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Bromine-lithium exchange on a *gem*-dibromoalkene

Part 2: comparative performance of flow micromixers

*Katia Pérez,^{a,b} Baptiste Picard,^a Daniela Vuluga,^b Fabrice Burel,^b Rainier Hreiz,^c Laurent Falk,^c
Jean-Marc Commenge,^c Aiichiro Nagaki,^d Jun-ichi Yoshida,^{d,e} Isabelle Chataigner,^{a,f} Jacques
Maddaluno,^a and Julien Legros^{a,*}*

a Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA, 76000 Rouen, France.

b Normandie Univ, INSA Rouen, UNIROUEN, CNRS, PBS, 76000 Rouen, France.

c Laboratoire Réactions et Génie des Procédés, Université de Lorraine, CNRS, LRGP, F-54000 Nancy, France.

d Department of Synthetic and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto, 615-8510, Japan.

e National Institute of Technology, Suzuka College, Shiroko-cho, Suzuka, Mie, 510-0294, Japan.

f Sorbonne Université, CNRS, Laboratoire de Chimie Théorique, LCT UMR7616, 75005 Paris, France.

Dedicated to Dr Danièle Bonnet-Delpon on the occasion of her 70th birthday

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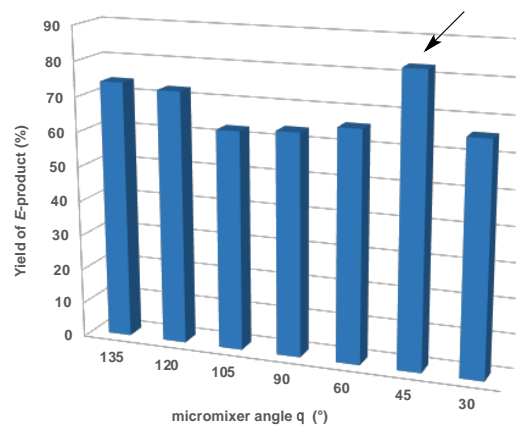
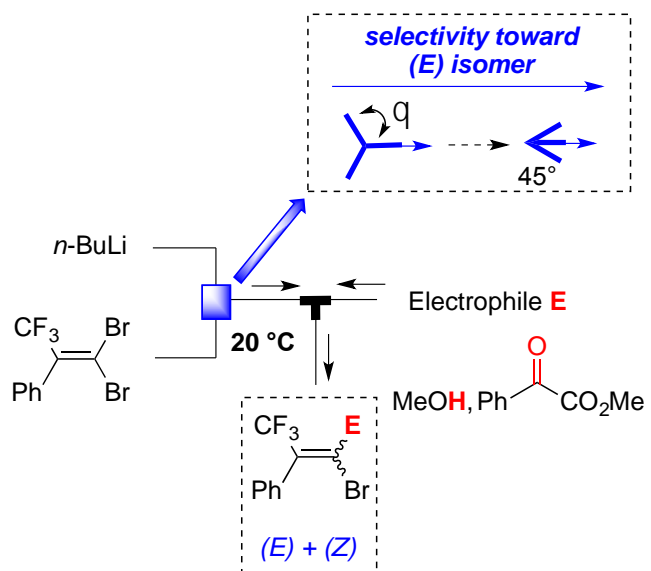


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ABSTRACT

The influence of sixteen passive mixers with eight different angles of 135, 120, 105° (Y mixers), 90° (T mixer), 75, 60, 45 and 30° (W mixers) and two internal diameters (ID = 500 and 250 μm) associated with a tubular microflow reactor of ID = 500 μm was measured in the stereoselectivity of lithium-bromine exchange on a *gem*-dibromo alkene, followed by proton trapping. The 45° W-shaped mixer with thinner ID gave the best selectivity for the monobrominated *E*-product over a range of flow rates without usual cryogenic conditions (20 °C). With methyl benzoylformate as electrophile, the corresponding polyfunctionalized product was obtained with a space time yield of 81 kg/L/h.

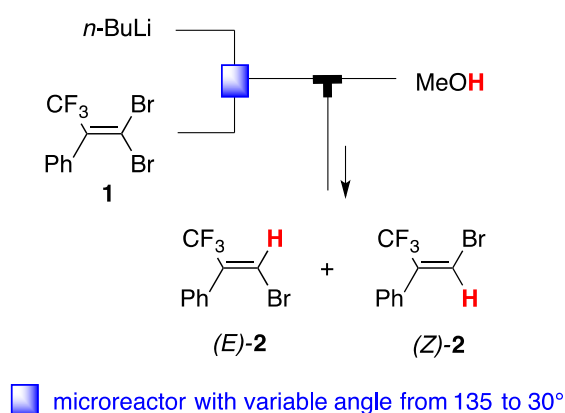
KEYWORDS microreactor shape, organolithium, carbenoid, stereoselectivity, microflow.

INTRODUCTION

Research concerning organic reactions generally focuses on the efficiency of the chemical transformation itself (mostly by assessing the yield of a target product of a specific molecular geometry) but sometimes neglects the tools used to perform the reaction. Thus, organic chemistry reports give little emphasis on some critical technical aspects, such as flask geometry, precise addition time or stirring rate. In contrast, in microflow chemistry engineering concerns are omnipresent and it is well-established that the design of the continuous flow reactor plays a fundamental role in the outcome of the reaction.¹⁻⁵ Microfluidic devices are generally considered as operating in the laminar flow regime because of the micrometric nature of the flow path and of the upper limit of the achievable in flow rates (indeed, because of their dimensions, those systems lead to tremendous pressure drops at high flow rates). As a result, two layers taken in the stream tend to move in a parallel fashion, without mixing with each other.⁶ Whereas computational fluid dynamics with square section mixers suggest that altering the angle between the inlet channels does not significantly impact the mixing performance,¹ Yoshida observed a significant difference in organolithium reactivity between circular section T-shaped and W-shaped (also known as V or anchor shaped) micromixers.^{7,8} The difference between these mixers lies in the angle between the channels, $\theta = 90^\circ$ for T-shaped and $\theta = 45^\circ$ for W-shaped (the inlets being each time separated by 2θ , with the outlet standing in-between in a “frontal encounter” setup; see Table 1).

These findings imply that the exact location where the two flows meet, and how these flows are behaving at this point influence the outcome of reactions, suggesting that the shape of the micromixer can be specifically designed to induce a local instability (local loss of the steady laminar behavior) favoring the mixing even under formal laminar regime. Indeed, as reported by

Galletti, the flow in the mixing zone of micromixers becomes chaotic and even turbulent at relatively moderate Reynolds number values.⁹ Along these lines we now report the influence of the shape of eight micromixers of circular cross-section from Y to W structure (angles $\theta = 135, 120, 105, 90, 75, 60, 45$ and 30°) with two internal diameters (500 and 250 μm) in the stereoselectivity of the lithium-halogen exchange of *gem*-dibromoalkene **1** under microflow conditions (Scheme 1 and Supporting informations).

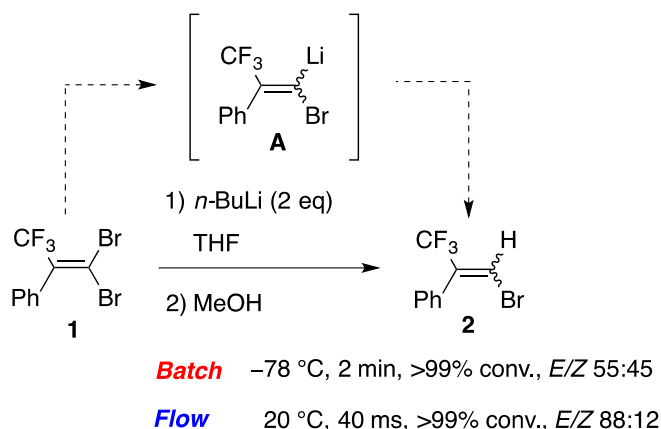


Scheme 1. Top: Lithium-halogen exchange on *gem*-dibromoalkene **1** with various Y-, T-, and W-shaped flow micromixers. Bottom: pictures of 3 micromixers (from left to right: 120° (Y), 90° (T) and 45° (W) angles).

RESULTS AND DISCUSSION

Lithiated vinyl carbenoids can be easily obtained by metal-halogen exchange from the corresponding *gem*-dihalogen alkene under cryogenic conditions. However these carbenoids are often particularly unstable since they may undergo fast Fritsch-Buttemberg-Wiechell

rearrangement (FBW) along with various side-reactions.¹⁰⁻¹² In a recent preliminary study, we showed that *gem*-dibromoalkene **1** was able to undergo lithium-bromine exchange and that the corresponding carbenoid intermediate **A** was stable enough to trap a proton to generate the corresponding monobromo olefin **2**.¹² Whereas the reaction was unselective under classical batch conditions, even at $-78\text{ }^{\circ}\text{C}$, a 88:12 *E/Z* ratio could be attained on a single run by using a continuous flow microreactor equipped with a T-shaped micromixer ($\theta = 90\text{ }^{\circ}$, $\text{ID}_{\text{mixer,tubing}} = 500\text{ }\mu\text{m}$, flow rate $Q_{(1+n\text{-BuLi})} = 9.4\text{ mL/min}$), even at $20\text{ }^{\circ}\text{C}$ within 30 ms (Scheme 2).



Scheme 2. Generation and trapping of a carbenoid **A** from *gem*-dibromoalkene **1** under batch and continuous flow conditions

We now extend this study to the influence of the design and sizing of the flow micromixer in the reaction between **1** (in THF) and *n*-BuLi (in hexanes) at $20\text{ }^{\circ}\text{C}$. Our first investigations are reported in Table 1 with the measure of the conversion rate of **1**, the selectivity of the transformation toward product **2** and the corresponding *E/Z* ratio, by using two micromixers ($\text{ID} = 500\text{ }\mu\text{m}$) with respective angles of 90° (Table 1, entries 1-6) and 45° (Table 1, entries 7-12) at various flow rates Q .

Table 1. Effect of T-shaped (90°) and W-shaped (45°) micromixers and flow rates on the conversion of **1** into *E*-**2**.^a

Entry	ID (μm)	Angle ($^{\circ}$)	Flow rate Q (mL/min)		t^R (ms)	Conversion (%) ^b	Product selectivity for 2 ^{b,c}	<i>E/Z</i> ratio ^b
			Substrate	<i>n</i> -BuLi				
1	500	90	1	0.625	220	59	98	93:07
2						31	64	71:29
3						30	91	84:16
4						71	72	88:12
5			6	3	40	98	99	77:23
6						99	99	72:28
7	500	45	1	0.625	220	88	70	55:45
8 ^d						–	–	–
9			4	2	60	100	95	65:35
10						100	97	61:39
11			5	2	50	100	96	64:36
12						98	99	69:31

^a Experiments were performed with: [**1**] = 0.1 M in THF, [*n*-BuLi] = 0.3 M in hexane. Reactor tubing: ID = 500 μm , L = 3 cm.

^b Measured by GC-MS and ¹⁹F NMR.

^c Product selectivity = [**2**]/([**2**] + [other products]) \times 100.

^d Clogging occurred

First experiments were conducted with the T-shaped mixer at a low flow rate Q = 1.625 mL/min (t^R = 220 ms; entries 1-4). The first assay gave a satisfactory result: 59% conversion of **1** almost exclusively into target product **2** and with an excellent *E* selectivity (93%). Unfortunately,

these results were not reproducible. Under the same conditions, the three following experiments (entries 2-4) gave significantly different results: conversion varied from 31 to 71% and selectivity for **2** could drop down to 64% (GC-MS suggesting some other products such as the incorporation of a butyl chain instead of the methanolic proton, as previously observed in batch mode). Moreover, the stereoisomeric ratio was still in favor of the *E* compound but never exceeded 88% (entry 4). In contrast, entries 5 and 6 shows that increasing the flow rate by >5-fold ($Q = 9$ mL/min) with the same reactor ($t^R = 40$ ms) afforded reproducible results: >98% conversion and selective formation of **2** albeit with a disappointing stereoisomeric selectivity (<77% *E*). This shows that high flow values are required to ensure flow stability and therefore reproducibility of reaction conditions.

Switching to a micromixer with $\theta = 45^\circ$ also demonstrated the importance of the flow rate conditions. At $Q = 1.625$ mL/min, the reaction could either take place or the flow system could clog (entries 7 and 8). Increasing Q to 6 and 7 mL/min brought reproducible results with full conversion into the desired monobrominated product with slight variations in the *E/Z* ratio from 61:39 to 69:31. From these experiments with two different micromixers the following conclusions could be drawn: 1) high flow rates ensure reproducibility of the experiments, 2) both 90 and 45° angles guarantee high conversions of the substrate **1** into the carbenoid **A** with subsequent trapping of a methanolic proton, 3) a clear tendency toward *E*-selectivity can be observed. 4) Despite some small discrepancies between identical experiments, *E*-selectivity seems significantly higher with a T-shape mixer rather than with a 45° W-shape in those conditions.

From these results, we extended the scope of the study to a broader range of eight micromixers from 135 to 30° (see Table 1 and Supporting information) with ID = 500 and 250

μm , and associated with the same reactor tubing as in Table 1, ($L = 3 \text{ cm}$, $\text{ID} = 500 \mu\text{m}$) at an intermediate flow rate $Q = 3.5 \text{ mL/min}$. Results are depicted in Table 2.

Table 2. Effect of micromixers with θ ranging from 135 to 30° at moderate flow rate (3.5 mL/min) on the conversion of **1** into *E*-**2**.^a

Entry	ID (μm)	Angle ($^\circ$)	Flow rate		Q (mL/min)	t^R (ms)	Conversion (%) ^b	Product selectivity for 2 ^{b,c} (%)	<i>E/Z</i> ratio ^b
			Substrate	<i>n</i> -BuLi					
1	500	135	2.5	1	100	46	79	80:20	
2		105				22	82	77:23	
3		90				60	85	90:10	
4		75				41	84	79:21	
5		60				56	89	84:16	
6		45				63	93	86:14	
7		30				56	88	86:14	
8	250	135	2.5	1	100	98	99	77:23	
9		120				49	98	89:11	
10		105				84	89	98:02	
11		90				91	90	80:20	
12		75				80	98	81:19	
13		60				69	>99	92:08	
14		45				92	>99	92:08	
15		30				95	88	82:18	

^a Experiments were performed with: $[\mathbf{1}] = 0.1 \text{ M}$ in THF, $[\textit{n}\text{-BuLi}] = 0.3 \text{ M}$ in hexane. Reactor tubing: $\text{ID} = 0.5 \text{ mm}$, $L = 3 \text{ cm}$.

^b Measured by GC-MS and ^{19}F NMR. Average value over 2 runs (reproducibility is $\pm 2\%$).

^c Product selectivity = $\frac{[\mathbf{2}]}{[\mathbf{2}] + [\text{other products}]} \times 100$.

With ID = 500 μm and $t^R = 100$ ms (entries 1-7), conversions were below 60% for each microreactor except for $\theta = 90$ and 45° (60 and 63% respectively) who also afforded the best *E/Z* selectivity (90:10 and 86:14 respectively; entries 3 and 7). Performing the experiments with a thinner ID (250 μm) had a tremendous effect on the Br-Li exchange with five reactors affording conversions >90% and in all eight cases affording the desired trapped carbenoid **2** >88% (entries 8-15). Regarding *E/Z* selectivity, the Y-shaped $\theta = 105^\circ$ and the W-shaped $\theta = 45^\circ$ microreactors led to the best isomeric ratios (entries 10 and 14, respectively). However, when considering the overall selectivity toward *E-2*, the micromixer W-45 led to 84% whereas Y-105 only provided 73% of *E-2*. These experiments therefore demonstrate the beneficial effect of small diameters for conversion and selectivity. Final assessments at a high flow rate (8.4 mL/min, $t^R = 40$ ms) are reported in Table 3).

Table 3. Effect of micromixers with θ ranging from 135 to 30° at high flow rate (8.4 mL/min)

on the conversion of **1** into *E*-**2**.^a

Entry	ID (μm)	Angle ($^{\circ}$)	Flow rate		Q t^R (ms)	Conversion (%) ^b	Product selectivity for 2 ^{b,c} (%)	<i>E/Z</i> ratio ^b
			Substrate	<i>n</i> -BuLi				
1	250	135	6	2.4	40	97	>99	77:23
2		120				78	>99	94:06
3		105				>99	>99	64:36
4		90				>99	>99	65:35
5 ^d		75				–	–	–
6		60				98	>99	68:32
7		45				90	>99	93:07
8		30				98	>99	68:32

^a Experiments were performed with: [**1**] = 0.1 M in THF, [*n*-BuLi] = 0.3 M in hexane. Reactor tubing: ID = 500 μm , L = 3 cm.

^b Measured by GC-MS and ¹⁹F NMR. Average value over 2 runs (reproducibility is $\pm 2\%$).

^c Product selectivity = [**2**]/([**2**] + [other products]) $\times 100$.

^d Clogging occurred

Higher flow rates unambiguously improved the conversion toward **2**: all mixers gave an increased or similar conversion compared to lower flow rates, despite the shortened residence time (as reactor length and width were kept constant). This strongly supports the hypothesis of a diffusion-ordered reaction and thus highlights the uttermost importance of mixing. However, such a clear trend could not be observed concerning stereoselectivity as the previous best ratio at lower flow rate was attained with Y-105 at 98:02 and now dropped to 64:36 while Y-120 increases from 89:11 to 94:06. The only clear conclusion that can be drawn is that the W-45 high

efficiency remained constant (83% overall for *E-2*). A histogram, summarizing the results from Tables 3 and 4, is represented in Figure 1.

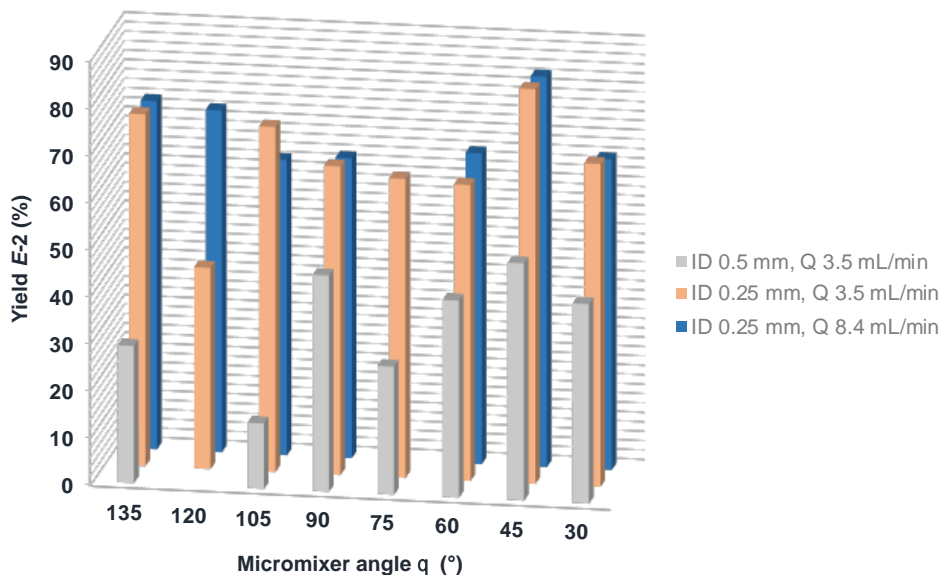
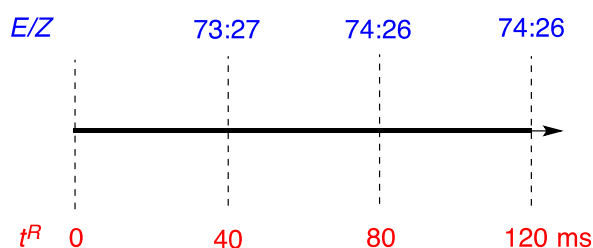


Figure 1. Yield of *E-2* according to the angle θ of the micromixer.

If the increased conversion in a shorter time can be adequately explained by an enhanced mixing, how this mixing affects the stereochemistry of the reaction remains unclear at this point. At least two non-exclusive hypotheses could explain the observed selectivities: the first could be a fast equilibrium between *Z* and *E* form of the intermediate carbenoid. One of the isomers would be the kinetic product, whereas the other one would gradually form, being the thermodynamically favored one. The second hypothesis is based on the particular reactivity of organolithium species associated to their aggregation state. This state strongly depends on the chemical environment, including solvents, additives,...^{13,14} For example, *n*-BuLi is hexameric in hexane whereas it is found under a mixture of tetramer/dimer in THF. It could be postulated that, depending on the quality of mixing, the chemical environment of lithiated species will be of various composition. In the worst case laminar regime and bad mixing would force THF and

hexane to flow side by side as well defined domains, whereas in the best case of perfect mixing, the whole solution would be homogeneous before reaction occurs. This would have a deep impact on the aggregation state of organolithium species *n*-BuLi and/or carbenoid **A** eventually modifying their reactivity. In order to check this, several experiments were performed by using the same solvent for the two streams. With hexane as common solvent (and *i*-PrOH used as protic quench to keep the reaction mixture homogeneous), the system immediately clogged whatever the angle of micromixer, probably due to LiBr precipitation. Preparing a solution of *n*-BuLi in THF proved very challenging, as THF solutions of *n*-BuLi are prone to rapid degradation at room temperature.^{15,16}

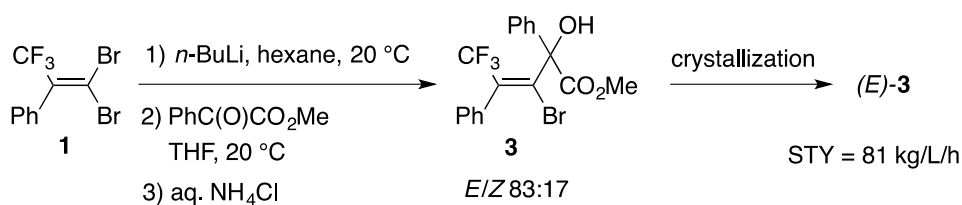
The equilibrium hypothesis, on the other hand, was ruled out by dedicated experiments: a microflow set-up was implemented with fixed flow rate $Q_{(1+n\text{-BuLi})}$ (9 mL/min) and micromixer ($\theta = 90^\circ$, ID = 500 μm), and only the length of the reactor tube was modified (with fixed ID = 500 μm ; Scheme 3).



Scheme 3. Evolution of *E/Z* ratio of **2** according to time in a flow set up.

With $L = 3$ cm ($t^R = 40$ ms), 6 cm ($t^R = 80$ ms) and 9 cm ($t^R = 120$ ms), full conversion into **2** was observed with almost no evolution in the *E/Z* ratio over time. Thus, it seems unlikely that the variations of stereoselectivity observed in a similar reaction time in experiments with various micromixers stems from a purely thermodynamic driven isomerization.

Finally, the potential of this set-up for the synthesis of functionalized scaffolds was assessed by trapping a solution of methyl benzoylformate in THF as an electrophile under best previous conditions reported in Table 3, entry 7. The reactor outlet was then collected into a flask containing methanol to afford product **3** (Scheme 4).



Scheme 4. Synthesis of compound (*E*)-**3** under microflow conditions (see Supporting information for details).

This reaction offered a >99% conversion of **1** with a 95% selectivity for **3** (*E/Z* ratio 84:16). Collecting the reactor outlet for 3 minutes followed by crystallization of the crude product yielded 338 mg of pure (*E*)-**3** with a productivity of 6.7 g/h and a high space-time yield (STY) of 81 kg/L/h due to the very small sizing of the global microreactor (83 μL).

CONCLUSION

In conclusion, we have studied the stereoselectivity of lithium-bromine exchange on a *gem*-dibromo alkene in a microflow system with sixteen passive mixers with eight different angles (from 135 to 30°) and two internal diameters (500 and 250 μm). The 45° W-shaped mixer with thinner ID gave the best selectivity for the *E*-monobrominated product at 20 °C at various flow rates. It is assumed that this effect stems from an excellent mixing of the two streams of *n*-BuLi and substrate and therefore disaggregate the organolithium species. Under these conditions, it is

possible to access to functionalized compounds with controlled geometry and very high space-time yield.

ASSOCIATED CONTENT

The Supporting Information is available free of charge:

Experimental and analytical details (PDF)

Design of micromixers (PDF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: julien.legros@univ-rouen.fr

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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