Novabiochem®

Merck Biosciences AG · Switzerland
Weidenmattweg 4
4448 Läufelfingen
Phone +41 (62) 285 2525
Fax +41 (62) 285 2520

www.novabiochem.com

Novabiochem a brand of Merck Biosciences AG.
An affiliate of Merck KGaA, Darmstadt, Germany

Microwave accelerated Suzuki coupling employing polymer-supported palladium phosphines

S. Barthélémy,[1] B. Baumeister[1] and P. White[2]

[1]Novabiochem, Merck Biosciences AG, Weidenmattweg 4, CH-4448, Läufelfingen, Switzerland and [2]Novabiochem, Merck Biosciences Ltd., Padge Road, Beeston, NG9 2JR.

Introduction

Palladium-mediated Suzuki cross-coupling of aryl halides and aryl boronic acids is an extremely important method for the synthesis of biaryls (Figure 1) [1].
The reaction is typically carried out by heating together the aryl halide and boronate in the presence of a palladium catalyst and an inorganic base, such as K_2CO_3. Even at elevated temperatures, coupling is often sluggish and, in some cases, can take a number of days to go to completion. Fortunately, this limitation can be overcome using microwave heating, enabling reaction times to be reduced to just a few minutes. The approach is particularly expedious if a polymer-supported palladium catalyst is used instead of the typical soluble $Pd(PPh_3)_4$ catalyst. Such insoluble catalysts offer significant benefits [2]: firstly, they can be easily removed at the end of the reaction by filtration; secondly, the products obtained typically contain much lower levels of residual palladium, which is particularly important if the compounds are for biological screening; finally, in contrast to many soluble catalysts, they are air stable and so can be handled under ambient conditions. The method is exemplified through the synthesis of a small library of biaryls.

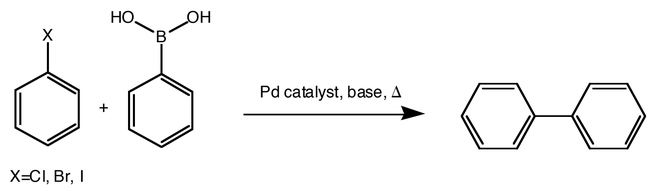

Figure 1: Suzuki coupling.

Library Synthesis

The library consisted of 14 compounds prepared from two boronic acids (**a**, **b**) and seven aryl bromides (**1** - **7**), as shown in Figure 2. All reactions were performed on an EMRYS™ Liberator from Personal Chemistry.
Dicyclohexylphenylphosphine polystyrene **8** (01-64-0394) loaded with Pd(0) (Method 1) was chosen as the catalyst for this study, since in comparative tests (Method 2) with supported triphenylphosphine polystyrene **9** (01-64-0308), diphenylphosphinomethyl polystyrene **10** (01-64-0351) and di-o-tolyl-phenylphosphine polystyrene **11** (01-64-0395), this material was found to be the most effective (Table 1).

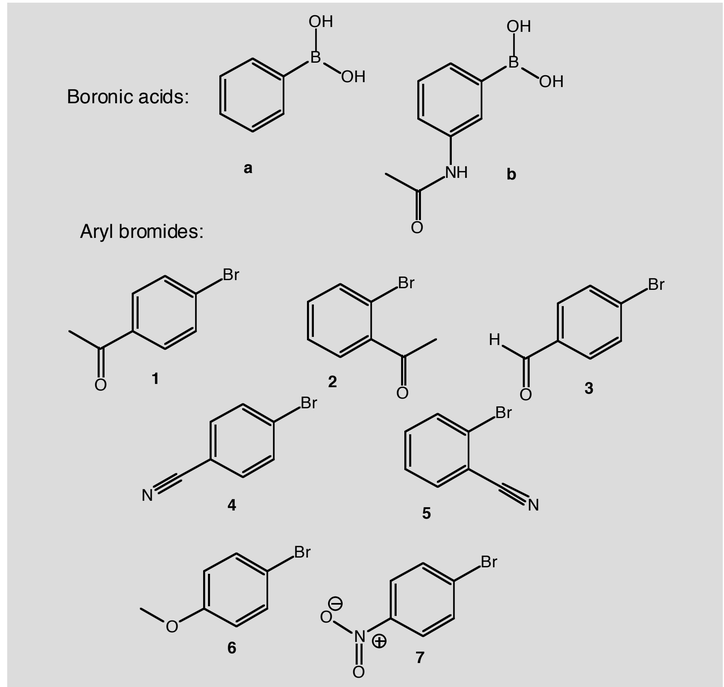

Figure 2: Boronic acid and aryl bromide building blocks.

Method 1: Catalyst preparation

1. Dicyclohexylphenylphosphine polystyrene (1.04 g, 1 mmole, 0.96 mmole/g) suspended in toluene was treated with $Pd(PPh_3)_4$ (0.04 mmole, 46 mg).
2. The mixture was heated at 80 °C under Ar.
3. The resin was isolated by filtration and washed with EtOH (3 x) and ether (3 x).
4. The loading of the resin was determined by elemental P and Pd analysis to be 0.037mmole/g.

Method 2: Preparation of 4-formylbiphenyl using different supported phosphines

1. 4-Bromobenzaldehyde (0.1 mmole) and phenylboronic acid (0.15 mmole) were dissolved in DMF or MeCN. 3M $CsCO_3$ aq. (65 µl) was added.
2. Pre-loaded palladium phosphine resin (0.001 mmole) was added and the reaction vessel was sealed.
3. The mixture was irradiated with microwave for 300 s. After this time, the crude reaction mixture was analyzed by HPLC.

Table 1: Conversion yields for 4-formylbiphenyl using four different polymer-supported phosphines loaded with palladium. P, product; S, starting material; H, homocoupling. Values were determined by HPLC using an ACE 3 AQ column; gradient: 10%–95% B in 2 min, 0.9 ml/min; A: 100% water; B: 100% acetonitrile.

Resin	Solvent	Temp (°C)	Volume (ml)	% P, S, H		
				P	S	H
8	MeCN	160	4	92	5	0
9	DMF	160	2	6	90	0
9	MeCN	160	4	86	6	3
10	MeCN	160	4	90	4	0
11	MeCN	160	4	42	42	14

For the library synthesis, Suzuki cross-couplings were performed in DME/water/EtOH as described in Method 3. The conversion yields of the reactions were determined by LCMS, and the results are given in Table 2. Compounds 1a, 1b and 4a (Figure 3) were isolated by chromatography on silica-gel eluted with EtOAc/hexane (1:3) in yields of 82, 43 and 79%, respectively, and characterized by HPLC and ^1H nmr spectroscopy (Figures 4-9).

Method 3: Library synthesis (Figure 3)

1. Aryl bromide (0.25 mmole) and arylboronic acid (0.375 mmole) were dissolved in DME/water/EtOH (9:2:9) containing $CsCO_3$ (0.5 mmole).
2. Pre-loaded palladium phosphine resin (0.003 mmole) was added and the reaction vessel was sealed.
3. The mixture was irradiated with microwave for 300 s at 170 °C. After this time, the crude reaction mixture was diluted with EtOH, filtered and concentrated.

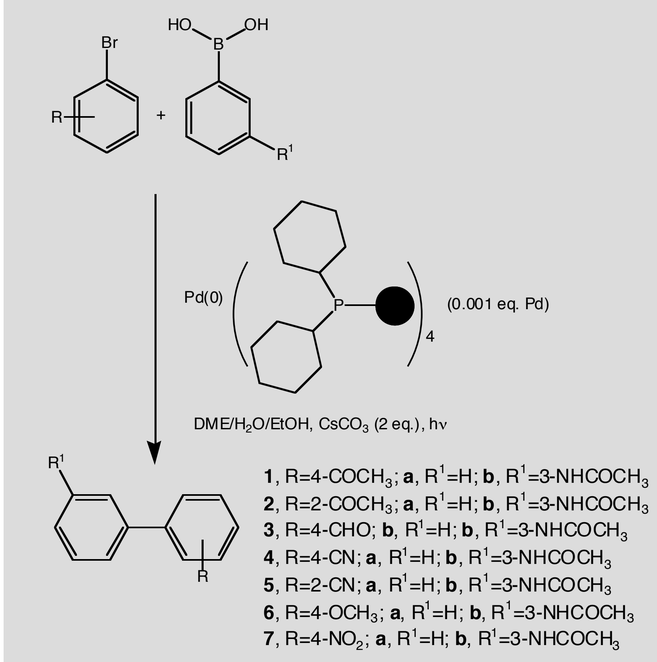

Figure 3: Preparation of biaryl library.

Table 2: Conversion yields for biaryl library. Values were determined by HPLC using an ACE 3 AQ column; gradient: 10%-95% B in 2 min, 0.9 ml/min; A: 100% water; B: 100% acetonitrile.

	Boronic acid a	Boronic acid b
Aryl-Br	% Yield	% Yield
1	79	70
2	75	65
3	84	74
4	95	82
5	97	75
6	97	67
7	84	80

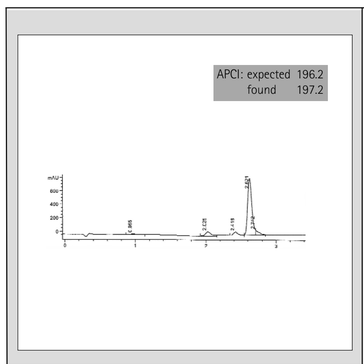

Fig. 4: HPLC elution profile of 1a. (HPLC conditions: ACE 3AQ; Gradient: 10%–95%B in 2 min, 0.9ml/min; A: water; B: acetonitrile.

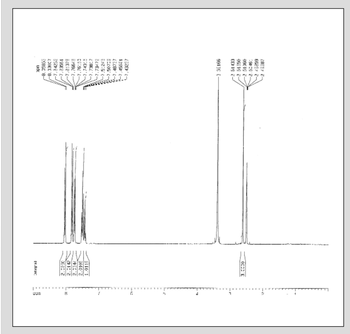

Fig. 5: ^1H nmr spectrum of 1a.

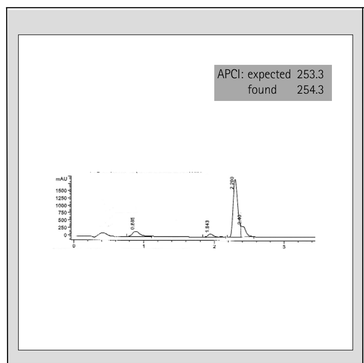

Fig. 6: HPLC elution profile of 1b. (HPLC conditions: ACE 3AQ; Gradient: 10%–95%B in 2 min, 0.9ml/min; A: water; B: acetonitrile.

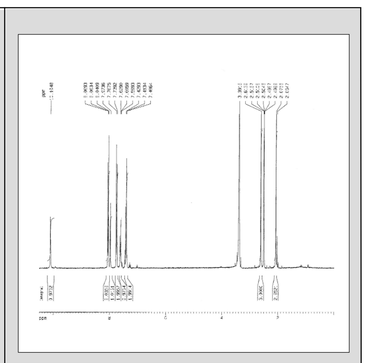

Fig. 6: ^1H nmr spectrum of 1b.

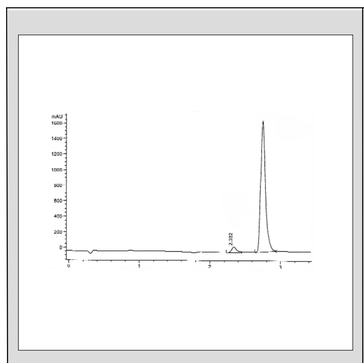

Fig. 8: HPLC elution profile of 4a. (HPLC conditions: ACE 3AQ; Gradient: 10%–95%B in 2 min, 0.9ml/min; A: water; B: acetonitrile.

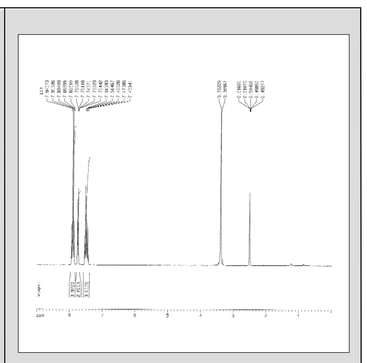

Fig. 9: ^1H nmr spectrum of 4a.

References

[1] Miyaura, N. & Suzuki, A., *Chem. Rev.* 1995; **95**: 2457.
[2] a) Jang, S.-B., *Tetrahedron Lett.* 1997; **38**: 1793; b) Fenger, I. & LeDrian, C., *Tetrahedron Lett.*; **39**: 4287; c) Parrish, C. A. & Buchwald, S. L., *J. Org. Chem.* 2001; **66**: 3820.

Acknowledgements

Ronny Lundin, Personal Chemistry AB, Uppsala, Sweden, is acknowledged for the microwave-assisted syntheses.

MERCK