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Enantioselective synthesis of *cis*-α-substituted cycloalkanols and *trans*-cycloalkyl amines thereof

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Abstract—The diastereo- and enantioselective syntheses of *trans*-cycloalkyl amines was accomplished through a three-step sequence consisting of: (1) asymmetric transfer hydrogenation through dynamic kinetic resolution of bicyclic and monocyclic α-substituted ketones using HCO_2H/Et_3N as the hydrogen source and TsDPEN-based Ru(II) catalysts, (2) nucleophilic hydroxyl to azide substitution of the resulting *cis*-cycloalkanols using diphenyl phosphoryl azide under modified Mitsunobu conditions, and (3) reduction of the *trans*-azide intermediates with $LiAlH_4$ of PPh_3/H_2O to the desired targets.

1. Introduction

Optically active amines are important building blocks for the synthesis of a variety of biologically active molecules, among other industrial applications. Consequently, numerous methods have emerged in the past few years for their preparation in enantiomerically pure or enriched form.[1] In spite of the considerable advances in asymmetric synthesis and catalysis, the resolution of racemates remains as the most important approach used by the chemical industry for the preparation of this type of compounds. In this context, dynamic kinetic resolution (DKR),[2] not limited by the theoretical 50% maximum yield associated with conventional separation techniques or classical kinetic resolutions, is established as the most efficient technique for the resolution of racemates wherever it is applicable. After the seminal work by the Noyori[3] and Genêt[4] groups on the catalytic hydrogenation of β-keto esters, the hydrogenation through DKR has found a number of applications and stimulated the development of related reactions, including the hydrogenation or transfer hydrogenation[5] of several types of monocyclic[6] and bicyclic[7] cycloalkanones.

On the other hand, cyclic chiral amines are key structural elements in several bioactive compounds such as inhibitors of acyl CoA:cholesterol acyltransferase (ACAT),[8] positive allosteric modulators at the AMPA [2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid] receptors,[9] acetylcholine esterase (AChE), and monoamine oxidase (MAO) inhibitors with potential for treatment of Alzheimer's and Parkinson's diseases,[10] compounds with potent hypoglycemic activity,[11] etc. (Fig. 1).

Inspired by the above-disclosed precedents, we have recently reported on the transfer hydrogenation of α-substituted cyclic ketimines as the first DKR process involving reduction of C=N bonds via DKR.[12] In order to complement this procedure, that is limited to the synthesis of cis products, we envisaged that the corresponding *trans*-α-substituted cyclic amines could be readily available from α-substituted ketones

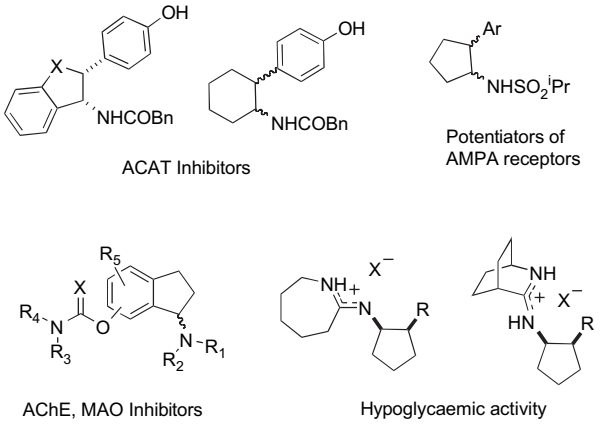

Figure 1. Bioactive cyclic amines.

Keywords: Asymmetric catalysis; Amines; Transfer hydrogenation; Dynamic kinetic resolution.
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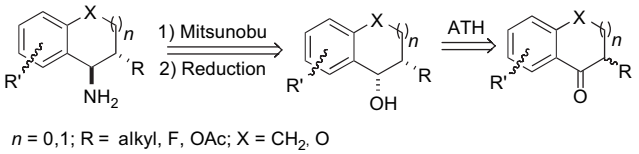
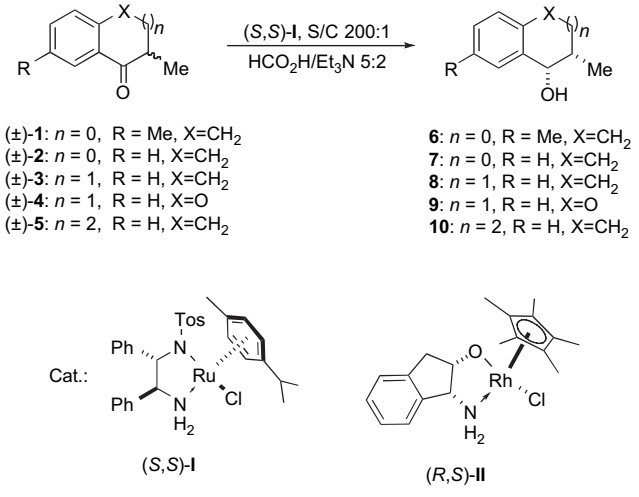
through a three-step synthetic route consisting of: (1) asymmetric transfer hydrogenation to *cis*-α-substituted cycloalkanols, (2) classical[13] or modified[14] Mitsunobu reaction with inversion of the configuration to *trans*-azido intermediates, and (3) reduction of the latter to the desired cycloalkyl amines (Scheme 1). In this paper, we report the results collected on the basis of this hypothesis and its extension to the synthesis of cyclic *cis*-1,2-diols and *trans*-1,2-fluoroamines.



Scheme 1. Retrosynthetic analysis for *cis*-cycloalkanols and *trans*-cycloalkyl amines thereof.

2. Results and discussion

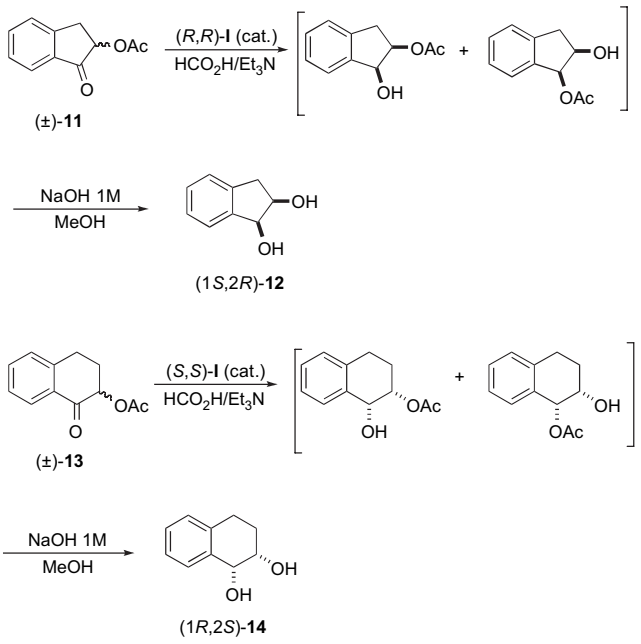
For the synthesis of the desired *cis*-cycloalkanols, initial experiments were performed with readily available racemic 2,6-dimethylindan-1-one (±)-**1** using 0.5 mol % of [RhClCp*(1*R*,2*S*)-*cis*-1-aminoindan-2-ol] [(*R*,*S*)-**II**] as the catalyst and ^{i}PrONa/^{i}PrOH as the hydrogen source.[15] The expected 2,6-dimethylindan-1-ol **6** was isolated in a moderate 45% yield as a 1:3 *cis*/*trans* diastereomeric mixture (Scheme 2), suggesting a thermodynamically controlled formation of the products. On the other hand, the use of Noyori/Ikariya [RuCl(TsDPEN)(*p*-cymene)] catalysts (*R*,*R*)- or (*S*,*S*)-**I** in 5:2 HCO_2H/Et_3N azeotropic mixture as the solvent and hydrogen source (method **A**)[16] was successfully applied to the reduction of racemic indanones (±)-**1**,**2** into the desired *cis*-(1*S*,2*S*)-indan-1-ol derivatives[17] **6** and **7**, obtained in excellent yields and stereoselectivities (Table 1, entries 1 and 2). No reaction was observed from α-aryl substituted indanones, even using substrate/catalyst ratio (S/C)=50 or 1.2:1 HCO_2H/Et_3N mixture (method **B**).[18] This result contrasts with the behavior of monocyclic substrates (see below) and also with that described by Wills and co-workers for 1-aryltetral-2-one derivatives,[7] and can be explained if a large proportion of unreactive enolic form is present in the keto/enol equilibrium in this case.



Scheme 2. Asymmetric transfer hydrogenation of (±)-**1**–**5** using (*S*,*S*)-**I** catalyst and 5:2 HCO_2H/Et_3N azeotropic mixture as hydrogen source.

The reactions of tetral-1-one and chroman-4-one derivatives (±)-**3**,**4** were accomplished using (*S*,*S*)-**I** as the catalysts and 5:2 HCO_2H/Et_3N azeotropic mixture to afford, respectively, *cis*-(1*S*,2*S*)-2-methyltetral-1-ol[19] (**8**) and *cis*-(3*S*,4*S*)-3-methylchroman-4-ol (**9**) in high yields, good *cis*/*trans* ratios, and excellent enantioselectivities (Table 1, entries 3 and 4). The longer reaction times required for completion of the reactions and the lower diastereomeric excesses observed with respect to indanone derivatives (±)-**1**,**2** can be explained by a less efficient epimerization of the less reactive (*R*)-**3** or (*R*)-**4** enantiomers. This fact can be in turn tentatively attributed to the lower acidity of the α-proton of tetralone and chromanone rings. Finally, it should also be mentioned that the seven-membered 2-methyl benzosuberone (±)-**5** showed a very poor reactivity under these conditions. By increasing the catalyst loading to 2 mol %, the corresponding alcohol **10** could be isolated in only 30% yield and with moderate diastereo- and enantioselectivity (entry 5).

The behavior of 2-acetoxyindan-1-one (±)-(**11**) and 2-acetoxytetral-1-one (±)-(**13**) as representatives of α-oxygenated cyclic ketones was investigated next. In this cases, use of (*S*,*S*)-**I** or (*R*,*R*)-**I** catalysts and 1.2:1 HCO_2H/Et_3N mixture as hydrogen source and reaction medium afforded the best results concerning reactivity and stereoselectivity, a result in line with that previously observed for the related α-fluoro ketones.[20] The primary products from these reactions were mixture of the expected *cis*-2-acetoxycycloindan-1-ols and *cis*-1-acetoxycycloindan-2-ols, formed through well established 1,2-migration of the acetyl group (Scheme 3). The corresponding *cis* vicinal diols **12**[21] and **14**[22] were obtained by in situ deacetylation using NaOH (1 M)/MeOH (Table 1, entries 6 and 7).



Scheme 3. Synthesis of diols **12** and **14**.