

Continuous Flow Zinc Salt-promoted Stereoselective Alkynylation of Aldehydes Using a Polymer-supported Chiral Ligand

Ricardo Labes¹ (PG), Sean Newton² (PQ), Claudio Battilocchio² (PQ), Francisco de Assis Marques¹ (PQ), Steven Ley^{2*} (PQ).

¹Depto. de Química, Universidade Federal do Paraná – UFPR, Centro Politécnico, 81531-990, Curitiba – PR, Brazil.

²Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, England, CB2 1EQ, United Kingdom.

*svl1000@cam.ac.uk

Keywords: Carreira Reaction, Stereoselective Alkynylation, Chiral Alkynols, Propargylic Alcohols, Continuous Flow.

Introduction

Chiral alkynols, or propargylic alcohols, are useful building blocks in asymmetric synthesis, particularly in the synthesis of natural products.¹

Among the available methodologies to obtain alkynols, the most used are the asymmetric reduction of an yne-one, and the stereoselective metal-catalyzed alkynylation of a carbonyl compound, which includes the addition of organozinc reagents that consists in a great methodology to obtain chiral alkynols, being able to joint two complex pieces while creating a new stereocenter. The zinc salt mediated stereoselective addition of alkynes to carbonyl compounds is very attractive, considering that all reagents are commercially available, including the chiral ligand, it doesn't make use of pyrophoric reagents such as diethylzinc, and the reaction can be conducted without prior purification of the reagents and solvents.² This methodology has been successfully applied in the synthesis of many natural products.^{3,4}

The present work describes our efforts to conduct this methodology in continuous flow using an easily obtained polymer-supported chiral ligand.

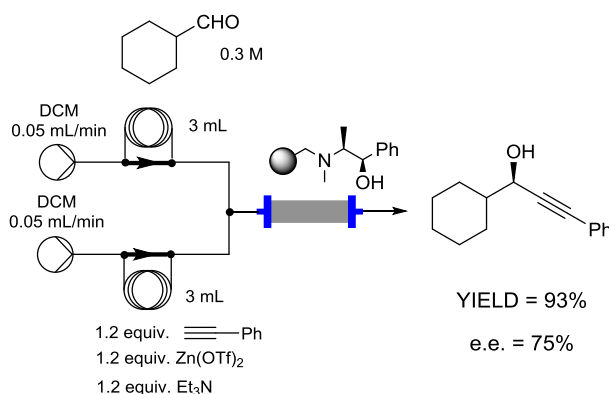
Results and Discussion

(-)-Ephedrine was the ligand of choice because once immobilized it has an analogy with the most used solution phase ligand for this methodology, (-)-*N*-Methylephedrine.² Merrifield resins differing in mesh, amount of divinilbenzene (DVB) and Cl, plus monolithic support had been screened for the preparation of supported ligand, being that Merrifield resin with 200-400 mesh, 1% DVB and 1.6 mmol/g of Cl performed the best. The supporting has been conducted as reported in the literature.⁵

Initially the selectivity and recyclability of the polymer supported (-)-ephedrine had been evaluated in batch, which delivered 71% isolated yield and up to 90% enantiomeric excess (e.e.), being successfully reused 10 times with a slight loss of enantioselectivity (84% in the 10th use).

Considering that the zinc triflate has a very low solubility in a non-polar solvents, and that non-polar

solvents are required to obtain good e.e. in this methodology,² we used many different systems to perform this methodology continuously, including the use of a cartridge charged with Zn(OTf)₂, and continuous stirring tank reactors (CSTR). The best system so far used a packed bed column containing the polymer-supported chiral ligand and dichloromethane (DCM) as solvent, which was efficient for the acetylide generation and delivered good enantioselectivity (**Scheme 1**).



Scheme 1: Asymmetric alkynylation of cyclohexanal in continuous flow.

Conclusions

A system for the continuous flow stereoselective alkynylation of aldehydes using a polymer-supported chiral ligand is successfully presented delivering the desired product in 93% yield and up to 75% e.e.

Acknowledgments

We are grateful to CAPES (RL, no 9865/13-6), Pfizer Worldwide Research and Development (CB), and the EPSRC (SVL, no EP/K0099494/1 and no EP/K039520/1) for financial support.

¹ Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, 351, 963.

² Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, 33, 373.

³ Reber, S.; Carreira, E. M. *Tetrahedron.* **2003**, 59, 6813.

⁴ Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, 126, 10313.

⁵ Frechet, J. M. J.; Bald E.; Lecavalier P. *J. Org. Chem.* **1986**, 51, 3462.