



# Continuous Flow Synthesis of Azobenzenes via Baeyer-Mills Reaction

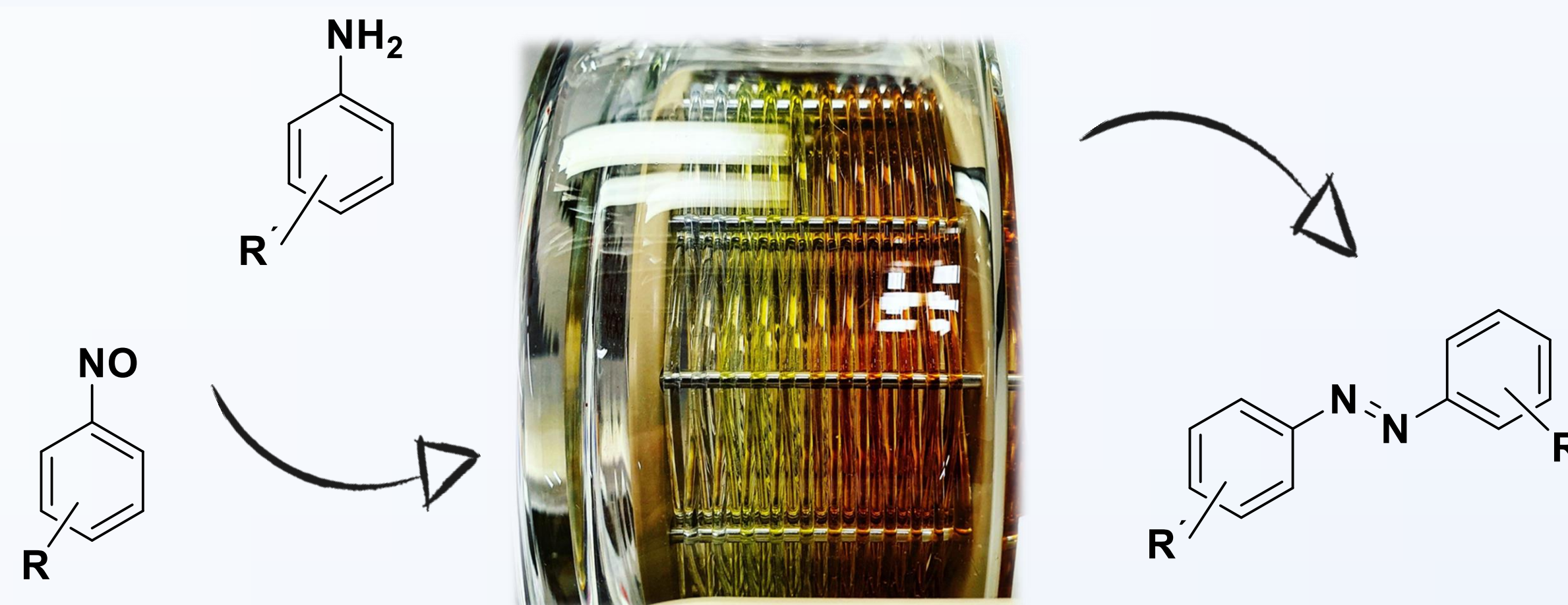
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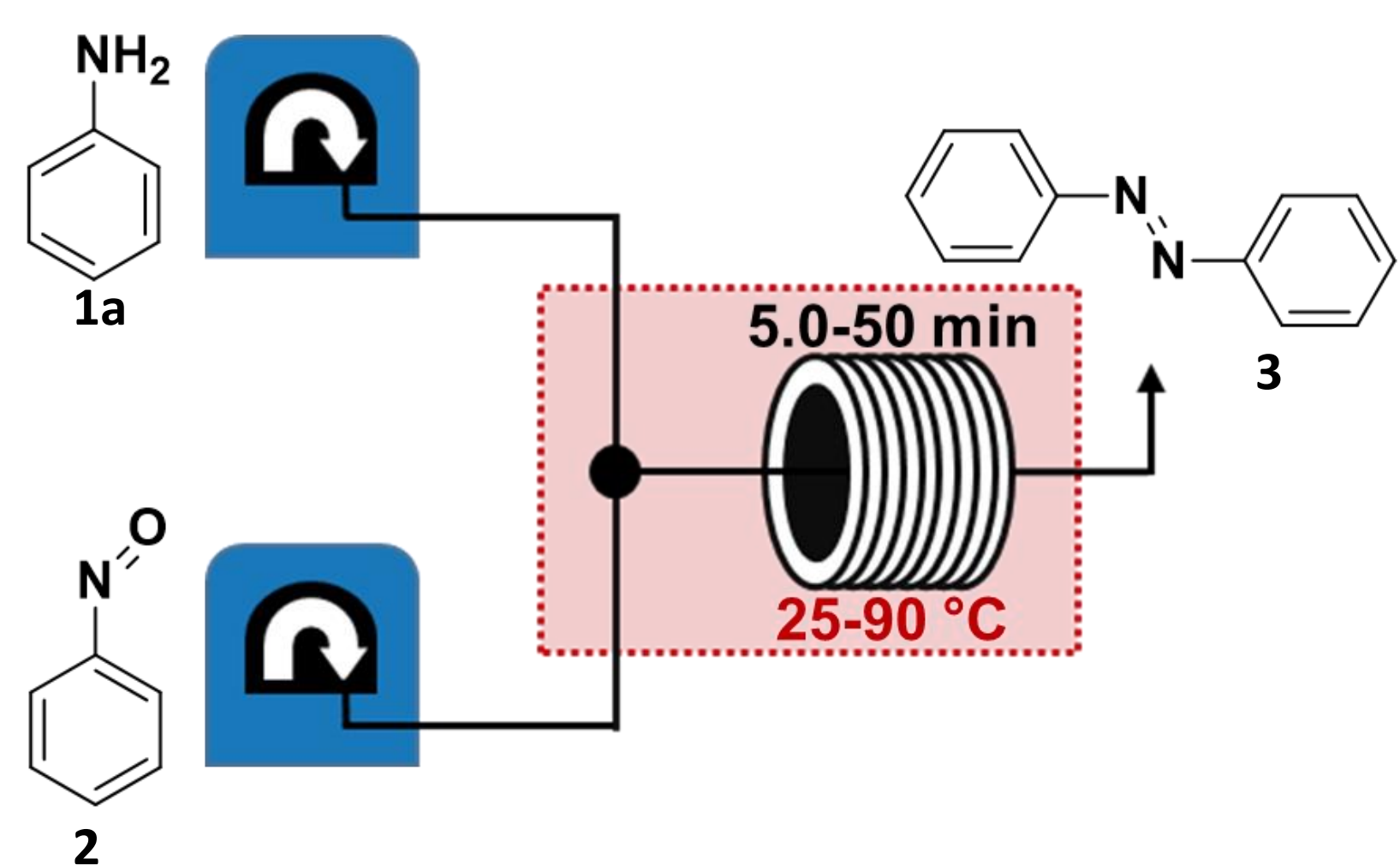
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## Synthesis of Azobenzenes in Flow

Azobenzenes (AB) are no longer just used as dyes, but also as information and energy storage systems. They were also examined in various other fields of research, such as organocatalysis, photobiology and photopharmacology.<sup>[1-6]</sup> In order to **reproducibly** synthesize non-symmetric as well as symmetric ABs **efficiently** and also in **large scale**, the Baeyer-Mills coupling reaction was transferred into a continuous flow setup.<sup>[7]</sup>



## Optimization

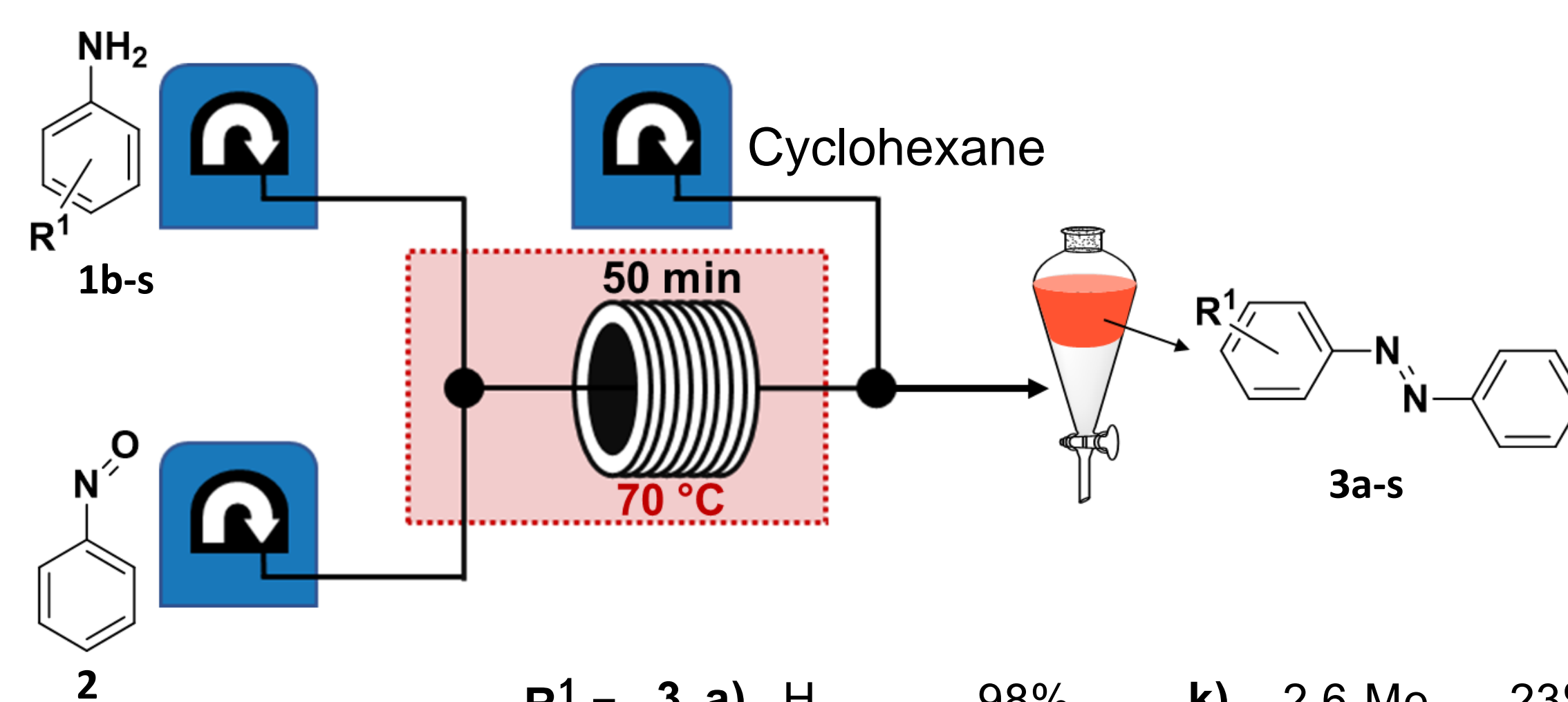



Both starting materials with the same concentration, dissolved in acetic acid, were pumped by a Vapourtec E-Series System. Temperature and residence time were optimized by analyzing the collected mixtures by HPLC.

temperature $\Theta$ / °C	residence time $T$ / min			
	5.0	10.0	16.7	50.0
25	5	5	12	31
40	12	20	29	52
50	19	31	45	67
60	31	42	58	77
70	42	56	69	83
80	53	67	76	81
90	55	69	79	86

## Substrate Scope

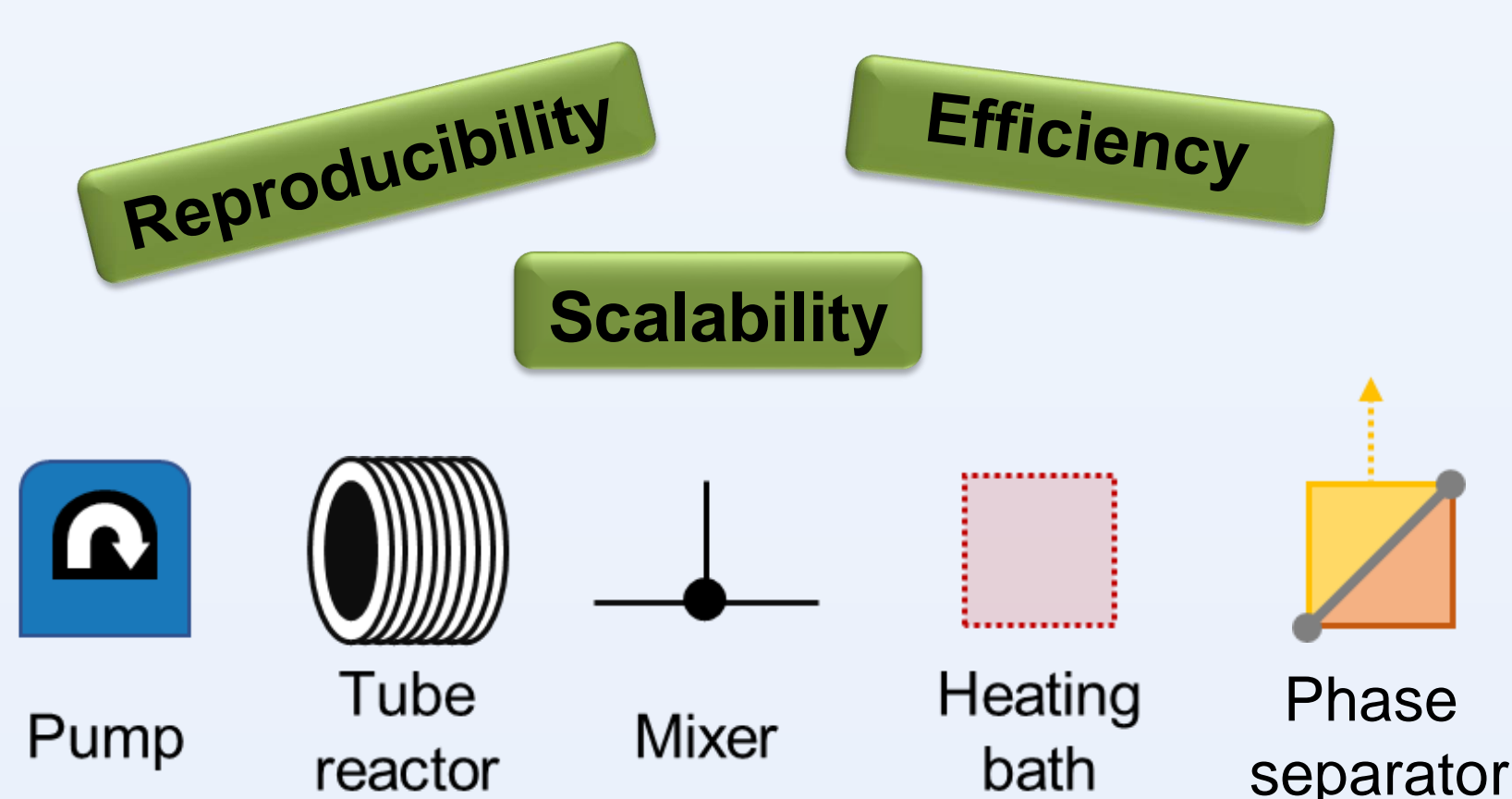
Comparison of *ortho*-, *meta*-, and *para*- derivatives revealed that for electron rich anilines, the *para*-substituted ABs are formed in better yields as *ortho*- and *meta*- analogues. Low yields of electron poor anilines can be rationalized by their poor nucleophilicity. For most of the compounds **no purification** was necessary.





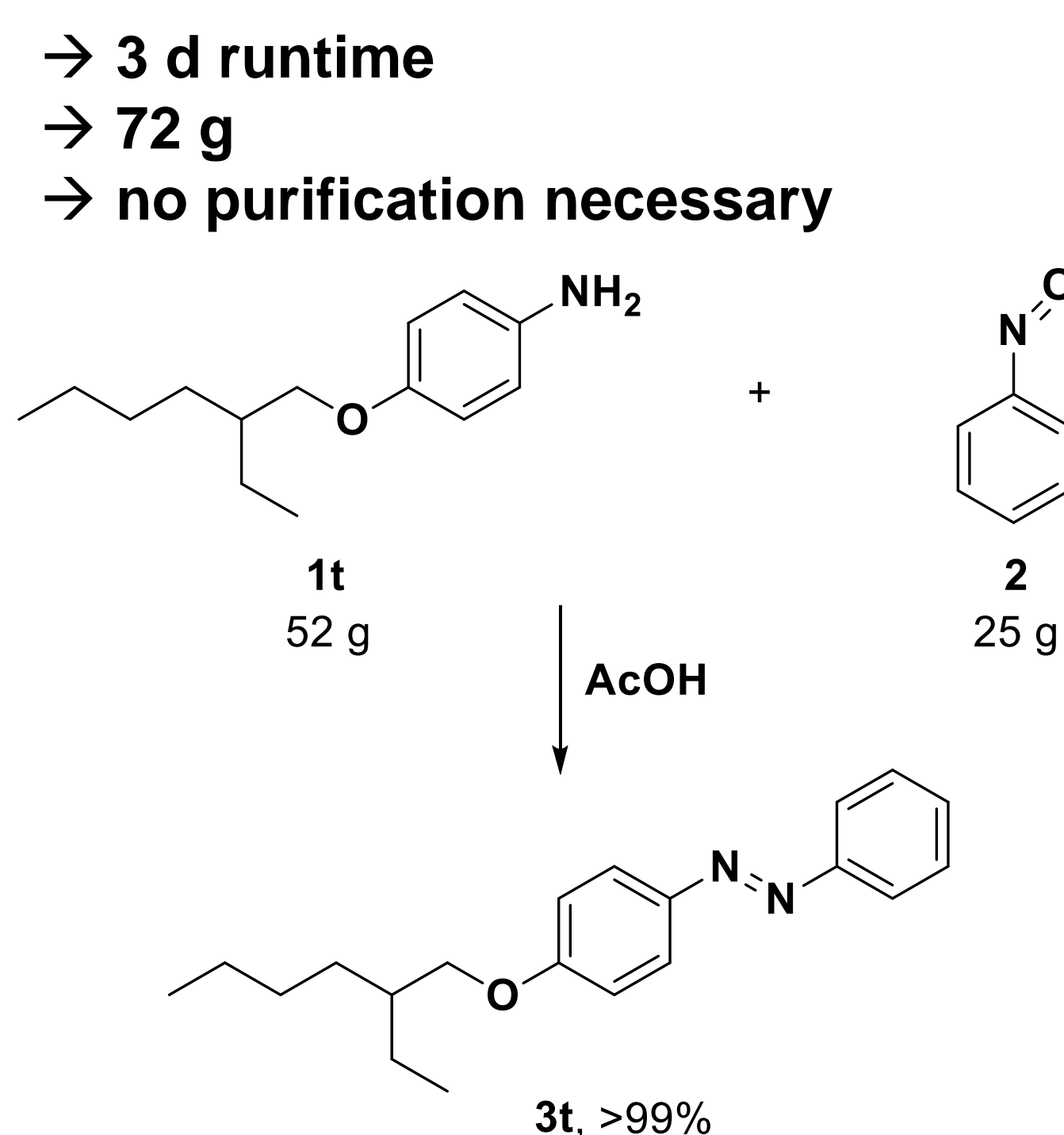
<b>R<sup>1</sup> =</b>	<b>3 a)</b>	<b>H,</b>	<b>98%</b>	<b>k)</b>	<b>2,6-Me,</b>	<b>23%</b>
	<b>b)</b>	<b>4-Br,</b>	<b>89%</b>	<b>l)</b>	<b>3-5-Me,</b>	<b>65%</b>
	<b>c)</b>	<b>3-Br,</b>	<b>77%</b>	<b>m)</b>	<b>2,4,6-Me,</b>	<b>70%</b>
	<b>d)</b>	<b>4-Me,</b>	<b>94%</b>	<b>n)</b>	<b>3,5-<i>t</i>Bu,</b>	<b>99%</b>
	<b>e)</b>	<b>3-Me,</b>	<b>79%</b>	<b>o)</b>	<b>4-CN,</b>	<b>7%</b>
	<b>f)</b>	<b>2-Me,</b>	<b>67%</b>	<b>p)</b>	<b>3-CN,</b>	<b>54%</b>
	<b>g)</b>	<b>4-<i>t</i>Bu,</b>	<b>&gt;99%</b>	<b>q)</b>	<b>4-OH,</b>	<b>68%</b>
	<b>h)</b>	<b>4-OMe,</b>	<b>96%</b>	<b>r)</b>	<b>4-CF<sub>3</sub>,</b>	<b>33%</b>
	<b>i)</b>	<b>3-OMe,</b>	<b>7%</b>	<b>s)</b>	<b>4-F,</b>	<b>95%</b>
	<b>j)</b>	<b>2-OMe,</b>	<b>72%</b>			

## Flow Chemistry

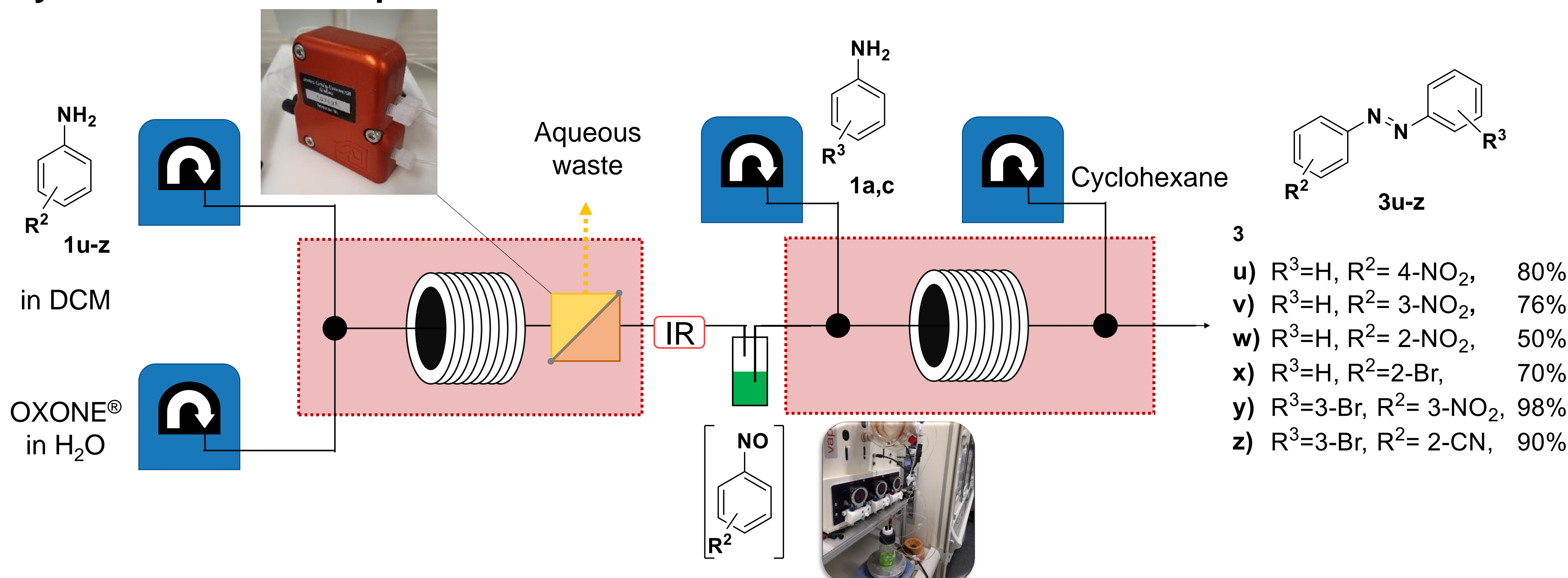


## Large Scale

**3t** is known for its potential use as molecular solar thermal energy (MOST)-system and was synthesized in large scale in this optimized flow setup.<sup>[1,8,9]</sup>



## Synthesis of electron poor ABs



To excess also electron poor substituents as well as both sides of the AB scaffold, the flow system was modified. Substituted nitrosobenzenes were synthesized *in situ* in a biphasic system and subsequent phase separation. The conversion to nitrosobenzene can be followed by in-line IR. Afterwards the optimized flow setup for the Baeyer-Mills reaction follows.

## Conclusion

The Baeyer-Mills coupling was successfully transferred to a continuous flow setup. This method provides **fast**, **high yielding** and easily **scalable synthesis** of a large number of non-symmetric ABs.



For electron poor ABs the setup was modified including *in situ* preparation of nitrosobenzenes.

