



## Halogen/lithium exchange in hydrocarbon media; basic and continuous reactor studies

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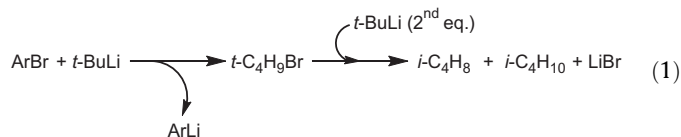
### ABSTRACT

The halogen/lithium (X/Li) exchange's usefulness is challenged by the extreme conditions employed during the conversion of a bromo or an iodo substituent to an organolithium intermediate. Our preliminary disclosure reveals that simple X/Li exchanges can be accomplished at ambient temperature and in doped hydrocarbon media using *n*-BuLi. Use of a continuous reactor featuring brief reaction times ( $\leq 1$  s) and large product throughputs further facilitates the production of a product resulting from a sequential X/Li exchange and nucleophilic addition.

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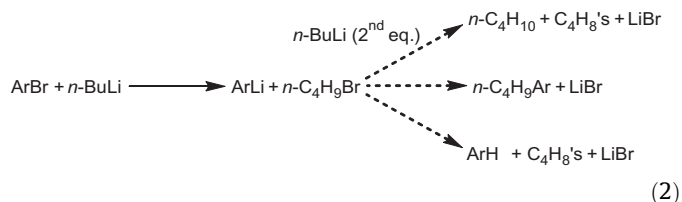
### 1. Introduction

The halogen/metal exchange is a time-honored procedure for regiospecific elaboration of arenes. Pioneered by Wittig<sup>1</sup> and Gilman,<sup>2</sup> the reaction has led to the publication of several review articles<sup>3</sup> and numerous articles describing its utilization. The customary conditions for the reaction ( $-78$  °C, ether media) virtually confine it to the laboratory as these conditions are too hazardous and expensive for scale-up. Added to these problems the customary reagent used for the exchange, *t*-BuLi, and the limitations of the exchange become apparent. Moreover, 2 equiv of *t*-BuLi is usually utilized to ensure a complete exchange (Eq. 1). To sum up, the conditions for the reaction are challenging, ethers are hazardous for several reasons and *t*-BuLi affords significant safety<sup>4</sup> and stoichiometry concerns.



Occasionally, *n*-BuLi is used for the exchange. Here a secondary reaction, namely, aryl substitution (Eq. 2b) can compete even if a second equivalent of *n*-BuLi is used (Eq. 2a). Lastly, loss of the de-

sired ArLi intermediate can occur by the reaction with the initially formed *n*-butylbromide (Eq. 2c). In our hands we find that the elimination reactions (2a and 2c) using *n*-BuLi are much slower (and less competing) than the substitution reaction (2b).



We set forth to establish a safer, greener, and atom-economical way to conduct these types of reactions. Several of our studies on metalations in hydrocarbon solvents illustrated that the activating equivalents of THF served to provide an extraordinary enhancement of the rate and the extent of *ortho*-lithiation.<sup>5</sup> It occurred to us that the ether-doped cyclohexane solutions or cyclohexane solutions themselves<sup>6</sup> might serve as equally viable media to affect X/Li exchange. With only small quantities of ethers present, their hazardous properties (low flashpoint, hygroscopic nature, instability toward alkyllithium reagents, and tendency to form explosive peroxides) would be minimized. We also speculated that the exchange could be run at ambient temperature whereby the need for expensive cryogenic equipment would be obviated. *n*-BuLi was selected for the study under these conditions to avoid the exposure to the dangerous reagent, *t*-BuLi. Lastly, to avoid the side reactions outlined in Eq. 2, short reaction times were examined,

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both in the batch processes and, more effectively, in a continuous reactor that afforded very short reaction times through enhanced mixing and rapid subsequent derivatization.

Our initial study explored the 1:1 exchange by the addition of bromobenzene in cyclohexane to *n*-BuLi at ambient temperature with analysis performed by treating 15 min sequential samples with CITMS (ClSiMe<sub>3</sub>) followed by GC analysis (Table 1). These results in and of themselves were gratifying, in that, better than an 80% average exchange took place at ambient temperature in cyclohexane with minimal formation of the substitution product, *n*-BuPh (runs 1–3). However, these exchange extents were not very reproducible. The relatively modest extent of exchange was attributable principally to lack of consumption of the starting material. Test runs in pentanes and hexanes indicated that the exchange was less efficient in these solvents (runs 4 and 5).

We then graduated to examination of the same system containing accelerating equivalents of THF (Table 2). Significantly higher and consistent exchange results were obtained. An average exchange extent of better than 95% was obtained in the presence of 1.0 equiv of THF (entries 1–4) with slightly lower extents of exchange noted when lower and higher accelerating equivalents of THF were present (entries 6–9). Use of an excess of *n*-BuLi did not provide any enhancement (entry 5). Runs 6–9 suggest that the extent of exchange versus the equivalents of THF in cyclohexane goes to a maximum at around 1.0 equiv THF. Since THF alone is most efficient in supporting the X/Li exchange, there is no obvious reason for THF-doped cyclohexane solutions exhibiting such a maximum. Again minimal formation of *n*-BuPh was noted although the data accrued after longer periods, that is, overnight, as well as an increased equivalent of THF (entry 6) afforded significant quantities of *n*-BuPh. The procedure of adding a 1.0-M solution of PhBr in cyclohexane containing 1 equiv of THF to *n*-BuLi (1.0 M in cyclohexane) at 20–22 °C under N<sub>2</sub> was ultimately adopted for this study. Four additional runs were performed using these conditions with maximum exchange results (typically at 90 min) of 94.4–97.4% along with 0.4–1.5% *n*-BuPh and 1.3–2.9% PhBr remaining unexchanged.

The next system examined was *p*-chlorobromobenzene (Table 3). In three separate small-scale batch processes, addition of the substrate to the *n*-BuLi solution resulted in an average extent of exchange of 96.8%, as determined by GC analysis of the *p*-chlorophenyltrimethylsilane product formed upon trapping with ClSiMe<sub>3</sub>. Side products observed were *p*-*n*-butylchlorobenzene (<1%) and *n*-butylbromobenzene(s) (<1%), the latter arising from the benzyne resulting from the loss of LiCl. Clearly, the order of addition is important for this system as well as for the addition of aryl substrate to the alkyllithium reagent producing superior extents of exchange. The overall reaction concentration was increased to 1.0 M in order to utilize the same flow rates of 2.0 M substrate with the commercial 2.0 M *n*-BuLi in cyclohexane. (Note there is minimal difference in the reaction profile as the concentration is increased.)

**Table 1**

Selected best results for bromobenzene X/Li exchanges in hydrocarbon media at ambient temperature<sup>a</sup>

Run #	Time	PhBr (%)	PhTMS <sup>e</sup> (%)	<i>n</i> -BuPh(%)
1	1.0 h	22.8	76.2	0.5
2	1.5 h	7.8	91.2	0.4
3	1.0 h <sup>b</sup>	13.8	85.5	0.2
4	30 min <sup>c</sup>	33.9	65.8	0.2
5	1 h <sup>d</sup>	32.3	66.1	0.6

<sup>a</sup> PhBr, *n*-BuLi (1:1), cyclohexane, 20–22 °C, 0.5 M.

<sup>b</sup> PhBr, *n*-BuLi each 0.87 M.

<sup>c</sup> Hexane media.

<sup>d</sup> Pentane media.

<sup>e</sup> ClSiMe<sub>3</sub>/GC analysis.

**Table 2**

Effect of equivalents of THF on X/Li exchange in hydrocarbon media at ambient temperature<sup>a</sup>

Entry #	Time	Equiv THF	PhBr (%)	PhTMS <sup>f</sup> (%)	<i>n</i> -BuPh (%)
1	30 min <sup>b</sup>	1.0	3.5	95.5	0.2
2	1.5 h <sup>b</sup>	1.0	1.3	97.4 <sup>g</sup>	0.7
3	30 min <sup>c</sup>	1.0	3.8	95.2 <sup>g</sup>	0.6
4	15 min <sup>d</sup>	1.0	2.3	95.9 <sup>g</sup>	0.8
5	20 min <sup>e</sup>	1.0	3.2	94.5 <sup>g</sup>	0.5
6	5 min	2.0	11.9	85.7 <sup>g</sup>	1.6
7	1 h <sup>b</sup>	0.75	28.5	70.9	0.2
8	2 h <sup>b</sup>	0.75	15.1	83.5 <sup>g</sup>	0.2
9	2 h	0.5	5.1	88.7 <sup>g</sup>	1.5

<sup>a</sup> PhBr, *n*-BuLi (1:1), cyclohexane, 20–22 °C, 0.5 M.

<sup>b</sup> Samples from the same reaction.

<sup>c</sup> PhBr, *n*-BuLi each 0.87 M.

<sup>d</sup> *n*-BuLi added to PhBr.

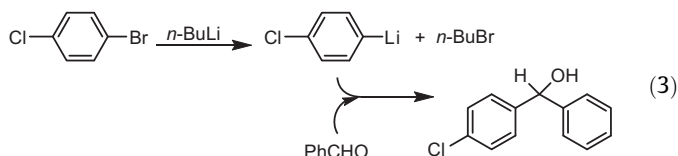
<sup>e</sup> 1.2 equiv *n*-BuLi.

<sup>f</sup> CITMS/GC analysis.

<sup>g</sup> Maximum extent of exchange for the reaction.

These results were sufficiently gratifying that a scaled-up investigation using a continuous reactor<sup>7</sup> was implemented. While performing X/Li exchange at ambient temperature is very advantageous, typical subsequent reaction steps will remain exothermic. One approach gaining a greater acceptance for controlling the reaction exotherms is the continuous flow reactor technology.<sup>7</sup> In an effort to maximize the utility of our newly developed X/Li exchange conditions we sought to implement this process within a continuous flow Synthetron™ reactor.<sup>8</sup> The Synthetron™ reactor technology is capable of processing concentrated reaction streams at flow rates of hundreds of milliliters per minute using reaction volumes of less than 0.5 mL. High flow rates lead to rapid exploration abilities and can quickly translate to produce larger quantities of the desired products.

To demonstrate the practicality and utility of our X/Li exchange method in continuous flow we began to explore the generation of *p*-chlorophenyllithium followed by trapping with benzaldehyde to provide the benzhydrol product, an intermediate in the manufacture of Cetirizine (Zyrtec®). We envisioned performing the X/Li exchange in one reactor and directing this newly formed reagent stream into a second reactor where the preformed intermediate *p*-chlorophenyllithium could react with benzaldehyde (Eq. 3).



After a few brief experiments to explore the use of the Synthetron™ reactor, we were able to realize a process whereby in fewer than 30 s, 50 mmol of the reactants were mixed and processed to provide a product solution indicating a GC conversion of 91% over the two reaction steps. The isolated yield for this small run was 8.7 g (80%). For processing a 400 g (2.09 mol) scale the continuous reaction was conducted on ca. 10 min of operating time using 2.0 M feed solutions to provide the benzhydrol product in 94% GC conversion over two steps (373 g isolated; 82% yield).<sup>9</sup> Comparatively, the two-step process conducted in a small batch (flask) reaction (35 mmol) provided 5.72 g isolated product (75% yield).

Ongoing studies of these relatively eco-friendly conditions for the halogen/lithium exchanges include the following uncorrected GC results (FID):

**Table 3**X/Li exchange of *p*-chlorobromobenzene at ambient temperature in cyclohexane doped with 1.0 equiv THF<sup>a</sup>

Time	Reaction (M)	Addition order	%PhCl	% <i>p</i> -TMS <sub>6</sub> H <sub>4</sub> Cl <sup>c</sup>	% <i>p</i> - <i>n</i> -BuC <sub>6</sub> H <sub>4</sub> Cl
15 min <sup>b</sup>	0.87	Ar→ <i>n</i> -BuLi	1.4	97.1 <sup>d</sup>	0
30 min <sup>b</sup>	0.87	Ar→ <i>n</i> -BuLi	1.5	96.9	0.2
15 min	0.87	<i>n</i> -BuLi→Ar	6.9	81.8 <sup>d</sup>	0.5
15 min	1.0	<i>n</i> -BuLi→Ar	3.5	89.7 <sup>d</sup>	0.4
15 min <sup>b</sup>	1.0	Ar→ <i>n</i> -BuLi	1.0	95.1	0.2
30 min <sup>b</sup>	1.0	Ar→ <i>n</i> -BuLi	1.1	96.7 <sup>d</sup>	0.2
30 min	1.0	Ar→ <i>n</i> -BuLi	1.0	96.5 <sup>d</sup>	0.5

<sup>a</sup> *p*-BrC<sub>6</sub>H<sub>4</sub>Cl, *n*-BuLi(1.0:1.05), cyclohexane, 20–22 °C.<sup>b</sup> Sequential samples from the same reaction.<sup>c</sup> CITMS/GC analysis.<sup>d</sup> Maximum extent of exchange for the reaction.**Batch***m*-ClC<sub>6</sub>H<sub>4</sub>Br/*n*-BuLi (1:1), 15 min,  
CITMS→*m*-ClC<sub>6</sub>H<sub>4</sub>TMS (97%)**Continuous reactor***m*-ClC<sub>6</sub>H<sub>4</sub>Br/*n*-BuLi (1:1)  
CITMS→*m*-ClC<sub>6</sub>H<sub>4</sub>TMS (96%)  
DMF→*m*-ClC<sub>6</sub>H<sub>4</sub>CHO (93%)  
*p*-ClC<sub>6</sub>H<sub>4</sub>Br/*n*-BuLi (1:1)  
DMF→*p*-ClC<sub>6</sub>H<sub>4</sub>CHO (94%)

For the batch reaction a 2 M solution of *m*-chlorobromobenzene (8 mmol) in cyclohexane containing 1 equiv of THF was prepared. This solution was added dropwise to an equal volume of 2 M *n*-BuLi in cyclohexane at 22 °C. The continuous reactor procedure for this same preparation involved simply feeding the same 2 M solutions of the reactants at the flow rate used for the *p*-isomer into the reactor and an exiting into a flask containing an excess of 2 M ClSiMe<sub>3</sub> in cyclohexane. For each of the DMF preparations, both the reactors were utilized. In the first the X/Li exchange was implemented as described above. For the aldehyde formation step, the generated ArLi solution was fed into the second reactor to which was also being fed a 2 M solution of DMF in THF. These reactions were exited into an aqueous saturated ammonium chloride solution and treated in a manner similar to that described for the benzhydrol product. It should be emphasized that on this small-scale the CITMS quench of *m*-chlorobromobenzene produces comparable results for both the batch and continuous reactor studies. On a larger scale, only the continuous reactor would produce similar results.

Further study of the ambient temperature halogen/metal exchange in batch and continuous flow is in progress. Concern must be expressed that at ambient temperature strong base side reactions will be more likely to compete than at cryogenic temperatures. This initial small-scale study has demonstrated that high yields of X/Li exchange products can be obtained in both the batch and continuous fashions using doped hydrocarbon media conditions. Using a continuous reactor in comparison to the conventional batch process provided advantageous yield and processing improvements. We anticipate that the advantages for continuous processes will be greater for larger scale comparisons. We also anticipate that the advantages of the continuous process will be much more obvious when more reactive substrates are employed. Additionally, this study has demonstrated that the Synthetron™ reactor technology is capable of providing hundreds of grams of products in only a matter of minutes and would make a valuable addition to laboratories interested in quickly producing larger quantities of products.

**2. Experimental**

All reagents were purchased from Aldrich Chemical Company and used without further purification unless otherwise noted. Ana-

lytical analysis was performed on an Agilent 6850 model GC with a BP-10 capillary column and FID detector. Identities of the products were confirmed by GC/MS analysis (Agilent 5973 MSD with 6890N Network GC system). CITMS-quenched reaction aliquots were allowed to sit for 1 h before addition of ca 2 mL of aqueous saturated sodium carbonate. They were then diluted with 2 mL of MTBE and shaken vigorously before injecting the organic layer.

**2.1. Lithium exchange of bromobenzene with 1 equiv THF (batch)**

To a clean, dry, nitrogen purged flask were added bromobenzene (1.26 mL, 8 mmol), anhydrous THF (0.65 mL, 8 mmol), and anhydrous cyclohexane to achieve a 1.0 M substrate concentration. In a separate clean, dry, nitrogen purged flask were added *n*-BuLi (2.0 M in cyclohexane; 4 mL, 8 mmol) and anhydrous cyclohexane (4 mL). The bromobenzene solution was then added dropwise at room temperature (water bath) to the *n*-BuLi solution to achieve an initial reaction concentration of 0.5 M for all reactants. Reaction aliquots were taken and quenched with CITMS; the maximum exchange of 97.4% occurred at 1.5 h.

**2.2. Lithium exchange of *p*-chlorobromobenzene with 1 equiv THF (batch)**

To a clean, dry, nitrogen purged flask were added *p*-chlorobromobenzene (6.70 g, 35 mmol), anhydrous THF (2.84 mL, 35 mmol), and anhydrous cyclohexane to achieve a 2.0-M substrate concentration. This solution was added dropwise at room temperature (water bath) to a clean, dry, nitrogen purged flask containing *n*-BuLi (2.0 M in cyclohexane; 18.4 mL; 36.8 mmol). The reaction aliquots were taken and quenched with a 2–3 equiv of a 2.0-M solution of CITMS in a clean, dry vial; the maximum exchange of 96.7% occurred at 30 min.

**2.3. Formation of (4-chlorophenyl)(phenyl)methanol (batch)**

The halogen/metal exchange was performed identically to the above-mentioned procedure except after 30 min, the reaction mixture was placed in an ice bath and slowly treated with benzaldehyde (4.0 M solution in cyclohexane, 9.1 mL) and allowed to stir for 1 h. The reaction was slowly quenched with aqueous saturated ammonium chloride. The quenched reaction mixture was then transferred to a separatory funnel with the aid of 20–30 mL of ethyl acetate. The aqueous layer was back-extracted with an additional 25 mL of ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to provide 7.6 g crude product of the benzhydrol product. Following trituration with 3.7 mL of hexanes and sitting overnight, a white solid formed was filtered and washed with cold hexanes to

afford 4.6 g pure product. A second crop of 1.12 g was obtained from the filtrate after sitting overnight. The resulting overall yield for the two crops was 5.72 g, 75%. Mp = 52–53 °C.<sup>10</sup>

#### 2.4. Exchange of *p*-chlorobromobenzene with 1 equiv THF (Synthetron™ S3T1 continuous reactor)

A 2.0 M solution of *p*-chlorobromobenzene in anhydrous cyclohexane including 1 equiv of anhydrous THF was prepared and coupled with a commercial 2.0 M solution of *n*-BuLi in cyclohexane. Reagent solutions were delivered through Teflon tubing using independent SYR-2200 dual programmable syringe pumps obtained from J-KEM Scientific. Initial trials were conducted using 25 mL of each reagent solution being fed into the reactor at room temperature and directing the exit stream into a stirring 2.0 M solution of CITMS in cyclohexane (60 mL) held at 0 °C in an ice bath. Reagent stream feed rates were 100 mL/min each, providing a reaction residence time of 0.034 s for the X/Li exchange. A 97% conversion by CITMS/GC analysis was attained which was utilized for the addition of benzaldehyde as described below.

#### 2.5. Production of (4-chlorophenyl)(phenyl)methanol (Synthetron™ S3T1 continuous reactor)

Utilizing conditions established for the X/Li exchange in a continuous fashion, a second S3T1 Synthetron™ reactor was coupled to the exit stream of the first reactor and chilled to 5 °C with a circulating chiller. A 1.0 M solution of benzaldehyde in THF was prepared and introduced to the second reactor at a flow rate of 200 mL/min (utilizing a Buchi pump, Model C-610). A combined flow rate of 400 mL/min in the second reactor provided a residence time of 0.017 s for the nucleophilic addition step. The exit stream from the second reactor was directed into a 12-L flask containing 1.2 L of aqueous saturated ammonium chloride. 1045 mL of 2.0 M *p*-chlorobromobenzene in anhydrous cyclohexane containing 1 equiv THF (170 mL; 2.09 mol), 1045 mL of commercial 2.0 M *n*-BuLi in cyclohexane, and 2090 mL of 1.0 M benzaldehyde were prepared to provide a continuous run time of 10.45 min. GC profiling of the collected reaction stream indicated 94% conversion over two steps with the crude product being produced at a rate of 43.7 g/min. The biphasic-quenched reaction mixture was transferred to a separatory funnel where the aqueous layer was

separated and back-extracted with 400 mL of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo to provide a viscous oil. The benzhydrol product was isolated as described above for the batch reaction except employing 200 mL of hexanes for the trituration to provide 373 g; 82% isolated yield, two crops. Mp = 54–55 °C.<sup>10</sup>

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