Synthetic Methods

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# Palladium-Catalyzed C–H Activation of N-Allyl Imines: Regioselective Allylic Alkylations to Deliver Substituted Aza-1,3-Dienes**

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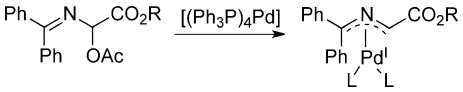
***Abstract:*** *A new mode of activation of an imine via a rare aza-substituted π-allyl complex is described. Palladium-catalyzed C(sp³)–H activation of the N-allyl imine and the subsequent nucleophilic attack by the α-alkyl cyanoester produced the 1-aza-1,3-diene as the sole regioisomer. In contrast, nucleophilic attack by the α-aryl cyanoester exclusively delivered the 2-aza-1,3-diene, which was employed in an inverse-electron-demand Diels–Alder reaction for heterobiaryl synthesis.*

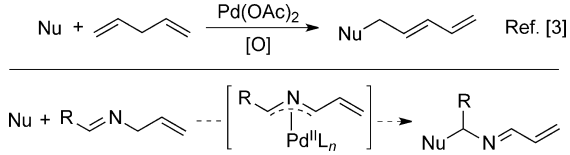
The use of π-allyl palladium chemistry for C–C bond formation plays an ever-increasingly important role in organic synthesis.[1] In this context, the direct C(sp³)–H activation for the generation of a π-allyl complex has gained more and more attention in recent years.[2,3] The importance of nitrogen-containing compounds[4] raises the question of accessibility of the aza analogue of the all-carbon π-allyl complex. To our knowledge, only one report of such a system has appeared involving an acetoxy glycine imine as a substrate which generates a 2-aza π-allyl palladium intermediate [Eq. (1)].[5]




(1)

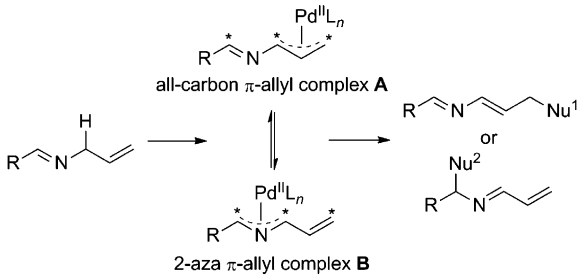
Indeed, the requirement of a hemiaminal as a precursor limits exploring such chemistry. Our recent interest in generating π-allyl palladium intermediates in allylic alkylation sequences by C(sp³)–H activation[3] led us to consider use of the readily available simple N-allyl imines as the aza-π-allyl precursors (Scheme 1). Herein, we report the first example of an aza-π-allylpalladium intermediate in an oxidative allylic alkylation.

The first question to address was the compatibility of N-allyl imines under palladium-catalyzed oxidative C–H activation conditions. A concern was the susceptibility of such a nitrogen atom towards oxidation to the nitrone with further




***Scheme 1.*** Palladium-catalyzed allylic alkylation by direct C(sp³)–H activation.

decomposition. Secondly, the anticipated C–H activation would produce a π-allyl palladium intermediate which could equilibrate between an all-carbon π-allyl and a 2-aza π-allyl intermediate (**A** and **B**, respectively; Scheme 2). Several electrophilic centers (marked with an *) would be generated




***Scheme 2.*** Generation of π-allyl complexes by oxidative C–H activation and possible outcomes from nucleophilic attacks.

during this process. Taking both the electronic and steric factors into consideration, the two termini of the π-allyl complexes are most prone to nucleophilic addition. Attack of a nucleophile on the imine terminus would generate an 1-aza-1,3-diene. Alternatively, if the incoming nucleophile approached the allyl terminus a 2-aza-1,3-diene would be produced. The π-allyl complexes **A** and **B** have not been available previously. If the reaction progresses through intermediate **B**, it would be an unprecedented generation of a 2-aza π-allyl complex by direct C–H activation.[6] Instead, if the reaction proceeds through **A**, it would be an unprecedented electrophilic activation of an imine by a π-allyl palladium moiety. This method would allow probing the reactivity of such nitrogen-containing systems.

Addition of an ester nucleophile to an electrophilic imine equivalent is an important class of chemical transformations as it can readily produce biologically relevant β-amino esters.[7] The α-methyl cyanoester **2** was chosen as a pronucleophile (Scheme 3).[8] *N*-benzylbenzylideneimine, *N*-allylbenzylideneimine (**1**), and *N*-propargylbenzylideneimine

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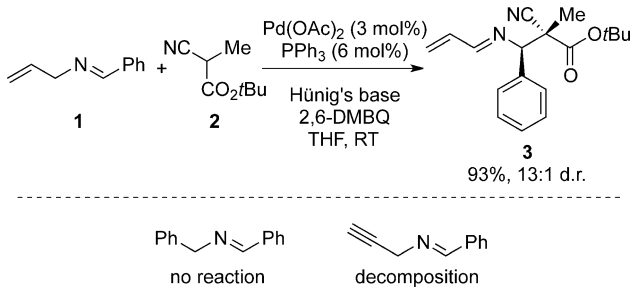
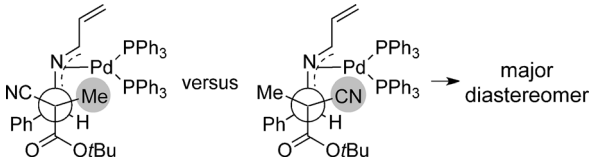


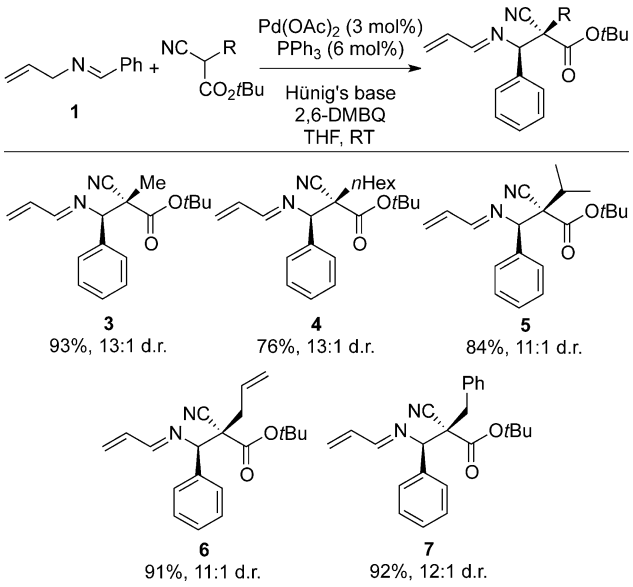

***Scheme 3.*** Preparation of α-cyano β-amino esters by C–H activation of *N*-allylbenzylideneimine. 2,6-DMBQ = 2,6-dimethylbenzoquinone, THF = tetrahydrofuran.

were considered as possible electrophilic imine sources. Interestingly, while *N*-benzylbenzylideneimine remained inert and *N*-propargylbenzylideneimine suffered decomposition under catalytic oxidative conditions, *N*-allylbenzylideneimine (**1**) furnished the 1-aza-1,3- diene **3** in excellent yield (93%) and with good diastereoselectivity (13:1 d.r.). The reaction proceeded in a completely regioselective manner with a high level of *E*/*Z* selectivity and the 2-aza-1,3-diene was not observed. 2,6-DMBQ was found to be the optimal oxidant and the amount of catalyst loading was reduced to 3 mol%. This outcome suggests that the reaction might progress through the aza π-allyl complex **B**.[9] Studies on the regioselectivity of nucleophilic addition on a conjugated π-allyl complex revealed that product distribution is dominated by $S_N2$ attack over $S_N2'$.[10] Additionally, considering the azaphilicity of the palladium metal, we propose that the allylic alkylation might advance via **B**. The observed diastereoselectivity originates from the minimization of the steric interactions between ligated palladium and substituents on the cyanoester.




From a practical point of view, while different N-protected imines usually require multistep preparation with an expensive protecting/activating moiety, N-allyl imines are readily prepared in a single step from the corresponding aldehyde and commercially available, cheap allyl amine. The inherent diastereoselectivity for which there is no precedent is an advantage for this method.[8] For a comparison, the same nucleophile, **2**, was subjected to a traditional Lewis acid catalyzed addition of *N*-Boc-phenylimine and the addition adduct (not shown here) was obtained with no preference in diastereoselectivity.[11]

We investigated the substrate scope for α-alkyl cyanoester nucleophiles (Scheme 4), all of which gave the allylic alkylation products in good yields and selectivity. For these examples, the reaction time varies from 12–18 hours.

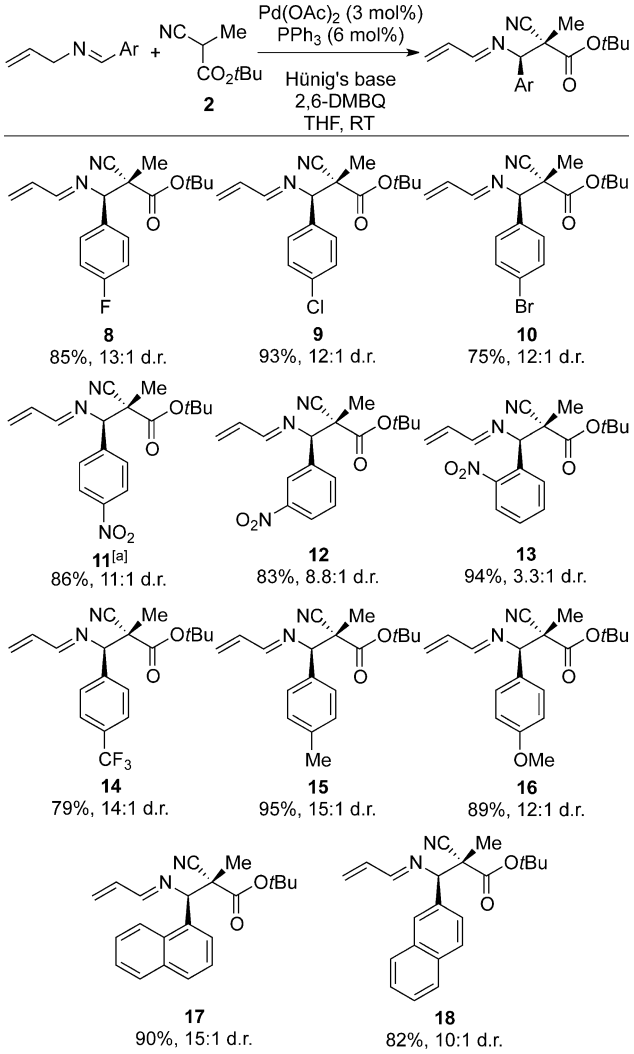



***Scheme 4.*** Substrate scope with respect to the nucleophile. Reactions were performed in THF (0.2 M) in the presence of $Pd(OAc)_2$ (3 mol%) and $PPh_3$ (6 mol%). The diastereoselectivity was determined by $^1$H NMR spectroscopy of the crude reaction mixture. The yields are of those of the isolated products.

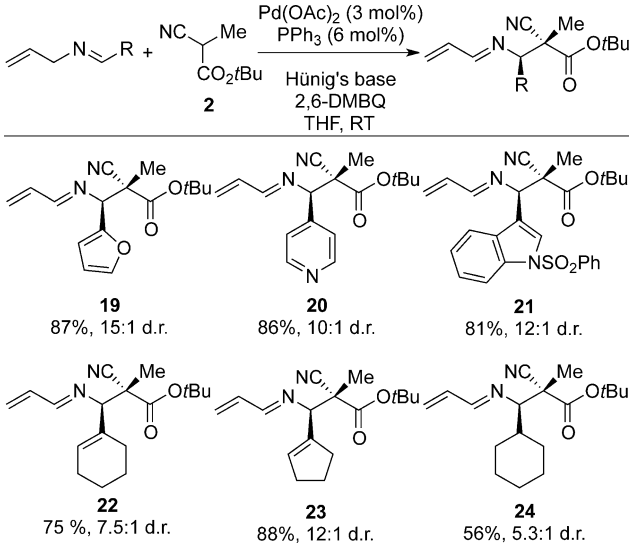
A wide selection of N-allylarylidene imines was subjected to the oxidative allylic alkylation conditions (Scheme 5) to give the adducts **8**–**18** within 10–18 hours. Electron-withdrawing aryl imines, even those bearing strong electron-withdrawing substituents cleanly furnished the corresponding β-amino esters (**8**–**14**) in good yields and diastereoselectivities. The position of the substituent on the aryl ring appeared to influence the diastereomeric ratios. The diastereoselectivity diminished when moving the substituents from the *para* to *meta* to *ortho* position (**11**–**13**). An electron-donating substituent (e.g., OMe) on the aryl system proved effective as well, thus yielding **16** in 89% yield. Both the 1-naphthyl and 2-naphthyl substituents on the imines performed equally efficiently (**17** and **18**, respectively) in spite of the steric crowding of the 1-naphthyl case. Curiously, better diastereoselectivity was observed for the 1-naphthyl variant (15:1 versus 10:1). The relative stereochemistry of the addition adducts was confirmed by an X-ray crystal structure of **11**.

We further extended this methodology to heteroaromatic and non-aromatic imines (Scheme 6). To our delight, electron-donating (e.g., furan) as well as electron-withdrawing (e.g., pyridine) heteroaromatic systems performed in a similar fashion. Cyclohexenyl as well as cyclopentenyl systems reacted to furnish the alkylation adducts (**22** and **23**), although with a slightly diminished selectivity for the cyclohexenyl derivative (7.5:1 versus 12:1 d.r.). Gratifyingly, oxidative allylic alkylation on the less electrophilic N-allyl alkylidene imine was effective and the adduct **24** was obtained in moderate yield and stereoselectivity. For these examples, the reaction times varied from 15–18 hours except for the formation of **24**. This substrate required a longer reaction time (60 h), presumably because of the slower rate of the C–H abstraction.

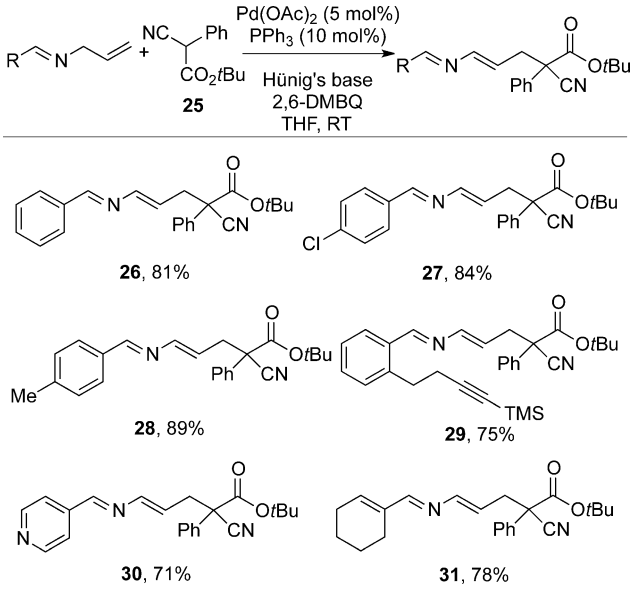
  




***Scheme 5.*** Substrate scope for electrophile. Reactions were performed in THF (0.2 M) in the presence of $Pd(OAc)_2$ (3 mol%) and $PPh_3$ (6 mol%). The diastereoselectivity was determined by $^1H$ NMR spectroscopy of the crude reaction mixture. The yields are those of the isolated products. [a] Compound **11** was characterized by X-ray crystallography.



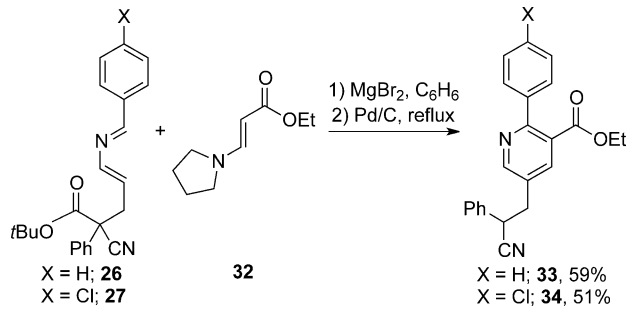

***Scheme 6.*** Extension of the substrate scope to heteroaromatic and nonaromatic systems. Reactions were performed in THF (0.2 M) in the presence of $Pd(OAc)_2$ (3 mol%) and $PPh_3$ (6 mol%). The diastereoselectivity was determined by $^1H$ NMR spectroscopy of the crude reaction mixture. The yields are those of the isolated products.




***Scheme 7.*** Preparation of 2-aza-1,3-dienes by oxidative allylic alkylation of N-allyl imines. Reactions were performed in THF (0.2 M) in the presence of $Pd(OAc)_2$ (5 mol%) and $PPh_3$ (10 mol%). The yields are those of the isolated products.

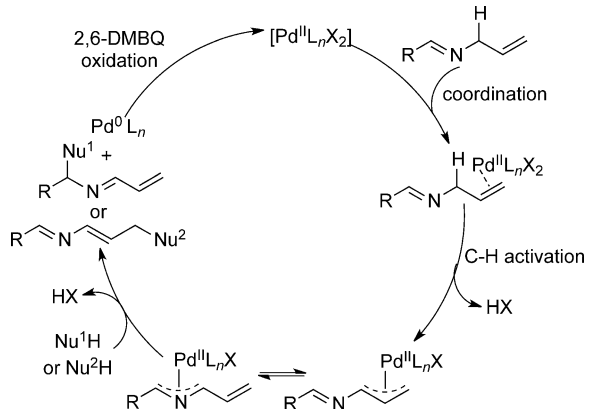
Can the reaction proceed through the alternate all-carbon π-allyl complex **A** to generate the thermodynamically more stable 2-aza-1,3-diene? 2-Aza-1,3-dienes are viable precursors for the hetero Diels–Alder reaction and can quickly assemble nitrogen-containing heterocycles.[12] Gratifyingly, the choice of the nucleophile allowed access to 2-aza-1,3-dienes as the sole regioisomer in the allylic alkylation. We reasoned that a bulkier and more stabilized carbanion, such as that from an α-aryl cyanoester, would prefer the formation of the 2-aza-diene. To our delight, the α-phenyl cyanoester **25** underwent smooth alkylation with **1** under oxidative conditions to deliver the 2-aza-1,3-diene **26** with complete regioselectivity (Scheme 7). Significantly longer reaction times (48–65 h) were required, thus suggesting that the nucleophilic addition has become the rate-determining step because of the lower reactivity of the more stabilized nucleophile. Electron-withdrawing as well as electron-donating aryl imines proved effective for the oxidative allylic alkylation. An alkyl substitution at the *ortho* position of the aryl ring as well as heteroaryl imine (pyridyl) performed efficiently. N-allyl alkenylidene imine was also found to be a good substrate for the oxidative alkylation reaction, thus generating the 3-aza-triene **31** in good yield (78%). The electron-deficient 2-aza-1,3-dienes were subjected to the inverse-electron-demand Diels–Alder reaction with the enamine **32**. A one-pot $MgBr_2$-promoted [4+2] cycloaddition




followed by Pd/C-mediated oxidation furnished the heterobiaryl systems (**33** and **34**) in 59 and 51% yields as single regioisomers. The *tert*-butyl ester removal and subsequent decarboxylation were observed under the reaction conditions.

A plausible catalytic cycle is outlined in Scheme 8. We propose that the initiation step involves coordination of $Pd^{II}$ to the allyl double bond rather than to the imine double bond. The failure of *N*-benzylbenzylideneimine and *N*-propargylbenzylideneimine to participate in the allylic alkylation supports this proposal. Then, the palladium(II)-mediated




***Scheme 8.*** Plausible catalytic cycle.

allylic C–H activation produces an all-carbon π-allyl complex which remains in equilibrium with the 2-aza π-allyl complex.[9] Subsequent nucleophilic attack reduces the catalyst to $Pd^0$ and releases the aza-1,3-diene products upon decomplexation. Finally, DMBQ-mediated oxidation regenerates the $Pd^{II}$ for the next catalytic cycle.

In summary, we have established an unprecedented selective palladium-catalyzed C($sp^3$)–H activation in lieu of alternative modes of oxidation of N-allyl imines. This selectivity may arise from coordination of the double bond to $Pd^{II}$, thus facilitating C–H insertion compared to other oxidative pathways. Support for this contention appears from the unique success of the N-allyl substrates compared to either N-benzyl or N-propargyl substrates. When α-alkyl cyanoester was employed as the nucleophile, biologically relevant β-amino esters were isolated with complete regioselectivity. The substrate scope was extended from arylidene imines to various alkenylidene and alkylidene imines. A complete reversal of regioselectivity was observed when a more stabilized and sterically more demanding α-aryl cyanoester was used as the nucleophile, and the 2-aza-1,3-dienes were obtained as the exclusive regioisomers. Oxidative C($sp^3$)–H activation of the N-allyl imine combined with two different nucleophilic addition modes promise further development of cost-effective preparation of amines and 2-aza-1,3-dienes. Expansion of this methodology to a wider variety of nucleophiles is currently underway and will be reported in due course, but preliminary results look promising.[13]

**Keywords:** allylic compounds · C–H activation · heterocycles · palladium · synthetic methods

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