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Towards a large scale approach to Milnacipran analogues using diazo compounds in flow chemistry

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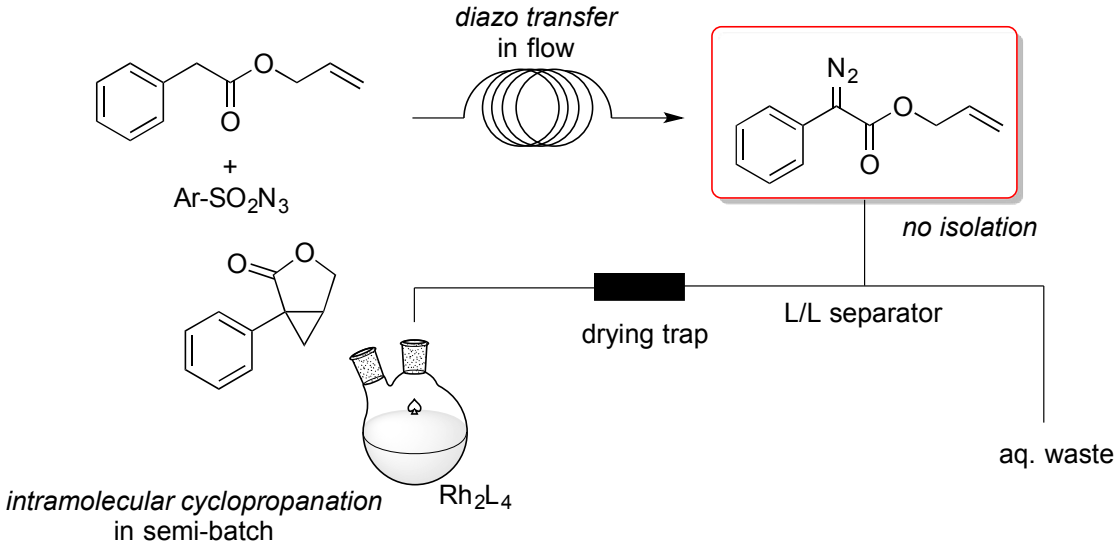
Graphics for the Table of Contents:



Abstract

The safe use of diazo reagents for the preparation of a key structure in the synthesis of milnacipran analogues is described herein. Using continuous flow technology, the diazo reagent is synthesized, purified, dried and subsequently used in semi-batch mode for an intramolecular cyclopropanation. Side products formed in the reaction are isolated and rationalized to optimize the process. Different separating techniques in flow are compared in their ability to produce pure and dry diazo reagents. The studies are yielding a scalable process to a key intermediate in the synthesis of milnacipran and possible substituted analogues.

Keywords: Cyclopropanation, Diazo-compounds, Diazo-tranzfer, Flow-Chemistry

Introduction

The 1*S*,2*R* enantiomer of milnacipran is called 'levomilnacipran' **1**, which is a serotonin-norepinephrine reuptake inhibitor (SNRI) used for the treatment of depression and fibromyalgia.[1] It is a more balanced reuptake inhibitor of serotonin and norepinephrine than other SNRIs.[2] Substituted milnacipran analogues have shown promising pharmaceutical properties and are interesting target molecules in drug development.[3] Several routes have been identified for the preparation of levominacipran **1**. One is the preparation of the bicyclic lactone **4** *via* the reaction of phenylacetonitrile **2** with non-racemic epichlorohydrin **3**. In this sequence, the epoxide **3** undergoes nucleophilic addition by phenylacetonitrile **2** to make the cyclopropane moiety. Treatment with sodium hydroxide transforms the nitrile group into a carboxylate which undergoes lactonization to **4** under treatment with hydrochloric acid. This compound is then treated with diethylamine and *n*-butyllithium to ring-open the lactone. Subsequently, an Appel reaction is used to make azide **5** which is transformed into levomilnacipran **1** by reduction using hydrogen.[4] Hu and Doyle showed that lactone **4** can also be obtained *via* a rhodium-catalyzed stereoselective intramolecular cyclopropanation using allyl phenyldiazoacetate with up to 95% *ee*.[5] Recently, such an approach to **4** was achieved through iron catalysis with good stereoselectivities using a spirobox ligand.[6] A diazo-based scale-up approach to **4** would give rapid access to functionalized milnacipran analogues. However, diazo compounds are challenging reagents for large scale applications because of their thermal properties.[7]

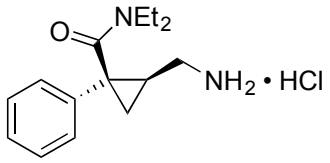


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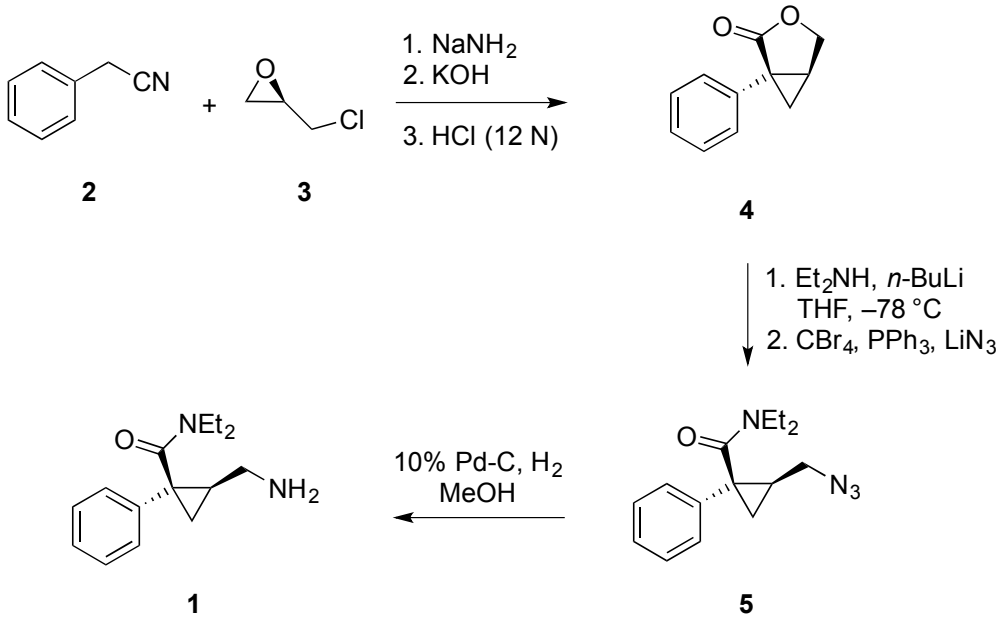
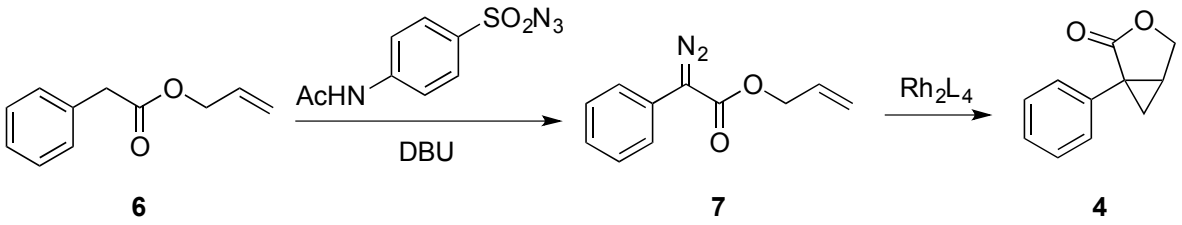
Figure 1: Levomilnacipran



2 **3** **4** **5** **1**

Scheme 1: Shuto synthesis of levomilnacipran **1**

Continuous flow microreactor technology promises to give rise to new opportunites for the large scale use of dangerous reagents.[8] Heat control is improved due to the high surface-to-volume ratio of microreactors.[9] Furthermore, no large quantities of dangerous materials are allowed to accumulate. Accordingly, several protocols for the preparation of highly energetic diazo reagents[10] such as diazomethane[11] and ethyl diazoacetate[12] using microstructured devices have been developed. Recently, we disclosed a flexible continuous flow protocol for the formation, purification and use of aryl diazoacetates which are versatile donor/acceptor substituted carbene precursors.[13] Considering the structural similarities to those, it was anticipated that the diazo transfer onto allyl phenylacetate **6** leading to diazo allyl phenylacetate **7** could be telescoped in flow with a selective extraction of **7** in an organic solvent, so that a subsequent intramolecular cyclopropanation to **4** is possible. This protocol should then be easily scalable to provide multigram quantities of key lactone **4**. Substituted analogues should be accessible *via* this route as well. The use of a chiral catalyst could provide enantioselective reactions to generate non-racemic **4**.



6 **7** **4**

Scheme 2: Diazo approach towards lactone **4**

Results

Safety & Feasibility test

Initially, the thermal properties for the reaction of **6** to **7** were investigated. DSC (differential scanning calorimetry) data for diazo transfer reagent *p*-ABSA had been obtained previously.[13] Diazo allyl phenylacetate **7** was found to have a decomposition on-set temperature of 77 °C which corresponds to a T_{D24} value of 6 °C. The enthalpy of the decomposition corresponds to ΔH = -182 kJ/mol which gives a ΔT_{ad} of 523 °C. C80 calorimetry for studying the heat released within a reaction was performed. The heat generated within the reaction and in a decomposition of the reaction mixture was recorded. It was found that the ΔH of the reaction was -150 kJ/mol corresponding to a ΔT_{ad} of 39 °C. Given the standard reaction temperature of 25 °C, the heat released would provide an operating temperature of 64 °C. This temperature would surpass the T_{D24} calculated for this reaction (52 °C). If the decomposition would take place at this time, it would lead to another ΔT_{ad} of 67 °C. At this point, a thermal runaway would be inevitable as the operating temperature would be at 131 °C and therefore well above the boiling point of the solvent, acetonitrile (b.p. 81 °C). In accordance to chemical risk classes defined by Stoessel *et al.*,[14] the diazo transfer described would have to be classified as risk class 5, the highest risk class for chemical reactions. This analysis shows that the move to a flow chemistry environment will dramatically reduce the risks associated with this process.

After this analysis, two-step batch methods were explored to investigate the feasibility of a two-step protocol without purification *via* column chromatography of diazo reagent **7**. Furthermore, the solubility of the rhodium catalysts in different solvents was studied to test the possibility of a completely continuous process. The diazo transfer from **6** to **7** was left stirring at 25 °C until no starting material could be observed *via* HPLC (24 h).[15] The yield of this reaction was 87%, providing diazo reagent **7** in pure form after work-up (HPLC analysis). For the two-step batch protocol, yields varied between 44% and 79%. Reactions with rhodium acetate as catalyst provided quite similar yields in all four solvent mixtures tested, however only chlorinated solvent mixtures with acetonitrile provided completely homogenous solutions (Table 1, entries 3 and 4). Therefore, these solvent mixtures are most promising for a continuous flow approach. Toluene in combination with acetonitrile provided the lowest yield of all examples (Table 1, entry 2). Dichloromethane with acetonitrile (Table 1, entry 4) required a longer reaction time until all diazo reagent was consumed as the operating temperature was limited by the boiling point of the solvents. Rhodium octanoate as catalyst was more active for the transformation of **7** to **4** providing the lactone in 79% HPLC yield over two steps (Table 1, entry 5). With these promising results in hand, continuous flow conditions for both steps were investigated.

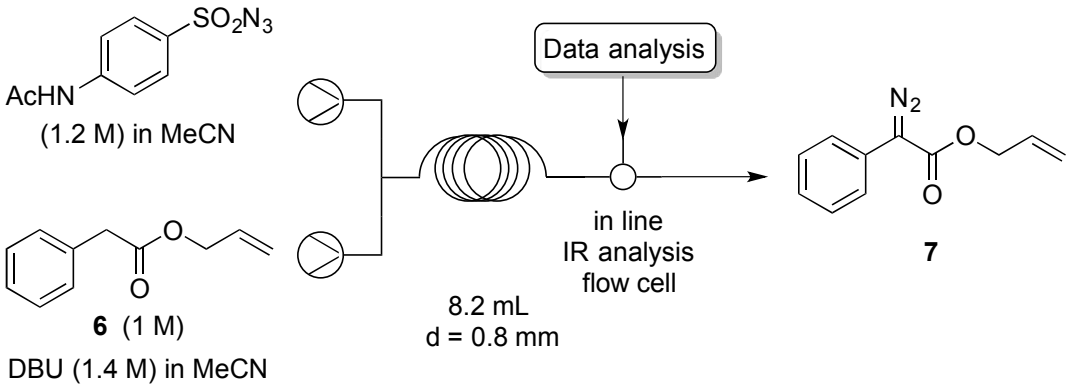
Table 1: Two step batch optimization from **6** to **4**

Entry	Catalyst	Solvent	Catalyst solubility	T [°C]	Time [h]	Yield [%][a]
1	$Rh_2(OAc)_4$	*n*-C_7H_{16}	Insoluble	60	1	59
2	$Rh_2(OAc)_4$	$C_6H_5CH_3$:CH_3CN 1:1	Traces of solid	60	1	44
3	$Rh_2(OAc)_4$	$CHCl_3$:CH_3CN 1:1	Homogeneous	60	1	59
4	$Rh_2(OAc)_4$	CH_2Cl_2:CH_3CN 1:1	Homogeneous	35	3.5	51
5	$Rh_2(C_7H_{15}COO)_4$	*n*-C_7H_{16}	Insoluble	60	1	79

[a] Two step yield as determined by HPLC assay.

Diazo transfer in flow

The diazo transfer reaction in flow was monitored using infrared in-line analysis techniques. The set-up is shown in Scheme 3. The diazo transfer onto **6** using commercially available *p*-acetamidobenzene sulfonylazide (*p*-ABSA) worked smoothly. In short reaction times (14 min), high yields (86%) were obtained at 65 °C (Table 2, entry 5) which could be increased by a longer residence time (Table 2, entry 6). A further increase in temperature however did not result in any additional diazo formation (Table 2, entry 7). Lower temperatures did result in slightly lower yields (Table 2, entries 1-4). It seems that the residence time of the reaction has a larger influence than the operating temperature. Interestingly, the diazo transfer onto allyl phenylacetate **6** was slightly more efficient than onto methyl phenylacetate.[13]



Scheme 3: Set-up for diazo transfer reaction optimization

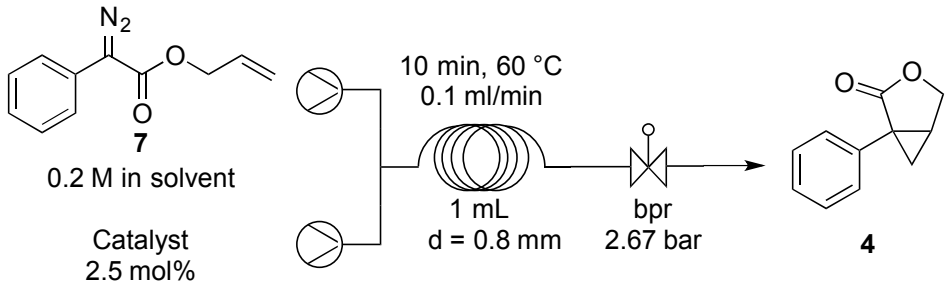
Table 2: Diazo transfer optimization in flow

Entry	Reaction time [min]	Temperature [°C]	Yield [%][a]
1	8	40	64
2	14	50	80
3	8	50	66
4	14	60	84
5	14	65	86
6	26	65	93[b]
7	14	75	86

[a] determined by IR spectroscopy; [b] conversion ^{1}HNMR

Intramolecular cyclopropanation in flow

The intramolecular cyclopropanation of the pure diazo reagent **7** was investigated under continuous flow conditions. The set-up is illustrated in Scheme 4. Solvents could be superheated in this continuous set-up (Table 3, entries 1 - 3, 7) due to the use of a back pressure regulator. Again, rhodium octanoate proved to be a more efficient catalyst for the diazo decomposition than rhodium acetate (Table 3, entries 1 and 3). Several reactions had only a limited solubility of the catalyst (Table 3, entries 1, 3, 5, 6) in the respective solvent as the precipitation of the catalyst could be observed in the syringe. In the case of *n*-hexane this led to a complete lack of reactivity (only starting material was recovered). To improve the solubility of the catalyst, a mixture of dichloromethane and acetonitrile was used (Table 3, entry 2) which improved the yield of the reaction slightly compared to pure dichloromethane (Table 3, entry 1). The best result was obtained using toluene as solvent (Table 3, entry 4).



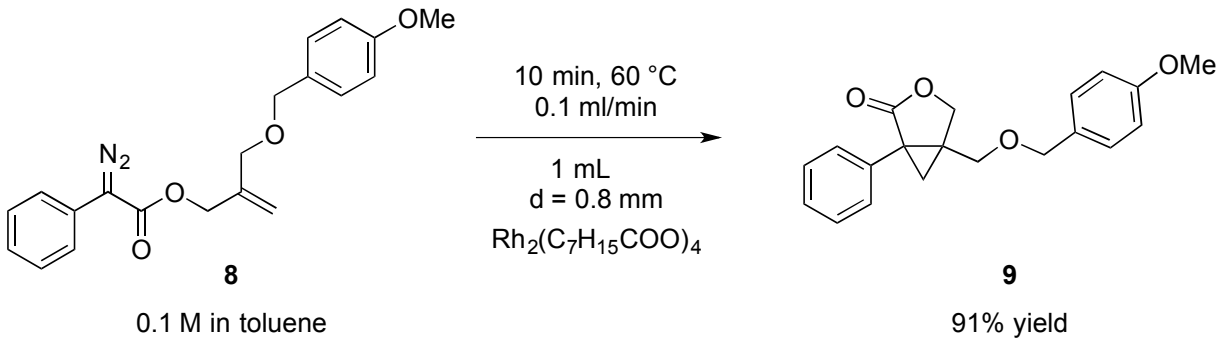
Scheme 4: Set-up for optimization of cyclization in flow

Table 3: Optimization of cyclization to **4** in flow

Entry	Solvent[a]	Catalyst [2.5 mol%]	Yield [%][b]
1	CH_2Cl_2	$Rh_2(OAc)_4$	27
2	CH_2Cl_2/CH_3CN 9/1	$Rh_2(OAc)_4$	31
3	CH_2Cl_2	$Rh_2(C_7H_{15}COO)_4$	63
4	CH_3CN	$Rh_2(C_7H_{15}COO)_4$	56
5	Toluene	$Rh_2(C_7H_{15}COO)_4$	82
6	*n*-C_6H_{14}	$Rh_2(C_7H_{15}COO)_4$	0
7	CH_2Cl_2	Fe(III)TPPCl	0

[a] all solvents were dried before use; [b] isolated yield

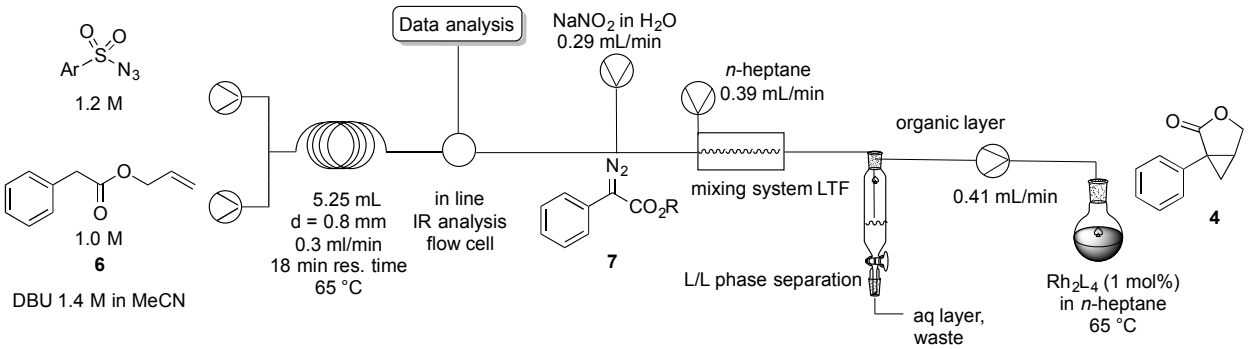
The best conditions for the one-step continuous flow protocol were used with the substituted diazo allyl ester **8** for the intramolecular cyclopropanation. Cyclopropane **9** was obtained in 91% yield within just 10 minutes residence time in toluene. However, again not all the rhodium octanoate dissolved in the syringe for the flow reaction which could prove problematic when scaling this reaction in a continuous flow set-up.



Scheme 5: Cyclization of substituted diazoester **8** in flow

Semi-batch and continuous two-step protocols

With the results obtained for each of the steps in batch and flow, a semi-batch set-up was designed (set-up **A**) with the formation of the diazoester in continuous flow, followed by an in-line liquid/liquid extraction and the use of a stream of the diazo compound in the organic layer into a flask containing the rhodium catalyst in the reaction solvent (Scheme 6). No significant accumulation of the diazo reagent was observed in the flask (HPLC analysis), making this process inherently safe. The formation of the diazo reagent was monitored using inline infrared analysis to verify that the diazo transfer reaction was stable over a longer period of time. Directly after the infrared analysis an aqueous sodium nitrite solution was added to quench residual azide moieties. The reaction mixture was extracted using a feed of *n*-heptane into a glass mixer. The mixture was then separated in-line and subsequently, the organic layer was pumped into a flask containing the rhodium catalyst in *n*-heptane.



Scheme 6: Continuous flow into semi-batch set-up **A**

For the extraction, a gravitational separating system was designed (Figure 2). A narrow bore glass column was filled with water and then stabilized with the reaction stream running into the column. The organic layer was pumped out of the top of the gravitational separator whereas the lower aqueous layer was

displaced from the separator via a siphon outlet. With this method, it was possible to have a stable interface of aqueous and organic layer at mid-height in the column.

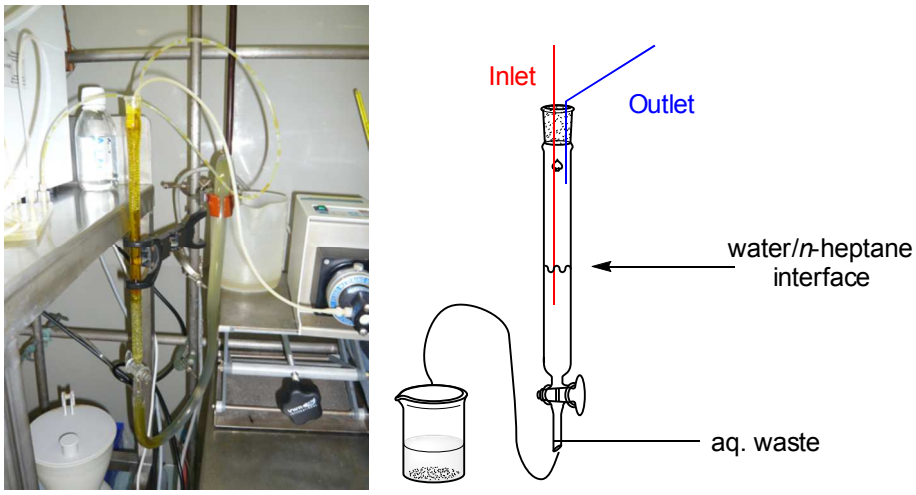
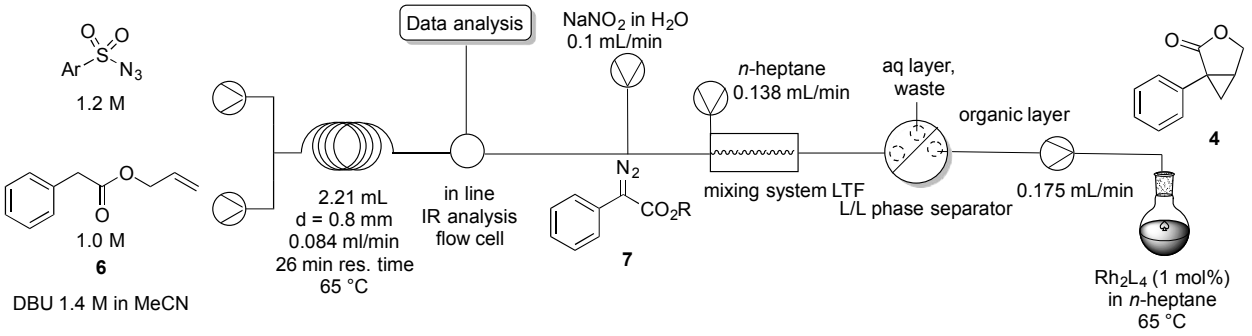


Figure 2: Gravitational separator left: photo; right: Scheme of gravitational separator[16]

Using this set-up, lactone **4** was obtained in low yields (31% yield; Table 4, entry 1). Considering the higher yields in the experiments developed before, this was surprising. The first step of the transformation worked well as could be monitored *via* in-line infrared analysis during the reaction. To determine if the liquid/liquid extraction was the source of the reduced yield of the cyclization, an alternative set-up with a membrane based liquid/liquid extraction was used (Figure 3).

Figure 3: Membrane separator

In the set-up using the membrane separator (Scheme 7), smaller quantities of reagents could be used as there was no need for the relatively large hold up volumes of the liquid/liquid extractor of set-up **A**. Surprisingly, in set-up **B** rhodium acetate was not capable of transforming **6** into lactone **4**. However, rhodium octanoate now provided lactone **4** in 33% isolated yield.



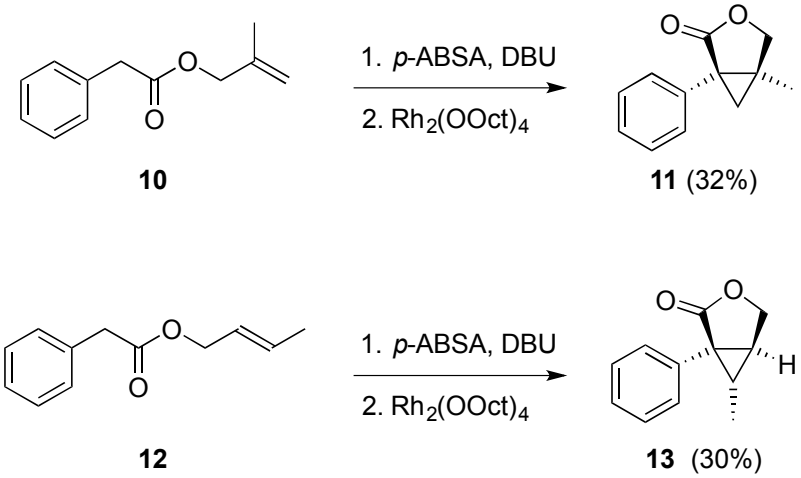
Scheme 7: Continuous flow into semi-batch set-up **B**

Table 4: Results of the two step continuous flow into semi-batch approach

Entry	Set-up	Catalyst (1 mol%)	Yield [%]
1	**A**	$Rh_2(OAc)_4$	31[a]
2	**B**	$Rh_2(OAc)_4$	0
3	**B**	$Rh_2(C_7H_{15}COO)_4$	33[b]

[a] HPLC yield; [b] isolated yield

As entry 3 provided the best results obtained to that point, it was briefly verified if substituted analogues of **4** could be synthesized *via* this route. The corresponding substituted alkenes were obtained by reacting phenylacetyl chloride with the substituted allylic alcohols. These were then subjected to reaction conditions of set-up **B**. Lactone **11** and **13** were obtained from substituted allyl phenylacetates **10** and **12** in 32% and 30% yield over two steps, respectively. Both reagents were obtained as single diastereomers (Scheme 8).[17]



Scheme 8: Substituted lactones prepared

It was hoped that a completely continuous process could increase the yield of this transformation. Therefore, a set-up utilizing the extraction system from set-up **A** was designed in which the outlet stream was fed into a continuous flow system. Rhodium octanoate was used as the catalyst. Dichloromethane was the solvent of this reaction as it provided a better solubility of the catalyst than *n*-heptane or toluene.

However, the completely continuous experiment did not improve the yield of the two-step protocol, providing lactone **4** in only 27% yield (determined by HPLC) over two steps.

Considering the inconsistent results obtained to that point, we decided to do a side product analysis to understand the competing reactions in the preparation of lactone **4**.

Side product and error analysis

LC/MS analysis of the crude reaction products and flash chromatography for isolation of the side products provided evidence for the main side products formed within the reactions. It was found that relatively large quantities of compounds **14** and **15** could be observed in the majority of reactions. We speculated that **14** could be explained by an O-H insertion reaction of the carbene into residual water within the reaction. It would then be possible that **14** could react with another molecule of **7** to generate **15**. Structure **16** was harder to explain. However, it is known that diazo compounds can react with nitriles to form oxazoles.[18] Therefore, it could be imagined that residual acetonitrile stemming from the diazo transfer reacts with diazo compound **7** to furnish oxazole **16**.

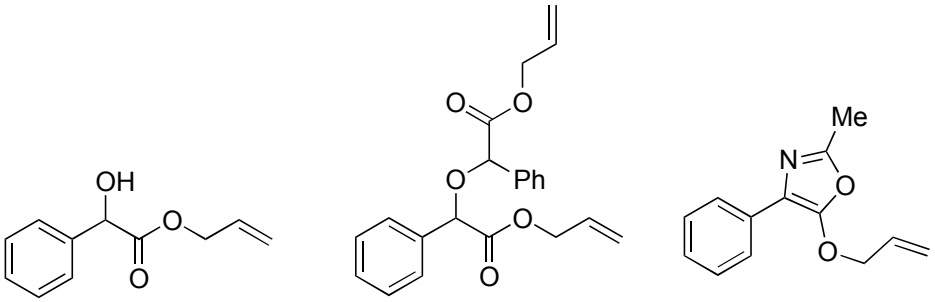
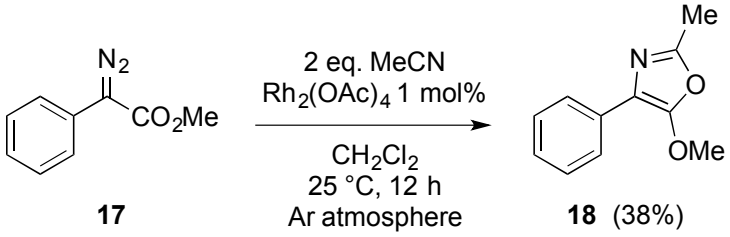


Figure 4: Isolated side products

To test this hypothesis for the formation of **16**, diazo methyl phenylacetate **17** was subjected to a mixture of acetonitrile in dichloromethane with 1 mol% rhodium acetate. Oxazole **18** was obtained in 38% yield which showed that acetonitrile could indeed react with aryl diazoacetates to yield oxazoles (Scheme 9).



Scheme 9: Formation of oxazoles from diazo methylphenylacetate

After isolation of the side-products, it was investigated which factors could have played a role in the formation of these side-products. The quality of the rhodium catalysts could have an impact on the transformation, therefore different batches of rhodium acetate were investigated for their ability to transform **6** into **4** (see supporting information). However, no differences were observed.

Another possible explanation of the results was that the extractions were inefficient and that too much water came through the work-up systems in set-up **A** and **B**. This was surprising as a completely continuous set-up based on set-up **B** had been efficiently employed for intermolecular reactions of diazo methylphenylacetate **17**.[13] To test this hypothesis, three batch experiments were performed using the diazo reagent **7** directly after the batch extraction protocol. One of the reactions was performed in acetonitrile (technical grade) to test if more of oxazole **16** could be observed (entry 1). The other two reactions used 0.1 (entry 2) and 1 equivalent (entry 3) of water respectively. The reactions were performed in *n*-heptane with rhodium acetate as catalyst in all three cases. The HPLC ratios of these reactions are shown below. Acetonitrile as solvent did reduce the formation of lactone **4** significantly which could be contributed in parts to the formation of larger quantities of oxazole **16** but also to the water content of the solvent. Although 0.1 equivalents of water are still tolerated by the reaction, 1 equivalent of water shuts down the reaction completely, only providing a mixture of alcohol **14** and dimer **15**. This means that even very small quantities of water passing by the liquid/liquid extraction would have a detrimental effect on the formation of lactone **4**.

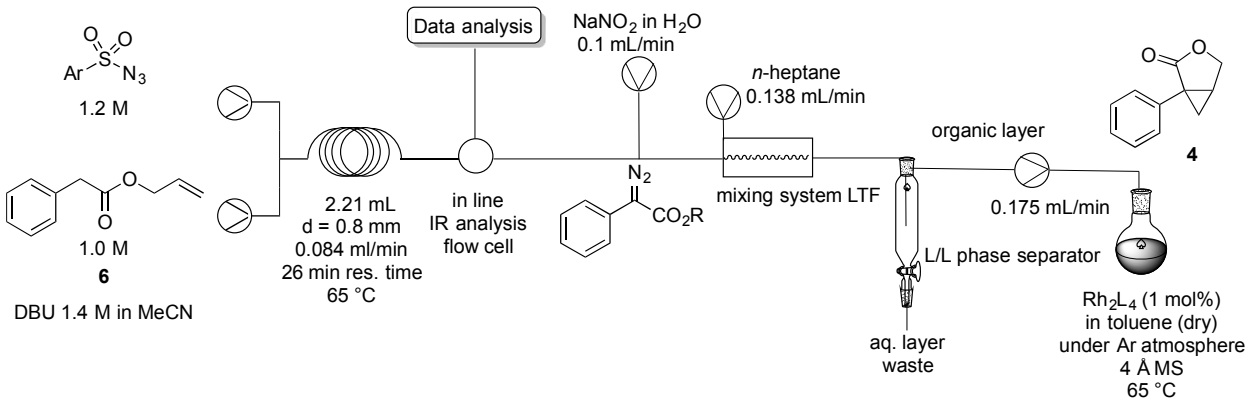
Table 5: Side product analysis

Entry	Conditions	Lactone **4** [%]	Alcohol **14** [%]	Dimer **15** [%]	Oxazole **16** [%]
1	CH_3CN as solvent	45	8	11	26
2	0.1 eq H_2O added	73	5	6	10
3	1 eq H_2O added	1	57	27	1

With the understanding of the influence of water for the reaction, we developed new approaches for the two-step continuous into semi-batch protocol (Set-up **C**).

Semi-batch protocols 2nd generation and scale-up

A simple initial alteration to the semi-batch protocol of the first generation was the use of dried solvents for the cyclization in batch. Beforehand solvents of technical grade had been used in the two-step protocol to reduce costs for an eventual scale-up. The flask was kept under argon atmosphere with molecular sieves as drying agents. Rhodium octanoate was used as the catalyst as it had outperformed rhodium acetate in previous reactions consistently. Furthermore, the gravitational separator was used as the separating system as it had given better results than the membrane separating system (see Table 4 entry 1 vs 3). A smaller column was used for the liquid/liquid extraction to reduce the scale needed to test the reaction set-up. Set-up **C** is shown in Scheme 10.



Scheme 10: Continuous flow into semi-batch set-up **C**

Set-up **C** provided the lactone in 40% yield (Table 6, entry 1). To further improve the yield of the flow/semi-batch protocol, a column containing $MgSO_4$ as water trap was included between the liquid/liquid extraction and the addition to the round bottom flask. This improved the yield, providing lactone **4** in 53% yield over two steps (Table 6, entry 2). Increasing the amount of the $MgSO_4$ in the trap did not lead to a further improvement in product formation (Table 6, entry 3).

Table 6: Results of the two step continuous flow into semi-batch approach

Entry	$MgSO_4$ trap	Yield [%]
1	n.A.	40
2	4 cm x 6 mm (1 g)	53
3	11 cm x 6 mm (2.7 g)	50

Having established a set-up with a significantly improved yield and being equipped with a good understanding of the dynamics of the two-step reaction, we proceeded to scale up the continuous flow into semi-batch system.

For the scale-up set-up **C** was employed with only few modifications. All flow rates were increased by a factor of 2.4 and a larger reactor coil (10 ml) was used for the diazo transfer reaction to account for the higher flow rates (Figure 5). The set-up was run for 8 hours with a final collection time of 6 hours (360 min). 2.04 g (33%) of **4** were obtained. The main side-product was dimer **15** of which 1.69 g (26%) were isolated. This result suggests that more water was passing through the system than in the small scale reaction. One possible explanation is that the $MgSO_4$ trap was saturated with water after a certain reaction time. Alternatively, the higher flow rates employed led to a less efficient trapping of residual water in the $MgSO_4$ column.

Figure 5: Upscale for multistep protocol to bicyclic lactone **4**

Conclusion

In conclusion, we have presented herein a diazo based continuous flow approach to the bicyclic lactone **4** which is a key intermediate on the route to milnacipran. All steps were carefully optimized in continuous flow and a 2-step process was established which circumvents the use of column chromatography of the diazo reagent. By analyzing the side products formed, it was found that water had a very strong negative impact on the reaction. Although a solution to trap the water from in the in-line liquid/liquid separation was found for small scale reactions using an in-line $MgSO_4$ trap, this system did not proof efficient for larger scale. This work presents a proof of concept for a flexible, safe and rapid generation of molecular complexity from simple starting materials which should give access to highly substituted milnacipran analogues. Albeit providing a reduced yield, the system was scalable to gram quantities of materials.

Experimental Section

General Information. Reactions were carried out in standard reagent grade solvents. All chemicals were purchased from Sigma Aldrich and Alfa Aesar and used without further purification. KR Analytical Ltd Fusion 100 Touch syringe pumps and Vapourtec E series pumps were used for cyclopropanation in flow as well as for set-up **B** and set-up **C**. Syrris Asia pumps and Ismatec piston pumps were used for diazo transfer optimization studies and set-up **A**. Mettler Toledo IR spectroscopy with flow diamond probe and flow silicon probe was used for reaction optimization and kinetics studies. Thermal analyses were performed with a Setaram C80 calorimeter. Purifications were performed on a Biotage® 25 g SNAP cartridge / Biotage Isolera system. Thin layer chromatography was performed on Merck Silica gel 60 F_{254}. Dried solvents were directly used from a SPS dry solvent system (toluene, heptane, acetonitrile) or distilled over CaH_2 (dichloromethane). ^{1}H and ^{13}C spectra were recorded on Bruker Fourier 300 and Bruker DPX 400 and referenced to the residual proton solvent peak (^{1}H: $CDCl_3$, δ 7.26 ppm) and solvent ^{13}C signal ($CDCl_3$, δ 77.16). Signals were reported in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, hep = septet, m = multiplet, b = broad), coupling constants in Hertz.

Optimization diazo transfer in flow for Allyl 2-diazo-2-phenylacetate (7) Allyl phenylacetate (35.24 g, 200 mmol) and DBU (42.6 ml, 280 mmol, 1.4 eq) were dissolved in acetonitrile for a total volume of

200 ml. *p*-Acetamidobenzenesulfonyl azide (57.66 g, 240 mmol, 1.2 eq) was dissolved in a total volume of 200 ml acetonitrile and subsequently filtered to remove residual solids. The two solutions were pumped through the flow system using Asia syringe pumps with flow rates of 0.5 ml/min each (combined flow rate 1 ml/min) for a residence time of 8.2 min and of 0.3 ml/min each (combined flow rate 0.6 ml/min) for a residence time of 13.7 min. The reaction mixture was analyzed using in-line infrared with the consumption of starting material used to determine the yield of the transformation. Calibration of allyl phenylacetate gave a R^2 of 0.993. Extraction of allyl 2-diazo-2-phenylacetate was performed using *n*-heptane (15 ml) and 1M $NaNO_2$ (11 ml) solution per 1 g allyl phenylacetate used. 964 mg Allyl 2-diazo-2-phenylacetate **7** (collection time 19 min, 4.77 mmol) was obtained without further purification in 84% yield as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.51 (m, 2H), 7.36-7.42 (m, 2H), 7.16-7.22 (m, 1H), 5.92-6.04 (m, 1H), 5.37 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.28 (ddd, *J* = 10.4, 2.5, 1.2 Hz, 1H), 4.78 (dt, *J* = 5.6, 1.4 Hz, 1H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 165.2, 132.1, 128.9, 125.9, 125.4, 123.9, 118.4, 65.4 ppm.

Optimization cyclopropanation in flow for 1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (4) Allyl 2-diazo-2-phenylacetate **7** (202 mg, 1 mmol) was dissolved in the reaction solvent to give the total volume of 5 ml. Catalyst (0.025 mmol, 2.5 mol%) was dissolved in the reaction solvent to give the total volume of 5 ml. Both solutions were charged into 5 ml syringes and pumped using a KR Analytical LtD Fusion 100 Touch syringe pump with a combined flow rate of 0.1 ml/min through a 1 ml reaction coil (residence time 10 minutes). The system was stabilized for 30 min and then collected for 60 min by running through a silica plug to quench the reaction mixture. The silica plug was washed with CH_2Cl_2 and the solvent was evaporated *in vacuo*. The crude reaction mixture was purified using column chromatography (10 g SNAP Ultra, 9:1 *n*-Hexane:EtOAc). 1-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one was obtained as colorless oil (for yields see Table 3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.27 (m, 5H), 4.47 (dd, *J* = 9.27, 4.6 Hz, 1H), 4.31 (d, *J* = 9.27 Hz, 1H), 2.57 (dt, *J* = 7.8, 4.6 Hz, 1H), 1.66 (dd, J = 7.8, 4.86 Hz, 1H), 1.38 (t, *J* = 4.58 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 134.5, 129.1, 128.8, 128.2, 68.6, 32.2, 25.5, 20.6 ppm

5-(((4-Methoxybenzyl)oxy)methyl)-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (9) The reaction mixture was collected for 60 minutes (combined flow rate 0.1 ml/min) and subsequently purified as described above. 178 mg (91%) of **9** were obtained as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (m, 5H), 6.98 (m, 2H), 6.74 (m, 2H), 4.45 (d, *J* = 9.06 Hz, 1H), 4.22 (d, *J* = 11.56 Hz, 1H), 4.15 (d, *J* = 11.56 Hz, 1H), 3.70 (s, 3H), 3.40 (d, *J* = 10.73 Hz, 1H), 3.15 (d, *J* = 10.73 Hz, 1H), 1.63 (d, *J* = 5.13 Hz, 1H), 1.31 (d, *J* = 5.13 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5, 159.3, 131.2, 130.4, 129.6, 129.2, 128.6, 128.2, 113.8, 72.9, 70.1, 68.3, 55.3, 36.8, 35.3, 20.5 ppm; IR (neat): ν 3958m, 2908m, 2858m, 1770s, 1612m, 1512s, 1454w, 1361m, 1303w, 1249s, 1091s, 1037m, 1014m, 910s cm^{-1}; HMRS: exact mass calcd for $C_{20}H_{20}O_4$ $[M]^+$: 324.1362, Found: 324.1360.

2-Step continuous flow / semi-batch protocol Allyl ester (4 mmol) was dissolved in acetonitrile and DBU (0.84 ml, 5.6 mmol, 1.4 eq) was added to give a total volume of 4 ml. *p*-ABSA (1.15 g, 4.8 mmol, 1.2 eq) was dissolved in acetonitrile to give a total volume of 4 ml. Both solutions were charged into 5 ml syringes. Flow rates were put to 0.042 ml/min for the ester and sulfonyl azide solution on a syringe pump. 1 M aqueous sodium nitrite quench solution was pumped via Vapourtec pump (blue tubing) with a flow rate of 0.101 ml/min and *n*-heptane for the extraction was pumped with a flow rate of 0.158 ml/min. After passing the L/L phase separator, the aqueous layer was discarded and the organic layer was added to the

solution. $Rh_2(OOct)_4$ (10.1 mg, 1 mol%) was dissolved in *n*-heptane (5 ml) and stirred at 65 °C. Addition of organic layer stream was performed for 30 minutes and the mixture stirred at 65 °C for another 30 min. Subsequently, solvent was evaporated *in vacuo* and the reaction mixture was purified via flash chromatography on an automated purification system using a 20g silica column.

5-Methyl-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (11)[19] 63 mg (32% yield; 161 mg of 198 mg of the crude reaction mixture was used for purification) of **10** were obtained as colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35-7.15 (m, 5H), 4.30 (d, *J* = 9.1 Hz, 1H), 4.12 (d, *J* = 9.1 Hz, 1H), 1.55 (d, *J* = 4.9 Hz, 1H), 1.32 (d, *J* = 4.9, 1H), 1.09 (s, 3H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.6, 132.2, 130.4, 128.9, 128.2, 73.4, 37.1, 31.4, 22.8, 15.4 ppm.

6-Methyl-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (13)[20] 66 mg (30% yield; 196 mg of 211 mg of the crude reaction mixture was used for purification) of **11** were obtained as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44-7.28 (m, 5H), 4.42 (dd, *J* = 9.1, 4.5 Hz, 1H), 4.32 (d, *J* = 9.1 Hz, 1H), 2.30 (t, *J* = 4.5 Hz, 1H), 1.50-1.42 (m, 1H), 0.80 (d, *J* = 6.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 130.6, 128.8, 128.2, 68.7, 37.2, 28.9, 26.4, 13.6 ppm.

Allyl 2-hydroxy-2-phenylacetate (14)[21] Obtained as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48-7.41 (m, 2H), 7.39-7.28 (m, 3H), 5.90-5.73 (m, 1H), 5.20 (s, 2H), 5.16 (dq, *J* = 5.14, 1.27 Hz, 1H), 4.60-4.68 (m, 2H), 3.40 (bs, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 138.3, 131.2, 128.6, 128.5, 126.6, 118.7, 72.9, 66.4 ppm.

Diallyl 2,2'-oxybis(2-phenylacetate) (15) Obtained as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.50 (m, 5H), 5.76-5.90 (m, 1H), 5.13-5.24 (m, 2H), 5.04 (d, *J* = 2.0 Hz, 1H), 4.57-4.64 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 135.5, 131.5, 128.9, 127.6, 127.5, 118.4, 78.7, 65.7 ppm; IR (neat): 3066m, 2085m, 1817w, 1801w, 1747s, 1685m, 1647w, 1496m, 1454m, 1361w, 1246m, 1203m, 1173s, 1103m, 987m, 935m, 732m, 698m cm^{-1}; HMRS: exact mass calcd for $C_{22}H_{25}O_5$ $[M]^+$: 366.1467, Found: 366.1468.

5-Methoxy-2-methyl-4-phenyloxazole (18) Methyl 2-diazo-2-phenylacetate **15** (176 mg, 1 mmol) was dissolved in dry CH_2Cl_2 (4 ml) and added via syringe pump over 1 h to a solution containing $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol; 1 mol%) in dry CH_2Cl_2 (4 ml) under argon atmosphere (Schlenk dried flask) at reflux. After completion of the reaction (*via* TLC analysis) the reaction mixture was cooled down to room temperature and then the solvent was evaporated *in vacuo*. The crude reaction mixture was immediately purified *via* flash column chromatography (12 g silica column with 0%-10% EtOAc in *n*-hexane over 25 column volumes) to furnish 71 mg of **16** (38%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.79 (m, 2H), 7.30-7.38 (m, 2H), 7.18 (tt, *J* = 8.37, 1.27 Hz, 1H), 4.00 (s, 3H), 2.41 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 151.9, 131.4, 128.5, 126.3, 124.8, 114.5, 60.1, 14.3 ppm. IR (neat) 3028w, 2949w, 1743s, 1647s, 1599s, 1500w, 1449m, 1369m, 1221s, 1173m, 1016m, 766m, 731m cm^{-1}. HRMS: Exact mass calc for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.0868, Found: 190.0862.

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Notes

The authors declare no competing financial interest.

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Supporting Information

The supporting information for this paper contains the results of reactions using different rhodium acetate batches.

References

1. Kasper, S.; Pletan, Y; Solles, A.; Tournoux, A. *Int. Clin. Psychopharmacol.* **1996**, *11*, 35-39.
2. Lopez-Ibor, J; Guelfi, J. D.; Pletan, Y.; Tournoux, A.; Prost, J. F. *Int. Clin. Psychopharmacol.* **1996**, *11*, 41-46.
3. Tamiya, J.; Dyck, B.; Zhang, M.; Phan, K.; Fleck, B. A.; Aparicio, A.; Jovic, F.; Tran, J. A.; Vickers, T.; Grey, J.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3328-3332.
4. a) Shuto, S.; Takada, H.; Mochizuki, D.; Tsujita, R.; Hase, Y.; Ono, S.; Shibuya, N.; Matsuda, A. *J. Med. Chem.* **1995**, *38*, 2964-2968; b) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamasihita, K.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 915-923.
5. Doyle, M. P.; Hu, W. *Adv. Synth. Catal.* **2001**, *343*, 299-302.
6. Shen, J.-J.; Zhu, S.-F.; Cai, Y.; Xu, H.; Xie, X.-L.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2014**, *53*, 13188-13191.
7. De Boer, T. J.; Backer, H. J. *Org. Synth.* **1956**, *36*, 16-19.
8. Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2015**, *54*, 6688-6728.
9. Wirth, T. *Microreactors in Organic Chemistry and Catalysis*, 2nd edition, Wiley: Weinheim, 2013.
10. For reviews on diazo compounds in flow: a) Deadman, B. J.; Collins, S. G.; Maguire, A. R. *Chem. Eur. J.* **2015**, *21*, 2298-2308; b) Müller, S. T. R.; Wirth, T. *ChemSusChem* **2015**, *8*, 245-250.
11. a) Procter, L. D.; Warr, A. J. *Org. Process Res. Dev.* **2002**, *6*, 884-892; b) Ferstl, W. F.; Schwarzer, M. S.; Löbbecke, S. L. *Chem. Ing. Tech.* **2004**, *76*, 1326-1327; c) Struempel, M.; Ondruschka, B.; Daute, R.; Stark, A. *Green Chem.* **2008**, *10*, 41-43; d) Maurya, R. A.; Park, C. P.; Lee, J. H.; Kim, D.-P. *Angew. Chem. Int. Ed.* **2011**, *50*, 5952-5955; e) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett.* **2011**, *13*, 320-323; f) Rossi, E.; Woehl, P.; Maggini, M. *Org. Process Res. Dev.* **2012**, *16*, 1146-1149; g) Mastronardi, F.; Gutmann, B.; Kappe, C. O. *Org. Lett.* **2013**, *15*, 5590-5593; h) Pinho, V. D.; Gutmann, B.; Miranda, L. S. M.; de Souza, R. O. M. A.; Kappe, C. O. *J. Org. Chem.* **2014**, *79*, 1555-1562.
12. a) Bartrum, H. E.; Blakemore, D. C.; Moody, C. J.; Hayes, C. J. *J. Org. Chem.* **2010**, *75*, 8674-8676; b) Delville, M. M. E.; van Hest, J. C. M.; Rutjes, F. P. J. T. Beilstein *J. Org. Chem.* **2013**, *9*, 1813-1818; c) Maurya, R. A.; Min, K.-I.; Kim, D.-P. *Green Chem.* **2014**, *16*, 116-120; d) Müller, S. T. R.; Smith, D.; Hellier, P.; Wirth, T. *Synlett* **2014**, *25*, 871-875.
13. Müller, S. T. R.; Murat, A.; Maillos, D.; Lesimple, P.; Hellier, P.; Wirth, T. *Chem. Eur. J.* **2015**, *21*, 7016-7020.
14. See Stoessel, F.; Fierz, H.; Lerena, P.; Killé, G. *Org. Proc. Res. Dev.* **1997**, *1*, 428-434.
15. Volumes correspond to the amount of starting material used. For a reaction using 1 g of starting material, 11 ml of *n*-heptane for the extraction were used.
16. a.) M. O'Brien, P. Koos, D. L. Browne, S. V. Ley, *Org. Biomol. Chem.* **2012**, *10*, 7031-7036; b.) D. X. Hu, M. O'Brien, S. V. Ley, *Org. Lett.* **2012**, *14*, 4246-4249.
17. Traces of another diastereomer were possibly observed in case of **13** in the crude ^{1}H NMR, however, isolation of this compound was unsuccessful and therefore determination of the structure was not possible.

18. Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657-3664.
19. Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145-1147.
20. Barluenga, J.; Aznar F.; Gutiérrez, I.; Martin, J. A. *Org. Lett.* **2002**, *4*, 2719-2722.
21. Alamsetti, S. K.; Sekar, G. *Chem. Commun.* **2010**, *46*, 7235-7237.