



Continuous Flow-Processing of Organometallic Reagents Using an Advanced Peristaltic Pumping System and the Telescoped Flow Synthesis of (*E/Z*)-Tamoxifen

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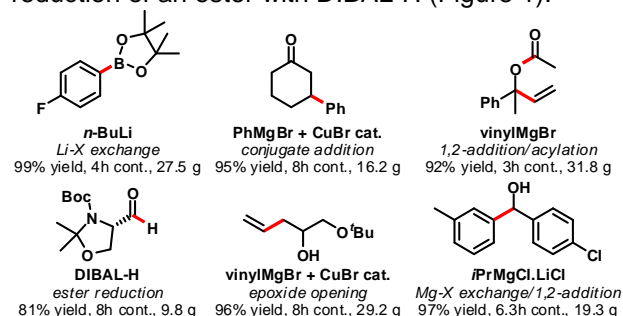
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INTRODUCTION

Flow chemistry offers potential utility to synthesis with organometallic reagents. The accurate temperature control of the potentially exothermic processes, the rapid and stoichiometric mixing of organometallic reagents and substrates, and the safe handling of the reactive components in a fully contained system are all examples of the potential benefits over traditional batch manipulations. However, organometallic reagents pose many technical hurdles with regard to continuous processing, not the least of which is the ability to pump these important and powerful reagents in a truly continuous fashion.

RESULTS AND DISCUSSION

A new flow system based on chemically resistant peristaltic pumps was developed.¹ To evaluate the reliability of this new system we selected several reactions, including lithium-halogen exchange, Grignard reagent addition, halogen-exchange and addition-elimination, transmetalation of Grignard reagents with copper catalysts and subsequent cuprate addition and conjugate addition, and partial reduction of an ester with DIBAL-H (Figure 1).



FFigure 1. Useful intermediates accessed through continuous processing of organometallic reagents.

Enhanced selectivities and yields over batch procedures were achieved, with examples of in line reaction telescoping. Commercially available organometallic reagents were pumped directly from the suppliers bottle to prepare multi-gram quantities of product in a continuous fashion, over periods of several hours without any manual intervention throughout the product collection. This work culminates in the continuous flow synthesis of the important breast cancer drug tamoxifen (Scheme 1).²

CONCLUSION

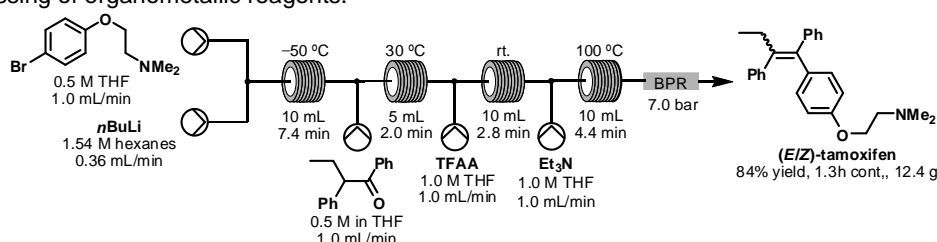
In conclusion, we report a new enabling-technology for the pumping of organometallic reagents such as *n*-BuLi, Grignard reagents and DIBAL-H. Several representative examples of its use in common transformations using these reagents, including metal-halogen exchange, addition, addition-elimination, conjugate addition and partial reduction are reported. This platform allows for truly continuous pumping of these highly reactive substances and examples are demonstrated over periods of several hours, to generate multi-gram quantities of products. This work culminates in an approach to the telescoped synthesis of tamoxifen, combining four chemically distinct transformations into one stream.

ACKNOWLEDGEMENTS

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REFERENCES

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Scheme 1. Telescoped flow synthesis of (*E/Z*)-tamoxifen.