Summer Scholar Report

An investigation of the synthesis and transmetalation chemistry of tris(aryl)tren ligands

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Introduction

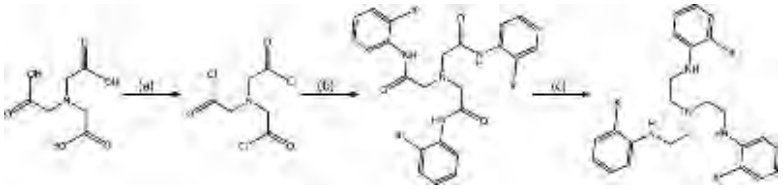
Tripodal ligands based on the tris(2-aminoethyl)amine (TREN) backbone have been used for more than 25 years to support a wide variety of interesting coordination compounds.[1] When fully deprotonated, the ligand is trianioinic, possessing three amido coordination sites and one amino coordination site, providing a tetradentate metal binding pocket. The ligand is able to stabilize metals in the +3 oxidation state, and favors a C_3 symmetric coordination environment, leaving an open coordination site on the metal at an axial position of a trigonal bipyramid (Figure 1). These ligands have been used to stabilize molybdenum compounds able to reduce dinitrogen,[2] zirconium compounds able to catalyze insertion reactions,[3] and novel actinide complexes.[4]

Figure 1. *The generic structure of the TREN ligand set, showing a metal bound in the tetradentate, tripodal tris(amido)amine binding pocket.*

To date, all TREN ligands possess a symmetric substitution pattern, with the same group on each of the three amido nitrogens of the ligand. A search of the Cambridge Structural Database reveals 436 metal complexes of TREN ligands. The vast majority of these complexes are tris(silyl)trens, where each amido nitrogen possesses trialkyl- or triaryl-silyl group. The synthesis of these ligands begins with the parent tris(2-aminoethyl)amine followed by a condensation with a chlorosilane.[1] Less common, but still studied, are tris(aryl)tren ligands (81 of 436 structures). The general synthesis of these ligands also begins with the parent tris(2-aminoethyl)amine and proceeds with a Buchwald-Hartwig coupling to generate the TREN ligands.[5] This synthesis is effective, though it requires the use of expensive catalysts and extensive purification.

Ligand Synthesis

In our lab, we have developed an alternative synthesis for TREN ligands, which rather than starting from the parent tris(2-aminoethyl)amine, starts from the significantly less expensive nitrilotriacetic acid.[6,7] We first convert nitrilotriacetic acid to nitrilotriacetic chloride through the use of phosphorus (V) chloride. This triacid chloride is then coupled with an aniline, using triethylamine as a sacrificial base, resulting in a nitrilotriacetamide. The nitrilotriacetamide is then reduced with lithium aluminum hydride or borane to generate the tris(aryl)tren ligand. The benefit of this synthesis, beyond the less expensive starting materials, is that it can be easily modified. By simply changing the aniline in the synthesis, the aromatic group on the tren ligand is altered. This synthesis offers many benefits, including a low cost, a scalable synthesis (>10 grams), simple purification steps, and is outlined in Scheme 1.



Scheme 1. *The modular synthesis of tris(aryl)tren ligands, where (a) is phosphorus (V) chloride, (b) is 3 equivalents of 2-X-aniline (X = H, Cl, Br, I, SMe, SPh), 3 equivalents of triethylamine and (c) is lithium aluminum hydride or borane.*

Figure 2 shows the crystal structures for some of the products of this synthesis. The initial product of the aniline coupling is a nitrilotriacetamide, which can itself function as a ligand.[8] The structures observed for the nitrilotriacetamides tend to be splayed out, with the three arms spread in a relatively planar fashion. There are N–H···O intermolecular hydrogen bonds in these ligands that enforce this geometry in the solid state. By contrast, the structures of the reduced TREN ligands demonstrate a C_3 symmetric crystal structure. There are three N–H···N intramolecular hydrogen bonds that hold the three arms up from the nitrogen of the tertiary amine. The NMR of both the nitrilotriacetamides and the TREN ligands demonstrate three equivalent arms in the solution phase.

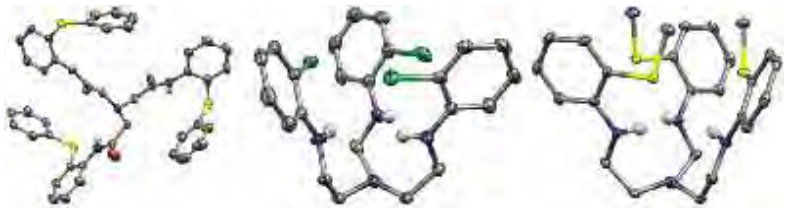


Figure 2. *The solid state structures of the nitrilotriacetamide formed from 2-(phenylthio)aniline (left), of the TREN formed from 2-chloroaniline (center) and the TREN formed from 2-(methylthio)aniline (right).*

When less electronegative anilines were used in the ligand synthesis, we began to observe the formation of a side-product in the aniline coupling to the nitrilotriacetic chloride. We were able to isolate one of these compounds, which turned out to be a dioxopiperazine compound, where there was a dangling amide arm and a six-membered ring in the product. In the synthesis, only two anilines replaced the chloride on the acid chloride; one of the amides that formed continues to attack the third acid chloride in a ring-closing reaction. This is observed with less electron rich aromatic rings because the rate is slowed, allowing for the intramolecular attack and ring-closing to occur. We can avoid this side-product by running the reaction in an excess of aniline, adding six equivalents or more, such that it functions as both the reagent and the sacrificial base.

Alternatively, we can intentionally generate this sideproduct and avoid the formation of the nitrilotriacetamide by adding just two equivalents of aniline with excess sacrificial base (triethylamine) to the nitrilotriacetic chloride (Figure 3). This also allows for the formation of this product with electron-rich anilines, where the side-product was not previously observed. The solid state structures of these dioxopiperazines show a single intramolecular N–H···N hydrogen bond, with one structure shown in Figure 3. These compounds shows two equivalent methylene groups in the six membered ring, on which there are two diastereotopic hydrogens, giving rise to a quartet in the ^{1}H NMR.

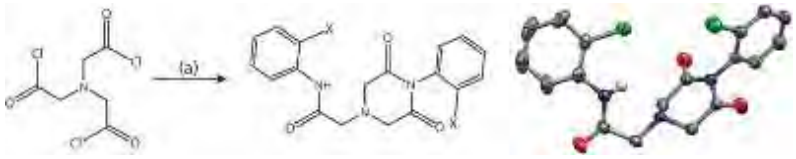


Figure 3. *The direct synthesis of dioxopiperazine products, where (a) is 2 equivalents of 2-X-aniline (X = H, Cl, Br, I, SMe, SPh), 4 equivalents of triethylamine. The solid state structures of the dioxopiperazine formed from 2-chloroaniline is shown at right.*

Metalation Chemistry

The TREN ligands, once synthesized can be deprotonated to generate viable transmetalation agents. The treatment of the TREN ligands with either *n*-butyllithium or *tert*-butyllithium leads to the formation of the trilithium salt of the tris(amido)amine. The structures of these complexes depend upon the steric bulk of the substituted aryl group. If Lewis basic groups are present at the 2-position of the aromatic rings, they interact with the bound lithium ions. There are also coordinated tetrahydrofuran solvent molecules present in the crystalline product. The structure of the 2-chlorophenyl variant of TREN is shown in Figure 4.

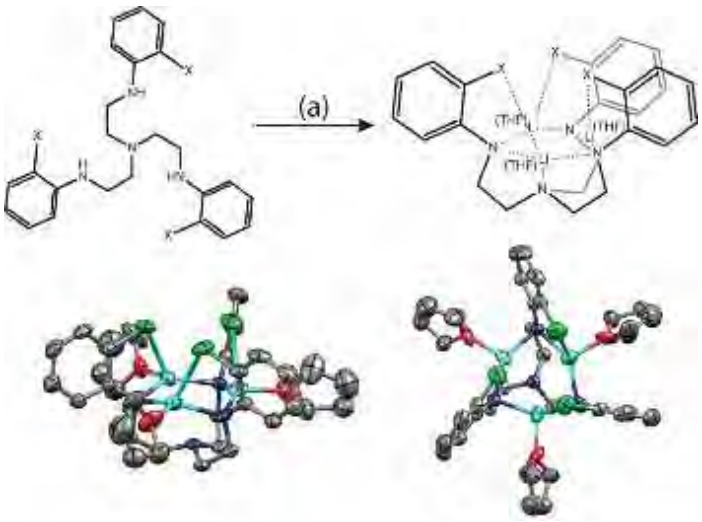


Figure 4. *The lithiation of the TREN ligands, where (a) is n-butyllithium or t-butyllithium. The solid state structure of the trilithium complex of the TREN formed from 2-chloroanline is shown with a side view (left) and a top view (right).*

The trilithium salts can be used as transmetalation agents with metal halide salts. One example of this transmetalation is the reaction of the trilithium complex of the 2-phenylthioaniline variant of TREN with antimony (III) chloride. This transmetalation gives the antimony TREN complex, with the antimony bound with a N_4 coordination pocket. There are three thioether ligands that remain uncoordinated above the antimony center. It is of note that this ligand design allows for the inclusion of different functional groups into the secondary coordination sphere of TREN ligands, as the thioethers above antimony demonstrate.

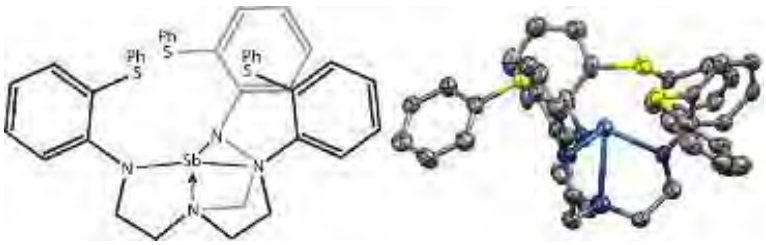


Figure 5. *The antimony complex of the TREN ligand generated from 2-(phenylthio)aniline, with the crystal structure shown at right.*

Future Directions

Moving forward, we have been exploring the reactivity of these ligands, in particular, examining other metalations and the reaction of internal aryl halides on the ligand for intramolecular cross-couplings. We have begun to study the dioxopiperazine complexes as precursors for the generation of TREN ligands with varied substitution at the amido nitrogens. We should have two publications coming soon to expand these syntheses, the metalation chemistry, and the reactivity therein.

Acknowledgements

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