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A stereoselective, catalytic strategy for the in-flow synthesis of advanced precursors of rasagiline and tamsulosin

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ABSTRACT

The diastereoselective, trichlorosilane-mediate reduction of imines, bearing different and removable chiral auxiliaries, in combination either with achiral bases or catalytic amounts of chiral Lewis bases, was investigated to afford immediate precursors of chiral APIs (Active Pharmaceutical Ingredients). The carbon-nitrogen double bond reduction was successfully performed in batch and in flow mode, in high yields and almost complete stereocontrol. By this metal-free approach, the formal synthesis of rasagiline and tamsulosin was successfully accomplished in micro(meso) flow reactors, under continuous flow conditions. The results of these explorative studies represent a new, important step towards the development of automated processes for the preparation of enantiopure biologically active compounds.

1. Introduction

Rasagiline mesylate (Scheme 1), also known as (*R*)-(+)-*N*-propargyl-1-aminoindan mesylate, is a commercially marketed pharmaceutically active substance, under the brand name azilect®. The racemic form of the drug was patented by Aspro Nicholas in the early 1979, and was later found to be indicated for treatment of Parkinson's disease (PD), being effective both as monotherapy in early PD, and as adjunctive in patients with advancing PD and motor fluctuations.[1] This chiral amine is a potent second-generation propargylamine pharmacophore that selectively and irreversibly inhibits the B-form of the monoamineoxidase enzyme (MAO-B) over type A by a factor of fourteen.[2] European drug-regulatory authorities approved this potent MAO-B inhibitor in February 2005 and the US FDA in May 2006.[3] Although the S-(−)-enantiomer of *N*-propargyl-1-aminoindane still exerts some neuroprotective properties, the potency of R-(+)-enantiomer against the MAO-B enzyme is approximately 1000-fold higher. Different strategies aimed to the preparation of the enantiopure compound have been explored,[4] but, at the best of our knowledge, a stereoselective organocatalytic approach for the preparation of rasagiline has never been reported so far. We report here a metal-free stereoselective strategy for the synthesis of rasagiline and of an advanced intermediate of another API, tamsulosin, sold under the trade name flomax as single enantiomer. Active as antagonist for α_{1a} adrenergic receptor, It is used to treat symptomatic benign prostatic hyperplasia and to treat urinary retention. Starting from this common precursor, different pharmaceutically active compounds could be prepared, having as biological targets different receptors such as cholinesterase and monoamine oxidase inhibition,[5] σ-receptors[6] and human adenosine A_{2A} receptor.[7]

The synthetic plan for the preparation of the two-target molecules involves a metal-free stereoselective reduction of imines, easily prepared starting from commercially available ketones (Scheme 1).[8]

2. Results and discussions

We initially explored the possibility to use a catalytic amount of chiral Lewis base (LB) for the stereoselective, trichlorosilane-mediated reduction of the imine prepared starting from 1-indanone. Two different chiral picolinamides, previously developed in our group, were tested.[9,10] Using ephedrine-derived catalyst **A**, the chiral amines were obtained in high yields, both using PMP (paramethoxyphenyl) and benzyl protected imines, but with modest

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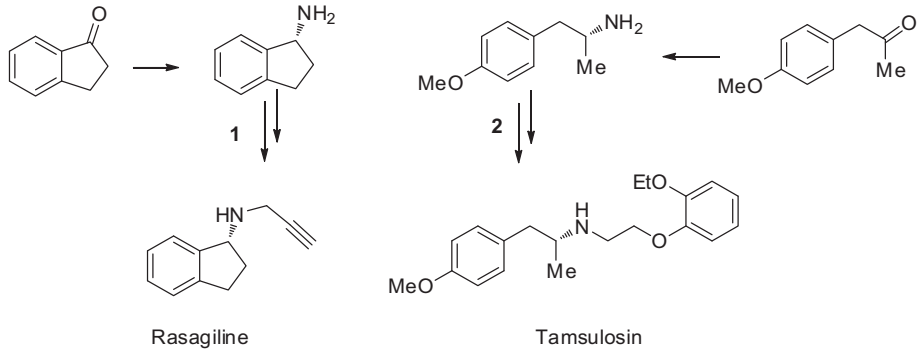


Scheme 1. Synthetic strategy for the synthesis of rasagiline and tamsulosin.

enantioselectivities, up to 60%. e.e. for the (*R*)-enantiomer. No better results were observed with catalyst type **B**, that is known to lead to the formation preferentially of the (*S*)-isomer (see Scheme 2).[10]

Then, we decided to explore the use of a chiral auxiliary, by employing α-methylbenzylamine as cheap and readily removable element of stereocontrol in the reduction, that was already successfully employed in previous works (Scheme 3).[8j] As achiral Lewis base, *N,N*-dimethyl formamide was selected as well established, inexpensive and efficient activator of trichlorosilane for the reduction of ketoimines.[8j,9]

Reductions were performed starting from a diastereoisomeric mixture of imine **3,** prepared from 1-(*R*)-phenylethylamine in a 9:1 (**3c:3d**) ratio, in favor of the *E* imine **3c**. The best results were achieved working at −20 °C, and performing the reaction for 36 h; the product was obtained in 55% yield and 98:2 diastereomeric ratio in favor of the (*R,R*) stereoisomer **4c** (Table 1, entry 5). To achieve complete conversion higher reaction temperature were needed (Table 1, entry 6), leading to a small decrease of diastereoselection (90:10 of *d.r.*).

Finally, in the attempt to increase further the efficiency of the process, the use of a match combination between the chiral auxiliary and the chiral catalyst was investigated. Based on previous works,[9] we selected the known favorable combination of catalyst **A** and 1-(*R*)-phenylethylamine as chiral auxiliary: the reduction was accomplished in 90% conversion and a 90:10 of *d.r.* ratio (Table 1, entry 7). Since the use of catalyst **B**, that leads to formation of products of (*S*) configuration,[10] afforded, as expected, the product in lower stereoselectivity (entry 8, mismatch couple with the chiral auxiliary that favours the formation of product with (*R*) configuration), the use of pseudo-enantiomer of catalyst **B** allowed to obtain the product **4c** in 80% conversion and a complete diasteroselectivity (Table 2, entry 9).

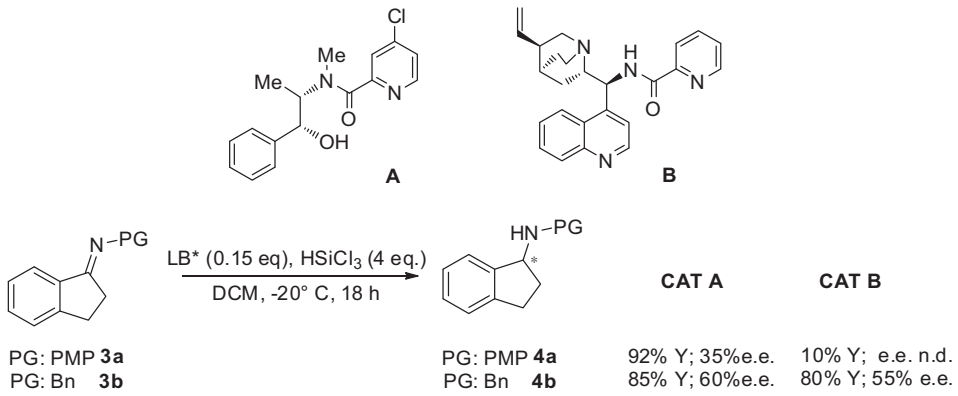
With the best reaction conditions in our hands, we decided to explore the possibility of employing different chiral auxiliaries. Since the removal of the α-methylbenzylamine tipycally requires palladium catalysts,[11] we focused our attention onto the use of a chiral auxiliary removable without the need of precious transition metals. In particular, we selected commercially available (*R*)-4-methoxy-α-methylbenzylamine and (*R*)-2-methyl-2-propanesulfinamide since they could be removed under metal-free conditions.[12,13]

Imines **5a** and **6a** were readily synthesized and their reduction was performed in the presence of 3.5 mol eq. of trichlorosilane and stoichiometric amounts of DMF or catalytic amounts of chiral picolinamide **A** (see Scheme 4).

Imine **5a** was efficiently reduced using DMF as achiral LB (Table 2, entry 1), with high conversion (80%) and a complete diasteroselectivity. In order to increase the yield, the reaction was then performed in the presence of catalyst **A** (Table 2, entry 2); complete conversion of the starting material into the chiral amine **5b** and a total stereocontrol of the reaction were observed.

Analogously, the reduction of imine **6a** was efficiently promoted by catalyst **A**, affording the product **6b**, that was *in situ* deprotected during the basic aqueous work up, to afford the primary chiral amine **1** in quantitative yield and 60% e.e. (entry 4, Table 2).

Considering the raising interesting for the flow preparation of API's,[14] based on these results and with the aim to further accelerate the reaction, we explored the possibility of developing



Scheme 2. Enantioselective reductions of imines for the synthesis of rasagiline intermediates.