

The Suzuki-Miyaura Cross Coupling Reactions on Solid Support. Link To Solution Phase Directed *ortho* Metalation. The Leznoff Acetal Linker Approach to Biaryl and Heterobiaryl Aldehydes

S. Chamoin,^a S. Houldsworth,^a C.G. Kruse,^b W. Iwema Bakker,^b and V. Snieckus^{a*}

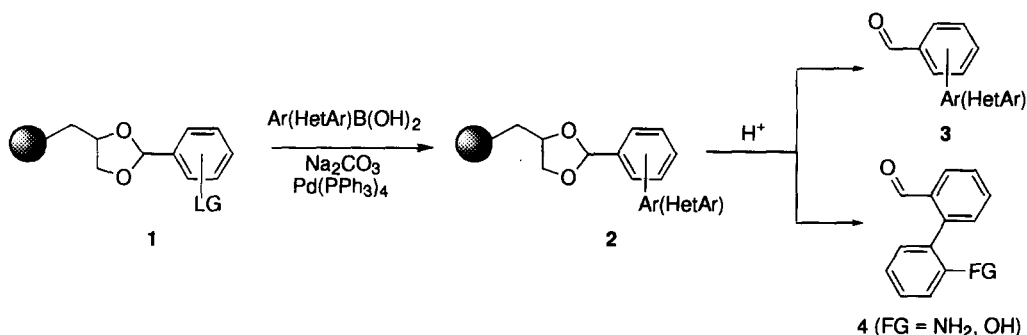
^a Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, ON N2L 3G1, Canada. E-mail: snieckus@buli.uwaterloo.ca

^b Solvay Pharmaceuticals Research Laboratories, P.O. Box 900, 1380 DA Weesp, The Netherlands

Received 24 December 1997; accepted 30 March 1998

Abstract: The synthesis of the titled compounds by Suzuki-Miyaura cross coupling on Merrifield resin - Leznoff acetal - linked halo benzaldehydes followed by mild acid hydrolysis is reported; synthetic utility for heterocycles based on solution phase Directed *ortho* Metalation chemistry is demonstrated. © 1998 Elsevier Science Ltd. All rights reserved.

As a sequel to the solid support (SS) Stille cross coupling,¹ we report herein a SS Suzuki-Miyaura cross coupling protocol based on the original excellent Leznoff acetal linker technology (1→2→3, Scheme 1). As for the SS Stille reaction, the Suzuki - Miyaura process² is connected to the Directed *ortho* metalation (DoM) reaction³ but, in addition, allows demonstration of the principle of cyclisation of released biaryl aldehydes 4 to heterocyclic products.

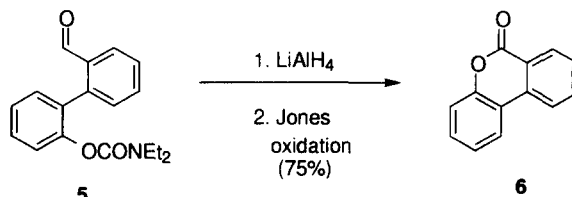


Scheme 1

Commercial Merrifield resin (1% cross linked, 1 mequiv Cl/g) was functionalised *via* the sodium alkoxide of solketal [prepared by treatment of solketal (Aldrich) with sodium metal] following the reported optimized conditions.⁴ Hydrolysis of the acetone (1.5M HCl/dioxan 1:1) enabled aldehydes to be loaded onto the solid support (3 equiv of the aldehyde/cat. PTSA/Na₂SO₄/toluene/80°C/24 h). Polymer loading was determined by cleavage from the SS (3M HCl/dioxane 1:1) and GC and/or NMR analysis.⁵ This cleavage method proved very reliable, although required prolonged reaction times.

Suzuki cross coupling reactions of a range of aryl and heteroaryl boronic acids with a sample of SS-attached bromo benzaldehydes were carried out using typical solution phase Suzuki conditions (excess of boronic acid / 5 mol% Pd(PPh₃)₄ / 2M aq Na₂CO₃ / DME / argon).⁶ The results are displayed in the **Table**. With the exception of one case of a boronate ester (entry 5), boronic acid aryl and heteroaryl (entries 2, 8, 14, and 15) coupling partners were used. In the absence of steric effects, excellent yields of the biaryl and heterobiaryl aldehydes were obtained. The problems of increasing steric demands could be circumvented in many cases (entries 1 - 5 and 13) by increasing the reaction times from 24 h to 48 h. However, in two cases (entries 10 and 11), even prolonged reaction times had minimal effects. Boronic acids prepared *via* DoM³ (entries 3, 5 and 13) afforded cross coupled products in excellent yields under slightly longer reaction times.

The demonstration of synthetic utility for heterocycles by virtue of the Suzuki - Miyaura - DoM connection was established in two prototype cases (entries 3 and 5). Thus cross coupling of SS - tethered 2-bromobenzaldehyde with the boronate ester of N-Boc aniline (entry 5) resulted, after cleavage, in cyclisation to phenanthridine in excellent combined yield (90%, two steps). Similarly, the hydrolysis product **5** (entry 3), upon treatment with LiAlH₄ and Jones oxidation furnished dibenzo[b,d]pyranone (**6**) in good yield (**Scheme 2**).



Scheme 2

In conclusion, SS Suzuki-Miyaura cross coupling reactions using the Leznoff acetal linker have been developed leading to biaryl and heterobiaryl aldehydes, a hitherto difficult to access class of molecules using currently available linker technologies.⁷ Furthermore, connection of this process to the Directed *ortho* Metalation strategy has been demonstrated. The application of this methodology to diverse libraries of biaryls, phenanthridines and dibenzopyranones may be anticipated. The transfer of Stille (ArSnR₃), Kumada (ArMgX) and Negishi (ArZnX) solution phase chemistry to SS, mindful of the DoM connection using the above linker technology, is under active investigation.⁸

Acknowledgment. We thank NSERC Canada and Monsanto/Searle/Ceregen for support under the Industrial Research Chair Program. We are most grateful to Bruce Hamper and Ceregen, St. Louis for tutoring S.C. in solid support techniques which greatly accelerated this program in our laboratories.

Table. Synthesis of Biaryl Aldehydes **3** and **4** by the Suzuki-Miyaura Reaction

Entries	Starting Polymer	Ar(HetAr)B(OH) ₂	Product 3	Yield ^a , %
1		PhB(OH) ₂		>95 ^b
2		(HO) ₂ B-		>95 ^b
3		 B(OH) ₂ OCONEt ₂		>95 ^b
4		 B(OH) ₂ NO ₂		87 ^b
5		 B(OH) ₂ NHBoc		90 ^b
6		PhB(OH) ₂		>95
7		 B(OH) ₂ OMe		>95
8		(HO) ₂ B-		85
9		PhB(OH) ₂		>95
10		 B(OH) ₂		60 ^{b,c}
11		 B(OH) ₂		45 ^{b,c}
12		 B(OH) ₂ OMe		>95
13		 B(OH) ₂ OCONEt ₂		>95 ^b
14		(HO) ₂ B-		>95
15		(HO) ₂ B-		65 ^c

^a Isolated yields after column chromatography^b 48 h Cross coupling reaction. ^c SM (%) in entry 10 (30%), 11 (45%), 14 (30%).

References and Footnotes

1. Chamoin, S.; Houldsworth, S.; Snieckus, V. *Tetrahedron Lett.* **1998**, 39, 4175.
2. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457. For recent cases on SS, see a) Backes, B.J.; Ellman, J.A. *J. Am. Chem. Soc.* **1994**, 116, 11171. b) Piettre, S.R.; Baltzer, S. *Tetrahedron Lett.* **1997**, 38, 1197. c) Ruhland, B.; Bombrun, A.; Gallop, M.A. *J. Org. Chem.* **1997**, 62, 7820.
3. Snieckus, V. *Chem. Rev.* **1990**, 90, 879; Snieckus, V. In *Chemical Synthesis: Gnosis to Prognosis*, Chatgililoglu, C.; Snieckus, V., Eds.; NATO ASI Series, Kluwer Academic Publishers: The Netherlands, **1996**, Series E: Applied Sciences, Vol. 320, p 191.
4. Leznoff, C.C.; Wong, J.Y. *Can. J. Chem.* **1973**, 51, 3756; Leznoff, C.C.; Sywanyk, W. *J. Org. Chem.* **1977**, 42, 3203.
5. The loading of the bromo-benzaldehydes were approximately 0.6 mequiv/g in each case.
6. *Typical Cross Coupling and Cleavage Procedure:* Resin **1** (0.15g) was swollen in anhydrous DME (5 mL) and the system was flushed with argon (30 min). Pd(PPh₃)₄ was added, the reaction mixture was stirred (10 min) and treated with degassed Na₂CO₃ solution (2 M, 8 equiv) and stirred (10 min). The boronic acid (3 equiv) was added, the reaction mixture was flushed with argon (15 min), heated to reflux for 24 h., cooled to rt, and treated with aq satd NH₄Cl solution (5 mL) and further stirred (10 min). The resin was removed by filtration (fritted glass funnel) and the filtrate was washed successively with DME (5 mL), DME:H₂O (1:1) (10 mL), 0.3 M HCl (10 mL), H₂O (15 mL), DMF (5 mL), EtOAc (10 mL), EtOAc:MeOH (1:1) (10 mL), MeOH (15 mL) and dried *in vacuo* (12 h). The resin **2** was swollen in dioxan (3 mL) for 30 min, a solution of 3 M HCl (3 mL) was added, and the mixture was stirred at 80°C (48 h). The reaction mixture was cooled to rt and subjected to filtration (fritted glass funnel). The resin was successively washed with H₂O (30 mL), H₂O:MeOH (1:1) (30 mL), MeOH (30 mL), CH₂Cl₂ (30 mL) and the filtrate was repeatedly extracted with CH₂Cl₂. The combined organic extract was washed with brine, dried (Na₂SO₄) and evaporated to dryness to give the aldehyde which was analyzed by GC and ¹H NMR.
7. Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D.C. *Tetrahedron* **1997**, 53, 5643.
8. All new compounds show satisfactory spectroscopic (NMR, HRMS) and analytical data.