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# Intermolecular Regioselective 1,2-Diamination of Allylic Ethers

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**Abstract:** Homogeneous palladium catalysis enables a novel intermolecular regioselective diamination of allylic ethers, which offers a convenient entry into 1,2,3-trisubstituted products. These represent suitable building blocks with differently protected nitrogen atoms for subsequent synthetic application.

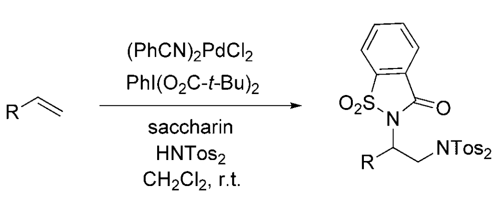
**Keywords:** alkenes; amides; diamines; oxidation; palladium

The 1,2-diamination of alkenes is an oxidation process to convert carbon-carbon double bonds into vicinal diamine derivatives,[1] which are of high significance in a variety of areas.[2]

Recent progress has demonstrated the ability of several transition metals to catalyze this transformation, including palladium,[3,4] copper,[5] nickel[6] and gold.[7] These reactions share a common concept of intramolecular aminometalation as the initial step and hence give rise to concomitant formation of heterocycles such as pyrrolidines.[8]

In addition to these diamination reactions of non-activated and activated alkenes, Shi has developed elegant sequential δ,γ-C–H activation/diamination reactions of terminal alkenes as well as diamination reactions of 1,3-butadienes.[9,10]

We recently developed a first strictly intermolecular palladium catalyzed diamination of alkenes (Scheme 1),[11] using high oxidation state palladium catalysis.[12] While quite general for terminal alkenes, we found that allylic ethers do not react under these conditions and are beyond the scope of the reaction. Since allylic ethers can be considered as versatile substrates for alkene oxidation because they lead to an interesting 1,2,3-trifunctionalization, we sought to develop a suitable protocol for this type of substrates. We here report on the regio- and chemoselective intermolecular diamination of allylic ethers and exemplify the utility of the products as versatile building blocks for subsequent organic synthesis.



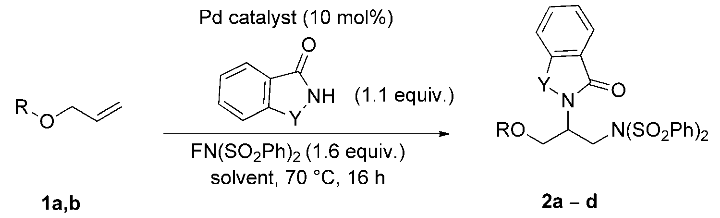
**Scheme 1.** Intermolecular diamination of alkenes.

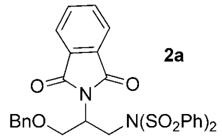
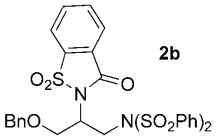
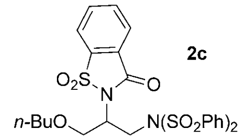
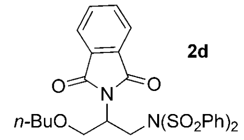
At the outset, we took inspiration in the seminal report on intermolecular aminoacetoxylation of allylic ethers by Stahl and Liu.[13,14] This work demonstrated the versatile combination of phthalimide and a palladium dichloride catalyst to initiate intermolecular aminopalladation. Initial efforts then focused on the exploration of *N*-fluoro-bis(phenylsulfonyl)imide (NFSI) as a suitable nitrogen source for the second carbon-nitrogen bond installment.[4,15,16]

For the diamination reactions of benzyl allyl ether **1a** with phthalimide as nitrogen source and NFSI as oxidant and nitrogen source, a screening of some common palladium salts led only to varyingly low amounts of diamination product (Table 1, entries 1–3). Only palladium bis(hexafluoroacetylacetonate) [Pd(hfacac)$_2$] as the catalyst precursor was able to induce moderate product formation (entry 4). Under these conditions, phthalimide could also be replaced by saccharin (entry 5). A subsequent screening of solvents revealed that ethyl acetate represented the optimum solvent for the present transformation (entries 5–9). For *n*-butyl allyl ether **1b**, similar reactivity was observed for the two nitrogen sources saccharin and phthalimide, giving rise to products **2c** and **2d**, respectively (entries 10 and 11).

These reactions proceed with complete regioselectivity and no other 1,2-dioxidation products than the diamine derivatives were obtained. However, the reaction suffered from low conversion and yields usually remained below 50%. Finally, addition of iodoso-

**Table 1.** Palladium-catalyzed diamination of alkenes: optimization of the process.



| Entry | R | Y | Pd Catalyst | Solvent | Diamine | Yield [%] |
|---|---|---|---|---|---|---|
| 1 | Bn (**1a**) | CO | $(MeCN)_2PdCl_2$ | EtOAc |  **2a** | <10 |
| 2 | Bn (**1a**) | CO | $Pd(OAc)_2$ | EtOAc | **2a** | <10 |
| 3 | Bn (**1a**) | CO | $Pd(O_2CCF_3)_2$ | EtOAc | **2a** | 15 |
| 4 | Bn (**1a**) | CO | $Pd(hfacac)_2$[a] | EtOAc | **2a** | 32 |
| 5 | Bn (**1a**) | $SO_2$ | | EtOAc |  **2b** | 37 |
| 6 | Bn (**1a**) | $SO_2$ | | $CH_2Cl_2$ | **2b** | <10 |
| 7 | Bn (**1a**) | $SO_2$ | | MeCN | **2b** | 25 |
| 8 | Bn (**1a**) | $SO_2$ | | acetone | **2b** | 28 |
| 9 | Bn (**1a**) | $SO_2$ | | dioxane | **2b** | <10 |
| 10 | *n*-Bu (**1b**) | $SO_2$ | | EtOAc |  **2c** | 35 |
| 11 | *n*-Bu (**1b**) | CO | | EtOAc |  **2d** | 32 |
| 12[b] | *n*-Bu (**1b**) | CO | | EtOAc | **2d** | 70 |

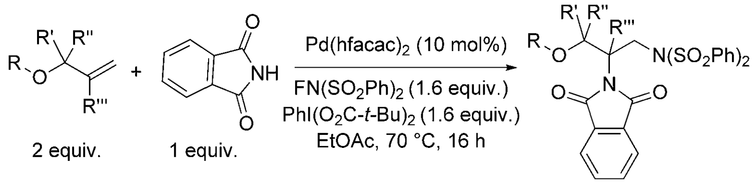
[a] hfacac = hexafluoroacetylacetonate.

[b] 2 mmol alkene, phthalimide (1 mmol), NFSI (1.6 mmol), $PhI(OPiv)_2$ (1.6 mmol).

benzene dipivalate to the reaction mixture containing phthalimide and NFSI led to a great improvement in yield and the diamination product **2d** could be isolated in 70% yield. Importantly, the corresponding reaction with saccharin does not experience this increase in yield.

This latter procedure was then employed for the synthesis of a series of different diamination products from allylic ethers. Table 2 shows representative examples. Various alkyl allyl ethers undergo clean diamination in 64–72% isolated yield with the expected complete regioselectivity as detected from the crude reaction mixture (entries 1–6). This chemoselectivity over potentially competing aminooxygenation reactions[12] is noteworthy. A benzoyl-protected allylic substrate was diaminated in 68% yield (entry 7) and two substrates with stereogenic allylic positions gave the corresponding diamination products as single diastereomers (entries 8 and 9). Their relative configuration was assessed by comparison with literature precedents and matches the outcome from the earlier aminoacetoxylation reaction.[13,17] A more sterically demanding ether with a *gem*-disubstituted allylic position still gave selective diamination (entry 10). Benzyl methallyl ether showed an equally reduced reactivity, but again the reaction proceeded with complete regio- and chemoselectivity (entry 11). Internal alkenes were found to be beyond the scope of the reac-

**Table 2.** Palladium-catalyzed intermolecular diamination of allylic ethers.



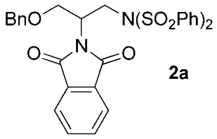
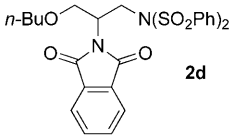
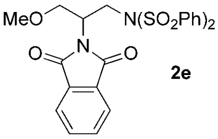
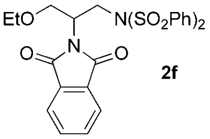
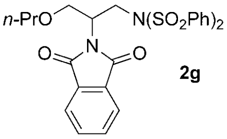
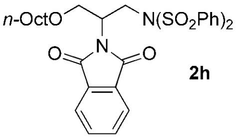
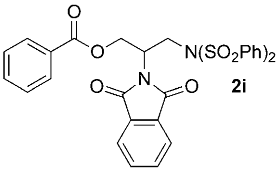
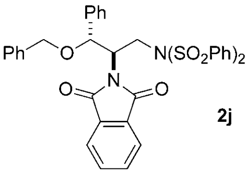
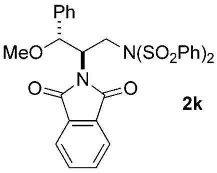
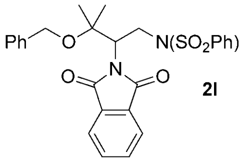
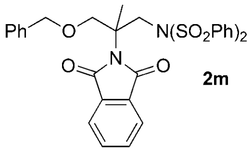
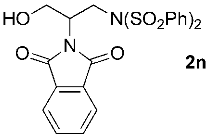
| Entry | R | R′ | R″ | R‴ | Diamine | Yield [%][a] |
|---|---|---|---|---|---|---|
| 1 | Bn | H | H | H |  **2a** | 72 |
| 2 | *n*-Bu | H | H | H |  **2d** | 70 |
| 3 | Me | H | H | H |  **2e** | 65 |
| 4 | Et | H | H | H |  **2f** | 64 |
| 5 | *n*-Pr | H | H | H |  **2g** | 68 |
| 6 | *n*-Oct | H | H | H |  **2h** | 67 |
| 7 | PhCO | H | H | H |  **2i** | 68 |
| 8 | Bn | Ph | H | H |  **2j** | 65[b] |
| 9 | Me | Ph | H | H |  **2k** | 55[b] |

**Table 2.** (Continued)

| Entry | R | R′ | R″ | R‴ | Diamine | Yield [%][a] |
|---|---|---|---|---|---|---|
| 10 | Bn | Me | Me | H |  **2l** | 40 |
| 11 | Bn | H | H | Me |  **2m** | 43 |
| 12[b] | H | H | H | H |  **2n** | 32 |

[a] Isolated yield after purification.

[b] 100% *de* according to the $^1$H NMR spectrum of the reaction crude.

tion. Finally, even free allylic alcohol could be oxidized under the present conditions (entry 12).

All products show the expected spectroscopic data in agreement with the depicted structures[17] and the constitution of the diamination products was unambiguously established by an X-ray crystallographic analysis of product **2d** (Figure 1).[18]

The synthetic utility of these diamination products as suitable building blocks was investigated within some representative reactions (Scheme 2). In order to allow for further differentiation of the two nitrogen groups, standard treatment of diamination product **2d** with methylhydrazine led to clean conversion of the phthalimide group into the free primary amine, which was isolated as the corresponding methyl carbamate **3** for the sake of convenient manipulation.

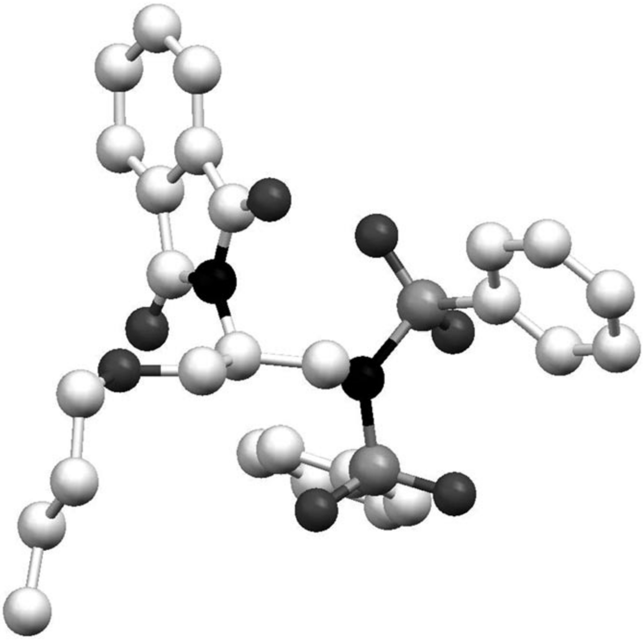
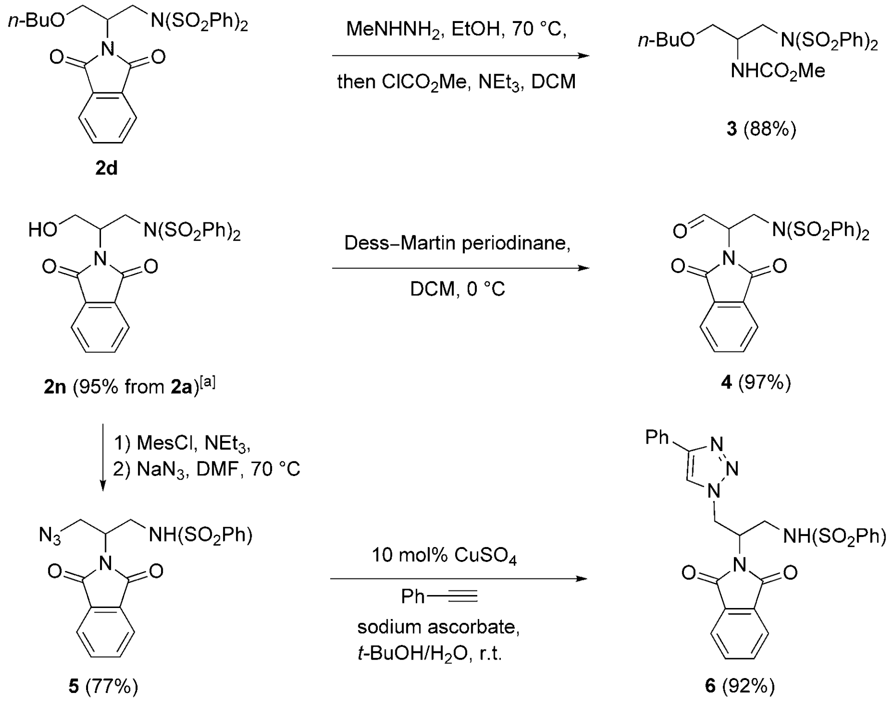


**Figure 1.** Structure of product **2d** in the solid state (N black, O dark grey, S light grey, C white).

The free alcohol **2n** as generated *via* direct diamination of allylic alcohol can be obtained otherwise *via* hydrogenolysis of the benzyl ether **2a**. By this route, **2n** is available in an overall 68% yield from benzyl allyl ether. Again, compound **2n** serves as an interesting starting compound for further derivatization. For example, it can selectively be oxidized to the corresponding 2,3-diaminopropionaldehyde **4** containing differentiated nitrogen groups. Alternatively, conversion of the free alcohol **2n** into the 1,2,3-triaminated azide-containing compound **5** proceeds with partial deprotection of the bis-sulfonimide. Compound **5** allows for a subsequent cycloaddition process to arrive at the triazole **6**, thereby demonstrating that the densely functionalized triamine derivative **5** can be successfully employed in "click chemistry".[19]

In summary, we have realized the catalytic intermolecular diamination of allylic ethers. The reaction employs catalytic amounts of palladium(II) compounds as catalyst source and proceeds with complete regioselectivity. It represents a significant advance in oxidative 1,2-difunctionalization of alkenes. Work in order to understand the underlying mechanism and the cooperative effect of the two oxidants as well as to extend the intermolecular diamination to internal alkenes is ongoing.



**Scheme 2.** Reactions employing 1,2,3-trifunctionalized diamination products. [a] 10 mol% Pd(OH)/C, 1 atm. $H_2$, EtOAc.

## Experimental Section

### Typical Procedure for the Diamination of Allylic Ethers with Phthalimide

Pd(hfacac)$_2$ (0.028 mmol, 14.5 mg), phthalimide (0.4 mmol, 60 mg), PhI[OC(O)*t*-Bu]$_2$ (0.64 mmol, 260 mg), *N*-fluorodibenzenesulfonimide (0.64 mmol, 200 mg) and the allyl ether substrate (0.8 mmol) were suspended in 0.4 mL of ethyl acetate (EtOAc) in a pyrex tube. The mixture was heated at 70 °C for 12 h. After cooling, the solution was evaporated under reduced pressure and the crude product was purified by chromatography on silica gel to give the diamination product.

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[17] Please see Supporting Information for details.

[18] Supplementary crystallographic data for the structure reported have been deposited with the Cambridge Crystallographic Data Centre under the deposition number CCDC 796289. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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