O	Tr	15
5	2	CsF (3)	—	H_2O	3	31
6	2	CsF (3)	—	—	6	70
7	1.5	CsF (3)	—	—	23	19
8	1.5	CsF (3)	CuI (10%)	—	90 (85)[c]	—
9	1.5	CsF (3)	CuI (10%)	—	30[d]	—

[a] Reaction carried out on 500mg (0.62mmol).
[b] GC yields.
[c] Isolated yield after column chromatography.
[d] Performed in absence of PPh_3.

Among suitable linkers, we chose the diethanolamino group known as an efficient boronic acid scavenger due to an additional boron chelation by the nitrogen lone pair.[6a] The supported 2-pyridinedioxazaborocane **3**[7] was obtained as a pale pink solid (1.25mequiv/g, 70% yield from **1**)[8] by refluxing 0.3equiv of aminodiol resin **1** (1.8mequiv/g)[8] in THF with the ate complex **2** prepared by in situ trapping of 2-lithiopyridine with triisopropylborate (Scheme 1).

The obtained supported reagent was then involved in Pd-catalysed Suzuki coupling under various conditions (Table 1). We chose to catalyze the reaction with 5mol% of the commonly used $PdCl_2(PPh_3)_2$ complex in DMF, a good solvent for both the Suzuki coupling and polystyrene swelling. As shown, the base had a large impact on the reaction selectivity. CsF was the most efficient (runs 8–9), may be due to the formation of a $PyrBF_3^-$ ate complex enhancing efficiently *trans*-metallation step.[9] A spectacular improvement was further obtained by addition of CuI, leading to **4a** in very good 85% isolated yield (run 9) with disappearance of homocoupling product **5**. Under these conditions a very clean reaction medium was obtained after simple filtration of the resin and subsequent elution of the filtrate through a short pad of silica. Moreover, elemental analysis of the resin after coupling revealed a quantitative release of the pyridine moiety.



3 **4b-k**

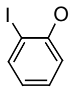
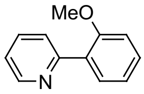
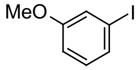
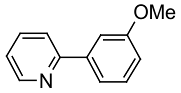
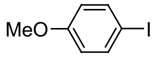
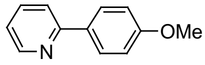
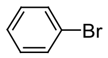
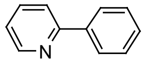
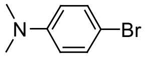
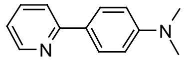
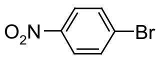
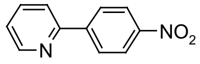
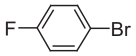
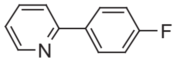
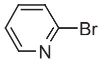
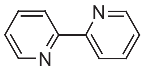
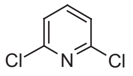
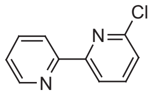
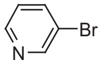
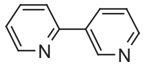
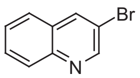
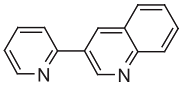
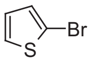
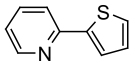
Scheme 2. Reagents and conditions: (i) (Het)ArX (1.25equiv), $PdCl_2(PPh_3)_2$ (5%), PPh_3 (10%), CuI (10%), DMF, 80°C, 30min, then CsF (3equiv), **3**, DMF, reflux, 12h.

The scope of the reaction was then examined by reacting **3** with a range of aromatic and heteroaromatic halides under the above determined best conditions (Scheme 2 and Table 2).[10]

All reactions led to the expected cross-coupling products in good yields with electron-rich and electron-deficient aryl and heteroaryl halides. Iodo aromatic compounds were reacted efficiently with an expected slight yield decrease with 2-iodo and 4-iodo anisole due to steric effects and deactivating electron-donor effect, respectively. 4-Bromo-N,N-dimethylaniline surprisingly gave **4d** in 77% yield. This kind of electron-rich bromo derivative generally led to poor yields in cross-coupling reactions.[5] Bromoarenes bearing electron-withdrawing groups also coupled efficiently. Very good yields were also obtained for preparation of dissymmetrical bis-heterocycles from both brominated or chlorinated substrates. Interestingly, the coupling of 2,6-dichloropyridine proceeded with full retention of the synthetically useful C–Cl bond in **4h**.

In summary, we have prepared the first supported stable source of 2-pyridylboronate.[11] This new useful organometallic reagent has been successfully reacted with a range of (het)aryl halides leading to coupling products in high yields. This study opens new perspectives for the Suzuki coupling in combinatorial chemistry especially for preparation of 2-x′ bisheterocycles. Work is now in progress to extend the reaction to immobilization of functional pyridines and other sensitive heterocyclic derivatives.

Table 2. Coupling of **3** with aromatic and heteroaromatic halides[a]

(Het)ArX	Product		Yield%[c]
		**4b**	60
		**4c**	82
		**4d**	67
		**4e**	50
		**4d**	77
		**4e**	56[b]
		**4f**	70
		**4g**	87
		**4h**	67
		**4i**	85[d]
		**4j**	78
		**4k**	79

[a] All reactions performed on 1 g (1.25 mmol) of resin **3**.

[b] 90% GC yield, material was lost by degradation during separation.

[c] Isolated yields after column chromatography.

[d] Bipyridine **4g** was obtained in trace amount.

References and notes

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7. From Ref. 5, the immobilized azaborocane **3** was assumed to have the structure depicted in Scheme 1. Investigations are in progress to obtain a more accurate structure using gel phase HRMAS NMR.
8. The loadings were obtained by elemental analysis.
9. Wright, S. W.; Hageman, D. L.; Mc Clure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
10. Typical procedure for Suzuki coupling with **3**. A mixture of the (het)aryl halide (1.56 mmol), $PdCl_2(PPh_3)_2$ (44 mg, 5%), PPh_3 (32 mg, 10%) and CuI (24 mg, 10%) in DMF (5 mL) was heated at 80 °C under inert atmosphere for 30 min. CsF (0.57 g, 3.75 mmol) was then added followed by resin **3** (1 g, 1.25 mmol). The suspension was then maintained under reflux for 12 h. After cooling the mixture was filtered and the filtrate passed through a short pad of silica. Evaporation and column chromatography afforded pure homocoupling products, which spectroscopic data were in full agreement with those of known compounds.
11. After preparation, the resin **3** was simply stored at room temperature into an argon flushed flask. The nitrogen content was found constant after 5 months and couplings proceeded with the same efficiency after such period.