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Disposable Cartridge Concept for On-Demand Synthesis of Turbo Grignards, Knochel-Hauser Amides and Magnesium Alkoxides

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Abstract

Magnesium organometallic reagents occupy a central position in organic synthesis. Freshness of these compounds is key for achieving high conversion and reproducible results. Common methods for the synthesis of Grignard reagents from metallic magnesium present safety issues and exhibit batch-to-batch variability. Tubular reactors of solid-reagents combined with solution phase reagents enable the continuous-flow preparation of organomagnesium reagents. The use of stratified packed bed columns of magnesium and lithium chloride for the synthesis of highly concentrated turbo Grignards is reported. A low-cost pod-style synthesizer prototype, which incorporates single-use prepacked perfluorinated cartridges and bags of

reagents, for the automated on-demand lab-scale synthesis of carbon, nitrogen and oxygen turbo magnesium bases is presented. This concept will provide access to fresh organomagnesium reagents on a discovery scale and will do so independent of operator's experience in flow and/or organometallic chemistry.

Keywords

Turbo Grignard Reagent; Knochel-Hauser Base; Magnesium; Lithium chloride; On-demand; Packed bed reactors; Plug and flow reactor; Synthesizer

Introduction

Flow chemistry has facilitated: (1) New application of high-energy or otherwise unsafe chemistry[1] – enabled by controlled/rapid heat removal and generation and immediate use of unstable species;[2] (2) Flash chemistry where rapid mixing can outcompete unimolecular side reactions;[3] (3) New chemistry by conducting reactions outside normal operating pressures and temperatures;[4] (4) New opportunities for the realization of automated chemistry including on-demand systems.[5] We have recently focused on systems where solid-reagent cartridges are combined with a solution phase reagent including: (1) Copper(I) oxide to produce N-heterocyclic carbene-Cu(I) complexes for use as catalysts;[6] (2) Proline to perform proline-based catalytic reactions;[7] (3) Zinc powder to produce organozinc halides in tandem with Negishi-couplings;[8] (4) Zinc-complexes to produce fluorescent species;[9] (5) Sodium borohydride to reduce carbonyls;[10] (6) Red phosphorous to produce polyphosphides.[11] Our initial foray into this area was born out of necessity. We wanted to conduct flow reactions that required solids and packed-beds facilitated use of solids without clogging. More recently, we began to think about this combination for

producing air and water sensitive reagents immediately prior to use. In particular, we were interested in addressing a dichotomy where discovery-scale (50-100mL) organometallic reagents are used with uncertain characteristics as opposed to large-scale where specs are often defined for all reagents including organometallics. The hypothesis is that unstable/unsafe reagents can be synthesized and used as needed for this discovery-scale instead of purchasing stock solutions that arrive with uncertain properties and require titration to determine concentrations.

Both commercial and academic flow systems are commonly oriented to experienced flow chemists and are designed to maximize versatile operation to explore a broad range of chemical transformations.[5c,12] These systems are designed to achieve generality of operation; this comes with an increase in cost and complexity of the instruments. Our on-demand approach targets the opposite end of the equipment design spectrum, it requires a low-cost systems designed to carry out only a few specific functions in a safe and robust manner; it also demands to be low cost in order to have any potential for real world application. In other words, to achieve the set goals, innovation is needed to reduce complexity/expense of (1) pumps; (2) reactors; (3) valves; (4) fittings and (5) chemical containers. The design presented here is based on a disposable cartridge concept, inspired by pod-based coffee machines (Figure 1). We take inspiration from recent efforts that demonstrate simple machines can do valuable chemistry.[5d] Our “cartridge” encompasses reagent bags, tubing, packed bed columns of solid reagents and product receptacle. These components are deployed in a low cost machine with design amenable for the automated lab-scale generation of organomagnesium reagents on-demand (Figure 1).

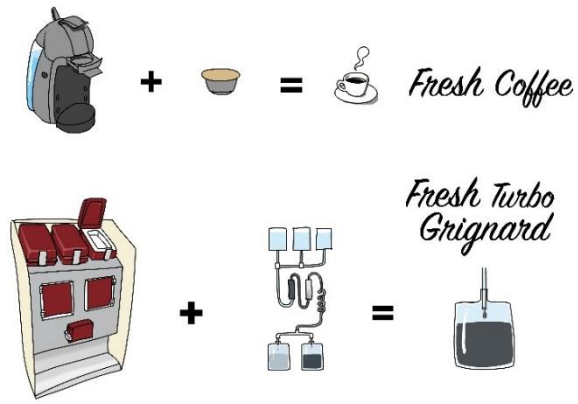


Figure 1: Comparing On-Demand Coffee and Turbo Grignard Pod-Style Machines.

Organomagnesium compounds are omnipresent reagents that serve as nucleophiles and bases. Grignard reagents react with oxygen and water yielding flammable gases and must be prepared, stored and handled under anhydrous inert atmosphere. Time consuming titration is recommended but is unreliable as only basicity is estimated. Freshness of these solutions is key for achieving high conversion because neutralization can alter aggregation states producing significant batch-to-batch variability. Direct insertion of magnesium metal with organic halides is the most common method used to prepare Grignard reagents but present difficulties: (1) sluggish reaction with ordinary magnesium turnings;[13] (2) formation of undesired byproducts by thermal decomposition and exothermic reaction not suitable for industrial processes;[14] (3) activation of metallic surface is required and can introduce safety issues due to the high reactivity of activated metal.

Flow chemistry technologies and cartridges containing activated metals can solve most of these issues: (1) The use of activated magnesium powder packed in a column increases reaction rate and facilitates safe separation of the metal and reagent solution; (2) Efficient heat transfer (large surface area to volume ratio) provides thermal control during metal activation and generation of concentrated organometallic

solutions; (3) Control over residence time reduces byproducts because the organometallic solution is not exposed to high temperatures longer than necessary. All these advantages allow a more straightforward production and use of these critical reagents.

Preparation of organozinc species using zinc-packed bed columns[8,15] provide examples of the progression toward on-demand synthesis of other organometallic reagents. While the concept of a reactive packed-bed is not new, many features must be considered and solved for success including: (1) The column packing – making sure the particle size range and how the column is packed provides a system with minimal channeling; (2) Selecting a column with the right properties such as materials of construction, pressure tolerance, heat conduction and diameter/particle size matching; (3) Column orientation and set-up – filters, etc.; (4) Activation of the solid phase. The activation issue is one of the most important when considering metal packing. Although our team had success with zinc packing, we still need to develop a new approach for magnesium. Magnesium when activated is more reactive compared to zinc due in part because magnesium is a stronger reducing agent than zinc. Beyond considerations of the packing, column and activation, the solubility of organomagnesiums is often lower than the corresponding zincates. The low solubility can clog the column or may reduce the insertion rate by forming a passivating layer over the metal particle surface.

Only five examples describe the production of organomagnesium species under flow conditions,[16] and only two use a practical system with a broad range of substrates.[17] The Alcázar group reported the generation and subsequent use of Grignard reagents.[17a] The most recent example, by the Loren group, extended organozinc reagents scope made in flow to aryl and tertiary alkyl halides by in situ

formation of the corresponding Grignard intermediate in presence of $ZnCl_2$ and LiCl, which are subsequently used in Negishi cross-coupling reactions.[17b]

However, in these publications, alkyl chloride substrates, which are generally more cost-effective than the corresponding bromide or iodide, are limited only to two compounds: 4-chloro-1-methylpiperidine and 3-(chloromethyl)-3-methyloxetane. Also, the use of LiCl solution as the reaction media to increase Grignard solubility was prepared from hygroscopic LiCl which implies thorough drying and storage under moisture-free atmosphere. Finally, concentration of Grignards were limited, in the range of 0.3 – 0.5 M, thereby limiting the discovery chemist's range of reaction conditions. In this study, we started selecting some of the most used organomagnesium halides in synthesis. For this purpose, a ranking of the 20 most cited as measured by citation value obtained from SciFinder was constructed (Figure 2). Based on our analysis, methyl, ethyl, isopropyl, butyl, benzyl and phenyl as the R group were selected as test cases for our proposed system.

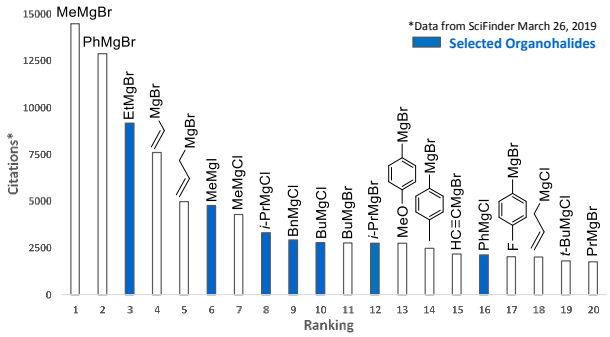


Figure 2: Ranking of the 20 Most Cited Grignard Reagents (SciFinder March 26, 2019).

Over the last two decades, Knochel demonstrated lithium chloride (LiCl) benefits on halogen-magnesium exchange rates[18] and on organomagnesium solubility.[19] The most known example of this class is isopropylmagnesium chloride lithium chloride

complex (*i*-PrMgCl•LiCl), known as turbo Grignard.[20] In addition to being widely cited, turbo Grignard is a popular discovery-scale tool in the pharmaceutical industry[14] and has shown excellent selectivity on large scale.[21] Halomagnesium amides LiCl adduct, e.g. Knochel-Hauser base (TMPMgCl•LiCl), are also useful reagents for selective deprotonation due to their strong basicity and low nucleophilicity.[22] Knochel-type alkoxides,[23] e.g. 2-methyl-2-propoxymagnesium chloride lithium chloride complex (*tert*-AmylOMgCl•LiCl), are less common in synthesis but their high reactivity and solubility combined with a high tolerance towards functional groups made them advantageous for selective transformation.

Herein, a novel disposable cartridge approach for on-demand, discovery-scale preparation of turbo Grignard reagents, Knochel-Hauser bases and new Knochel-type alkoxide using a stratified bi-component packed bed column of magnesium and lithium chloride is presented. Critical insights such as column packing, particle size, metal excess, reagent scope, order of addition, column stability, reproducibility and consideration of solid-liquid reaction models are presented. In addition, a proof of concept, automated pod-type synthesizer prototype designed to generate up to 100 mmol of fresh reagents on-demand is described. Our objective is to help others integrate this approach into their quotidian workflow to enable discovery-scale researchers increase the reliability of their developed routes and processes by increasing the quality of their organomagnesium reagents.

Results and Discussion

1. On-Demand Reagent Prototype.

Objective: To design and create a simple, robust, disposable and low cost system capable of producing on-demand reagents for lab-scale purposes using a combination of liquid and solid pods or cartridges. We envisioned a system that required: (1) pumps; (2) tubular reactors; (3) valves; (4) fittings and (5) chemical containers.

Challenges: Need to develop new design concepts to achieve low cost (1) high pressure pumps (10 bar); (2) disposable tubular reactors; (3) robust valve; (4) leakproof bonding process and (5) chemically compatible and high pressure containers.

System Design: The pod-style concept is achieved by making the entire fluidic circuit needed to run a specific chemistry with pre-arranged, custom made and thermally bonded parts. Parts were built of fully perfluorinated material providing excellent chemical resistance. We choose thermal bonding because this type of bond can provide a leakproof system without the need of fittings. All the fluidic items and reagents assembled together represent the “cartridge” (Figure 3E). Pre-built disposal cartridges have long shelf life and can be deployed on demand. The instrument we produced provides the necessary pumping (Figure 3A), heating (Figure 3C), and valving (Figure 3B) and united in an enclosed unit that can be loaded with self-contained cartridges (Figure 3E). In order to build the disposable cartridges, we developed bonding protocols to carry out the different types of connections needed (i.e. tube to tube, tube to cartridge, tube to bag, tee, etc…).

Pump concept: Pumping is achieved by developing flexible reservoirs made with perfluorinated polymer film (PFA); the bags are filled with the fluid to dispense. Pumping is accomplished by enclosing the bag in a metal clamshell with contact surfaces made with an elastomer (Figure 3A). When compressed air is pumped in the clamshell, it squeezes the bag through the elastomer thus dispensing fluid. The elastomer sheets fully embrace the reagent bag providing mechanical support, in this way a soft polymer bag can be squeezed at a relatively high pressure: our prototype achieved pumping pressures up to about 1 MPa (10 bar). This type of pressure driven pump, where dispensed liquid is enclosed in a plastic reservoir, provides the advantage of not dissolving any gas into the liquid during operation, which is the case with pressurized tanks. Additionally, all the wetted parts of the pump are fully disposable (Figure 3E). The metering function required to keep constant back pressure and flow rate is achieved by the tubing length and diameter downstream of the pump or by the fluidic network for more complex cases. Flow is pulseless as a result of the fact that is driven by compressed air.

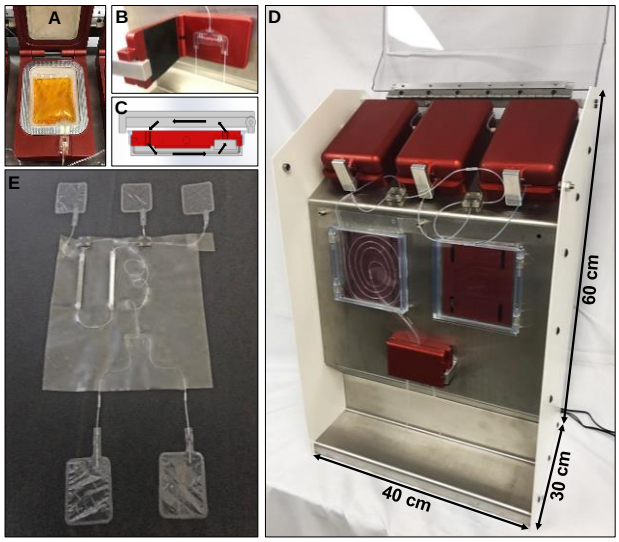


Figure 3: On-Demand Prototype. (A) Inside View of Pump with Flexible Bag Containing Yellow Liquid Laying on Elastomer Membrane. (B) Detail of Manifold Used to Select Waste or Product Collection. (C) Heater Cross Section, Arrows Indicate the

Air Convection Flow Path. (D) Reagents On-demand System Assembled with Coil Reactor Placed in Left Reactor Area. (E) Example of Disposable Cartridge.

On Demand Reagent (ODR) System Design: The ODR prototype (Figure 3D) is essentially composed by three clamshell pumps, in order to have up to three process fluids. Each bag contains valving so that only specified fluids can be dispensed when required by the process. The instrument offers up to two reaction areas made by aluminum plates; convention of air is generated with small fans embedded in the aluminum plate to improve the quality of the heat transfer to the reactor. A manifold (Figure 3B) is placed downstream of the reaction areas, where actuators control the direction of the outcome stream. Solvent priming and activation solution are discarded into waste and only when product is generated the manifold starts to collect. The systems heating, temperature control and valving are controlled by an Arduino card (not shown – on the back of the system). Different control routines can be loaded into the Arduino card as needed.

2. Grignard Reagents via Magnesium Packed-Beds.

Objective: Generate concentrated organomagnesium solutions from alkylhalides using a standardized and reproducible packed-bed of magnesium, develop a consistent activation protocol using a single activation solution and optimize conditions for quantitative organic chlorides conversion.

Challenges: Metal surface activation, organomagnesium solubility, formation of a black byproduct, performance and degradation over time.

System Set-up: A commercial flow chemistry system[24] equipped with a temperature controlled glass manifold reactor[25] was used (Figure S1). We have found that both glass and perfluoroalkoxy alkane (PFA) columns with similar dimensions can be used. To reduce the costs, the flow chemistry system can be replaced by syringe or HPLC pumps and reactor heating can be accomplished using standard heating tools (water/oil bath, heating jacket or suitable oven). The 10 x 100 mm (ID x length) column was filled with magnesium. Back pressure regulator (BPR) was added to prevent gas/liquid separation and increase solvent boiling temperature.

We started reproducing Alcázar's conditions to obtain organomagnesium bromide reagents from the corresponding alkylbromides. Activation protocol was slightly modified, a single activating solution composed by 1-bromo-2-chloroethane, TMSCl and DIBAL-H in THF/toluene was pumped through magnesium powder (98 %; 20–230 mesh) at 1 mL/min and 40 ^{o}C (Supporting Information 1.2.2.). Organomagnesium bromide reagents (15 mL) were generated in THF at 0.5 mL/min flow rate and 25 ^{o}C. For each experiment, concentration was determined in duplicate by reaction with a known mass of two different indicators until color change: 2-hydroxybenzaldehyde phenylhydrazone[26] or a mixture of benzoic acid and 4-(phenylazo)diphenylamine.[27] Iodine also can be used.[28] Similar concentrations were obtained by NMR titration with 1,5-cyclooctadiene as standard (Supporting Information 1.2.10.).[29]

Heat released from the exothermic Grignard reaction was not fully dissipated by the heat exchanger and we decided to measure temperature evolution during the conversion of EtBr 0.5 M at 0.5 mL/min flow rate with no heat controller. Three thermocouples were placed at different points along the glass column (Figure 4 right).

Results showed ~35 ^{o}C increment, which is an underestimation because measurements were taken on the outer surface of the glass column. The data features a hot spot moving upward during the reaction (Figure 4 left) suggesting that magnesium is consumed by layers at 0.5 mL/min flow rate and the reaction occurs almost exclusively at the interphase EtBr-Mg* and not along the whole column. Since reactive interphase moves upward at the same rate that Mg is getting consumed, heat release is not constant along the column and steady state temperature only occurs during a short amount of time at localized area. Even with no temperature control, exothermic Grignard reaction can be controlled under our conditions using a 10 mm internal diameter packed bed column.

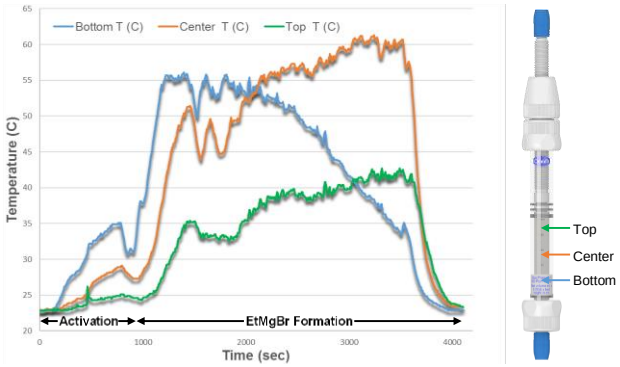


Figure 4: Temperature Evolution Measured With Thermocouples Along the Column Outer Surface at Three Different Points.

During isopropylmagnesium bromide optimization (Table S4), solubility issues hindered the formation of a concentrated solution (> 0.8 M). Crystallization of *i*-PrMgBr in the collection flask forced us to reduce the organic halide initial concentration to 0.9 M, yielding *i*-PrMgBr 0.75 M (82 %; note: yields reported herein refer to the amount of halide converted vs. organometallic reagent produced; no detectable halide is recovered and organometallic reagent purity was high unless otherwise stated.) (Table S4, Entry 3). Reactivity order of organic halide against oxidative addition reaction is R-

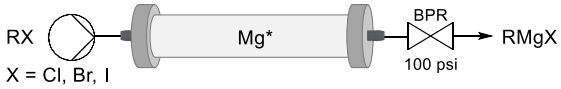
I > R-Br > R-Cl. To achieved direct insertion of 2-chloropropane, the temperature was increased and the best result was obtained at 80 ^{o}C, yielding *i*-PrMgCl 0.78 M (87 %) (Table S4, Entry 7). Since *i*-PrMgCl is more soluble in THF than the corresponding bromide,[30] we were able to use initial concentration up to 2.5 M, yielding to *i*-PrMgCl 2.23 M (89 %) (Table S4, Entry 8). At temperature higher than 60 ^{o}C, 100 psi BPR was required to prevent solvent boiling inside the packed bed column.

During preliminary experiments, we observed the formation of a black residue left after magnesium consumption. While the residue did not affect the column performance for the conversion of 10 mL of *i*-PrCl 2.5 M solution, larger volumes generate increased the pressure drop and eventually clogging of the system. Analysis of the black residue via X-ray Photoelectron Spectroscopy (Figure S6) revealed the presence of magnesium, oxygen, carbon and chlorine. Although we do not understand the mechanism, we sought a solution that would enable column performance to remain constant. During optimization, we tested Mg chips (99.98 %, 6–35 mesh) and observed less black residue. Thus, we explored the reaction using different ratios of Mg chips/powder (Figure S7). We found that Mg 1:1 chip/powder provided more consistent results over relatively large amount (~100 mmol) of organic halide converted. We offer two explanations: (1) the higher purity of Mg chips (99.98 %) and (2) the higher surface area (SA) of Mg powder (~130 mesh) SA ≈ 30 cm^2/g than Mg chips (~20 mesh) SA ≈ 4 cm^2/g. We hypothesize that these features provide a large activated Mg surface for initial quantitative conversion and a purer but less reactive material that generates less byproducts resulting in *i*-PrMgCl yield up to 97 %. The optimal amount of Mg was determined to be 2 equivalents. Yield drop after consumption of 1 eq. of Mg, was first attributed to channeling through the packed bed. We proposed that channeling might be responsible for the evolution of the column. To test this hypothesis, we followed the

changes in the column using 4K webcam for two types of columns: (1) a firmly packed column and (2) a loosely packed column. The well packed Mg column did not consume all the Mg due to channeling (Figure S8A) as we proposed. The loosely packed column to our surprise behaved like fluidized bed, allowing *i*-PrCl to be in contact with a larger surface of Mg (Figure S8B) and provide better performance than a well-packed column: 98 %.

System Scope: Next, we probed the limit of this transformation for primary (bromoethane, bromooctane, chlorobutane and iodomethane), secondary (2-bromopropane, 2-chloropropane and 2-chlorobutane) alkyl halides as well as benzyl (chloromethylbenzene) and aryl (chlorobenzene) chlorides.

Table 1: Reaction of Organic Halides with a Packed Bed Column of Activated Magnesium. Scope of Grignard Reagents Prepared Under Flow Conditions.[a]



Entry	RX	T (C)	Solvent	[RX] (M)[b]	[RMgX] (M)	Yield (%)[c]
1	*i*-PrBr	25	THF	0.9	0.74	82[d]
2	EtBr	25	THF	1.2	1.08	90
3	EtBr	25	2-MeTHF	2.5	2.21	88
4	EtBr	25	Et_2O	2.5	2.39	96
5	*n*-OctBr	25	THF	0.6	0.51	85
6	*n*-OctBr	25	Et_2O	1.2	1.08	90
7	*i*-PrCl	80	THF	2.5	2.38	95
8	*sec*-BuCl	80	THF	2.5	2.23	89
9	*n*-BuCl	80	THF	2.5	2.37	95
10	PhCl	100	THF	2.5	2.32	93
11	BnCl	60	2-MeTHF[e]	1.2	0.99	83[f]
12[g]	MeI	25	Et_2O	2.5	2.36	94

[a] RX solution (20 mL) was pumped at 0.5 mL/min flow rate through a column (ID = 10 mm) of Mg* (2 eq.) chips/powder 1:1 ratio; [b] Quantitative RX conversion; [c] Determined by titration of overall RMgX solution (~15 mL) collected at steady state; [d]

2-methylpropene obtained as mayor byproduct; [e] 10 % of THF; [f] 1,2-Diphenylethane obtained as single byproduct; [g] BPR 140 psi.

Good to excellent yields were obtained (Table 1). In general, bromo-Grignards tend to be less soluble in THF than chloro-Grignards and other ethereal solvents can be more appropriate: 2-methyltetrahydrofuran (2-MeTHF) or diethyl ether (Et_2O). Higher solubility of EtMgBr in these solvents allows us to obtain 2.21 M (88 %) in 2-MeTHF and 2.40 M (96 %) in Et_2O but only EtMgBr 1.08 M (90 %) in THF (Table 1; Entry 2-4). Concentration of *n*-OctMgBr is also limited to 0.51 M (85 %) in THF (Table 1; Entry 5). The use of Et_2O increases solubility up to 1.08 M (90 %) (Table 1; Entry 6). Even chlorobenzene, considered a deactivated specie, was converted to PhMgCl in excellent yield 2.32 M (93 %) (Table 1; Entry 10) heating the column to 100 ^oC. In the case of benzyl chloride, a mixture 2-MeTHF/THF (9:1)[31] was found to be optimal to reduce the formation of Wurtz-type byproduct (1,2-diphenylethane) (Table S5), yielding BnMgCl 0.99 M (83 %) (Table 1; Entry 11). Noteworthy, iodomethane (bp = 42 ^oC) solution in Et_2O can be converted to the corresponding methylmagnesium iodide (MeMgI) in good yield and good mass balance using a 140 psi BPR (Table 1; Entry 12).

3. Turbo Grignards via Stratified Packed Bed Columns Containing Magnesium and LiCl.

Objective: Generate organomagnesium lithium chloride complexes (turbo Grignards) from alkylchlorides using stratified bi-component packed bed column composed of magnesium and lithium chloride.

Challenges: Metal passivation by lithium chloride coating, handling of LiCl (hygroscopic), LiCl equivalent optimization due to solubilization over time.

System Set-up: Same flow system was used as for the generation of Grignard reagents (Figure S2). The 10 x 100 mm (ID x length) column was half filled with magnesium (chips/powder 1:1 ratio) and the second half with anhydrous lithium chloride (Figure 5). The two components were separated by fiber glass previously dried at 120 ^{o}C overnight. A 100 psi back pressure regulator (BPR) was added to prevent gas/liquid separation and increase solvent boiling temperature.

Clogging is a common concern in flow chemistry and during our scope exploration we observed that concentration of organomagnesium reagents generated were mostly limited by their solubility. Knochel pioneered the use of lithium chloride to solubilize organometallic reagents and to increase reactivity most probably due to disaggregation of oligomers.[18,19] We used this approach to overcome the solubility issue under continuous conditions. First, we verified that similar results are achieved in presence and absence of LiCl in solution for EtMgBr formation (Supporting Information 2.2.). Because organomagnesium halide lithium chloride complexes are believed to be RMgX•LiCl 1:1 dimer and considering LiCl solubility limitation of ~0.5 M in THF, we decided to design a new system for the generation of highly concentrated turbo Grignard reagents. Instead of using a solution of starting material and LiCl, a bi-component packed bed column was assembled. First ~4.5 cm of the Omnifit column was filled with magnesium (chips/powder 1:1 ratio) and the upper ~4.5 cm with anhydrous lithium chloride (Figure 5). The two components were separated by fiber glass previously dried at 120 ^{o}C overnight. We first tested this column with EtBr 1.5 M solution and comparable EtMgBr•LiCl concentration was obtained 1.30 M (87 %) (Table 2; Entry 1) in comparison with dissolved LiCl 1.27 M (86 %) (Table S6; Entry 6).

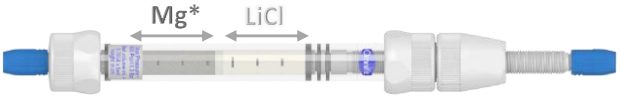
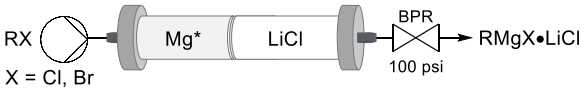


Figure 5: Stratified Bi-Component Column (Diba Omnifit EZ Solvent Plus) Composed of Magnesium (Chips/Powder 1:1 Ratio) and Lithium Chloride Separated with Fiber Glass for Turbo Grignard Reagents Synthesis.

The separation of the two components is crucial to obtain reproducible results. When Mg and LiCl are intimately mixed together, re-activation of the column failed, likely due to magnesium surface passivation. The separation of Mg/LiCl allows reuse of the column several times with different substrates. Nevertheless, we do not recommend its reutilization. For optimal results, 2 equivalents of Mg* (chips/powder 1:1 ratio) and 2 equivalents of LiCl must be used a single time.

System Scope: The bi-component column was employed to obtain turbo Grignard (isopropylmagnesium chloride lithium chloride complex)[20] as well as *sec*- and *n*-butylmagnesium chloride lithium chloride complexes as THF solutions (~10 mL). Very good yields were obtained: *i*-PrMgCl•LiCl 2.19 M (88 %); *s*-BuMgCl•LiCl 2.15 M (86 %) and *n*-BuMgCl•LiCl 2.13 M (85 %) (Table 2; Entry 2-4).

Table 2: Reaction of Organic Halides with a Stratified Packed Bed Column of Activated Magnesium and Lithium Chloride. Scope of Turbo Grignard Reagents Prepared Under Flow Conditions.[a]



Entry	RX	T (C)	[RX] (M)[b]	[RMgX•LiCl] (M)	Yield (%)[c]
1	EtBr	25	1.5	1.30	87
2	*i*-PrCl	80	2.5	2.19	88
3	*sec*-BuCl	80	2.5	2.15	86
4	*n*-BuCl	80	2.5	2.13	85

[a] RX solution (15 mL) in THF was pumped at 0.5 mL/min flow rate through a bi-component column (ID = 10 mm) composed by activated Mg* (2 eq.) chips/powder 1:1 ratio and anhydrous LiCl (2 eq.) separated with fiber glass; [b] Quantitative RX conversion; [c] Determined by titration of overall RMgX·LiCl solution (~10 mL) collected at steady state.

Formation of turbo Grignard reagent (*i*-PrMgCl•LiCl) was scaled up to ~100 mmol using a 15 x 100 mm column and the results were compared with Knochel batch protocol.[32] Using our flow procedure, generation of higher *i*-PrMgCl•LiCl concentration (2.10 M instead of 0.89 M) in shorter reaction time (1.5 h instead of 12 h) causes a 7-fold throughput and 15-fold space-time yield improvement (Table 3).

Table 3: Comparison Between Batch and Flow Conditions for the Synthesis of *iso*-Propylmagnesium Chloride Lithium Chloride Complex (*i*-PrMgCl•LiCl).

***i*-PrMgCl•LiCl**	**Batch**[a]	**Flow**
mmol of 2-chloropropane	100	100
2-Chloropropane concentration (M)	0.92	2.50
Reaction time (hour)	12	1.5
i-PrMgCl•LiCl concentration (M)	0.89	2.10[b]
Conversion of 2-chloropropane (%)	100	100
Throughput (mmol h^{-1})	7	50
Normalized space-time yield[c]	1	15

[a] A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; [b] Propene and 2,3-dimethylbutane as byproducts; [c] Space-time yield (mmol mL^{-1} h^{-1}): batch = 0.065; flow = 0.980.

4. Knochel-Hauser Bases via Stratified Packed Bed Columns Containing Magnesium and LiCl.

Objective: Generate amidomagnesium lithium chloride complexes (Knochel-Hauser Bases) from turbo Grignard formed in situ and the corresponding amine using stratified bi-component packed bed column composed of magnesium and lithium chloride.

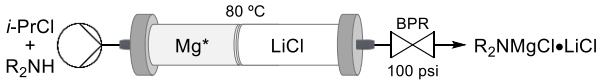
Challenges: Gas formation from amine deprotonation, residence time optimization due to variation in amine and amide properties.

System Set-up: Same flow system was used as for the generation of turbo Grignard reagents (Figure S2). In the case of TMPH, a coil (V = 10 mL; ID = 0.03”) was added downstream to increase residence time (Figure S3).

We synthesized amidomagnesium chloride lithium chloride complexes ($R_2NMgCl•LiCl$) by in situ formation of turbo Grignard in presence of the corresponding amine. The reactions were carried out flowing a *i*-PrCl/amine 1:1 ratio dissolved in THF/toluene 1:1 mixture at 0.5 mL/min flow rate and 80 ºC. Toluene was required to solubilize magnesium amides species. During the process, propane is generated but no overpressure was observed. The flammable gas was released after the BPR together with the $R_2NMgCl•LiCl$ solution in the collection flask, away from a heat source.

System Scope: Bis(trimethylsilyl)amine (HMDS), diphenylamine (Ph_2NH), aniline ($PhNH_2$) and 2,2,6,6-tetramethylpiperidine (TMPH) were selected as substrates. Ph_2NH, HMDS and $PhNH_2$ due to their lower pKa (25, 30 and 31 respectively in DMSO)[33] and TMPH due to its broad application in synthesis (Knochel-Hauser base, pKa = 37 in DMSO).[22a,33,34] Excellent yields were obtained: HMDSMgCl•LiCl 1.15 M (98 %), $Ph_2NMgCl•LiCl$ 1.16 M (97 %) and PhNHMgCl•LiCl 1.15 M (96 %) (Table 4; Entry 1-3).

Table 4: Reaction Between Amines and isoPropylmagnesium Chloride Generated *in Situ*. Knochel-Hauser Bases Synthesis Using a Stratified Packed Bed Column of Activated Magnesium and Lithium Chloride.[a]



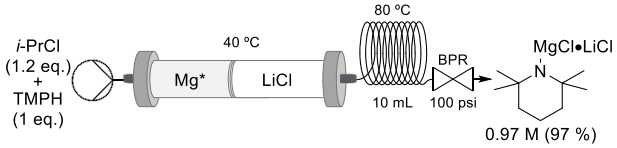
Entry	R_2NH	[RX] (M)[b]	[$R_2NMgX•LiCl$] (M)	Yield (%)[c]
1	HMDS	1.2	1.17	98
2	Ph_2NH	1.2	1.16	97
3	$PhNH_2$	1.2	1.15	96

[a] A 2-chloropropane (1 eq.) and amine (1 eq.) THF/toluene (1:1) 1.2 M solution (30 mL) was pumped at 0.5 mL/min flow rate and 80 ºC through a column (ID = 10 mm) of activated Mg* (2 eq.) chips/powder 1:1 ratio and anhydrous LiCl (2 eq.) separated with

fiber glass; [b] Quantitative RX conversion; [c] Determined by titration of overall $R_2MgCl{\cdot}LiCl$ solution (~25 mL) collected at steady state.

In the case of TMPH, a 10 mL coil (20 min residence time; t_R) was added due to slower reaction rate and the *i*-PrCl amount was optimized to 1.2 equivalents (Scheme 1). Even if the addition of a coil increases the residence time for TMPMgCl•LiCl synthesis up to 25 min, our flow set-up is 9 times faster than the batch version which usually takes 24 h at room temperature.[22a,34h] The reaction was carried out flowing a *i*-PrCl/TMPH 1.2:1 ratio dissolved in THF/toluene 1:1 mixture at 0.5 mL/min flow rate and 80 ºC.

Scheme 1: Continuous Flow Synthesis of TMPMgCl•LiCl with a Stratified Packed Bed Column of Activated Magnesium and Lithium Chloride.



As drawback, we observed LiCl precipitation in the flask ~2 h after collection. Clear solution can be recovered by filtration through dried fiber glass using a cannula without drastic concentration decrease. The same reaction was done in batch using turbo Grignard generated in flow and the same result was observed, proving that LiCl is coming from *i*-PrMgCl•LiCl. Analysis of the precipitate by NMR and GC-MS, after being washed with pentane at 0 ºC and dried under vacuum, showed no evidence of organic compounds. It seemed that TMPMgCl•LiCl coordinates less LiCl than the corresponding *i*-PrMgCl•LiCl and triggers LiCl crystallization. To solve this issue, the packed bed column temperature was decrease from 80 ºC to 40 ºC to reduce the amount of LiCl dissolved in the *i*-PrMgCl•LiCl solution. Under this conditions, we were

able to obtain TMPMgCl•LiCl 0.97 M (97 %) as a solution (~40 mL) that remained clear for much longer (Scheme 1). We suggest to directly react TMPMgCl•LiCl solution in flow or to telescope the reagent in batch with the next step. Knochel-Hauser base was also scaled up to ~100 mmol using a 15 mm ID column. Using our flow procedure, similar TMPMgCl•LiCl concentration was obtained (~1.0 M) compared with Knochel protocol[22a,34h] but reaction time was reduced from 36 h to 4 h providing a 10-fold increment in throughput and space-time yield (Table 5).

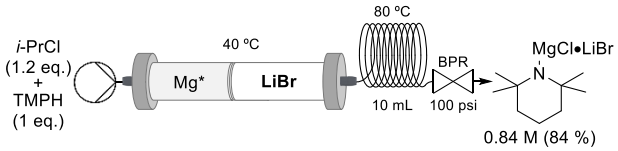
Table 4: Comparison Between Batch and Flow Conditions for the Synthesis of 2,2,6,6-Tetramethylpiperidinylmagnesium Chloride Lithium Chloride Complex (TMPMgCl•LiCl).

TMPMgCl•LiCl	**Batch[a]**	**Flow**
mmol of 2-chloropropane	100	100
2-Chloropropane concentration (M)	1.20	1.20
TMPH concentration (M)	1.05	1.00
Reaction time (hour)	36	4
TMPMgCl•LiCl concentration (M)	1.03	0.97
Throughput (mmol h^{-1})	2	22
Normalized space-time yield[b]	1	10

[a] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; D. Göbel, N. Clamor, B. J. Nachtsheim, *Org. Biomol. Chem.* **2018**, *16*, 4071; [b] Space-time yield (mmol mL^{-1} h^{-1}): batch = 0.016; flow = 0.160.

We also found that LiBr could be used. The reaction was carried out under the same conditions. The high solubility of the LiBr provided solutions that remained clear for days (TMPMgCl•LiBr 0.84 M (84 %); Scheme 2).

Scheme 2: Continuous Flow Synthesis of TMPMgCl•LiBr with a Stratified Packed Bed Column of Activated Magnesium and Lithium Bromide.



5. Alkoxide Bases via Stratified Packed Bed Column Containing Magnesium and LiCl.

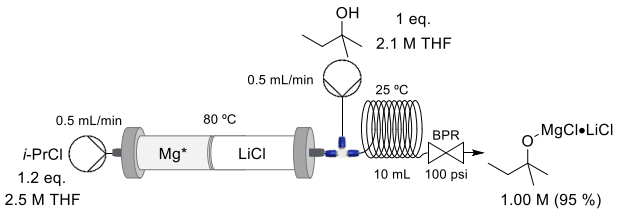
Objective: Generate magnesium alkoxide lithium chloride complexes by telescoped reaction of turbo Grignard with *tert*-amyl alcohol using stratified bi-component packed bed column composed of magnesium and lithium chloride, T-mixer and coil reactor.

Challenges: Alcohol incompatibility with activating solution and alkoxide solubility.

System Set-up: Same flow system was used as for the generation of turbo Grignard reagents. Extra feed was added between the packed bed column and the coil (V = 10 mL; ID = 0.03”) for *tert*-amyl alcohol addition (Figure S4).

Finally, we explored the formation of sterically hindered oxygen bases by direct alcohol deprotonation. Knochel-type *tert*-amyl magnesium alkoxide (*t*-AmylOMgCl•LiCl) 1.00 M (95 %) was obtained (~15 mL) by the reaction of the corresponding alcohol (1.0 eq.) and turbo Grignard (1.2 eq.) under flow conditions at 25 °C (Scheme 3). In the case of *t*-AmylOMgCl•LiCl concentration was determined using a mixture of benzoic acid and thymolphthalein as indicator.[35]

Scheme 3: Continuous Flow Synthesis of *t*-AmylOMgCl•LiCl with a Stratified Packed Bed Column of Activated Magnesium and Lithium Chloride.



6. On-Demand Reagent Proof of Concept.

Objective: To reiterate turbo Grignard and Knochel-Hauser base synthesis on the ODR prototype.

Challenges: Change in reactor material – from reusable glass to disposable perfluorinated columns; and modification in bi-component (Mg/LiCl) configuration – from a single stratified column to two separated mono-component columns.

System Set-up: Internal diameter of perfluorinated tubular reactor used on the ODR prototype was limited to 6.3 mm to maintain efficient heat transfer. Due to this ID limitation and the heater dimensions we decided to separate Mg and LiCl in two tubular reactors.

First, concentration stability at steady state and scalability up to ~100 mmol was verified using two perfluorinated tubular reactors of 9.5 mm (ID) on the Vapourtec flow system. The first column containing Mg was heated at 80 °C using a temperature controlled glass manifold.[25] LiCl column was kept at 25 °C. Concentration was followed over time during the conversion of 2-chloropropane in THF (56 mL; 2.2 M) into *i*-PrMgCl·LiCl (50 mL; 1.91 M) (Figure 6). Ten samples of 5 mL were collected and

concentration was determined by duplicate with 2-hydroxybenzaldehyde phenylhydrazone.

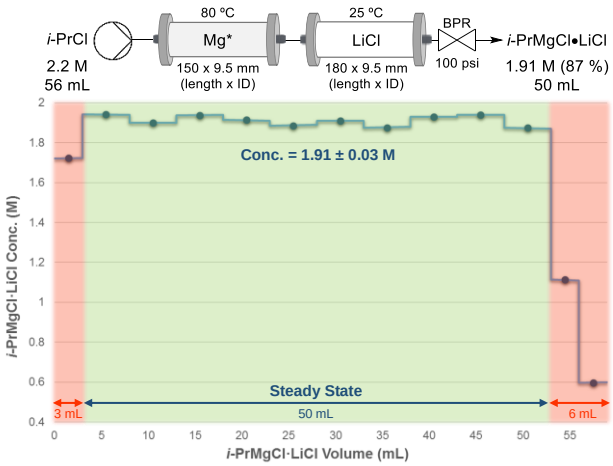
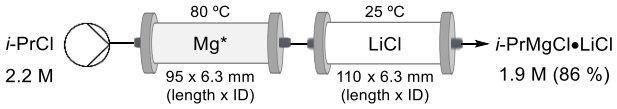


Figure 6: Steady State Concentration Stability during the Conversion of *i*-PrCl in THF (56 mL; 2.2 M) into *i*-PrMgCl·LiCl (50 mL; 1.91 M) using Two Perfluorinated Disposable Mono-Component Tubular Reactors.

Results demonstrate continuous and stable generation of *i*-PrMgCl•LiCl (~100 mmol) at steady state under similar ODR prototype conditions. A certain volume of starting material solution (6 mL) was discarded to prevent dilution of *i*-PrMgCl•LiCl at the beginning and end of the experiment due to solvent diffusion. We stipulate that these results illustrate that our system provides high quality material for the discovery scale needs. This approach is not suitable for large-scale and is not designed to be scaled. The goal is to aid discovery efforts to increase reagent reliability.

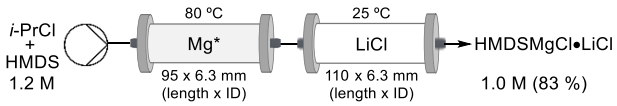
The synthesis of turbo Grignard (*i*-PrMgCl•LiCl) (~10 mL) and Knochel-Hauser base derived from HMDS (HMDSMgCl•LiCl) (~10 mL) were reiterated on the ODR prototype. Similar *i*-PrMgCl•LiCl yield (86 %) was obtained (Scheme 4) using the optimized conditions established on commercial flow system with a single reusable bi-component glass column (Table 2; Entry 2) and with two separated disposable mono-component columns (Figure 6). The cartridge is composed by three solution bags (THF, activating solution and *i*-PrCl solution) and two tubular reactors (Mg chips/powder and LiCl) connected in-series (Figure S5).

Scheme 4: Synthesis of *i*-PrMgCl•LiCl on the ODR prototype.



In the case of HMDSMgCl•LiCl, the same cartridge configuration was used (Figure S5) and slightly lower yield (83 %) was obtained (Scheme 5) compared with the reaction done on the Vapourtec flow system (Table 4; Entry 1). This variation was attribute to unsteady flow rate produced by propane released during the reaction, thus affecting fluid dynamics and back pressure control.

Scheme 5: Synthesis of HMDSMgCl•LiCl on the ODR prototype.



Product purities, *i*-PrCl quantitative conversion and yields were confirmed by NMR (Supporting Information 5.) demonstrating ODR prototype ability to safely produce high quality organomagnesium reagents on demand.

Conclusion

We have developed a new flow setup for the on-demand synthesis of highly concentrated (~2 M) turbo Grignards from alkyl chlorides using a stratified packed bed column of activated magnesium and lithium chloride. The volumes we can produce reliably are consistent for the target discovery-scale audience. Magnesium activation in packed bed column is safer and faster in comparison with batch protocols. LiCl enhances organomagnesium compounds solubility and reactivity, and our moisture free setup makes possible to directly use hygroscopic LiCl in solid form. Back pressure control allows high temperature oxidative addition reaction and enables quantitative conversion of less reactive, but more cost-effective, alkyl chlorides. Furthermore, a low-cost pod-style synthesizer prototype has been designed and built. The reagents are prepacked in disposable perfluorinated assembly – bags, cartridges and tubings – sealed together using a new thermal bonding method. This on-demand concept was demonstrated by preparing turbo Grignard reagent and Knochel-Hauser base (optimized on a commercial flow system). We predict that with small modifications this system could be configured to produce many different reagents. Our group is currently working on an organolithium version of this on-demand reagent approach.

Experimental

Turbo Grignard: isopropylmagnesium chloride lithium chloride complex (*i*-PrMgCl•LiCl). 2-Chloropropane (2.975 g, 3.46 mL, 37.5 mmol, 1 Eq.) is dissolved in THF (11.5 mL) in a flask under argon. Organic halide 2.5 M solution is flowed through a column (ID = 10 mm; length = 100 mm) of activated magnesium (chips/powder 1:1 wt%) (1.86 g, 75 mmol, 2 Eq.) and anhydrous lithium chloride (3.21 g, 75 mmol, 2 Eq.) with BPR (100 psi) at 0.5 mL/min and 80 ^{o}C. After ~4 min, the outcome solution is

collected in a vial under inert containing 2-hydroxybenzaldehyde phenylhydrazone (20 - 40 mg). When the yellow color solution turns orange, turbo Grignard reagent is collected in a flask under argon. When the starting material solution run out, organomagnesium collection is maintained during 4 min (~2 fold the residence time), flowing THF at 0.5 mL/min. Yielding 88 % of isopropylmagnesium chloride lithium chloride complex as clear 2.19 M solution (~10 mL).

Knochel-Hauser Base: Lithium dichloro(2,2,6,6-tetramethylpiperidinato)-magnesate (TMPMgCl•LiCl). 2-Chloropropane (4.284 mg, 4.99 mL, 54.0 mmol, 1.2 Eq) and 2,2,6,6-tetramethylpiperidine (TMPH) (6.420 g, 7.67 mL, 45.0 mmol, 1.0 Eq) are dissolved in THF (16.2 mL) and toluene (16.2 mL) in a flask under argon. Organic halide 1.2 M and amine 1.0 M mixture solution is flowed through a column (ID = 10 mm; length = 100 mm) of activated magnesium (chips/powder 1:1 wt%) (2.23 g, 90 mmol, 2 Eq.) and lithium chloride (3.85 g, 90 mmol, 2 Eq.) at 0.5 mL/min, 40 ^{o}C and atmospheric back pressure. After ~4 min, the outcome solution is collected in a vial under inert containing 2-hydroxybenzaldehyde phenylhydrazone (20 - 40 mg). When the yellow color solution turns orange, the mixture is flowed through the coil at 0.5 mL/min, 80 ^{o}C and 100 psi back pressure. When the starting material solution run out, THF/toluene (1:1) is pumped at 0.5 mL/min to maintain the mixture flowing. After ~20 min, gas released is observed and the outcome solution is collected in a vial under inert containing 2-hydroxybenzaldehyde phenylhydrazone (20 - 40 mg). When the yellow color solution turns orange, the Knochel-Hauser base (TMPMgCl•LiCl) solution is collected in a flask under argon. Organomagnesium collection is maintained during 20 min or until gas release starts to decrease. Yielding 97 % of 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (TMPMgCl•LiCl) solution as clear 0.97 M solution (~40 mL).

Knochel-type Magnesium Alkoxide (*tert*-amylOMgCl•LiCl). 2-Chloropropane (1.983 g, 2.31 mL, 25.00 mmol, 1.2 Eq.) is dissolved in THF (7.7 mL) in a flask under argon. 2-Methyl-2-butanol (1.87 g, 2.32 mL, 21.0 mmol, 1.0 Eq) is dissolved in THF (7.7 mL) in a second flask under argon. Organic halide 2.5 M solution is flowed through a column (ID = 10 mm; length = 100 mm) of activated magnesium (chips/powder 1:1 wt%) (1.49 g, 60 mmol, 2.4 Eq.) and lithium chloride (2.57 g, 60 mmol, 2.4 Eq.) at 0.5 mL/min, 80 ^{o}C and 100 psi back pressure. After ~4 min, the outcome solution is collected in a vial under inert containing

Supporting Information

All details for the flow procedures and reactors assembly (full part list, flow system photos and ODR prototype protocols) and all experimental data of the chemical reactions (optimization, packed bed particle size study and concentration determination) and NMR spectra.

Supporting Information File 1:

File Name: Organomagnesiums On-demand SI v_final

File Format: Word Document

Title: Supporting Information - Disposable Cartridge Concept for On-Demand Synthesis of Turbo Grignards, Knochel-Hauser Amides and Magnesium Alkoxides

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