



^{15}N -D-labeled ionic probes for mass spectrometry

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ABSTRACT

An effective ^{15}N - and deuterium (D)-labeled 2,6-bis(oxazolin-2-yl)pyridine (pybox)–La complex based probe ionization method that produces a distinct isotopic shift was developed. The distinct isotopic shift was detected by using the newly synthesized ^{15}N -D-labeled pybox complexes. Moreover, O-[3-(tetramethylpybox)-propyl]-hydroxylamine (oxime–TMpybox) was prepared for attachment to the carbonyl group of the target molecule. Distinct isotopic shifts and multiple charged ions were detected for various compounds having amino, thiol, carboxyl, and carbonyl groups and fullerenes, using the TMpybox ionic probe series in cold-spray ionization mass spectrometry.

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1. Introduction

Bis(oxazoliny)pyridine tridentate ligands were first developed by Nishiyama et al. for enantioselective organometallic catalysis,¹ and have been used to generate chiral Lewis acid catalysts with transition metals and lanthanides. Recently, chiral mass spectrometry (MS) was reported to be a new approach for stereochemical analysis because of its speed and simplicity.² In particular, using an isotope-labeled pybox–metal complex, Arakawa et al. reported an excellent method for the determination of heterochirality, which uses electrospray ionization (ESI)-MS.³ Isotope

labeling is highly useful for precise structure analysis as well as trace analysis in MS.⁴

Previously, we developed MS probes, including NHS–TMpybox **1**, Mal–TMpybox **2**, BrAc–TMpybox **3**, and Sar–TMpybox **4**. These probes can donate multiple charges contained in their respective metal charged sites to the target compound in order to analyze large complex molecules, including biomolecules,⁵ and large carbon clusters, such as fullerenes,⁶ in soft ionization conditions (Fig. 1). These ionic probes enable us to obtain ^{15}N -labeled compounds by complexation with ^{15}N -labeled pybox–La complex, as exemplified by (1+6), thereby allowing comparison of the isotopic

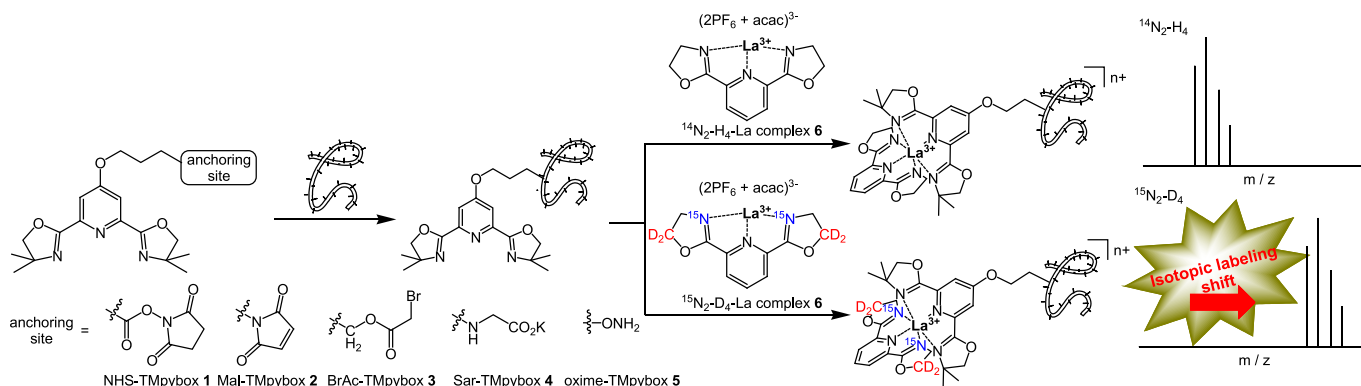


Fig. 1. Ionic probe attachment ionization mass spectrometry.

shifts between labeled and non-labeled ionic probe attached biomolecules and fullerenes.^{6,7} However, the isotopic shift induced by ^{15}N labeling was not distinct because the difference was only 0.7–1.3 u. Therefore, we prepared $^{15}\text{N}_2\text{-D}_4$ -labeled pybox–La

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complex **6** ($^{15}\text{N}_2\text{-D}_4\text{-6}$) in an attempt to observe the extended isotopic shift clearly. We also prepared a new MS probe, oxime-TMpybox **5**, which can react with the carbonyl group of the target molecule. Various carbonyl compounds are important for human physiology and a major concern in environmental chemistry. Testosterone, an important hormone, shows low ionization efficiency because of its steroid moiety.⁸ In this paper, we describe the preparation of the $^{15}\text{N}_2\text{-D}_4$ -labeled ionic probes, including oxime-TMpybox **5**, which can selectively react with the carbonyl group, for isotope-labeled MS in soft ionization conditions by using cold-spray ionization MS (CSI-MS).⁹

2. Results and discussion

Oxime-TMpybox **5** and $^{15}\text{N}_2\text{-D}_4\text{-6}$ were prepared as follows (Scheme 1). Pybox **9** was obtained by alkylation of 4-hydroxypybox **7**,⁵ which was prepared from chelidamic acid in six steps in 32% yield, with phthalimide **8**.¹⁰ Treatment of **9** with hydrazine monohydrate gave oxime-TMpybox **5** in quantitative yield. After ethyl ester **10**, which was prepared from pyridine 2,6-dicarbonyl dichloride and glycine- ^{15}N ethyl ester in 77% yield,⁵ was reduced with NaBD_4 and LiCl to furnish diol **11** in 79% yield,³ diol **11** containing two hydroxyl groups was converted into dichloride **12** in 76% yield. Finally, $^{15}\text{N}_2\text{-D}_4\text{-6}$ was obtained by construction of an oxazoline ring and complexation with La. Synthesized probe **5** and $^{15}\text{N}_2\text{-D}_4\text{-6}$ were then introduced to testosterone (TS) and cinnamaldehyde (CA), and CSI-MS measurement was conducted to confirm the specific probe attachment of **5** and the ^{15}N and D isotope labeling.¹¹

5-Bound molecules were prepared as follows (method E). After a pyridine solution of target carbonyl compound and **3** was stirred at 80 °C, the solution containing the derivative was poured into a MeCN solution of $^{14}\text{N}_2\text{-H}_4$ - or $^{15}\text{N}_2\text{-D}_4\text{-6}$.

The CSI mass spectra of $^{14}\text{N}_2\text{-H}_4$ -, $^{15}\text{N}_2\text{-H}_4$ -, and $^{15}\text{N}_2\text{-D}_4$ -carbonyl compounds are shown in Fig. 2. In the case of ($^{14}\text{N}_2\text{-H}_4\text{-6+5}$)- and ($^{15}\text{N}_2\text{-H}_4\text{-6+5}$)-bound CA, doubly charged ions of $[\text{M}+\text{acac}^-]^{2+}$ (m/z : 465 and 466) were detected, respectively (Fig. 2a and b). Similarly, the ion of $[\text{M}+\text{acac}^-]^{2+}$ (m/z : 468) was detected in ($^{15}\text{N}_2\text{-D}_4\text{-6+5}$)-bound CA (Fig. 2c). This isotope-labeled ion was partially exchanged from 'D' to 'H' (m/z : 467.4; $^{15}\text{N}_2\text{-H}_2\text{-D}_2$ and m/z : 467.9; $^{15}\text{N}_2\text{-H}_1\text{-D}_3$). In the case of ($^{14}\text{N}_2\text{-H}_4\text{-6+5}$)- and ($^{15}\text{N}_2\text{-H}_4\text{-6+5}$)-

bound TS, doubly charged ions of $[\text{M}+\text{acac}^-]^{2+}$ (m/z : 543 and 544) were detected, respectively (Fig. 2d and e). Similar to CA, the isotope-labeled ion $[\text{M}+\text{acac}^-]^{2+}$ (m/z : 546), together with the partially exchanged composition from 'D' to 'H' (m/z : 545.5, $^{15}\text{N}_2\text{-H}_2\text{-D}_2$ and m/z : 546.0, $^{15}\text{N}_2\text{-H}_1\text{-D}_3$), was detected. Compared with $^{14}\text{N}_2\text{-H}_4$ - and $^{15}\text{N}_2\text{-D}_4$ -bound carbonyl compounds, the isotopic shift of m/z ca. 3.0, corresponding to the increase in mass induced

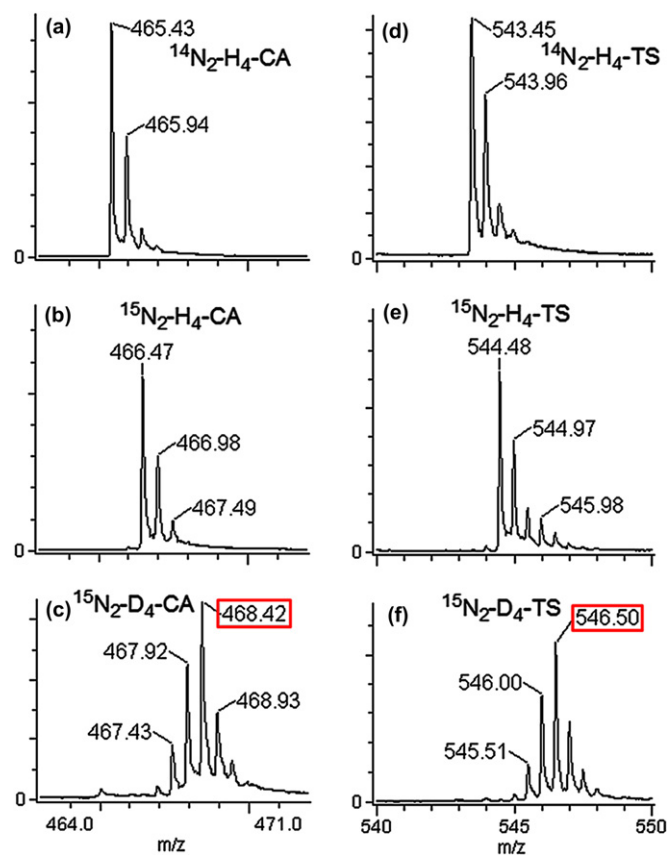
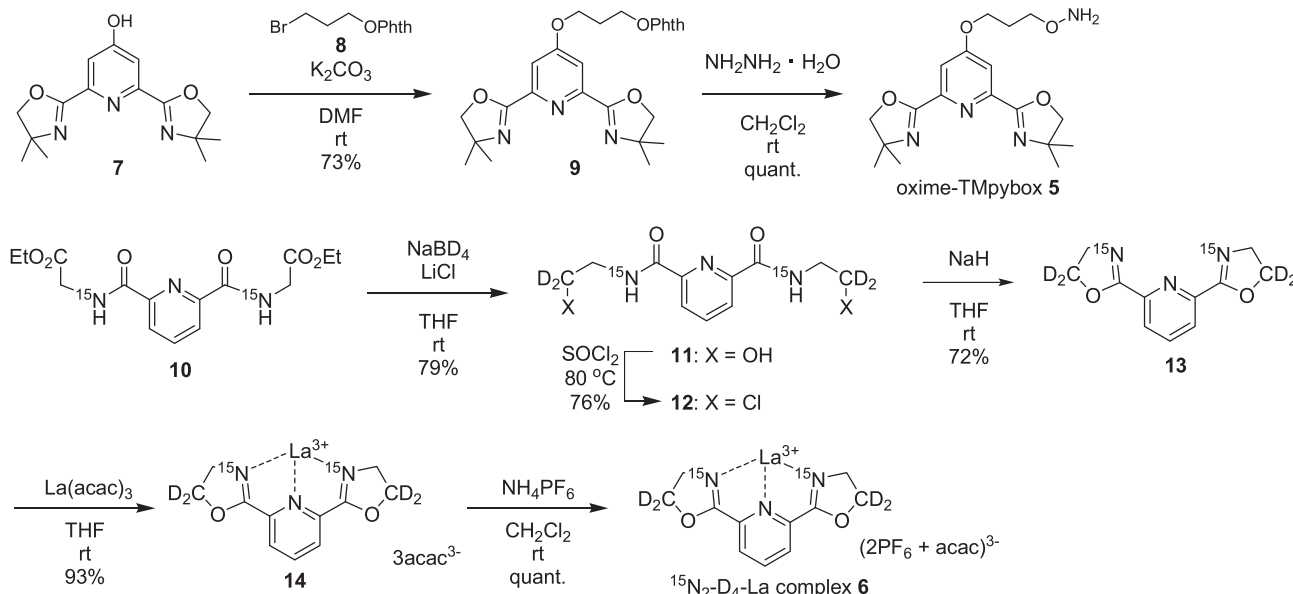


Fig. 2. CSI mass spectra of (a) ($^{14}\text{N}_2\text{-H}_4\text{-6+5}$)-CA, (b) ($^{15}\text{N}_2\text{-H}_4\text{-6+5}$)-CA, (c) ($^{15}\text{N}_2\text{-D}_4\text{-6+5}$)-CA, (d) ($^{14}\text{N}_2\text{-H}_4\text{-6+5}$)-TS, (e) ($^{15}\text{N}_2\text{-H}_4\text{-6+5}$)-TS, and (f) ($^{15}\text{N}_2\text{-D}_4\text{-6+5}$)-TS.



Scheme 1. Preparation of oxime-TMpybox **5** and $^{15}\text{N}_2\text{-D}_4\text{-6}$.

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