Synthesis of a 2(1H)-pyridone library via rhodium catalyzed formation of isomunchones

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RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)

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Experimental Section:

General Methods:

**General:** Unless noted all reagents were obtained from commercial sources and used without further purification. All solvents used in the reactions were dried prior to use unless reported. ¹H and ¹³C NMR spectra were recorded on JEOL ECX-400 NMR spectrometer (at 400 MHz and 100 MHz respectively) or JEOL ECA-500 NMR spectrometer (at 500 MHz and 125 MHz respectively) at 297 K (24 °C). Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS). NMR spectra were run in CDCl₃, acetone-d6 or DMSO-d6. Thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ plates from EMD Chemical Inc. and components were visualized by ultraviolet light (254 nm) and/or phosphomolybdic acid, 20 wt% solution in ethanol. SiliFlash silica gel (230-400 mesh) was used for all column chromatography.
1-(Phenylsulfonyldiazoacetyl)pyrrolidin-2-one (5): was prepared following Padwa et al. protocol.¹

**General procedure for the rhodium catalyzed [3+ 2]-cycloaddition and subsequent triflates formation 10{1-3}**:¹

A solution containing 2.0 g (6.8 mmol) of diazoimide (5), 34.0 mmol (5.0 equiv.) of appropriate dipolarophile 7{1-3}, and 2 to 5 mg of rhodium(II) acetate in 20 mL of toluene was heated at 80 °C for 14 h in a pressure tube. The completion of the reaction was monitored either by ¹H NMR or LC-MS. The solvent was removed under reduced pressure, and the crude product was used for the next step without further purification. The resulting hydroxyl pyridone (9) and 5.0 equiv. of N-phenyl trifluoromethanesulfonamide were dissolved in 25 mL of CH₂Cl₂. The mixture was allowed to stir for 20 min at 0 °C, during that time 1.8 mL (13.6 mmol) of triethylamine was added slowly. Afterwards the mixture was stirred at room temperature for 16 h, the solvent was removed under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give the corresponding triflates, 10{1-3} as white solid.

**General procedure for the Suzuki coupling reaction:**

A pressure tube was (10 mL) charged with one of the triflates 10{1-3} (0.2 mmol), the appropriate boronic acid (1.2 equiv.) and THF. A solution of 1M of Cs₂CO₃ (3.0 equiv.) was added to the reaction mixture followed by [Pd(dppf)Cl₂]•CH₂Cl₂ (2 mol %) catalyst. The pressure tube was evacuated, backfilled with nitrogen and sealed. The reaction vessel was heated to 80 °C for 14-15 hours in an oil bath. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexane : ethyl acetate as eluent. The ratio of the solvents in the eluent was adjusted such that the product spot on TLC had a Rf value between 0.25 and 0.30.

**Analysis of the library:**

Four of the components used in the PCA were LogP, molecular weight, volume and polar surface area. Below the minimum, maximum and mean of these parameters are presented. Additionally, the histograms of these parameters are also presented (Figs 1-4).
Table 1. Properties of synthesized libraries

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<th>Property</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
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<td>Volume (Å³)</td>
<td>308.65</td>
<td>565.87</td>
<td>408.23</td>
<td>44.10</td>
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</table>

NMR Spectra
X: parts per Million: 1H
$^{1}H$ NMR spectrum

**Chemical Shifts:**
- 1.9 ppm
- 1.87 ppm
- 1.86 ppm
- 1.8 ppm
- 1.7 ppm

$X$ : parts per Million : $^{1}H$
(1, 30)

X : parts per Million : 1H
also same as sd-04-145
X : parts per Million : 1H

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X : parts per Million : 1H

(2, 11)
X : parts per Million : 1H
(2,19)
(2, 20)
\((2, 3)\)
(2, 57)

X : parts per Million : 1H
$^1$H NMR recorded at 600 MHz.
(2, 79)

X : parts per Million : 1H
(2, f0)
(3, 1)
(3,3)
$^{10}(3,6)$
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$$(3, 11)$$
X : parts per Million : 1H

(3, 23)
$$(3, 29)$$
(3,4S)
(3.47)
(3.48)

X: parts per Million: 1H
X : parts per Million : 1H