Tetrahedron: *Asymmetry* 26 (2015) 1273–1280

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of a series of ω-dimethylaminoalkyl substituted ethylenediamine ligands for use in enantioselective catalysis

Subrata K. Ghosh [a], Carola Ganzmann [b], John A. Gladysz [a,*]

[a] *Department of Chemistry, Texas A&M University, PO Box 30012, College Station, TX 77842-3012, USA*
[b] *Institut für Organische Chemie and Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Henkestrasse 42, 91054 Erlangen, Germany*

ARTICLE INFO

Article history:
Received 5 September 2015
Accepted 24 September 2015
Available online 22 October 2015

ABSTRACT

The title compounds $H_2NCH((CH_2)_nNMe_2)CH_2NH_2$ **L1**–**L4** (n = 1–4) are efficiently synthesized in enantiopure form. The commercial starting materials, L-asparagine, (*S*)-5-hydroxymethyl-2-pyrrolidinone, and (*S*)-6-(((benzyloxy)carbonyl)-amino)-2-((*tert*-butoxycarbonyl)amino)hexanoic acid, are elaborated in 6–9 standard steps to give **L1** (18% overall), **L2** (13%), **L3** (36%) and **L4** (38%) or the corresponding tris(hydrochloric acid) salts $[H_3NCH((CH_2)_nNHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$, which are preferable for long term storage. The sequences make use of isobutyl carbamate, Cbz, and Boc protecting groups and Hofmann type rearrangements; the dimethylamino groups are introduced at late stages, either via reductive dimethylations or nucleophilic displacements involving mesylates and $HNMe_2$. **L1**–**L4** chelate to $[Co(en)_2]^{3+}$ fragments to give octahedral complexes that catalyze numerous enantioselective reactions.

1. Introduction

Over the last fifteen years, a variety of small molecule hydrogen bond donor catalysts have been developed and found diverse applications in enantioselective syntheses.[1] Some of the most useful catalysts have been based upon urea and thiourea moieties.[2] These readily bind to a number of Lewis basic organic functional groups, as demonstrated by a series of crystal structures.[3] Importantly, some of the most effective urea and thiourea catalysts are bifunctional, incorporating an auxiliary tertiary amine group.[2b,4] This can serve as either a Lewis or Brønsted base during the catalytic cycle.

We have begun to study Werner complexes as possible NH hydrogen bond donor catalysts for enantioselective organic syntheses.[5,6] This includes the historically important chiral-at-metal tris(ethylenediamine)cobalt trication $[Co(en)_3]^{3+}$, which was among the first few inorganic species to be resolved into enantiomers,[7] as well as analogues with substituted diamines, such as 1,2-diphenylethylenediamine (dpen).[6] We have also developed cationic ruthenium complexes in which NH bonds remote from the metal effect the catalysis.[8,9] Dramatic improvements in the performance of this catalyst family were realized when dimethylamino substituents were incorporated into the NH containing ligand.[8b] Closely related themes have also received attention from Meggers et al.[10]

In our first communication, which focused on the additions of malonates to enones in organic media, we were only able to realize modest enantioselectivities using lipophilic salts of $[Co(en)_3]^{3+}$.[5] We speculated that the adducts of ethylenediamine ligands containing an ω-dimethylaminoalkyl substituent might give improved results. Hence, we sought to synthesize a series of ligands $H_2NCH((CH_2)_nNMe_2)CH_2NH_2$ in enantiopure form, so that they could be incorporated into cobalt complexes such as $\mathbf{I}^{3+}$ (Fig. 1) without increasing the numbers of diastereomers.

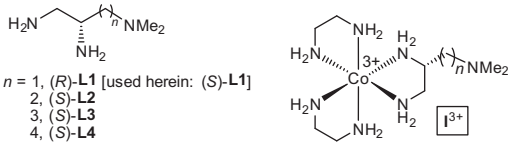


Figure 1. Target ligands and complexes.

Curiously, we could only locate one such triamine in the literature, that with n = 2.[11] The overall yield was modest, and only the ^{1}H NMR spectrum and specific rotation were reported. Hence, we set out to prepare ligands with n = 1–4, termed **L1**–**L4** (Fig. 1), and/or the functionally equivalent tris(hydrochloric acid) salts. Herein, we describe practical six to nine step syntheses for all of these species from inexpensive, commercially available enantiopure starting materials in 38–13% overall yields (average: 26%),

* Corresponding author.
E-mail address: gladysz@mail.chem.tamu.edu (J.A. Gladysz).

http://dx.doi.org/10.1016/j.tetasy.2015.09.012
0957-4166/

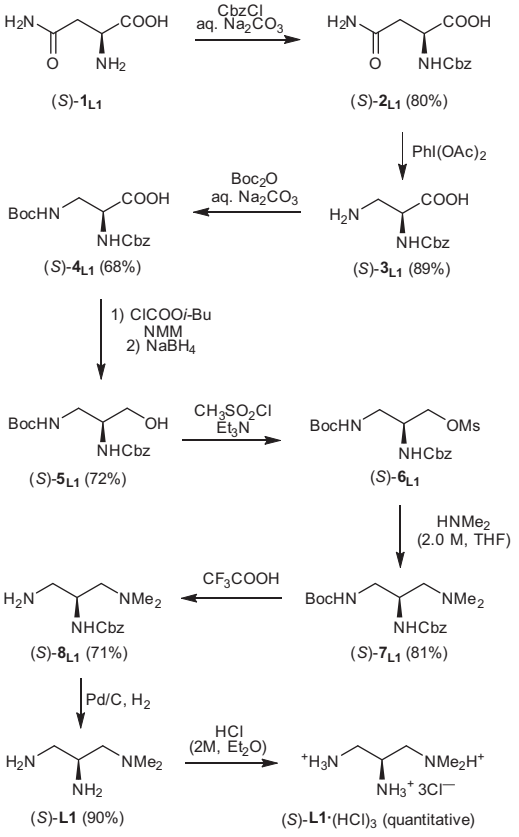
and their detailed characterization. The applications of these ligands will be described separately.[12]

2. Results

2.1. Synthesis of ligand L1

As shown in Scheme 1, commercial (*S*)-asparagine [L-asparagine or (*S*)-**1$_{L1}$**][13a] was elaborated in a series of five known steps.[14,15] The first step involved treatment with CbzCl to give the Cbz protected amine (*S*)-**2$_{L1}$** (our yield/lit: 80/84%).[14a] A Hofmann type rearrangement was then effected with PhI(OAc)$_2$ to give ß-amino acid (*S*)-**3$_{L1}$** (our yield/lit: 89/89%),[14b] which was protected with Boc to afford (*S*)-**4$_{L1}$** (our yield/lit: 68/91%).[14a,16] Following a patent procedure, the carboxylic acid was activated with isobutyl chloroformate, after which a reaction with $NaBH_4$ gave the primary alcohol (*S*)-**5$_{L1}$** (our yield/lit: 72/55%).[15,16] Mesylation was effected to give (*S*)-**6$_{L1}$**,[15] the last known compound in this sequence, which was employed in the following step assuming a quantitative yield.

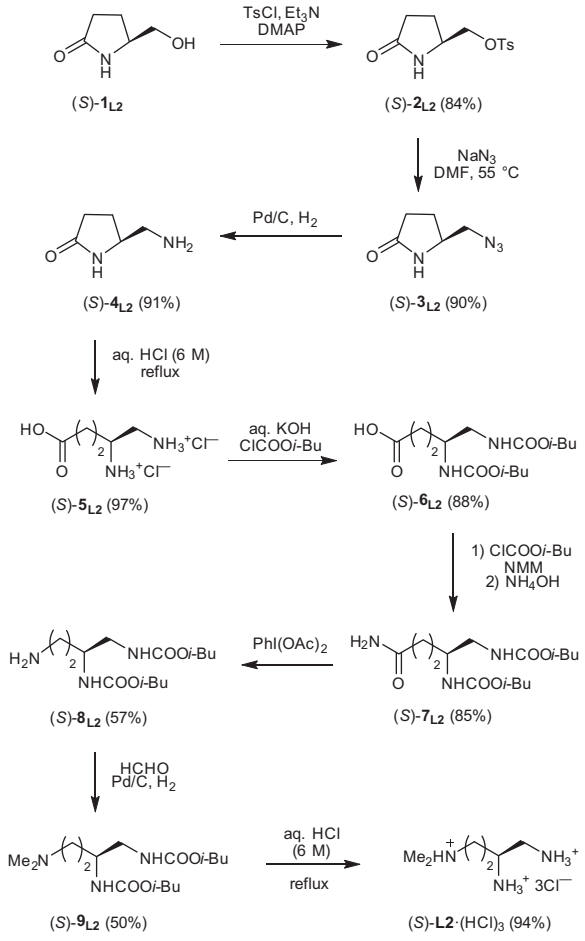
In order to introduce the dimethylamino group, (*S*)-**6$_{L1}$** and a THF solution of $HNMe_2$ were refluxed (Scheme 1). Work up gave the protected triamine (*S*)-**7$_{L1}$** (81%, two steps). The addition of CF_3CO_2H removed the Boc protecting group, to afford the diamine (*S*)-**8$_{L1}$** (71%). Hydrogenolysis then detached the Cbz group, to give the target triamine (*S*)-**L1** (90%) in 18% overall yield from (*S*)-**1$_{L1}$**. For long term storage, this was converted into the tris(hydrochloric acid) salt (*S*)-[$H_3NCH((CH_2)NHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$ ((*S*)-**L1**·$(HCl)_3$) in 99% yield. This sequence has been repeated by several coworkers, sometimes with even higher yields than those indicated above and in the experimental section (maximum values for the first five yields in Scheme 1: 85%, 90%, 80%, 80%, 86%).



Scheme 1. Synthesis of the tris(hydrochloric acid) salt of (*S*)-**L1**.

2.2. Synthesis of ligand L2

As shown in Scheme 2, commercial (*S*)-5-hydroxymethyl-2-pyrrolidinone (*S*)-**1$_{L2}$**[13b] was elaborated in a series of five known steps.[17] The first involved treatment with tosyl chloride to give the tosylate (*S*)-**2$_{L2}$** (our yield/lit: 84/93%).[17a] Subsequent reaction with NaN_3 afforded (*S*)-**3$_{L2}$** (our yield/lit: 90/99%).[17a] The azide was reduced to the primary amine (*S*)-**4$_{L2}$** with Pd/C and H_2 (our yield/lit: 91/99%).[17a] Hydrolysis (6 M HCl) then provided (*S*)-**5$_{L2}$** (our yield/lit: 97/83%).[17b] Both primary amine groups were protected using isobutyl chloroformate to give (*S*)-**6$_{L2}$** (our yield/lit: 88/88%).[17b]



Scheme 2. Synthesis of the tris(hydrochloric acid) salt of (*S*)-**L2**.

We next sought to remove a methylene group from the carboxylic acid chain. Thus, (*S*)-**6$_{L2}$** was first converted into the corresponding amide (*S*)-**7$_{L2}$** (85%), a new compound. A modified Hofmann rearrangement was then carried out using PhI(OAc)$_2$. The resulting primary amine (*S*)-**8$_{L2}$** (57%) was a known compound.[17b] A reductive dimethylation (aqueous HCHO, Pd/C, H_2) yielded the new tertiary amine (*S*)-**9$_{L2}$** (50%). Refluxing aqueous HCl afforded the tris(hydrochloric acid) salt (*S*)-[$H_3NCH((CH_2)_2NHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$ (*S*)-**L2**·$(HCl)_3$ as a colorless sticky compound in 13% overall yield from (*S*)-**1$_{L2}$**. As noted above, this compound has been previously synthesized, but in only 7% overall yield, although the sequence involved one fewer step.[11]

2.3. Synthesis of ligand L3

As shown in Scheme 3, **L3** can be accessed using (*S*)-**6$_{L2}$** from Scheme 2. The carboxylic acid was first activated with isobutyl