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Pyridylic anions are soft nucleophiles in the palladium-catalyzed C(sp³)-H allylation of 4-alkylpyridines†

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We report a mild palladium-catalyzed method for the selective allylation of 4-alkylpyridines in which highly basic pyridylic anions behave as soft nucleophiles. This method exploits alkylidene dihydropyridines, which are semi-stable intermediates readily formed using a 'soft-enolization' approach, in a new mechanistic manifold for decarboxylative allylation. Notably, the catalytic generation of pyridylic anions results in a substantially broader functional group tolerance compared to other pyridine allylation methods. Experimental and theoretical mechanistic studies strongly suggest that pyridylic anions are indeed the active nucleophiles in these reactions, and that they participate in an outer-sphere reductive elimination step. This finding establishes a new p*K*_a boundary of 35 for soft nucleophiles in transition metal-catalyzed allylations.

Introduction and background

Pyridines and related aza-arenes bearing a stereogenic carbon at the heterobenzylic position are widely represented in drug candidates,^{1,2} bioactive natural products³ and agrochemicals (Fig. 1a). In pharmaceuticals, the stereogenic carbon in these compounds is often responsible for their increased target selectivity,⁴ and therefore transformations that install stereogenicity at the pyridylic position^{5,6} are highly valuable.^{7,8} Due to the high p*K*_a value of alkyl pyridines, however, methods to functionalize the pyridylic C(sp³)-H require some form of pre-activation of the pyridine ring to enable functionalization. One strategy involves coordination of the pyridine nitrogen to a Lewis acid prior to deprotonation with a stoichiometric base (Fig. 1b).⁹⁻¹³ Most of the reported methods using this strategy require superstoichiometric amounts of strong bases (*e.g.* *n*-BuLi and/or MHMDS), severely limiting the functional group content, with Sawamura's method¹¹ being a notable exception. Furthermore, these reactions are limited to 2-alkylpyridines. A second strategy requires a pre-existing carboxylate group to further activate the pyridylic C(sp³)-H bond, thus narrowing the substrate scope (Fig. 1c).¹⁴

Here we report a new mechanistic framework for C(sp³)-H allylation of pyridines, which exploits their metal-free soft-enolization¹⁵ to form alkylidene dihydropyridines¹⁶ (ADHPs) as semi-stable intermediates that are primed for a palladium-catalyzed decarboxylative allylation reaction (Fig. 1d). This approach imparts complete selectivity for 4-alkylpyridines and stands in contrast to all other methods which are either selective for 2-alkylpyridines or display no selectivity. Importantly, the use of a very mild base for the synthesis of the ADHPs and the catalytic generation of pyridylic anions in the allylation step allows the presence of a very broad range of functionality in the substrates, including enolizable and electrophilic carbonyls (*e.g.* free aldehydes) and acidic N-H groups (*e.g.* carbamates).

Reaction design and development

At the outset of this work we envisioned the mechanistic framework outlined in Scheme 1(b). Thus, treatment of ADHPs such as **1'**, readily prepared from the corresponding pyridine **1** (Scheme 1(a), see ESI† for full details), with a Pd(0) catalyst would result in ionization of the allyl group, releasing CO₂(g), a pyridylic anion and a cationic allyl-Pd(II) intermediate (**I**). Since 4-alkylpyridines have p*K*_a values¹⁷ above the currently established limit for 'soft' nucleophiles in palladium-catalyzed allylation reactions,^{12a} it seemed likely that the pyridylic anion would behave as a 'hard' nucleophile and form alkyl palladium intermediate **II**.¹⁸ Reductive elimination would give the expected allylation product **1A**.

Catalyst screening reactions were conducted using Pd(dba)₂ as the Pd(0) source and a 1 : 2 ratio of palladium to phosphine (Scheme 1(c)). Use of triphenylphosphine provided the desired

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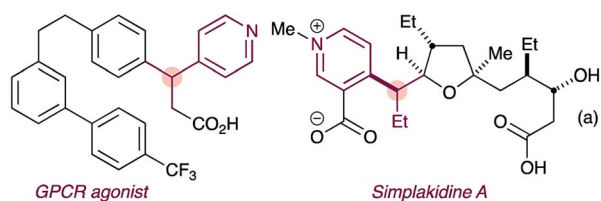
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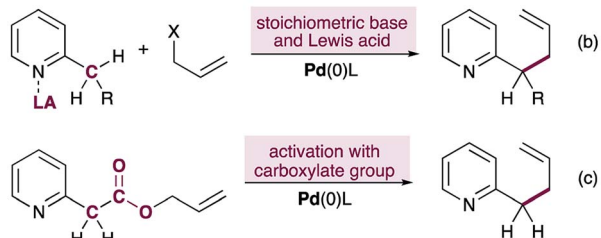
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc03304a



4-Alkylpyridines are found in synthetic and naturally occurring compounds



Existing strategies for allylation of alkyl pyridines



A mild and selective allylation of 4-alkylpyridines.

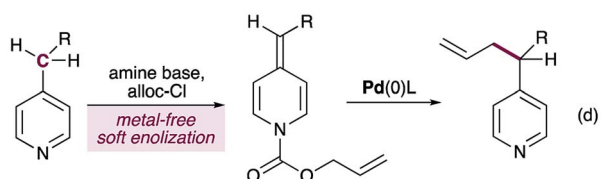
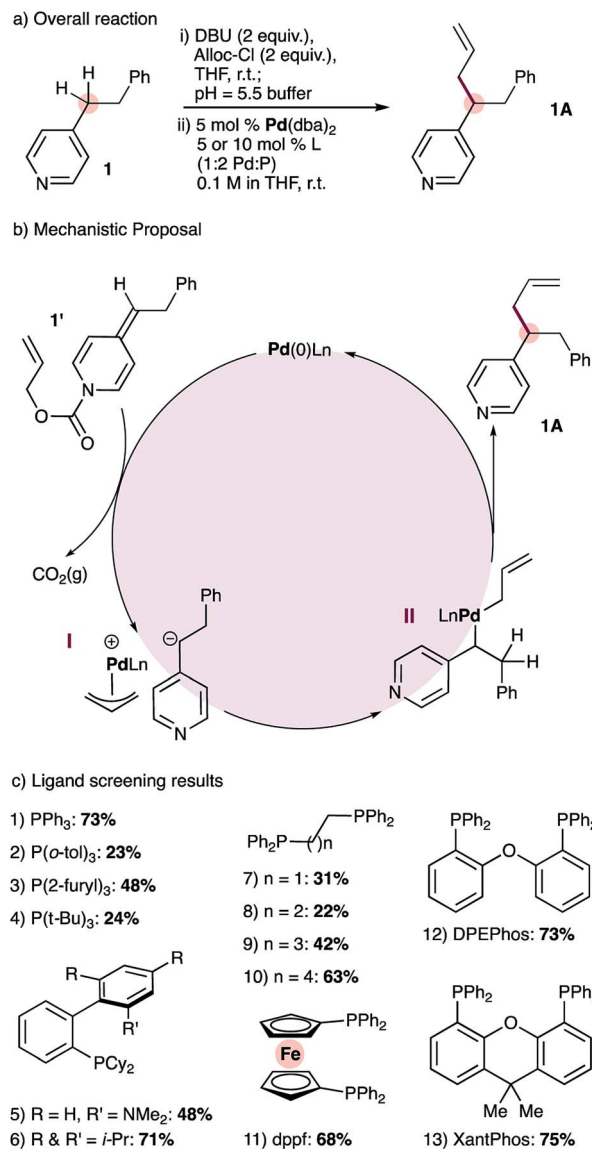


Fig. 1 4-Alkylpyridines with stereogenic pyridylic carbons are featured in synthetic and naturally occurring biologically active molecules (a). Current approaches to palladium-catalyzed C(sp³)-H allylation of alkylpyridines involve pre-activation with a Lewis acid (b) or require a pre-existing carboxylate group (c). Our new approach exploits alkylidene dihydropyridines for selective C(sp³)-H allylation of 4-alkylpyridines (d).

allylation product **1A** in 73% yield, while tri(*o*-tolyl)phosphine provided a lower yield (entries 1 & 2). More electron-rich monodentate ligands gave moderate or low yields of the allylated product (entries 3 & 4). The use of monodentate biaryl ligands (Buchwald ligands) gave the allylated product, but did not prove superior to triphenylphosphine (entries 5 and 6). Tethered alkyl diphenylphosphines with small bite angles (entries 7 & 8) gave low yields of **1A**, and the yield increases with wider bite angles (entries 9 & 10). Bidentate ligands with large bite angles (entries 11 to 13) provided consistently good results but none was significantly superior to triphenylphosphine. Nonetheless, we chose XantPhos for future reaction development reasoning that catalysts bearing bidentate ligands should display greater stability than those with monodentate ligands.

We also noted that during our ligand-screening study, reaction yields reached a plateau of 70–75% with ligands of varying structure, including triphenylphosphine, XPhos, as well as bidentate phosphines with large bite angles such as DPEPhos and XantPhos (Scheme 1c, entries 1, 6, 12 and 13 respectively). Therefore, we suspected that yield losses were a result of the mildly acidic work-up step required to remove DBU, which was used during the formation of ADHP **1'** (Scheme 1a). To mitigate this problem, we developed an alternative high-yielding method for the synthesis of ADHPs that uses triethylamine and avoids



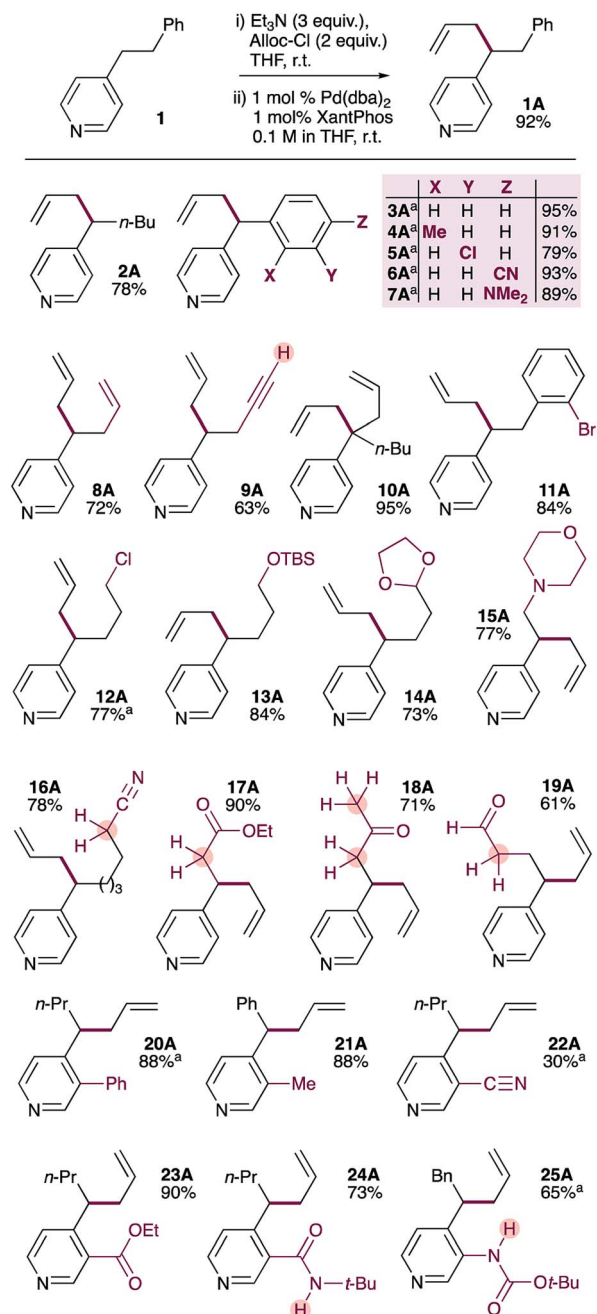
Scheme 1 Reaction development: overall reaction (a), mechanistic proposal (b) and ligand screening results (c).

aqueous work-up (Scheme 2, see ESI† for full details). With this modification, and using 1% catalyst loading, 4-phenethylpyridine could be allylated in 92% isolated yield, and therefore these conditions were adopted for substrate scope studies.

Substrate scope

We were pleased to find that the optimized conditions are suitable for a wide range of 4-substituted pyridines (Scheme 2). 4-*n*-Pentylpyridine provided the allylation product **2A** in 78% yield. Benzylpyridines bearing methyl-, chloro-, cyano- and dimethylamino-substituents on the benzene ring could also be allylated in uniformly good yields (**3A–7A**). It should be noted that 4-benzylpyridines have significantly lower pK_a values than 4-alkylpyridines (26.7 and 35 respectively)¹⁷ and very likely act as soft nucleophiles in these reactions,¹⁸ in contrast to the proposed mechanism (Scheme 1) for 4-alkylpyridines.





Scheme 2 Substrate scope of the selective palladium-catalyzed allylation of 4-alkylpyridines. ^a Pd₂dba₃·CHCl₃ used instead of Pd(dba)₂.

Substrates bearing alkenes or terminal alkynes were also tolerated, giving the corresponding products in good yields (**8A** and **9A**). It is also possible to generate products with a quaternary pyridylic carbon in excellent yield (**10A**). Interestingly, a substrate bearing an aryl bromide gives allylation product **11A** in good yield, with no evidence of oxidative addition across the C(sp²)-Br bond. Similarly, a primary alkyl chloride is well tolerated (**12A**). In contrast to other pyridine allylation methods that use Lewis acids (e.g. BF₃·OEt₂), our method tolerates acid-sensitive TBS-protected primary alcohols (**13A**) and acetal-

protected aldehydes (**14A**). Amines do not interfere with the reaction, giving the allylated product **15A** in good yield. Due to the relatively low acidity of alkylpyridines (pK_a = 35) it is common to use strong bases (e.g. *n*-Buli or MHMDS, M = Li, Na or K) alone or in combination with Lewis acid to generate pyridylic nucleophiles,^{9,10,12} which limits functional group tolerance. In contrast, our method avoids the use of aggressive reagents and tolerates the presence of functional groups with activated C-H or N-H groups with pK_a values well below 35. Indeed, pyridines bearing electrophilic functional groups with acidic α-protons, including nitriles (**16**, pK_a ~ 32), esters (**17**, pK_a ~ 30), ketones (**18**, pK_a ~ 24), and even aldehydes (**19**), are allylated in good-to-excellent yields.

It is also possible to allylate 4-alkylpyridines bearing substituents at the 3-position. 3-Phenyl-4-*n*-butyl pyridine (**20**) and 3-methyl-4-benzyl pyridine (**21**) provide allylated products in excellent yield. Substrates bearing electrophilic and strongly coordinating functional groups at the 3-position are also tolerated, and generally provide the allylated products in good yields (**22A**–**25A**). The low yield obtained with 3-cyano-4-butylpyridine (**22**) reflects its low nucleophilicity, which results in incomplete conversion to the corresponding ADHP. It is notable that the acidic N-H protons in the amide (**24**, pK_a ~ 26) and carbamate (**25**, pK_a ~ 21) groups do not interfere with the reaction.

Pyridylic selectivity

To our knowledge, all existing methods for transition metal-catalyzed pyridylic allylation are selective for the 2-pyridylic position in substrates with multiple pyridylic sites,^{9–11} or do not display positional selectivity at all,¹² unless guided by pre-existing functionality.^{13,14} Therefore, selective allylation of 4-alkylpyridines in substrates bearing multiple pyridylic positions would be a valuable synthetic advance. Our strategy for achieving selective allylation exploits the divergent behaviour of 2-, 3- and 4-alkylpyridines towards activation by chloroformate and subsequent deprotonation with mild base (Fig. 2a). 4-Alkylpyridines are readily activated by chloroformate

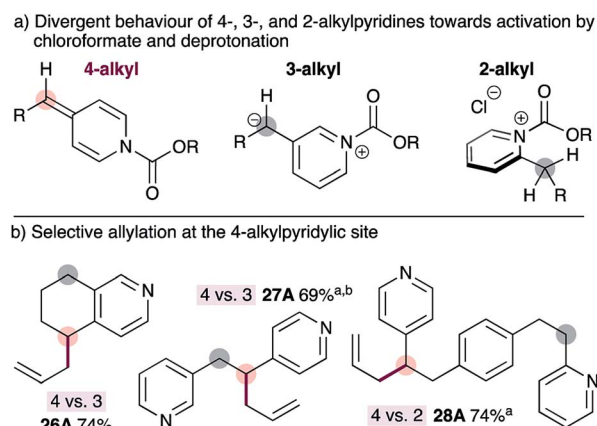
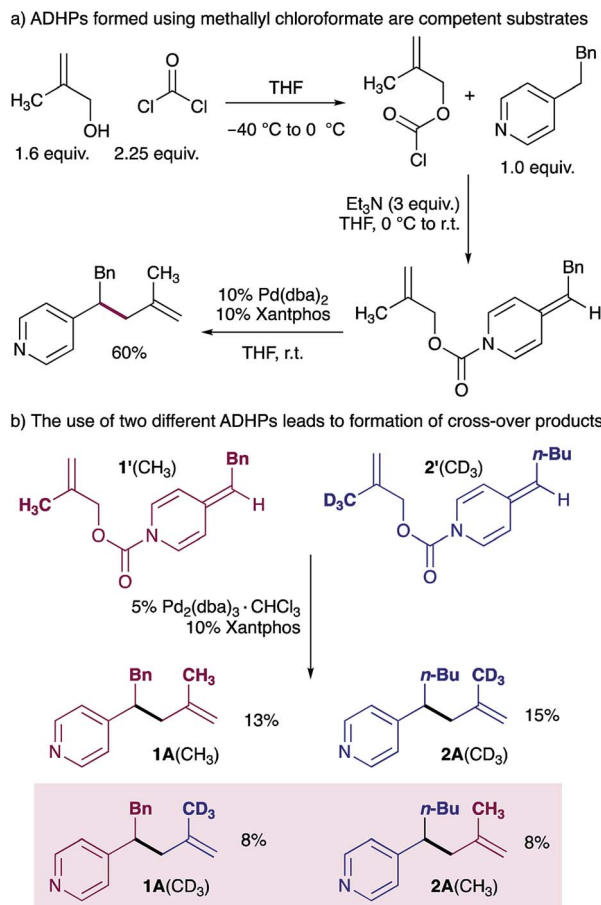


Fig. 2 Divergent reactivity of alkylpyridines towards chloroformates enables selective allylation at the 4-pyridylic position in substrates with multiple pyridylic sites. ^aPd₂dba₃·CHCl₃ used instead of Pd(dba)₂. ^bDioxane used instead of THF.

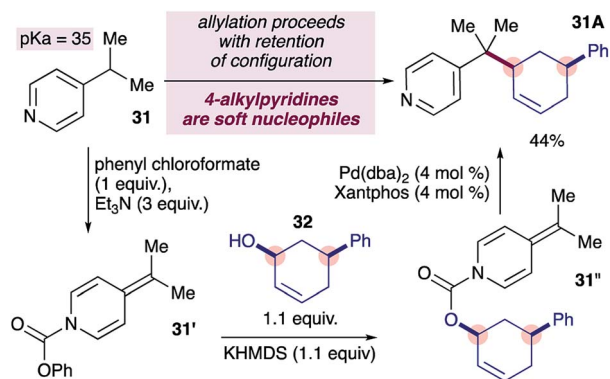




Scheme 3 Establishing the presence of ion pairs.

and ADHP 2' revealed that all four possible cross-over products are observed, supporting the participation of ion pairs. It is interesting to note that the product distribution suggests that ion separation is slow relative to reductive elimination.

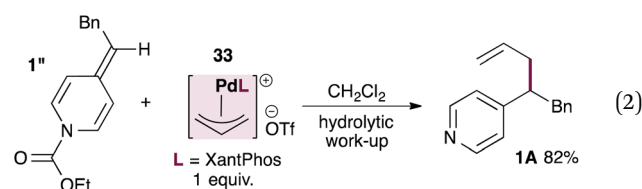
We became interested in the mode of reductive elimination in these reactions because this would inform the future development of an enantioselective variant. Following the dogma of palladium-catalyzed allylations¹⁸ and assuming fast decarboxylation, 4-alkylpyridines are expected to behave as 'hard' nucleophiles, undergoing inner-sphere reductive elimination, owing to their high pK_a values, as suggested in Scheme 1b. Recently however, it has been shown that nucleophiles with pK_a values of up to 32 can also behave as soft nucleophiles,^{12a} at least under some conditions. The pK_a range for 4-substituted pyridines spans from 26 to 35 (ref. 23) and covers the current limit of 32 for soft nucleophiles, and therefore it is of fundamental interest to determine the behaviour of 4-alkylpyridines ($pK_a = 35$ in DMSO) in transition metal-catalyzed allylations. Ideally, the stereochemical probe required (*i.e.* ADHP 31'' in Scheme 4) would be prepared from the corresponding chloroformate, however we were unable to prepare the required chloroformate cleanly (not shown) using a variety of conditions.^{24a} We therefore prepared the required probe by forming the ADHP 31' using phenylchloroformate, and substituting phenoxide with the potassium alkoxide of alcohol 32, as previously



Scheme 4 Alkylpyridines undergo outer-sphere reductive elimination with allyl electrophiles in palladium-catalyzed allylation reactions.

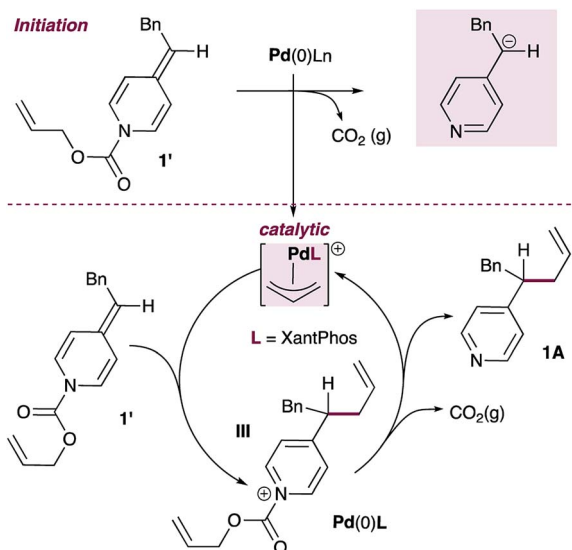
reported.^{24b,c} Subjecting stereochemical probe 31' to standard conditions provided coupled product 31A in 44% yield.²⁵ Notably, the cross-coupling product formed displayed complete retention of configuration (*i.e.* double inversion), consistent with outer-sphere reductive elimination.²⁶ This is a remarkable finding because it would establish a new pK_a boundary for soft nucleophiles in transition metal-catalyzed allylations if pyridylic anions are indeed involved, as suggested by prior experiments (*i.e.* eqn (1)).

The unexpected outcome of the stereochemical probe experiment, together with the broad functional group tolerance of this reaction, raises the possibility that ADHPs themselves could be sufficiently nucleophilic towards allylpalladium intermediates. To test this hypothesis we prepared the known, cationic XantPhos-stabilized allylpalladium(II) complex²⁷ and subjected it to a stoichiometric reaction with ADHP 1'' prepared using ethyl chloroformate and therefore unable to react with palladium (eqn (2)). Interestingly, this reaction provided the allylated product in 82% yield after hydrolytic work-up. It is worth noting however, that the allylpalladium complex proved insoluble in THF (which is the standard solvent) and therefore the reaction was conducted in DCM. Furthermore, the rate of this reaction is significantly slower than that of the parent reaction despite the fact that it is stoichiometric in palladium.



Given this finding, a different mechanism that accounts for the broad functional group tolerance observed can be proposed (Scheme 5). Under standard conditions, the Pd(0)L catalyst would undergo oxidative addition to ADHP 1' to generate a cationic allylpalladium(II) intermediate and a pyridylic anion (inset). The allylpalladium complex could then be attacked by a second ADHP to generate a pyridinium intermediate (III) and a Pd(0)L catalyst. These two partners would combine to



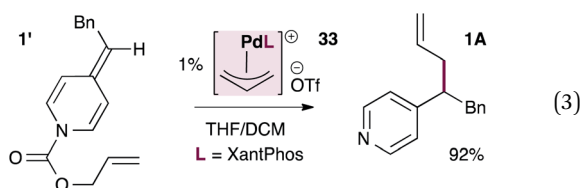


Scheme 5 An alternative mechanistic proposal with ADHPs as active nucleophiles in palladium-catalyzed pyridylic allylation.

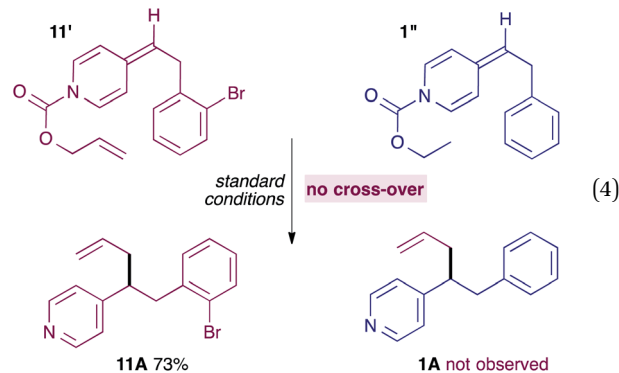
regenerate the cationic allylpalladium(II) intermediate and release allylated product **1A**.

The viability of this proposal is predicated on (i) the cationic allylpalladium complex acting as a competent catalyst in the allylation reaction, and (ii) ADHPs outcompeting pyridylic anions in the nucleophilic addition to the allylpalladium(II) intermediate. A liability in this proposal is that the fate of the pyridylic anion remains unclear.

As shown in eqn (3), the XantPhos-stabilized allylpalladium(II) complex is indeed catalytically active in these reactions, providing the allylated product in 92% isolated yield, lending some support to the mechanism in Scheme 5.



It seemed unlikely however, that a neutral ADHP would be more nucleophilic than a pyridylic anion, casting doubt on the proposal in Scheme 5. Previous experiments have shown that ADHPs prepared from allyl chloroformate generate solvent separated ion pairs and give cross-over products under standard conditions (see Scheme 3). Therefore, it is possible to test the ability of an ADHP to outcompete pyridylic anions by subjecting ADHP **11'** to standard reaction conditions and in the presence of an equal amount of ADHP **1''**, which is prepared using *ethyl* chloroformate and therefore unable to generate allylpalladium(II) intermediates itself (eqn (4)). Not surprisingly, this reaction only yields the expected allylation product **11A**, along with the unreacted ADHP **1'**, and with no evidence of allylated pyridine **1A**. This strongly suggests that ADHPs are not competent nucleophiles in the presence of pyridylic anions.



Finally, we conducted a head-to-head comparison of the allylation reaction of ADHP **1'**, using the standard catalytic system (*i.e.* 1% Pd(0) and XantPhos) and the allylpalladium(II) complex **33** (Fig. 4). The relative rates of these reactions were compared by monitoring the disappearance of the substrate and appearance of the product using NMR signal of the indicated protons. In both cases the reactions are high yielding, however it is clear that the reaction under standard conditions, likely proceeding through generation of pyridylic anions as nucleophiles, occurs at a significantly faster rate than that using complex **33**, in which neutral ADHPs act as nucleophiles. This indicates that the rate of nucleophilic attack on an allylpalladium complex by a pyridylic anion is significantly faster than the rate of attack by a neutral ADHP,²⁸ making the catalytic cycle proposed in Scheme 5 highly unlikely.

Computational study

While our experimental mechanistic probes provided some insight into the mechanism and allowed us to exclude some possibilities, they did not allow us to firmly establish the nature of the nucleophile in these reactions. In view of seemingly

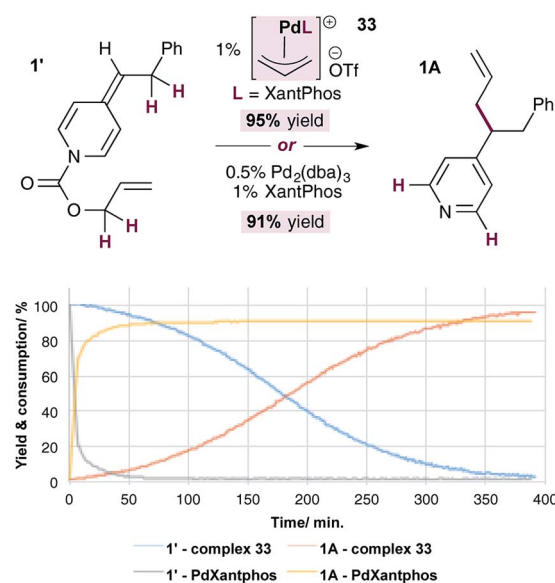
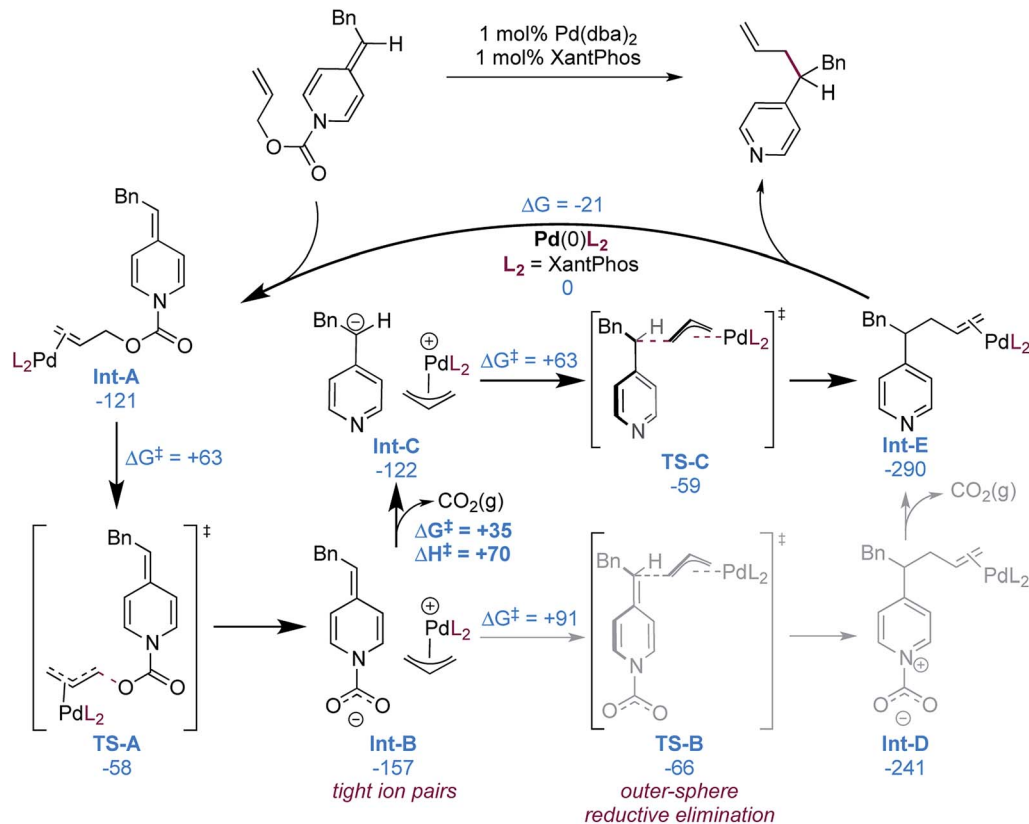


Fig. 4 Comparison of the rate of pyridylic allylation using standard conditions (Pd(0) and XantPhos) and cationic complex **33**.

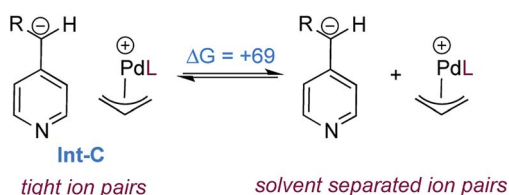




Scheme 6 Computationally supported catalytic cycle (free energies in kJ mol^{-1}), most probable pathway illustrated in bold.

conflicting data, specifically the wide substrate scope (particularly acidic functional groups, Scheme 2) and catalyst decomposition (suggesting a strongly basic intermediate, eqn (1)), it remained unclear if a free pyridylic anion or a carboxylate-stabilized pyridylic anion is involved. To gain a better understanding of the mechanism, we therefore performed a computational investigation using DFT (M06-D3/6-311++G(d,p) + SDD(Pd)//wB97XD/6-311+G(d,p) + SDD(Pd))²⁹ using substrate 1, as it is a typical and high-yielding example. The mechanistic possibilities supported by the calculations are illustrated in Scheme 6.

As expected, formation of the catalyst–substrate complex (**Int-A**) is found to be exergonic. At this point, oxidative addition occurs (**TS-A**) and leads to the formation of the cationic allylpalladium(II) complex and a carboxylate-stabilized pyridylic anion. The proximity of the charges is significantly stabilizing



Scheme 7 Dissociation of the ion pair **Int-C** (free energies in kJ mol^{-1}).

and thus the two species form the tight ion pair **Int-B**, the separation being endergonic (Scheme 7).

This ion pair (**Int-B**) can undergo outer-sphere allylation *via* **TS-B** with a free energy barrier of 91 kJ mol^{-1} . Calculation of an inner-sphere transition state resulted in an even higher free energy barrier of 126 kJ mol^{-1} (see ESI†). It is thus not involved in the mechanism, in line with the experimental observations (Scheme 4). The allylation product **Int-D** can then undergo exergonic decarboxylation to form the final product.

An alternative mechanistic pathway can be envisioned, where **Int-B** decarboxylates prior to addition, to form the ion pair **Int-C**. This new intermediate was also found to undergo preferentially the allylation *via* an outer-sphere mechanism (**TS-C**). The calculations suggest that the decarboxylation is endergonic, with a computed free energy cost of 35 kJ mol^{-1} . However, no decarboxylation transition structure could be found by performing relaxed scan of the elongation of the N-CO_2^- bond length, suggesting a fast process. To estimate the upper activation barrier of decarboxylation, we computed the enthalpy of the process, which was found to be $+70 \text{ kJ mol}^{-1}$. The actual free energy barrier should then be between $+35$ and $+70 \text{ kJ mol}^{-1}$, which is lower than the activation barrier from **Int-B** to **TS-B** in the previously discussed mechanistic alternative (see above).

We also calculated the free energy to convert the tight ion pair **Int-C** to its solvent separated ion pair (Scheme 7). While endergonic, the cost of dissociation is close in energy to the



allylation step (+69 vs. +63 kJ mol⁻¹). This would enable possible kinetic competition between ion exchange and allylation, but the kinetic preference for allylation would result in the non-crossover products as the major components in the mixture. This is consistent with the product distribution observed in the cross-over experiment (Scheme 3b). Finally the product to substrate exchange on the Pd(0) catalyst was found to be exergonic, hence no product inhibition is expected to be observed.

Discussion

The original mechanistic proposal for this study (Scheme 1b) invoked the formation of strongly basic pyridylic anions. Consistent with the widely accepted behaviour of strongly basic anions in transition metal-catalyzed allylation reactions, this proposal also invoked an inner sphere reductive elimination event. The wide functional group tolerance of this reaction seemed at odds with the presence of a strongly basic anion and prompted us to study the mechanism in some detail. Furthermore, the recent finding that substrates with pK_a values as high as 32 act as soft nucleophiles in transition metal-catalyzed allylation reactions, coupled with the fact 4-alkylpyridines have pK_a values that are not significantly higher, also raised questions about the reductive elimination step in this reaction.

The results of our mechanistic probe experiments together with a theoretical treatment support a mechanism that proceeds *via* catalyst coordination to substrate (Scheme 6) and oxidative addition, resulting in an ion pair consisting of carboxylate-stabilized pyridylic anion and a cationic allylpalladium(II) intermediate (**Int-A** to **Int-B** *via* **TS-A**). Two mechanistic pathways were identified from **Int-B**, one involving pre-decarboxylative allylation (**Int-B** to **Int-E** *via* **TS-B** and **Int-D**), and the other proceeding *via* decarboxylation followed by allylation (**Int-B** to **Int-E** *via* **Int-C** and **TS-C**). Our calculations show that both mechanistic pathways are reasonable, with **TS-B** being lower in energy than **TS-C**, and decarboxylation having a lower energy barrier than either **TS-B** and **TS-C**. Assuming reversible decarboxylation, these computations would suggest a Curtin-Hammett regime, with the reaction proceeding *via* **TS-B**. Alternatively, if decarboxylation is irreversible, then the reaction must proceed through **TS-C**. Thus, the preferred mechanism hinges the reversibility of decarboxylation.

There remains some debate regarding the reversibility of decarboxylation processes. For example, it has been suggested that slow separation of the carbanion and CO₂(g) is the key factor responsible for reversibility.³⁰ However, using calculations and experimental kinetic isotope effects it has been shown that there is no significant reversibility in simple decarboxylations.³¹ Recently it was also shown that decarboxylation of the potassium salt of 4-pyridylic acetic acid in DMF solution, generating a 4-pyridylic anion, is reversible under a CO₂(g) atmosphere.³² Further, exchange of CO₂(g) and ¹³CO₂(g) directly demonstrates that CO₂(g) diffuses away from the anion, countering the notion that separation of a carbanion and CO₂(g) is limiting.

In view of the relatively low calculated barrier to decarboxylation (**Int-B** to **Int-C**), insignificant reversibility of decarboxylation of pyridylacetic acids³¹ as well as evidence for diffusion of CO₂(g) from pyridylic anions,³² and the suggested presence of strongly basic anions in our reaction (eqn (1)) we favour the mechanistic pathway in which decarboxylation occurs prior to allylation (shown in bold in Scheme 6). If correct, this mechanism is notable because it would implicate highly basic pyridylic anions as reactive intermediates in the presence of other reactive functional groups. Palladium-catalyzed cross-coupling reactions of highly basic and nucleophilic reagents in the presence of electrophilic functional groups are known,³³ and can be synthetically useful if the rate of transmetalation to palladium is faster than the rate of addition to the electrophilic site.³⁴ In our case, the concentration of the pyridylic anion is low throughout the reaction because it is catalytically generated, the decarboxylation is predicted to be endergonic, and ion separation is disfavoured (Scheme 7). Thus, the observed functional group tolerance is likely a reflection of a fast rate of allylation relative to the reaction of the pyridylic anion with an electrophilic or acidic function. It is possible, however, that the reaction proceeds through allylation prior to decarboxylation (**Int-B** to **Int-D** *via* **TS-B**). This mechanistic alternative could be supported by observing **Int-D**, which we will investigate in future studies. Irrespective of the precise mechanism, our work shows that anions derived from 4-alkylpyridines (pK_a = 35 in DMSO) behave as soft nucleophiles towards allylpalladium intermediates. This study therefore suggests a new pK_a limit for soft nucleophiles in transition metal-catalyzed allylation reactions.

Conclusions

We have developed a practical, mild and selective palladium-catalyzed method for the allylation of 4-alkylpyridines. This method exploits the conversion of 4-alkylpyridines to alkylidene dihydropyridines (ADHPs) under metal-free soft enolization conditions using inexpensive and broadly available reagents. The strategic use of ADHPs as semi-stable substrates provides a new entry into transition metal-catalyzed allylation reactions of pyridines, which complements all known methods in terms of positional selectivity. This reaction tolerates a very broad range of functional groups in the substrates, including electrophilic groups and acidic protons, which is notable given the low acidity of alkylpyridines. In addition, the reaction allows allylation at the 4-alkyl pyridylic position in substrates bearing multiple pyridylic sites. Experimental and computational mechanistic studies revealed that catalytically generated pyridylic anions are the likely nucleophiles in these reactions and that reductive elimination proceeds through an outer-sphere mechanism. Together, these findings are of fundamental importance, suggesting a new pK_a limit of 35 for soft nucleophiles in transition metal-catalyzed allylation reactions.

Conflicts of interest

There are no conflicts to declare.



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