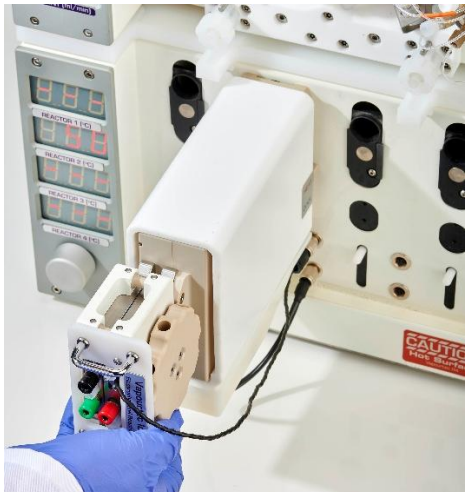

Application Note 63:

Reductive Electro-Organic Synthesis

Produced for Vapourtec by New Path Molecular Ltd

Abstract

This application note demonstrates the use of the Vapourtec Ion electrochemical reactor for the reductive cross-electrophile coupling of organic halides, constructing a Csp^2-Csp^3 bond. After optimization of this key reaction, the desired product was afforded in a yield of 81%.

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Background

Electrochemistry represents one of the most intimate ways of interacting with molecules [1]. In the past few years, a large number of various types of reactions using electrochemical reactors have been reported. These technologies have yet to be integrated into a tailor-made device, which has forced chemists to engineer their own apparatus prior to attempting any electrochemical reaction.

In 2017, Pfizer revealed a reductive cross coupling reaction to construct Csp^2-Csp^3 bonds from organic halides in a batch electrochemical system [2]. An electrochemical protocol was used to reduce a catalyst (Ni^{II} to Ni^0 or Ni^{III} to Ni^{II} according to literature).

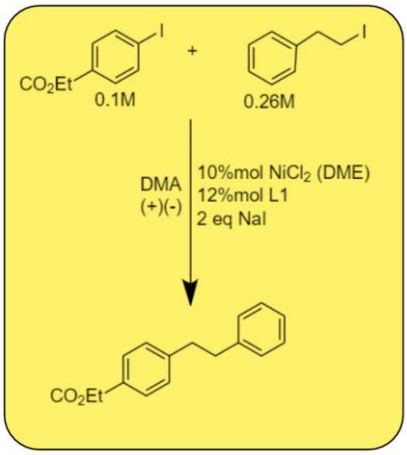


Figure 1 – The reductive cross coupling between aryl iodide and alkyl iodide.

Vapourtec has recently developed the Ion electrochemical reactor compatible with the Vapourtec R- and the E-Series flow chemistry systems. This reactor takes advantage of the extremely large surface-to-volume ratios that a flow microreactor provides [3] to make this reaction more efficient. One of the key features of

the Ion electrochemical reactor is its versatility to operate at different conditions:

- It can be both heated and cooled (-10 °C to 100 °C)
- It can work at pressures of up to 5 bar (allowing to work over solvent's boiling point and with gas mixtures)
- The reactor's volume can be easily changed from 0.15 ml to 1.20 ml
- Any electrode of dimensions 50 mm x 50 mm and up to 2.0 mm thick can be fitted in the reactor. Vapourtec supplies 20 different electrodes. Exotic electrodes can be sourced elsewhere.

In this application note, we illustrate the reductive cross coupling reaction to form sp^2-sp^3 bonds using this pioneering electrochemical reactor. The reaction proceeded simply and smoothly, producing the corresponding product from organic iodides which are readily commercially available compounds.

Setup

All the experiments were performed using the Vapourtec R-Series equipped with an R2C+ pump module as well as the new Ion electrochemical reactor.

Reagents

All materials, except for the ligand 2-amidinopyridine hydrochloride (L1), were purchased from commercial suppliers:

- Fluorochem - Aryl iodide, dimethylacetamide (DMA) and Dtbbpy
- Sigma-Aldrich -Alkyl iodide, $NiCl_2$ (DME), and NaI

Ligand L1 was synthesized according to the literature [4].

System solvent - DMA

Reagent solution - A 20 ml vial was dried overnight in an oven at 105 °C. It was equipped with a stir bar and a septum and then cooled down to room temperature under vacuum conditions. The vial was backfilled with N_2. Then, 0.1 eq of $NiCl_2$ (DME), 0.12 eq of L1 and 2 eq of NaI were charged into the vial. After this, the vial was evacuated and backfilled with N_2 three times. 2.0 ml of DMA was added via syringe and it was stirred for 5 min.
Then the aryl iodide (0.2 mmol, 1 eq) and alkyl iodide (0.52 mmol, 2 eq) were added to the mixture.

System Parameters

Working electrodes

- Cathode: Carbon electrode
- Anode: Zinc electrode

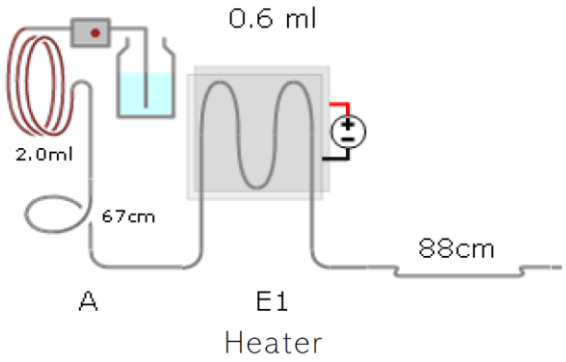


Figure 2: Schematic of the R-Series used during this application note.

The reaction was set to constant current (0.02 A) at 1 atm without a back-pressure regulator. Two working temperatures were studied, 30 and 50 °C.

The final reagent was loaded into the sample loop using a 2 ml syringe. The reagent passed into the Ion electrochemical reactor, with a volume between electrodes of 0.6 ml.

In order to evaluate the effect of residence time, two flowrates were evaluated, 0.030 ml/min and 0.060 ml/min.

Results and Discussion

The reaction output was collected into a vial and an aliquot was analyzed by HPLC. 4-Bromoanisole was used as internal standard to determine yields.

Table 1 collates the reaction optimization results and conditions. When the reaction was performed in the presence of a catalytic amount of nickel complex and ligand at room temperature, 18% of the desired product was obtained with starting material (Entry 1).

In order to improve conversion and yield, reactions were conducted with increasing temperature or extending residence time (Entries 2 and 3). Gratifyingly, the corresponding product was given in higher yield. Furthermore, the combination of these increased the yield to 50 % (Entry 4). During the ligand screening, it was found that picoline amide derivative L1 was the best ligand (Entry 5). Finally, extending residence time and collection time made the yield higher and the cross coupling product was afforded in 81 % (Entry 6).

Table 1 – Reaction conditions vs yield

Entry	Temperature (°C)	Flow (ml/min)	Residence time (min)	Collection mode	Ligand	SM (%)[a]	TM (%)[a]
1	30	0.06	10	Auto (for 40min)	Dtbbpy	38	18
2	30	0.03	20	Auto	Dtbbpy	5	40
3	50	0.06	10	Auto	Dtbbpy	9	38
4	50	0.03	20	Auto	Dtbbpy	0	50
5	50	0.06	10	Auto	L1	5	55
6[b]	50	0.03	20	Manual (for 157min)	L1	0	81 (92)[c]

a) HPLC yields with 4-bromoanisole as internal standard
b) Collection time was extended from 40 min to 157 min
c) Isolated yield

Conclusion

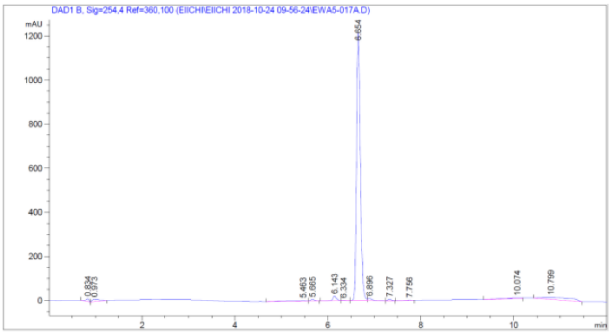
By using the newly developed Ion electrochemical reactor, we have successfully achieved a reductive cross coupling between an aryl iodide and alkyl iodide. By selecting the right ligand, increasing temperature, residence and collection time, yield was improved to 81 %. This enhanced electrochemical approach will be a highly useful method for forming Csp^2-Csp^3 bond from commercially available compounds.

Acknowledgements

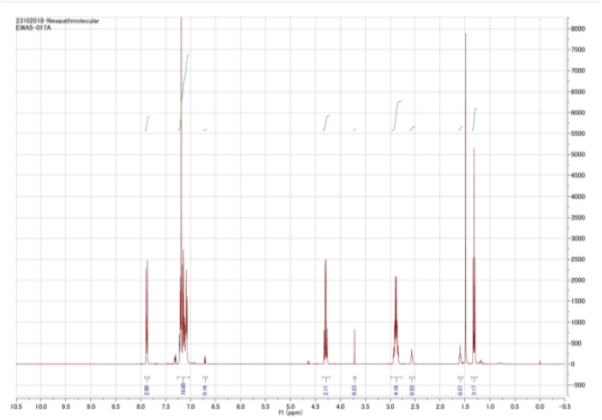
Vapourtec wish to thank the team at New Path Molecular for undertaking the research that this note shows.

Supporting information

HPLC analysis



NMR analysis



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