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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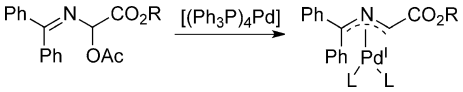
Abstract: *A new mode of activation of an imine via a rare aza-substituted π-allyl complex is described. Palladium-catalyzed C(sp³)–H activation of the N-allyl imine and the subsequent nucleophilic attack by the α-alkyl cyanoester produced the 1-aza-1,3-diene as the sole regioisomer. In contrast, nucleophilic 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.*

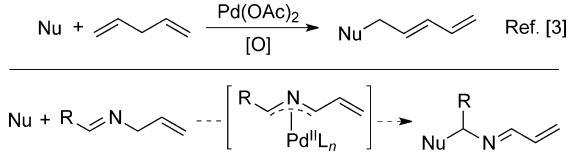
The use of π-allyl palladium chemistry for C–C bond formation plays an ever-increasingly important role in organic synthesis.[1] In this context, the direct C(sp³)–H activation for the generation of a π-allyl complex has gained more and more attention in recent years.[2,3] The importance of nitrogen-containing 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)

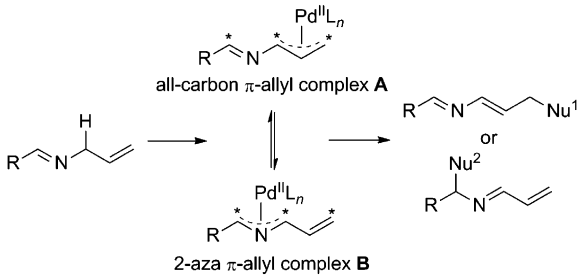
Indeed, the requirement of a hemiaminal as a precursor limits exploring such chemistry. Our recent interest in generating π-allyl palladium intermediates in allylic alkylation sequences by C(sp³)–H activation[3] led us to consider use of the readily available simple N-allyl imines as the aza-π-allyl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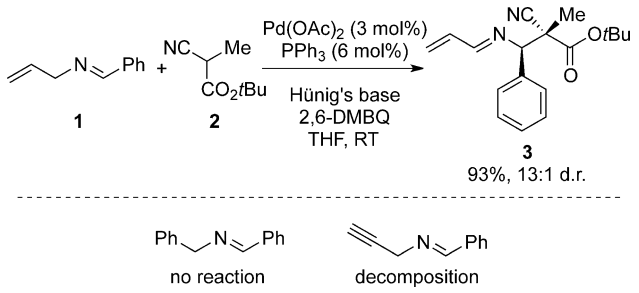
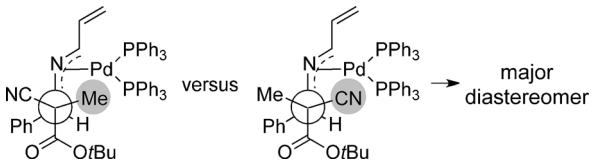


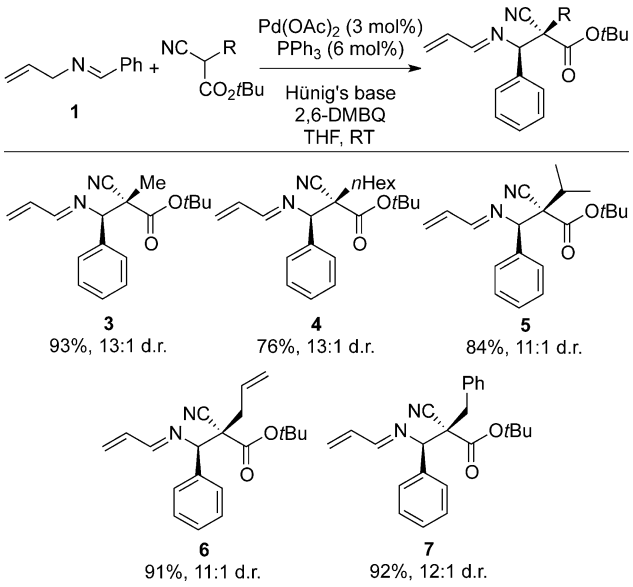
Scheme 3. Preparation of α-cyano β-amino esters by C–H activation of *N*-allylbenzylideneimine. 2,6-DMBQ = 2,6-dimethylbenzoquinone, THF = tetrahydrofuran.

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]

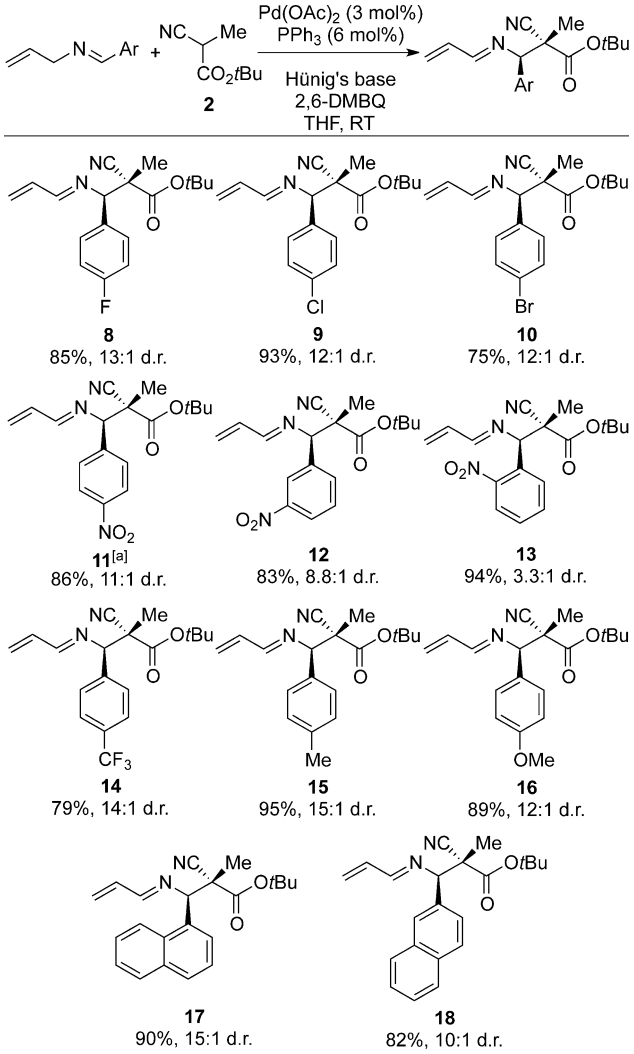
We investigated the substrate scope for α-alkyl cyanoester nucleophiles (Scheme 4), all of which gave the allylic alkylation products in good yields and selectivity. For these examples, the reaction time varies from 12–18 hours.



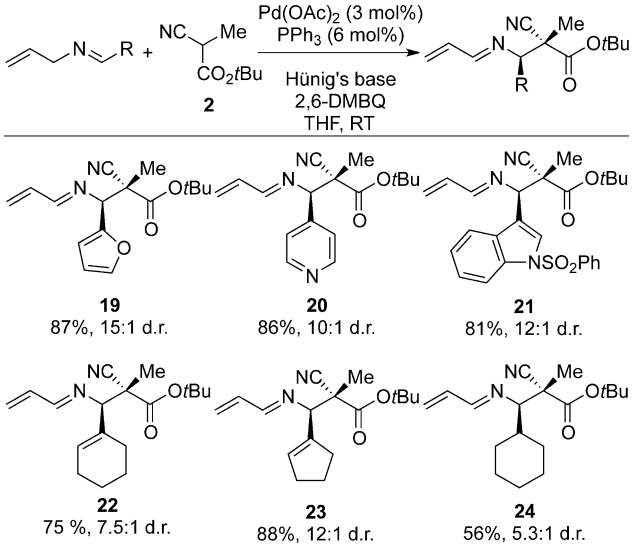
Scheme 4. Substrate scope with respect to the nucleophile. Reactions were performed in THF (0.2 M) in the presence of $Pd(OAc)_2$ (3 mol%) and PPh_3 (6 mol%). The diastereoselectivity was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The yields are of those of the isolated products.

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**.

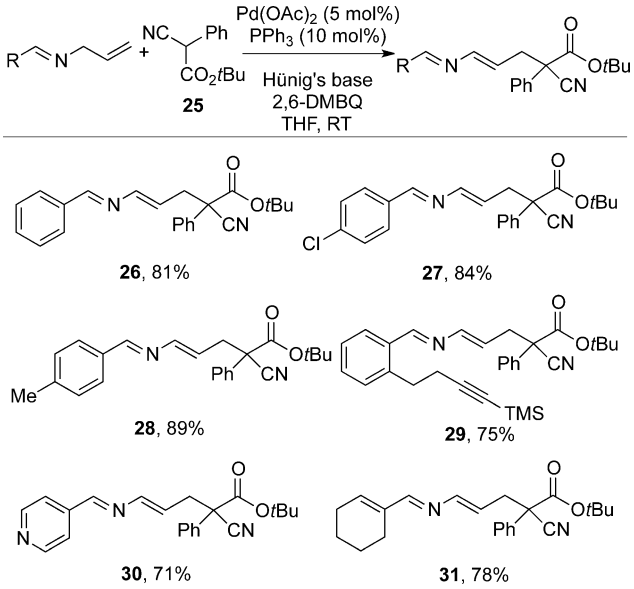
We further extended this methodology to heteroaromatic and non-aromatic imines (Scheme 6). To our delight, electron-donating (e.g., furan) as well as electron-withdrawing (e.g., pyridine) heteroaromatic systems performed in a similar fashion. Cyclohexenyl as well as cyclopentenyl systems reacted to furnish 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.

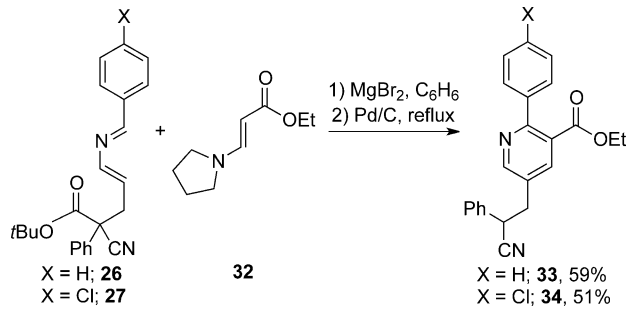


Scheme 6. Extension of the substrate scope to heteroaromatic and nonaromatic systems. Reactions were performed in THF (0.2 M) in the presence of $Pd(OAc)_2$ (3 mol%) and PPh_3 (6 mol%). The diastereoselectivity was determined by ^1H NMR spectroscopy of the crude reaction mixture. The yields are those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



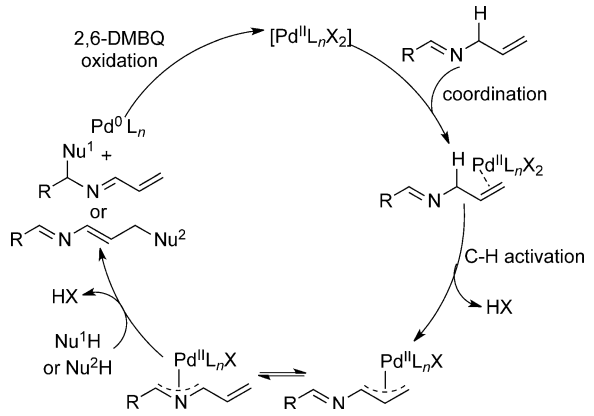
Scheme 7. Preparation of 2-aza-1,3-dienes by oxidative allylic alkylation of N-allyl imines. Reactions were performed in THF (0.2 M) in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%). The yields are those of the isolated products.

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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