Asymmetric enzymatic reduction and Suzuki-Miyaura coupling for the synthesis of odanacatib

Raquel de Oliveira Lopes, Benedikt Reichart, Toma Glasnov, C. Oliver Kappe, Wolfgang Kroutil, Leandro Soter de M. e Miranda, Ivana Correa R. Leal, Rodrigo O. M. A. de Souza*

Grupo de Biocatálise e Síntese Orgânica, Instituto de Química,
Programa de Pós-graduação em Química, Universidade Federal do Rio de Janeiro – UFRJ, Ilha do Fundão, Rio de Janeiro-RJ.
**raquellopes25@gmail.com*

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INTRODUCTION

The odanacatib (**1**) (Figure 1) is a specific inhibitor of cathepsin K acting as an antiresorptive agent that preserves bone-formation for the osteoporosis treatment.[1,2] The clinical trial (phase III) of odanacatib (**1**) accomplished early due to the potencial efficacy, safety and favorable benefit-risk profile. [3]

By considering the important role of odanacatib (**1**) for the osteoporosis treatment, the aim of this work is to develop new biocatalysts synthetic routes for building blocks of **1** by using microwave and continuous flow as strategy tools for reaction process optimization.

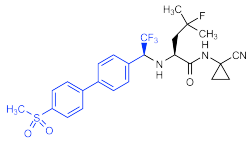
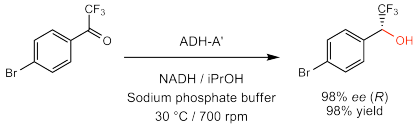


Figure 1. Odanacatib (**1**)

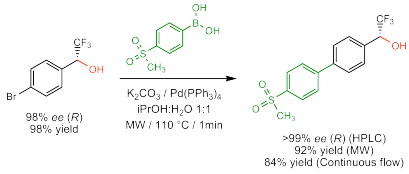
RESULTS AND DISCUSSION

Initially, the lyophilized *E. coli* cells containing the overexpressed alcohol dehydrogenase (ADH-A') were rehydrated with sodium phosphate buffer (850 µL, 50 mM, pH 7.5) assembling the cofactor NADH (1 mM). Then, the 4'-Br-2,2,2-trifluoroacetophenone (50 mM) dissolved in isopropanol (150 µL) was added. The reaction mixture was shaken at 30 °C and 700 rpm in different times. Afterwards, the reaction was stopped by extraction with ethyl acetate (3 x 2 mL). The organic layer was separated by centrifugation (10 min, 5.000 rpm) and dried (Na_2SO_4). Conversions and enantiomeric excess of the corresponding alcohol were determined by GC (Scheme 1).[4] The GC-FID analysis showed that conversions over than 99% and enantiomeric excesses of 98% are achieved by adopting the following parameters: 10 mg of lyophilized cells for 6 hours or 20 mg of lyophilized cells for 2 hours.



Scheme 1. Asymmetric reduction of the ketone by using lyophilized cells of *Escherichia coli* (ADH-A')

After that, the Suzuki-Miyaura coupling was optimized under microwave irradiation (Monowave 300 – Anton Paar) using the alcohol *R* (1 eq.), boronic acid (1 eq.), potassium carbonate (2 eq.), tetrakis palladium(0) (0.2 mol%) and a solution of distilled water and isopropanol 1:1, in different times and temperatures. Then, the solvent was evaporated and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and conversions were determined by GC-FID (Scheme 2).[5] The same reaction was performed by continuous flow (Syrris). The reaction mixture was pumped through the coil reactor (4 mL PFA-*Coil*; 5 minutes residence time; flow rate 0.8 mL/min) and heated at 110 °C. The complete reaction mixture was collected for 10 minutes. The isolated yield achieved 92% by using the microwave conditions and 84% by using continuous flow, and in both reactions the enantioselectivity desired was preserved.



Scheme 2. Suzuki–Miyaura coupling

CONCLUSION

Lyophilized *E. coli* cells containing the overexpressed ADH are able to reduce 4'-Br-2,2,2-trifluoroacetophenone to *R* alcohol, in excellent conversions rates and high enantiomeric excess, and the Suzuki-Miyaura coupling preserved the enantioselectivity in good conversion rates by using microwave or continuous flow conditions.

ACKNOWLEDGEMENTS

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