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Palladium-catalyzed regioselective azidation of allylic C–H bonds under atmospheric pressure of dioxygen†

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A palladium-catalyzed allylic azidation of alkenes with sodium azide under atmospheric pressure of dioxygen was developed. This methodology provides a new efficient and simple route for accessing allylic azides. Furthermore, the one-pot process consisting of Pd-catalyzed allylic azidation of alkenes and Cu-catalyzed 1,3-dipolar cycloaddition led directly to the 1,2,3-triazole from the alkene. The formed allylic azide can be also *in situ* reduced to the allylic amine or oxidized to the alkenyl nitrile.

The selective transformations of C–H bonds have been significantly developed and have played vital roles in organic synthesis.[1] Recently, palladium-catalyzed direct functionalization of allylic C–H bonds leading to oxygenation,[2] alkylation,[3] amination,[4] carbonylation,[5] silylation[6] or dehydrogenation[7] is a valuable complement to the well-known Trost–Tsuji reaction. The new procedure shows that unnecessary functional group manipulations (FGMs) can be bypassed which presents a highly efficient approach for the synthesis of functionalized olefins, thereby reducing synthetic steps and increasing the overall yield.

Azides are typically prepared from the substitution of organic halides with sodium azide, but this approach requires the prior synthesis of the organic halides.[8] Recently, the groups of Carreira, Barluenga and Jiao have independently developed novel and elegant methods for the synthesis of organic azides while avoiding the use of halides.[9–11] In connection with our previous research,[2n,5] we reasoned that use of the azide anion as a nucleophile would provide straightforward access to diverse allylic azides by the palladium-catalyzed regioselective azidation of alkenes, which would provide a new allylic azidation in synthetic methodologies and palladium chemistry. Herein we report the first example of regioselective palladium-catalyzed directly oxidative azidation of allylic C–H bonds of terminal alkenes using molecular oxygen[12] as the sole oxidant. The *in situ* formed allylic azides[13] can also undergo Cu-catalyzed azide–alkyne cycloaddition to furnish 1,2,3-triazoles,[14] thus allowing for the direct ligation of alkenes to biomolecular frameworks *via* a triazole linker, an approach that could be used in bioconjugate chemistry.[15] The developed C–H azidation/1,3-dipolar cycloaddition sequence is also suitable for use in discovery of lead compounds by target-directed synthesis[16] as well as in the design of novel peptidomimetics.[17] Furthermore, the 1,2,3-triazoles can be employed for the synthesis of other heterocyclic systems.[18]

We commenced our study by investigating the allylic C–H azidation of allylbenzene with sodium azide. Optimization of the reaction condition showed that

- the solvent played a very important role in reaction efficiency and selectivity. DMSO was the unique solvent to fulfill the allylic azidation under atmospheric pressure of dioxygen.

- $Pd(OAc)_2$ was superior to any other Pd catalysts (such as $PdCl_2$, $PdBr_2$, PdI_2, $Pd(PPh_3)_4$ and $Pd(CH_3CN)_2Cl_2$).

- increasing the temperature led to a higher reaction rate, but the yield or conversion was not improved.

Finally, the optimal reaction conditions found for azidation of the allylic C–H bond involved treatment of allylbenzene with sodium azide at 100 °C in the presence of palladium(II) acetate (5% mol) using O_2 (1 atm) as an oxidant.

With the optimized conditions in hand, we turned our attention to the allylic azidation reaction by different allyl arenes. Allyl arenes with electron-withdrawing (Table 1, **2g–2h** and **2i–2l**) and -donating groups (Table 1, **2b–2f** and **2m–2n**) as well as with halogen substituents (Table 1, **2g–2h**) are perfectly compatible with the optimized reaction conditions. Substituents at the *para*, *meta*, and *ortho* positions of the arene ring did not affect the efficiencies (Table 1, **2b–2d**). Reactive functional groups, such as vinyl, nitrile, ketone, carboxylic ester, amide and carbamate, could be tolerated in this allylic C–H azidation (Table 1, **2i–2n**). 2-Naphthylpropene gave the corresponding product in 81% yield (Table 1, **2o**). Notably, hetero-

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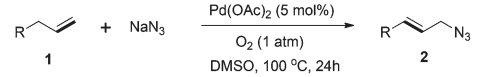
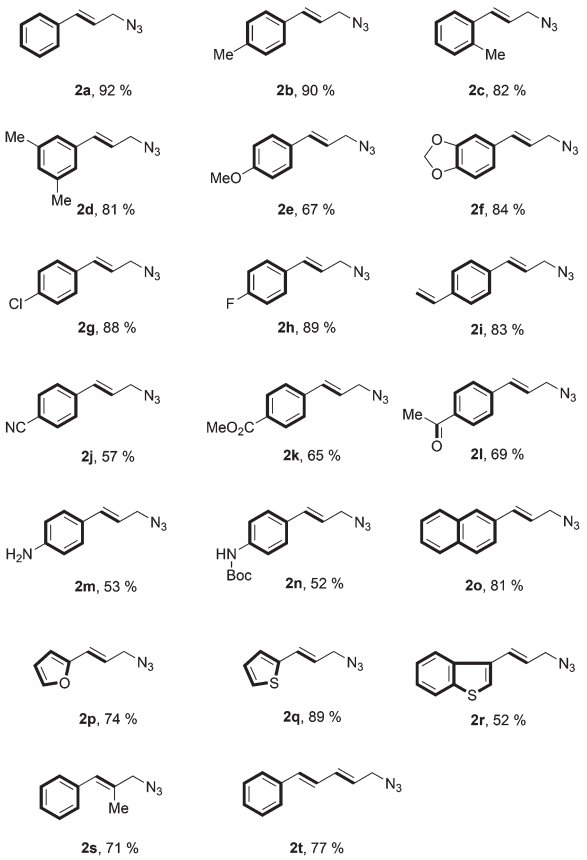
Table 1 Pd-catalyzed allylic azidation of alkenes with NaN_3[a,b]



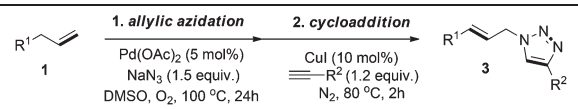


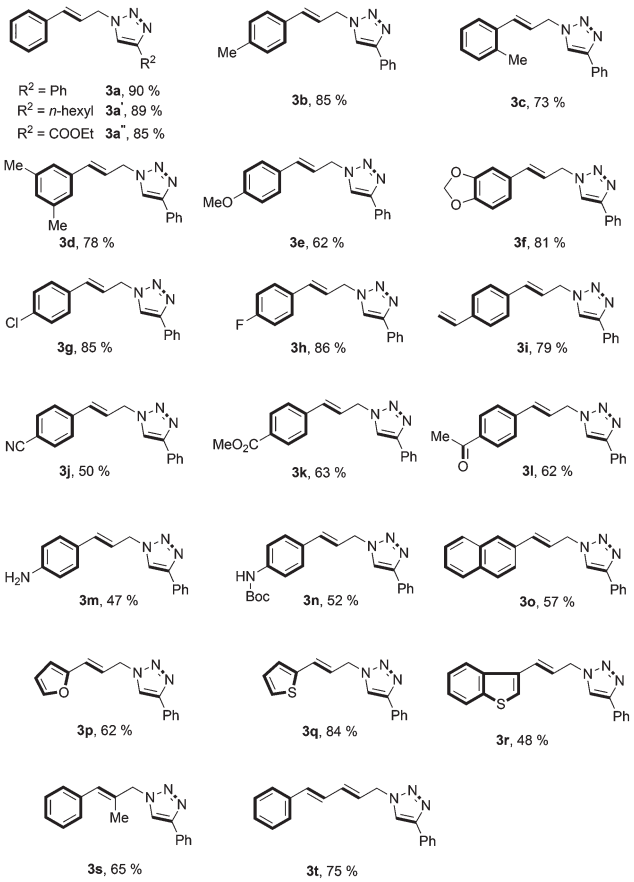
[a] Reaction conditions: alkenes (0.5 mmol), NaN_3 (0.75 mmol), $Pd(OAc)_2$ (5 mol%), 2.5 mL DMSO, O_2 (1 atm), 100 °C, 24 h. [b] Isolated yields are given.

aryl-substituted propenes, 1-allyl-2-furan, 1-allyl-2-thiophene and 1-allyl-3-benzothiophene, provided **2p**, **2q** and **2r** in moderate to good yields (Table 1, **2p**, **2q** and **2r**). 2,3-Disubstituted propene performed well in this transformation, leading to the corresponding allylic azide **2m** in moderate yield. Moreover, the alkenyl-substituted propene survived well, generating **2t** in 77% yield (Table 1, **2t**). However, simple alkenes, such as 1-octene, did not proceed in this process.

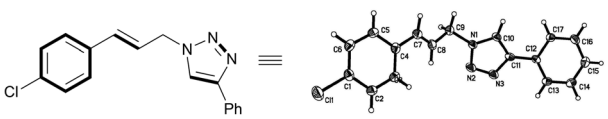
Subsequently, we considered the possibility of using these substrates in the classical click ligation with a terminal acetylene. We found a procedure that was not necessary to isolate the *in situ* formed azide prior to the 1,3-dipolar cyclization step with the alkyne. Indeed, it can be achieved in a straightforward one-pot process consisting of Pd-catalyzed allylic azidation of alkenes and Cu-catalyzed 1,3-dipolar cycloaddition.[14] A series of substrates were subsequently subjected to an azidation–cycloaddition sequence to show the scope of the developed methodology. All substrates that can form azides in the reaction are suitable substrates (Table 2, **3a–3t**). In addition, the

Table 2 One pot, two-step synthesis of 1,2,3-triazoles from alkenes[a,b]





[a] Allylic azidation conditions: alkenes (0.5 mmol), NaN_3 (0.75 mmol), $Pd(OAc)_2$ (5 mol%), 2.5 mL DMSO, O_2 (1 atm), 100 °C, 24 h; cycloaddition conditions: CuI (10 mol%), alkynes (0.6 mmol), N_2, 80 °C, 2 h. [b] Isolated yields are given.



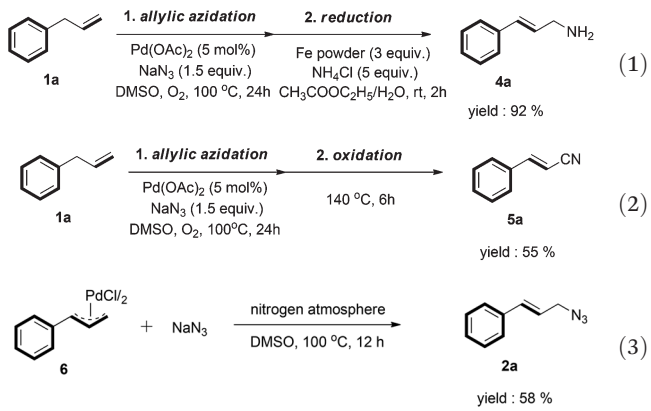
Scheme 1 X-ray crystal structure of **3g**.

structure of **3g** was further confirmed by X-ray diffraction (Scheme 1). This one-pot sequence led directly to the 1,2,3-triazole from the alkene, a type of transformation without precedent and of great synthetic interest.

The resulting allylic azide **2a** could also be converted to the corresponding allylic amine **4a** by the reduction[19] with Fe/NH_4Cl at room temperature within 2 hours; after the azide

had been synthesized from the alkene, the solvent was removed with water, and subsequently the reagents that were needed to achieve the reduction were added (eqn (1)). In general, the one-pot sequence allows for amination of allylic C–H bonds under mild conditions and in high overall yields. Alternatively, the formed allylic azide **2a** could be oxidized by increasing the temperature under O_2 (1 atm) to provide the alkenyl nitrile **5a** (eqn (2)). This is indeed an unprecedented transformation of aerobic oxidative synthesis of nitriles from primary azides with palladium catalysis.[20]

The products of these reactions are consistent with a mechanism in which allylic C–H activation proceeds with subsequent attack of the nitrogen nucleophile at the terminal position of the π-allyl intermediate. The alternative possibility, anti-Markovnikov aminopalladation and then β-hydride elimination, seems less likely because the intermolecular Wacker oxidation reactions of terminal alkenes exhibit Markovnikov regioselectivity.[21] Experimental support for an allylic C–H activation mechanism was obtained by preparing π-allylpalladium complex **6** [22] and investigating its reactivity with sodium azide. When the reaction was performed under a nitrogen atmosphere, allylic azide **2a** was formed in 58% yield (eqn (3)). It indicated that the π-allylpalladium should be involved in this allylic C–H azidation.



Conclusions

In summary, a versatile approach to azides *via* palladium-catalyzed allylic C–H azidation of alkenes using molecular oxygen as the sole oxidant has been developed. Additionally, the one-pot process consisting of Pd-catalyzed allylic azidation of alkenes and Cu-catalyzed 1,3-dipolar cycloaddition led to the direct formation of 1,2,3-triazoles from alkenes. The newly formed allylic azide can be *in situ* reduced to allylic amine. Alternatively, the allylic azide can be oxidized by increasing the temperature under O_2 (1 atm) to provide alkenyl nitrile. The developed procedure is suitable for a variety of allyl arenes and alkenyl-substituted propene. Further studies to expand the scope of nucleophiles in the palladium-catalyzed regioselective fragmentation of alkenes are ongoing in our laboratory.

Acknowledgements

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