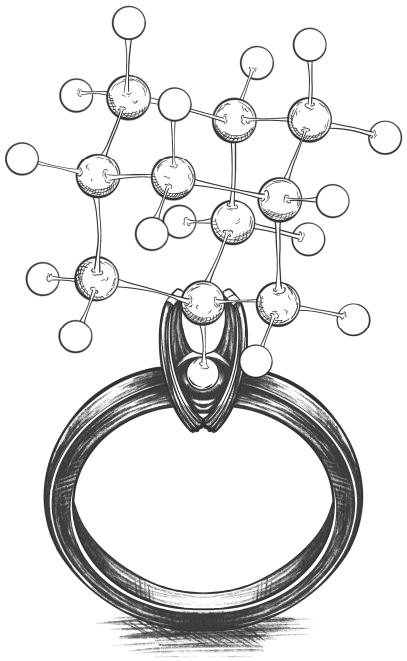
Ligand properties augmentation through modification with diamondoids

Inauguraldissertation zur Erlangung des Doktorgrades

der Naturwissenschaftlichen Fachbereiche

im Fachgebiet Organische Chemie (Fachbereich 08)

an der Justus-Liebig-Universität Gießen



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angefertigt im Zeitraum von Marz 2017 bis Dezember 2021

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Abstract

Diamondoids, a type of polycyclic hydrocarbons resembling small diamond cages, are long established in research and industry. Their chemical stability, conformational rigidity, spatial bulkiness, and excellent electron-donor abilities make them versatile lattices for numerous applications through their further functionalization or the augmentation of existing molecules. In this dissertation we explore further the impact of diamondoid modification by investigating a novel series of adamantane-containing NHCs based on the original Arduengo carbene. We also demonstrate the first application of diamantane functionalization in generating a potent ligand for the platinum family of anticancer drugs.

In the first publication, in collaboration with the research group of Prof. Dr. Grzegorz Mlostoń from University of Łódź we reported on a series of adamantylated oxyimidazolium salts that could be used to generate N-alkoxyheterocyclic carbenes analogous to the first stable carbene isolated by Arduengo. We isolated the carbene that showed the largest upfield ^{13}C NMR shift compared to common NHCs. We further analyzed the properties of investigated carbenes through their gold(I) and selenium complexes.

The second publication builds upon discovering a straightforward way to previously inaccessible 1,2-vicinal diamantane derivatives, particularly chiral 1,2-diaminodiamantane. It is used to generate bulky and lipophilic Pt(II) dichloride and oxalate complexes. *R*,*R*-enantiomeric dichloride complex, tested on human ovarian cancer cell lines A2780 and cisplatin-resistant A2780cis, showed superior activity to the potent anticancer drug cisplatin.

Zusammenfassung

Diamantoide, ein Typ polyzyklischer Kohlenwasserstoffe, die kleinen Diamantkäfigen ähneln, sind seit langem in Forschung und Industrie fest etabliert. Ihre chemische Stabilität, Konformationssteifigkeit, räumliche Fülle und hervorragende Elektronendonor-Fähigkeit machen sie zu vielseitigen Grundgerüsten für zahlreiche Anwendungen. Diese werden durch ihre weitere Funktionalisierung oder die Vergrößerung bereits bestehender Moleküle erreicht. In dieser Dissertation erforschen wir die Auswirkungen diamantartiger Modifikationen, indem wir eine neue Reihe adamantanhaltiger NHCs auf der Grundlage des ursprünglichen Arduengo-Carbens untersuchen. Desweiteren demonstrieren wir die erste Anwendung der Diamantan-Funktionalisierung bei der Erzeugung eines wirksamen Liganden für die Platin-Familie der Krebsmedikamente.

In der ersten Veröffentlichung berichteten wir in Zusammenarbeit mit der Forschungsgruppe von Prof. Dr. Grzegorz Mlostoń von der Universität Łódź über eine Reihe von adamantylierten Oxyimidazoliumsalzen, die zur Erzeugung von N-Alkoxyheterocyclen analog zum ersten von Arduengo isolierten stabilen Carben verwendet werden können. Wir isolierten das Carben, das im Vergleich zu herkömmlichen NHCs die größte ^{13}C-NMR-Verschiebung im Hochfeld zeigte. Wir haben die Eigenschaften der untersuchten Carbene anhand ihrer Gold(I)- und Selenkomplexe weiter analysiert.

Die zweite Veröffentlichung basiert auf der Entdeckung eines einfachen Weges zu bisher unzugänglichen 1,2-vicinalen Diamantanderivaten, insbesondere chiralem 1,2-Diaminodiamantan. Sie wird zur Erzeugung von sperrigen und lipophilen Pt(II) Dichlorid- und Oxalat-Komplexen verwendet. Der *R*,*R*-enantiomere Dichloridkomplex, der an den menschlichen Eierstockkrebs-Zelllinien A2780 und dem Cisplatin-resistenten A2780cis getestet wurde, zeigte eine höhere Aktivität als das starke Krebsmedikament Cisplatin.

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1 Introduction

Diamonds captivated humanity with their brilliance and unique properties for millennia. With time, from gemstones to nanoelectronics smaller and smaller diamonds found their applications. This includes the molecular level as well, which is occupied by diamondoids – the hydrogen-terminated diamond units or cages (Figure 1).[1] These cage hydrocarbons are conformationally rigid, highly chemically stable molecules with well-established functionalization methods resulting in readily tunable electronic properties.[1–8] Diamondoids are good electron donors for ligand modification, and in bulk their negative electron affinity makes them useful in nanoelectronics.[9,10] As hydrogen saturated hydrocarbons they are highly lipophilic, which is useful in drug design.[11,12] The smallest diamondoid adamantane (**1**) found significant use e.g., in pharmaceuticals and catalysis, while the larger diamondoids—chiefly diamantane (**2**), triamantane (**3**), and *anti*-tetramantane (**4**)—are used predominantly in the research of nanoelectronics and nanomaterials.

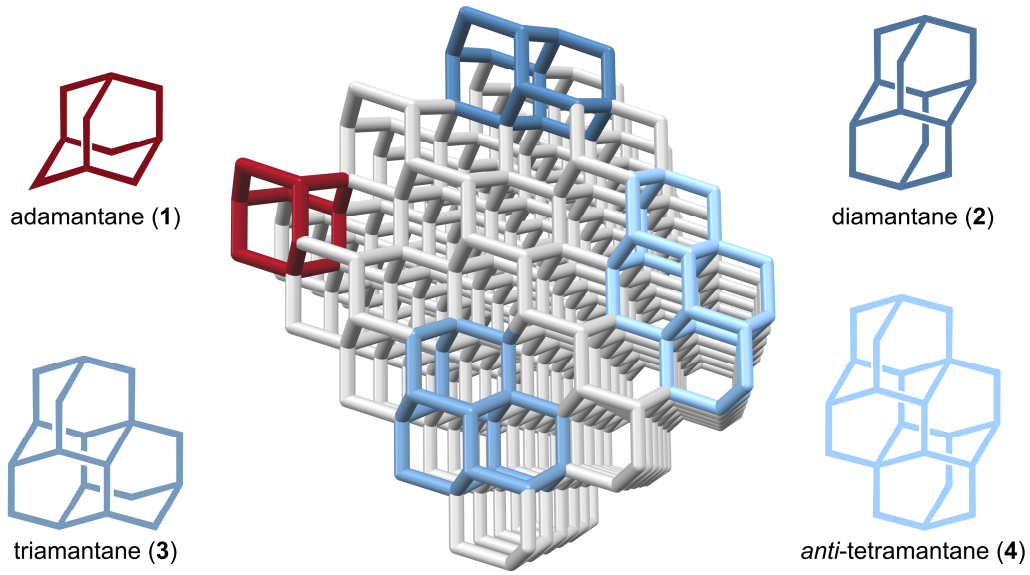


Figure 1. Diamondoids superimposed on the diamond lattice.[8,13,14]

The aim of this thesis is to investigate the impact and utility of diamondoid molecules for the tuning of ligand properties. The impact is demonstrated by synthesizing modified adamantane-substituted N-heterocyclic carbenes (NHCs). Similar to the first crystalline carbene reported by Arduengo *et al.,* the stabilization effect of adamantane substituents as well as their electron donor abilities allowed us to further push the electron donation abilities of the NHCs. The further aim is to extend the versatility of diamantanes for ligand modification. We extended the available chemistry of diamantane by developing a straightforward access to its vicinal 1,2-derivatives. This substitution pattern, which has functional groups attached to the neighboring carbon atoms, is commonly found in bidentate ligands. Vicinal diamine derivative of diamantane is then investigated as ligand for platinum complexes used as the anticancer agents.

1.1 Diamondoids in nature and laboratory

The simplest member of the diamondoid family adamantane (**1**, $C_{10}H_{16}$) has a structure of three fused cyclohexane rings in a chair conformation (Figure 1). Two adamantane units fused with their cyclohexane faces produce diamantane (**2**, $C_{14}H_{20}$), three produce triamantane (**3**, $C_{18}H_{24}$), and so on. Starting from tetramantane (**4**-**7**, $C_{22}H_{28}$) there are more than one way to face-fuse the diamondoid units. In the case of tetramantane, there are four possible isomers (Figure 2). To provide a simpler alternative to the IUPAC nomenclature for polycyclic hydrocarbons, they are named analogous to the conformers of butane: *anti*-tetramantane, *iso*-tetramantane and two *skew*- isomers, which due to their helical structure[15] form an enantiomeric pair. An alternative nomenclature suggested by Balaban and Schleyer is also widely used (Figure 2).[16]

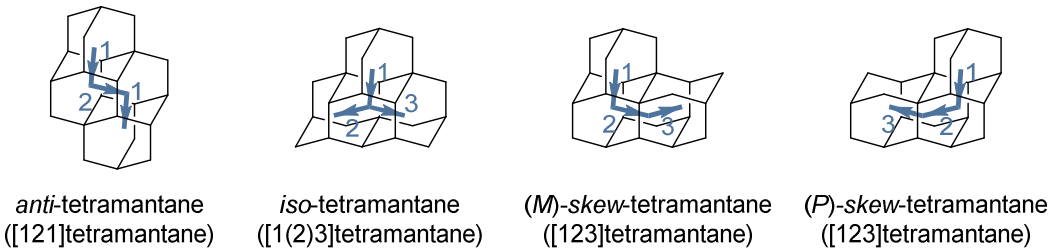
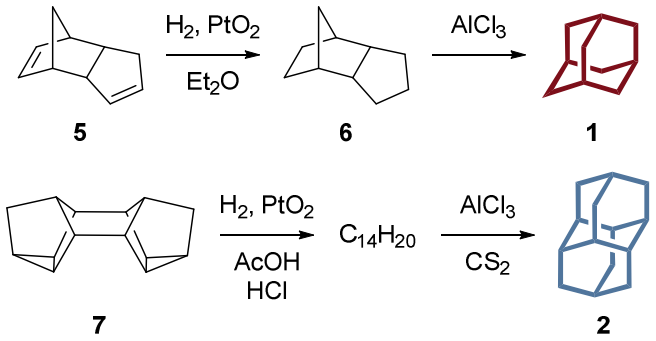


Figure 2. Diamondoid isomers of tetramantane and their common nomenclature.

A mixture of diamondoids was first extracted from crude oil in the early 1930s.[17] The largest isolated member to date from such mixtures is undecamantane obtained from gas condensate.[13] In the laboratory, adamantane synthesis was first published by Prelog and Seiwerth[18] as a multistep process resulting in small overall yield. The first simple synthesis of adamantane was published by Schleyer in 1957 and involved the so-called stabilomeric[19] rearrangement of the isomeric *endo*-tetrahydrodicyclopentadiene (**6**) catalyzed by Lewis acids (Scheme 1).[20] Polycyclic **6** is quantitatively obtained from the reduction of inexpensive dicyclopentadiene (**5**). Diamantane (**2**) was first synthesized by Schleyer *et al.* in 1965 from norbornene dimer through its rearrangement with $AlCl_3$ in trace yields.[21] Readily available dimer of norbornadiene known as Binor-S[22,23] (**7**) was found to be a much more convenient precursor for the rearrangement. Hydrogenated **7** is a mixture of hydrocarbons with the general formula $C_{14}H_{20}$, which is then rearranged in the presence of $AlCl_3$ to diamantane. These



Scheme 1. Example synthesis of **1** and **2** via Lewis acid–catalyzed rearrangement.[19–21]

rearrangements are further promoted by stronger acid catalysts.[24–26] The single step conversion from **7** to **2** was later achieved by Olah *et al.* using $NaBH_4$ together with CF_3SO_3H.[27] Several other hydrocarbons also can be rearranged into **2**.[25,28,29] Triamantane (**3**) can be synthesized through rearrangement as well.[26,27,30–32] Although, only *anti*-tetramantane (**4**) among the four possible isomers (Figure 2) has been synthesized in significant quantities and it is the largest diamondoid synthesized so far. This was achieved using a step-wise procedure starting from **2**.[33,34] Synthesis of higher diamondoids is problematic due to the increasing number of possible isomers and synthesis steps. The best source of these diamondoids is still the separation of mixtures obtained as a byproduct from the oil and gas industry.[13,35,36]

Diamondoid structures form not only in oil wells deep underground or through laboratory synthesis. Cage hydrocarbons are well-represented in nature,[37] among which adamantane (**8**) and homoadamantane [a] (**9**) structures are found in molecules isolated from the plants of *Guttiferae* (*Clusiaceae*) family.[38,39] Diamondoid cages with oxygen heteroatoms can be found in an extremely potent neurotoxin tetrodotoxin (**10**) and its analogues (**11**), extracted from pufferfish and other organisms an containing 2,4-dioxaadamantanes in their structures.[40,41] Another 2,4-dioxaadamantane cage was found in perforalactone A (**12**) isolated from *Harrisonia perforate*.[42] A nitrogen-containing 2-azadiamantane fragment was found in alstoscholarisine K (**13**), which is an alkaloid extracted from the gall-infected leaves of *Alstonia scholaris*.[43] Emergence of such cage structures in nature is another point in favor of the three-dimensional lattices in pharmaceutical applications.

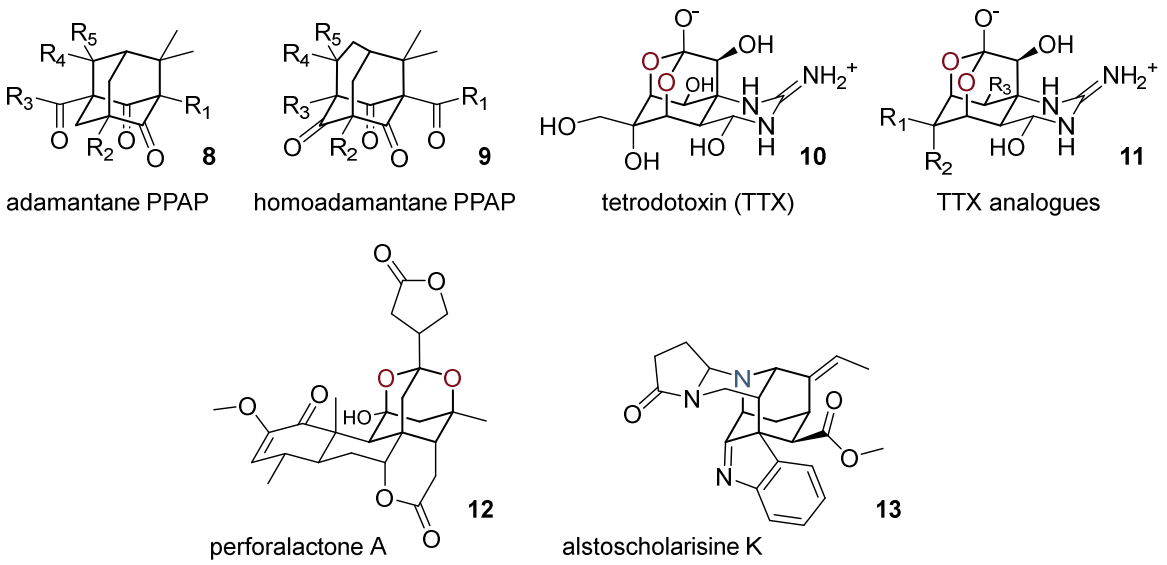


Figure 3. Examples of adamantane and heteroadamantane lattices found in nature.[38,39] (PPAP = polycyclic polyprenylated acylphloroglucinol)

Currently, diamondoids are relatively common fragments helping to achieve desired properties of the molecules in the roles of bulky substituents or backbones. In the latter role, rigid diamondoid scaffolds provide a more predictable molecular geometry due to the decreased degrees of freedom. Furthermore, diamondoids, in contrast to diamond, are distinct

[a] Homoadamantane ($C_{11}H_{18}$) contains ethylene bridge in place of one methylene bridge in adamantane.

molecules and not bulk materials. This allows them to be modified and used as monomers providing the resulting polymers[44] significant thermal and chemical stability among other properties. During the last three decades, many functionalized diamondoids (Figure 4) were used in preparation of major types of polymers such as polyamides and polyimides,[45–54] polyesters,[55] polyacrylates,[51,56–60] polycarbonates,[61] polyvinyls,[59,62,63]polyvinyl ethers,[64–66] polystyrenes,[67] polyurethanes.[68–71] Together with enhanced thermal and chemical stability, bulky diamondoid units tend to increase the glass transition temperatures of the modified polymers as well.[72] Incorporation of diamondoid compounds in polymers can significantly change their plasticity, depending on the type of polymer. Thus, the modified polypropylenes show increased plasticity, whereas the polycarbonates become more brittle.[73] The polymer modification with diamondoids also greatly impacts their optical properties. Such modifications generally provide the high optical transparency in the UV-visible range while keeping the polymers light.[59,66,74] Adamantane-modified polymers have shown low light dispersion and relatively high refractive index comparable to those achieved with aromatic moieties while being more UV stable.[75] Modification of polymers with diamondoid fragments can also be used to modulate their electronic properties. Polyamides and polyimides with adamantane moieties have low enough dielectric constants to be used as insulation materials and coatings in electronic applications.[76,77] Adamantane fragments can act as π-conjugation interrupter in light emitting polymers that provide blue and green light.[78]

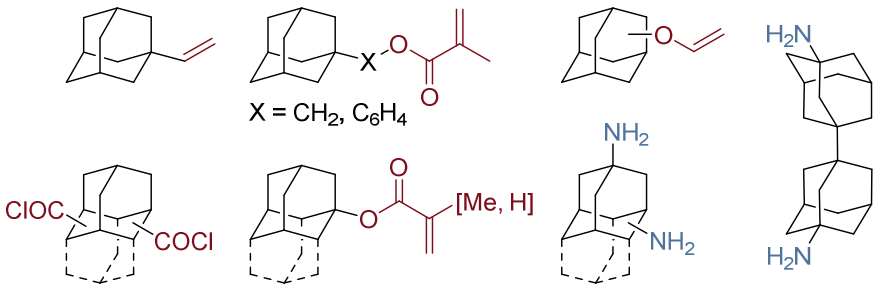


Figure 4. Examples of monomers with diamondoid fragments.

Diamondoids can be used to form thin coating on a substrate, in particular through the formation of the self-assembled monolayers (SAMs). Thiols are long known to form monomolecular coats on gold substrates.[79,80] A variety of diamondoid thiols (**14**–**18**) have been synthesized[81–84] as well as adamantanetrithiols (**19**), which resemble tripods.[85] These compound form highly-ordered monolayers that help to utilize the negative electron affinity of diamondoids and serve as electron sources.[86] In particular, the experiments with **18** deposited on gold and silver substrates showed mostly monochromatic electron emission.[87,88] Electronic emission is critical for many imaging technologies, where **18** provides air-stable coating and beneficial electronic properties.[89] The monochromatic emission was used to improve the spatial resolution in X-ray photoemission electron microscopy by reducing chromatic aberration.[90] Despite convenience of thiol groups in forming monolayer-metal attachment, depending on the conditions diamondoid thiols can be prone to oxidation or thermal displacement.[91,92] For that reason more firm covalent bonding was formed by reaction of diamantane phosphoryl dichloride (**20**) and the tungsten oxide surface.[93] Formation of stronger P–O bonds significantly increased thermal stability and allowed for stronger currents before degradation and can be used to form nanocomposites with other metals like Pd.[94]

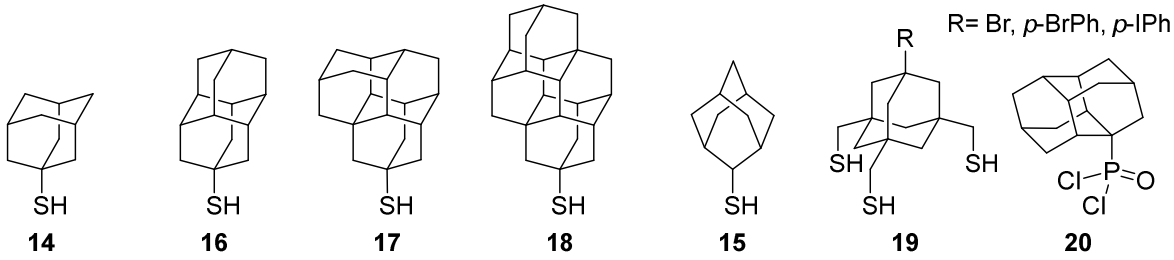


Figure 5. Diamondoid derivatives for the SAM generation.[79–85,93]

Furthermore, diamondoids were investigated in production of materials like liquid crystals,[95] nanowires[96] as well as in supramolecular chemistry as guests.[97–99] Although, the two major uses of diamonds are in ligands for use in catalysis and in medications, which will be discussed in the next chapters.

1.2 Diamondoids in ligands for catalysis

Higher diamondoids' steric bulk and rigid structure makes them highly suitable for promoting metal coordination.[100–102] An increase in steric bulk achieved by substituting adamantane moieties with diamantane can lead to a significant increase in catalytic effect.[103] Adamantane in particular, can be encountered as a fragment in many effective catalysts[10] Even simple adamantane derivative like 1-aminoadamantane (**21**) by itself can be an effective ligand in vanadium[104,105] or molybdenum[106,107] complexes.

Two major groups of ligands benefiting from incorporation of diamondoids in their structures are phosphines and carbenes. Phosphine ligand utility in catalysis is hard to overestimate considering their wide commercial availability and their use on an industrial scale. Many of these phosphine ligands already employ bulky substituents that tune the spatial and electronic properties of the ligand.[108–110] Tri-*tert*-butyl phosphine [P(*t*-Bu)$_3$] is one of the most prominent examples of potent and versatile ligands in the range of crowded trialkyl phosphines.[111–113] Despite the similarity in steric demand, diamondoid fragments often have a significant advantage over *tert*-butyl and other substituents by providing the necessary electronic and steric push to promote catalysis of many challenging reactions or improve their selectivity.[10,114]

Even primary diamondoid phosphines (Figure 6) can be effective ligands in various reactions despite their pyrophoricity through electronic stabilization provided by the ancillary functional groups as in the case of **22** possessing a remarkable air stability.[115] The substituted primary diamantane phosphine **22** is usable in selective Pd-catalyzed C–H arylation of unprotected indoles.[116] The reaction is occurring with an access to air and in biphasic mixture with water, which generates the phosphine oxide **23** acting as the ligand and forming a Pd complex with its trivalent tautomeric phosphinol form (Figure 6). The hydroxyphosphine **22** and its corresponding oxide **23** also used to make sp^3-carbon-based gas sensors via chemical vapor deposition. The sensors showed significant sensitivity towards NO_2 achieving ppb levels of detection and NH_3 with ppm levels of detection by forming aggregates with specific porosity enforced by rigid diamantane cages.[117]

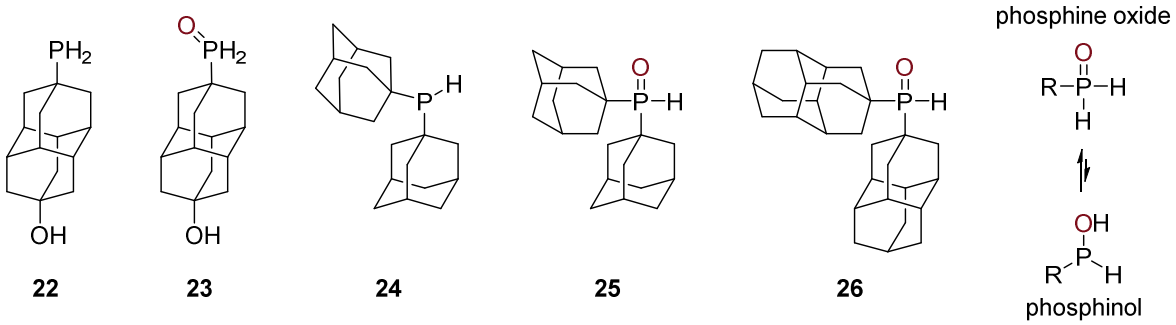


Figure 6. Primary and secondary phosphines and their phosphine oxides used in catalysis.

In contrast to primary phosphine ligands, secondary diamondoid phosphines has much more prominence as ligands in catalysis. Diadamantylphosphine (**24,** Ad_2PH) is an affordable phosphine ligand that is easily available through a reaction of plain adamantane with PCl_3 followed by reduction.[118] Even secondary Ad_2PH by itself provides enough bulkiness and nucleophilicity to effectively activate aryl chlorides in the Heck reaction.[119,120] Furthermore, it showed superior activity than more basic and sterically hindered P(*t*-Bu)$_3$ with selected substituents and can activate much less reactive electron-rich aryl chlorides. The phosphine **24** can promote Suzuki reaction and shows superior yields and enantioselectivity than other dialkylphosphines in Ni(II)-catalyzed hydrophosphination of methacrylonitrile providing high enough steric demand to reach >90% ee.[121] When used with just $PdCl_2$, **24** can activate aryl chlorides to undergo cross-coupling with malononitrile.[122]

Derived from diadamantylphosphine oxide **25** has the necessary steric bulk to outperform analogous di-*tert*-butyl- and diphenyl-phosphine oxides as well as several other bulky ligands in Ru-catalyzed arylations via C–H bond functionalization using aryl chlorides.[123] The oxide **25** also shows higher performance than multiple commercially-available phosphines in Pd-catalyzed C–H bond arylations and benzylations of oxazoles and oxazolines.[124] The influence of steric crowding was further demonstrated using even bulkier di(4-diamantyl)phosphine oxide (**26**) formed from the corresponding phosphine,[125] which outperformed adamantyl and *tert*-butyl analogues in similar reactions.[103]

The much larger group of trisubstituted phosphines reveals the extent of applicability of diamondoid modification on phosphine ligands. Starting with diadamantyl phosphine **24** (Figure 7) simple alkylation can yield us multiple tertiary phosphines usable in catalysis.[126] In particular alkylating secondary phosphine **24** with the flexible *n*-butyl moiety gives PAd_2(*n*-Bu) (**27,** cataCXium A) first isolated by Beller and co-workers in 2000.[127,128]. It showed higher performance than potent P(*t*-Bu)$_3$ in promoting reactions of deactivated aryl chlorides in Heck,[127] Suzuki,[128] Sonogashira[129] and Buchwald-Hartwig[130–132] cross-coupling reactions. In the case of the Suzuki reactions, **27** better retained its activity even when halving the amount of Pd source and the ligand itself compared to P(*t*-Bu)$_3$.[128] Furthermore, **27** used in the Pd-catalyzed α-arylation of ketones allows the use of the less active aryl chlorides.[133] It also showed superior yields compared to other alkyl- or aryl-phosphines in the direct Pd-catalyzed *ortho*-arylation of electron-rich and electron-poor benzoic acids with aryl chlorides.[134]

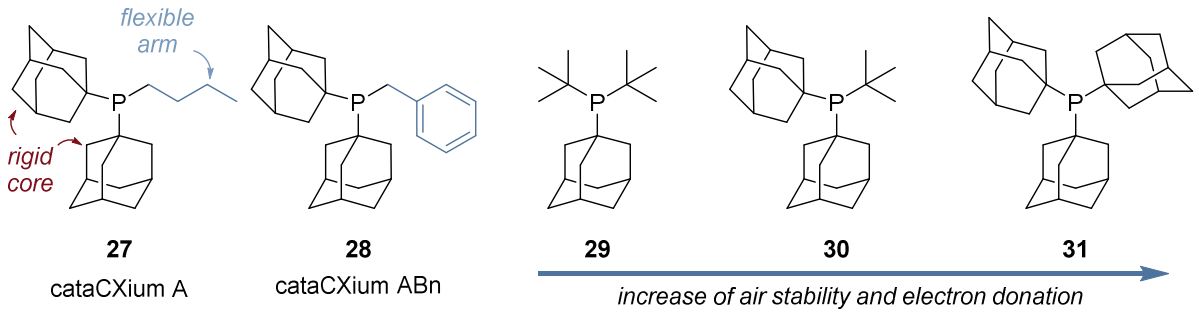


Figure 7. Trialkyl phosphine ligands with diamondoid substituents. [127–129,132,135–137]

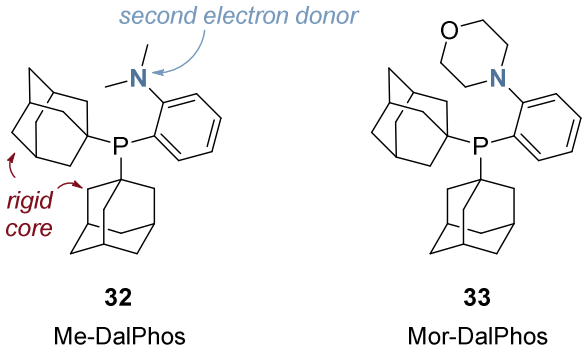
Beller and co-workers demonstrated that trialkylphosphines and **27** in particular promote a wide range of carbonylation reactions with aryl halides.[138–143] The tolerance towards the electronic properties of the substrates lets the versatility of PAd_2(*n*-Bu) to be extended to the challenging arylation of electron-rich heterocycles with aryl chlorides.[144] The combination of adamantyl substituents and a much smaller and mobile *n*-butyl chain more actively promote Pd-catalyzed synthesis of enamides from thioesters than bulkier ligands.[145] The ligand **27** can outpace even newer ligands in Au-catalyzed hydrohydrazination of terminal alkynes.[146] Overall, it often outperforms other phosphine ligands in many catalytic applications, while being inexpensive due to the straightforward synthesis from cheap reagents.

The combination of two bulky and sterically demanding adamantane moieties and linear alkyl chain made **27** a versatile and inexpensive ligand available commercially. A second widely available phosphine ligand with similar structure is PAd_2Bn **(28,** cataCXium ABn) with a flexible benzyl arm instead of *n*-butyl chain. It is also useful in Pd-catalyzed reactions like Sonogashira couplings with aryl chlorides,[129,147,148] or in Pd-catalyzed conversion of thioesters to thioethers.[149] Phenyl ring could be further functionalized to optimize the performance of the ligand.[150] For instance, benzyl moiety can be easily modified with polymer tails which makes the catalyst stay in either polar[151] or nonpolar[152] phase of a biphasic mixture allowing for an efficient recycling of the catalyst in heterogenous Sonogashira and Suzuki couplings. Diamondoid fragments in these polymers provide most of the steric crowding necessary for the efficient ligand performance. Similar polymers were tested in multiple homogenous Pd-catalyzed reactions with the recovery through nanofiltration.[153] In ligand **28**, the straightforward functionalization of the benzyl arm provides an access to various functionalities, while two adamantane units provide the baseline activity.

Even one adamantane unit substituting *tert*-butyl moiety in P(*t*-Bu)$_3$ is enough to noticeably affect the performance of the ligand. PAd(*t*-Bu)$_2$ **(29)** despite the modest increase in bulk has significantly increased air and moisture stability compared to P(*t*-Bu)$_3$ while having similar performance in Pd-catalyzed reactions.[132,135,136,154] The bulkier PAd_2(*t*-Bu) **(30)** with two adamantane substituents is even more hindered and has more distinct reactivity than P(*t*-Bu)$_3$ providing significantly better yields or significantly slower rates of reactions depending on the steric parameters of the substrates.[135,136,147,155] The bulkiest tri(1-adamantyl)phosphine **(31,** PAd_3) was first isolated by Carrow and co-workers in 2016.[137] It is a highly air-stable phosphine with significantly increased electron-donor ability compared to P(*t*-Bu)$_3$ that approaches that of *N*-heterocyclic carbenes. Despite higher steric demand of adamantanes, P(*t*-Bu)$_3$ is somewhat

flatter than **31**, likely due to the dispersion interaction of the adamantanes.[156] The higher polarizability of adamantane compared to smaller substituents is another contributing factor that can explain the difference of reactivity of PAd_3 and other phosphines.[157] In tested Suzuki–Miyaura reactions with chloroarenes, **31** showed much greater catalytic activity and reaction rates than P(*t*-Bu)$_3$, PAd_2(*n*-Bu), XPhos, SPhos, PCy_3, and PEPPSI-IPr.[137,157] Much faster rates of Suzuki–Miyaura reactions promoted by more active PAd_3 ligand allows to use room temperature conditions and weaker bases which is especially important in reactions with base-sensitive polyfluorinated boronic acids or esters due to the competing protodeboronation side-reactions.[158–160] High steric demand of adamantanes helps **31** to show higher stereoselectivity in Suzuki–Miyaura cross-couplings of chiral alkylboron nucleophiles.[161] High chemical stability of the catalysts formed from PAd_3 eliminates the need for Schlenk line and glovebox techniques[162] and tolerates water-based solvents[163] leading to higher turnover numbers in Pd-catalyzed,[164] and Ni-catalyzed[165] polymerizations than other phosphines. Ligand **31** gives improved yields compared to other commercial phosphine ligands in Pd-catalyzed *α*-arylation of indolin-3-ones[166] and Au-catalyzed synthesis of indolizines.[167] Overall, PAd_3 exemplifies a unique combination of diamondoid features and their influence on the ligand performance as a notable addition to the privileged class of trialkyl phosphine ligands.[168]

Substantial use of the adamantane moieties in ligand modification comes from combining their properties with those of aryl rings to form various dialkylaryl phosphines. Stradiotto and co-workers developed a series of diadamantylaryl phosphine ligands with an additional electron donor functional with the most successful representatives being Me-DalPhos (**32**) and Mor-DalPhos (**33**).[169–173] Diadamantyl phosphine fragment attached at the *ortho*-position of several aniline derivatives gave a widely applicable set of commercially available P,N-bidentate ligands. In a structure-activity investigations of similar ligands, **32** showed higher performance in Pd-catalyzed aminations of aryl and heteroaryl chlorides with ammonia, anilines and other amines.[172] Concurrently, **33** achieved even higher yields than **32** and structurally similar ligands in Buchwald-Hartwig aminations of aryl chloride with ammonia[169,174] or hydrazine.[173] Mor-DalPhos acting as a bidentate ligand in Buchwald-Hartwig amination provides an access to wide range of substrates from various amines to imines and hydrazones and tolerating some competitor nitrogen-containing functional groups.[175,176] In Pd-catalyzed mono-α-arylation of acetone with various aryl halides and tosylates **33** outclassed ferrocene, NHC and dialkylbiaryl phosphine ligands.[177]



32 Me-DalPhos **33** Mor-DalPhos

Figure 8. *P,N*-bidentate diamondoid ligands.

Furthermore, DalPhos ligands are able to stabilize gold(III) species, known for their instability preventing oxidative additions,[178–180] exploiting their bidentate nature by forming more stable four coordinate complexes.[181] Thus, **33** can promote Au-catalyzed hydroaminations of internal alkynes with dialkylamines with significant regioselectivity,[171] and stabilize *α*-oxo gold carbenes intermediates derived from terminal alkynes allowing them to easily react with various nucleophiles.[182–187] **32** allows challenging Au-catalyzed C–N and C–C couplings between aryl iodides and amines[188,189] or arenes[190] correspondingly. Gold(III) complexes stabilized with DalPhos ligands exploit gold's π-acidity to activate alkenes producing two C–C[191] or C–C with C–X bond formations.[192–195] Usage of biocompatible gold in catalytic systems can be preferable to conventional but more toxic Pd.[196,197] Consequently, **32** in complex with AuCl can successfully promote arylation of cysteine in peptides and proteins.[198] In the case of triflomethylthiolation and trifloromethylselenolation of unsaturated halides, **32** helps to activate not only aryl halides but also alkenyl and alkynyl halides at moderate conditions and Au-catalyst loadings compared to other catalysts based on Pd, Co, Ni, and Cu.[199] Although dimethylamino- and morpholino- phenyl moieties are the most widely used DalPhos ligands and generally give good performance, some reactions can benefit from diadamantylaryl phosphine ligands with other aryl substituents.[146,183,200–203] Overall, DalPhos-type ligands are very potent widely commercially available ligands for many reactions catalyzed by Pd and gold[204] and even some catalyzed by platinum[170]

Another prominent subgroup of dialkylaryl phosphine ligands is dialkyl*bi*aryl phosphines introduced and popularized by Buchwald and co-workers (Figure 9).[205] Their work in 1999 demonstrated the benefits of the simplest dialkylbiphenyl phosphines (JohnPhos ligands) in Pd-catalyzed reactions with electron-rich aryl chlorides to produce diaryl ethers.[206] AdJohnPhos (**34**) with two adamantyl substituents showed superior yields in reactions with highly electron-rich aryl chlorides compared to ligands with other alkyl substituents. The increase in catalytic activity provided by adamantyl substituents is further demonstrated in the Au-catalyzed hydrohydrazination of terminal alkynes, where switch from JohnPhos with *tert*-butyl substituents to AdJohnPhos with adamantyl substituents increased yield from 20% to 60% in the test reaction.[146] Following investigations and the catalytic screening that showed the benefit of conformational rigidity of the active Pd complex, more active BrettPhos ligands were synthesized.[207] Notably, the bulky AdBrettPhos (**35**) can promote the reductive elimination step in Pd-catalyzed amidations of smaller five member ring heterocycles significantly outcompeting other dialkylbiaryl phosphines.[208] The ligand **35** is generally useful in C–N cross-couplings under mild conditions.[209–212]

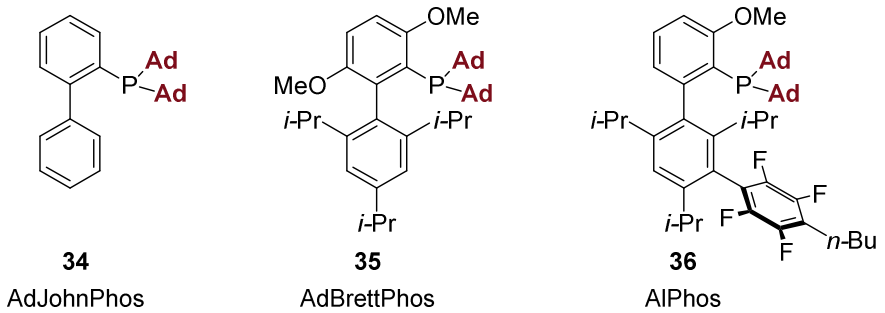


Figure 9. Diadamantylbiaryl phosphines developed by Buchwald group.[206–208,213,214]

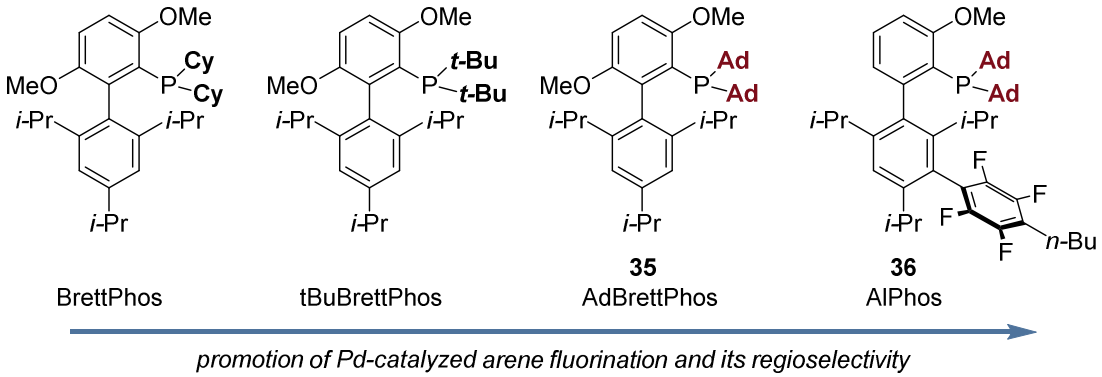


Figure 10. Commercially available ligands for the Pd-catalyzed fluorination and their relative activity.[215]

Introduction of fluorine in molecules is of great interest due to the importance of fluorine in pharmaceutical drugs.[216,217] The BrettPhos ligands developed by Buchwald's group showed remarkable ability to promote Pd catalyzed aryl fluorination.[218] Adamantyl variant **35** is particularly effective in helping to transform aryl triflates into the corresponding aryl fluorides in higher yields than other similar ligands.[219] With further optimizations of the ligand for C–F coupling reactions, Buchwald's group found the benefits of the substitution at the C3′ position[220,221] leading to the development of the modified AdBrettPhos ligand with a fluorinated aryl substituent. The new ligand AlPhos (**36**) is used for regioselective fluorination of (hetero)aryl triflates and the less activated and more accessible bromides.[213,214] It showed improved results compared to AdBrettPhos, which was already an improvements over earlier BrettPhos ligands (Figure 10), and required even milder reaction conditions with high yields achieved even at room temperature.[213] In both **35** and **36**, adamantyl substituents play a large role in facilitating reductive elimination.[215] High reactivity under mild conditions also allows AlPhos to facilitate Pd-catalyzed C–N cross-coupling using common soluble bases like DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[212] The ligand is suitable for aminations involving anilines, amides, and primary amines. Furthermore, **36** promotes C–S cross-couplings of various (hetero)aryl bromides at room temperature.[222]

Modularity of the Buchwald group's Phos-type ligands allows for easy fine-tuning (Figure 11). Screening of ligands for the Pd-catalyzed alkyl aryl ether synthesis led to the development of AdCyBrettPhos (**37**), which combines adamantyl and cyclohexyl alkyl substituents with already optimized biaryl moiety of **35**.[223] It facilitates C–O cross-coupling of variety of primary alcohols with unactivated (electron-rich) aryl halides under mild conditions.[224] Beneficial steric configuration assists the rate-limiting reductive elimination step in C–O cross-coupling, which is slower compared to C–N cross-coupling.[225] AdCyBrettPhos enables C–O cross-coupling between (hetero)arenes and secondary alcohols under mild conditions.[226] Multiple activated and unactivated (hetero)arenes formed ethers with the secondary alcohols used in a small excess at room temperature or 40 °C compared to preceding metal-catalyzed C–O cross-coupling reactions requiring larger excess of alcohol and higher temperatures.[227–229] The second tactic of tuning is to change the biaryl part. AdBippyPhos (**38**) featuring bipyrazolyl moiety instead of biphenyl shows high performance in C–O cross-couplings, specifically arylation of branched alcohols or arylation of alcohols with *ortho*-substituted arenes.[230–233] In Pd-catalyzed arylation

of fluoroalkylamines, **38** allows to use milder conditions and weaker bases to prevent decomposition of the resulting fluroalkylaniline.[234] The third option is to combine bulky adamantanes and chiral biaryl moieties to achieve stereoselective synthesis[235–237] *e.g.*, binaphthyl ligand **39**, which enables highly selective asymmetric gold catalysis.[238–241] The versatility of diadamantyl phosphine core results in many commercially available ligands with distinct advantages over analogs and constant research of novel ligands.[242,243]

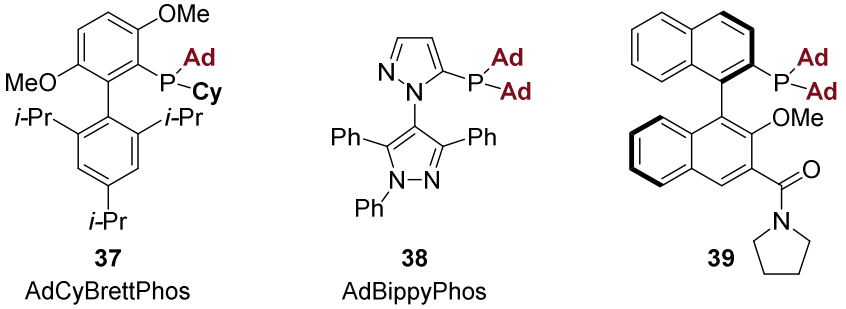


Figure 11. Purpose-tuned diadamantylbiaryl phosphines.[223,230,238]

The second large group of highly extensible ligands is *N*-heterocyclic carbenes (Figure 12) comprising a large variety of *N*-heterocycles used to stabilize the carbene center.[244,245] While some earlier examples of such compounds were known earlier in 20th century, the explosive interest from the scientific community has started with the isolation of the first stable crystalline carbene IAd (**40**) 1991 by Arduengo *et al.*[246] Imidazolylidene heterocycle **40** features two adamantane *N*-substituents that provide kinetic stabilization in addition to the electronic stabilizing effect of heteroatoms on the carbene center. Relative ease of structural modification of such heterocycles soon led to a family of NHCs (Figure 12) many of which are widely commercially available and are commonly used in metal catalysis,[247–249] organocatalysis,[250–254] material science[244,255] and medicine.[256,257] Generally strong σ-donors and variable π-acceptors due to the electronic contributions of the nitrogen atoms, NHCs are stronger ligands than phosphines and more readily stabilize reactive species from singular elements[258–264] to nanoparticles and nanoclusters.[265–267]

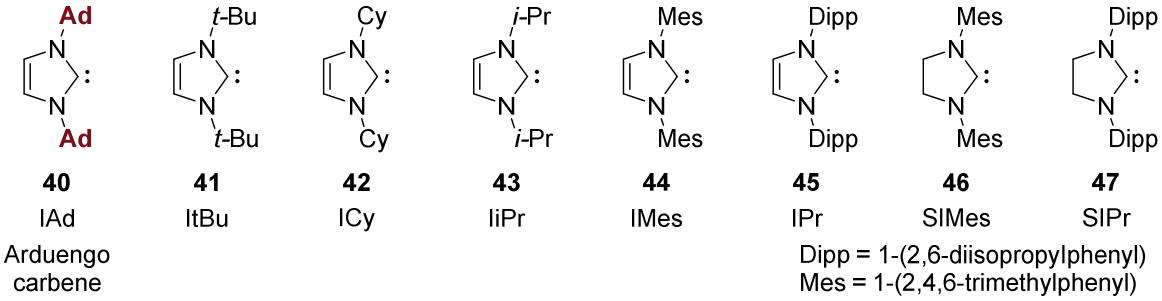


Figure 12. Arduengo carbene and its commonly used commercially available analogues.[245]

Transition metal carbene complexes formed from IAd provide distinct electronic end steric properties that are beneficial in metal complex stabilization and in catalyzing numerous reactions sometimes significantly exceeding the results obtained with other commercially available NHCs (Figure 12). Arduengo carbene by itself catalyzes transesterification,[268] and outperforms other NHCs in Mukaiyama aldol additions.[269]With corresponding metals, IAd

promotes Cu-catalyzed formation of alkenyl boronate compounds from terminal alkynes with >98% *E*-selectivity;[270] Co-catalyzed selective anti-Markovnikov hydrosilylations,[271] and Co-catalyzed Suzuki–Miyaura cross-coupling of aryl triflates.[272] It is significantly superior than I*t*Bu, IPr, and IMes in: Ni-catalyzed *exo*-selective hydroacylations generating *α*-methyl ketones;[273] oxidative cross-coupling of alcohols and olefins in synthesis of mono-α-arylated ketones;[274] and C–O bond activation of esters to form 3-acylbenzo[*b*]furans.[275] Furthermore, **40** performs better than other common NHCs in Pd-catalyzed intramolecular acylation of aryl chlorides to selectively synthesize benzocyclobutenones.[276] Bulky Pd(0)-complex with two IAd units promotes Pd-catalyzed Suzuki–Miyaura couplings of aryl chlorides at room temperature.[277] Arduengo carbene more selectively promotes Ru-catalyzed hydrogen isotope exchange reactions through C–H activation better than other common NHCs.[278] Easily accessible Au-complexes of **40** also promote the synthesis of furanones from propargylic alcohols better than **41**, **44**–**47**,[279] and synthesis of indoles from 2-alkynyl arylazides.[280] Notably, many reactions where IAd outperforms other carbenes are the reactions requiring selective formation of products. **40** and its derivatives can be also used as an alternative catalyst in polycarbonate synthesis to reduce branching.[281]

Arduengo carbene **40** properties can be augmented through various modifications (Figure 13). Exchanging N-substituents of **40** to the bulkier 1-diamantyl (**48**) or 4-diamantyl (**49**) substituents showed slightly slower turnover due to increased steric demand with similar to noticeably better activity in tested Sonogashira coupling reactions and organocatalyzed silyl enol ether formations.[282] Changing the heterocycle core from imidazole to benzimidazole (**50**) is than **40**–**44** and some common phosphine ligands in Ru-catalyzed hydroesterification of alkenes.[283] Unsymmetrical NHCs with one adamantane and another *N*-substituent provide different steric demands in one ligand, which, depending on the substrate, can be used more successfully than each symmetrical analogue. The favorable combinations of *N*-substituents helps Ru-catalyzed *Z*-selective olefin metathesis with Grubbs catalyst formed from **51** and **52**,[284–289] Ni-catalyzed synthesis of indolo[2,1-*a*]isoquinolines using **53**,[290] and Pd-catalyzed Suzuki coupling of aryl bromides using **54** that features alkylferrocene.[291]

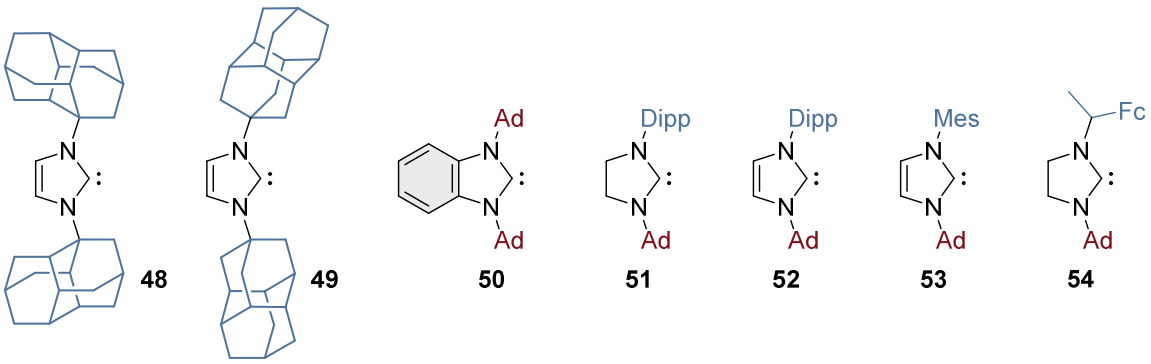


Figure 13. Arduengo carbene modifications.[282–291]

Modification of the NHC backbone and introduction of other N-substituents provided numerous carbenes with a variety of steric and electronic properties, which could be selected for depending on the application. In search for new NHCs, many methods are used like changing the alkyl or aryl *N*-substituents and changing the backbone or the whole heterocycle.

Much less investigated approach towards broadening the range of NHCs is the introduction of heteroatom spacers to the *N*-substituents forming N–X–R_n moieties. The *N*-substituents connected through a nitrogen spacer show an increase in the *σ*-donor properties of these carbenes.[292–294] NHCs with P–R_2 *N*-substituents provide extra binding to metals through phosphorus atom in addition to changing the electronic properties of the carbene center.[295–300] Much less is known about carbenes with N–O–R substituents. Their parent heterocycles can be also regarded as substituted heterocyclic *N*-oxides. *N*-Oxidation significantly alters the electronic properties of heterocycles due to the strong *σ*-acceptor and good *π*-donor properties of the oxygen atom leading to drastically different chemical activity.[301–303]

To investigate how the *N*-oxide-based heterocyclic carbenes differ from the more conventional imidazolium NHCs, we decided to investigate a small series of N-alkoxyheterocyclic carbenes named NOHCs. This was done in collaboration with the Grzegorz Mlostoń group from the University of Łódź, which is experienced in imidazole N-oxide chemistry.[304–307] We synthesized a small series of the *N*-adamantyloxy imidazolium salt precursors to synthesize carbenes analogous to the Arduengo carbene (Figure 14) due to its remarkable stability provided by bulky adamantane substituents.[246,308] We obtained the NOHC precursor salts to **55** and **57** through *O*-adamantylation of the corresponding N-oxides[304,305,309] and the symmetrical **56** was formed via the one-pot condensation forming the imidazole core.[305] After numerous trials we were able to isolate a free carbene **57** through the deprotonation with LiHMDS base.[310] As far as we can tell, this was the first time a free carbene with heterotricyclic *N*-oxide in its core was synthesized.[294,311–314]

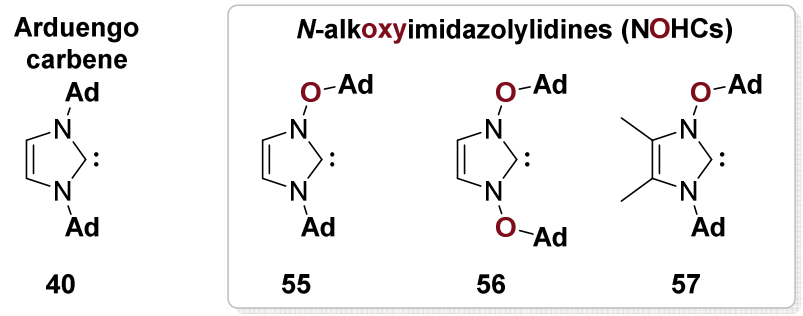


Figure 14. Original Arduengo carbene and its *N*-alkoxy analogues.

Adamantyl substituents in **40** in addition to the carbene stabilization also increase electron density on the carbene center demonstrated by an upfield shift of the C2 atom on the ^{13}C NMR spectra (Figure 15). Carbene **57** which we were able to isolate shows even greater upfield shift to 203.9 ppm, which makes the carbene center of **57** the most shielded among imidazolium or imidazolinium carbenes reported to date. Upfield shift of the carbene center of **57** compared to Arduengo carbene is reflected in a similar shift in a AuCl complex further indicating an increase in electron density at the carbene center. To disentangle the contributions of *σ*-donor and *π*-acceptor parts in the carbene bonding we prepared the corresponding NHC-Se adducts called selones. Similar to phosphines,[315–317] the ligand-selenium bond character can be examined through the sensitive ^{77}Se NMR shifts (Figure 16).[318–322] Selone **58** formed from **40** is notable due to its comparatively large electron shift pointing at the significant carbon-selenium double

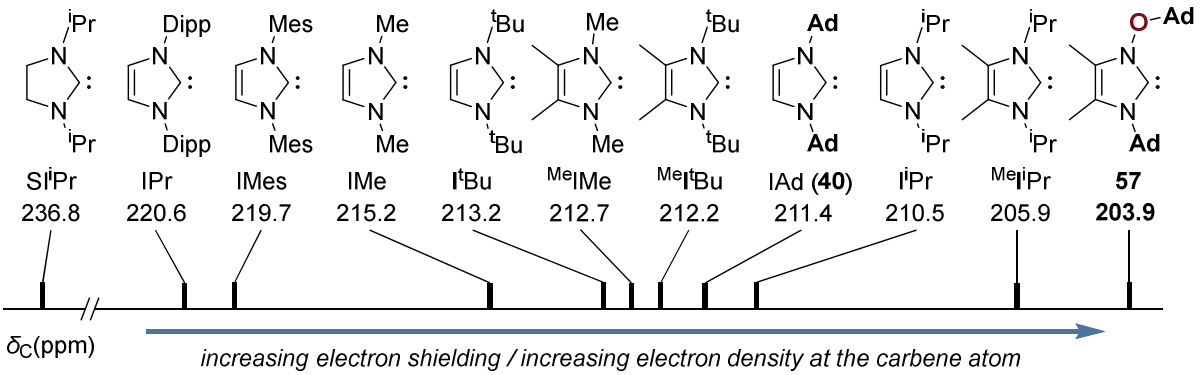


Figure 15. Comparison of the ^{13}C NMR shifts of selected NHCs.[310,323]

bond character, which is getting reduced by introduction of the oxygen atoms shifting **59** and **60** upfield. This effect is counterbalanced by the methyl backbone substituents in the case of **61** shifting it even farther downfield than the selone **58** indicating even greater π-accepting ability. These findings were confirmed through the selone ^{15}N NMR shifts, which are sensitive to charge delocalization on the carbene atom and the contribution of the *N*-substituents due to proximity.[322] Higher ratio between σ-donor and π-accepting components in the carbene bonding can be seen in the downfield ^{15}N NMR shifts caused by the N–C–N π-electron delocalization. NOHCs **55**–**57** and the parent Arduengo carbene **40** are predominantly σ-donors, and less π-acidic **57** gave the most downfield shifted ^{15}N NMR signal. Overall, NOHCs **55**–**57** further extend the range NHCs demonstrating the drastic change in the electron density of the carbene center and its character pushing it in the case of **57** beyond the normal rage of similar carbenes. This further widens the potential applicability on NHCs as ligands.

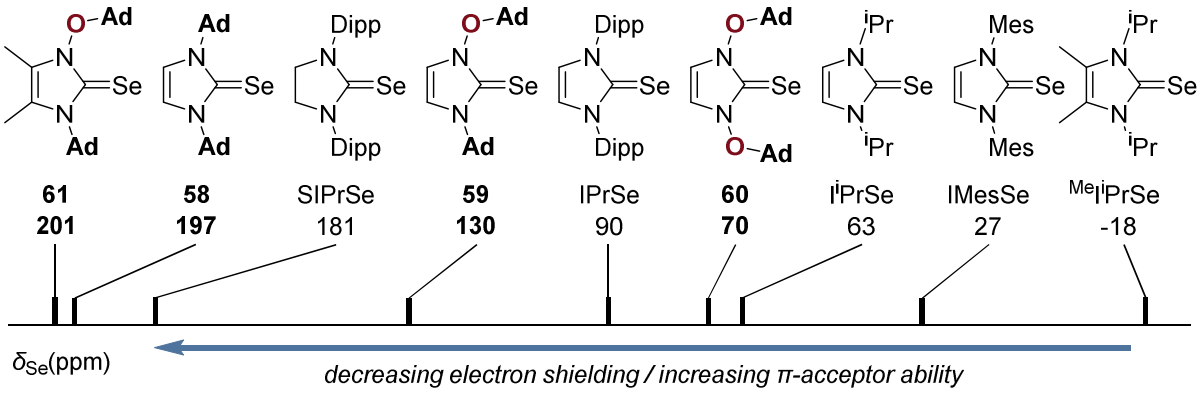


Figure 16. Comparison of the ^{77}Se NMR shifts of selected selones.

Thus far, diamondoids have been a notable part of numerous potent ligands. A majority of the diamondoid ligands described in this chapter are commercially available and excel in their domain, while being similar in cost to their analogues if such exist. Through the inclusion of diamondoid latices in the ligand structures their properties can be expanded further by increasing the electron density at the bonding atom or providing steric bulk around it for stabilization or shaping of the catalytic cell.

1.3 Diamondoids in medications

Bulky lipophilic diamondoid fragments are also well represented in pharmaceutical compounds. They offer a diverse set of pharmaceutically-relevant properties and are used as a way to mimic known structural motifs from natural products.[12] A history of diamondoid fragments in medications started shortly after a more efficient procedure for the synthesis of adamantane published by Schleyer (see Chapter 1.1).[20] A simple functionalization of the adamantane cage with an amino group in the tertiary (bridgehead) position gave the first diamondoid pharmaceutical amantadine [1-aminoadamantane] (Figure 17, **21**). Its antiviral activity towards *Influenza A* was reported in 1963[324] and subsequent *in vivo* studies confirmed the potency of amantadine as an antiviral agent.[325,326] Amantadine was shown to be a well-tolerated drug with low toxicity. It was approved by the Food and Drug Administration (FDA) for use against Asian influenza in 1966 and later also against *Influenza A*.[327] At the same time, some reports started to show that patients with Parkinson's disease (PD) treated for influenza with amantadine experienced relief in PD symptoms such as tremors.[328] It was shown to be effective as mono and combinational therapy and was approved by the FDA in 1973.[327] Currently, amantadine is no longer recommended for the treatment of *Influenza A* due to the dissemination of resistant strains.[329,330] Although it is still widely used in PD therapies, where it enhances dopamine release and acts as an *N*-methyl-D-aspartate (NMDA) antagonist, to treat dyskinesia caused by PD as well as side-effects of the L-DOPA therapy.[327,331]

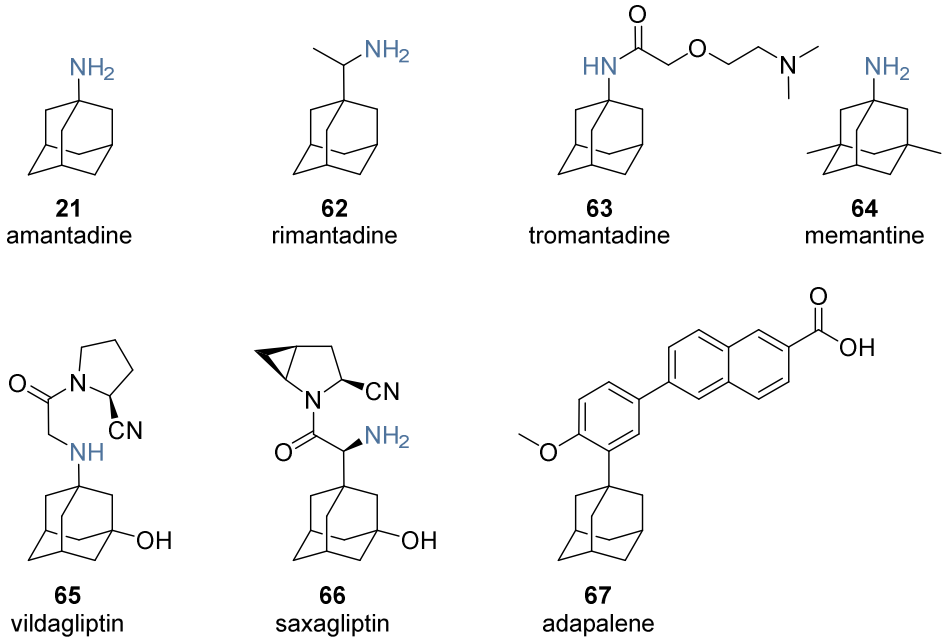


Figure 17. A selection of adamantane derivatives approved for medical use.[12]

SAR investigations of amantadine analogues lead to the discovery of a more potent antiviral agent for *Influenza A*, which was called rimantadine [α-methyl-1-adamantane-methylamine] (**62**).[332,333] Rimantadine produces less side effects, has a much lower elimination half-life and an even higher lipophilicity. Approved in 1993 by the FDA, by 2005–06 the resistant strains became predominant, and in 2011 it was no longer recommended together with **21** against

Influenza A.[334] The established mechanism of action of aminoadamantanes is in binding to the M2 proton channel using both the lipophilic adamantane center and hydrophilic amino group resulting in its blockage, which inhibits viral replication.[335,336] Drug-resistance arises when the mutated protein has larger pore sizes preventing an effective blockage by the aminoadamantane drugs. Another antiviral aminoadamantane derivative named tromantadine (**63**) showed effectiveness against *Herpes simplex virus* (HSV) and *Varicella zoster virus*,[337,338] building up on a moiety with the already established antiviral properties. Approved in some European, Asian, and South American countries, **63** showed a comparable activity to acyclovir, which is a standard antiviral agent against HSV, chickenpox, and shingles.[339] While the exact mechanism of action is not yet known, **63** inhibits virus replication and impedes the absorption of the virus by changing the glycoproteins of the host cell.[337,340]

Neurological activity of **21** incited further search of potent derivatives. One of such derivatives is memantine (1-amino-3,5-dimethyladamantane, **64**). Although it was first tested as another PD treatment, it did not show higher effectiveness compared to **21**. Memantine acts as a potent non-competitive NMDA antagonist.[341] It is a well-tolerated drug in treatment of moderate to severe Alzheimer's disease (AD), used as a monotherapy and in a combination with acetylcholine-esterase inhibitors.[342] It was approved in 2002 for medicinal use by European Medicines Agency (EMA) and in 2003 by the FDA. Aside from protecting the neurons from chronic excitotoxicity by blocking the NMDA receptors, **64** prevents amyloid-β toxicity and possibly inhibits its production.[343] It has also shown promising results in treatment of OCD, schizophrenia, bipolar disorder, and major depressive disorder.[344,345]

Vildagliptin[346] (**65**) and saxagliptin[347] (**66**) are another adamantane derivatives containing proven functional cores of amantadine and rimantadine. Vildagliptin (approved by EMA in 2007) and saxagliptin (approved by the FDA and EMA in 2009) are dipeptidyl peptidase-4 (DPP-4) inhibitors, which are used to treat type 2 diabetes.[348] These drugs are taken as monotherapy or in a combination with metformin, which is a main hyperglycemic agent, enhancing its effect. While based on aminoadamantane, additional cage functionalization with the hydroxyl group was associated with even more favorable active cite interactions.[349] Furthermore, adamantane also acts a bulky substituent that inhibits intramolecular cyclization reactions with the cyano group, which is directly responsible for the binding with DPP-4.[346]

Aminoadamantane derivatives are not the only approved diamondoid-derived drugs. Adapalene (**67**) is an approved topical treatment for moderate and severe acne in 1996 by the FDA. As a synthetic retinoid, its main mode of therapeutic interaction is the binding with retinoic acid receptors (RARs). Adapalene is a third-generation retinoid with specific affinity for two out of three RAR isotypes RAR-β and RAR-γ.[350] Suggested as an alternative to tretinoin (all-*trans* retinoic acid) in the topical treatment of acne, adapalene showed better photostability as well as chemical stability even when combined with benzoyl peroxide, which is one of the main acne treatments.[351,352] As other topical retinoids, adapalene not only normalizes differentiation and keratinization of follicular epithelial cells, but also provides anti-inflammatory activity.[353] The adamantyl tail provides lipophilicity, facilitating access to the follicular unit. Its bulkiness, which modulates the skin penetration, was connected to the decrease in adverse effects such as skin irritation.[354] Adapalene can be also used in treatment of other skin conditions, like

Darier's disease[355] or some types of rosacea.[356,357] Retinoid adapalene analogues also showed a significant antibacterial activity, specifically against methicillin-resistant *S. aureus* strains.[358]

Earlier successes of simple adamantane derivatives like aminoadamantane and further discoveries of effective diamondoid-containing drugs contributed to a wide adoption of the adamantane fragment for scientific research with its numerous derivatives available commercially.[359] Higher diamondoids require different approaches for chemoselective functionalization due to greater structural complexity.[2,3,9] In contrast to adamantane, which has tertiary carbon bridgeheads and secondary carbon bridges, diamantane has two bridgehead carbon types: six "medial" carbon atoms forming a "belt" and two "apical" carbon atoms along the main axis of symmetry (Figure 18). This presents many more possible functional group positions compared to diamantane.

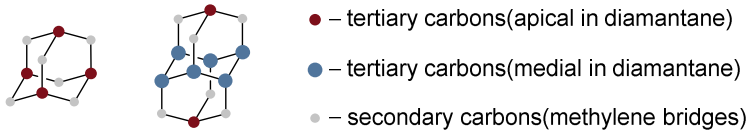
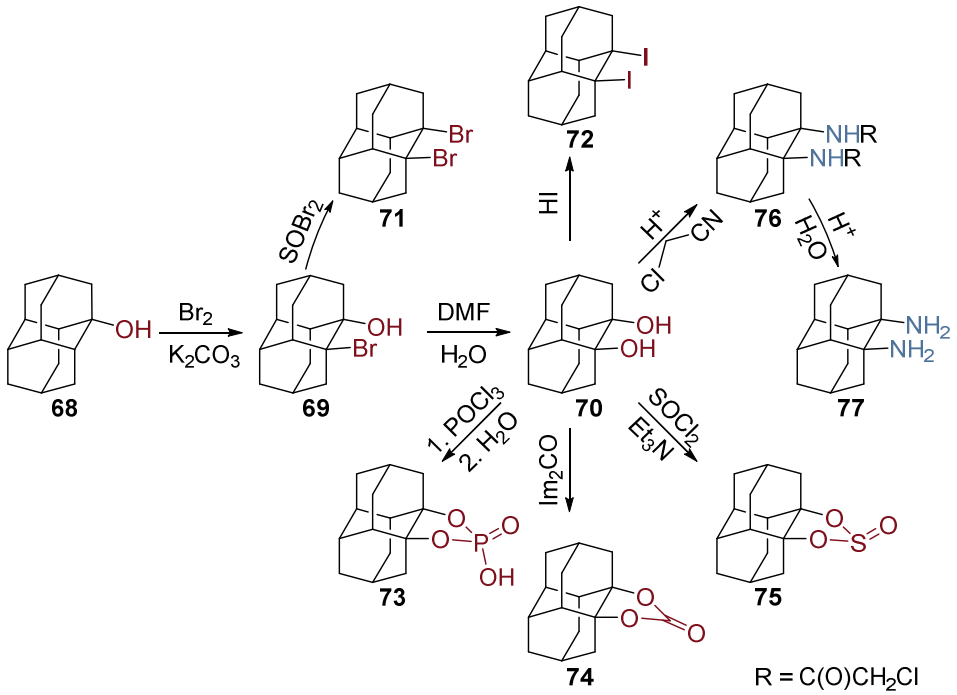


Figure 18. Types of carbon atoms in adamantane and diamantane.

Known diamondoid functionalization methods derived from adamantane often involve sequential introduction of functional groups via the reactions with electrophiles, which leads to inactivation of adjacent cites sterically and electronically.[360,361] This prevents an easy access to vicinal derivatives. In our research we were able to synthesize such derivatives via the retro-Barbier type fragmentation reaction of 1-diamantyl alcohol (**68**) to extend the available chemistry of diamantane to 1,2-derivatives (Scheme 2).[362] Single step reaction allowed us to



Scheme 2. Vicinal derivatives obtained from 1-hydroxydiamantane.

isolate 2-bromo-1-hydroxydiamantane (**69**) for the first time. We then demonstrated how **69** can then be easily converted to a series of 1,2-diamantane derivatives (**70**–**77**, Scheme 2). Among them a special attention is given to 1,2-diamine (**77**) since vicinal diamines are privileged structures featured in many natural compounds, pharmaceuticals and catalysts.[363] As all 1,2-diamantane derivatives, vicinal diamines have only two possible stereoisomers: *R*,*R*- and *S*,*S*-enantiomers, which can be isolated in high yields following a simple procedure.[364] These 1,2-diamine diamantane derivatives could be used not only as vicinal diamine ligands or building blocks but as a more bulky and rigid 1,2-diaminocyclohexane (1,2-DACH) analogues. 1,2-DACH is a common ligand that is commercially available in both enantiomeric forms as ligand or a chiral building block for pharmaceutical agents, catalysts or materials.[365,366]

One of the most impactful examples of diamine fragment use is in the class of platinum anticancer drugs (Figure 19). The first member of this family is cisplatin [*cis*-dichlorodiamineplatinum(II)] (**78**), which has potent antiproliferative activity in 1968 and was approved for a wide variety of cancer types worldwide in 1978.[367] Currently cisplatin is still the drug of choice in treatments of the ovarian cancer. In the testicular cancer cisplatin provides 90% cure rate even for advanced stages of the disease.[368,369] Current mechanistic investigations suggest that the action of platinum(II) complexes with a general formula $[PtX_2(RNH_2)_2]$ involves their hydrolysis in tissues forming a charged aqua-complex $[Pt(RNH_2)_2(H_2O)_2]^{2+}$. Labile water ligands can quickly dissociate allowing the platinum center to form inter- and intra-strand crosslinks with the DNA,[370] blocking their repair mechanisms. Formation of the platinum adducts leads to cell apoptosis caused by the inhibited DNA replication mechanism.[371] A strong antiproliferative effect of cisplatin is counterbalanced by severe adverse effects like nephrotoxicity, peripheral neurotoxicity, gastrointestinal toxicity, ototoxicity, and hematotoxicity.[372–377] Furthermore, multiple cancer cell types have an intrinsic or acquired resistance to cisplatin.[378–380]

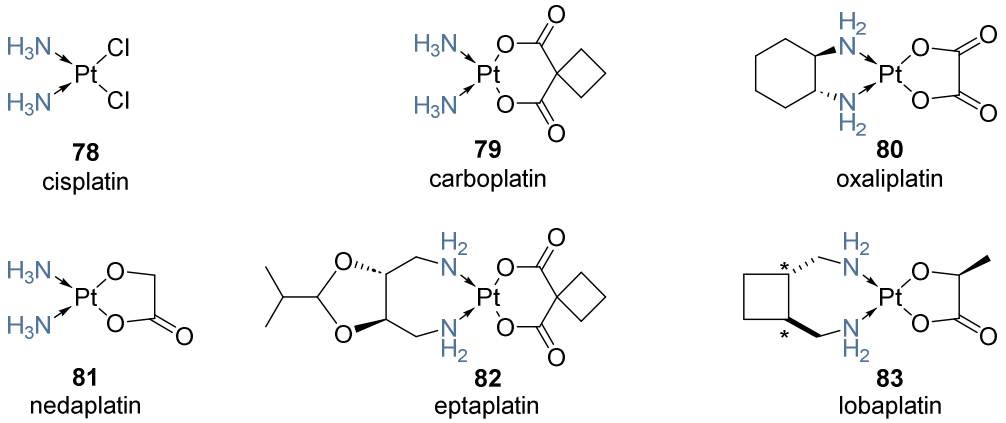


Figure 19. Approved platinum-based antitumor drugs

The second-generation platinum drug carboplatin (**79**) with a bulky bidentate dicarboxylate ligand is a more stable complex. This prevents hydrolysis before reaching the targeted tissue unlike with cisplatin[381] making carboplatin significantly less toxic, although with a higher required concentration to reach the equivalent effect to cisplatin.[369,377] Carboplatin is still actively used to treat ovarian cancer.[369,377,382] The hydrolysis of carboplatin leads to the same

charged $[Pt(NH_3)_2(H_2O)_2]^{2+}$ complex as in case of cisplatin and, as a result, cisplatin-resistant cancers has cross-resistance to carboplatin as well.[377,383,384] To counter cisplatin resistance, a third generation of platinum complexes with different amino ligands was developed. The most notable member is oxaliplatin (**80**) with its name derived from bidentate oxalate ligand it possesses instead of two chloride ions in cisplatin.[385,386] But the main difference is much larger and more lipophilic diamine ligand (1*R*,2*R*)-DACH that helps to circumvent the cisplatin resistance by forming different Pt-DNA lesions.[385,387] This changes the antineoplastic properties of oxaliplatin making it particularly effective against colorectal cancer, where cisplatin and carboplatin are much less viable.[386,387] Nedaplatin (**81**), eptaplatin (**82**), and lobaplatin (**83**) are approved in Japan, South Korea, and China correspondingly.[388] As second and third generation drugs they also employ more stable leaving ligands and larger lipophilic carrier ligands in an attempt to lessen adverse effects and to combat cross-resistance to cisplatin.

Investigations in antineoplastic activity of platinum complexes points at the significant contribution of amine carrier ligands in modulating the activity of resulting complexes as well as counteracting resistance by forming distinct DNA lesions. More bulky and lipophilic ligands showed increased accumulation and absorption of platinum complexes in cancer cells as well as slower hydrolysis aiding excretion.[381,389] Thus, the search for more viable carrier ligands is one of the main approaches for the development of new platinum antineoplastic agents and combating rising cross-resistance.

As we previously synthesized diamantane-1,2-diamine, we decided to investigate it as a carrier ligand in platinum antineoplastic agents.[390] Enantiopure diamine ligands were used to synthesize complexes (Figure 20) with Pt(II) dichloride (**84**) and Pt(II) oxalate (**85**). Oxalate complexes **85** were found to be insoluble and discarded, while dichloride complexes **84** named diaplatins were investigated further.

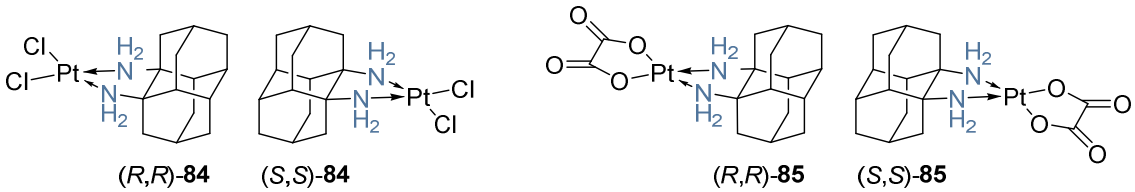


Figure 20. Diamantane-based platinum complexes generated from vicinal dimines.

We completed *in vitro* cytotoxicity assay using human ovarian cancer cell line A2780 and its cisplatin-resistant variant A2780cis for both *R*,*R*- and *S*,*S*-enantiomeric complexes (Table 1). *R*,*R*-**84** showed higher ability to inhibit growth of both A2780 and A2780cis cell lines compared to cisplatin. Higher potency of *R*,*R*-complex echoes that of oxaliplatin which is based on enantiopure (1*R*,2*R*)-DACH.[391,392] Diamantane-1,2-diamine here can be thought of as more lipophilic and conformationally locked (1*R*,2*R*)-DACH, where R,R-configuration is advantageous for the formation of DNA crosslinks or inhibition of their repair.[393–398] As the crosslinks are known to form preferentially with guanosine,[370] we investigated the interaction of platinum complexes with nucleotides guanosine monophosphate (GMP) and deoxyguanosine monophosphate (dGMP). Purine fragments of these nucleotides formed bisadducts even faster with platinum in larger *R*,*R*-diaplatin compared to smaller cisplatin. Consequently, diamantane

Table 1. In vitro cytotoxicity assay of (*R*,*R*)-**84**, (*S*,*S*)-**84**, and cisplatin.

Cell line	IC_{50} (μM)[a]		
	(*S*,*S*)-**1**	(*R*,*R*)-**1**	Cisplatin
A2780	6.85 ± 1.21	2.27 ± 0.65	3.28 ± 0.63
A2780cis[b]	20.15 ± 0.91	11.2 ± 0.66	16.81 ± 0.56

[a] IC50 values derived as mean ± SD of results of eight parallel experiments done in triplicate for each platinum complex paired with each cell line and incubated for 72 h at 37 °C. [b] Cisplatin-resistant variant of A2780 cell line.

stands as a viable base to build upon for the specific site targeting and further exploration of the pharmaceutical uses of diamondoids.

1.4 Concluding remarks

Diamondoids continue to be popular scaffolds with wide utility in material science, catalysis, and medicine. Numerous NHC are synthesized to cover the wide range of electronic and steric properties. We synthesized modified *N*-heterocyclic carbenes with *N*-adamantyloxy substituents providing altered σ-donor and π-acceptor properties. High electron shielding of the carbene center provided by the adamantyloxy arm led to the most upfield shifted imidazolium carbene and the first isolated free *N*-alkoxy carbene pushing the boundaries of common NHCs. Further research can be directed to extend the range of NOHCs to include other types of NHCs beyond imidazolium and to find catalytic applications or reactive species to stabilize.

In biomedical applications diamondoids found a significant recognition as well. Although it is focused mostly on adamantanes, which can be encountered in compounds commonly found in pharmacies. We were able to develop a way to synthesize vicinal diamantane derivatives and produce a chiral hindered diamantane diamine. We used it to produce Pt(II) complexes of the cisplatin family of anticancer compounds. While the Pt(II) dichloride complex showed higher cytotoxicity than cisplatin on the targeted cell line and its cisplatin-resistant variant, oxalate complex proved to be insoluble. Introduction of more hydrophilic leaving ligand can further improve solubility and performance of the diamantane diamine complex. This can be followed by the more comprehensive cytotoxicity assay using more cell lines. Other vicinal derivatives of diamantane with additional cage functionalization are also available and can be converted to the corresponding diamines. This may also enhance the cytotoxic properties of the Pt-DNA lesions through impairing their recognition by the DNA-repair mechanism.

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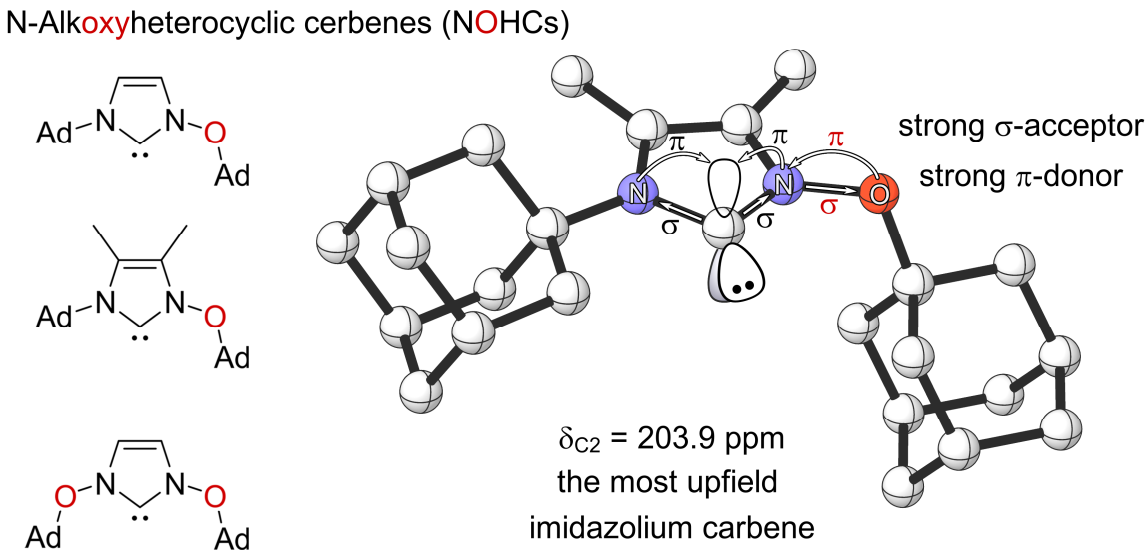
2 Publications

2.1 N-Alkoxyimidazolylidines (NOHCs): nucleophilic carbenes based on an oxidized imidazolium core



Abstract

We report the first preparation of *N*-alkoxyimidazolylidene (NOHC), a nucleophilic carbene based on an oxidized imidazolium core. The Arduengo-type analogous carbene center shows the most upfield ^{13}C NMR shift compared to common NHCs. The obtained gold(I) complex of the carbene follows the ^{13}C NMR upfield trend and shows the marked influence the alkoxy substituents. Similarly, the ^{77}Se and ^{15}N NMR shifts of a range of NOHC-selenium adducts show increased σ-donation and decreased π-back donation in the bonding with the nucleophile. This extension of the NHC family provides altered electronic properties for the use of such carbenes as ligands or catalysts.

Reference

V. V. Bakhonsky, J. Becker, G. Mlostoń and P. R. Schreiner, *Chem. Commun.*, 2022, **58**, 1538–1541.

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2022, **58**, 1538

Received 8th October 2021,
Accepted 23rd December 2021

DOI: 10.1039/d1cc05696d

rsc.li/chemcomm

N-Alkoxyimidazolylidines (NOHCs): nucleophilic carbenes based on an oxidized imidazolium core†‡

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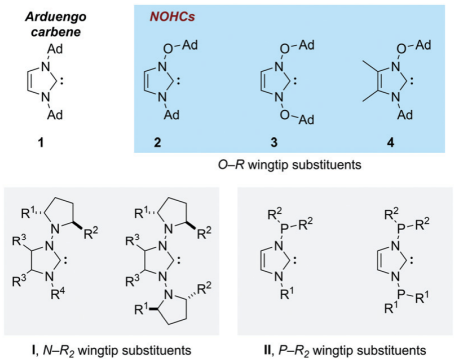
We report the first preparation of *N*-alkoxyimidazolylidene (NOHC), a nucleophilic carbene based on an oxidized imidazolium core. The Arduengo-type analogous carbene center shows the most upfield ^{13}C NMR shift compared to common NHCs. The obtained gold(I) complex of the carbene follows the ^{13}C NMR upfield trend and shows the marked influence the alkoxy substituents. Similarly, the ^{77}Se and ^{15}N NMR shifts of a range of NOHC-selenium adducts show increased σ-donation and decreased π-back donation in the bonding with the nucleophile. This extension of the NHC family provides altered electronic properties for the use of such carbenes as ligands or catalysts.

N-Heterocyclic carbenes (NHCs) are a firmly established class of ligands and organocatalysts.[1,2] Starting from the synthesis of the first stable, crystalline NHC by Arduengo *et al.*,[3] this compound class rapidly attained popularity. Numerous applications of these NHCs were quickly realized such as their use in organometallic catalysis,[4–9] organocatalysis,[10,11] and later in materials and pharmaceutical chemistry.[12,13] The versatility of NHCs plays a major part in their adoption because by changing the substituents near the carbene center or the backbone as well as by changing the heterocyclic core, the properties of NHCs can be varied greatly, allowing to adjust the resulting properties for a specific application. The effect of these modifications on the resulting structural and electronic properties has been well investigated.[14,15] Substituents near the carbene center act in multiple ways: by providing steric bulk for carbene stabilization,[16] by modifying steric demand for catalysis, and by influencing the carbene's electronic properties.

Imidazolium-based carbenes, one of the first NHC subclasses, have been modified extensively and there are now numerous commercially available derivatives. Much less is known of imidazole derivatives modified at the nitrogen with a heteroatom connection. Chiral 1,3-bis(*N*,*N*-dialkylamino)imidazolin-2-ylidenes are very rare examples displaying an N–N linkage with the substituent (**I**, Scheme 1).[17,18] These carbenes were found to have enhanced σ-donor abilities. Electron-rich and bulky *N*-phosphanyl-substituted NHCs (**II**) have been studied more[19–23] as these substituents provide not only modification of the steric and electronic parameters, but also offer an additional coordination center.

To our surprise, carbenes with an N–O linkage to the substituent of the carbene's imidazole core are extremely scarce. A very recent publication describes metal complexes of symmetric 1,3-bis(benzyloxy)imiadzol-2-ylidenes, prepared with a mechanochemical approach.[24] As oxygen also is a good π-donor but a stronger σ-acceptor as compared to nitrogen,



Scheme 1 Arduengo carbene and some of its analogues.

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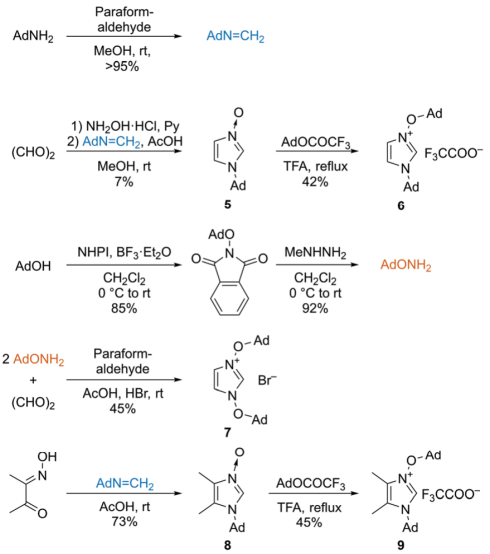
† We dedicate this work to Prof. Akihiro Ohta (Tokyo) on the occasion of his 88th birthday.

‡ Electronic supplementary information (ESI) available. CCDC 2098148. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc05696d

we expect that these types of carbenes, which we term *N*-alkoxyimidazolylidines (NOHCs) here, also would be highly nucleophilic. Hence, we set out to prepare and characterize a series of ''Arduengo-like'' NOHCs (Scheme 1) and evaluate the effects of the alkoxy substituents on their electronic properties utilizing spectroscopic methods. Earlier attempts at providing spectroscopic evidence for *N*-alkoxy carbenes were, to the best of our knowledge, unsuccessful.[25–29]

1-(Methyleneamino)adamantane (AdN=CH_2) was prepared by condensation of 1-adamantylamine with paraformaldehyde with methanol in excellent yield.[30] The precursor to carbene **2** was synthesized by condensation of glyoxal with hydroxylamine followed by *in situ* cyclocondensation with AdN=CH_2 (Scheme 2). The resulting crude product had to be purified by multiple column chromatographies resulting in rather poor yield of *N*-oxide **5**. The following *O*-adamantylation was achieved by refluxing **5** in TFA with an excess of 1-adamantyl trifluoroacetate, which can be prepared from 1-adamantanol and trifluoroacetic anhydride in quantitative yield. As adamantylations occur exclusively *via* an S_N1 mechanism, TFA was used to facilitate the dissociation of 1-adamantyl trifluoroacetate giving the resulting imidazolium salt **6** in 42% yield. The symmetric imidazolium salt **7** can be prepared[31] by one pot cyclocondensation of glyoxal, paraformaldehyde, and 1-adamantyloxyamine, which can be synthesized by alkylation of *N*-hydroxyphthalimide with 1-adamantanol followed by hydrazinolysis.[32] Imidazolium salt **9** was accessed by adamantylating *N*-oxide **8**, which was obtained as the cyclocondensation product of diacetyl monoxime with AdN=CH_2.[33]

We spectroscopically identified the carbene **4** by deprotonation of the corresponding imidazolium salt **9** with LiHMDS in THF at −78 to −30 °C followed by evaporation and extraction



Scheme 2 Synthetic routes to imidazolium salt precursors for the preparation of NOHCs.

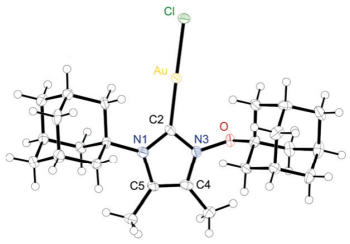


Fig. 1 The molecular structure obtained by X-ray diffraction analysis of gold(I) complex **10**. Ellipsoids drawn at 50% probability. Selected distances and angles: C2–N3 = 1.348(8) Å, C2–N1 = 1.356(8) Å, N1–C5 = 1.434(7) Å, N3–C4 = 1.373(7) Å, N3–O = 1.385(6) Å, C2–Au = 2.005(5) Å, N1–C2–N3 = 104.0(4)°, N3–C2–Au = 121.2(4)°, N1–C2–Au = 134.5(5)°, C2–Au–Cl = 178.8(2)°.

with *n*-pentane, concentration, and preparing a solution in THF-d_8, which was then analyzed *via* ^{13}C NMR at rt. Using neat KHMDS also furnished **4** (Fig. S20, ESI‡) but the isolation was impossible because of rapid decomposition.This reaffirms that the complexation of **4** with the TFA salts is highly unlikely. The carbene significantly decomposes at rt within several hours and is therefore not amenable to crystallization. However, we were able to synthesize the Au(I) chloride complex of **4** *via* the transmetallation route.[34,35] Salt **9** was reacted with Ag_2O producing the silver(I) complex of **4** that is then *in situ* reacted with chloro(dimethyl sulfide)gold(I) forming the gold(I) complex **10**. After purification *via* column chromatography on neutral alumina, we were able to obtain crystals of **10** suitable for X-ray structure determination (Fig. 1). The C2–Au bond is 2.005(5) Å, which is in line with similar NHC-Au(I) complexes with C–Au bond lengths typically around 2.0 Å.[36] The bond between C4 and N3 is considerably shortened compared to the bond between C5 and N1, which bears the adamantyl substituent, causing the AuCl moiety to tilt towards N3.

These structural findings point toward an increased electron density at the carbene center, which we were also able to confirm by comparisons of NMR chemical shifts. The carbene center of **4** has a ^{13}C NMR shift of 203.9 ppm, which is the most upfield shift of all ''Arduengo-like'' imidazolium carbenes, showing the remarkable electron-donor ability of the N–O–Ad moiety, by increasing the electron density at the carbene center. Fig. 2 shows a comparison with common imidazolium-based NHCs and some of their 4,5-dimethylated derivatives. As **1** displays a signal shifted downfield by 7.5 ppm from **4**, this suggests additional electron donation from the oxygen atom. The 165.8 ppm ^{13}C NMR shift of the carbene center in the Au-complex **10** follows the upfield trend of the carbene.[36] The upfield chemical shift is generally connected to an increased electron density at the carbene center. ''Wing tip'' substituents (*cf.* Scheme 1) or in some instances fused rings involved in conjugation with nitrogen atoms strongly influence the electron density of the heterocyclic core.[37] To investigate the electronic properties of NOHCs more deeply, we set out to deconvolute the contributions of *N*-alkoxy substituents on their resulting σ-donating and π-accepting properties. In this context,

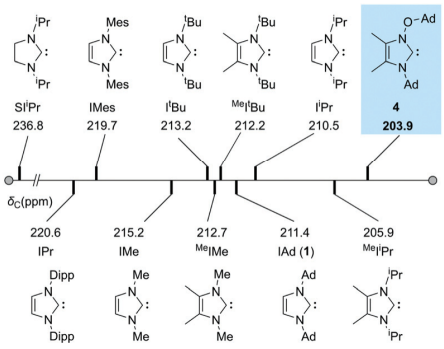


Fig. 2 Comparison of ^{13}C NMR chemical shifts between novel **4** and known carbenes.[43]

NHC-selenium adducts have been utilized to assess the carbene's electronic properties through the relative position of the highly sensitive ^{77}Se NMR shifts.[38–42]

Increased π-back donation from selenium to the carbene center contributes to the double-bond resonance form of the adduct and the deshielding of the selenium atom results in downfield shifts of the ^{77}Se NMR peaks (Fig. 3). Hence, we synthesized a series of NOHC-selenium adducts through deprotonation of the corresponding imidazolium salts **6**, **7**, and **9** and reaction with elemental selenium. The ^{77}Se NMR shifts of the corresponding adducts were compared to other selones formed with common NHCs (Fig. 3). Selone **12**, which has one N–O–Ad moiety, demonstrates the influence of the oxygen atom that shifts the Se signal 67 ppm upfield relative to the selenium adduct of **1**. Furthermore, selone **11** with two *N*-alkoxy groups has its Se signal shifted another 60 ppm upfield. This implies

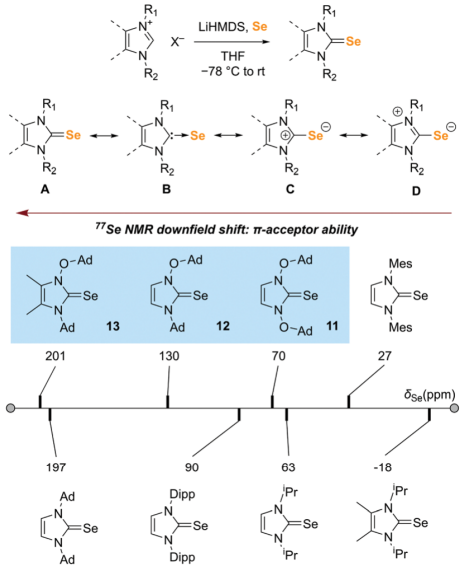


Fig. 3 General synthesis of selones and ^{77}Se NMR shifts of selected adducts.

the successive stabilization of resonance contributor **D** echoing the observed chemical structure of the gold(I) complex **10** (Fig. 1).

Contrary to the observed trend of electron donating groups on the imidazolium backbone shifting the selenium signal upfield, in case of adduct **13** the signal shifts strongly downfield providing one of the most π-Lewis-acidic imidazolium carbenes placing it downfield even from the adduct of the Arduengo carbene (**1**). This could be attributed to a combination of steric and electronic effects of the backbone substituents.[44] Overall, the N–O–Ad moiety decreases the π-acidity of carbenes, although the favorable combination of steric hindrance and a +I effect of the methyl substituents in **13** leads to overall lesser resonance stabilization and lesser π-electron density on the backbone reflected in the downfield shift of the corresponding ^{13}C NMR signals compared to **12** and the ^{77}Se NMR shift downfield from the selenium adduct of **1**. The Se-adducts were used further to investigate the carbene π-acceptor and σ-donor properties based on the method by Roesky *et al.* by measuring the ^{15}N NMR chemical shifts.[42] The imidazolium nitrogen atoms are excellent reporters regarding charge delocalization and stabilization of carbenes as well as being substituent attachment points. We carried out ^{1}H–^{15}N HMBC experiments that utilize ^{15}N in natural isotopic abundance (Table 1).

The resulting data show the combined effect of π-donation from the *N*-substituents to the carbene center. The N–C2–N π-electron delocalization causes deshielding that is enhanced by alkoxy fragments. A strong correlation of the ^{15}N shifts with the increased π-donation from the N-substituents to the carbene center demonstrates the influence of the oxygen electron pairs and puts the NOHCs in the range of strongly σ-donating ligands, even more so than typical imidazolium NHCs (Table 1). Thus, selone **11** has a 12 ppm downfield shift compared to the selone of **1**. The unsymmetric selones **12** and **13** gave two ^{15}N signals with 2–3 ppm difference in chemical shifts between their corresponding nitrogen atoms pointing at the electron donor contribution of the methyl substituents on **13**. Note that the ^{15}N NMR shifts of the nitrogen atoms connected to the alkoxy substituents in **12** and **13** are shifted downfield more than the analogous symmetric **11** by around 12 ppm. The ^{15}N shifts of the *N*-alkyl substituents are upfield relative to the selone of **1** and also display a 12 ppm difference. The chemical shift differences of the unsymmetric selones **12** and **13** compared to symmetric selone **11** and the selone of **1** could be attributed to an increased polarizability of **12** and **13** resulting in the push–pull effect by alkyl and alkoxy substituents, which was suggested for imidazoles[45] as well as for other push–pull systems[46,47] as

Table 1 ^{15}N NMR shifts of selected carbene adducts with selenium

	IAdSe	11	12	13
δ_N (ppm)	−179	−167	−156, −189	−154, −192

CH_3NO_2 used as reference.

derived from ^{13}C and ^{15}N NMR experiments. The ^{15}N NMR shifts show that increased π-donation by *N*-alkoxy substituents decreases the π-acidity of the carbene center, which confirms the ^{77}Se NMR studies.

In conclusion, we synthesized a new class of *N*-alkoxyheterocyclic (NOHC) carbenes that display a significant influence of the N–O-linkage on the carbene's electronic properties. To the best of our knowledge, the carbene has the most upfield ^{13}C NMR shift of any imidazolylidene. The NOHC-Au(I) chloride complex shows a shortening of the N3–C4 bond around the N–O–R moiety, which leads to tilting of the AuCl moiety towards the *N*-alkoxy substituent. The ^{13}C NMR shift of the carbene center of the Au-complex follows the trend as it is shifted upfield from similar imidazolylidene-Au(I) complexes. The ^{77}Se and ^{15}N NMR spectra were analyzed for a range of NOHC-selenium adducts demonstrating the contribution of the N–O-linkage to the electronic structure of the NOHCs. Remarkably, the ^{77}Se NMR chemical shift of the 4,5-dimethyl-substituted NOHC is the highest reported to date for an imidazolylidene Se adduct, indicating a very high π-acidity of the carbene center. These properties are likely to make NOHCs attractive for applications as ligands and catalysts that will be explored next and reported in due course.

This research was supported through the Deutsche Forschungsgemeinschaft (DFG, Germany, Schr 597/34-1) and the National Science Center (NCN, Poland, 2016/23/G/ST5/04115/l) within the Beethoven-2 program. We thank Prof. Andrey A. Fokin for fruitful discussions. We also acknowledge the preparation of some of the imidazolium salts used for the synthesis of imidazol-2-selones by Mateusz Kowalczyk (University of Lodz). This project was elaborated within the Justus Liebig University Giessen and University of Lodz Partnership agreement.

Conflicts of interest

There are no conflicts to declare.

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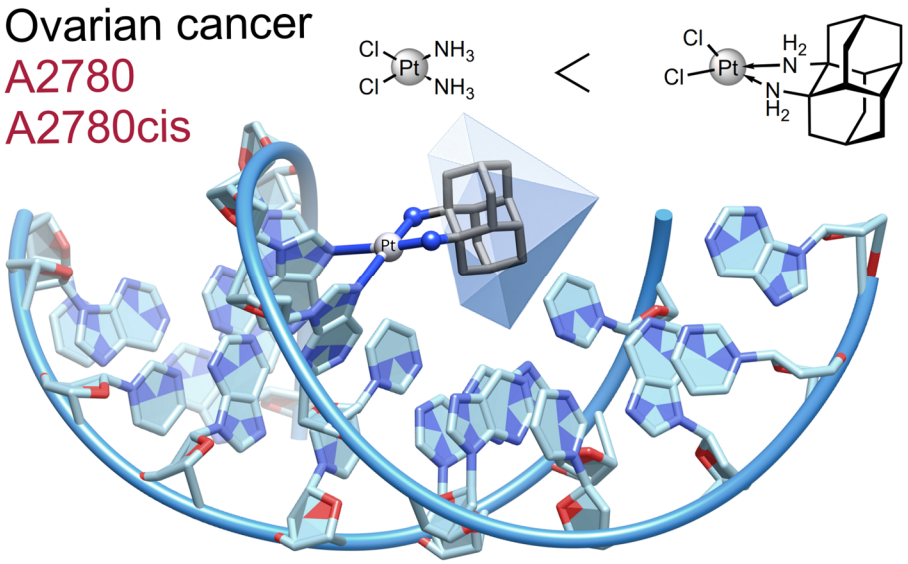
2.2 Synthesis and antiproliferative activity of hindered, chiral 1,2-diaminodiamantane platinum(II) complexes



Abstract

Platinum-based antineoplastic agents play a major role in the treatment of numerous types of cancer. A new bulky, lipophilic, and chiral ligand based on 1,2-diaminodiamantane in both of its enantiomeric forms was employed for the preparation of new platinum(II) complexes with chloride and oxalate ligands. The dichloride complexes have a higher solubility and were evaluated as anti-proliferation agents for human ovarian cancer cell lines A2780 and cisplatin-resistant A2780cis. Its *R*,*R*-enantiomer showed increased efficacy compared to cisplatin for both cancer cell lines. A chromatographic approach was used to estimate the solvent partition coefficient of the dichloride complex. The binding of diamondoid-based platinum complexes to nucleotides was tested for both enantiomers with guanosine monophosphate (GMP) and deoxyguanosine monophosphate (dGMP) and occurs at a similar or faster rate for both isomers compared to cisplatin despite greatly increased steric demand. These findings highlight the potential in 1,2-diaminodiamantane as a viable pharmacophore.

Reference

V. V. Bakhonsky, A. A. Pashenko, J. Becker, H. Hausmann, H. J. M. De Groot, H. S. Overkleeft, A. A. Fokin and P. R. Schreiner, *Dalton Trans.*, 2020, **49**, 14009–14016.

Dalton Transactions

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Cite this: DOI: 10.1039/d0dt02391d

Synthesis and antiproliferative activity of hindered, chiral 1,2-diaminodiamantane platinum(II) complexes†

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Received 6th July 2020,
Accepted 28th August 2020

DOI: 10.1039/d0dt02391d

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Platinum-based antineoplastic agents play a major role in the treatment of numerous types of cancer. A new bulky, lipophilic, and chiral ligand based on 1,2-diaminodiamantane in both of its enantiomeric forms was employed for the preparation of new platinum(II) complexes with chloride and oxalate ligands. The dichloride complexes have a higher solubility and were evaluated as anti-proliferation agents for human ovarian cancer cell lines A2780 and cisplatin-resistant A2780cis. Its *R,R*-enantiomer showed increased efficacy compared to cisplatin for both cancer cell lines. A chromatographic approach was used to estimate the solvent partition coefficient of the dichloride complex. The binding of diamondoid-based platinum complexes to nucleotides was tested for both enantiomers with guanosine monophosphate (GMP) and deoxyguanosine monophosphate (dGMP) and occurs at a similar or faster rate for both isomers compared to cisplatin despite greatly increased steric demand. These findings highlight the potential in 1,2-diaminodiamantane as a viable pharmacophore.

Introduction

Cisplatin [*cis*-dichlorodiamineplatinum(II)] (Fig. 1), first tested in 1968, was approved worldwide in 1978 after being accidentally discovered to have antiproliferative activity by Rosenberg during electrochemical treatment of living cells using platinum electrodes.[1] This discovery dramatically changed cancer treatment regimens with platinum-based drugs being incorporated as effective agents by themselves or in combination with other antineoplastic medication in >50% of formulations for a wide variety of cancer cell types. Cisplatin is still the preferred drug for ovarian and testicular cancer providing 90% cure rate for the latter.[2,3] There is converging evidence that the mechanism of action of cisplatin and its analogues with the general formula $[PtX_2(RNH_2)_2]$ involves hydrolysis of the diamine complexes inside cancer cells producing the charged $[Pt(NH_3)_2(H_2O)_2]^{2+}$ complex that quickly loses water and forms inter- and intrastrand DNA cross-links blocking repair mechanisms. The majority of cross-links are guanosine–guanosine d(GpG) and, to lesser extent, adenosine-guanosine d(ApG) intrastrand cross-links formed by platinum diamine complexes and adjacent purine bases.[4] The resulting platinum adducts interfere with DNA replication triggering cell apoptosis.[5] Despite beneficial cytotoxicity used to target cancer cells, cisplatin treatment has drawbacks such as dose-limiting peripheral neurotoxicity, gastrointestinal toxicity, ototoxicity, hematological toxicity and severe nephrotoxicity, being potentially lethal for patients without modern hydration techniques.[6–11] Furthermore, it quickly became evident that numerous cancer cell types have intrinsic or acquired resistance towards cisplatin.[12–14] In an attempt to overcome the limitations of cis-

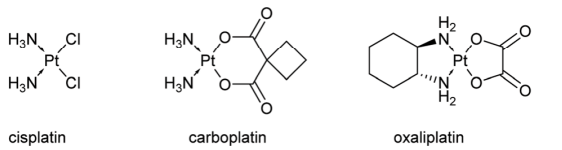

Fig. 1 Chemical structures of platinum anticancer drugs approved worldwide.

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†Electronic supplementary information (ESI) available: NMR spectra and crystallographic data. CCDC 1956841 and 1956840. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0dt02391d

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platin, carboplatin was developed. This second-generation platinum agent has chlorine ligands substituted by a bidentate cyclobutanedicarboxylate moiety. Carboplatin has a greatly reduced toxicity profile, allowing adjustment of the active dosage to individual patients, although it has decreased anticancer activity requiring 20–40 fold increase in concentration to achieve the same effect as for cisplatin.[3,11]

Despite being actively used in treatment of ovarian cancer, the dose-limiting myelosuppression (thrombocytopenia and to lesser extent neutropenia and anemia) still remains a significant drawback.[3,11,15] Carboplatin has the same mechanism of action inside the cell as cisplatin. Consequently, numerous cancer cell types, known to acquire cisplatin resistance, exhibit cross-resistance to carboplatin as well.[11,16,17]

The third-generation platinum drugs were developed to further counter cisplatin resistance. Oxaliplatin, the most recent worldwide-approved anticancer drug based on platinum,[18,19] displays a bidentate oxalate moiety instead of the two chloride anions in cisplatin, as well as amino ligands derived from (1*R*,2*R*)-1,2-diaminocyclohexane [(*R*,*R*)-DACH]. The larger and more lipophilic 1,2-diaminocyclohexane [1,2-DACH] significantly changes the cytotoxicity profile and provides very limited cross-resistance to cisplatin, which is linked to the steric properties of the DACH adduct that hinders the DNA repair mechanism within tumor cells.[18,20] Differences in activity manifest themselves in the particular effectiveness of oxaliplatin in the treatment of colorectal cancer, which is unresponsive to cisplatin and carboplatin.[19,20]

New generations of platinum-based anticancer drugs with diverse cytotoxicity profiles require different diamine carrier ligands that are responsible for interactions with DNA inside cancer cells. The lipophilicity of these ligands increases absorption and accumulation of the platinum complex within the cell while decreasing the requirement for renal excretion, thus reducing toxic side effects.[21,22] *trans*-1,2-Diaminocyclohexane is the most popular diamine pharmacophore, although other hydrocarbon backbones receive increasing attention. For instance, kiteplatin [$PtCl_2$(*cis*-1,4-DACH)], first synthesized in 1994, incorporates a 1,2-DACH isomer; it lacks cross-resistance with already approved anticancer drugs.[23,24] The more bulky and lipophilic 2,3-diaminobicyclo [2.2.1]heptane, 2,3-diaminobicyclo[2.2.1]heptane, camphor-1,2-diamine, and their analogues (Fig. 2) were recently utilized as carrier ligands, some of which exhibited promising antiproliferative properties when paired with appropriate leaving ligands in platinum complexes.[25–31]

We suggest 1,2-diaminodiamantane as a viable alternative to known lipophilic diamine pharmacophores. Diamondoids among other polycyclic hydrocarbons have already displayed potential as promising scaffolds for medicinal chemistry.[32,33] Our recent work on diamantane functionalization[34] provides direct access to previously unknown 1,2-disubstituted diamondoids and 1,2-diaminodiamantane in particular. The bulky diamantane backbone provides high lipophilicity in a compact and extraordinarily stable lattice. Being conformationally rigid, 1,2-diaminodiamantane may present significant steric and kinetic hindrance to the DNA repair mechanism, which may further increase the efficacy of its platinum-DNA adduct. The two available stereoisomers of 1,2-diaminodiamantane are the *R*,*R* and *S*,*S* enantiomers that introduce chirality into their corresponding platinum complexes, which is known to play a major role in platinum drug efficacy.[35]

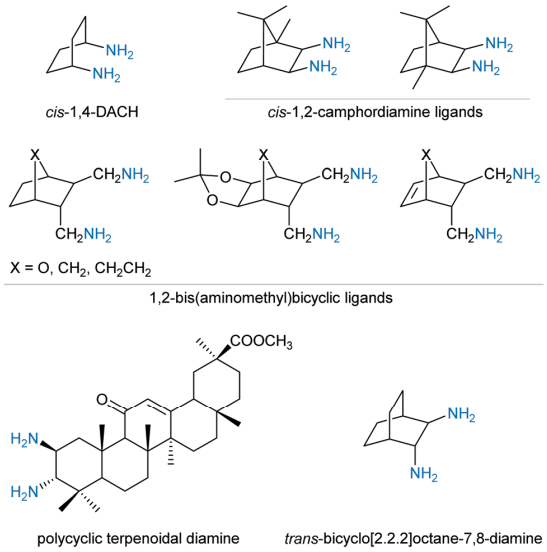

Fig. 2 Bulky diamine ligands known to be tested in various platinum complexes for antiproliferative activity.

In this study we synthesized two diamantane based platinum complexes in both of their enantiopure forms (Fig. 3) and tested them in cancer cell assays. The (*R*,*R*)-**2** and (*S*,*S*)-**2** complexes were found to have extremely low solubility and were not used in activity studies. Although these complexes (termed *diaplatins*) generally exhibit decreased solubility compared to cisplatin, we were able to grow a crystal of (*S*,*S*)-**1** and compare its geometry to the structures of 1,2-diaminocyclohexanedichloroplatinum(II) [$PtCl_2$(1,2-DACH)] and cisplatin. Using reverse phase high pressure liquid chromatography (RP-HPLC), we were able to estimate the lipophilicity of the

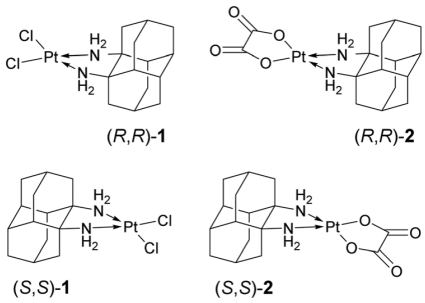

Fig. 3 Investigated diamondoid-based platinum complexes.

dichloride complex using a range of reference compounds with known partition coefficients. The diaplatin enantiomers were tested for their cytotoxicity *via* a cell viability assay conducted on the human ovarian cancer cell line A2780 and its cisplatin-resistant variant A2780cis. (*R*,*R*)-**1** displays higher cytotoxicity than cisplatin for both cell lines, while (*S*,*S*)-**1** shows lower or similar activity as compared to cisplatin, which shows similar to the known reactivity of oxaliplatin comprising (*R*,*R*)-DACH and its *S*,*S*-diamine-based counterpart.[36–38] We evaluated GMP and dGMP binding rates for both (*R*,*R*)-**1** and (*S*,*S*)-**1** complexes using NMR spectroscopy. Despite the increased steric demand, charged diamantanediaminoplatinum complexes have binding rates comparable to cisplatin. (*R*,*R*)-**1** shows increased activity and cytotoxicity compared to cisplatin, thereby benefiting from its bulky backbone with inherent chirality.

Experimental

Preparation of platinum complexes

Materials and methods. Chemicals, solvents, and reagents for biological assays were of analytical or equivalent grade and were used as received. Melting points were measured in closed capillaries on Krüss KSP1N melting point meter. NMR spectra were recorded on Bruker DPX-300 300 MHz spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C, 64 MHz for ^{195}Pt) using DMF-d7 as a solvent. Chemical shifts are given in parts per million (ppm). High-resolution mass spectra were recorded on Bruker Daltonics micrOTOF mass spectrometer using ESI (electrospray ionization). Elemental analysis was performed on Thermo FlashEA 1112 Series CHN elemental analyzer. IR spectra were recorded on Bruker Optics VERTEX70/Platinum ATR. Purity was confirmed *via* HPLC using Dionex P680 pump, Rheodyne 8125 injector and Shodex RI-101 ELSD. 1,2-Diaminodiamantane was synthesized and separated on enantiomers according to the published procedure.[34]

***cis*-[1,2-Diaminodiamantane]dichlorideplatinum(II) (1).** 1,2-Diaminodiamantane (0.1 g, 0.46 mmol) was added to a solution of K_2PtCl_4 (0.19 g, 0.46 mmol) in water (2 mL) and the resulting mixture was stirred for 24 h at rt. The yellow precipitate formed and was filtered, washed with acetone, recrystallized from a water/DMF mixture, and dried under reduced pressure at 40 °C for 24 h. We obtained yellow crystals of **1** (0.085 g) in 37% yield. Mp 314 °C (dec.). ^{1}H NMR (300 MHz, DMF-d7): δ 5.18–4.84 (m, 4H, NH_2), 2.78–2.66 (m, 2H), 2.65–2.51 (m, 2H), 2.04–1.93 (m, 4H), 1.77–1.66 (m, 4H), 1.66–1.55 (m, 4H), 1.47–1.35 (m, 2H). ^{13}C NMR (75 MHz, DMF-d7): δ 64.5 (C), 43.5 (CH), 40.2 (CH), 38.2 (CH_2), 38.0 (CH_2), 31.7 (CH_2), 28.8 (CH). ^{195}Pt (64 MHz, DMF-d7): δ 2251. HRMS (ESI): calcd for $C_{14}H_{22}N_2Cl_2NaPt^+$ $[M + Na]^+$ = 506.0700 found 506.0702. HPLC (Chiralpak IB, 35% methanol, 65% *tert*-butyl methyl ether, 1.0 mL min^{-1}): (*R*,*R*)-**1** ret. time 6.04 min >99% purity, >99% ee; (*S*,*S*)-**1** ret. time 5.76 min >99% purity, >99% ee.

***cis*-[1,2-Diaminodiamantane]oxalatoplatinum(II) (2).** A solution of 1,2-diaminodiamantane (0.1 g, 0.46 mmol) in isopropanol (5 mL) was added to a solution of $K_2[Pt(ox)_2]\cdot 2H_2O$ (0.187 g, 0.41 mmol) in water (5 mL) preheated to 50 °C. The resulting mixture was stirred at 70 °C for 72 h in the dark. The precipitated off-white powder was filtered, washed with water and acetone, and dried under reduced pressure. We obtained off-white crystals of **2** (0.06 g) in 29% yield. Mp 267 °C (dec.). IR ν_{max}/cm^{-1}: 2913br, 1694s, 1667s, 1598w, 1357s, 818s, 561w, 459w. Due to the insolubility of the obtained solid material, no further purification and analysis could be completed. Therefore, the complex was not used in further investigations.

Crystallographic structure measurements

Crystallographic data for 1,2-diaminodiamantane dihydrochloride and (*S*,*S*)-**1** were collected at 100 K using φ- and ω-scans on a BRUKER D8 Venture system equipped with dual IμS microfocus sources, a PHOTON100 detector and an OXFORD CRYOSYSTEMS 700 low temperature system. Mo-Kα radiation with a wavelength of 0.71073 Å and a collimating Quazar multilayer mirror were used. Semi-empirical absorption corrections from equivalents for 1,2-diaminodiamantane dihydrochloride and numerical absorption corrections for (*S*,*S*)-**1** were applied using SADABS-2016/2.[39] The space groups were determined by systematic absences using XPREP and the structures were solved by direct methods using SHELXT.[40] Refinement for all structures was performed against F^2 on all data by full-matrix least squares using SHELXL.[41] All non-hydrogen atoms were refined anisotropically and C–H hydrogen atoms were positioned at geometrically calculated positions and refined using a riding model. O–H and N–H hydrogen atoms were located in the Fourier difference map and set to ideal distances. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2× or 1.5× (CH_3 and OH hydrogens) the U_{eq} value of the atoms they are linked to.

Deposition Numbers 1956841, 1956840† contain the supplementary crystallographic data for this paper.

Lipophilicity measurements

The lipophilicity of complex **1** was studied with its *R*,*R*-enantiomer using RP-HPLC. Measurements were done on with a setup comprising a Dionex LPG-3400A pump, VWD-3100 detector, ASI-100 sampler, and a Degasys DG-1310 degasser. The reverse-phase column was a Knauer Eurospher IIC18 4 × 250 mm for all experiments. Various mixtures of acetonitrile in water were used as mobile phases. To establish the dead time of the column, potassium iodide was used as a dead volume marker. A series of compounds with known log *P* values were injected in the same reverse-phase column to establish a reference curve. The flow rate was kept constant at 1 mL min^{-1} for all experiments. A UV detector was used at 210 nm. A series of retention times, measured for each compound, was used to calculate capacity factors *k* according to eqn (1):

$$k = \frac{t_R - t_0}{t_0} \quad (1)$$

where t_R is the retention time and t_0 the dead time of the column. The capacity factor *k* was determined at least three

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times for each compound using different combinations of acetonitrile and water. The results were analyzed using a linear regression as a relationship between log k and concentration of acetonitrile in the mobile phase (ϕ). This allowed to extrapolate the log k_w values corresponding to capacity factor of the compound in 100% water. The calculated log k_w values for the reference compounds were plotted against their experimental log P values and analysed using a linear regression to establish the relationship curve. The partition coefficient for complex **1** was then estimated with a 95% confidence interval.

Cell viability assay

The human ovarian cancer cell line A2780 (ECACC 93112519) and its cisplatin-resistant variant A2780cis (ECACC 93112517) were grown as a monolayer at 37 °C in an atmosphere containing 5% CO_2 in RPMI medium (Gibco BRLTM, Invitrogen Corporation, Netherlands) with 10% fetal bovine serum (Hyclone, Perbio Science, Netherlands), benzylpenicillin sodium salt (Penicillin G sodium salt, 100 units per mL; Dufecha, Biochemie BV, Netherlands), streptomycin (100 μg mL^{-1}; Dufecha, Biochemie BV, Netherlands), and 2 mM Glutamax × 100 (Gibco BRLTM, Netherlands). The cells were seeded at 20000 cells cm^{-2} in 96-well plates after transferring them with a micropipette from the source culture after trypsinization. Diaplatins and cisplatin as the standard were introduced as solutions in DMF. The concentration in the first well was 270 μM and 1% DMF for (*R*,*R*)-**1**, (*S*,*S*)-**1**, cisplatin and 1% DMF for the control experiment. In every following well, the concentration of the platinum complexes and DMF was progressively halved. Cells were incubated for 72 h at 37 °C in an atmosphere containing 5% CO_2. The cell viability was then analyzed by addition of resazurin sodium salt (Alamar Blue) to cell cultures followed by incubation for 6 h and fluorescence assay of the thus produced resorufin. The evaluation of cell survival was performed with an Epoch Microplate Spectrophotometer (BioTek Instruments) to measure absorbance at 570 nm. All conducted cytotoxicity experiments for (*R*,*R*)-**1**, (*S*,*S*)-**1**, cisplatin, and the control solution containing DMF were run eight times in parallel for each cell line and were done in triplicate. The cytotoxicities of the platinum complexes were calculated using non-linear regression analysis of dose–response data and expressed as half maximal inhibitory concentrations (IC_{50}). Statistical analysis was performed with GraphPad Prism 7.

Nucleotide binding experiments

The rates of (*R*,*R*)-**1**, (*S*,*S*)-**1**, and cisplatin binding with guanosine monophosphate (GMP) and deoxyguanosine monophosphate (dGMP) nucleotides were studied using ^{1}H NMR spectroscopy. A platinum complex solution in DMF-d7 (0.27 mL, 6.9 mM) reacted with GMP or dGMP in a molar ratio 1 : 3.5 introduced with a $NaClO_4$ solution in D_2O (0.33 mL, 100 mM). The reaction mixture was immediately transferred into an NMR tube and ^{1}H NMR data were collected every hour for 66 h at 37 °C. The pH was measured immediately after the reaction mixture was prepared and at the end of the reaction at rt.

Results and discussion

Platinum complexes synthesis and structure analysis

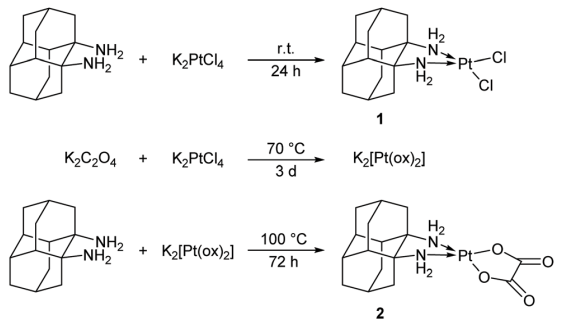
For the synthesis of diaplatin complexes **1** and **2** we decided to utilize silver-free methods to prevent microscopic concentrations of silver from contaminating the samples. Silver is a potent cytotoxic agent and multiple crystallizations in addition to other purification procedures are required to remove its traces and avoid its influence on the cytotoxicity profile of platinum samples.

To prepare (*R*,*R*)-**1** and (*S*,*S*)-**1**, the pure 1,2-diaminodiamantane enantiomers were reacted with K_2PtCl_4. The reaction mixture was stirred for three days protected from light and followed by filtration. The (*R*,*R*)-**2** and (*S*,*S*)-**2** oxalate complexes, $K_2[Pt(ox)_2]$ prepared from K_2PtCl_4 and potassium oxalate, were reacted with the 1,2-diaminodiamantane enantiomers in a similar fashion. This procedure gives diamantane-based platinum complexes in good yields (Scheme 1).

The oxalate complexes are off-white and the dichloride complexes are yellow, which is common for this class of platinum structures, and they have notably decreased solubility compared to cisplatin. Furthermore, (*R*,*R*)-**2** and (*S*,*S*)-**2** are insoluble in most common solvents including *N*,*N*-dimethylformamide (DMF), known to dissolve platinum complexes. However, **1** displays good solubility in DMF and is somewhat soluble in methanol. It can be stored as a solution in these solvents for months in a closed vial without significant decomposition. Solutions in DMSO cause a precipitate to form and show significant decomposition (NMR), which is known for platinum complexes.[42] After initial tests (*R*,*R*)-**2** and (*S*,*S*)-**2** were discarded because they were not soluble enough to reach active concentrations for cytotoxicity assays.

Crystallization of the 1,2-diaminodiamantane dihydrochloride from methanol gave crystals suitable for X-ray single diffraction analysis. The solved structure (Fig. 4A) shows the absolute configuration of (*S*,*S*), determined *via* anomalous dispersion, with a high degree of purity reflected in the Flack parameter[43] being close to zero (Table S1†).

Using a two-phase diffusion technique with DMF as the primary solvent and diethyl ether as the second phase, we were able to grow a crystal of (*S*,*S*)-**1** and obtain its crystal structure



Scheme 1 Preparation of the diaplatin complexes **1** and **2**.

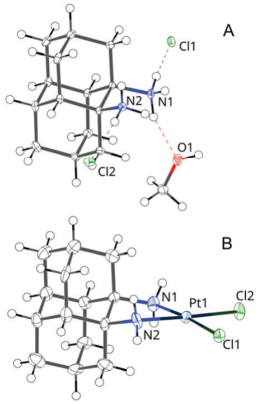


Fig. 4 The molecular structures obtained by crystal structure analysis of (*S*,*S*)-1,2-diaminodiamantane dihydrochloride in a cell with a methanol molecule (A) and of (*S*,*S*)-**1** (B). Ellipsoids drawn at 50% probability.

Table 1 Diaplatin **1**, [$PtCl_2$(1,2-DACH)], and cisplatin geometry comparisons[a]

	Diaplatin **1**	[$PtCl_2$(1,2-DACH)][b]	Cisplatin[c]
Pt–N	2.027(5)	2.036(6)	2.048(3)
Pt–Cl	2.304(1)	2.321(2)	2.321(8)
C–N	1.511(8)	1.497(9)	—
C(1)–C(2)	1.530(7)	1.4965(85)	—
∠(NPtCl)	91.49(14)	90.83(20)	88.87(9)
∠(ClPtCl)	92.83(5)	94.73(7)	91.65(3)
∠(NPtN)	84.25(19)	83.65(20)	90.62(12)

[a] Bonds lengths in Å, angles in deg., SD in parentheses. [b] Ref. 44. [c] Ref.45.

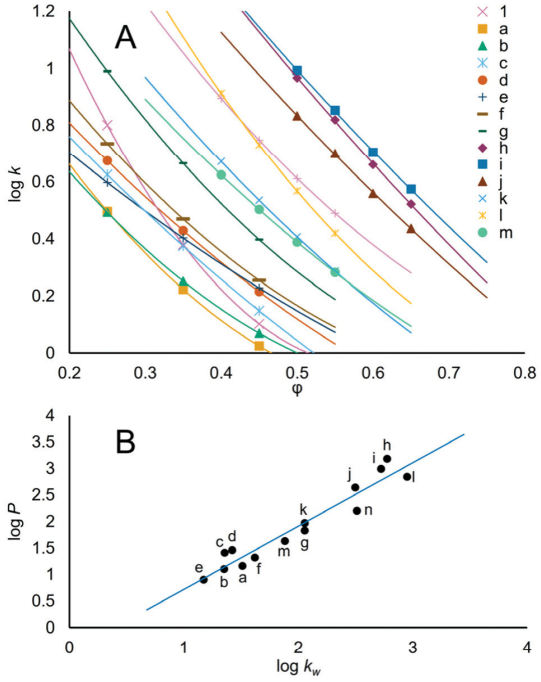


Fig. 5 The capacity factor (log *k*) dependence on acetonitrile concentration (*ϕ*) in moving phase (A) and correlation of experimental log *P* values of reference compounds with their measured capacity factor (log k_w) in 100% water (B): (1), (*R*,*R*)-**1**; (a), acetanilide; (b), benzylic alcohol; (c), phenylacetic acid; (d), phenol; (e), aniline; (f), guaiacol; (g), *p*-cresol; (h), benzophenone; (i), bromobenzene; (j), ethyl benzoate; (k), *p*-chloroaniline; (l), 1-naphthol; (m), acetophenone; (n), methyl benzoate.

(Fig. 4B). The structure for the (*S*,*S*)-**1** crystal was solved in the hexagonal space group *P*622 and the absolute structure could be determined again with a Flack parameter close to zero (Table S7†). We compared the crystal structure of **1**, [$PtCl_2$(1,2-DACH)], and cisplatin (Table 1). Overall, the geometry of 1 is very close to the geometries of [$PtCl_2$(1,2-DACH)] and cisplatin with a few differences imposed by the rigid diamondoid moicty.

Lipophilicity measurements

The octanol–water partition coefficient (*P*) is a widely used value for estimating membrane permeability in drug discovery. One of the most commonly employed methods is RP-HPLC[46] based on measuring the capacity factor (log k_w) values, which directly correlate with experimental log *P* values.[47] Furthermore, RP-HPLC is known for producing reliable results for platinum complexes.[48,49] We chose to assess the (*R*,*R*)-**1** and a range of organic compounds with known log *P* values[50,51] for reference. Retention times were measured at different isocratic concentrations of acetonitrile in water as mobile phase and using eqn (1) were converted to capacity factors log *k* for every measurement (Fig. 5A). Capacity factors in 100% water (log k_w) were extrapolated from these values *via* linear regression analysis. The experimental log *P* values of the reference compounds were used to establish relationship curves between partition coefficients and capacity factors (Fig. 5B) using linear regression analysis. Log *P* ± 95% CI of (*R*,*R*)-**1** was then found to be 2.50 ± 0.16, which is more than four logarithmic units higher than cisplatin[52–55] reported in the range from −2.13 to −2.45. Hence, the compact diamondoid ligand offers an alternative to long alkyl chains with different pharmacological activity and significantly increased lipohilicity.

Cell viability assay

The platinum complexes (*R*,*R*)-**1**, (*S*,*S*)-**1** were tested against the human ovarian cancer cell line A2780 and its cisplatin-resistant variant A2780cis. Compounds (*R*,*R*)-**1**, (*S*,*S*)-**1**, and cisplatin were introduced to cell cultures in ten different concentrations and incubated for 72 h at 37 °C. We used standard procedures for adding a fluorescent dye to cell wells and, using spectrophotometry, we collected dose–response data (Fig. 6) to determine the IC_{50} values (Table 2). (*R*,*R*)-**1** shows superior cytotoxicity compared to cisplatin for both cancer cell lines while (*S*,*S*)-**1** has the lowest efficacy. The difference in activity

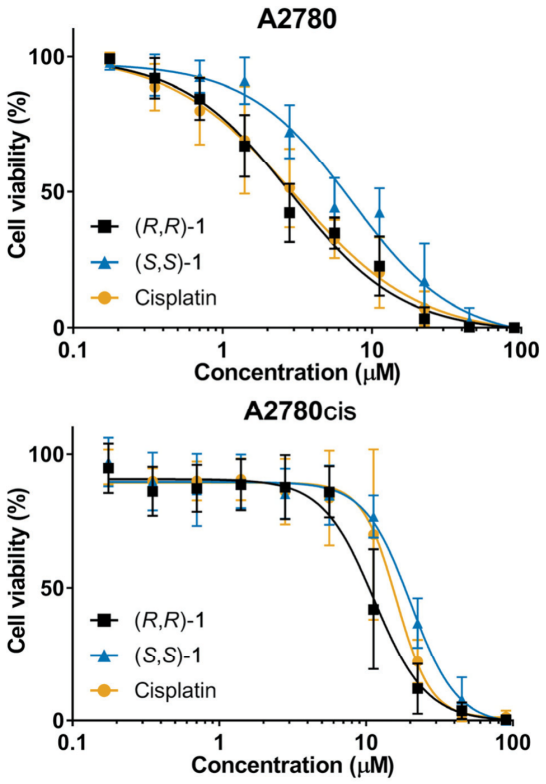


Fig. 6 Dose–response curves for (*R*,*R*)-**1**, (*S*,*S*)-**1**, and cisplatin on human ovarian cancer cell lines A2780 (top) and A2780cis (bottom).

Table 2 *In vitro* cytotoxicity of (*R*,*R*)-**1**, (*S*,*S*)-**1**, and cisplatin against human ovarian cancer lines A2780 and A2780cis

	IC_{50} (μM)[a]		
Cell line	(*S*,*S*)-**1**	(*R*,*R*)-**1**	Cisplatin
A2780	6.85 ± 1.21	2.27 ± 0.65	3.28 ± 0.63
A2780*cis*[b]	20.15 ± 0.91	11.2 ± 0.66	16.81 ± 0.56

[a] IC_{50} values derived as mean ± SD of results of eight parallel experiments done in triplicate for each platinum complex paired with each cell line and incubated for 72 h at 37 °C. [b] Cisplatin-resistant variant of A2780 cell line.

between the diaplatin stereoisomers is in line with previously observed pattern for oxaliplatin, which contains the (*R*,*R*)-DACH fragment.[37,38] The difference in reactivity of oxaliplatin and its stereoisomer is attributed to a more favorable configuration of the resulting DNA cross-link.[56–61] The cisplatin-resistant cell line A2780cis shows a notable decrease in response to platinum complexes in the same range of concentrations, although (*R*,*R*)-**1** retains its superior activity compared to cisplatin. The observed efficacy of simplest 1,2-diaminodiamantane platinum complexes can be further enhanced by substituting the chloride groups for other leaving ligands, which is a general approach to achieve enhanced solubility, and decreased overall toxicity for the human body.[15,21,28,62–66]

Nucleotide binding experiments

Formation of DNA cross-links is the crucial part of the platinum cytotoxicity mechanism. To study diaplatin complex **1** activity on nucleotides in comparison to cisplatin we chose guanosine monophosphate (GMP) and deoxyguanosine monophosphate (dGMP) as substrates (Fig. 7). The reaction between platinum complexes and GMP or dGMP causes substitution of their leaving ligands with corresponding nucleotide to form monoadducts that quickly lose a second leaving ligand forming bisadducts. The N7 atom of the purine fragment is known to be the preferred binding site

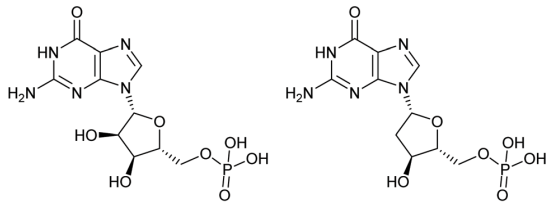


Fig. 7 Structures of used nucleotide substrates.

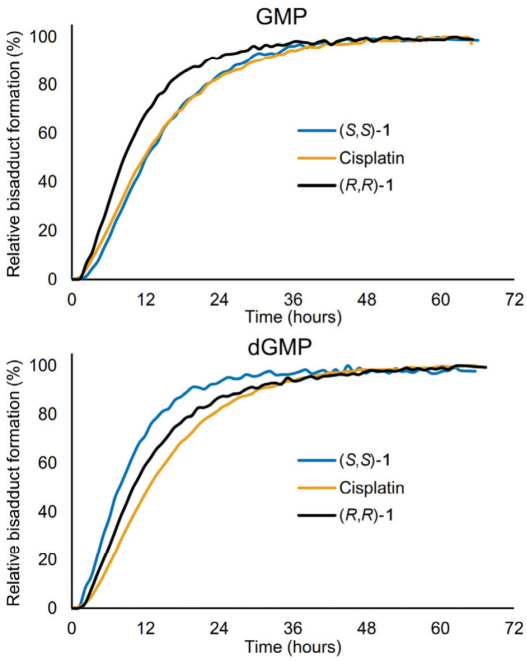


Fig. 8 Rates of nucleotide-platinum bisadduct formations for GMP (top) and dGMP (bottom).

to platinum,[67] thus causing easily observable downfield NMR shifts of the adjacent H8 atom. The collected ^{1}H NMR data during incubation of the reaction mixtures provide time-dependent changes of the H8 atom integral, thereby providing insights into the binding rates for the studied complexes (Fig. 8).

Both nucleotides form bisadducts faster with (*R*,*R*)-**1** than with cisplatin despite the bulky diamantane backbone. The (*S*,*S*)-**1** bisadduct with GMP has a rate of formation close to cisplatin, but binding to deoxyguanosine proceeds faster than for (*R*,*R*)-**1** and cisplatin illustrating the impact of backbone chirality. Overall, diaplatin **1** showed noticeably faster reaction towards bisadduct formation despite greatly increased steric requirements posed by the diamantane moiety.

Conclusions

Here we put forward 1,2-diaminodiamantane as a viable non-leaving ligand for platinum-based anticancer drugs. We were able to prepare (*R*,*R*)-**1** and (*S*,*S*)-**1** featuring chloride ligands despite decreased solubility compared to cisplatin. The analogous platinum complexes with oxalate moieties were found to have negligible solubility preventing them from being studied further. The crystallographic data allowed us to confirm the absolute configurations of the newly prepared complexes. The diamondoid moiety predictably changed the platinum complex towards significantly increased lipophilicity. A cytotoxic assay demonstrates the superiority of (*R*,*R*)-**1** relative to cisplatin on both the human ovarian cancer cell line A2780 and its cisplatin-resistant variant A2780cis. Complex (*S*,*S*)-**1** was found to be less potent than cisplatin on either cell line. This further demonstrated the difference in reactivity caused by the chiral diamine backbone interactions with DNA. Similar to oxaliplatin, which contains the *R*,*R*-enantiomer of *trans*-1,2-diaminocyclohexane as the diamine ligand, (*R*,*R*)-1,2-diaminodiamantane yields the more potent cytotoxic complex. Nucleotide binding studies of the diaplatin enantiomers showed activities similar to other platinum(II) complexes. Despite the increased steric demand, both GMP and dGMP bind faster to (*R*,*R*)-**1** than to cisplatin. The (*S*,*S*)-**1** binding kinetics towards GMP are close to cisplatin, but in case of dGMP the rate is higher compared to (*R*,*R*)-**1** or cisplatin.

1,2-Diaminodiamantane provides an opportunity to utilize a pharmacophore with an unusual set of properties. At the cost of decreased solubility, the simplest platinum(II) complex based on this diamantane backbone already proved to be more potent than cisplatin on the studied cell lines while being as fast at binding with nucleotides as cisplatin despite considerably increased bulk. Furthermore, the straightforward diaplatin synthesis allows simple modifications of both the diamine and the leaving ligands as a way to improve solubility[29] in addition to augmenting its pharmacokinetics.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The work in Giessen was supported in part by the U.S. Department of Energy (Contract No. DE-AC02-76SF00515). A. E. P. thanks Erasmus+Programme for support.

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3 Acknowledgement

My work and this thesis would not be possible without the help and contributions of many people over the years. I would like to thank:

Prof. Dr. Peter R. Schreiner, PhD for his support, guidance, and giving me an opportunity to grow as a scientist in his group.

Prof. Dr. Andrey A. Fokin for his support, guidance, and always being ready to share his wealth of knowledge.

Prof. Dr. Grzegorz Mlostoń for the collaboration on the carbene project.

Alexander E. Pashenko, PhD for his friendship, collaboration and giving me the passion for organic synthesis many years ago.

Dr. Heike Hausmann, Dr. Jonathan Becker, Anika and Stefan Bernhardt, Steffen Wagner, and Dr. Raffael Wende for their help with analysis and measurements.

Dr. Denis Gerbig and Dr. Henrik Quantz for their help with computational chemistry.

Michaela Richter, Doris Verch, and Dr. Jörg Neudert for their organizational and administrative support.

Dr. Boryslav Tkachenko for discussions and company, especially during evening lab work.

Colleagues from Room B218 **Dr. Fumito Saito, Dr. Nataliya Fokina Dr. Marina Šekutor, Dr. Oana Moncea, Dr. Tizian Müller, and Gowrisankar Saravanan, PhD** for the nice working atmosphere and for the discussions scientific and not.

The whole **PRS group** for being kind and accommodating.

Ben, Jenny, Martin, Jan, Olga, and Julia for their friendship and for their consistent motivation and support on my academic path.

My parents and my sister for their love and encouragement.