



Green asymmetric synthesis of tetrahydroquinolines in carbon dioxide medium promoted by lipophilic bifunctional tertiary amine – squaramide organocatalysts

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ARTICLE INFO

Article history:

Received 18 September 2017
 Received in revised form
 10 November 2017
 Accepted 20 November 2017
 Available online 23 November 2017

Keywords:

Asymmetric organocatalysis
 Green chemistry
 Carbon dioxide
 Domino reactions
 Tetrahydroquinolines

ABSTRACT

Novel pseudo-enantiomeric bifunctional tertiary amine-squaramides modified with long-chained alkoxy or polyfluoroalkoxy groups, have been synthesized. They catalyzed the asymmetric double-Michael cascade reactions of *o*-*N*-tosylaminophenyl α,β -unsaturated ketones with α -nitroolefins in carbon dioxide medium at significantly lower pressure (75 bar) and temperature (35 °C), than known less lipophilic catalysts. Both enantiomers of the pharmacologically valuable methoxy-substituted tetrahydroquinoline derivatives can be prepared in moderate to high yield with promising enantioselectivity (up to 98% *ee*) under the optimized conditions.

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1. Introduction

An important place in current organic chemistry is occupied by organocatalysis – a rapidly developing methodology for asymmetric synthesis, which is based on the use of relatively simple metal-free, enantiomerically pure organic molecules as activators and stereoinductors.¹ Bifunctional chiral tertiary amines bearing the thiourea or squaramide fragments have recently attracted considerable attention due to their ability to activate reagents via stereoselective formation of hydrogen bonds in the transition state of catalytic reactions² (non-covalent catalysis). These catalysts are resistant towards moisture and air and, in some cases, can be readily isolated from corresponding reaction mixtures and repeatedly used in the catalytic process.³

The pioneering work of Jacobsen,⁴ Takemoto,⁵ Rawal⁶ and some other prominent chemists has inspired researchers to look for novel efficient H-bonding organocatalysts. Catalysts promoting practically important enantioselective transformations under eco-friendly conditions, in particular, in water⁷ and liquid carbon dioxide media are especially attractive. Water is a unique medium where enzymatic reactions (prototypes of organocatalytic processes)

occur in nature. Carbon dioxide, which is steadily produced from renewable natural (plants) and industrial (burning of fuels) sources, is currently considered as widely available, non-toxic and potentially recyclable Green chemistry solvent for laboratory and industrial use.⁸

There are only a few examples of non-covalent organocatalysis in carbon dioxide medium. Asymmetric Michael reactions, catalyzed by bifunctional tertiary amines, in particular compound **I** (Fig. 1), can be efficiently carried out in liquid or supercritical (sc) CO₂.⁹ Very recently, we successfully applied this solvent¹⁰ to the double-Michael domino reactions of *o*-*N*-tosylaminophenyl α,β -unsaturated ketones **1** with α -nitroolefins **2** catalyzed by quinine-derived squaramide **II** to afford pharmacologically valuable functionalized chiral tetrahydroquinolines **3** with promising diastereo- (*dr* > 99:1) and enantioselectivity (up to 98% *ee*).¹¹ However, high yields of products could be attained here only under severe supercritical (sc) conditions (200 bar, 75 °C) which demanded expensive high-pressure equipment. The reactions significantly slow down at lower pressures, that may be attributed to a reduction of the carbon dioxide density¹² which leads to lower solubility of catalyst **II** and reagents in this solvent (the experiments in an autoclave equipped with sapphire windows showed a heterogeneity of the reaction mixtures).

Commonly, organic compounds bearing lipophilic structural fragments are more soluble in the non-polar carbon dioxide

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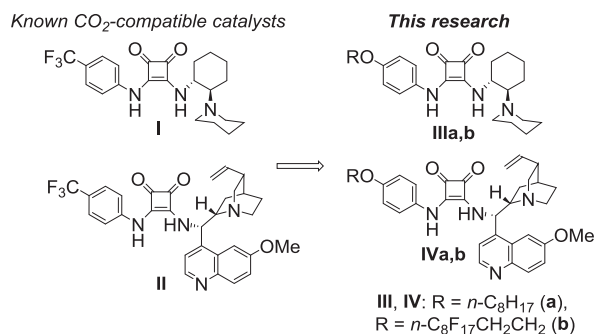


Fig. 1. Research strategy.

medium.¹³ The lipophilicity may be improved by long-chained alkyl groups, which reduce the cohesion energy density and hence, improve solubility of organic molecules.¹⁴ Incorporating polyfluorinated structural fragments also significantly enhances the affinity of polar organic compounds with carbon dioxide,¹⁵ suppressing their self-associating ability¹⁶ and/or reducing the polarity of organic molecules.¹⁷ These experimental results are in accordance with results of theoretical studies (DFT calculations and COSMO-RS).¹⁸

Based on these data, we expected that substitution of the trifluoromethyl group in catalysts **I** and **II** for a long-chained alkoxy or polyfluorinated alkoxy group would improve the solubility of the resulting molecules **III** and **IV** in carbon dioxide medium, allowing catalytic reactions to be performed at lower pressure, thus making them less resource- and energy-consuming (Fig. 1).

2. Results and discussion

To verify this hypothesis, we synthesized novel bifunctional tertiary chiral amines **III** and **IV** bearing *n*-octyloxy or fluorinated *n*-decyloxy groups on the aromatic ring attached to the squaramide fragment (Scheme 1). Potassium *p*-nitrophenoxide and 4-fluoronitrobenzene were converted to 4-nitrophenol derivatives **4a** and **4b** by the *O*-alkylation (arylation) reactions with 1-chloro-*n*-octane or polyfluorinated *n*-decanol, respectively. Catalytic (Pd) hydrogenation of compounds **4a** and **4b** afforded the corresponding aniline derivatives **5a** and **5b**. The latter were transformed into squaramide half-esters **6a** and **6b** by careful treatment with an equimolar amount of dimethyl squarate in methanol. Exhaustive

amidation of **6a** and **6b** with (1*R*,2*R*)-cyclohexane-1,2-diamine **7** or quinine-derived primary amine **8** furnished the target lipophilic bifunctional catalysts **IIIa,b** and **IVa,b** in 17–48% overall yield (for details, see Experimental section).

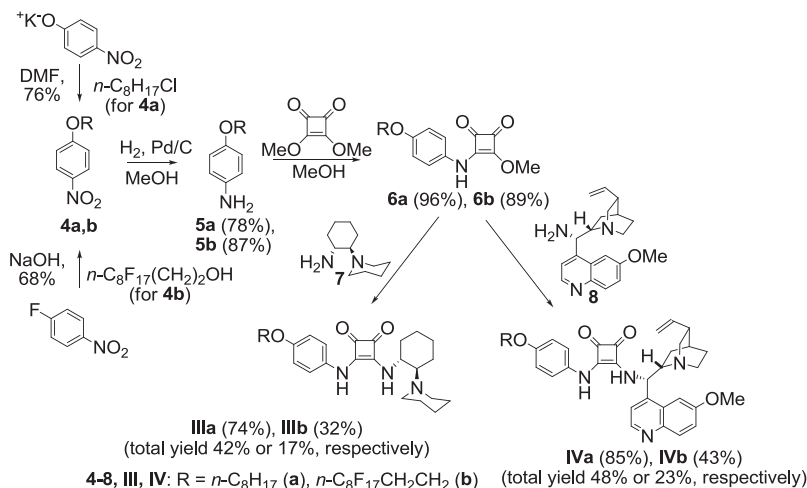
We compared the catalytic performance of novel (**III** and **IV**) and known (**I** and **II**) catalysts (5 mol % of each) in the model reaction of chalcone **1a** with *o*-chloro- β -nitrostyrene **2a**. The experiments were carried out at 75 bar and 35 °C, the values being very close to the corresponding parameters of the CO₂ critical point (72.8 bar, 31.1 °C) (Table 1). In all cases, functionalized tetrahydroquinoline **3aa** bearing three contiguous stereocenters was generated as a single diastereomer in the carbon dioxide medium. The trifluoromethylated compounds **I** and **II** were the least efficient catalysts in these conditions: yields of corresponding adducts **3aa** and *ent*-**3aa** were only 9% and 13%, respectively, over 3 h (entries 1 and 2). Significantly improved product yield (81%) and reasonable enantioselectivity (88% *ee*) was attained in the presence of (1*R*,2*R*)-cyclohexane-1,2-diamine-based *n*-octyloxy squaramide **IIIa** over the same period (entry 3). The enantioselectivity was further improved (up to 89% *ee*) by carrying out the **IIIa**-catalyzed model reaction at 23 °C and 100 bar pressure, yet at the expense of a noticeable decrease in the yield of **3aa** (entry 3, data in parenthesis). Quinine-derived squaramide **IVa** bearing an *n*-octyloxy group provided the antipodal *ent*-**3aa** in inferior yield to catalyst **IIIa** (58%), though, with better stereoselection (93% *ee*) (entry 5).

Table 1

Catalytic performance of **I** – **IV** in the model reaction.

Entry	Catalyst	Product	Yield, %	<i>ee</i> , %
1	I	3aa	9	90
2	II	<i>ent</i> - 3aa	13	91
3	IIIa	3aa	81 (55 ^a)	88 (89 ^a)
4	IIIb	3aa	83	74
5	IVa	<i>ent</i> - 3aa	58	93
6	IVb	<i>ent</i> - 3aa	59	90

^a The reaction was carried out at 100 bar and 23 °C.⁸

Scheme 1. Synthesis of lipophilic catalysts **III** and **IV**.

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