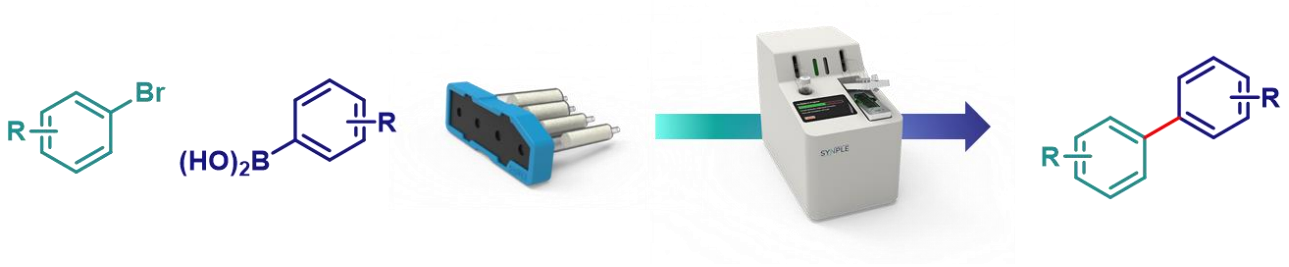
Application Note – Suzuki-Miyaura cross-coupling

Introduction

The Suzuki-Miyaura cross-coupling reaction is a remarkably useful tool in organic synthesis. It is a catalyzed-palladium reaction and it allows to generate carbon-carbon bond from an organoboron compound with an organic halide or pseudo-halide. The reaction has largely been employed in academic laboratories as well as in pharmaceutical and fine chemical industries to synthesise a large variety of organic molecules. This transformation presents a lot of advantages such as: i) the use of boronic acids, which are very available, less toxic and safer for the environment than organotin or organozinc compounds used for other cross-coupling reactions; ii) a wide variety of aryl halides / pseudo-halides can be used with the following reactivity: R-I > R-OTf > R-Br > R-Cl.

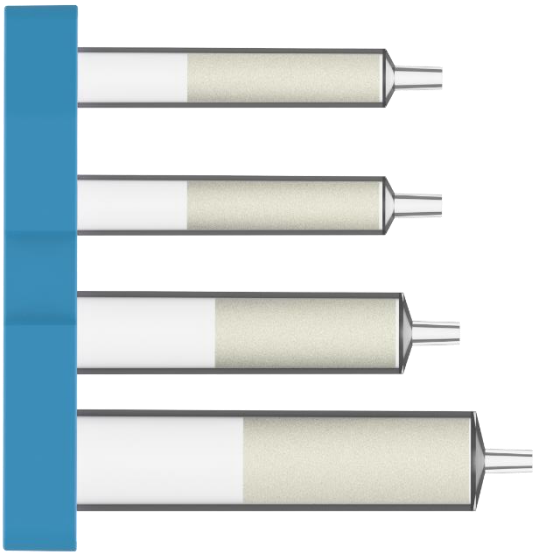
Though lot of different Pd catalysts can be used for Suzuki-Miyaura cross-coupling reactions, under homogeneous conditions, it can generate Pd black. To avoid the usage of homogeneous catalysis, the use of heterogeneous catalysis represents a good alternative to reduce by a lot palladium leaching. By using pre-packed solid-supported palladium cartridge and solid-phase purification method, Suzuki-Miyaura cross-coupling reaction has become safer and more user-friendly.



Using the approach in this application note, the Synple Chem synthesizer offers an easy and fast-automated method for the Suzuki-Miyaura cross-coupling between aryl bromides and aryl boronic acids.

Cartridge Contents

The cartridge contains a set of reagents to carry out a Suzuki-Miyaura cross-coupling reaction at a scale up to 0.8 mmol.



Sand / Celite / solid-supported Pd / Cs_2CO_3

–

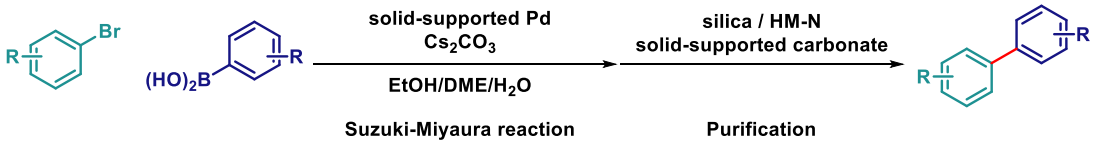
solid-supported carbonate

silica / HM-N

Contact: info@synplechem.com www.synplechem.com
Cartridge product numbers: C001, C101

Reaction Scheme

This section describes the general course of the Suzuki-Miyaura cross-coupling:



Reaction Procedure

1) Solubilization of the aryl bromide and aryl boronic acid

The starting aryl bromide and aryl boronic acid in the vial are dissolved in DME/EtOH/ H_2O (2:2:1).

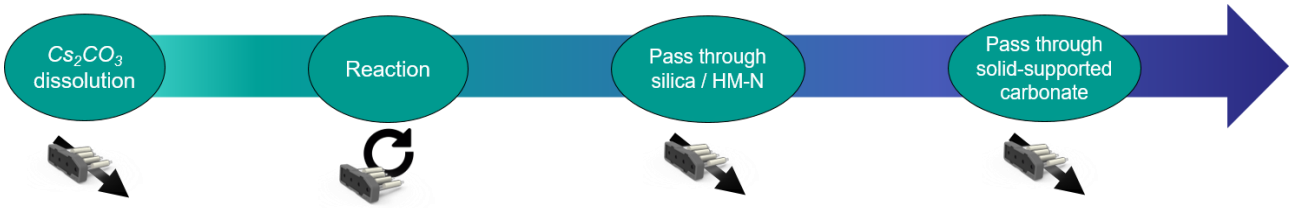
2) Suzuki-Miyaura cross-coupling reaction

In the first step, the pre-mixed solution of aryl bromide and aryl boronic acid is heated up to 65 °C and circulated through compartment 1 (solid-supported Pd and Cs_2CO_3) at 1 mL/min at 65 °C for 3 hours. The compartment 1 is cooled down to room temperature and further rinsed with EtOAc, which goes into the vial.

3) Purification

The reaction mixture is then passed through compartment 4 (silica / HM-N) at 1 mL/min. The compartment 4 is further rinsed with EtOAc, which goes into the vial. The reaction mixture is circulated through the compartment 3 (solid-supported carbonate) for 1.5 hour. The compartment 4 is further rinsed with EtOAc, which goes into the vial.

After purification, the solution in the vial contains the Aryl-Aryl product.

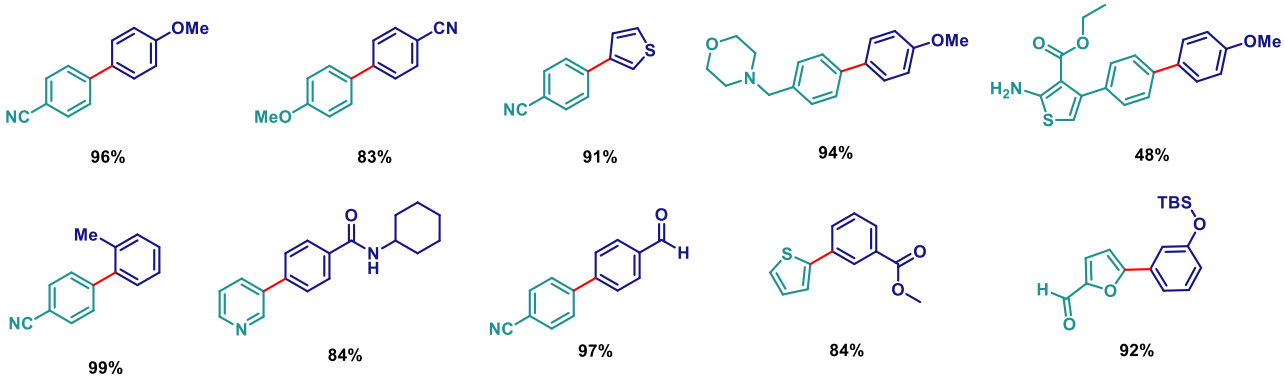


Substrate Scope

Tolerated functional groups

A wide range of functional groups are tolerated including aldehydes, amides, esters, ethers, ketals, nitriles, silyls and various heterocycles (furan, morpholine, pyridine, thiophene, etc.),

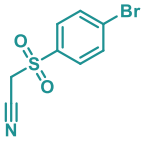
Example substrate scope (from 0.8 mmol aryl bromide)



Contact: info@synplechem.com www.synplechem.com
Cartridge product numbers: C001, C101

Identified Chemistry Limitation

Insoluble starting materials
Some starting materials were insoluble in any solvents and couldn't be used for an automated Suzuki-Miyaura cross-coupling reaction.



Reaction Parameter Editing

Editing parameters:

Parameter 1	Reaction time of Suzuki-Miyaura step (seconds) e.g. 12 hours = 43200 seconds

Enabling and Disabling parts:

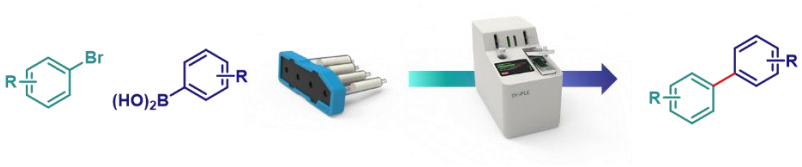
Part 1: Purification step:
The purification step of the sequence can be disabled. Then synthesizer will then provide the crude product in solution in the vial after the coupling step.

Reaction Planning

Solubility of reactants
The starting amine shall be soluble in a solution of DME/EtOH/H_2O (2:2:1). If insoluble, 10% of NMP or DMF can be used to help for the solubilisation of starting materials.

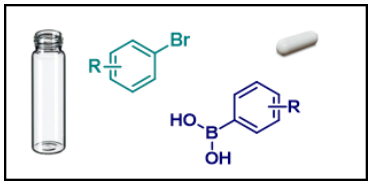
Tolerance of air and/or moisture
Suzuki-Miyaura cross-coupling reaction using Synple Chem synthesizer is insensitive toward moisture. All the reaction solvents should be degazed (with nitrogen or argon) 30 minutes before use.

Sample Preparation



Precaution
To ensure a successful reaction in the Synple Chem synthesizer, automated CH_2Cl_2 wash shall be run before setting up a Suzuki-Miyaura cross-coupling reaction.

Setup



Components for sample preparation:

- Vial
- Stir bar
- Aryl bromide and aryl boronic acid (up to 0.8 mmol)
- Reaction solvent (4 mL – DME/EtOH/H_2O = 2:2:1)

1) **Tips for sample preparation**
    - *Sonication may help dissolving poorly soluble materials.*

Contact: info@synplechem.com www.synplechem.com

- *Pre-grinding the aryl bromide or aryl boronic acid may help dissolving poorly soluble materials.*
- *For insoluble starting materials in DME/EtOH/H_2O (2:2:1), addition of 10% of NMP or DMF can be used to get everything soluble.*

Machine Solvents for the use with Suzuki-Miyaura cross-coupling cartridge

Please connect the following solvent to the color-coded solvent lines:

	S1: CH_2Cl_2, 99.8% anhydrous, 50 ppm amylene tolerate
	S2: EtOAc, HPLC grade
	S3: MeOH, >99.9%
	S4: –
	S5: –

Machine Cleaning after Suzuki-Miyaura cross-coupling Reaction

1) Run automated MeOH/H_2O (1:1) wash after the Suzuki-Miyaura cross-coupling reaction.
2) Run automated MeOH wash after the automated MeOH/H_2O (1:1) wash.
3) Run automated CH_2Cl_2 wash before starting a new Suzuki-Miyaura cross-coupling reaction.

Solvent Consumption and Run Time

SEQUENCE RUNTIME	
Reaction Sequence	**Time**
Suzuki-Miyaura	7 h 07 min

SOLVENT COMSUMPTION FOR BOC DEPROTECTION	
For Reaction Setup	**Amount**
1,2-Dimethoxyethane (DME)	2 mL-
Ethanol (EtOH)	2 mL
Water (H_2O)	
Machine Solvents	
Dichloromethane (CH_2Cl_2)	20 mL
Ethylacetate (EtOAc)	57 mL

Contact: info@synplechem.com www.synplechem.com