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Functionalized organolithium reagents in the synthesis of chiral ligands for catalytic enantioselective addition of diethylzinc to aldehydes

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ABSTRACT

Series of functionalized organolithium compounds were prepared and added to chiral bicyclic ketones (1*R*-(+)-camphor analogue **2** and 1*R*-(−)-fenchone **3**), resulting in the preparation of a small "library" of chiral aminoalcohols able to serve as ligands in metal mediated asymmetric synthesis. The configuration of the chiral ligands was approved by applying advanced NMR experiments. The absolute configurations of 1,2-disubstituted planar chiral ferrocene-based aminoalcohols **15**, **18** and **19** were determined by means of NMR experiments and confirmed by X-ray crystallography. The new chiral ligands were tested as pre-catalysts for the addition of diethyl zinc to benzaldehyde. The reactions proceeded with excellent conversions and a moderate degree of enantioselectivity.

1. Introduction

The considerable interest in the synthesis and application of new enantiomerically pure β-, γ- and δ-aminoalcohols by utilizing different sources of chirality has been an obvious result of their efficiency as pre-catalysts for enantioselective addition of diorganozinc compounds to aldehydes, discovered first by Oguni and Omi [1]. The phenomenon of chirality amplification (the non-linear relationship between the enantiomeric purity of the ligand used and the enantiomeric excess of the product obtained) has attracted particular interest and has been studied in detail by Noyori [2] with the example of *N*,*N*-dimethylaminoisoborneol (DAIB). In recent years, a large number of aminoalcohols structurally based on the bicyclic camphane core have been synthesized using camphor [3], fenchone [3b,4], camphor-10-sulfonamide [5] and similar chiral sources [6] as the starting materials. The variation of the substituents attached to the camphane skeleton allows data collection to study the influence of the ligand structure on the degree and sense of enantioselectivity.

Over the few past years, we have been interested in the utilization of (+)-camphor and (−)-fenchone within the addition reactions of functionalized organometallic reagents, leading to various aminoalcohols [3a,3b,7] showing, in several cases, high efficiency as pre-catalysts to form *in situ* organozinc complexes that are able to provide enantioselective addition of diethylzinc to aldehydes.

In the present paper we are applying an organometallic approach to obtain *N*- and *S*-functionalized hydroxy-camphane derivatives of type **A** and **B** (Scheme 1) that possess a similar substitution at C-1 and C-3 of the bicyclic skeleton, but different stereochemistry at C-2, realized through the different *exo*/*endo*-selectivity of the addition of organolithiums to compounds **2** and **3**. Chiral compounds of type of **A** and **B** are versatile ligands for diverse metal catalyzed transformations and they could be employed in applications beyond the organozinc additions used to test them in the present work.

2. Results and discussion

2.1. Synthesis of chiral aminoalcohols and analogues by addition of functionalized organolithiums to bicyclic ketones

For the planned addition reactions, the commercially available 1*R*-(+)-camphor **1** was transformed into the ketone **2** applying a known procedure [8a,8c] (Scheme 1). Ketone **2** has been rarely used for transformations [8b–e]. To the best of our knowledge, addition reactions of organometallics to **2** have not been studied. Only the reduction with $LiAlH_4$ leading to the corresponding *iso*-borneol analogue has been described [8c]. A set of organolithium reagents was selected to perform addition reactions to these ketones, leading to dimethylaminoalcohols (with reagents **4**–**6**, **12**) and alcohols containing an *N*-heterocyclic moiety (with reagents **7**, **13**–**14**), which in the case of **13** and **14** possess an additional

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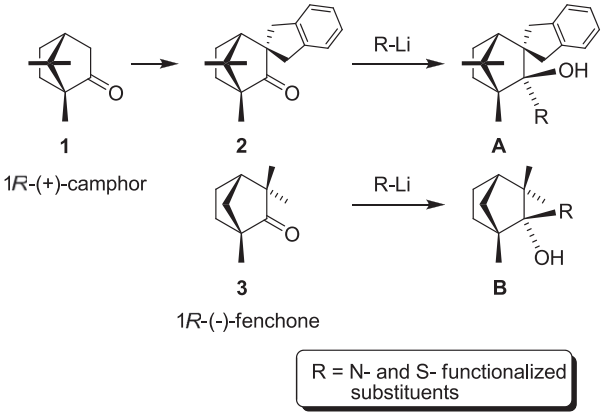
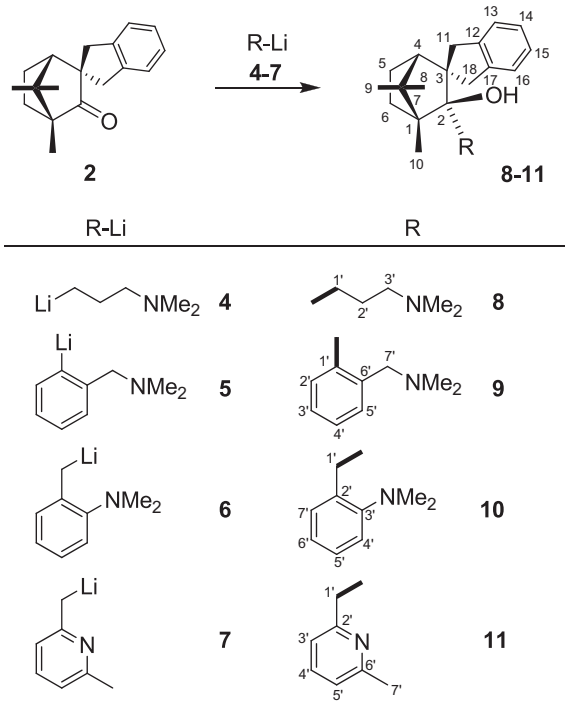


Scheme 1. The addition of organolithiums to **2** and **3** proceeds in a highly diastereoselective manner, leading to products of type **A** and **B** with defined stereochemistries.

Me_2N-group (Schemes 2 and 3). The organolithium reagents were prepared or generated *in situ* by using known or modified published procedures [9–17].[1]

Addition of organolithium **4** [9] occurred in hexane at room temperature leading to aminoalcohol **8**, isolated in excellent yield (Scheme 2). In this case the assistance of anhydrous $CeCl_3$ was not necessary compared with previously published results [3b]. The reaction of **5** [10] and **2** was performed in hexane/Et_2O at room temperature, with the formation of **9** in good yield. The addition of the *in situ* generated **6** [11] to **2** occurs in a low yield (in hexane/Et_2O). The similar addition of **6** to (−)-fenchone (**3**) was also low yielding and an inseparable mixture of the corresponding *endo*/*exo* fenchol isomers was formed in this case (the ratio of both diastereoisomers was determined by NMR as 8:1, without unambiguous identification). Organolithium reagent **7**, possessing low thermal stability, was generated *in situ* at −60 °C [12] and the addition was performed at the same temperature to obtain **11** in good yield. Similar results have been published for the addition of **7** to (+)-camphor [18].

The addition of reagents **12**–**14** to ketones **2** and **3** is presented in Scheme 3. The 1,2-disubstituted ferrocenyllithium compound **12** was formed and used as a racemate in respect of the chirality plane [13]. Therefore after addition of **12** to **2**, the formation of two diastereoisomers is to be expected, provided only *endo*-addition occurs. Remarkably, only one diastereoisomer, **15**, was observed and isolated. No experimental evidence for the formation of other diastereoisomers could be obtained. Compound **15** was identified as the *endo*-addition product (for the configuration determination see discussion below). Additionally, 60% of the *N*,*N*-dimethylaminomethyl-ferrocene used to generate **12** was recovered after performing the addition reaction, followed by aqueous work-up procedure (see Section 4). Therefore, these results indicate that only one of the planar chiral enantiomers of **12** took part in the addition reaction, probably due to steric reasons. This suggestion is strongly supported by the results of the addition reaction of **12** to **3** in respect of the lower steric hindrance in this case during the course of the nucleophilic attack. The reaction of **12** and **3** furnished the expected two diastereoisomers **18** and **19** in respect of the chirality plane and as a result of *exo*-addition (78% overall yield, ratio **18**:**19** = 1:2). It should be pointed out that in fact the normal addition of nucleophiles to bicyclo [2.2.1]-heptan-2-ones with respect to the stereoselectivity is *exo* due to the significant repulsion caused by the *endo*-protons. However, the presence of the methyl group at the C-7 position in the case of **2** executes additional hindrance, forcing reagent **12** to add against the repulsion of the



Scheme 2. Addition of organolithiums **4**–**7** to the camphor analogue **2**.

endo-protons. The application of organolithiums **13** [14] and **14**[1] provided, in the case of **2**, products **16** and **17**, and in case of **3**, compounds **20** and **21** respectively, isolated in moderate yields.

For the synthesis of β-heteroatom functionalized derivatives of type **B** (Scheme 1), the organolithium reagents **22a**–**d** [15], **23a**–**c** [15] and **24**–**27** [15–17] were prepared *in situ* from the corresponding heterocycles [19–21] and added to ketone **3** (Scheme 4). The products **28**–**34** were isolated in moderate to excellent yields as single diastereoisomers (see Section 4) as a consequence of the expected *exo*-addition selectivity. In the case of 2-lithio-thiophene (**26**), small amounts of the bis-substituted derivative **33** were isolated. This is obviously a result of the formation of 2,5-dilithio-thiophene during the lithiation of thiophene with *n*-BuLi. The addition reactions of reagents **22**–**27** to ketone **2** were abandoned because of the discouraging enantioselectivities, achieved with products **28**–**34** applied as ligands for the addition of Et_2Zn to benzaldehyde (see below).

For the synthesis of γ-aminoalcohols, the reagent $LiCH_2CN$ (generated *in situ* from *n*-BuLi and CH_3CN) was added to ketones **2** and **3** (Scheme 5). The addition reaction was performed at −78 °C in THF to give the compounds **35** and **36**, respectively, in excellent yields, which were then reduced quantitatively to the corresponding aminoalcohols **37** and **38** (the synthesis of **36** and **38** has been previously described [3a]). Compounds **37** and **38** were the starting materials for the preparation of the dialkylamino derivatives **39**–**43**, obtained in moderate to excellent yields using a standard procedure (RX/K_2CO_3 in refluxing THF/water). Surprisingly, an attempt to prepare the *N*,*N*-dimethyl substituted aminoalcohol from **37** using HCHO/HCOOH (Eschweiler–Clarke procedure) led, under the reaction conditions, to a new undesired product, assigned as the heterocyclic derivative **44**.

The structures of the new chiral compounds were established by NMR experiments and mass spectra. The unambiguous assignment

[1] To best of our knowledge there is no published procedure for the preparation of reagent **14**, so we have successfully used the *in-situ* procedure described for the preparation of **13**, starting from 2-(*N*,*N*-dimethylamino)-pyridine.