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## Synthetic Methods for the Preparation of Platinum Anticancer Complexes

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### 1. Introduction

The demonstration in the 1960's that *cis*-diamminedichloroplatinum(II), or cisplatin, inhibits cellular division of *Escherichia coli*<sup>1</sup> led to the subsequent discovery that this simple coordination compound is also an effective antitumor agent in mouse models.<sup>2</sup> Subsequent studies validated cisplatin as an effective anticancer agent in humans as well,<sup>3–7</sup> and FDA approval of cisplatin for the treatment of metastatic ovarian and testicular cancers was granted in 1978.<sup>8</sup> Its introduction as a chemotherapeutic agent significantly improved the survival outlook for many cancer patients; the cure rate for testicular cancer before the approval of cisplatin was less than 10%, significantly lower than the 90% cure rate attained with modern platinum chemotherapy.<sup>9,10</sup>

Cisplatin kills cancer cells primarily by cross-linking DNA and inhibiting transcription.<sup>11</sup> The chemical origin of this process begins when cisplatin enters the cell and undergoes aquation involving loss of one or both chloride ligands. The resulting platinum(II) aqua complexes are potent electrophiles that readily react with a number of biological ligands with loss of the bound water molecules. The purine bases of nucleic acids are strongly nucleophilic at the N7 position. Thus, cisplatin binds readily to DNA, forming primarily bifunctional adducts with loss of both chloride ligands. The major cisplatin-DNA adduct is the intrastrand 1,2-d(GpG) cross-link, which accounts for 60–65% of the bound platinum.<sup>12</sup> The resulting Pt-DNA adducts, which distort and bend the DNA structure,<sup>13–15</sup> impede transcription.<sup>16</sup> The downstream effects of transcription inhibition ultimately lead to cell death.

Despite its great curative success in testicular cancer, cisplatin is not universally effective in other cancer types and induces a number of toxic side effects.<sup>17–19</sup> Additionally, certain cancers are resistant to cisplatin therapy. This resistance is either intrinsic or developed during prolonged treatment.<sup>20,21</sup> To circumvent these problems, new platinum complexes have been pursued and investigated for their antitumor properties. Although well over a thousand complexes have been prepared and tested thus far,<sup>22</sup> only two other platinum drugs are approved for clinical use worldwide, and three additional compounds are approved for

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regional use in Asia.<sup>23</sup> These complexes, displayed in Chart 1, operate with a mechanism of action similar to that of cisplatin, which involves DNA binding and transcription inhibition.

In designing a new platinum anticancer agent, several structural features can be strategically modified. As shown in Figure 1, three different ligand types generally comprise a platinum anticancer complex. The ligands L are typically nitrogen donors. They are referred to as “non-leaving group” ligands because they form thermodynamically stable bonds with platinum and are retained in the final platinum-DNA adduct. Modifications of these ligands directly affect the nature of the resulting platinum-DNA adducts<sup>24–26</sup> and therefore the manner by which cellular repair pathways respond to those adducts. Complexes that contain amine ligands different from the amines in cisplatin usually exhibit a different spectrum of activity in cancer cell lines and are usually not cross-resistant with cisplatin.<sup>27</sup> Oxaliplatin, with its chelating and chiral 1,2-diaminocyclohexane ligand, *trans*-1*R*,2*R*-DACH (DACH), falls into this category. Modifications of the leaving group ligands X, so named because they are lost upon DNA-binding, can alter the overall reaction stoichiometry and aquation kinetics for a platinum anticancer complex. Complexes that react quickly, such as those with labile nitrate ligands, are generally more toxic because of indiscriminate binding to off-target biological nucleophiles.<sup>28</sup> Carboplatin, on the other hand, contains a relatively stable chelating CBDCA (CBDCA = 1,1-cyclobutane-dicarboxylato) ligand as its leaving group. By comparison to cisplatin, carboplatin can be administered at higher doses because of its lower toxicity profile.<sup>29,30</sup> Although less toxic, carboplatin has a similar spectrum of activity and exhibits cross-resistance to cisplatin, which is a result of the same non-leaving group ammine ligands.<sup>27,31</sup> The axial ligands R comprise the third category. Axial ligands are present only in higher-valent platinum complexes, such as those of platinum(III) and platinum(IV). These ligands can ultimately dissociate after biological reduction of the platinum complex, although there is no guarantee that reduction will lead to their specific departure from the coordination sphere. They provide convenient points for installation of tumor-targeting moieties or attachment to nanoparticles. Any of the three ligand types can be modified in order to alter the lipophilicity and water solubility of the resulting platinum complex. Both of these properties are important in the design of an effective drug. The stereochemistry and the number of each respective ligand type can be altered as well.

In this review, we present an overview of known synthetic strategies for the synthesis of platinum anticancer complexes. Previous review articles have focused on the mechanistic details of platinum-based drugs at the cellular level,<sup>32–37</sup> the chemistry of platinum under biological conditions,<sup>38,39</sup> and new trends for the rational design of platinum anticancer agents.<sup>40–46</sup> The present article provides synthetic inorganic chemists with practical advice on the synthesis and purification of potential platinum anticancer agents. The coordination chemistry principles employed for the preparation of such compounds are emphasized and are therefore useful to a broader readership. There are two major sections, which describe the synthesis of platinum(II) and platinum(IV) complexes. These sections are further divided based on the nature and stereochemistry of the target complexes. In each section, a short overview is provided of the anticancer properties of the target complexes. Multinuclear platinum complexes, some of which are excellent drug candidates,<sup>47,48</sup> have been omitted from this review to maintain the focus on single-site reactivity. The reaction schemes do not

display fully balanced chemical reactions, but instead illustrate only the major platinum-containing products. This choice stems from the complexity of many seemingly simple reactions of platinum compounds, the chemistry of which can be deceptively complicated. Two generic ligand types, L and X, are utilized (Figure 1), with ligands symbolized by “L” representing either an amine or *N*-heterocyclic unit. When “(L<sub>2</sub>)” is used, the ligand is bidentate. Ligands designated with an “X” are monoanionic, like halides or carboxylates.

## 2. Synthesis of Platinum(II) Complexes

All clinically used platinum drugs (Chart 1) contain the element in the +2 oxidation state having almost exclusively square-planar coordination geometries. The major reaction pathways involved in the synthesis of platinum(II) and other square-planar d<sup>8</sup> complexes involve associative ligand substitution. These reactions proceed through five-coordinate trigonal-bipyramidal intermediates. The stereochemistry of the resulting products is dictated by the relative trans effect of the ligands within the complex. Synthetic strategies discussed in the following sections therefore rely heavily on the trans effect principle. For more detailed summaries of substitution reactions of platinum(II) and other d<sup>8</sup> complexes, as well as the trans effect, the reader is referred elsewhere.<sup>49–51</sup> An early review on the synthesis of monodentate amine complexes of platinum(II) is also available.<sup>52</sup>

### 2.1. Synthesis of *cis*- and *trans*-[PtL<sub>2</sub>X<sub>2</sub>] Complexes

*cis*- and *trans*-Diamminedichloro–platinum(II), are stereoisomers, representative members of the class of complexes having the general formula [PtL<sub>2</sub>X<sub>2</sub>], where L is an amine or *N*-heterocycle and X is a halide or other labile ligand. Both cisplatin and its trans isomer were first prepared over 100 years ago by Peyrone and Reiset, respectively,<sup>53,54</sup> and were commonly known as Peyrone's chloride and Reiset's second chloride. Cisplatin and the trans isomer, both yellow solids, were recognized to be isomers of Magnus' green salt, [Pt(NH<sub>3</sub>)<sub>4</sub>][PtCl<sub>4</sub>]. Structural differences between these three compounds helped validate Werner's theory of coordination chemistry.<sup>55</sup>

Following Peyrone's initial preparation of cisplatin, several different synthetic routes have been described. The common starting material for these procedures is K<sub>2</sub>[PtCl<sub>4</sub>], a water-soluble salt, which can be prepared directly from platinum metal in two steps.<sup>56</sup> As with Peyrone's initial synthesis, several protocols for the synthesis of cisplatin involve the direct action of aqueous ammonia on the tetrachloroplatinate ion.<sup>57,58</sup> This reaction inevitably results in the formation of Magnus' green salt and the trans isomer as undesired byproducts, both of which must be removed by additional purification steps.<sup>57,58</sup> Recently, the use of microwave irradiation for the synthesis of cisplatin directly from K<sub>2</sub>PtCl<sub>4</sub> and NH<sub>4</sub>OAc was reported.<sup>59</sup> The adaptation of this method with flow chemistry techniques enables cisplatin to be synthesized on the gram scale in one step with no contaminating impurities from Magnus' green salt or the trans isomer.

The most widely used method for preparing cisplatin is that reported by Dhara in 1970.<sup>60</sup> For this multistep reaction (Scheme 1), aqueous [PtCl<sub>4</sub>]<sup>2-</sup> is first converted to [PtI<sub>4</sub>]<sup>2-</sup> upon treatment with 4 equiv of KI. The addition of ammonium hydroxide to the dark brown solution of [PtI<sub>4</sub>]<sup>2-</sup> yields the yellow precipitate, *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>I<sub>2</sub>]. Removal of the iodide

ligands from this complex with 2 equiv of  $\text{AgNO}_3$  in water gives the diaqua cation, *cis*- $[\text{Pt}(\text{NH}_3)_2(\text{OH}_2)_2]^{2+}$ , from which isomerically pure cisplatin can be isolated as a yellow solid following treatment with excess chloride ion. The absence of the trans isomer is attributed to the much higher trans effect of the iodide compared to that of the chloride ligand. The key intermediate in the formation of cisplatin from the tetrahaloplatinate anions is the monosubstituted complex,  $[\text{Pt}(\text{NH}_3)\text{X}_3]^-$ . When X is I, the large trans effect ensures that the next  $\text{NH}_3$  ligand departs from a position trans to an iodide to give the desired cis isomer. When X is Cl, the lower trans effect of the latter renders substitution trans to  $\text{NH}_3$  kinetically competitive with substitution trans to the halide, thus yielding a small proportion of the trans isomer. Dhara's method has been adapted to prepare cis complexes with other amine or *N*-heterocyclic ligands,<sup>61–63</sup> cisplatin with  $^{15}\text{N}$ -labeled am–mines,<sup>64–66</sup> and radiolabeled  $^{195}\text{mPt}$ -cisplatin.<sup>67</sup> When chelating diamines are used, this method is preferred as well.<sup>68,69</sup> In cases where the desired amine or *N*-heterocyclic ligands are not water-soluble, an alternative synthetic route is employed, involving the addition of 2 equiv of the amine ligand to  $\text{K}_2\text{PtCl}_4$  in a solvent mixture of water and an alcohol at elevated temperatures.<sup>70–73</sup> The use of DMF instead of ethanol or methanol as a cosolvent for this reaction has also been reported.<sup>74,75</sup>

Purification of cisplatin can be accomplished by recrystallization from hot water containing either 0.1 M HCl or 0.9% NaCl.<sup>66,67</sup> The high chloride ion concentration inhibits the formation of platinum aqua or hydroxo complexes. The use of amide solvents to recrystallize cisplatin is also an effective means of purification.<sup>76</sup> Dissolution of cisplatin in *N,N*-dimethylacetamide (DMA) to a concentration of 18 mg/mL, followed by the addition of three volume equiv of 0.1 N HCl and incubation in an ice bath, affords analytically pure material.<sup>67</sup> Alternatively, storing a concentrated solution (~22 mg/mL) of cisplatin in DMF at 3 °C overnight yields yellow cube-like crystals of a DMF solvate, cisplatin·DMF.<sup>77</sup> Removal of DMF from the crystal lattice under vacuum gives solvent-free cisplatin of very high purity.<sup>77</sup> Care should be taken when recrystallizing new complexes of the general formula, *cis*- $[\text{PtL}_2\text{Cl}_2]$ , from hot solvents. Although not observed for cisplatin, several other compounds having this formula isomerize upon recrystallization from hot acetone or DMF, giving instead the pure trans isomer.<sup>78–80</sup> Thus, stereochemistry should be confirmed after each purification step.

A quick way to test for the presence of isomeric impurities in cisplatin, its trans isomer, or related  $[\text{PtL}_2\text{Cl}_2]$  complexes is the Kurnakow test.<sup>18</sup> This test is performed by adding an excess of thiourea (tu) to an aqueous mixture of *cis/trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ . The trans isomer converts to a white, poorly water-soluble powder, *trans*- $[\text{Pt}(\text{NH}_3)_2(\text{tu})_2]\text{Cl}_2$ , whereas cisplatin becomes the yellow, soluble complex  $[\text{Pt}(\text{tu})_4]\text{Cl}_2$  (Scheme 2). The formation of different products from the two isomers is a consequence of the high trans effect of thiourea. The first equiv of thiourea displaces a chloride ligand. For cisplatin, this substitution places the thiourea trans to an ammine ligand, whereas for *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$  the thiourea binds trans to a chloride. The ammine of cisplatin is sufficiently labilized by the thiourea ligand such that it can be displaced. The amines of the trans isomer are never found in a position trans to the thiourea ligand and therefore remain coordinated. The use of the Kurnakow test in conjunction with HPLC provides a powerful and sensitive method to detect isomeric

impurities.<sup>82,83</sup> In contrast to *cis*- and *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>], the thiourea-coordinated products exhibit significantly different retention times and contain stronger UV-vis absorbance features, properties that make them amenable for HPLC analysis. NMR spectroscopy provides another potential tool to distinguish between isomers. Unfortunately, the <sup>195</sup>Pt NMR chemical shifts of the *cis* and *trans* isomers are very similar, with  $\delta = -2104$  ppm for cisplatin and  $-2101$  ppm for *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>].<sup>84</sup> The evaluation of 3-bond Pt–H coupling constants (<sup>3</sup>J<sub>PtH</sub>) determined by <sup>1</sup>H NMR spectroscopy, however, revealed that these values are 8–14 Hz greater for the *cis* isomers of these complexes,<sup>85</sup> indicating that the magnitudes of these coupling constants can be used to distinguish the two isomers. A potential limitation to this method is the need for a low-field NMR spectrometer in order to minimize chemical-shift anisotropy effects of the <sup>195</sup>Pt nucleus, which broaden resonances and obscure coupling.

The discovery that *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] lacks the biological activity of cisplatin influenced the early structure-activity relationships derived for platinum-based anticancer agents.<sup>28,86,87</sup> In contradiction to these structure-activity relationships, which prescribe *cis* geometry for activity, it was later discovered that some *trans* complexes of general formula [PtCl<sub>2</sub>L<sub>2</sub>] are cytotoxic when L is an *N*-heterocycle like pyridine or thiazole.<sup>88–90</sup> Several methods have been described for the synthesis of these symmetric *trans* compounds from the [PtCl<sub>4</sub>]<sup>2-</sup> ion. To prepare *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>], excess ammonia is added to the [PtCl<sub>4</sub>]<sup>2-</sup> anion to generate the cationic complex, [Pt(NH<sub>3</sub>)<sub>4</sub>]<sup>2+</sup>. The [Pt(NH<sub>3</sub>)<sub>4</sub>]Cl<sub>2</sub> salt forms colorless aqueous solutions from which *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] can be precipitated as a yellow solid after the addition of hydrochloric acid (Scheme 3).<sup>57</sup> This synthetic pathway also exemplifies the *trans* effect principle. After treatment of [Pt(NH<sub>3</sub>)<sub>4</sub>]Cl<sub>2</sub> with HCl, an ammine ligand is replaced by a chloride, forming [Pt(NH<sub>3</sub>)<sub>3</sub>Cl]<sup>+</sup>. The *trans* effect of chloride is greater than that of ammonia. Hence, the next incoming chloride ion preferentially displaces the ammine *trans* to the coordinated chloride, selectively giving rise to the *trans* isomer. This general scheme is applicable to other amine ligands and *N*-heterocycles as well.<sup>90</sup> *Trans* complexes can also be prepared directly from [PtL<sub>4</sub>]X<sub>2</sub> compounds without the use of hydrochloric acid. Upon heating [PtL<sub>4</sub>]X<sub>2</sub> as a suspension in an organic solvent or as a solid under vacuum, the outer-sphere halides substitute the inner-sphere amine or *N*-heterocycle, exclusively generating the *trans* isomer.<sup>90–93</sup> In an attempt to make *trans*-[PtL<sub>2</sub>Cl<sub>2</sub>], where L is imidazole, [PtL<sub>4</sub>]Cl<sub>2</sub> was treated with HCl. Instead of obtaining the expected product, *trans*-[PtL<sub>2</sub>Cl<sub>2</sub>], only platinum(IV) complexes were obtained.<sup>61</sup> The reaction of [PtL<sub>4</sub>]Cl<sub>2</sub> with excess Et<sub>4</sub>NCl in refluxing DMF ultimately gave the desired *trans* complexes.<sup>61</sup> Interestingly, for the analogous complex where L is pyrazole, *trans*-[PtL<sub>2</sub>Cl<sub>2</sub>] could be obtained from [PtL<sub>4</sub>]Cl<sub>2</sub> and HCl without any reported difficulties.<sup>94</sup>

As described in Section 1, leaving group ligands can have profound effects on the biological properties of the resulting platinum complexes. The importance of this behavior is exemplified by the clinically used drugs carboplatin and nedaplatin (Chart 1), which differ from cisplatin only by substitution of the chloride leaving groups with chelating ligands. The chloride ligands of complexes of general formula *cis*- and *trans*-[PtL<sub>2</sub>Cl<sub>2</sub>], where L is an amine or *N*-heterocyclic ligand, can readily be replaced by other desired ligands. A number of different synthetic routes are available for substitution of the halides with other ligands.

For the synthesis of dicarboxylato species, these synthetic routes and their practical applications have been reviewed in great detail.<sup>95</sup> Here, we summarize these reactions schemes and reiterate some practical aspects.

Typically, a water-soluble silver(I) salt, such as AgNO<sub>3</sub>, is allowed to react with a suspension of the platinum(II) complex in water. Silver chloride or iodide is formed as a white or yellow solid, respectively, and removed by filtration. The filtrate contains the substitution-labile complex [PtL<sub>2</sub>(OH<sub>2</sub>)<sub>2</sub>]<sup>2+</sup>. The protonation state and charge on this cation depend on the pH of the solution. At high pH, substitution-inert platinum(II) hydroxo compounds form. These species readily oligomerize to form multinuclear platinum(II) complexes containing bridging hydroxide ligands, which are similarly resistant to conventional ligand substitution reactions.<sup>39,65,96</sup> At slightly acidic pH, however, the aqua ligands are readily displaced by other nucleophiles. Treatment of *cis*-[PtL<sub>2</sub>(OH<sub>2</sub>)<sub>2</sub>]<sup>2+</sup> in water with sodium salts of anionic nucleophiles, NaNu, forms the complexes *cis*-[PtL<sub>2</sub>(Nu)<sub>2</sub>] (Scheme 4a). This reaction proceeds best when the resulting product is insoluble in water and can then be isolated by filtration without the need to evaporate the solution to dryness. In cases where the desired product is water soluble, contamination of the final product with NaNO<sub>3</sub> is a problem.<sup>97</sup> In addition to preparing diamine dicarboxylato platinum(II) complexes, this reaction has been used to synthesize platinum(II) diazido complexes,<sup>98,99</sup> which are precursors to photoreactive platinum(IV) prodrugs.<sup>100</sup> The platinum(II) dinitrato complexes, [PtL<sub>2</sub>(ONO<sub>2</sub>)<sub>2</sub>], can also be prepared independently and isolated as solids, as evidenced in part by an early report of the X-ray crystal structure of *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>(ONO<sub>2</sub>)<sub>2</sub>].<sup>101</sup> An efficient synthesis of *cis*-[PtL<sub>2</sub>(ONO<sub>2</sub>)<sub>2</sub>] is accomplished by treating *cis*-[PtL<sub>2</sub>I<sub>2</sub>] with AgNO<sub>3</sub> in acetone.<sup>62,102</sup> The reaction proceeds substantially faster in acetone compared to water. Solid *cis*-[PtL<sub>2</sub>(ONO<sub>2</sub>)<sub>2</sub>] dissolves in water with heating to form the diaqua species described above, which can then be used to install new leaving group ligands.

An alternative reaction for preparing water-soluble complexes with modified leaving groups utilizes a silver(I) salt of the desired new ligand. The silver(I) salts react directly with cisplatin and related diaminedihalidoplatinum(II) complexes in water, yielding insoluble AgX as the only byproduct (Scheme 4b). The resulting silver(I) halide can be removed by filtration, leaving the soluble product to be recovered from the filtrate by evaporation of the solvent. This strategy was employed for an optimized synthesis of radiolabeled <sup>195m</sup>Pt-carboplatin.<sup>103</sup> In cases where the silver(I) salt of a desired carboxylate ligand is not readily available, a one-pot strategy can be employed, in which the diaminedihalidoplatinum(II) complex, Ag<sub>2</sub>CO<sub>3</sub>, and the carboxylic acid are mixed together.<sup>95</sup> In another approach, the sulfate salt of [PtL<sub>2</sub>(OH<sub>2</sub>)<sub>2</sub>]<sup>2+</sup>, generated by the reaction of Ag<sub>2</sub>SO<sub>4</sub> with [PtL<sub>2</sub>X<sub>2</sub>] in water, is used in conjunction with Ba(II) salts of the carboxylates, usually formed in situ from Ba(OH)<sub>2</sub>, to synthesize the desired platinum(II) carboxylate (Scheme 4c).<sup>97,104,105</sup> The byproduct of this reaction, insoluble BaSO<sub>4</sub>, can be easily removed by filtration. This reaction has been used to attach β-diketonate<sup>106</sup> and sulfonate<sup>107</sup> ligands to platinum(II). Another synthetic approach, which has not found widespread use, requires a platinum(II) oxalate complex and the calcium salt of a ligand. The mixture of these two species generates



insoluble calcium(II) oxalate and the target complex, the latter remaining in solution (Scheme 4d).<sup>107</sup>

Various other interesting leaving groups have also been attached to platinum to generate anticancer drug candidates. Platinum(II) diamine complexes with squarate,<sup>108</sup> selenite,<sup>108</sup> tellurate,<sup>109</sup> ascorbate,<sup>110–112</sup> and methyl sulfinyl carboxylate<sup>113,114</sup> leaving groups have been prepared using the protocols described above. Additionally, the complex [Pt(*trans*-1*R*, 2*R*-DACH)(B<sub>2</sub>O<sub>5</sub>H<sub>2</sub>)] with a chelating borate ligand was prepared from [Pt(*trans*-1*R*, 2*R*-DACH)(OH)<sub>2</sub>] and a mixture of boric acid and tetraborate in water.<sup>115</sup> These novel complexes demonstrate the synthetic versatility of the methods described above for preparing new platinum compounds with different leaving group ligands, some of which may have therapeutic potential.

## 2.2. Synthesis of *cis*- and *trans*-[PtLL'X<sub>2</sub>], Complexes with Mixed Am(m)ine Ligands

Platinum(II) complexes that bear two different amine or *N*-heterocyclic ligands have gained importance in recent years as a new class of anticancer agents. The complexes *cis*-[Pt(NH<sub>3</sub>)(2-picoline)Cl<sub>2</sub>] (picoplatin)<sup>116,117</sup> and *cis*-[Pt(NH<sub>3</sub>)(cyclopentylamine)(hydroxybutanedioato)] (cycloplatam)<sup>118</sup> (Chart 2), for example, have undergone clinical trials.<sup>23</sup> *cis*-[Pt(NH<sub>3</sub>)(cyclohexylamine)Cl<sub>2</sub>] (JM-118) (Chart 2), an active metabolite of the clinically investigated platinum(IV) complex satraplatin,<sup>119,120</sup> is another member of this class of compounds. *Trans* platinum complexes of mixed amine or *N*-heterocyclic ligands are also of importance. Some members of these “*trans* planar amine” (TPA) class of compounds having the general formula *trans*-[Pt(NH<sub>3</sub>)LX<sub>2</sub>], where L is an *N*-heterocycle, exhibit potent anticancer activity and are not cross-resistant with cisplatin.<sup>121</sup> Moreover, they serve as precursors for the preparation of phototoxic platinum(IV) diazido complexes.<sup>98,122</sup>

The most straightforward synthetic route to mixed amine platinum(II) complexes with *cis* stereochemistry involves the use of the [PtLCl<sub>3</sub>]<sup>-</sup> anion as an intermediate. Treating this ion with another amine or *N*-heterocycle, L', is expected to yield the complex *cis*-[PtLL'X<sub>2</sub>]. A limitation to this approach, however, is the difficulty in preparing am(m)inetrichloridoplatinate(II) ions. Initial reports of the syntheses of K[Pt(NH<sub>3</sub>)Cl<sub>3</sub>] (Cossa's salt) appeared over a century ago.<sup>123,124</sup> Since then, researchers have focused on finding straightforward, high yielding protocols for obtaining this and related ions. The treatment of K<sub>2</sub>PtCl<sub>4</sub> with one equiv of L more readily generates 0.5 equiv of the highly insoluble *cis*-[PtL<sub>2</sub>Cl<sub>2</sub>] complex rather than the soluble salt K[PtLCl<sub>3</sub>]. An early, inefficient preparation of K[Pt(NH<sub>3</sub>)Cl<sub>3</sub>] involved treatment of cisplatin with hydrochloric acid in the presence of a catalytic amount of Pt metal at elevated temperatures.<sup>125</sup> After removing unreacted cisplatin and Pt metal by filtration, the [Pt(NH<sub>3</sub>)<sub>4</sub>]<sup>2+</sup> cation was added to precipitate the salt [Pt(NH<sub>3</sub>)<sub>4</sub>][Pt(NH<sub>3</sub>)Cl<sub>3</sub>]<sub>2</sub>. This salt was then treated with K<sub>2</sub>PtCl<sub>4</sub>, giving insoluble Magnus' salt, [Pt(NH<sub>3</sub>)<sub>4</sub>][PtCl<sub>4</sub>], and Cossa's salt, K[Pt(NH<sub>3</sub>)Cl<sub>3</sub>], in the filtrate. A typical yield was not reported for this method, but the large quantity of undesired platinum-containing byproducts makes this approach expensive and undesirable. The reaction was later optimized to obtain Cossa's salt in 60% yield from cisplatin.<sup>126</sup> In this case, the salt was isolated by anion-exchange chromatography and therefore did not require formation of

the platinum double salts. With careful control of temperature and reaction time, the ammonium salt of  $[\text{Pt}(\text{NH}_3)\text{Cl}_3]^-$  was reportedly isolated in 90% yield, also by the action of hydrochloric acid on cisplatin, but in the absence of a Pt metal catalyst.<sup>127</sup>

An alternative, more commonly used route for the preparation of the  $[\text{Pt}(\text{NH}_3)\text{Cl}_3]^-$  anion employs *N,N*-dimethylacetamide (DMA) as the solvent.<sup>128,129</sup> At high temperatures (100 °C) with a stream of nitrogen gas bubbling through the DMA solution, the direct reaction between an excess amount of tetraethylammonium chloride and cisplatin affords the desired anion, which can be subsequently precipitated from an aqueous solution as the  $\text{PPh}_4^+$  salt.<sup>128</sup> The use of other *cis*- $[\text{PtL}_2\text{Cl}_2]$  complexes as starting materials in this reaction generally affords the corresponding  $[\text{PtLCl}_3]^-$  ions. This transformation, however, is only successful if the leaving amine ligand is sufficiently volatile, driving the reaction by evaporation of the amine. Because of this limitation, the anion  $[\text{Pt}(\text{cyclohexylamine})\text{Cl}_3]^-$  could not be prepared by this method.<sup>128</sup> The high temperatures employed, which result in the eventual decomposition of cisplatin to insoluble platinum black, restrict the overall yield and efficiency of the reaction. The introduction of substoichiometric amounts of  $\text{NH}_4\text{Cl}$  (0.25 mol%) prevents formation of platinum black (Scheme 5).<sup>130</sup> The reported yield in this case was 58%, but unreacted cisplatin could be recovered for later use.<sup>130</sup> Water-soluble forms of the  $[\text{Pt}(\text{NH}_3)\text{Cl}_3]^-$  ion as either its sodium or potassium salt can be isolated using an ion-exchange resin,<sup>129,130</sup> or metathesis with either  $\text{KPF}_6$ <sup>131</sup> or  $\text{NaBPh}_4$ .<sup>132</sup> An HPLC method was described recently to assess the purity of the potassium salt.<sup>133</sup> To prepare the analogous anions where L is an *N*-heterocycle instead of an amine, direct reaction between  $\text{K}_2\text{PtCl}_4$  and one equiv of L in DMF at 75 °C can be used. This reaction also produces some of the disubstituted neutral product *cis*- $[\text{PtL}_2\text{Cl}_2]$ .<sup>134,135</sup> The amount of this undesired species formed depends on the steric bulk of the incoming heterocycle.<sup>135</sup> For example, much higher yields of the anion were afforded with 2,4-lutidine than with pyridine. Presumably, the steric properties of the ortho methyl groups of 2,4-lutidine disfavor simultaneous coordination of two such ligands to a single platinum center. The use of steric effects to synthesize of  $[\text{PtLCl}_3]^-$  directly from  $\text{K}_2\text{PtCl}_4$  in water, where L is an aliphatic amine, has also been described.<sup>136</sup> The sterically crowded amines, isopropyl and *tert*-butyl amine, substantially retard the formation of *cis*- $[\text{PtL}_2\text{Cl}_2]$ , enabling isolation of  $[\text{PtLCl}_3]^-$  in 16–36% yields.<sup>136</sup> For either reaction, the desired soluble anion can be separated from the insoluble disubstituted complex by extraction into water.

The  $[\text{PtLCl}_3]^-$  ions are suitable precursors for the synthesis of mixed ligand complexes of the type *cis*- $[\text{PtLL}'\text{X}_2]$ . The reaction between L' and  $[\text{PtLCl}_3]^-$  in water or DMF gives the mixed amine complex with the expected *cis* stereochemistry.<sup>128,137–139</sup> Under these conditions, however, a small amount of *cis*- $[\text{PtL}'_2\text{Cl}_2]$  can also be formed, presumably arising from  $[\text{PtCl}_4]^{2-}$  impurities in the starting material.<sup>129</sup> By analogy to Dhara's method for the synthesis of cisplatin,<sup>60</sup> the preparation of *cis* mixed amine complexes was improved by first treating the  $[\text{PtLCl}_2]^-$  anion with 2 equiv of NaI or KI in water (Scheme 5).<sup>126</sup> Multinuclear NMR spectroscopic studies verified that the addition of two equiv of iodide, when L =  $\text{NH}_3$ , forms primarily the *trans*- $[\text{PtI}_2\text{Cl}(\text{NH}_3)]^-$  ion, resulting from substitution of two chloride ligands.<sup>140</sup> The large *trans* effect of the iodide favors the amine substitution reaction. The addition of an amine, L, to *trans*- $[\text{PtI}_2\text{Cl}(\text{NH}_3)]^-$  readily yields the mixed



halide species  $[\text{PtL}(\text{NH}_3)\text{ClI}]$ , where L is trans to the iodide ligand. In this case, some impurity resulting from  $[\text{PtCl}_4]^{2-}$  is present in the form of *cis*- $[\text{PtL}'_2\text{I}_2]$ . This impurity, however, can be readily removed from the desired product by its dissolution in acetone.<sup>129</sup> The mixed halide intermediate can then be converted to the dichloride by removal of the iodide ligand with  $\text{Ag}^+$  and addition of  $\text{Cl}^-$  to the resulting platinum aqua complex (Scheme 5). In the case where both L and L' are quinoline derivatives, the direct reaction of  $[\text{PtLCl}_3]^-$  and L' in mixed aqueous and organic solvent directly afforded the desired compound in its pure form without the need to proceed through the mixed halide species.<sup>141</sup>

The other commonly used route for preparing mixed *cis* amine platinum(II) complexes utilizes iodido-bridged dimers,  $[\text{PtLI}(\mu\text{-I})_2]$ , as intermediates. The reaction of *cis*- $[\text{PtL}_2\text{I}_2]$  with perchloric acid forms these species, which are generally insoluble and brown in color (Scheme 6).<sup>142</sup> The scope of this reaction extends to a range of aliphatic<sup>143</sup> and aromatic amines,<sup>144</sup> and *N*-heterocycles.<sup>145</sup> For sterically hindered amines, such as *tert*-butyl amine, the analogous iodido-bridged dimers form directly upon reaction with  $\text{K}_2\text{PtI}_4$ ; formation of the expected product, *cis*- $[\text{PtL}_2\text{I}_2]$ , does not occur, presumably owing to the large steric hindrance of the bulky amine ligands.<sup>143</sup> The perchloric acid serves to remove an amine ligand from *cis*- $[\text{PtL}_2\text{I}_2]$  by protonolysis. The vacant coordination site on the platinum(II) center is then filled by an iodide ligand from another complex. Because both the starting material and products are poorly soluble in water, the reaction can take an exceedingly long time to reach completion; for cyclopropyl amine, a reaction time of three weeks was necessary to achieve full conversion.<sup>143</sup> Furthermore, the lack of solubility of both species makes it difficult to gauge the extent of the reaction. For reactions that have not gone to completion, the final product may be contaminated by starting material. The iodido-bridged dimers exist in two isomeric forms, *syn* and *anti* (Scheme 6), depending on the disposition of the two amine ligands about the Pt–Pt vector. Solution NMR spectra display resonances from both isomers, but in the solid-state only *anti* isomers have been observed by X-ray crystallography.<sup>143,146</sup>

Although several recent publications have reported that some of these iodido-bridged dimers exhibit anticancer activity,<sup>147,148</sup> their primary use is to prepare *cis* mixed amine complexes. In this context, it should be noted that these iodido-bridged dimers can also serve as precursors for the  $[\text{PtLCl}_3]^-$  3 anion discussed above. Treatment of  $[\text{PtLI}(\mu\text{-I})_2]$  with excess  $\text{AgNO}_3$  in water, followed by the addition of excess  $\text{KCl}$ , provides another route to the  $[\text{PtLCl}_3]^-$  ion.<sup>149</sup> More useful, however, is the direct reaction of these dimers with another amine or *N*-heterocycle to form the mononuclear mixed amine complexes, *cis*- $[\text{PtLL}'\text{I}_2]$  (Scheme 6).<sup>131,142</sup> Despite the presence of both *anti* and *syn* isomers in the iodido-bridged dimer starting material, only *cis*- $[\text{PtL}_2\text{I}_2]$  is obtained from this reaction. The iodide ligands can be exchanged for other halides using an appropriate silver (I) salt as described above. Analogous chlorido-bridged dimers can be synthesized by the photolysis of *trans*- $[\text{Pt}(\text{ethylene})\text{LCI}_2]$ .<sup>150</sup> Cleavage of these chlorido-bridged dimers with another amine ligand, however, leads to formation of both the *trans* and *cis* isomers of the mixed amine complex,<sup>150</sup> rendering this procedure less useful.

When a bidentate oxygen ligand is desired as the leaving group instead of monodentate halides, a different synthetic route can be used to access the mixed amine complex. The first

step in this pathway requires the synthesis of  $cis$ -[Pt(DMSO)<sub>2</sub>(O<sub>2</sub>Chel)], where O<sub>2</sub> Chel is a typically anionic chelating ligand with oxygen donor atoms. This intermediate is prepared by the reaction of  $cis$ -[Pt(DMSO)<sub>2</sub>Cl<sub>2</sub>], which itself is obtained from commercially available K<sub>2</sub>PtCl<sub>4</sub> and DMSO,<sup>151</sup> and the disilver salt of the chelating ligand in water (Scheme 7).<sup>152</sup> The first DMSO ligand of  $cis$ -[Pt(DMSO)<sub>2</sub>(O<sub>2</sub>Chel)] can be substituted by an amine L at 40 °C in water to form isolable complexes of the type  $cis$ -[PtL(DMSO)(O<sub>2</sub>Chel)]. The addition of a different amine, L', to this complex at higher temperatures (100 °C) in water enables substitution of the second DMSO ligand to afford the mixed amine complex  $cis$ -[PtLL'(O<sub>2</sub>Chel)] (Scheme 7).<sup>152</sup> The difficulty in removing the second DMSO ligand is emphasized by the fact that even the use of chelating diamine ligands requires heating to 100 °C to enforce bidentate coordination. For bidentate *N*-heterocycles like 2,2'-bipyridine, lower temperatures (refluxing methanol) can be used to substitute both DMSO ligands.<sup>153</sup> The concentrations of the reactants are also important because, when high concentrations of chelating diamine ligands are used, both the DMSO ligands and oxygen chelate get displaced, forming [Pt(L<sub>2</sub>)<sub>2</sub>]<sup>2+</sup>.<sup>154</sup> Despite the apparent utility of this method, it has not been widely applied.<sup>95,155–157</sup>

The processes for preparing mixed amine complexes with *trans* stereochemistry are more straightforward than those discussed above for *cis* complexes. These compounds, having the general formula  $trans$ -[PtLL'Cl<sub>2</sub>], are of interest because many of them display *in vitro* anticancer activity superior to that of cisplatin, despite their *trans* stereochemistry.<sup>158–163</sup> Additionally, they exhibit no cross-resistance with cisplatin.<sup>158,159,161</sup> Their preparation begins with the complex  $cis$ -[PtL<sub>2</sub>Cl<sub>2</sub>], the synthesis of which has been described earlier. The addition of greater than two equiv of L' to a suspension of this complex in boiling water typically gives rise to a colorless solution containing the salt,  $cis$ -[PtL<sub>2</sub>L'<sub>2</sub>]Cl<sub>2</sub> (Scheme 8). The solubility and color can vary slightly, depending on the hydrophobicity and electronic properties of the amine or *N*-heterocycle ligands. Addition of concentrated hydrochloric acid to this salt at elevated temperatures leads to substitution of one L and one L' ligand by chloride, forming  $trans$ -[PtLL'Cl<sub>2</sub>] (Scheme 8).<sup>158</sup> The stereochemistry of the product is dictated by the kinetic *trans* effect. The first chloride substitution can yield either of the intermediates, [PtL<sub>2</sub>L'Cl] or [PtLL'<sub>2</sub>Cl<sub>2</sub>]. The larger *trans* effect of chloride compared to those of amines or *N*-heterocycles ensures that the second chloride substitutes *trans* to the first chloride. Further substitution to form [PtLCl<sub>3</sub>]<sup>2-</sup> is impeded by the low solubility of  $trans$ -[PtLL'Cl<sub>2</sub>], which precipitates from solution as a yellow solid immediately upon its formation.

### 2.3. Synthesis of Monofunctional Platinum(II) Complexes

Platinum(II) complexes containing only one substitution-labile ligand are designated as 'monofunctional' in contrast to cisplatin and carboplatin, both of which contain two substitution-labile coordination sites and are referred to as 'bifunctional.' Among the first monofunctional platinum(II) complexes investigated for their potential anticancer activity were [Pt(dien)Cl]Cl (dien = diethylenetriamine) and [Pt(NH<sub>3</sub>)<sub>3</sub>Cl]Cl. The observation that these two complexes are inactive helped establish the traditional structure-activity relationships for platinum therapeutics, which state that, among other requirements, charge neutrality and bifunctionality are necessary for activity.<sup>28,164</sup> Despite their lack of anticancer

properties, these two monofunctional complexes have been useful in modeling the reactions of platinum complexes with biologically relevant nucleophiles because the presence of only one exchangeable ligand site simplifies interpretation of the results.<sup>165–168</sup>

Optimized synthetic routes to these salts are available.<sup>169,170</sup> The synthesis of  $[\text{Pt}(\text{NH}_3)_3\text{Cl}]\text{Cl}$  commences by treatment of *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$  with one equiv of KI to form the mixed halide complex, *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}]\text{Cl}$ . The addition of 1 equiv of  $\text{AgNO}_3$  in water selectively precipitates AgI and gives *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}(\text{OH}_2)](\text{NO}_3)$ . Aqueous ammonia readily replaces the labile aqua ligand, yielding  $[\text{Pt}(\text{NH}_3)_3\text{Cl}]\text{Cl}$  as a colorless to pale yellow solid after precipitation from the aqueous solution with a mixture of ethanol and diethyl ether (Scheme 9).<sup>169</sup> The aqua intermediate, *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}(\text{OH}_2)](\text{NO}_3)$ , could also conceivably be used as a synthon for complexes of the general type, *trans*- $[\text{Pt}(\text{NH}_3)_2\text{LCl}](\text{NO}_3)$ . The optimized preparation of  $[\text{Pt}(\text{dien})\text{Cl}]\text{Cl}$  utilizes the reaction of either *cis/trans*- $[\text{PtCl}(\text{SMe } 171 \text{ or } \text{cis-}[\text{Pt}(\text{DMSO})_2\text{Cl}_2]151$  with dien in refluxing methanol. Isolation of  $[\text{Pt}(\text{dien})\text{Cl}]\text{Cl}$  as a white solid in yields of >90% is accomplished by the addition of either  $\text{CHCl}_3$  or  $\text{CH}_2\text{Cl}_2$  to the resulting methanolic reaction mixture.<sup>170</sup>

More recently, a number of monofunctional platinum(II) complexes have been discovered that break the traditional structure-activity relationships by exhibiting anticancer properties.<sup>172–176</sup> The most thoroughly investigated members of this class are complexes of general formula *cis*- $[\text{PtL}_2\text{L}'\text{Cl}]^+$ , where L is a monodentate or bidentate amine and L' is either an *N*-heterocycle,<sup>172</sup> a sulfoxide,<sup>173,177,178</sup> or a thiourea derivative (Chart 3).<sup>179</sup>

For the sulfoxide and thiourea complexes, chelating diamines are used exclusively because the strong trans effect of these ligands labilizes monodentate amines, leading to their dissociation. Although we define the sulfoxide compounds, *cis*- $[\text{Pt}(\text{L}_2)(\text{RR}'\text{SO})\text{Cl}]^+$ , as monofunctional because of the presence of only one labile Pt–Cl bond, these complexes form bifunctional DNA-adducts.<sup>180</sup> Rapid substitution of the chloride for water or nucleobases is followed by the slow substitution of the sulfoxide ligand. The kinetics of the sulfoxide substitution reaction are effectively modulated by its steric bulk.<sup>173,177,180</sup> The synthesis of these complexes proceeds either by the addition of the chelating amine ligand to *cis*- $[\text{PtCl}_2(\text{RR}'\text{SO})_2]$  or the addition of one equiv of sulfoxide to *cis*- $[\text{Pt}(\text{L}_2)\text{Cl}_2]$  (Scheme 10). The latter reaction pathway is the preferred route; the use of *cis*- $[\text{PtCl}_2(\text{RR}'\text{SO})_2]$  as the starting material in the former pathway gives variable amounts of *cis*- $[\text{Pt}(\text{L}_2)\text{Cl}_2]$  as an undesired byproduct.<sup>173</sup>

Complexes of the type *cis*- $[\text{Pt}(\text{NH}_3)_2\text{L}]^+$ , where L is an *N*-heterocycle, have attracted significant attention since the initial discovery of their antitumor properties in 1989.<sup>172</sup> In contrast to the sulfoxide complexes discussed above, these cations bind to DNA and nucleobases in a monofunctional manner with no indication of ammonia or *N*-heterocycle loss to form bifunctional adducts.<sup>181</sup> Although the monofunctional lesions do not significantly bend DNA,<sup>26,182</sup> they still manage to effectively destabilize the structure of the double helix<sup>183–185</sup> and impede DNA replication<sup>186</sup> and transcription.<sup>26,187</sup> The characteristic monofunctional DNA adducts may be responsible for the different spectrum of activity observed for these compounds in comparison to those for clinically used bifunctional platinum drugs.<sup>188</sup> A number of derivatives of *cis*- $[\text{Pt}(\text{NH}_3)_2\text{L}]^+$  have been

synthesized, with L being a wide range of different *N*-heterocycles. These *N*-heterocycles include derivatives of pyridine with different substituents<sup>172</sup> and fused aromatic rings,<sup>189</sup> pyrimidines,<sup>190</sup> a fluorescently labeled pyridine,<sup>191</sup> steroid functionalized pyridines,<sup>192,193</sup> imidazothiazoles,<sup>194</sup> 9-aminoacridine,<sup>195</sup> the antimalarial drug chloroquine,<sup>195</sup> ethidium,<sup>196</sup> the anticancer drug 5-fluorouracil,<sup>197</sup> and several antiviral agents.<sup>198,199</sup> Of these drug candidates, the complex utilizing phenanthridine as its *N*-heterocyclic ligand, termed phenanthriplatin, exhibits in vitro cytotoxicity greater than that of cisplatin across a wide range of cell lines.<sup>189</sup> As phenanthriplatin illustrates, the judicious choice of the *N*-heterocycle can give rise to very potent monofunctional complexes.

The synthesis of monofunctional complexes can be accomplished by stirring a mixture of cisplatin and one equiv of the *N*-heterocycle in water at 50–60 °C for several days.<sup>172</sup> This reaction proceeds by direct substitution of the chloride ligand by the *N*-heterocycle. This method, however, typically gives low yields of impure compounds. The major impurity is the disubstituted species, *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>L<sub>2</sub>]Cl<sub>2</sub>, which arises from substitution of both chloride ligands. Pretreatment of cisplatin with one equiv of AgNO<sub>3</sub> in water to generate the reactive mono aqua complex, *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>]<sup>+</sup>, followed by the addition of another ligand has also been reported.<sup>190</sup> This method gave rise to a substantial portion of unreacted cisplatin and unidentified byproducts. The reaction mixture containing one equiv AgNO<sub>3</sub> and cisplatin in water has been analyzed by <sup>195</sup>Pt NMR spectroscopy. The mono aqua complex, *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl(OH<sub>2</sub>)]<sup>+</sup>, comprises 57% of the total platinum in solution, whereas the diaqua complex, *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>(OH<sub>2</sub>)<sub>2</sub>]<sup>2+</sup>, and unreacted cisplatin account for 39 and 4%, respectively. The large quantity of the diaqua complex should lead to the formation of an equally large proportion of the undesired disubstituted complex. Treating cisplatin with one equiv of AgNO<sub>3</sub> in DMF, however, gives a much more favorable product distribution; 79–86% of the total platinum is in the monosolvated form *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl(solv)], where “solv” is either DMF or nitrate, whereas only 9% and 9–12% of the platinum comprises doubly solvated species and unreacted cisplatin, respectively.<sup>172,195</sup> The preferred synthetic route to monofunctional complexes, therefore, involves the reaction of cisplatin with one equiv of AgNO<sub>3</sub> in DMF followed by the addition of the *N*-heterocyclic ligand (Scheme 11).<sup>172,200</sup> Care must be taken to purify the final monofunctional product from unreacted cisplatin and disubstituted byproducts. Because cisplatin is not soluble in methanol, it can be removed by filtration after dissolving the crude product in this solvent. A final recrystallization step from either dilute HCl or methanol is necessary to separate the monofunctional complex from disubstituted byproducts. The mononitrato species, *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl(NO<sub>3</sub>)], has reportedly been isolated as a solid by evaporation of an aqueous solution containing a 1:1 mixture of cisplatin and AgNO<sub>3</sub>.<sup>199</sup> This complex was then used as a precursor for new monofunctional complexes. Only CHN analyses were presented as characterization for *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl(NO<sub>3</sub>)]; it is most likely that the isolated solid comprised the mixture of species found in solution by <sup>195</sup>Pt NMR spectroscopic studies, as discussed above.

Another important class of monofunctional platinum anticancer agents contains complexes of the general formula *cis*-[Pt(L<sub>2</sub>)Cl(tu)]<sup>+</sup>, where L<sub>2</sub> is a chelating diamine ligand and tu is a derivative of thiourea, coordinated through the sulfur atom (Chart 3, right side).<sup>201,202</sup> Although the first generation analogues of these complexes with underivatized thiourea

ligands exhibit only poor to moderate in vitro cytotoxicity,<sup>203</sup> the second generation compounds with acridine-functionalized thioureas are typically more cytotoxic than cisplatin.<sup>174,204,205</sup> These Pt-acridinylthiourea, or PT-ACRAMTU, conjugates form hybrid DNA adducts;<sup>206</sup> the Pt center binds preferentially to *N7* of guanine bases and the acridine intercalates between base pairs. Several dichloridoplatinum(II) complexes tethered to acridine through a modified ethylenediamine ligand, first reported in the late 1980s, also exhibit dual intercalation and covalent DNA-binding modes.<sup>74,75,207</sup> The covalent adducts of these complexes, however, are bifunctional as opposed to the monofunctional adducts formed by PT-ACRAMTU compounds. In contrast to the monofunctional sulfoxide complexes discussed above, the thiourea ligand does not get displaced by nucleobases and therefore only monofunctional covalent DNA adducts are formed.<sup>203</sup> The unique hybrid DNA-binding motif of these complexes gives rise to a profile of activity in a wide range of cancer cells substantially different from those of cisplatin and related platinum anticancer drugs.<sup>179</sup> The synthesis of PT-ACRAMTU complexes follows a protocol similar to that used for the monofunctional *cis*-diammine complexes. A 1:1 mixture of *cis*-[Pt(L<sub>2</sub>)Cl<sub>2</sub>] and AgNO<sub>3</sub> is stirred in DMF, and the filtrate is treated with one equiv of the thiourea ligand (Scheme 12).<sup>208</sup> This reaction fails when monodentate amine ligands are used; the addition of thiourea induces full substitution of the monodentate amine ligands, forming [Pt(tu)<sub>4</sub>]<sup>2+</sup>,<sup>208</sup> consistent with the expected results of the Kurnakow test, as discussed above.

#### 2.4. Platinum(II) Complexes Synthesized by Ligand-Based Reactivity

The synthetic strategies discussed in the previous sections all rely on ligand substitution reactions at the platinum(II) center. Alternative synthetic pathways involve the use of outer-sphere, ligand-based reactivity. These reactions are facilitated by the ability of transition metal ions to activate coordinated ligands, making them more susceptible to certain reactivity pathways that would otherwise be inaccessible to them in the unbound form. This section covers several examples of these reactions that have been utilized to synthesize of novel platinum anticancer drug candidates.

Iminoether complexes of platinum(II) of general formula [Pt(iminoether)<sub>2</sub>Cl<sub>2</sub>] display potent anticancer activity both in vitro and in vivo. As for traditional platinum anticancer agents, this activity is proposed to arise from DNA binding.<sup>209</sup> For the trans isomers, monofunctional adducts<sup>210,211</sup> and protein-DNA cross-links<sup>212</sup> are invoked as the predominant cytotoxic lesions. The trans isomers tested initially proved to be more active than their cis congeners,<sup>213</sup> although some recent studies have reported the opposite observation for new members of this class of compounds.<sup>214,215</sup> The cis and trans structure-activity relationships for these compounds, therefore, depend on the exact chemical nature of the iminoether ligand. In addition to the stereochemistry at the square-planar platinum center, the iminoether ligands can exist in either *E* or *Z* configuration, depending on the orientation of the substituents about the C–N double bond. As a result, there are six isomers for [Pt(iminoether)<sub>2</sub>Cl<sub>2</sub>] complexes, neglecting rotational isomers involving hindered rotation about the Pt–N bond vector (Chart 4). For both cis and trans isomers, the stereochemistry of the ligand has a substantial effect on the biological activity of the complex.<sup>213,216</sup> Therefore, precise synthetic control over the total stereochemistry of the final complex is important for further biological applications.

The nitrile complexes, *cis*- and *trans*-[PtCl<sub>2</sub>(NCR)<sub>2</sub>], are precursors for preparing *cis*- and *trans*-[PtCl<sub>2</sub>(iminoether)<sub>2</sub>] complexes. The reaction of *cis*- or *trans*-[PtCl<sub>2</sub>(NCR)<sub>2</sub>] in alcohols<sup>217</sup> or alcohol-dichloromethane mixtures<sup>218</sup> with a catalytic amount of KOH affords the iminoether complexes by nucleophilic attack of the alkoxide on the coordinated nitrile ligand (Scheme 13). Formation of the iminoether occurs with retention of the starting stereochemistry of the platinum complex, but generally a mixture of *E* and *Z* ligand-based isomers is obtained. Formation of the *Z* iminoether is kinetically preferred; isomerization to the *E* isomer occurs in the presence of catalytic amounts of base, which is present under the reaction conditions.<sup>219</sup> Carrying out the reaction at low temperature (0 °C) also significantly impedes isomerization to the *E* isomer, giving predominantly *Z* isomers.<sup>220</sup> The *ZZ*, *EZ*, and *EE* isomers can be separated on the basis of solubility differences by fractional crystallization or silica gel column chromatography.<sup>219</sup> Recently, the reaction of *cis*- and *trans*-[PtCl<sub>2</sub>(NCR)<sub>2</sub>] with thiols was disclosed.<sup>221</sup> Utilizing *n*-BuLi as the base and THF as the solvent at rt, both *cis* and *trans* complexes afford bis(imino thioether) platinum(II) compounds. The reaction proceeds cleanly, forming only imino thioether ligands with *E* configurations.<sup>221</sup>

Mixed iminoether-amine platinum(II) complexes of formula [PtCl<sub>2</sub>(NH<sub>3</sub>)(iminoether)] also exhibit *in vitro* and *in vivo* anticancer activity.<sup>220,222</sup> These complexes are prepared from mixed amine-nitrile complexes by the attack of an alkoxide on the coordinated nitrile ligand under conditions similar to those employed for the bis(iminoether) complexes described above. The synthetic protocols for the precursor complexes, *cis*- and *trans*-[PtCl<sub>2</sub>(NH<sub>3</sub>)(NCR)], are similar to those described for mixed amine platinum(II) complexes described above. To prepare *trans*-[PtCl<sub>2</sub>(NH<sub>3</sub>)(NCR)], *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>I<sub>2</sub>] is treated with two equiv of AgNO<sub>3</sub> in water to form the diaqua complex, from which *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>(NCR)<sub>2</sub>] can be formed by addition of a large excess of nitrile at 70 °C. Excess aqueous KI displaces two ligands; the large *trans* effect of iodide enforces *trans* stereochemistry in the final product, *trans*-[PtI<sub>2</sub>(NH<sub>3</sub>)(NCR)]. The iodide ligands can be replaced by chlorides via sequential treatment with AgNO<sub>3</sub> and KCl. The synthesis of *cis*-[PtCl<sub>2</sub>(NH<sub>3</sub>)(NCR)] is accomplished more simply by action of a large excess of nitrile on Cossa's salt, K[Pt(NH<sub>3</sub>)Cl<sub>3</sub>].<sup>220</sup>

In addition to alcohols, alkoxides, and thiols, platinum(II) nitriles are also activated for nucleophilic attack by amines to form amidine complexes. Amidine complexes of formula *cis*- and *trans*-[PtCl<sub>2</sub>(amidine)<sub>2</sub>], *cis*- and *trans*-[PtCl<sub>2</sub>(NH<sub>3</sub>)(amidine)], and *trans*-[Pt(amine)<sub>2</sub>(amidine)<sub>2</sub>]Cl<sub>2</sub> have been investigated for anticancer potential, both *in vitro* and *in vivo*.<sup>223–228</sup> Like their iminoether analogues, these complexes generally show good activity in both cisplatin-sensitive and -resistant cell lines. Additionally, both metal- (*cis* or *trans*) and ligand-based (*EE*, *EZ*, or *ZZ*) stereoisomers are possible, as for the related iminoether complexes. The syntheses of *cis*- and *trans*-[PtCl<sub>2</sub>(amidine)<sub>2</sub>], like those for the analogous iminoether complexes, begin with *cis*- and *trans*-[PtCl<sub>2</sub>(NCR)<sub>2</sub>]. Low temperature reactions (–10 °C) of the bis(acetonitrile) complexes with secondary or primary amines in CH<sub>2</sub>Cl<sub>2</sub> affords the amidine complexes (Scheme 14).<sup>229</sup> For the *cis* isomer, five equiv of the amine are required, whereas for the *trans* isomer 50 equiv of amine are required for complete conversion to the diamidine product.<sup>230</sup> The metal stereochemistry is initially



retained in both cases, but in pure water these complexes isomerize, forming an equilibrium mixture of *cis* and *trans* species.<sup>231</sup> This isomerization is prevented in the presence of 100 mM NaCl.<sup>231</sup> The stereochemical outcome of the amidine ligand (*E* vs *Z*) appears to be dictated by the nature of the coordinated nitrile ligand and the nucleophilic amine. In the reaction with the bis(acetonitrile) or bis(benzylcyanide) platinum complexes, primary amines selectively give *ZZ* isomers and secondary amines give *EE* isomers.<sup>225,232</sup> When the coordinated nitrile is benzonitrile, a mixture of *EE* and *ZZ* isomers is obtained.<sup>233</sup> Preparative TLC can be used to separate and isolate some of these isomers.<sup>223</sup>

The action of ammonia on both *cis*- and *trans*-[PtCl<sub>2</sub>(NCR)<sub>2</sub>] has also been investigated.<sup>224,234</sup> For *cis* dinitrile complexes, addition of aqueous ammonia in THF affords the expected diamidine species.<sup>224</sup> When gaseous ammonia is bubbled through a CH<sub>2</sub>Cl<sub>2</sub> solution of the *trans* dinitrile complex at -10 °C, the major product is *trans*-[PtCl(NH<sub>3</sub>)(amidine)<sub>2</sub>]Cl, which results from substitution of a chloride ligand by ammonia in addition to the expected attack on the coordinated nitrile.<sup>234</sup> This complex is also the major product when the *trans* dinitrile complex is treated with aqueous ammonia in THF.<sup>224</sup> At room temperature and with 24 h reaction times, both chlorides of *trans*-[PtCl<sub>2</sub>(NCR)<sub>2</sub>] can be substituted by aliphatic amines or ammonia to form the salts, *trans*-[Pt(amine)<sub>2</sub>(amidine)<sub>2</sub>]Cl<sub>2</sub> (Scheme 14)<sup>235</sup>, which also exhibit anticancer activity.<sup>227</sup> The greater tendency of the *trans* dinitrile complex to lose its chloride ligands in comparison to that of the *cis* is proposed to be a consequence of the greater solubility of the intermediate diamidine complex, *trans*-[PtCl<sub>2</sub>(amidine)<sub>2</sub>], which makes it susceptible to further reactivity with the nucleophilic amines. For the *cis* complex, the diamidine complex precipitates from solution, thus impeding further substitution reactions.

Using the abovementioned amidine-forming reactions, new analogues of the monofunctional PT-ACRAMTU complexes, discussed above, were prepared.<sup>236</sup> These complexes have the general formula, *cis*-[PtCl(L<sub>2</sub>)(amidine)](NO<sub>3</sub>), where L<sub>2</sub> is either two ammine ligands or a chelating diamine, and the amidine ligand is tethered to an intercalating acridine unit. These complexes display excellent activity against non-small cell lung cancer (NSCLC) cell lines, having no cross-resistance to cisplatin.<sup>236</sup> Furthermore, compared to first generation thiourea analogues, these amidine complexes react less readily with cysteine sulfur,<sup>237</sup> yet bind more rapidly to DNA.<sup>238</sup> By comparison to cisplatin, these complexes display a significantly larger degree of intracellular accumulation and DNA platination.<sup>239</sup> The syntheses are accomplished by first treating *cis*-[PtL<sub>2</sub>(NCR)Cl]Cl with 1 equiv of AgNO<sub>3</sub> to exchange the outer-sphere chloride with a nitrate counterion, followed by addition of an acridinyl amine to a DMF solution of the complex at -10 °C (Scheme 15).<sup>236</sup> Acidic workup with HNO<sub>3</sub> yields the product in its protonated form. The low temperature conditions employed during addition of the amine are presumably necessary to prevent it from displacing the chloride ligand. The mononitrile precursor complex, *cis*-[PtL<sub>2</sub>(NCR)Cl]Cl, is synthesized by refluxing a mixture of *cis*-[PtL<sub>2</sub>Cl<sub>2</sub>] and excess nitrile in dilute HCl (Scheme 15).<sup>236,240</sup> This straightforward, amidine-forming reaction has recently been applied to screen combinatorially a number of new platinum complexes that differ in the starting nitrile ligand and the acridinyl amine.<sup>241</sup> The method was used to

delineate some structure-activity relationships for this new class of platinum anticancer complexes.<sup>241</sup>

In addition to nitriles, amines and ammonia are also activated for novel reactivity pathways when coordinated to platinum. Such ligands can engage in condensation reactions to form coordinated imines or iminates. For example, reactions of  $[\text{Pt}(\text{NH}_3)_6]^{4+}$  and  $[\text{Pt}(\text{en})_3]^{4+}$  with acetylacetone afford  $\beta$ -diketiminate complexes.<sup>242,243</sup> Additionally, both *cis*- and *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$  react with 2-pyridinecarboxaldehyde to form  $[\text{Pt}(\text{pmpa})\text{Cl}]$ , where pmpa = *N*-(2-picolyl)picolinamide, presumably by condensation of the coordinated  $\text{NH}_3$  group with the aldehyde (Scheme 16).<sup>244</sup> Ammine insertion into a carbon-carbon double bond of the axial ligand of a platinum(IV) complex has also been observed.<sup>245</sup> Acetonimine complexes of platinum(II), *cis* and *trans*- $[\text{PtX}_2(\text{acetonimine})_2]$  where X = Cl or I, were synthesized by the reaction of *cis* and *trans*- $[\text{Pt}(\text{NH}_3)_2\text{X}_2]$  with acetone in the presence of KOH (Scheme 16).<sup>246</sup> These complexes are of therapeutic interest because they display good *in vitro* anticancer activity against a panel of human cancer cell lines without exhibiting cross-resistance to cisplatin.<sup>246</sup> *cis*- and *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$  react more slowly with acetone than their corresponding iodide analogues, with complexes of *cis* stereochemistry being more reactive than the *trans* complexes. Based on these observations, the ligand *trans* to the amines is proposed to modulate the condensation reactivity, which occurs first by deprotonation of the ammine to form a nucleophilic amido ligand. Higher *trans* effect ligands lower the ammine  $\text{p}K_a$  by stabilizing the anionic amido ligand. Another route to bis(acetonimine) platinum(II) complexes was also reported; direct ligand substitution reaction of  $[\text{PtL}_2\text{Cl}_2]$  (L in this case is a phosphine) by  $[\text{Ag}(\text{acetonimine})_2]\text{ClO}_4$  affords such species.<sup>247</sup>

Ligand-based reactivity does not necessarily require activation by platinum coordination. If the ligand has a functional group that is not in direct interaction with the platinum ion, this functional group can display its typical reactivity, provided that the reaction conditions or byproducts do not lead to decomposition of, or ligand dissociation from, the platinum complex. The platinum(II) complexes  $[\text{Pt}(\text{edma})\text{Cl}_2]$  and  $[\text{Pt}(\text{edda})\text{Cl}_2]$ , where edma = ethylenediaminemonoacetic acid and edda = ethylenediamine-*N,N'*-diacetic acid, can engage in reactions associated with their free carboxylic acid groups (Scheme 17). The reaction of  $[\text{Pt}(\text{edma})\text{Cl}_2]$  with thionyl chloride in methanol converts the acid to a methoxy ester group, presumably through an intermediate acid chloride.<sup>248</sup> Furthermore, the carboxylic acids of both  $[\text{Pt}(\text{edma})\text{Cl}_2]$  and  $[\text{Pt}(\text{edda})\text{Cl}_2]$  can be converted to amides after activation with 1,1'-carbonyldiimidazole (CDI) and treatment with an amine.<sup>249,250</sup> In both cases, the platinum coordination sphere remains unaffected. Platinum(II) complexes of a chelating diamine ligand having a pendant azide have also been synthesized.<sup>251</sup> The azide functional group was employed for a Cu(I)-catalyzed click reaction with terminal alkynes. This chemistry was used to attach a number of different groups to the platinum complex (Scheme 17). Notably, the coordination sphere of the platinum(II) core remained intact in the presence of the Cu(I) catalyst.<sup>251</sup> Platinum(II) complexes with thiol-reactive maleimide derivatives attached to both the non-leaving<sup>252</sup> and leaving group ligands<sup>253</sup> were prepared. As expected, the maleimide moiety readily reacted with thiols. This reaction was used to link carboplatin derivatives to human serum albumin for improved tumor delivery.<sup>253</sup>

### 3. Synthesis of Platinum(IV) Anticancer Complexes

Several platinum(IV) complexes have undergone clinical trials, but to date none has been approved for use in the USA. Examples include iproplatin, tetraplatin, and satraplatin (Chart 5).<sup>23</sup> An advantage of platinum(IV) complexes over their platinum(II) analogues is their six-coordinate octahedral coordination geometry. The introduction of two additional ligands allows for further tuning of the properties and confers the ability to attach functional or targeting groups. Moreover, being complexes of  $d^6$  octahedral metal ions, platinum(IV) compounds are substantially more inert than those of platinum(II). Thus, undesirable side reactions with proteins or intracellular thiols can generally be avoided using platinum(IV) complexes. The kinetic inertness of satraplatin is most likely the reason why it could be administered orally, in contrast to all other platinum drugs, which are delivered intravenously.

Because platinum(IV) complexes are inert, they usually undergo reduction to platinum(II) before binding to their ultimate intracellular target, DNA.<sup>254,255</sup> Reduction of platinum(IV) occurs with loss of two ligands, giving a square-planar geometry for the platinum(II) product. It has generally been assumed that the two ligands lost upon reduction are located trans to each other and that both derive from positions along the axis orthogonal to the original plane of four ligands. This longstanding notion has been challenged by number of recent studies, which show that the composition of the reduced platinum(II) products depends on the nature of the reducing agent.<sup>256–259</sup> Furthermore, the kinetics of intracellular platinum(IV) reduction depend both on the cell type<sup>260</sup> and the ligands that define the coordination sphere of the complex.<sup>261</sup> The ability to rationally design new platinum(IV) anticancer drug candidates using well defined synthetic chemistry is critical for discovering new therapeutic agents and for further elucidating structure-activity relationships.<sup>262</sup>

#### 3.1. Oxidation of Platinum(II)

A common synthetic route to complexes of platinum(IV) proceeds via two-electron oxidation of an appropriate platinum(II) precursor. For potential platinum(IV) anticancer agents, the most widely used oxidizing agents are hydrogen peroxide<sup>263</sup> and chlorine.<sup>264</sup> These two molecules react with platinum(II) to give trans oxidative addition products (Scheme 18). The equatorial ligands of the resulting platinum(IV) complex are generally retained with the stereochemistry of the starting platinum(II) compound. For some diamine dicarboxylato platinum(II) complexes, however, the action of chlorine leads to undesired displacement of the carboxylate groups to form diaminetetrachloridoplatinum(IV) compounds.<sup>265</sup>

Platinum(IV) dihydroxo compounds, obtained by oxidation of platinum(II) complexes in water, are important starting materials for the synthesis of further derivatized platinum(IV) compounds (vide infra). The treatment of a yellow-orange suspension of cisplatin in water with 10–100 fold excess of  $H_2O_2$  at 50 °C gives rise to a pale-yellow suspension comprising *cis,cis,trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)<sub>2</sub>].<sup>266</sup> This reaction is general, proceeding equally well for cis and trans platinum(II) isomers.<sup>267</sup> When isolated directly from the mother liquor, this complex crystallizes with a molecule of hydrogen peroxide that forms hydrogen bonds with the hydroxo ligands.<sup>268</sup> Hydrogen peroxide is also retained in the crystal lattice of the

related complex, *cis,cis,trans*-[Pt(<sup>i</sup>PrNH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)<sub>2</sub>] (iproplatin).<sup>269</sup> The observation that these complexes are able to cleave DNA<sup>270,271</sup> is a consequence of hydrogen peroxide in the lattice rather than the platinum(IV) complex. The hydrogen peroxide can be removed by recrystallization from pure water.<sup>266,267</sup> For the all trans isomer, *trans,trans,trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)<sub>2</sub>], which does not contain lattice-bound hydrogen peroxide, recrystallization from water leads to isomerization, giving *trans,cis,cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)<sub>2</sub>].<sup>267</sup> Diphenyl phosphate (DPP) can also be incorporated into the crystal lattice of trans-platinum(IV) hydroxo compounds.<sup>272</sup> In these crystals, the diphenyl phosphate forms strong hydrogen bonds with the coordinated hydroxide or water ligands.<sup>272</sup> The DPP adducts exhibit improved aqueous solubility. Thus, the use of an appropriate co-crystallization agent may enhance the pharmacological properties of the complex. The abovementioned results point to a large degree of complexity for the H<sub>2</sub>O<sub>2</sub> oxidation of anticancer platinum(II) complexes. Care should be taken to avoid co-crystallized molecules which themselves might have biological activity. Additionally, isomerization may impede purification attempts.

The mechanism of platinum(II) oxidation by hydrogen peroxide and chlorine has important implications for the composition of the isolated products. Studies of hydrogen peroxide-oxidation of platinum(II) complexes using <sup>18</sup>O-labeled water revealed that only one of the hydroxide ligands on the platinum(IV) complex originates from hydrogen peroxide; the other comes from water.<sup>275</sup> Recently, the oxidation of [Pt(*cis*-1,4-DACH)Cl<sub>2</sub>] by chlorine gas was investigated in several different solvents.<sup>276</sup> By NMR spectroscopy, an intermediate corresponding to the addition of one solvent molecule and one chloride ligand, *fac*-[Pt(*cis*-1,4-DACH)(solv)Cl<sub>3</sub>]<sup>+</sup>, was detected. The remaining outer-sphere chloride counterion then substitutes for the labile solvent molecule, giving the expected tetrachlorido species.<sup>276,277</sup> Further support for this mechanism comes from the crystal structure of a mixed *trans*-chloridoaqua complex obtained by the aqueous chlorine oxidation of a platinum(II) oxazole complex.<sup>278</sup> Some early studies report the observation of a transient red or orange color upon oxidation of cisplatin or [Pt(en)Cl<sub>2</sub>] with chlorine.<sup>264,279</sup> The color then changes to the characteristic yellow of the tetrachlorido complexes.<sup>264,279</sup> In our lab, we observed similar behavior following the oxidation of cisplatin and related platinum(II) complexes with hypervalent iodine reagents. The transient red color has been proposed to arise from dinuclear metal-metal bonded platinum(III) complexes, some of which are also red and readily form tetrachloridoplatinum(IV) complexes by disproportionation.<sup>280,281</sup> These dinuclear intermediates probably only occur at high platinum concentrations.

The use of coordinating solvents enables isolation of mixed *trans* oxidative addition products. For example, oxidation of platinum(II) in alcohols with H<sub>2</sub>O<sub>2</sub> gives *trans* hydroxo-alkoxo complexes (Scheme 18).<sup>273–275,282–284</sup> An optimized protocol for the synthesis of cisplatin analogues of these species, *cis,cis,trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)(OR)], utilizes high dilution conditions in neat alcohol and oxidation with 50% aqueous H<sub>2</sub>O<sub>2</sub>.<sup>274,284</sup> The use of 50% rather than 30% H<sub>2</sub>O<sub>2</sub> presumably minimizes the amount of water in solution, which can compete with the alcohol for coordination to platinum. Addition of hydrogen peroxide to a platinum(II) complex with a 9-fluorenylideneprapanedioate (fpd) ligand in refluxing methanol afforded a complex with two axial methoxide ligands instead of the expected

mixed hydroxo-methoxo complex.<sup>282</sup> The formation and stability of the dimethoxo complex is proposed to arise from an intramolecular stabilizing interaction between the methoxide and fpd ligands,<sup>282</sup> and therefore this reaction is probably not general for most platinum(II) complexes. The use of ethyleneglycol as a solvent for the hydrogen peroxide-oxidation of platinum(II) affords a trans hydroxo-ethyleneglycolato complex.<sup>283</sup> The terminal alcohol group of the ethyleneglycolate ligand can presumably be further functionalized by electrophiles, but such reactions have not yet been investigated.

The hydrogen peroxide-oxidation of platinum(II) complexes in the presence of carboxylic acids has also been explored. The oxidation of [Pt(CBDCA)(DPDA)] (DPDA = 2,2-dimethyl-1,3-propanediamine) in acetic acid with hydrogen peroxide gave the unexpected cis diacetate complex, *cis*-[Pt(CBDCA)(DPDA)(OAc)<sub>2</sub>].<sup>285</sup> In contrast, the use of acetic anhydride mixed with a small amount of acetic acid, formed by hydrolysis of the anhydride, as a solvent selectively afforded the trans diacetate complex, *trans*-[Pt(CBDCA)(DPDA)(OAc)<sub>2</sub>] (Scheme 19).<sup>285</sup> The mechanistic details and reasons for the isomeric preferences of these reaction products have not yet been elucidated. The oxidation of the platinum(II) dihydroxo compound, [Pt(DPDA)(OH)<sub>2</sub>], with hydrogen peroxide in carboxylic acids at room temperature gave an unexpected species of general formula and stereochemistry, *fac*-[Pt(DPDA)(OH)(O<sub>2</sub>CR)<sub>3</sub>] (Scheme 19).<sup>286</sup> In our lab, we also explored the oxidation of cisplatin with hydrogen peroxide in neat formic acid. The major product obtained is the diformate complex, *cis,cis,trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(O<sub>2</sub>CH)<sub>2</sub>] (Scheme 19).<sup>287</sup>

Recently, the oxidation of oxaliplatin with hydrogen peroxide in the presence of greater than 40 equiv of carboxylic acid in a minimum volume of THF was reported.<sup>288</sup> The major products observed were the monocarboxylato species, *trans*-[Pt(*trans*-1,2-DACH)(oxalate)(OH)(O<sub>2</sub>CCR)].<sup>288</sup> When bromoacetic acid was used, however, a large quantity of the dicarboxylato species was obtained.<sup>288</sup> This observation was rationalized based on the lower p*K*<sub>a</sub> of bromoacetic acid (2.9) compared to those of the other acids screened (≈ 4.8). With its greater acidity, the bromoacetic acid can protonate the second hydroxo ligand and displace it, as discussed below. Unlike hydrogen peroxide-oxidations carried out in alcohols where one alkoxide and hydroxide are added, there is a greater tendency to add at two carboxylate ligands when the oxidation is performed in organic acids. The species initially formed are most likely mixed hydroxo-carboxylato complexes, analogous to the mixed chlorido-solvento species observed in chlorine oxidations.<sup>276</sup> The highly acidic conditions, not present in alcohol solutions, lead to protonation and subsequent substitution of the hydroxide ligand by a carboxylate, as discussed below. The relative p*K*<sub>a</sub> values of the hydroxo ligands and carboxylic acids most likely dictate whether the major product will be the mono or dicarboxylato complex. Another strategy to prepare mixed hydroxo-acetato complexes employs a different oxidant and solvent mixture.<sup>261,288</sup> Oxaliplatin and *trans*-[PtLL'Cl<sub>2</sub>] complexes, suspended in a 1:1:1 mixture of DMF, CH<sub>2</sub>Cl<sub>2</sub>, and acetic acid, can be oxidized with *tert*-butyl hydroperoxide (in decane) to afford *trans*-[Pt(*trans*-1,2-DACH)(oxalate)(OH)(OAc)] and *trans,trans,trans*-[PtLL'Cl<sub>2</sub>(OH)-(OAc)].<sup>261,288</sup> The use of entirely non-aqueous solvent and peroxide for these reactions prevents formation of the dihydroxo compound. These complexes can serve as precursors for the synthesis of mixed dicarboxylato species.

Oxidation with hydrogen peroxide can also be used to increase the denticity of a ligand. Platinum(II) complexes with the formulas  $[\text{Pt}(\text{edma})\text{Cl}_2]$ ,  $[\text{Pt}(\text{edda})\text{Cl}_2]$ , and  $[\text{Pt}(\text{edta})\text{Cl}_2]$  contain one, two, and four uncoordinated carboxylic acid groups, respectively. Upon oxidation of  $[\text{Pt}(\text{edma})\text{Cl}_2]$  with  $\text{H}_2\text{O}_2$ , the carboxylate coordinates and the ligand binds in a facial, tridentate manner, forming *fac*- $[\text{Pt}(\text{edma})\text{Cl}_2(\text{OH})]$  (Scheme 20).<sup>248</sup> Similarly, both carboxylates of  $[\text{Pt}(\text{edda})\text{Cl}_2]$  coordinate upon oxidation with  $\text{H}_2\text{O}_2$ .<sup>248,289</sup> For  $[\text{Pt}(\text{edta})\text{Cl}_2]$ , only two of the four free carboxylates bind upon oxidation.<sup>290</sup> The remaining two carboxylates can potentially be functionalized by standard amide-bond coupling chemistry, as for the platinum(II) analogues described above. These ring-closing reactions provide a general synthetic route to stable platinum(IV) complexes with multidentate ligands. The design of ligands for platinum(II) complexes with strategically placed donors can facilitate such reactions upon oxidation.

Apart from chlorine and hydrogen peroxide, few other oxidants have been explored for the synthesis of platinum(IV) anticancer agents. One such alternative oxidant is the dithiobis(formamidinium) cation. The dichloride salt of the dithiobis(formamidinium) cation oxidized cisplatin, adding a thiourea and a chloride to the axial positions (Scheme 21).<sup>291</sup> The oxidation of *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$  with this reagent afforded initially the all trans isomer, *t,t,t*- $[\text{PtCl}_2(\text{NH}_3)_2(\text{tu})\text{Cl}]$ , but over time it isomerized to give the same product obtained by the oxidation of cisplatin, *cis,cis,trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2(\text{tu})\text{Cl}]$ .<sup>292</sup> Notably, the tetrafluoroborate salt of the dithiobis(formamidinium) cation does not give any oxidation products, thus highlighting the important role of the coordinating chloride counterion in facilitating the oxidative addition.<sup>291,292</sup> Bromine, like chlorine, also oxidizes diamine platinum(II) complexes, generally forming trans dibromido complexes (Scheme 21).<sup>293</sup> The bromine oxidation of several dichlorido platinum(II) complexes, however, failed to give the expected trans dibromido products; instead, a mixture of complexes with different ratios of chloride and bromide ligands was obtained.<sup>250,294</sup> For diphosphine complexes, this halide scrambling reaction is initiated by light.<sup>295</sup> Oxidations of cisplatin with  $\text{KMnO}_4$ <sup>296</sup> or ozone<sup>297</sup> in water reportedly both lead to the formation of the dihydroxo compound, *cis,cis,trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2(\text{OH})_2]$ , which can also be obtained by oxidation with hydrogen peroxide. The use of peroxydisulfate,  $\text{S}_2\text{O}_8^{2-}$ , as an oxidant, primarily gives trans hydroxo-sulfato platinum(II) complexes.<sup>296,298</sup> The reaction of diamine diamidate complexes of platinum(II) with  $\text{NaOCl}$  yields the corresponding trans hydroxo-chlorido platinum(IV) complexes (Scheme 21).<sup>299</sup> The tetrachloroaurate ion,  $[\text{AuCl}_4]^-$ , can also oxidize platinum(II). The complex *cis*- $[\text{Pt}(\text{NH}_3)_2(1\text{-methylthymine})_2]$  was oxidized by  $\text{NaAuCl}_4$  to afford *cis,cis,trans*- $[\text{Pt}(\text{NH}_3)_2(1\text{-methylthymine})_2(\text{OH})(\text{OH}_2)]$ .<sup>300</sup> The addition of two ligands originating from water was unexpected and rationalized on the basis of steric crowding at the axial sites by the 1-methylthymine ligands. In contrast, the oxidation of a platinum(II) terpyridine complex by  $\text{AuCl}_4^-$  added two chloride ligands to the resulting platinum(IV) coordination sphere.<sup>301</sup> Nitrogen dioxide gas can also oxidize cisplatin in an aqueous solution containing one equiv of  $\text{KCl}$  (Scheme 21).<sup>302</sup> The product,  $[\text{PtCl}_3(\text{NO}_2)(\text{NH}_3)]$ , which could not be isolated as analytically pure material, comprised primarily the facial isomer, as determined by NMR spectroscopy. Analysis by X-ray diffraction revealed a disordered mixture of facial and meridional isomers.<sup>302</sup> Potassium dichromate,  $\text{K}_2\text{Cr}_2\text{O}_7$ , and potassium chlorochromate,  $\text{KCrO}_3\text{Cl}$ , can also oxidize cisplatin.<sup>303</sup> On the basis of



spectroscopic data, the products were proposed to be a dimetallic heteronuclear Pt–Cr complex and a trimetallic Pt–Cr<sub>2</sub> complex, respectively, with oxo ligands bridging the metal centers (Scheme 21).<sup>303</sup> Similarly, cisplatin was oxidized by iron(III) complexes of the general formula, *cis*-[Fe(bpy')<sub>2</sub>(CN)<sub>2</sub>](NO<sub>3</sub>), where bpy' is derivative of 2,2'-bipyridine, to form trinuclear cyanide-bridged complexes (Scheme 21).<sup>304,305</sup> The photochemistry of these complexes was explored, and in some cases the release of aquated cisplatin as a photoproduct occurred,<sup>304,305</sup> thus signifying the potential use of such complexes as photoactivated anticancer agents.

Hypervalent iodine species are a class of powerful oxidizing agents with utility in organic synthesis. Iodobenzene dichloride (PhICl<sub>2</sub>),<sup>306</sup> which can be isolated as a crystalline solid, acts as an easy-to-handle surrogate for chlorine gas. It efficiently converts cisplatin and related diaminedichloridoplatinum(II) complexes to their corresponding tetrachloridoplatinum(IV) analogues (Scheme 22).<sup>249,250</sup> A recent report describes the action of PhICl<sub>2</sub> on an organoamide platinum(II) complex in a mixture of acetone and basic water.<sup>307</sup> A mixed *trans* hydroxo-chlorido platinum(IV) complex is obtained (Scheme 22),<sup>307</sup> consistent with a solvent-assisted mechanism, similar to that observed for oxidations by chlorine and hydrogen peroxide.

The oxidations of *cis*- and *trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>], where NH<sub>2</sub>Cy is cyclohexylamine, with PhI(OAc)<sub>2</sub> in dichloromethane have been investigated.<sup>308</sup> The major products derive from the oxidative addition of two acetate ligands in a *cis* orientation. For *cis*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>], the major product is *cis,cis,cis*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>(OAc)<sub>2</sub>], whereas, when the starting material is *trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>], the major product is *cis,trans,cis*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>(OAc)<sub>2</sub>] (Scheme 22). In addition to the major product, minor products *mer*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl(OAc)<sub>3</sub>] and *fac*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)(OAc)Cl<sub>3</sub>] also form upon PhI(OAc)<sub>2</sub> oxidation of *cis*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>], indicative of intermolecular ligand substitution reactions. The apparent limitations of using PhI(OAc)<sub>2</sub> in contrast to PhICl<sub>2</sub> are the formation of products without predictable stereochemistry and unexpected ligand stoichiometries. Given the large number of hypervalent iodine complexes in the literature, further investigations of their reactivity with platinum(II) complexes is certainly warranted, for they may lead to new, valuable synthetic routes to novel platinum(IV) complexes.

### 3.2. Outer-Sphere Ligand-Based Reactivity

Outer-sphere ligand-based reactivity pathways for the preparation of new platinum(IV) complexes is a valuable synthetic route because their kinetic inertness limits the utility of ligand substitution reactions. A reaction of key importance in this regard is that of Pt(IV)-hydroxo compounds with electrophiles. The coordinated hydroxide ligand of platinum(IV) complexes is sufficiently nucleophilic to enable such transformations. The acetylation of *cis,cis,trans*-[Pt(<sup>i</sup>PrNH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)<sub>2</sub>] with trifluoroacetic anhydride to form *cis,cis,trans*-[Pt(<sup>i</sup>PrNH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub>(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub>] was first demonstrated in 1983.<sup>309</sup> This chemistry was further expanded to include a broader range of acid anhydrides, pyrocarbonates, and isocyanates as electrophiles to afford dicarboxylate, dicarbonate, and dicarbamate platinum(IV) complexes, respectively.<sup>129</sup> In all cases, the stereochemistry of the starting dihydroxo platinum(IV) compound is retained. For acetylation of *trans,trans,trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>(OH)<sub>2</sub>] with

acetic anhydride, however, light-induced isomerization of the initial product, *trans,trans,trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>(OAc)<sub>2</sub>], to *trans,cis,cis*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>(OAc)<sub>2</sub>] occurred.<sup>308</sup>

Since the initial report, a wide variety of *trans* platinum(IV) dicarboxylate complexes have been synthesized in this manner. The carboxylate ligands have significant effects on both the lipophilicity and reduction potentials of the resulting platinum(IV) complexes.<sup>310–313</sup> Furthermore, the ubiquitous nature of the carboxylate functional group in many different organic molecules enabled the synthesis of platinum(IV) complexes bearing biologically active ligands, attached via the carboxylate.<sup>314–317</sup> Different protocols have called for the use of excess anhydride, either neat,<sup>129</sup> or together with acetone,<sup>129</sup> dichloromethane,<sup>66,310</sup> acetonitrile,<sup>318,319</sup> or DMSO<sup>320,321</sup> as the solvent (Scheme 23). Similarly, tetracarboxylato platinum(IV) complexes, some of which exhibit anticancer activity when administered orally,<sup>322</sup> can be synthesized from *cis*-[PtL<sub>2</sub>(OH)<sub>4</sub>]<sup>293,308,323</sup> and excess anhydride in dichloromethane (Scheme 23).<sup>308,324</sup> This reaction demonstrates that equatorial *cis* hydroxide ligands also display nucleophilic properties. Acyl chlorides also react with *trans* dihydroxo platinum(IV) complexes to form dicarboxylates. A difficulty in this reaction, noted early on,<sup>129</sup> is the formation of hydrochloric acid as a byproduct, which can remove the hydroxo ligands of platinum(IV) by protonation. Optimized reaction conditions utilize refluxing acetone as a solvent and an excess of pyridine as a base to sequester the HCl that is formed (Scheme 23).<sup>325,326</sup> Aromatic carboxylate ligands can be installed on platinum(IV) with this method as well.<sup>314,327</sup>

A third route to *trans* platinum(IV) dicarboxylates utilizes the ring opening reactions of the platinum(IV) hydroxo complexes with cyclic anhydrides. Succinic,<sup>154,328,329</sup> maleic,<sup>154,245</sup> glutaric,<sup>154,330</sup> phthalic,<sup>327</sup> and naphthalic<sup>331</sup> anhydrides have all been used in this reaction, together with the traditional Chinese medicine cantharidin.<sup>315</sup> Early protocols for this reaction involved the treatment of a platinum(IV) hydroxo compound with the cyclic anhydride in refluxing dichloromethane for two days.<sup>154,330</sup> Currently, the most commonly used method utilizes either DMF<sup>329</sup> or DMSO<sup>328</sup> as solvent at 50–80 °C for 6–24 h (Scheme 23). Activating carboxylic acids with an appropriate coupling reagent has also been an effective means of forming *trans* dicarboxylate complexes. For example, the reaction of a platinum(IV) analogue of oxaliplatin, *trans*-[Pt(*trans*-1,2-DACH)(oxalate)(OH)<sub>2</sub>], with 3 equiv of carboxylic acid, triethylamine (TEA), and the coupling reagent *O*-benzotriazol-1-yl-*N,N,N,N*-tetramethyluronium tetrafluoroborate (TBTU) readily yields the dicarboxylato complex, *trans*-[Pt(*trans*-1,2-DACH)(oxalate)(O<sub>2</sub>CR)<sub>2</sub>] (Scheme 23).<sup>288</sup> This one pot procedure may provide a useful alternative to the abovementioned methods because it avoids the need to prepare anhydrides or acyl chloride as intermediates.

The synthesis of mixed platinum(IV) carboxylate complexes can introduce greater molecular complexity and provide a means of installing different functional or targeting groups. The reaction of a platinum(IV) dihydroxo complex with a mixture of different anhydrides gives rise to a statistical mixture of symmetric and asymmetric platinum(IV) dicarboxylates that can be separated by silica gel chromatography.<sup>129</sup> Similarly, mixed tetracarboxylates were synthesized by the reaction of a platinum(IV) tetrahydroxo complex with different ratios of anhydrides.<sup>332</sup> The resulting products required purification by either

silica gel chromatography or preparative reverse-phase HPLC.<sup>332</sup> Another, more elegant pathway to mixed platinum(IV) dicarboxylates requires the isolation of a trans mixed hydroxo-carboxylato platinum(IV) complex. The remaining hydroxo ligand could then be derivatized with a different carboxylate ligand. The synthesis of several mixed hydroxo-carboxylato complexes by the peroxide oxidation of platinum(II) in the presence of an excess of carboxylic acid was described above, as shown in Scheme 19.<sup>261,288</sup> These complexes can react with another acid anhydride to yield a mixed-dicarboxylate complex. The selective acetylation of a single hydroxo ligand is another potential strategy. One way to accomplish this selective reaction is with steric control. Initially, the acetylation of a platinum(IV) analogues of sterically hindered picoplatin, *cis,cis,trans*-[Pt(NH<sub>3</sub>)(2-pic)Cl<sub>2</sub>(OH)<sub>2</sub>], with acetic anhydride was reported to be unsuccessful because the ortho methyl group of the picoline ligand impedes the hydroxo nucleophilic attack.<sup>145</sup> It was later shown, however, that the acetylation of this complex can be successfully executed with a number of different anhydrides to give symmetric dicarboxylate complexes.<sup>333</sup> Thus the steric effects of the 2-picoline ligand did not successfully lead to the formation of the monohydroxo complex. The platinum(IV) complex *cis,cis,trans*-[Pt(en')Cl<sub>2</sub>(OH)<sub>2</sub>], where en' is *N,N*-dimethylethylenediamine, is selectively acetylated at only one of the hydroxo ligands in the presence of excess succinic anhydride (Scheme 24).<sup>334</sup> The inability to form the dicarboxylate was attributed to steric repulsion induced by the additional methyl groups on the ethylenediamine ligand.<sup>334</sup> This strategy was expanded with other bulky derivatives of ethylenediamine to selectively functionalize only one hydroxide ligand with isocyanates and acyl chlorides using mild reaction conditions.<sup>335</sup> The isolation of other mixed hydroxo-carboxylato platinum(IV) complexes as synthons for mixed dicarboxylates was described recently.<sup>331</sup> These complexes were obtained by careful control of the reaction conditions. The room temperature reactions of platinum(IV) dihydroxo complexes with an acid anhydride in DMSO were used to increase the yield of the desired monocarboxylate complexes with respect to that of the dicarboxylate species (Scheme 24). These reaction conditions were employed to prepare complexes with axial aromatic carboxylates<sup>331</sup> and succinate.<sup>258,336</sup> In general, the desired mixed hydroxo-carboxylato complexes are insoluble in acetone, thereby enabling the undesired dicarboxylate complexes to be removed by dissolution in this solvent.<sup>129</sup> An alternative procedure utilizes a carboxylic acid preactivated by *N,N'*-dicyclohexylcarbodiimide (DCC).<sup>288</sup> The one pot reaction of a *trans*-[Pt(*trans*-1,2-DACH)(oxalate)(OH)<sub>2</sub>] with only slightly greater than one equiv of DCC and a carboxylic acid in DMF at room temperature preferentially gave the monocarboxylato species (Scheme 24).<sup>288</sup>

In addition to acid anhydrides and acid chlorides, several other electrophiles react with platinum(IV) hydroxo complexes. The reactivity of platinum(IV) hydroxides with pyrocarbonates and isocyanates to form platinum(IV) carbonates and carbamates has been known for over 15 years.<sup>129</sup> The reactions of *cis, cis, trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)<sub>2</sub>] with both alkyl and aromatic isocyanates were recently investigated in detail.<sup>337</sup> The optimal conditions utilized four equiv of the isocyanate and DMF as the solvent at room temperature for several hours (Scheme 25). The action of trimethylsilyl chloride (TMSCl) on the tetrahydroxo complex, *cis*-[Pt(DPDA)(OH)<sub>4</sub>] has also been explored.<sup>323</sup> At room temperature in THF with TEA as a base, the main reaction product is the *trans* disiloxide

complex, *cis, trans, cis*-[Pt(DPDA)(OSiMe<sub>3</sub>)<sub>2</sub>(OH)Cl], whereas refluxing conditions afforded *cis, trans, cis*-[Pt(DPDA)(OSiMe<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] (Scheme 25)<sup>323</sup>. The substitution of the hydroxide ligands most likely arises from the HCl byproduct, which acts as the source of protons to labilize the hydroxide ligands and as the source of the nucleophilic chloride ligands.

The additional axial ligands available in platinum(IV) but not platinum(II) complexes can be selected for introducing reactive organic functionalities. For example, the ring-opening reaction of platinum(IV) hydroxides with cyclic acid anhydrides yields platinum(IV) complexes with free terminal carboxylic acids. The terminal carboxylic acids can undergo amide and ester coupling reactions with the octahedral platinum(IV) center remaining intact (Scheme 26). These reactions have been used to covalently modify platinum(IV) complexes with estrogen,<sup>328–341</sup> and nano-delivery devices.<sup>274,342–348</sup> Additionally, a wide variety of amines and alcohols have been coupled to such platinum(IV) complexes in order to systematically adjust their lipophilicities.<sup>284,329,349–354</sup> For coupling reactions carried out in DMF, *N, N'*-diisopropylcarbodiimide (DIPC),<sup>328</sup> *O*-(7-azabenzotriazol-1-yl)-*N, N, N', N'*-tetramethyluronium hexafluorophosphate (HATU),<sup>342</sup> and 1,1'-carbonyldiimidazole (CDI)<sup>329</sup> were all used with success, whereas for aqueous coupling reactions the combination of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) works well.<sup>336,338,341</sup>

Two platinum(IV) complexes with axial ligands containing aldehyde and ketone functional groups have also been reported recently.<sup>355,356</sup> The reaction of these functional groups with organic hydrazines and hydroxylamines leads to the formation of hydrazones and oximes, providing a new convenient method to conjugate platinum(IV) to different units (Scheme 26). This strategy has already been employed to attach platinum(IV) to a short peptide<sup>356</sup> and a polymeric nanoparticle.<sup>355</sup> A platinum(IV) complex containing an axial carboxylate ligand with a pendant azide has also recently been described.<sup>288</sup> In the presence of CuI, the azide ligand reacts with an alkyne to form the expected triazole, and the intact platinum(IV) complex can be isolated by preparative HPLC in approximately 50% yield (Scheme 26).<sup>288</sup> A possible limitation of this reaction for use in the preparation of other platinum(IV) complexes could be undesired reduction of the platinum(IV) center by the Cu(I) ion. In another recent report, a thiol-reactive maleimide functional group was installed in the axial positions of two platinum(IV) complexes via carbamate linkages.<sup>357</sup> The maleimide was used to attach the platinum(IV) complex to human serum albumin at its single exposed cysteine residue (Scheme 26).<sup>357</sup>

### 3.3. Ligand Substitution Reactions

Because of the inert nature of platinum(IV) complexes, direct ligand substitution reactions are generally very slow and require harsh conditions. As a result, such reactions are rarely employed to prepare anticancer platinum(IV) prodrug candidates. Complexes of the type [Pt(L<sub>2</sub>)Cl<sub>4</sub>], where L<sub>2</sub> is a chelating diamine ligand, however, can be synthesized by the reaction of the [PtCl<sub>2</sub>]<sup>2-</sup> anion with L<sub>2</sub> in water, usually under refluxing conditions.<sup>358–362</sup> For more complicated structures, different strategies can be utilized to facilitate ligand substitution of platinum(IV), as discussed below.

Hydroxide ligands bound to platinum(IV) complexes can be substituted under acidic conditions. A popular synthetic route to *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>4</sub>] and other diamine tetrachlorido complexes utilizes *cis, cis, trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(OH)<sub>2</sub>] as a platinum(IV) starting material. Treatment of this compound with hydrochloric acid affords the tetrachlorido (Scheme 27).<sup>310</sup> This reaction most likely proceeds via protonation of the hydroxo ligands, converting them to labile water ligands, followed by displacement with the nucleophilic chloride ion. This reaction also works for hydrobromic acid to substitute bromide for hydroxide ligands.<sup>363</sup> When hydrochloric acid is added to the tetrahydroxo compound, [Pt(*trans*-1,2-DACH)(OH)<sub>4</sub>], all four hydroxides are replaced by chloride ligands.<sup>364</sup> In contrast, suspending [Pt(*trans*-1,2-DACH)(OH)<sub>4</sub>] in neat carboxylic acid affords the trisubstituted species, *fac*-[Pt(*trans*-1,2-DACH)(OH)(O<sub>2</sub>CR)<sub>3</sub>] (Scheme 27).<sup>364</sup> It is hypothesized by the authors of these studies that the p*K*<sub>a</sub> of the last hydroxide ligand is too low to be protonated by a carboxylic acid (p*K*<sub>a</sub> ≈ 5), but not lower than that of the stronger acid HCl. This hydroxo ligand, however, still retains its nucleophilic character as it can be acetylated with other carboxylic anhydrides to rationally make mixed carboxylate complexes.<sup>365</sup> When trifluoroacetic anhydride is added to these tricarboxylate complexes in the absence of a base, the unexpected product *cis, cis, cis*-[Pt(*trans*-1,2-DACH)(O<sub>2</sub>CR)<sub>2</sub>(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub>] is obtained (Scheme 27).<sup>366</sup> The hydroxide is most likely initially acetylated by trifluoroacetic anhydride, releasing the strong acid, trifluoroacetic acid, as a byproduct. Trifluoroacetic acid can then protonate and release a coordinated carboxylate ligand and bind to the platinum(IV) center. Consistent with this hypothesis is the observation that adding a base with the trifluoroacetic anhydride gives rise only to the expected complex, *fac*-[Pt(*trans*-1,2-DACH)(O<sub>2</sub>CCF<sub>3</sub>)(O<sub>2</sub>CR)<sub>3</sub>], presumably by neutralizing the trifluoroacetic acid byproduct.<sup>366</sup>

Just as acidic conditions favor ligand substitution reactions in platinum(IV) complexes by protonolysis, basic conditions can also induce ligand substitution, albeit by a different mechanism. Under basic conditions, platinum amine complexes can undergo ligand substitution via the base hydrolysis mechanism.<sup>367–369</sup> In general, these reactions result in the net substitution of a chloride by a solvent ligand. The first step is the deprotonation of an amine ligand to form an amido ligand. The high *trans* effect of the amido ligand favors dissociation of a *trans* chloride ligand, yielding a five-coordinate intermediate. The addition of a solvent molecule to this five-coordinate intermediate results in the observed product. In the realm of platinum-based anticancer agents, this reaction mechanism has been proposed, albeit without supporting kinetic data, for the formation of several new derivatives of satraplatin.<sup>308,370</sup> The reaction of *cis, cis, trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>(O<sub>2</sub>CC<sub>3</sub>H<sub>7</sub>)<sub>2</sub>] with sodium methoxide in methanol resulted in substitution of the chloride *trans* to the cyclohexylamine for a methoxide ligand, forming *cis, cis, trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl(OMe)(O<sub>2</sub>CC<sub>3</sub>H<sub>7</sub>)<sub>2</sub>] (Scheme 28)<sup>370</sup>. Similarly, in basic water *cis, cis, trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl<sub>2</sub>(O<sub>2</sub>CCH<sub>3</sub>)<sub>2</sub>] converts to the monohydroxide complex, *cis, cis, trans*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl(OH)(O<sub>2</sub>CCH<sub>3</sub>)<sub>2</sub>], where the hydroxide ligand is also *trans* to the cyclohexylamine (Scheme 28).<sup>308</sup> In DMA containing 2 M LiCl, the addition of TEA as a base to *cis*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)(OAc)<sub>4</sub>] afforded the monochlorido complex *mer*-[Pt(NH<sub>3</sub>)(NH<sub>2</sub>Cy)Cl(OAc)<sub>3</sub>] (Scheme 28).<sup>308</sup> In this case, the base hydrolysis route was able to substitute an acetate ligand rather than a chloride. This reaction also demonstrates that, if a non-coordinating solvent is used, other ligands besides solvent can be added to the

platinum(IV) complex. In a recent study, it was demonstrated that platinum(IV) complexes with electronegative halocarboxylate ligands can be directly hydrolyzed, undergoing substitution of the carboxylates for hydroxides.<sup>371</sup> These reactions are accelerated under basic conditions,<sup>371</sup> suggesting that a conjugate base mechanism might be operative.

#### 4. Concluding Remarks

The chemistry of cisplatin and its isomers was first explored over one hundred years ago. The discovery of its anticancer properties in 1969 motivated further exploration into its coordination chemistry and that of related species,<sup>372,373</sup> with the ultimate goal of finding new complexes with improved therapeutic properties. The development of new synthetic methodologies can give access to new platinum complexes with novel structures and possibly novel modes of biological activity. This review summarizes the known reactivity patterns and synthetic strategies for a range of platinum anticancer complexes. Notably, much of this chemistry has only been developed within the last 20 years. Thus, as long as the need for new platinum anticancer agents persists, new chemistry will be developed and investigated in order to obtain such compounds.

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#### Biographies



Justin J. Wilson completed his undergraduate education at U.C. Berkeley where he received his B.S. in Chemistry with Highest Honors and the Departmental Citation. At Berkeley, he carried out undergraduate research in the laboratory of Professor Jeffrey R. Long on the topic of single-molecule magnetism. After Berkeley, he attended the Massachusetts Institute of Technology for graduate studies. At MIT, he worked in the laboratory of Professor Stephen J. Lippard and completed his thesis on platinum-based anticancer agents for which he received the Davison Award, an annual prize for the best inorganic PhD thesis. Justin is currently a Seaborg Institute Postdoctoral Research Fellow at Los Alamos National Laboratory.





Stephen J. Lippard is the Arthur Amos Noyes Professor of Chemistry at MIT, where he was head of department from 1995–2005. His work on platinum complexes began with initial studies that provided electron dense reagents for use in electron microscopy and macromolecular crystallography, continued with work that elucidated the nature of 'platinum blues,' and for many years has contributed to our understanding and designed improvement of platinum anticancer drugs and drug candidates. He recently co-founded Blend Therapeutics to help advance novel platinum compounds for cancer therapy. He is shown here with his late wife Judy, a constant companion for 50 years to whom this article is dedicated.

## Abbreviations

<b>bpy</b>	2,2'-bipyridine
<b>CBDCA</b>	1,1-cyclobutanedicarboxylato
<b>CDI</b>	1,1'-carbonyldiimidazole
<b>DACH</b>	diaminocyclohexane
<b>dien</b>	diethylenetriamine
<b>DMA</b>	<i>N,N</i> -dimethylacetamide
<b>DCC</b>	<i>N,N'</i> -dicyclohexylcarbodiimide
<b>DPDA</b>	2,2-dimethyl-1,3-propanediamine
<b>DIPC</b>	<i>N,N'</i> -diisopropylcarbodiimide
<b>DPP</b>	diphenyl phosphate
<b>edda</b>	ethylenediamine- <i>N,N'</i> -diacetic acid
<b>edma</b>	ethylenediaminemonoacetic acid
<b>EDC</b>	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)
<b>edta</b>	ethylenediametetraacetic acid
<b>en</b>	ethylenediamine
<b>fpd</b>	9-fluorenylidenepropanedioate
<b>HATU</b>	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
<b>pmpa</b>	<i>N</i> -(2-picolyl)picolinamide
<b>NHS</b>	<i>N</i> -hydroxysuccinimide
<b>TBTU</b>	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
<b>TEA</b>	triethylamine

<b>TMSCI</b>	trimethylsilyl chloride
<b>tu</b>	thiourea

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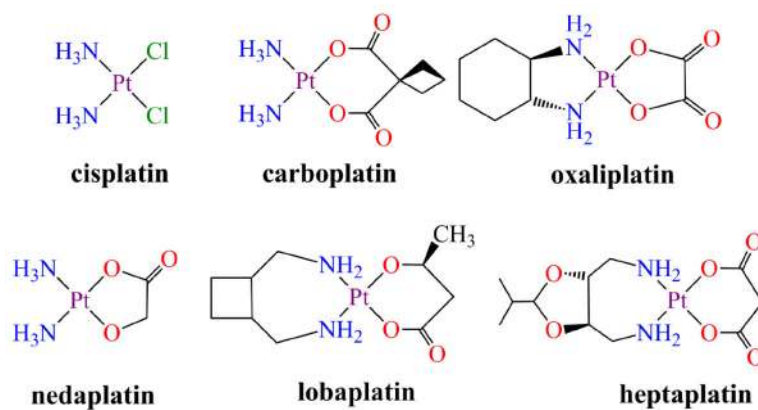
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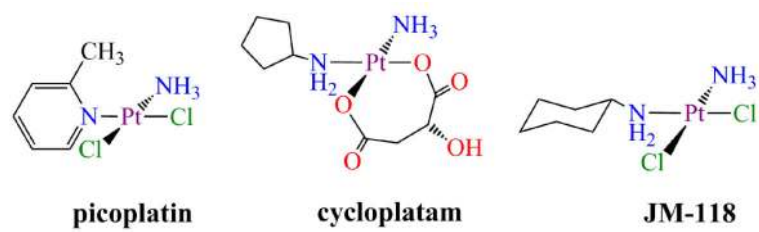


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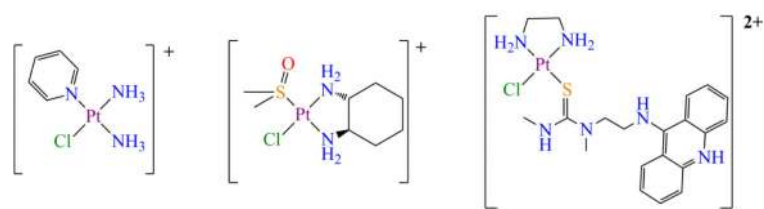
**Chart 1.**

Chemical structures of the clinically used platinum-based anticancer drugs. The top three complexes, cisplatin, carboplatin, and oxaliplatin, are approved for use worldwide. The bottom three complexes, nedaplatin, lobaplatin, and heptaplatin, are approved for use in Japan, China, and Korea, respectively.

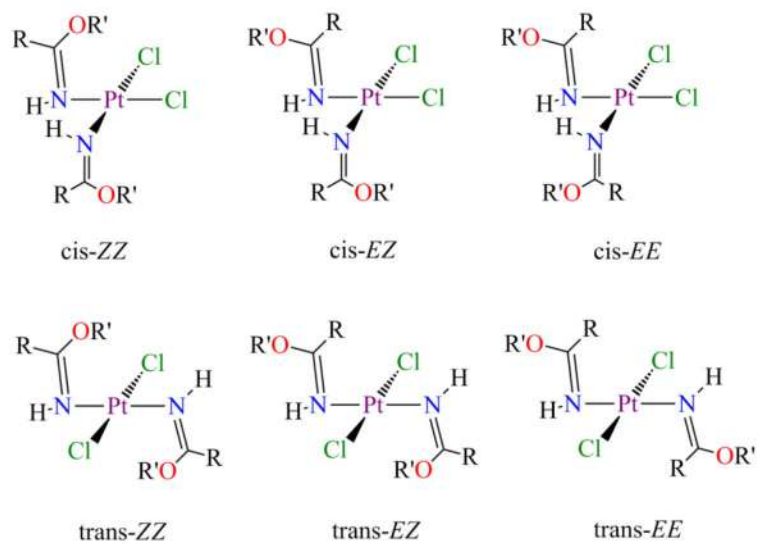


**Chart 2.**

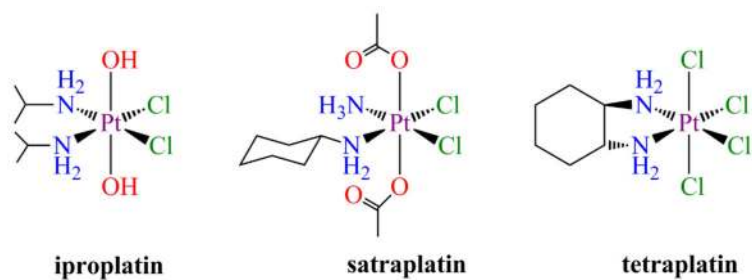
Structures of mixed amine platinum(II) complexes that have undergone clinical trials.

**Chart 3.**

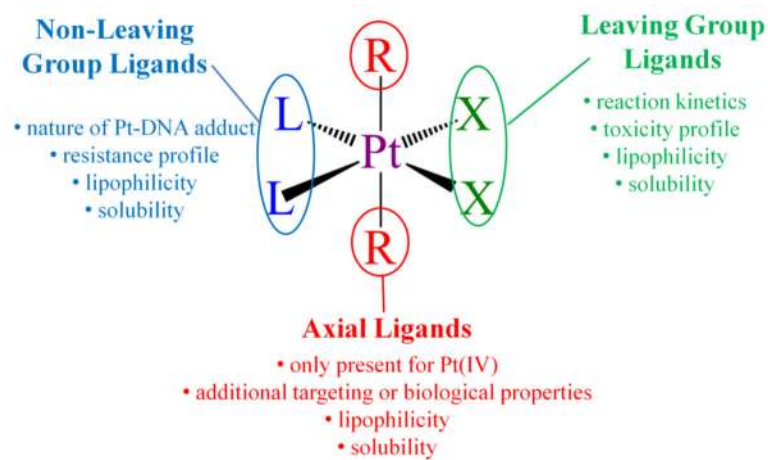
Examples of cationic monofunctional platinum(II) complexes that exhibit anticancer activity.<sup>172–174</sup>

**Chart 4.**

Depiction of the six different stereoisomers of [PtCl<sub>2</sub>(iminoether)<sub>2</sub>]. The terms cis and trans refer to the stereochemistry at the platinum(II) center, whereas *E* and *Z* denote the stereochemistry at the C–N double bond of the iminoether ligands.<sup>213</sup>

**Chart 5.**

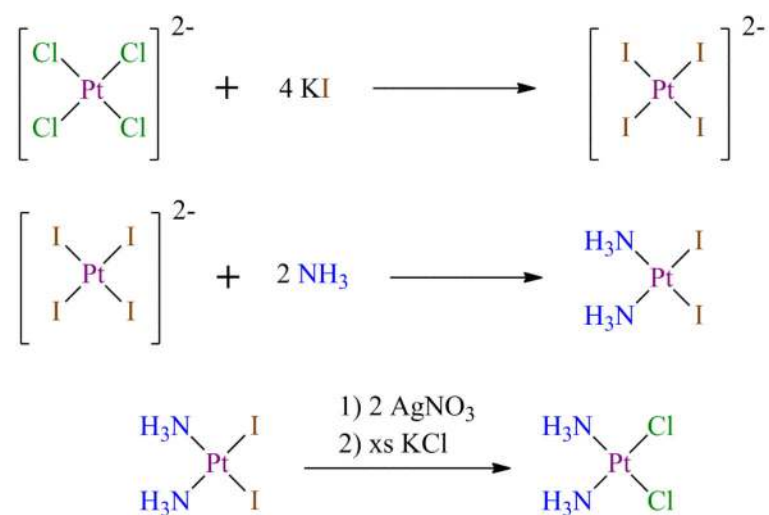
Examples of several clinically investigated platinum(IV) anticancer agents.



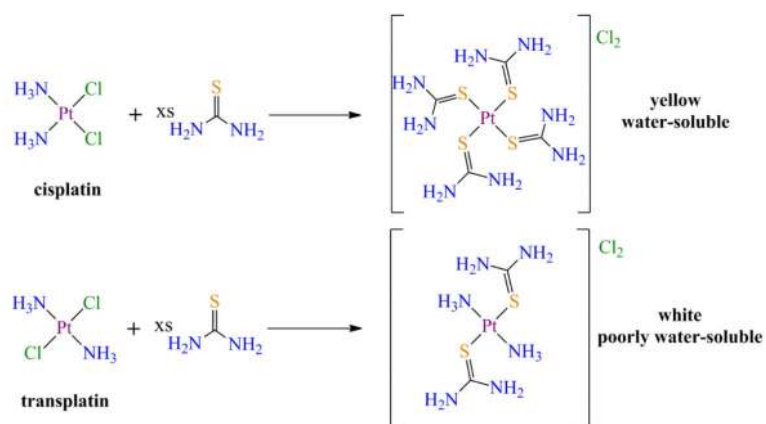
**Figure 1.**

Different components of platinum anticancer agents. Additional factors that can be varied are the stereochemistry and the respective number of non-leaving and leaving group ligands.

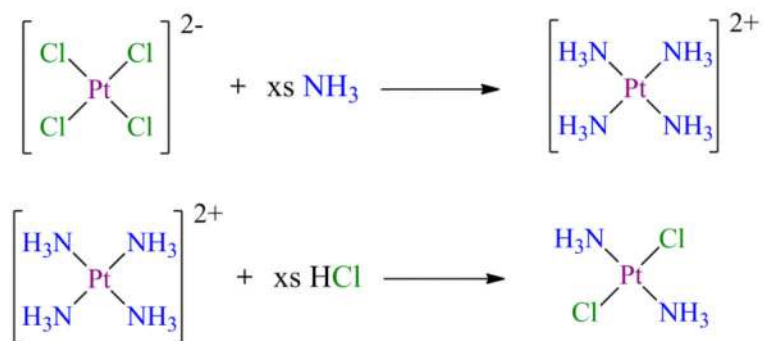


**Scheme 1.**

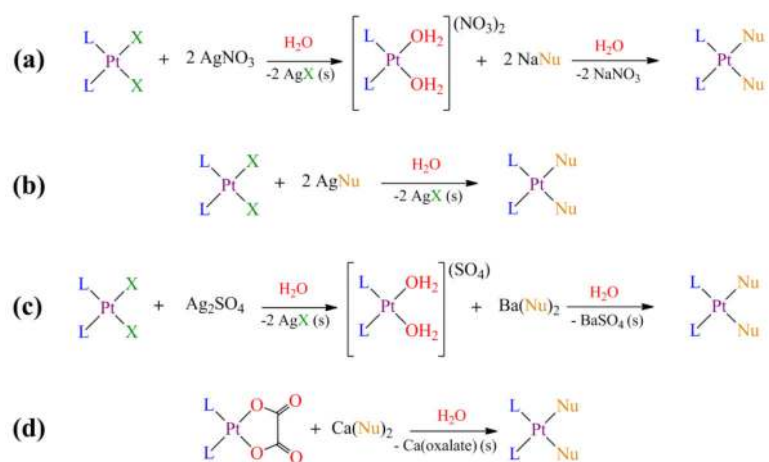
Synthesis of cisplatin using the method of Dhara.<sup>60</sup> All reactions steps are carried out in aqueous solution.

**Scheme 2.**

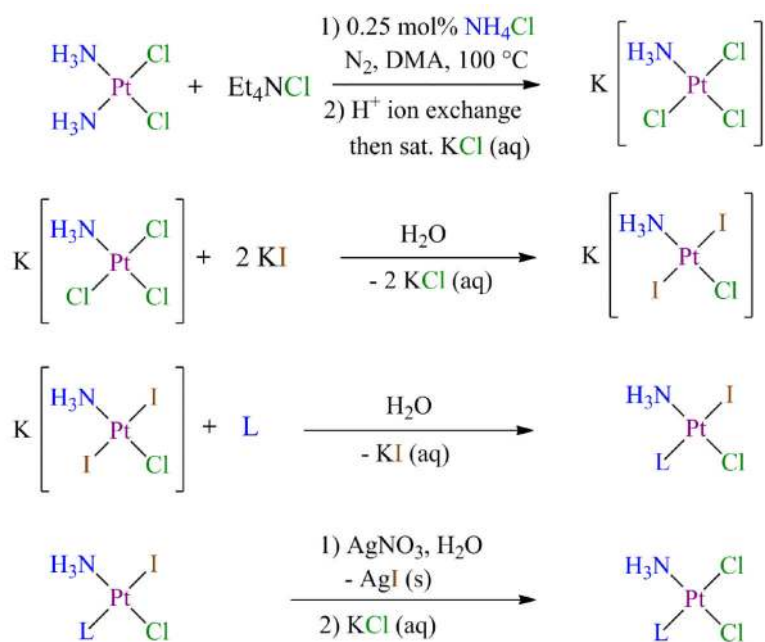
The use of the Kurnakow test<sup>81</sup> to distinguish *cis*- and *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>]. Reactions with thiourea are carried out in sub-boiling water.

**Scheme 3.**

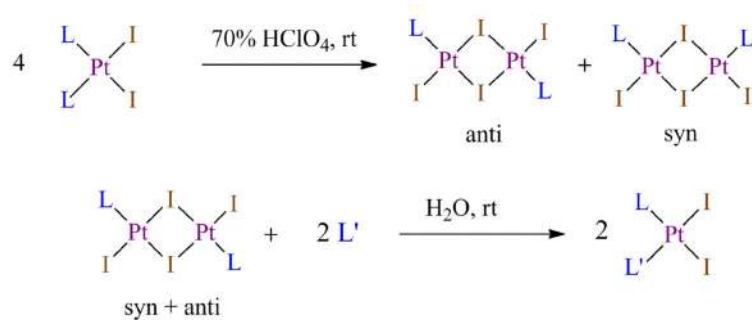
Synthesis of *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ .<sup>57</sup> Reactions are carried out in water at elevated (50–100 °C) temperatures.

**Scheme 4.**

Different synthetic routes to replace halide leaving group ligands.<sup>95,107</sup>

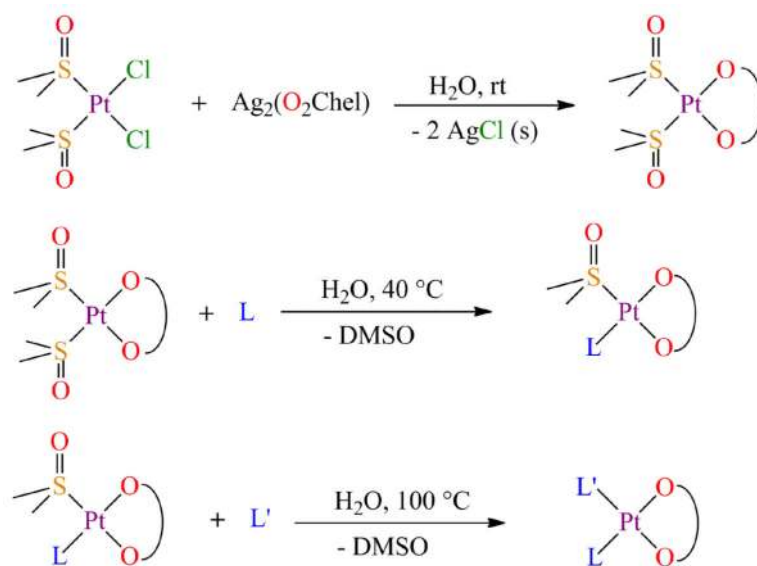
**Scheme 5.**

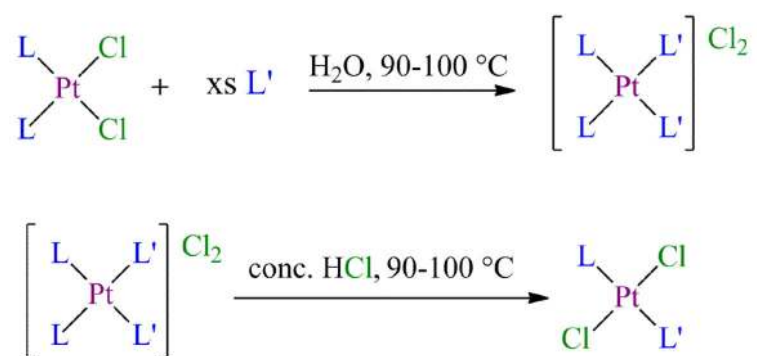
Synthesis of *cis*-[Pt(NH<sub>3</sub>)LCl<sub>2</sub>] starting from cisplatin using the [Pt(NH<sub>3</sub>)Cl<sub>3</sub>]<sup>-</sup> ion as an intermediate.<sup>126,130</sup>

**Scheme 6.**

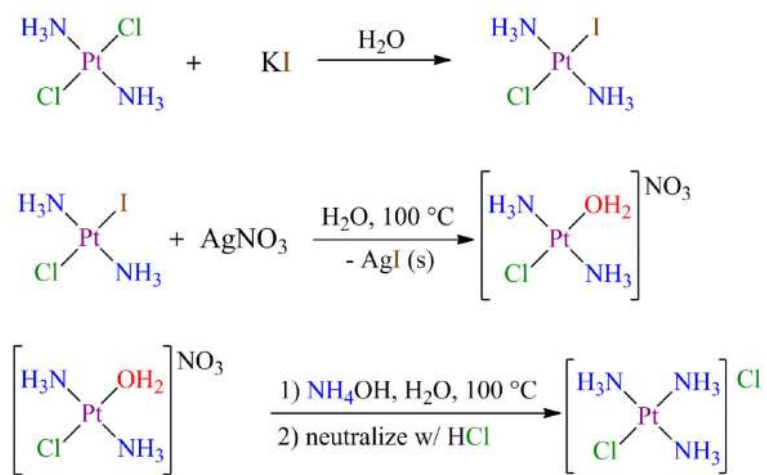
Synthesis of mixed amine complexes, *cis*- $[\text{PtLL}'\text{I}_2]$ , via iodido-bridged dimer intermediates.<sup>131,142</sup>



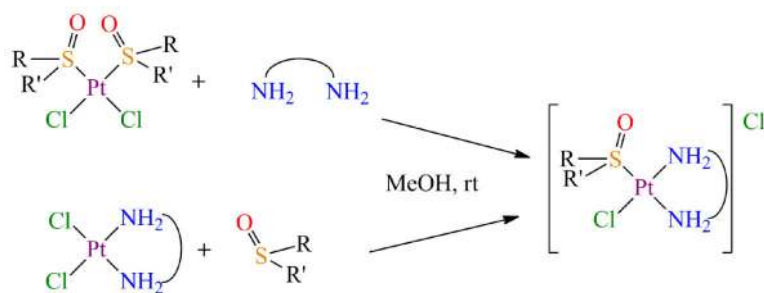
**Scheme 7.**Synthesis of mixed amine complexes with a chelating oxygen donor leaving group.<sup>152</sup>



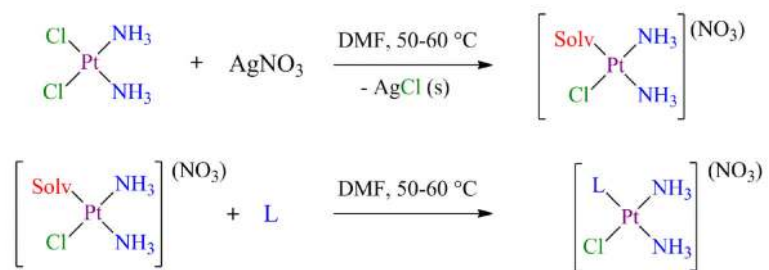
**Scheme 8.**  
Synthesis of *trans*-[PtLL'Cl<sub>2</sub>].<sup>158</sup>



**Scheme 9.**  
Synthesis of  $[\text{Pt}(\text{NH}_3\text{Cl})\text{Cl}]$ .<sup>169</sup>

**Scheme 10.**

Two different synthetic routes for the preparation of *cis*-[Pt(L<sub>2</sub>)(RR'SO)Cl]Cl.<sup>173</sup>

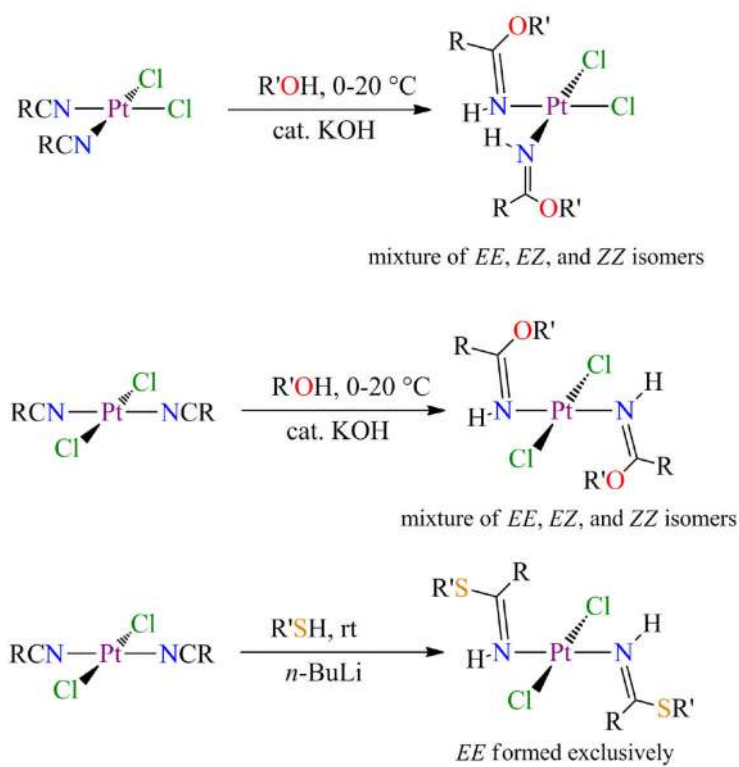


**Scheme 11.**  
Synthesis of *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>LCl]NO<sub>3</sub>.<sup>172,189</sup>

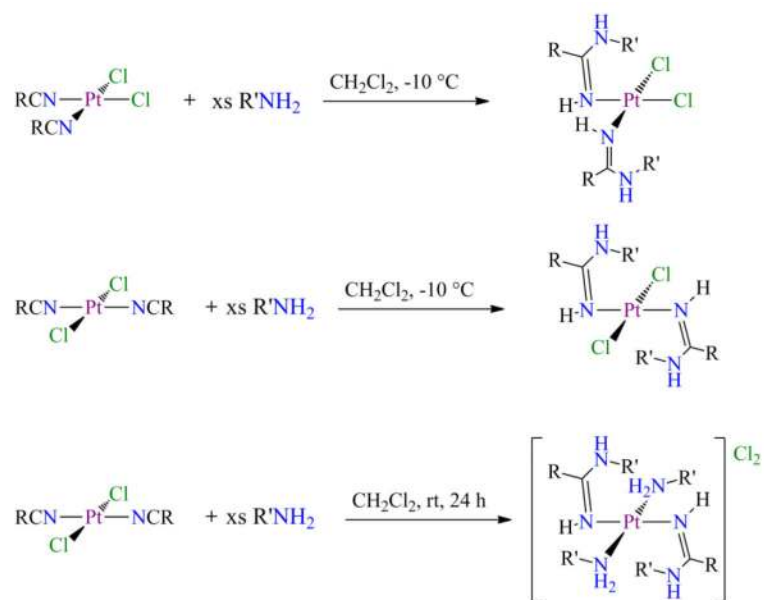


**Scheme 12.**  
Synthesis of monofunctional, thiourea platinum(II) complexes.<sup>208</sup>

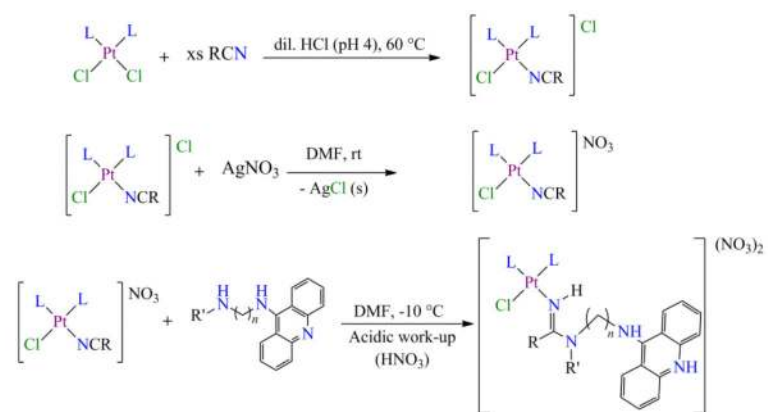


**Scheme 13.**

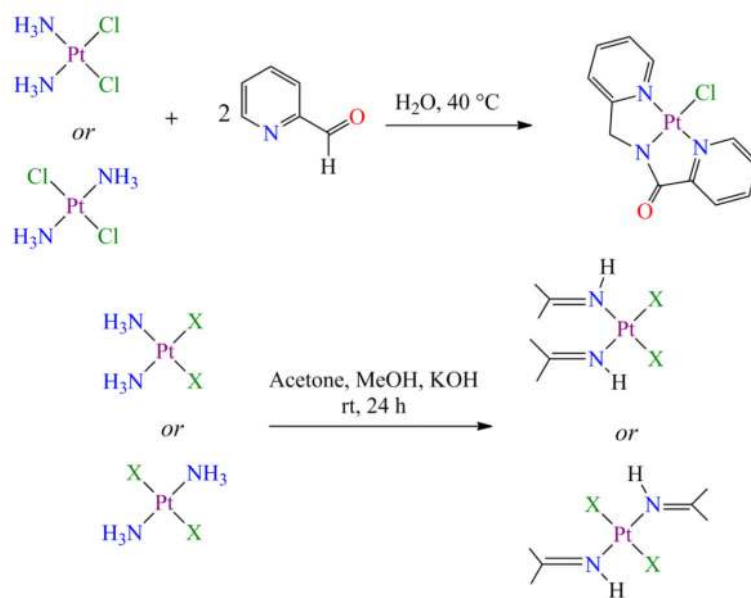
Synthesis of *cis*- (top), *trans*- $[\text{PtCl}_2(\text{iminoether})_2]$  (middle), and *trans*- $[\text{PtCl}_2(\text{imino thioether})_2]$ .<sup>213,219,221</sup>

**Scheme 14.**

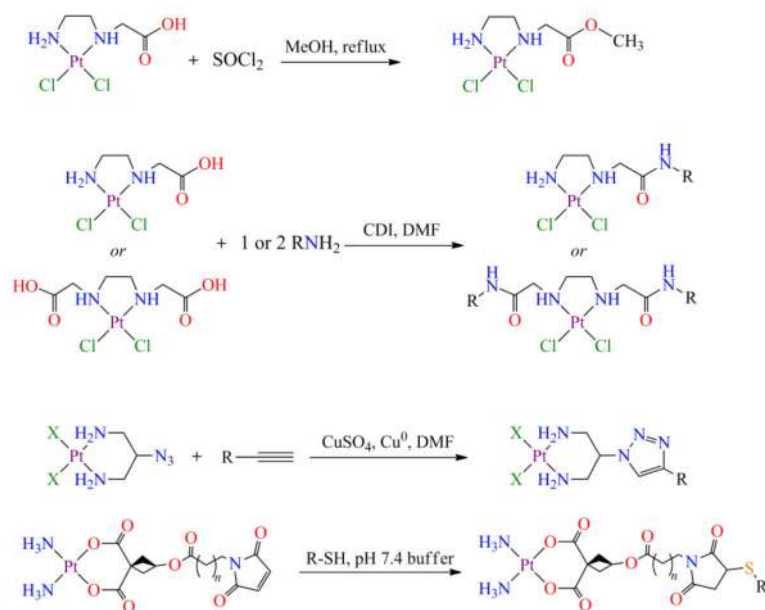
Synthesis of *cis*- (top) and *trans*-[PtCl<sub>2</sub>(amidine)<sub>2</sub>] (middle).<sup>229</sup> Room temperature conditions and extended reactions times lead to the formation of primarily *trans*-[Pt(NH<sub>2</sub>R')<sub>2</sub>(amidine)<sub>2</sub>] from *trans*-[PtCl<sub>2</sub>(NCR)<sub>2</sub>] (bottom).<sup>235</sup>

**Scheme 15.**

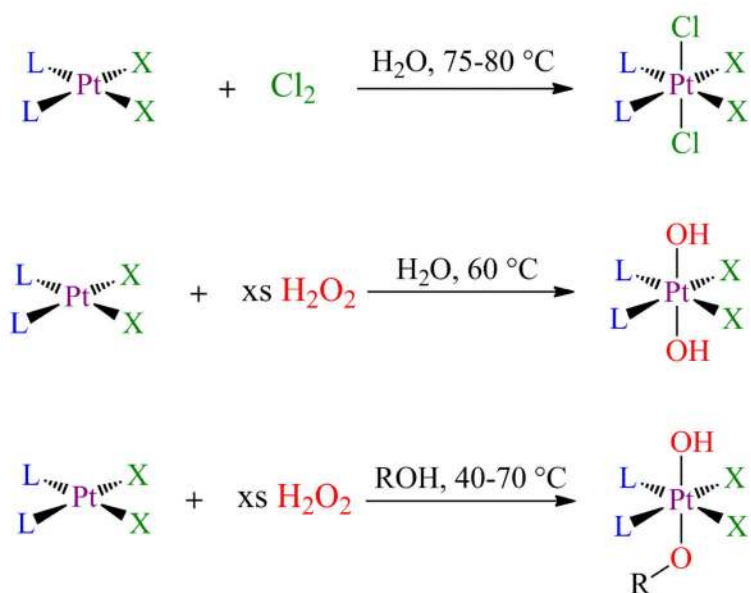
Multi-step synthetic scheme for the preparation of monofunctional platinum-amidine complexes.<sup>236</sup>

**Scheme 16.**

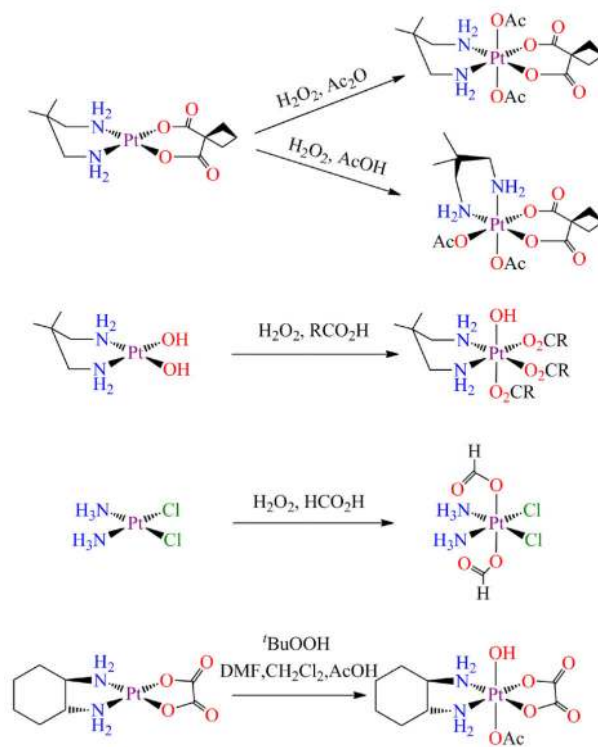
Condensation reactions involving the coordinated ammine ligands of *cis*- and *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>], as well as their diiodido analogues.<sup>244,246</sup>

**Scheme 17.**

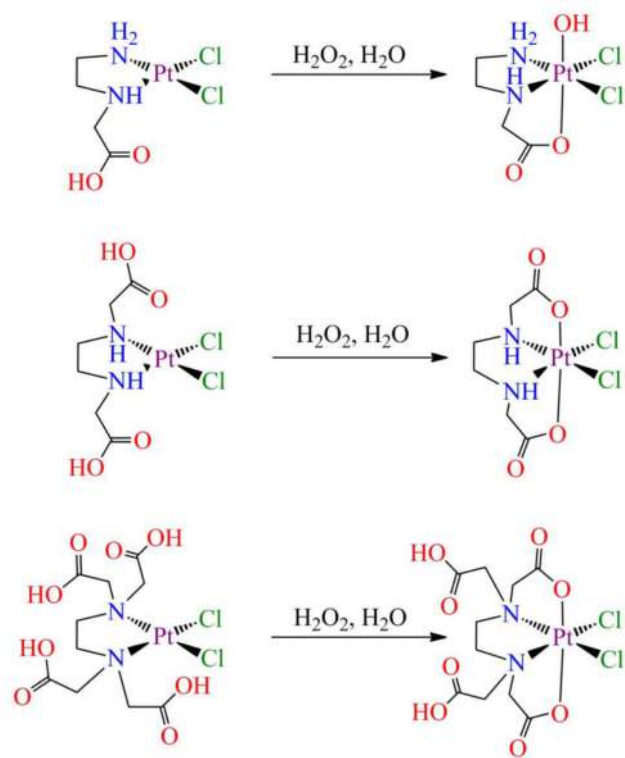
Outer-sphere ligand-based reactivity pathways of several platinum(II) complexes.<sup>248–253</sup>

**Scheme 18.**

Oxidation of a platinum(II) complex with chlorine (top)<sup>264</sup> and hydrogen peroxide<sup>266</sup> (bottom). The products obtained for the hydrogen peroxide-oxidation are dependent on the solvent used.<sup>273,274</sup>

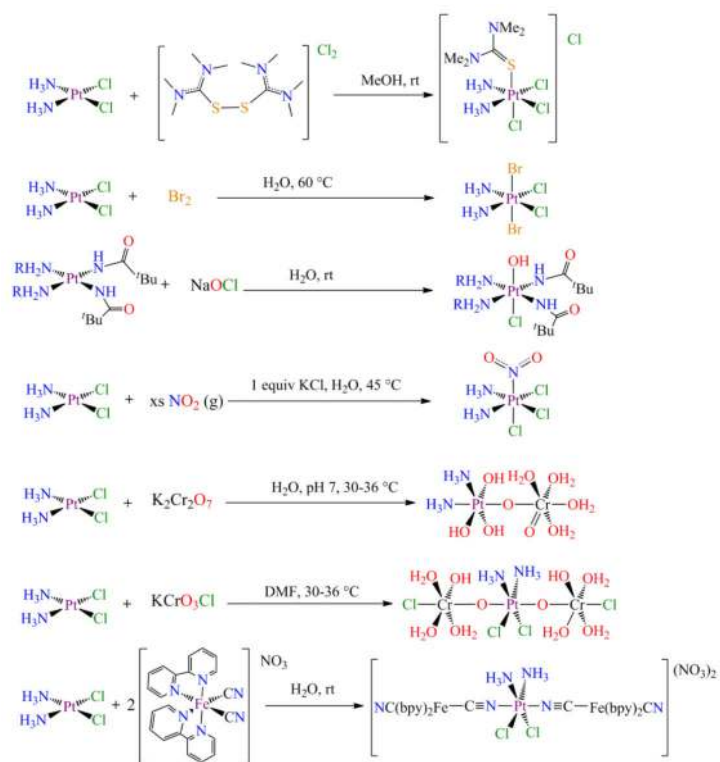
**Scheme 19.**

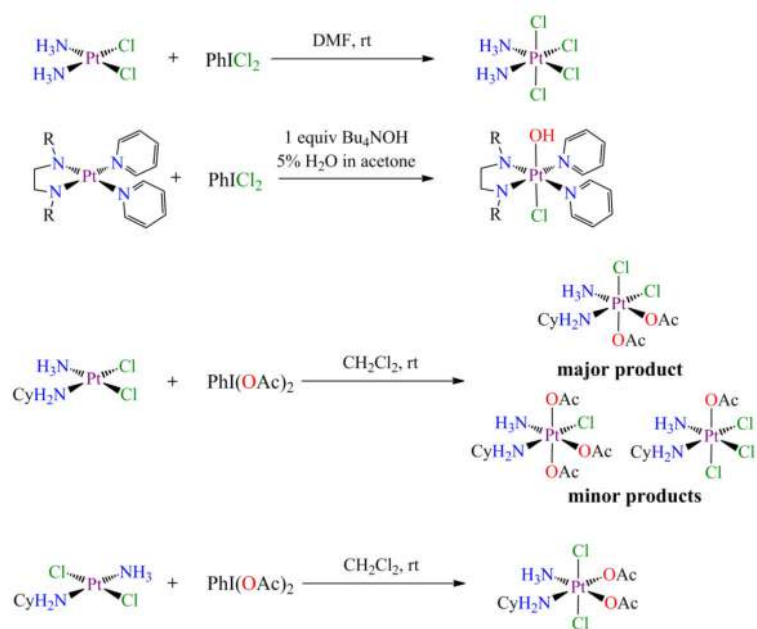
Peroxide oxidations of platinum(II) complexes in various acidic solvents.<sup>261,285,286,288</sup>

**Scheme 20.**

Ring-closing oxidation reactions of  $[\text{Pt}(\text{edma})\text{Cl}_2]$  (top),<sup>248</sup>  $[\text{Pt}(\text{edda})\text{Cl}_2]$  (middle),<sup>248,289</sup> and  $[\text{Pt}(\text{edta})\text{Cl}_2]$  (bottom).<sup>290</sup>

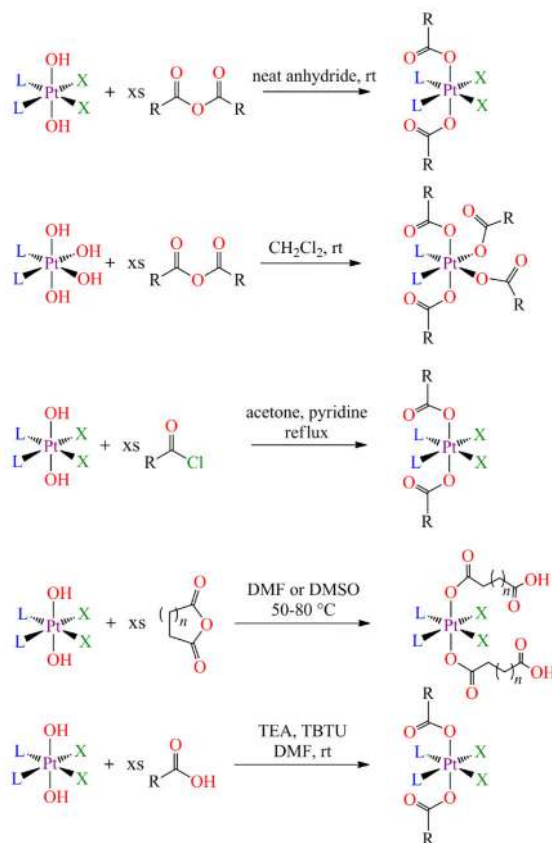


**Scheme 21.**Preparation of platinum(IV) complexes using different oxidizing agents.<sup>291–293,299,303–305</sup>

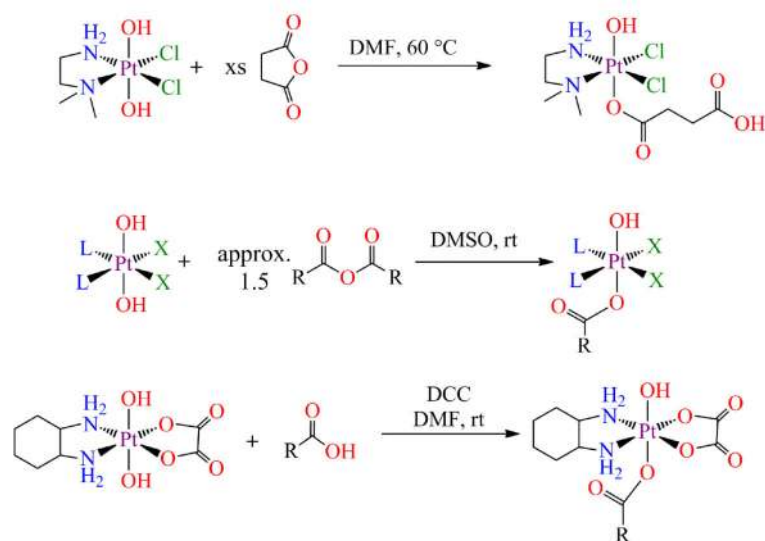


Scheme 22.

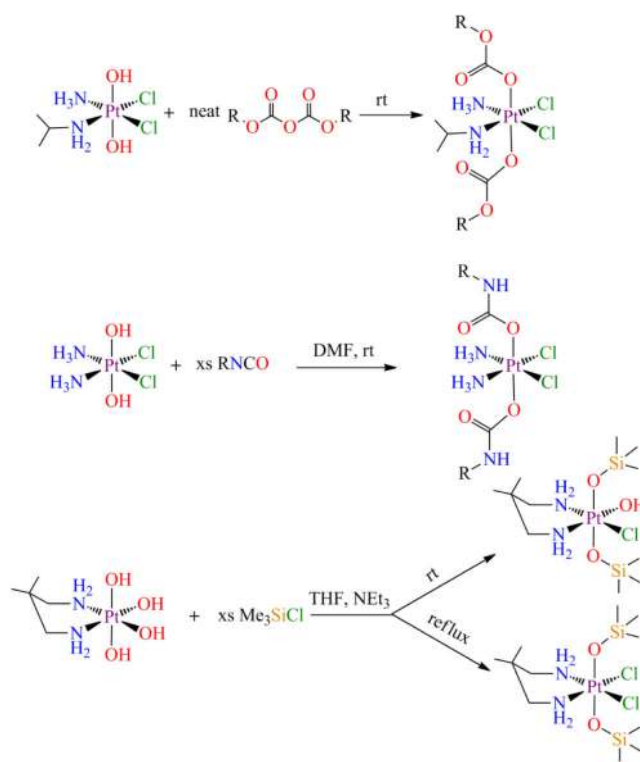
Oxidation of platinum(II) complexes with hypervalent iodine reagents.<sup>307,308</sup>

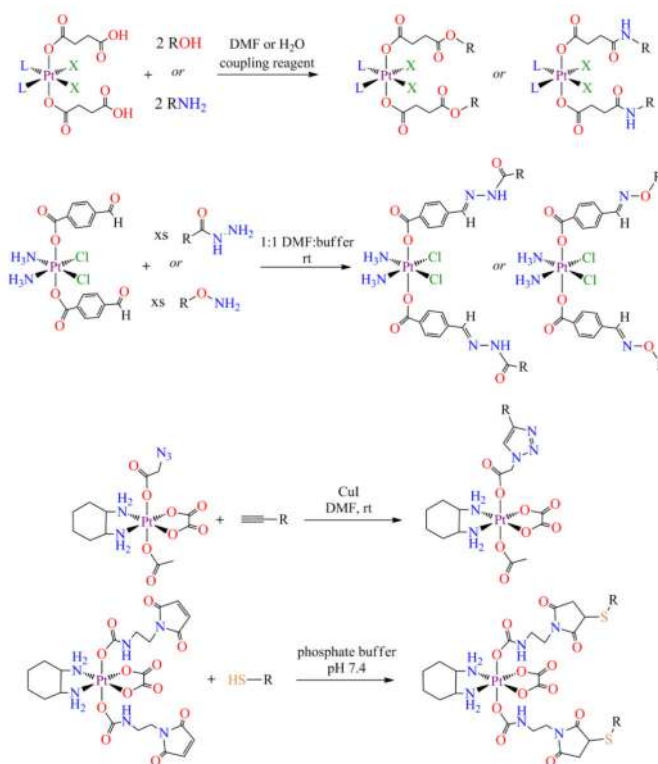
**Scheme 23.**

Synthetic methods for the preparation of platinum(IV) carboxylates.<sup>129,288,324,325,328</sup>

**Scheme 24.**

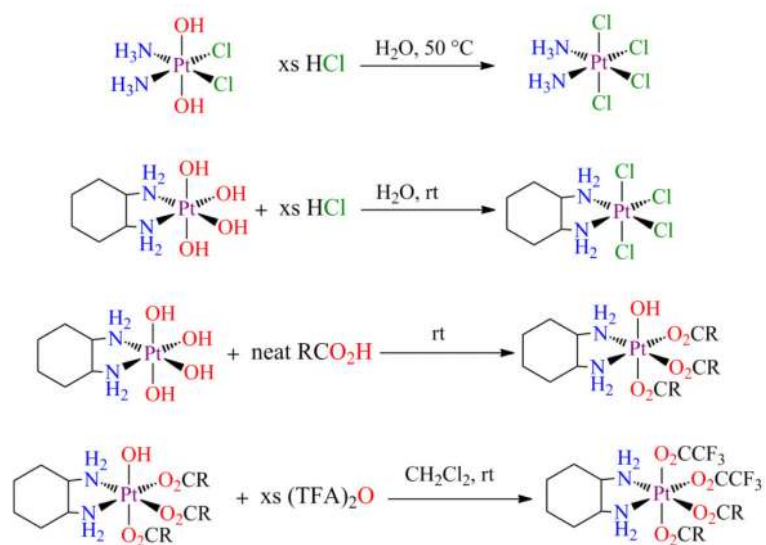
Synthesis of mixed trans hydroxo-carboxylato platinum(IV) complexes.<sup>258,288,331,336</sup>

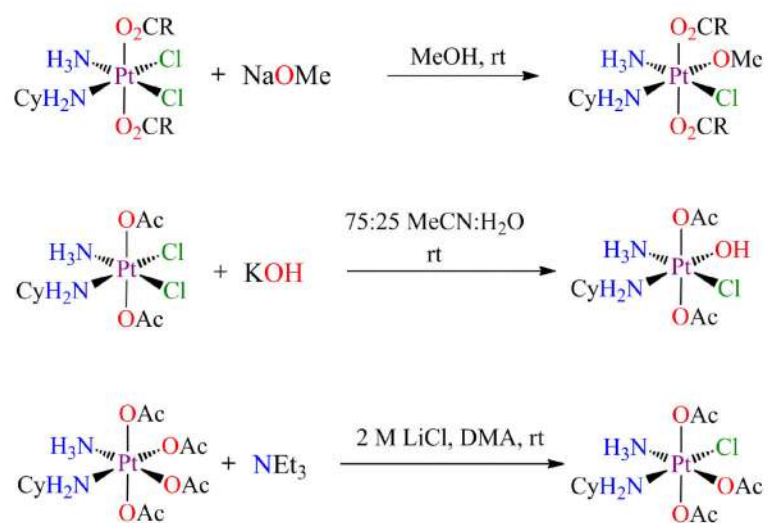
**Scheme 25.**Reactivity of platinum(IV) hydroxides with electrophiles.<sup>129,323,337</sup>



Scheme 26.

Outer-sphere reactivity of platinum(IV) complexes with organic functional groups.<sup>288,328,329,355–357</sup>

**Scheme 27.**Ligand substitution reactions facilitated by acidic conditions.<sup>310,364,366</sup>

**Scheme 28.**

Ligand substitution reactions facilitated by basic conditions, presumably through a base hydrolysis mechanism.<sup>308,370</sup>