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Magnetically Driven Agitation in a Tube Mixer Affords Clog-Resistant Fast Mixing Independent of Linear Velocity

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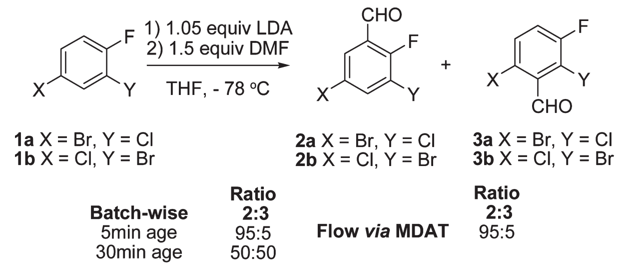

An economical and simple flow mixer based on magnetically driven agitation in a tube (MDAT) is reported. Mixing via MDAT compared favorably to both Tee and multilaminar mixers at low flow and was successfully used to screen and optimize two challenging organometallic reactions at low temperature without clogging or the need for high dilution.

Flow chemistry has been a topic of considerable recent interest[1] with many reports of the utility of microchannel mixers. The degree of mixing afforded by such mixers is highly dependent on the linear velocity of the fluid through the reactor, with fast mixing being observed only at the highest flow rates.[2] This dependence of mixing on flow rate is especially problematic, as researchers often adjust the residence time of reagents within a reaction zone by changing reagent flow rates, a change that also alters mixing behavior. The advantage of these microchannel-based systems over batch continues to be a controversial subject.[3] Furthermore, these systems are prone to clogging even when using seemingly homogeneous solutions, and require >1 s for complete diffusive mixing in nonturbulent flow.[4] While the issue of clogging can sometimes be addressed through dilution, this approach results in both longer processing times and greater solvent volumes, a negative impact on the product mass intensity and environmental impact of the process.[5] To support the overarching goal of rapid scale up of continuous processes, with minimal development efforts, we desired a more suitable format for small-scale experimentation (<1 g of starting material).

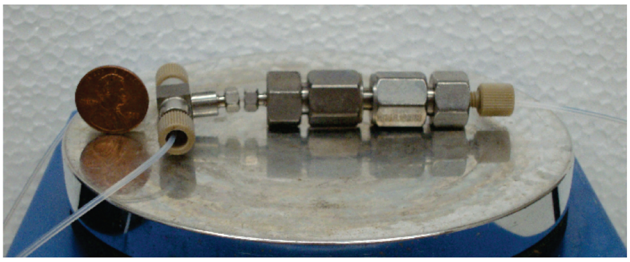

FIGURE 1. Magnetically driven agitation in a tube (MDAT) mixer.

We sought a simple mixer for small-scale screening that would afford fast mixing independent of flow rate, yet resist clogging. Inspired by early HPLC solvent mixing work that utilized agitation via magnets in stainless-steel tubing,[6] we placed two small magnets inside an empty HPLC column, which was connected to a Tee mixer (500 μm). Placement of this tube over a magnetic stir-plate afforded the magnetically driven agitation in a tube (MDAT) apparatus illustrated in Figure 1. Characterization of the mixing time in the MDAT mixer was accomplished via the fourth Bourne competition reaction (Scheme 1),[7] an experimental protocol that compares the rate of acid-catalyzed hydrolysis of 2,2-dimethoxypropane (DMP) to methanol vs neutralization of NaOH with HCl. If the mixing time is faster than the reaction time, minimal methanol is produced, as the rate constant for neutralization ($k_1 = 1.4 \times 10^8$ (m^3/mol)/s) is several orders of magnitude greater than that for hydrolysis ($k_2 = 0.6$ (m^3/mol)/s).[8,9] We compared three different mixers: (1) a multilaminar mixer (possessing 50 μm channels (Institut für Mikrotechnik Mainz, GmbH), (2) a 500 μm Tee mixer

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[1] Some recent publications include: (a) Illg, T.; Lob, P.; Hessel, V. *Bioorg. Med. Chem.* **2010**, *18*, 3707. (b) Ye, X.; Johnson, M. D.; Diao, T.; Yates, M. H.; Stahl, S. S. *Green Chem.* **2010**, *12*, 1180. (c) Kockmann, N.; Gottsponer, M.; Zimmerman, B.; Roberge, D. *Chem.—Eur. J.* **2008**, *14*, 7470. (d) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2009**, *48* (45), 8547. (e) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem., Int. Ed.* **2009**, *48* (22), 4017. (f) Odedra, A.; Seeberger, A. *Angew. Chem., Int. Ed.* **2009**, *48* (15), 2699. (g) Gross, T. D.; Chou, S.; Bonneville, D.; Gross, R. S.; Wang, P.; Campopiano, O.; Ouellette, M. A.; Zook, S. E.; Reddy, J. P.; Moree, W. J.; Jovic, F.; Chopade, S. *Org. Process. Res. Dev.* **2008**, *12* (5), 929. (h) Carter, C. F.; Lange, H.; Ley, S. V.; Baxendale, I. R.; Wittkamp, B.; Goode, J. G.; Gaunt, N. L. *Org. Process. Res. Dev.* **2010**, *14* (2), 393.

[2] (a) Yoshida, J.-I. *Flash Chemistry*; John Wiley & Sons: New York, 2008; pp 105−135. (b) Yoshida, J.-I. *Chem.—Eur. J.* **2008**, *14* (25), 7450.

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[4] Falk, L.; Commenge, J. M. *Chem. Eng. Sci.* **2009**, *65*, 405.

[5] (a) Chin, P.; Barney, W. S.; Pindzola, B. A. *Curr. Opin. Drug Discovery Dev.* **2009**, *12* (6), 848. (b) Hessel, V. *Chem. Eng. Technol.* **2009**, *32* (11), 1655.

[6] Gugger, R. E.; Mozersky, S. M. *Anal. Chem.* **1973**, *45* (8), 1575.

[7] (a) Bladyga, J.; Bourne, J. R. *Turbulent Mixing and Chemical Reaction*; John Wiley & Sons: New York, 1999. (b) Bladyga, J.; Bourne, J. R.; Walker, B. *Can. J. Chem. Eng.* **1998**, *76*, 641.

[8] Johnson, B. K.; Prud'homme, R. J. *AIChE J.* **2003**, *49*, 2264.

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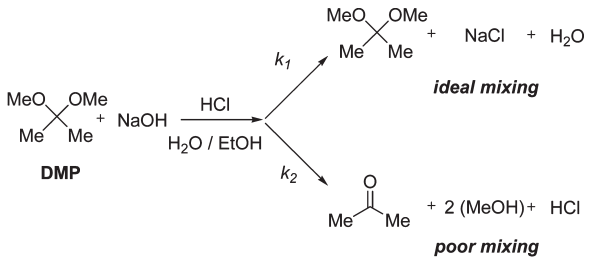
SCHEME 1. Fourth Bourne Competition Experiment



(UpChurch Scientific), and (3) the MDAT mixer placed on an IKA RCT basic ICAMAG magnetic stirrer at 1200 rpm. As illustrated in Figure 2, a strong dependence of mixing time on flow rate was exhibited by the Tee mixer while both the multilaminar and MDAT mixers showed less dependence. Furthermore, the data suggest that the MDAT system was able to achieve more rapid mixing at a lower flow rate than the multilaminar mixer. We postulate that mechanical energy added by the tumbling stir bars is responsible for this improved mixing efficiency. As expected, turning off the magnetic stirrer results in very poor mixing via the MDAT that is considerably worse than that observed with stirring.

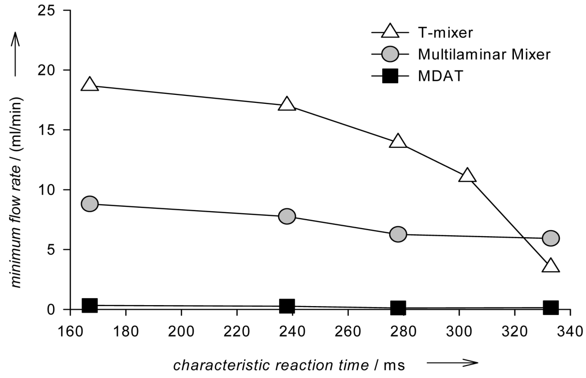
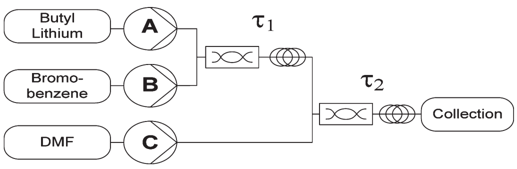


FIGURE 2. Required flow rates for complete mixing.

TABLE 1. Flow Synthesis of Benzaldehyde[a]



entry	mixer arrangement	τ_1[b] (s)	flow 1 (mL/min)	τ_2[b] (s)	flow 2 (mL/min)	conv[c] (%)
1	Tee, Tee	24	0.75	14	1.27	62
2	Tee, Tee	12	1.50	7.0	2.54	52
3	Tee, Tee	6.0	3.00	4.0	5.08	71
4	Tee, Tee	3.0	6.00	2.0	10.17	100
5	Tee, MDAT	24	0.75	14	1.27	35
6	Tee, MDAT	12	1.50	7.0	2.54	24
7	Tee, MDAT	6.0	3.00	4.0	5.08	78
8	Tee, MDAT	3.0	6.00	2.0	10.17	99
9	MDAT, MDAT	24	0.75	14	1.27	100
10	MDAT, MDAT	12	1.50	7.0	2.54	100
11	MDAT, MDAT	6.0	3.00	4.0	5.08	99
12	MDAT, MDAT	3,0	6.00	2.0	10.17	100

[a] All reactions run at −78 °C. Solution A: 2.5 M BuLi in hexane. Solution B: 0.5 M bromobenzen in THF. Solution C: 1.0 M DMF in THF. [b] Residence times in holding coils. [c] Conversion of bromobenzene to benzaldehyde, as determined by HPLC.

At cryogenic temperatures the Einstein−Stokes equation predicts that the solute diffusion coefficient will be decreased.[10] Therefore, results obtained with use of the rt fourth Bourne reaction cannot be directly translated to low-temperature operation. We chose to investigate the cryogenic synthesis of benzaldehyde from bromobenzene as a model for such low-temperature syntheses. A flow reactor was fashioned by linking two mixers in series, using various combinations of the multilaminar, MDAT, and Tee mixers. Unfortunately, all attempts to include the multilaminar mixer at either position resulted in clogging when used at −78 °C with 2.5 M butyllithium and 1.0 M bromobenzene;[11] thus only results for combinations of the T and MDAT mixers are shown. Series arrangement of two T mixers (Table 1, entries 1−3) afforded incomplete conversion at −78 °C for flow rates ≤3 mL/min. When the more rapid flow rate of 6 mL/min was used, complete conversion was obtained (entry 4). Similarly, when a T mixer was used in the first position (for metal−halogen exchange) followed by the MDAT for the second position (electrophilic quench) conversion was incomplete at flow rates ≤3 mL/min (entries 5−7) but complete for 6 mL/min (entry 8), a result of mixing-dependence on flow-rate with the Tee mixer. In contrast, when the MDAT mixers were used for both positions, > 99% conversion was obtained for all flow rates tested (entries 9−12). These observations point to the superior mixing efficiency of the MDAT vs Tee mixers across a range of cryogenic flow rates.

We next investigated the use of the MDAT mixer to address an actual synthetic chemistry challenge involving a kinetically favored, but thermodynamically unstable, reactive intermediate. Regioselective lithiation of arene **1a** followed by trapping with DMF was expected to afford aldehyde **2a**.[12] However, treatment of commercially available **1a** with LDA at −78 °C, followed by aging the incipient aryllithium for 30 min, and addition of DMF afforded an equimolar mixture of the desired product **2a** and the regioisomeric aldehyde **3a**. When deprotonation and quench operations were carried out within <10 min (Table 2, entries 1 and 2) a 90:10 ratio of the desired aldehyde was

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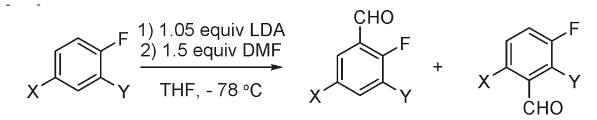
(9) Characteristic mixing time can be identified when mixing and reaction time are equivalent. For the fourth Bourne reaction, the mixing time equals the reaction time, defined as $\tau_{\mathrm{rxn}} = 1/(k_2[\mathrm{DMP}])$, when 4% conversion of DMP to methanol is achieved for the slower reaction. The half-life for reaction of caustic with HCl is on the order of a few nanoseconds while the half-life for DMP hydrolysis is in milliseconds. Since DMP is in solution with a slight excess of caustic, the hydrolysis of DMP by acid to generate acetone and methanol can only take place if segregation of fluid takes place, and the excess caustic is neutralized by a local excess of acid.

(10) Nguyen, N.-T. *Micromixers − Fundamentals, Design and Fabrication*; William Andrew Publishing: New York, 2008.

(11) Successful use of microreactors at cryogenic temperatures has been reported; however, examination of experimental details reveals conditions involved high dilution. (a) Usutani, H.; Tomida, Y.; Okamoto, H.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2007**, *129* (11), 3046. (b) Nagaki, A.; Kim, H.; Yoshida, J.-I. *Angew. Chem., Int. Ed.* **2009**, *48* (43), 8063.

(12) For regioselective lithiations adjacent to fluorine, see: (a) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7495. (b) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7499.

TABLE 2. Batch Deprotonation/Quench Experiments on Polyhaloarene 1[a]



1a X = Br, Y = Cl
1b X = Cl, Y = Br

2a X = Br, Y = Cl
2b X = Cl, Y = Br

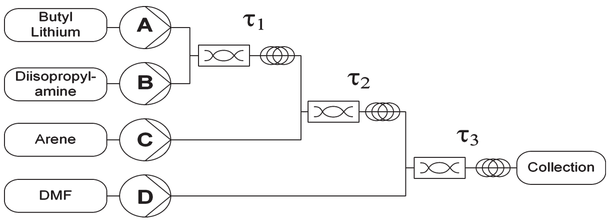
3a X = Br, Y = Cl
3b X = Cl, Y = Br

entry	substrate	ArLi age[b] (min)	ratio **2**:**3**[c]
1	**1a**	5	95:5
2	**1a**	10	90:10
3	**1a**	30	50:50
4	**1b**	5	95:5
5	**1b**	30	50:50

[a] Reaction conditions: *n*-BuLi added to *i*Pr_2NH in THF at −78 °C, followed by 10 min age; polyhalobenzene **1** was added to this solution, keeping the internal temp < −70 °C. After the age time indicated, DMF was added and the solution was warmed to 22 °C. [b] Time aryllithium aged prior to addition of DMF. [c] Determined by HPLC.

obtained. Conversely, extended aging afforded an equimolar mixture of **2a** and **3a** (entry 4). These results clearly suggested that batch-wise preparation of significant quantities of aldehyde **2a** would be challenging, as maintenance of cryogenic conditions would require slow addition of LDA (≫5 min). We initially fashioned a flow reactor by series arrangement of two Tee mixers (500 μm), but were disappointed to observe incomplete conversion even after 1 min residence time. Small-scale (0.25 mL **1a**) batch experiments proved that both deprotonation of **1a** and DMF-quench are complete within 30 s at −78 °C if mixing is sufficient. When the Tee mixers were replaced with multilaminar mixers all attempts to run the transformation below −50 °C resulted in clogging.

TABLE 3. Flow Experiments with MDATs on Arene 1a[a]



entry	flow rates for pumps A, B, C, D (mL/min)	time[b] τ_1, τ_2, τ_3 (s)	conv (%)	ratio[c] **2a**:**3a**
1	0.104, 0.052, 0.260, 0.260	64, 60, 44	89	96:4
2	0.104, 0.052, 0.260, 0.260	160, 60, 44	94	95:5
3	0.208, 0.104, 0.520, 0.520	80, 30, 22	93	93:7

[a] All reactions carried out at −78 °C. Solution A: 1.25 M *i*Pr_2NH in THF. Solution B: 2.5 M BuLi in hexane. Solution C: 0.5 M arene in THF. Solution D: 1.0 M DMF in THF. [b] Residence times in holding coils. [c] Determined by HPLC.

In contrast, when MDAT mixers were used in the reactor setup, we were able to generate LDA, treat with arene, and quench with DMF in one continuous and clog-free system. Our initial attempt afforded excellent regioselectivity (96:4), but incomplete conversion (Table 3, entry 1). Some desbromo-product was also observed, suggesting incomplete LDA formation. Upon increasing the length of the reactor zone for LDA generation (Table 3, entry 2) nearly 95% conversion was obtained while maintaining excellent selectivity of **2a**:**3a** (95:5). We were pleased to find that use of the MDAT mixing elements in the flow-reactor facilitated rapid mixing, yet remained resistant to clogging, even after several hours of continuous operation. Moving to even more rapid flow rates, we saw a slight loss in both conversion and selectivity. Utilizing optimized conditions (Table 3, entry 3), we were able to produce material with excellent regioselectivity in 84% crude yield, with a ratio of 95:5 for the desired isomer.

In a related study, the aryllithium derived from polyhalobenzene **1b** was also found to undergo rearrangement upon aging. While a 95:5 ratio of **2b**:**3b** is obtained upon rapid quench, longer aging significantly degrades that ratio (Table 2, entries 4 and 5). We were pleased to find that use of the optimized conditions for production of **2a** (flow rates noted for Table 3, entry 2) for the MDAT-based flow reactor also worked successfully for production of polyhalobenzaldehyde **2b**, affording an 84% yield, with < 7% isomer **3b** observed.

In summary, we have developed a general, economical, and simple mixer based on magnetically driven agitation in a tube (MDAT). This mixer provides clog-resistant, flow rate-independent, fast mixing that is superior to both simple Tee mixers and multilaminar mixers as evidenced by studies using the fourth Bourne reaction. Importantly, we have successfully used these mixers to perform several metal−halogen exchange/electrophile quench reactions at cryogenic (−40 °C) temperatures, *without* clogging or the need for high dilution. The MDAT mixer offers a significant advance over conventional approaches, and provides an inexpensive and simple way to test reactions using continuous flow reactors.

Experimental Section

Flow Reactor Setup (Used for Synthesis of 2a and 2b). For the reactor 1/16 in. outer diameter, 0.04 in. inner diameter, 316 stainless-steel (SS) tubing was used; all MDATs and SS tubing reactors were submerged in a CO_2/acetone bath to hold the internal temperature below −78 °C. Solutions A and B were flowed into an MDAT connected to 1000 μm ID SS tubing (R_1, variable length and volume) to form reactor 1 with residence time τ_1. This tubing was connected to a second MDAT through which solution C was introduced, and the resultant mixture aged via passage through SS tubing (R_2, variable length and volume), for τ_2. This tubing was connected to a third MDAT through which solution D was introduced, and the resultant mixture aged via passage through SS tubing (R_3, variable length and volume), for τ_3. The output solution was collected into vials precharged with a 12% water−AcOH/MTBE mixture in order to immediately halt the reaction. Commercial *n*-butyllithium (2.5 M in hexane) was used as received; solutions of *i*Pr_2NH, **1a**/**1b**, and DMF were prepared in volumetric flasks from inhibitor-free anhydrous THF (KF < 200 ppm).

Organometallic Flow Reaction. Stock solutions were pumped through the reactor described above ($R_1 = R_2 = R_3 = 0.5$ mL) at optimized flow rates (as detailed in Table 3) and collected into a flask precharged with a 12% water−AcOH/MTBE mixture. After collection was complete, the biphasic mixture was separated and the organic layer washed twice with water, followed by saturated $NaHCO_3$. The solution was passed through solkafloc, concentrated in vacuo to afford a slowly crystallizing oil. Analysis was performed by HPLC versus standards prepared from batch reactions.

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Supporting Information Available: Full details of reactor setup, experimental procedures, analytical data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.