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The conjugate addition of enantiomerically pure lithium amides as chiral ammonia equivalents part III: 2012–2017

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ABSTRACT

This review covers further applications of the conjugate addition of enantiomerically pure lithium amides as chiral ammonia equivalents in asymmetric synthesis and provides an update since our last review of this area, which was published in 2012.

Contents

1. Introduction

We published a comprehensive review concerning the development, scope and applications of the conjugate additions of enantiomerically pure lithium amides (which act as chiral ammonia equivalents) in 2005[1] and an update covering 2005–2011 was published 2012.[2] Since then, this methodology has continued to be employed in asymmetric synthesis: particularly, numerous applications have been reported which elaborate the resultant β-amino esters/amides to a wide range of biologically important targets. Accordingly, several synthetic methodologies have also been developed which utilise the enantiopure β-amino esters/amides to access various other synthetic motifs. This review will provide a further update on reports and applications of the conjugate additions of enantiomerically pure lithium amides in asymmetric synthesis covering the period of 2012 to date.

2. The conjugate addition of enantiomerically pure lithium amides

The highly diastereoselective conjugate addition of enantiomerically pure lithium *N*-benzyl-*N*-(α-methyl benzyl)amide **2** to α,β-unsaturated esters was originally reported in 1991.[3] The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**2** to methyl *p*-benzyloxycinnamate **1** in THF at −78 °C gave β-amino ester **3** in 78% yield as a single diastereoisomer (>99:1 dr). Hydrogenolysis of the *N*-benzyl and *O*-benzyl groups in the presence of $Pd(OH)_2/C$ and subsequent acid-mediated ester hydrolysis in aq HCl under reflux gave (*S*)-β-tyrosine·hydrochloride **5**·HCl in

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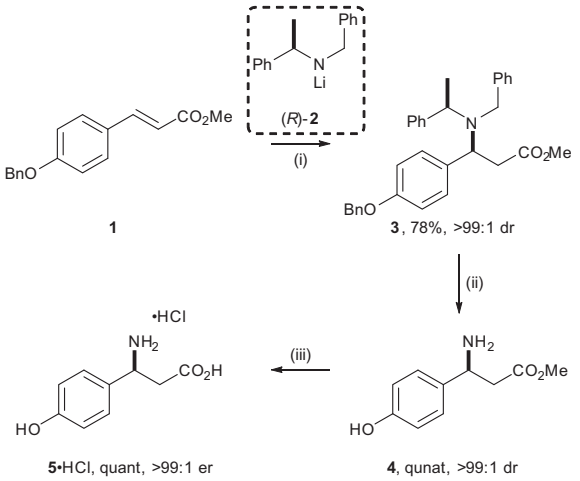

Scheme 1. *Reagents and conditions*: (i) (*R*)-**2**, THF, −78 °C, 15 min; (ii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH/H_2O/AcOH (v/v 40:4:1), 20 °C, 18 h; (iii) aq HCl, reflux, 16 h.

quantitative yield and >99:1 er (Scheme 1). Since this original report, this methodology has been employed routinely in organic synthesis,[4] demonstrating a wide range of substrate scope (~300 examples) and consistently high diastereoselectivity (typically >95:5 dr).

In addition to lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **2**, which has been utilised most commonly, several other enantiomerically pure lithium amides have also been employed. The lithium amide reagents that appeared in the literature since 2011 are listed below (Fig. 1).

Based upon molecular modelling calculations, a transition state mnemonic was proposed to rationalise the diastereoselectivity observed upon conjugate addition.[5] In order to gain further insight into the mechanism of this process, some studies towards elucidating the structure of lithium amide reagents in solution have been reported more recently.[6] We have determined the solution structure of both enantiopure and racemic, doubly labelled ^{6}lithium ^{15}*N*-benzyl-^{15}*N*-(α-methylbenzyl)amide, which exists as dimers in THF, as determined by ^{6}Li and ^{15}N NMR spectroscopic analysis at low temperature.[7,8] Garrido et al. employed QM calculations in combination with MM sampling to explore the conformational structure of the transition state in this reaction. Their results suggested that the main potential transition state geometries are two conformers in a "V-stacked" orientation of the lithium amide's phenyl rings.[9]

2.1. Conjugate addition of enantiomerically pure lithium amides to β-alkyl- and β-aryl-α,β-unsaturated esters and amides

The conjugate addition of enantiomerically pure lithium amides has been applied to a number of α,β-unsaturated esters and amides, with a wide range of functionality including protected amino groups, halides, protected and free-hydroxyl groups, carboxylic acids, alkenyl groups, and heterocycles. All of the recent examples, reported since 2011, are listed below (Table 1).

2.2. Conjugate addition to chiral substrates: doubly diastereoselective reactions

The stereochemical outcome of conjugate additions of enantiomerically pure lithium amide reagents to chiral α,β-unsaturated carbonyl compounds is also influenced by the stereochemistry of the substrate in a doubly diastereoselective reaction. When the two chiral species (i.e., chiral lithium amide reagent and chiral α,β-unsaturated carbonyl compound) favour formation of the same diastereoisomeric product, this reaction would lead to very high diastereoselectivity, which is called a "matched" reaction, whereas when the two chiral species favour opposite stereochemical outcomes, lower diastereoselectivity is generally observed, which is termed a "mismatched" reaction. The inherent level of substrate control of the chiral α,β-unsaturated ester can be predicted upon conjugate addition of an achiral lithium amide, such as *N*-benzyl-*N*-isopropylamide, which we have found to be a good model for lithium *N*-benzyl-(*N*-α-methylbenzyl)amide **2**. In general, reagent control from the chiral lithium amide is dominant over substrate control for chiral α,β-unsaturated carbonyl compound, with a few notable exceptions. Depending on the nature of the chiral α,

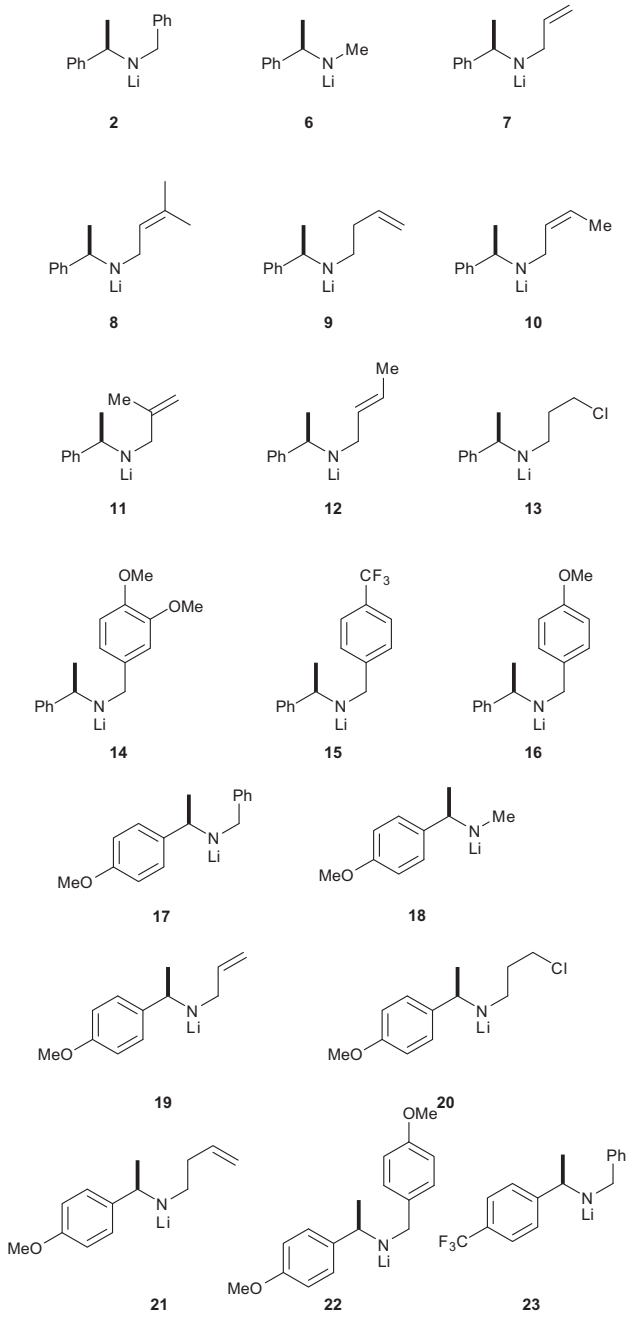

Figure 1. Enantiomerically pure lithium amides **2** and **6**–**23** as chiral "ammonia equivalents". Chiral lithium amide reagents are depicted here as their (*R*)-enantiomers in all cases, regardless of which antipode was employed in the original reports.