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Facile and green synthesis of [Pd(NHC)(η³-R-allyl)Cl] complexes and their anticancer activity†

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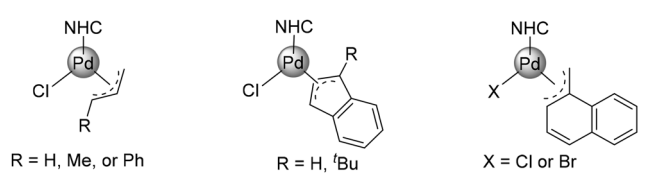
A facile and environmentally friendly method for synthesizing a range of palladium-N-heterocyclic carbene (NHC) complexes—[Pd(NHC)(η³-R-allyl)Cl]—is described. This improved approach, which is based on the use of aqueous ammonia as weak base, is effectively exemplified with different NHC structures bearing R-allyl groups, achieving good to excellent yields while significantly reducing reaction times, temperature, cost, and overall environmental impact compared to previous methods. The synthesized complexes were evaluated for *in vitro* anticancer activity against several human cancer cell lines. Most complexes, except those with highly bulky and lipophilic ligands, showed excellent cytotoxicity—comparable to cisplatin in cisplatin-sensitive tumors and up to 100 times more potent than the reference drug in highly aggressive or resistant cancers. Structural variations such as the type of palladium fragment or imidazol ring saturation had minimal impact on cytotoxic performance.

In transition metal-catalyzed reactions, the accessibility of the catalyst is a crucial factor in determining the practicality and efficiency of a catalytic system. In this vast landscape, palladium-catalyzed cross-coupling reactions stand out as one of the most powerful and widely utilized chemical transformations, enabling the formation of carbon–carbon (C–C) and carbon–nitrogen (C–N) bonds.[1–3] Among various palladium complexes used in these reactions, the ones supported by N-heterocyclic carbene (NHC) ligands (Pd–NHC well-defined complexes) are oftentimes preferred over their phosphine-based counterparts due to their superior air and moisture stability, along with the stronger σ-donor properties of NHCs compared to aryl phosphines.[4–6] These complexes and their ability to mediate organic transformations have been extensively explored during the last decades in cross-coupling reactions.[7–9]

Complexes of the type [Pd(NHC)(η³-R-allyl)Cl] bearing various throw-away ligands (R-allyl = allyl, methyl allyl, cinnamyl, and indenyl) have proven to be valuable in this context (Scheme 1, left).[10–15] Even two decades after our report of palladium–NHC complexes with the allyl ligand in 2002,[16] the η³-R-allyl type complexes remain a subject of intense study.

For instance, Hazari and co-workers investigated the nature of the throw-away ligands and the deactivation pathways of η³-R-allyl (^{t}Bu-indenyl and indenyl) containing NHC–Pd complexes (Scheme 1, middle), highlighting the critical role of the bulky R-substituent on the ally moiety in the catalyst activation step.[15,17] Similarly, Nolan and co-workers recently explored the effect of substituted cinnamyl moieties on catalytic efficiency, demonstrating that mesityl modification (2,4,6-trimethyl) on the cinnamyl group enhanced the catalytic activity in Buchwald–Hartwig amination compared to the unsubstituted counterpart.[18] This class of Pd–allyl complexes was further expanded in 2021 by Gooßen and co-workers with the development of allyl-type complexes [Pd(NHC)(MeNAP)X] (MeNAP =



Scheme 1 [Pd(NHC)(η³-R-allyl)Cl] complexes.

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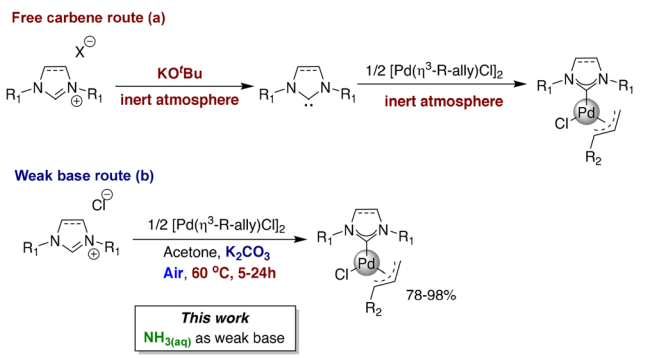
methylnaphthyl, X = Br or Cl) (Scheme 1, right).[19] Notably, these MeNAP-type complexes, along with the cinnamyl-type complexes have enabled challenging cross-coupling reactions to assemble very bulky tetra-*ortho*-substituted biaryls under mild conditions.[19,20]

In this respect, designing a straightforward and efficient method for synthesizing these well-defined allyl-type NHC–Pd complexes is highly important, and this has been a focus of our research team since their first isolation. Notably, well-defined complexes are essential for in-depth studies of catalytic systems as well as for biological purposes.[18]

The most widely used method for synthesizing [Pd(NHC)(η^3-R-allyl)Cl]-type complexes involves generating a free carbene under an inert atmosphere with a strong base (*e.g.* KO^{t}Bu), followed by the addition of palladium dimers such as [Pd(η^3-allyl)(μ-Cl)]$_2$ or [Pd(η^3-cin)(μ-Cl)]$_2$ (Scheme 2a, "Free carbene route").[21,22] Given the drawbacks of this method (two steps, the use of strong bases and strictly anhydrous and inert atmosphere conditions), we have focused on developing a more efficient and cost-effective strategy.

During our studies related to the synthesis of other NHC metal complexes (Au[23] and Cu[24]) using a weak base (K_2CO_3) under milder conditions, we discovered in 2017 that this "weak-base" approach was also effective for the synthesis of [Pd(NHC)(η^3-R-allyl)Cl]-type complexes (Scheme 2b, "Weak-base route").[25] In this one-step approach, palladium dimers such as [Pd(η^3-allyl)(μ-Cl)]$_2$ or [Pd(η^3-cin)(μ-Cl)]$_2$ were combined with various NHC salts in acetone with K_2CO_3 under air. While conventional NHC salts such as IPr·HCl, SIPr·HCl, and SIMes·HCl reacted under moderately harsh conditions (60 °C, 5 h, 78–98% isolated yield), bulkier NHC precursors (IPr*·HCl, IPr*^{OMe}·HCl, IPr^{2Np}·HCl, IPent·HCl, and IHept·HCl) required increased amount of base and harsher condition (60 °C, 24 h, 81–94% isolated yield). Although the weak-base approach using K_2CO_3 has shown promising results for preparing [Pd(NHC)(η^3-R-allyl)Cl]-type complexes, there is still room for improvement in mitigating the harsh reaction conditions. Additionally, the workup protocol requires a large amount of dichloromethane (22 mL per 50 mg of NHC salts), a solvent recently restricted by the U.S. Environmental Protection Agency (EPA).[26] Moreover, to remove inorganic salts as well as the excess of azolium salt (which was found to be necessary to prevent the formation of by-products), the reaction mixture requires filtration through silica gel. Given these challenges, developing a more efficient and environmentally friendly synthetic approach for this important class of complexes is highly desired.



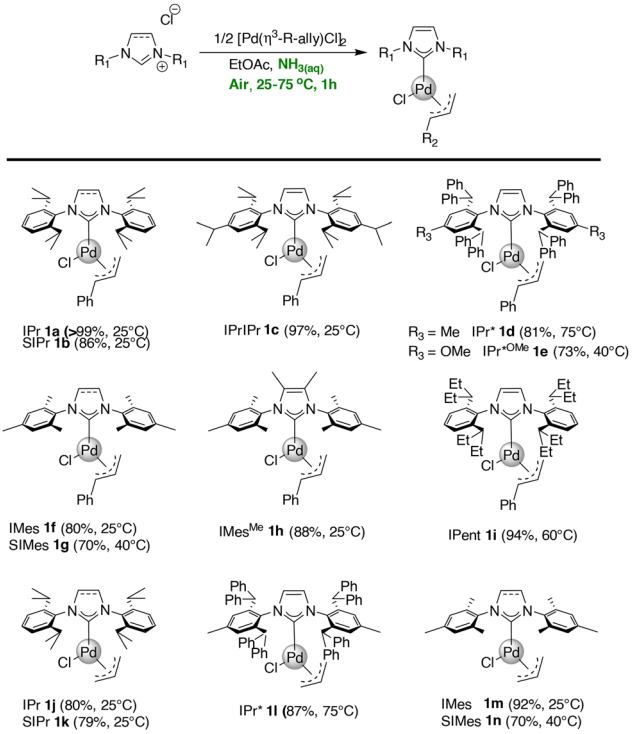
Scheme 2 Synthetic routes to [Pd(NHC)(η^3-R-allyl)Cl]-type complexes.

In this context, the reports of exploration of alternative weak bases remains limited, as only K_2CO_3 has been tested in this reaction to date. To this end, we recently reported the use of aqueous ammonia ($NH_{3(aq.)}$) as a cost-effective and green weak base for the synthesis of [Au(NHC)Cl] complexes and their functionalization.[27] In the report, aqueous ammonia showed comparable results to the original method with K_2CO_3 despite its weaker basicity.

We report now on our efforts to examine the use of aqueous ammonia as a weak base in the synthesis of [Pd(NHC)(η^3-R-allyl)Cl]-type complexes and propose improved reaction conditions and workup protocols, emphasizing key factors such as reaction time, temperature, cost-effectiveness, and environmental impact. Moreover, we report the first systematic study on the anticancer activity of neutral Pd–allyl and Pd–cinnamyl complexes. The main objective here was to assess the impact of both the nature of the NHC ligand and of the organopalladium fragment (Pd–allyl or Pd–cinnamyl) on the cytotoxicity towards cancer cells. We initiated this study by investigating the optimal reaction conditions for converting both saturated and unsaturated azolium salts into the corresponding [Pd(NHC)(η^3-R-allyl)Cl]-type complexes, employing aqueous ammonia as a mild base.

The optimized protocol outlined in Scheme 3 can be conducted in air with technical grade ethyl acetate to generate a series of [Pd(NHC)(η^3-R-allyl)Cl]-type complexes from NHC·HCl salts (1.0 equiv.) and [Pd(η^3-allyl)(μ-Cl)]$_2$ or [Pd(η^3-cin)(μ-Cl)]$_2$ metal source (0.5 equiv.) in the presence of aqueous ammonia (3 equiv.). Compared to the state-of-the-art approach with K_2CO_3, full conversion can be achieved on both cinnamyl and allyl complexes in only one hour with equally high yields. Notably, using the current approach, an excess of NHC·HCl salt was not required, whereas in the state-of-the-art method, an excess (1.2 equivalent) of the NHC salts relative to the palladium source was necessary to suppress by-product formation.[25]

With the optimized conditions (see ESI Table S1†), a variety of [Pd(NHC)(η^3-R-allyl)Cl]-type complexes were prepared to assess the generality of this protocol. [Pd(IPr)(η^3-cin)Cl] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) can be isolated in quantitative yield (**1a**), and the saturated equivalent, SIPr, in an 86% yield (**1b**). While IPrIPr (**1c**) can be synthesized in an excellent yield (97%), lower yields were observed with more sterically hindered ligands such as IPr* (**1d**) and IPr*^{OMe} (**1e**), 81% and 73%, respectively. Even though higher temperatures were required for bulkier ligands, such as IPr* (**1d**), IPr*^{OMe} (**1e**), and IPent (**1i**) in order to achieve full conversion in one hour, significantly faster conversion (1 h *vs.* 24 h) can be achieved with this method with respect to the previous approach. Lastly, IMes (**1f**), SIMes (**1g**), and the recently

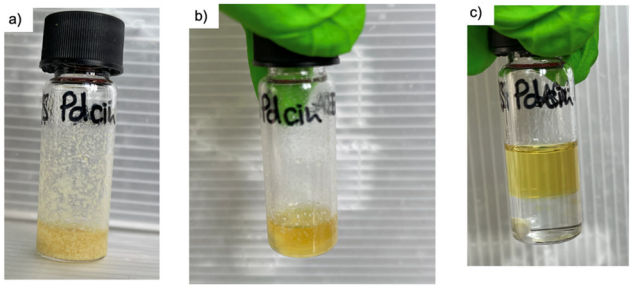


Scheme 3 Scope of Pd–NHC complexes using aqueous ammonia. Reaction condition: NHC·HCl (50 mg, 1.0 eq.), $[Pd(\eta^3\text{-allyl})(\mu\text{-Cl})]_2$ or $[Pd(\eta^3\text{-cin})(\mu\text{-Cl})]_2$ (0.5 eq.), NH_3 (3 eq.), EtOAc (0.5 mL), mixed for 1 h. For the detailed condition, see the ESI.†

reported $IMes^{Me}$ (**1h**)[28] can be isolated in 80%, 70%, and 88% yield, respectively. Notably, complex **1h** showed excellent results in Miyaura borylation for a series of aryl chlorides.[28] In fact, current approach can shorten the reaction time from 5 h to 1 h with an increased yield. Similar results were observed for allyl complexes, where $[Pd(IPr)(\eta^3\text{-allyl})Cl]$ can be synthesized in an 80% yield (**1j**) and other NHC ligands in 70 to 92% yield. It is worth noting that all complexes can be prepared within just 1 hour using this approach, in contrast to the 5–24 hours required by the state-of-the-art method employing K_2CO_3.[25]

In addition to the improved reaction conditions, another advantage of this approach is its environmentally friendly and straightforward workup protocol. Upon completion of the reaction, the reaction mixture transforms from a yellow suspension into a yellow solution (Scheme 4a and b). The following workup then is a simple aqueous extraction performed directly in the reaction vessel, using minimal amounts of ethyl acetate to isolate the product complex ('phase-cut' workup Scheme 4c) thereby reducing solvent consumption and operation time. Notably, dichloromethane was eliminated from all workup steps, representing a clear environmental improvement over the previous method employing K_2CO_3.

Encouraged by these results, the *E*-factor for our reaction condition to evaluate the environmental footprint was calculated. The E factor is one of the oldest metrics to estimate the environmental impact of a synthetic process and was introduced by Roger Sheldon in 1992.[29] It is defined as the mass ratio of waste to the target product, including atom efficiency, stoichiometry, solvent usage, and yield. While extremely useful to rapidly evaluate the amount of waste associated with a reaction, atom efficiency alone does not consider solvent waste or any of the ESI† that are necessary to isolate the final product. Therefore, the *E*-factor reflects the actual amount of waste generated by a process on a very practical level. Calculation of the *E*-factor reveals that the proposed protocol significantly reduced the environmental footprint of the synthetic process compared to the standard procedure with K_2CO_3 (22 *vs.* 537 in the case of **1a**, and 26 *vs.* 572 in the case of **1j**, see Tables S2–S4 in ESI†).[30] In practice, solvent use represents the largest cost during the purification process. This improvement was achieved through the environmentally friendly and facile workup procedure.



Scheme 4 The evolution of the reaction over 1 hour. (a) The beginning of the reaction. A suspension due to insoluble IPr·HCl in EtOAc. (b) After completion of the reaction. Insoluble IPr·HCl is fully reacted and the product is soluble in EtOAc. (c) "Phase-cut" workup with EtOAc/H_2O.

Overall, aqueous ammonia demonstrated superior efficiency compared to the state-of-the-art weak base K_2CO_3 for the synthesis of a broad range of $[Pd(NHC)(\eta^3\text{-R-allyl})Cl]$ complexes. This newly established standard method leads to shorter reaction times, a significantly more facile workup process, and a significantly improved *E*-factor for the overall synthetic process. A detailed comparison highlighting the benefits of this method for the synthesis of $[Pd(IPr)(\eta^3\text{-cinnamyl})Cl]$ complexes is presented in Table 1 below.

Table 1 The comparison between K_2CO_3 and $NH_{3(aq)}$ weak bases for $[Pd(IPr)(\eta^3\text{-cinnamyl})Cl]$ synthesis with some key parameters

	K_2CO_3 method (2017)[25]	$NH_{3(aq)}$ method (this work)
Solvent	Acetone	EtOAc
Temp. [°C]	60	25
Time [h]	5	1
Yield	98	>99
Base [€ per mol][a]	33	2
Workup	Evaporation Filtration (silica + 22 mL DCM)	Phase-cut
E-factor	537	22

[a] The prices are calculated from the Sigma-Aldrich website at the time of writing.

In the last five years, Scattolin and Visentin have uncovered that some Pd–allyl complexes exhibit high cytotoxicity against a broad spectrum of cancer cell lines, making them promising anticancer agents.[31–33] However, while cationic Pd–allyl complexes have been widely studied, neutral species remain unexplored. Cationic complexes of the general formula [Pd(NHC)(PTA)(η^3-allyl)]X (PTA = 1,3,5-triaza-7-phosphaadamantane; X = BF_4, ClO_4, OTf) induce cancer cell death through an apoptotic mechanism involving early mitochondrial damage.[34] Moreover, these organopalladium derivatives significantly inhibit thioredoxin reductase (TrxR), a key enzyme in cellular redox balance often overexpressed in cancer cells.

In parallel, there is growing interest in anionic Pd–allyl complexes, known as palladates. Palladate complexes exhibit a unique interaction between the proton of an azolium salt and two chlorides of the Pd–allyl fragment, and they inhibit TrxR even more effectively than cationic Pd–allyl complexes and the gold-based drug auranofin.[35,36] A 2024 computational study suggested that both cationic Pd–allyl complexes and palladates inhibit TrxR by forming a covalent Pd–Se bond with the enzyme's selenocysteine residue, irreversibly impairing its activity.[37]

A recent collaboration with the Gandin group has expanded palladate chemistry to include BIAN-based (BIAN = bis(imino) acenaphthene) azolium ligands, yielding compounds with potent cytotoxicity and the ability to trigger immunogenic cell death (ICD) in multiple human cancer cell lines.[38] These findings highlight the potential of palladium–allyl derivatives as dual-action anticancer agents that combine cytotoxic and immunostimulatory properties.

One of the aims of the present study is to fill the existing gap in the literature regarding the limited and sporadic examples of neutral Pd–allyl complexes investigated as potential anticancer agents. To this end, the *in vitro* anticancer activity of the synthesized complexes **1a–n** was assessed against a panel of human cancer cell lines. The selected lines, provided by Sigma-Aldrich/Merck, included A2780 (cisplatin-sensitive ovarian carcinoma), A2780*cis* (cisplatin-resistant ovarian carcinoma), MDA-MB-231 (triple-negative breast cancer), and U87 (glioblastoma). For reference, the cytotoxicity of cisplatin, a commonly used platinum-based chemotherapeutic agent, was also evaluated under identical experimental conditions. The findings, reported as IC_{50} values, are presented in Table 2. The collected data clearly show that many of the complexes bearing extremely bulky and lipophilic ligands, such as IPr* and IPr*^{OMe} (complexes **1d**, **1e**, and **1l**), exhibit the lowest cytotoxicity. Notably, complex **1l** can be considered inactive (IC_{50} > 100 μM). In contrast, all other complexes demonstrated excellent cytotoxicity across all cancer cell lines tested. Their activity was comparable to that of cisplatin in the cisplatin-sensitive A2780 cell line, while in highly aggressive tumors—including cisplatin-resistant ovarian cancer, triple-negative breast cancer, and glioblastoma—the cytotoxicity of our compounds exceeded that of cisplatin by up to two orders of magnitude. From a structure–activity relationship (SAR) perspective, the nature of the organopalladium fragment (Pd–allyl *vs.* Pd–cinnamyl) appeared to have negligible impact on the observed cytotoxicity. Similarly, no clear trend was identified regarding the effect of imidazole ring saturation.

Table 2 Effects of neutral Pd(II)–NHC allyl complexes on the proliferation of A2780, A2780*cis*, MDA-MB-231 and U87 cancer cells. The inhibition of cell growth is represented as IC_{50}[a]

	IC_{50} (μM)			
Complex	A2780	A2780*cis*	MDA-MB-231	U87
Cisplatin	**2.5 ± 0.2**	**70 ± 10**	**60 ± 10**	**30 ± 10**
1a	1.3 ± 0.1	0.5 ± 0.1	0.37 ± 0.03	0.24 ± 0.01
1b	0.4 ± 0.1	0.4 ± 0.1	0.12 ± 0.03	0.14 ± 0.01
1c	1.0 ± 0.2	0.4 ± 0.1	0.98 ± 0.02	1.0 ± 0.1
1d	4.0 ± 0.4	1.5 ± 0.8	1.5 ± 0.4	0.64 ± 0.07
1e	30 ± 10	1.7 ± 0.4	2.4 ± 0.3	3.2 ± 0.3
1f	0.30 ± 0.05	0.21 ± 0.05	0.30 ± 0.02	0.36 ± 0.01
1g	3.9 ± 0.3	4.1 ± 0.3	3.3 ± 0.4	2.8 ± 0.1
1h	0.37 ± 0.04	0.47 ± 0.09	0.38 ± 0.05	0.42 ± 0.02
1i	4.2 ± 0.4	0.6 ± 0.2	0.5 ± 0.2	0.16 ± 0.02
1j	0.31 ± 0.04	0.30 ± 0.08	0.28 ± 0.02	0.42 ± 0.02
1k	0.28 ± 0.06	0.3 ± 0.1	0.29 ± 0.04	0.33 ± 0.02
1l	>100	>100	>100	>100
1m	0.29 ± 0.05	0.4 ± 0.1	0.3 ± 0.1	0.31 ± 0.04
1n	0.28 ± 0.08	0.21 ± 0.04	0.25 ± 0.09	0.28 ± 0.02

[a] Data after 96 h of incubation. Stock solutions in DMSO for all complexes; stock solutions in H_2O for cisplatin. A2780 (cisplatin-sensitive ovarian cancer cells), A2780*cis* (cisplatin-resistant ovarian cancer cells), MDA-MB-231 (triple-negative breast cancer), U87 (glioblastoma) and MRC-5 (normal lung fibroblasts).

Overall, although these compounds are *ca.* 5–10 times less active than the best examples of cationic Pd(II)–allyl complexes reported in the literature ([Pd(NHC)(PTA)(η^3-allyl)]X),[34] their significantly simpler and more straightforward synthesis access makes them highly attractive candidates within the emerging field of organopalladium anticancer agents.

Further studies focusing on the activity and selectivity of these complexes towards cancer cells in more complex biological systems, such as patient-derived organoids and animal models, are currently ongoing in our laboratories. These investigations aim to validate the promising *in vitro* results and to better understand the therapeutic potential and safety profile of the most active compounds. Future biological studies of these organopalladium complexes will be rendered much simpler considering their facile synthetic access. Findings on the elaboration of the aqueous ammonia protocol to other metals and on the fascinating potential of these complexes in biology will be reported shortly.

Author contributions

All authors contributed to the writing and revision of the manuscript. The final version of the manuscript has been approved by all authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

All primary data associated with this manuscript are provide in the accompanying ESI.†

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