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Memory of chirality in a flow-based system: enantioselective synthesis of quaternary α-amino acids using flow microreactors

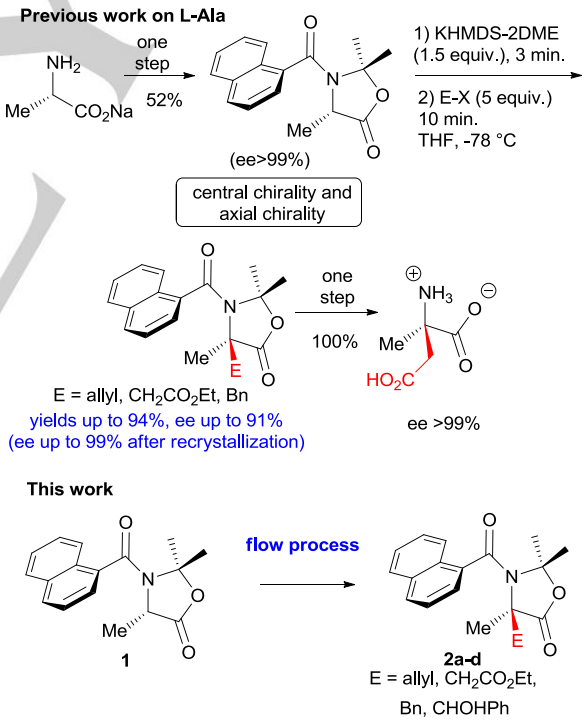
Antonin Mambrini,[a] Didier Gori, [a] Cyrille Kouklovsky, [a] Heejin Kim, [b] Jun-ichi Yoshida, [c] and Valérie Alezra*[a]

Abstract: Enantioselective synthesis of quaternary α-amino acids based on alkylation of a conformationally unstable enolate according to a Memory of Chirality strategy was successfully adapted to a flow-based system. This allows for the scale up of this enantioselective process with reaction residence times of less than 3 minutes. The enantiomeric excesses are similar to those obtained in batch process.

Introduction

Memory of Chirality (MOC)[1–10] is an original strategy in asymmetric synthesis based on the chiral pool but in which the initial stereogenic center is temporarily destroyed and recovered in an enantioselective fashion. The principle relies on a memorization of the initial chirality by a global chiral conformation of the intermediate. Therefore this strategy is very sensitive to reaction conditions in particular reaction rate and temperature, and many MOC reactions are either intramolecular[11–15] or performed at low temperature[16–20] or both.[21,22] We have already developed a 3-step asymmetric synthesis of quaternary α-amino acids based on MOC.[23–26] The key step is an intermolecular alkylation of an enolate and the initial chirality of the starting α-amino acid is "memorized" at only low temperatures by a chiral conformation of a tertiary aromatic amide (Scheme 1). This reaction is very efficient and enantioselective but not scalable because strict temperature control (and consequently the pre-cooling of the base, transferred by cannulation) is essential to achieve high enantioselectivity. Thus, we thought that we could use continuous flow chemistry[27,28] to optimize the heat exchange and to be able to access to large quantities of quaternary α-amino acids.

Continuous flow chemistry has been recently found as an attractive method for organic chemistry as it increases the safety (by better heat and mass transfer) and it is easy to adapt to scale-up.[29,30] Among flow chemistry, flash chemistry,[31–33] is referring to very fast reactions conducted in a highly controlled manner using microflow reactors. Flash chemistry is very promising as it allows transformations that are difficult even impossible to perform in batch. Highly unstable intermediates can be used for the next reaction before they decompose or isomerize by virtue of extremely short reaction times. It is also really interesting in the field of labile organometallic anion chemistry.[34–38] This concept of flash chemistry seemed thus to be perfectly adapted to our MOC reactions and it has never been tried before for enantioselective synthesis by MOC. We describe here our results on L-alanine in this field, which consist in the very first application of MOC in a flow-based system, as well as a large scale synthesis of a quaternary α-amino acid derivative.



Scheme 1. Previous work on L-Ala alkylation and adaptation to flow process.

Results and Discussion

We used a simple flow-based system composed of 3 syringe pumps, stainless steel tubing and T-mixers. We first tried to perform alkylation of compound **1** under the conditions similar to the batch reaction, with KHMDS as a base at -78 °C. It

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completely failed as formation of insoluble potassium salt (KBr or KI) occurred in situ and thus clogged the system. Attempts to use an ultrasonic bath led also to overpressure at low temperatures (at 0°C, no overpressure was observed but the alkylated compound was racemic). Therefore, we decided to use LDA as a base to produce soluble lithium salts and reinvestigated batch experiments.

We first conducted the reaction with LDA under batch conditions, and the results are shown in Table 1. Several reaction conditions were modified according to the experimental requirements of the flow mode. In particular, the reaction solution was a bit more diluted (0.10 M) than the experiments in our previous reports (0.27 M), because highly concentrated solution having high viscosity is easy to clog in flow (in aldol reaction, use of even higher concentration improved the enantiomeric excess). The enantiomeric excesses obtained with LDA (entries 1–3 Table 1) were a bit lower than with KHMDS (entries 4–6) but are acceptable. Unexpectedly, DME, which was the best additive for KHMDS, gave very disappointing results with LDA but DMPU was a convenient additive for this reaction (reaction was not possible without it for allyl iodide). And the reaction with ethyl iodoacetate gave better yield and enantiomeric excess, probably because of high reactivity (entry 7).

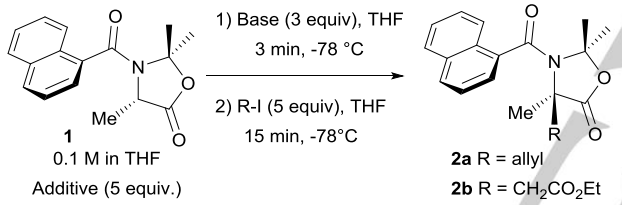


Table 1. Batch tests

Entry	R	Additive	Base	Yield (%)	ee (%)[a]
1	Allyl	-	LDA	NR[b]	NR[b]
2	Allyl	DMPU	LDA	81	64
3	Allyl	DME	LDA	33	59
4	Allyl	-	KHMDS	81	65
5	Allyl	DMPU	KHMDS	81	65
6	Allyl	DME	KHMDS	75	70
7	CH_2CO_2Et	-	LDA	74	65

[a] Determined by chiral stationary-phase HPLC. [b] No reaction

We then decided to investigate alkylation with LDA in a flow-based system. We first conducted reactions using ethyl iodoacetate as an electrophile, because it was a better reactant as confirmed in Table 1. We optimized the reaction time for deprotonation (t^1) by changing the length of the tubing as well as the deprotonation temperature (T^1; Table 2). This reaction led successfully to the expected compound **2b** with, not surprisingly, the same absolute configuration as in batch. Temperature variations showed that the enantiomeric excess is pretty stable below -55 °C whereas the conversion drops at -78 °C (entries 2 and 6). Deprotonation was complete at -50 °C in 35 seconds but we had also high conversion with higher enantiomeric excesses at lower temperatures (entries 1 and 2). Use of 10 equivalents of electrophile did not improve the yield (entry 4). The best compromise seemed thus deprotonation at -55 °C for 35 s (entry 2).

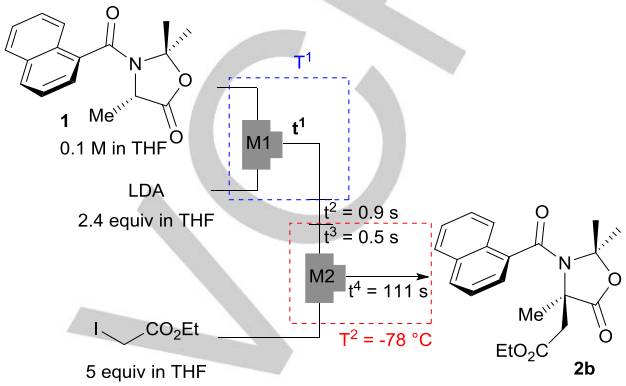


Table 2. Optimization of deprotonation time and temperature in a flow-based system – alkylation with ethyl iodoacetate

Entry	t^1 (s)	T^1 (°C)	Conv. (%)[a]	ee (%)[a]
1	35	-50	100	62
2	**35**	**-55**	**88**	**75**
3	7.7	-55	83	77
4[b]	35	-60	75	72
5	17	-65	72	78
6	35	-78	61	78

[a] Determined by chiral stationary-phase HPLC. [b] 10 equiv. of electrophile were used.

We then optimized the alkylation step and used allyl iodide as electrophile because it was less reactive. The length of tubing reactor for alkylation was extended to 20 m to improve the conversion (longer tubing induced overpressure). We fixed the deprotonation temperature (-60 °C) and time (35 s), then varied the temperature of the reaction with allyl iodide. We also investigated the role of DMPU as it improved the yield in batch. We first added this additive with the base but it systematically induced clogging. We thus added it with the electrophile. The results are gathered in table 3. DMPU improved the conversion (entries 3 and 4). Increasing temperature from -78 °C to -55 °C does not affect the enantiomeric excess but improved the conversion (entries 1 and 3). At -30°C, the conversion was complete, but the enantiomeric excess completely dropped (entry 5). Finally, at -60 °C, the isolated yield was 74% with an enantiomeric excess of 57% (entry 6). This result was a bit inferior to the batch experiment but acceptable, probably because of the lower concentration or of the temperature increase.

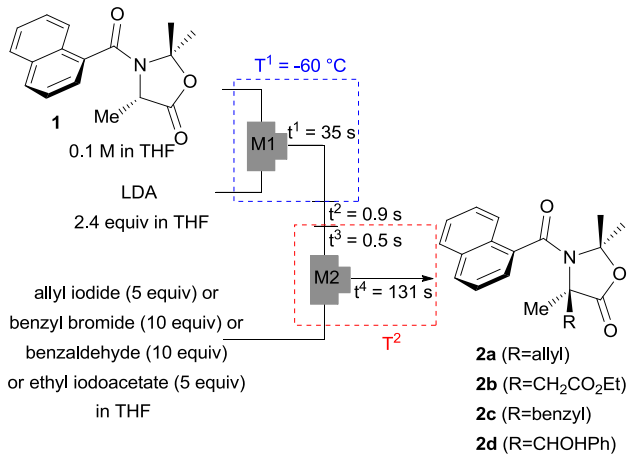


Table 3. Optimization of alkylation in a flow-based system alkylation with allyl iodide, benzyl bromide, ethyl iodoacetate and aldol reaction with benzaldehyde

Entry	Electrophile	Additive[a]	T^2 (°C)	Conv. (%)[b]	ee (%)[b]
1	Allyl iodide	-	-78	37	50
2	Allyl iodide	DMPU	-78	56	44
3	Allyl iodide	-	-55	46	49
4	Allyl iodide	DMPU	-55	99	52
5	Allyl iodide	-	-30	97	18
6	**Allyl iodide**	**DMPU**	**-60**	**74[c]**	**57**
7	**BnBr**	**DMPU**	**-60**	**68[c]**	**75**
8	**PhCHO**	**DMPU**	**-60**	**42[c],[d]**	**67/90[d]**
9	**ICH_2CO_2Et**	**-**	**-70**	**82[c],[e]**	**89**

[a] 6 equiv. of DMPU was mixed with an electrophile and used for flow reaction. [b] Determined by chiral stationary-phase HPLC. [c] isolated yield. [d] de = 74%, ee(major dia) = 67%, ee(minor dia) = 90%. [e] reaction performed on 1.33 g of compound **1**; 1.20 g of **2b** was obtained.

We then applied these conditions (entry 6, table 3) to benzyl bromide (10 equiv.) and obtained the expected compound **2c** (E = Bn) in 68% yield and 75% enantiomeric excess (entry 7). We also performed aldol reaction with benzaldehyde and get a separable mixture of diastereomers (de= 74%, yield = 42%) in 67% (major diastereomer) and 90% (minor diastereomer) enantiomeric excess.

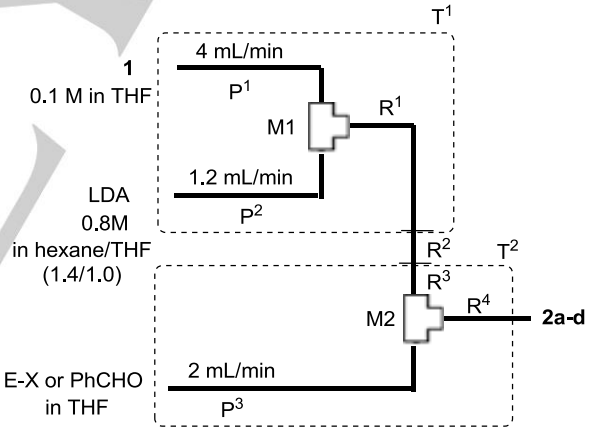
As our goal was to demonstrate that thanks to flow chemistry, we would be able to access large quantities of quaternary amino acids, we launched the alkylation on a larger quantity of oxazolidinone **1** with ethyl iodoacetate. For experimental reasons (temperature control) we chose to perform the large-scale reaction at -70 °C, which is possible thanks to the high reactivity of ethyl iodoacetate. When using 1.33 g of **1**, we were pleased to get 1.20 g of the final compound **2b** in 82% yield and 89% enantiomeric excess (entry 9, table 3), which is very close to our previous batch result. Obviously, larger quantities are reachable by just increasing the collecting time. Unexpectedly, these flow results show that the enantiomeric excess is highly dependent of the nature of the electrophile, much more than in our previous batch reactions. This may be due either to a lower conformational stability of the lithium enolate in flow than of the potassium enolate in batch, or to a reduced reactivity of a lithium enolate, compared to our former potassium enolate, rendering the reactivity of the electrophile more important for the control of the racemization.

Conclusions

To conclude, we successfully adapted our MOC reaction to a flow-based system. In particular, we were able to synthesize a large amount of quaternary amino acid derivative **2b** in high yield and high enantiomeric excess, at a temperature slightly superior than in batch and mostly in a very short time, with reaction residence time of less than 3 minutes. We thus showed for the first time that MOC synthesis of quaternary amino acids could be adapted to the concept of flash chemistry allowing larger scale synthesis.

Experimental Section

Flow alkylation general procedure



A microfluidic system consisting of two T-shaped micromixers (M1 and M2), four microtubes reactors (R^1, R^2, R^3 and R^4) and three tubes pre-temperature-retaining units (1000 µm of inner diameter (ø) and 100 cm of length (L)) were used at temperature T^1 for P^1 and P^2 and T^2 for P^3. A solution of (*S*)-3-(1-naphthoyl)-2,2,4-trimethyloxazolidin-5-one (**1**; 0.10 M in THF) and a solution of lithium diisopropylamine (0.80 M in hexane/THF (1.4/1.0) were individually introduced to M1 (ø:500 µm) by syringe pumps. The resulting solution was passed through R^1 (various lenghts, ø: 1000 µm, temperature: T^1), R^2 (10 cm, ø: 1000 µm, temperature: room temperature), R^3 (5 cm, ø: 1000 µm, temperature : T^2) and was mixed with a solution of electrophile (various electrophiles and various concentration in THF) in M2 (ø: 500 µm). The resulting solution was passed through R^4 (various sizes, ø: 1000 µm, temperature: T^2). The flow rates for (*S*)-3-(1-naphthoyl)-2,2,4-trimethyloxazolidin-5-one **1**, LDA and the electrophile were 4 mL/min, 1.2 mL/min and 2 mL/min respectively. After a steady state was reached, the product solution was collected for 1 min while being quenched with saturated aqueous NH_4Cl solution (2 mL). Then, DCM (6 mL) and brine (2 mL) were added, and then the organic

phase was concentrated and analyzed by ^{1}H NMR spectroscopy and HPLC stationary phase or purified as following procedures.

Acknowledgements

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Keywords: Flash chemistry • Asymmetric synthesis • Amino acids • Memory of Chirality • Flow chemistry

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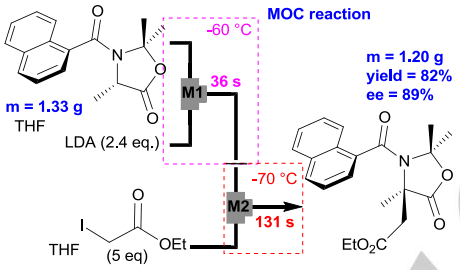
Entry for the Table of Contents

COMMUNICATION

The first Memory of Chirality reaction in flash chemistry is reported: it allows enantioselective synthesis of quaternary α-amino acid derivatives with reaction residence times of less than 3 minutes. This proof of concept shows that larger quantities of compound can be synthesized in short reaction time.



Asymmetric synthesis

*Antonin Mambrini, Didier Gori, Cyrille Kouklovsky, Heejin Kim, Jun-ichi Yoshida, Valérie Alezra**

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