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In search of diamine analogs of the α,α-diphenyl prolinol privileged chiral organocatalyst. Synthesis of diamine derivatives of α,α-diphenyl-(*S*)-prolinol and their application as organocatalysts in the asymmetric Michael and Mannich reactions

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ABSTRACT

This paper describes improved reaction conditions for the substitution of the hydroxyl group in (*S*)-diphenyl(pyrrolidin-2-yl)methanol by the azide group, which was then reduced to the diamine derivative. We examined two protecting groups (*N*-Bn and *N*-Boc) on the pyrrolidine nitrogen in order to functionalize the primary amino group into various amide, alkylated amine, sulfonamide, thiourea and triazole derivatives. Notably, carefully controlled conditions were required to generate the desired derivatives from the sterically hindered benzhydrylamine moiety. Unexpectedly, upon removal of the *N*-protecting group in derivatives containing electrophilic polar double bonds (C=S, C=O) cyclization took place, affording products such as amidines. The target compounds were evaluated as bifunctional organocatalysts in the asymmetric Michael and Mannich addition reactions. (*S*)-2-(Azidodiphenylmethyl) pyrrolidine (*S*)-**7** was identified as the most efficient organocatalyst among the various diamine derivatives of α,α-diphenyl-(*S*)-prolinol prepared in this work.

1. Introduction

Chiral β-aminoalcohols containing bulky substituents, in particular the geminal diphenyl segment, constitute an important group of ligands with diverse applications in asymmetric synthesis and catalysis. In this regard, oxazaborolidine derivatives prepared from α,α-diphenyl-(*S*)-prolinol have been extensively applied in the enantioselective reduction of prochiral ketones.[1] Emblematic organocatalysts containing the α,α-diaryl-(*S*)-prolinol segment do not only include free β-amino alcohols as bifunctional molecules,[2] but also the corresponding silyl ether derivatives.[3] As anticipated, the high stereoinduction achieved by means of these organocatalysts originates for the most part from the distinctive geminal biaryl group.[4]

In 2008 our research group accomplished the first synthesis of the *N*-benzylated (*S*)-proline-azide (*S*)-**3**, by means of the replacement of the tertiary hydroxyl group in (*S*)-**2** with azide anion as nucleophile, via a S_N1 type substitution. This substitution reaction required the use of strongly acidic conditions (aq H_2SO_4), which provided the corresponding carbocation precursor of azide (*S*)-**3** and hence, of diamine (*S*)-**5**. Enantiopure diamine (*S*)-**5** was treated with borane in order to afford the desired diazaborolidine precatalyst for the asymmetric reduction of carbonyl compounds (Fig. 1).[5] It should be noticed that also in 2008, Ooi et al.[6] described the preparation of several chiral diamines derived from L-valine, L-isoleucine and L-*tert*-leucine via azidation of the corresponding diarylamino alcohols.

In subsequent years, the synthesis and application of analogs of azide (*S*)-**3** and diamine (*S*)-**5** aroused considerable interests. It can be appreciated that the key step in the preparation of novel diamine (*S*)-**5** corresponds to the replacement of the tertiary hydroxyl group in aminoalcohol (*S*)-**6** by azide, by means of strong Brønsted acids (Fig. 2). While we initially employed aqueous sulfuric acid to replace the hydroxyl group via a S_N1 reaction, Zhong and co-workers[7] obtained azide (*S*)-**7** by means of TFA instead of H_2SO_4, and used it directly as catalyst in a novel asymmetric formally [4+1] annulation to generate *cis*-isoxazoline *N*-oxides.

In order to synthesize *N*-protected azide (*S*)-**3**, Asami and coworkers employed a mixture of H_2SO_4 and CF_3CO_2H in biphasic media under reflux.[8] These researchers also employed azide (*S*)-**3** as precursor of diamine (*S*)-**5**, whose primary amine functionality

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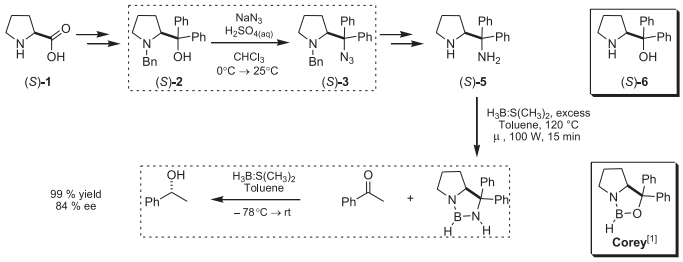


Fig. 1. Synthesis and application of a diazaborolidine analog of the Corey–Bakshi–Shibata (CBS) oxazaborolidine catalyst.

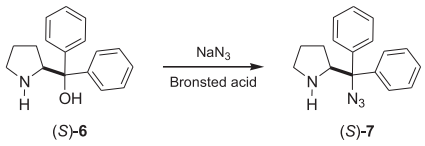


Fig. 2. Azidation reaction of tertiary alcohol (*S*)-**6** via S_N1 substitution of the hydroxyl group by means of strong Brønsted acid.

was *N*-phenylated to obtain an analog of the diazaborolidine catalyst. On the other hand, Lee and co-workers obtained a series of chiral aminoazides, including (*S*)-**7**, employing a biphasic reaction media of H_2SO_4-toluene.[9,10]

Recently, Connon and co-workers evaluated *N*-acylated derivatives of (*S*)-**7** in the kinetic resolution of alcohols,[11] while Bez and co-workers[12] examined several Cu(II) complexes of azide (*S*)-**3** and their derivatives as catalysts in the asymmetric Henry reaction, achieving moderate results. Recently, Kesavan and co-workers[13] developed an *N*-methylated pyrrolidine-thiourea derivative from (*S*)-**7**, which was evaluated as potential catalyst in the Michael addition of 1,3-dicarbonyl compounds to nitroolefins; however, this derivative was not effective in this specific reaction.

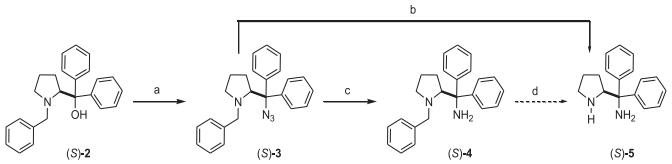
Nevertheless, it is worth mentioning that there are some important structural features of this class of pyrrolidine diamine derivatives that have not been properly addressed in the literature. Indeed, despite the apparent structural similarity of diamine (*S*)-**5** and aminoalcohol (*S*)-**6**, particular reactivity patterns decisively affect the possibility of handling and applying the former diamine (*S*)-**5** and derivatives thereof in asymmetric organocatalysis.

Hence, we revisited some proline diamine derivatives that were already described in the literature, and developed several novel derivatives as well. Nevertheless, in the present work we focused mainly in the preparation of compounds presenting an unsubstituted N–H pyrrolidine nitrogen, so that they could be evaluated as bifunctional organocatalysts. In this regard, asymmetric organocatalysis via enamine has proven to be one of the most effective methods to carry out enantioselective α-functionalizations on aldehydes and ketones. In particular, asymmetric Michael and Mannich addition reactions seemed to be attractive applications of our proline-derived catalysts because of their structural resemblance with the intensively studied (*S*)-2-[diphenyl(trimethylsilyloxy) methyl] pyrrolidine (Jørgensen–Hayashi catalyst[3]).

2. Results and discussion

2.1. Synthesis of (*S*)-(*N*-benzylpyrrolidin-2-yl)diphenyl-methanamine, (*S*)-4, and derivatives

Azide (*S*)-**3** was prepared via azidation reaction of tertiary alcohol (*S*)-**2** using the methodology developed in our group[5] with some minor modifications. Specifically, it was found that best results are obtained when employing 70% aqueous sulfuric



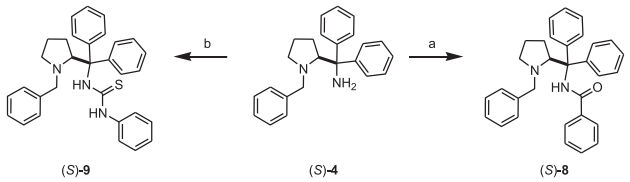
Reagents and conditions: (a) $H_2SO_{4(aq)}$ 70 %-v, $CHCl_3$, 5 equiv. NaN_3, 10 °C, 15 h; (b) 120 psi H_2, 20 %-w $Pd(OH)_2/C$, MeOH, 60 °C, 99 %; (c) 4 equiv. $LiAlH_4$, THF, reflux, 4 h, 95 %; (d) 60 psi H_2, 10 %-w Pd-C, AcOH, MeOH, rt, 24 h, 99 %.

Fig. 3. Azidation reaction of (*S*)-**2** in the preparation of key intermediate (*S*)-**3**, and subsequent reduction to afford diamines (*S*)-**4** and (*S*)-**5**.

acid and temperatures around 10–15 °C (Fig. 3). Indeed, the homogeneity of the reaction emulsion was improved at this acid concentration and slightly higher reaction temperature (10–15 °C instead of 0 °C, as initially used[5a]). Under these conditions, agglomeration and precipitation of alkyl ammonium sulfate is prevented, and this facilitates the subsequent reaction with hydrazoic acid.

With the desired amino azide (*S*)-**3** at hand, diamine (*S*)-**5** could be directly obtained through catalytic hydrogenation with $Pd(OH)_2$ at 120 psi H_2 and heating to 60 °C. On the other hand, diamine (*S*)-**4** was prepared in good yield by reducing the azido functionality in (*S*)-**3** with $LiAlH_4$ under THF reflux, as previously described[5a] (Fig. 3).

In the initial attempts to functionalize (*S*)-**4**, neither alkyl halides nor *p*-toluenesulfonyl chloride were sufficiently reactive to afford the expected *N*-alkylated or *N*-sulfonylated products. This lack of reactivity was observed when bulky amine (*S*)-**4** was treated with the corresponding reagents either at room temperature, under conventional heating, or even with microwave activation. By contrast, reactions carried out with electrophilic reagents containing polarized carbon-heteroatom double-bond did give rise to the desired N-functionalization of the sterically hindered exocyclic nitrogen. In particular, treatment of (*S*)-**4** with benzoyl chloride generated amide (*S*)-**8** and thiourea (*S*)-**9** was obtained by means of Edman's reagent (Fig. 4).



[a]Reagents and conditions: (a) 1.2 equiv. BzCl, 1.3 equiv. Et_3N, 0.5 equiv. DMAP, THF, rt, 72 h, 78 %; (b) 1.6 equiv. Ph–N=C=S, THF, rt, 72 h, 92 %.

Fig. 4. Successful functionalization of the sterically hindered primary amino group in (*S*)-**4**.[a]

Debenzylation of derivatives (*S*)-**8** and (*S*)-**9** was attempted under the conditions that previously had been effective in the hydrogenolysis of (*S*)-**3**, i.e. 20% $Pd(OH)_2/C$ in AcOH/methanol under hydrogen pressure (Fig. 5). However, instead of obtaining the desired N–H products, amide (*S*)-**8** generated cyclic amidine (*S*)-**10** by water loss (Fig. 5), while thiourea (*S*)-**9** produced cyclic thiourea (*S*)-**11** by loss of aniline (Fig. 6). These unanticipated processes are explained by an intramolecular attack of the free pyrrolidine nitrogen towards the electrophilic carbonyl or thiocarbonyl functions. The formation of cyclic derivatives (*S*)-**10** and (*S*)-**11** was corroborated by means of X-ray crystallography.

Examination of the X-ray crystallographic structure of thiourea (*S*)-**9** (Fig. 6) makes evident the proximity between the pyrrolidine