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Palladium Catalysis

# Palladium-Catalyzed Vicinal Difunctionalization of Internal Alkenes: Diastereoselective Synthesis of Diamines**

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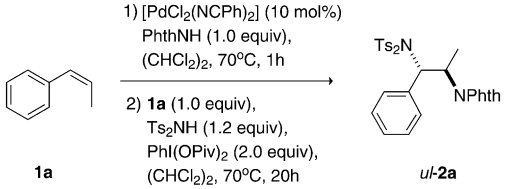
The seminal protocols by Sharpless et al. for the osmium-(VIII)-catalyzed dihydroxylation[1,2] and aminohydroxylation[3,4] of alkenes introduced the metal-catalyzed 1,2-difunctionalization of unsaturated hydrocarbons as a broadly applicable concept in modern organic synthesis. Recently, palladium catalysis has emerged as an conceptual alternative for this type of intermolecular vicinal difunctionalization reaction of alkenes.[5] While the osmium(VIII)-catalyzed reactions proceed through the concerted transfer of two heteroatoms to the alkene,[6] the alternative palladium-catalyzed reactions involve the stepwise process of nucleopalladation followed by the formation of the second carbon–heteroatom bond accompanied by release of the palladium catalyst. This approach should generally enable a broader range of reactions; however, transformations of this type such as chlorohydrin syntheses,[7] dibrominations,[8] diacetoxylations,[9] aminoacetoxylations,[10] and aminofluorinations[11] have so far been applied to only terminal alkenes.

Therefore, the application of internal alkenes in difunctionalization reactions remains a significant challenge in this particular area of palladium catalysis. One reason for this is the general problem of developing selective reaction conditions that disable undesired competing pathways such as isomerization reactions[12] and β-hydride elimination of the σ-alkyl palladium intermediates.[13] Currently, dioxygenation reactions of substituted 2-vinyl phenols represent the only more general oxidation reaction in this area. These reactions were developed independently by Muzart und Sigman[14] and show relatively broad applicability. However, they require a 2-hydroxyphenyl substituent, which is rather difficult to modify at later stages.

Our palladium-catalyzed intermolecular diamination reactions of terminal alkenes[15] constitute another example of the vicinal difunctionalization of alkenes using palladium in a high oxidation state.[5a,b] Despite ongoing efforts, we had not succeeded in transferring the conditions of the Pd/PhI-$(O_2CR)_2$ catalyst system to reactions with internal alkenes. Herein, we now describe the successful development of the first more generally applicable protocol for the palladium-catalyzed intermolecular diamination of internal alkenes, which proceeds with complete regio- and diastereoselectivity.

In view of the lack of methodology for the difunctionalization of internal alkenes, we started an investigation using (*Z*)-β-methylstyrene (**1a**) as a standard substrate. The initial attempt to transfer our conditions for the related intermolecular diamination of terminal alkenes[15a] to a reaction with substrate **1a** was not successful. Imitating the diamination of allylic ethers,[15b] we employed phthalimide (PhthNH) as the nitrogen source in a limiting amount together with an excess of **1a**. In the presence of a combination of iodobenzene dipivalate ($PhI(OPiv)_2$) as the oxidant and bistosylimide as the second nitrogen source[15a] this approach led to the desired diamination product **2a** (Table 1, entry 1). Compound **2a** was obtained as a single regio- and diastereoisomer. After some additional experimentation we found that preheating the catalyst precursor $[Pd(NCMe)_2Cl_2]$ together with phthalimide for a period of one hour significantly enhanced the yield (Table 1, entry 2). When the catalyst precursor was the corresponding benzonitrile complex, a significant increase in yield was observed (Table 1, entry 3). A second cycle of optimization adjusting the ratio between the iodine(III) oxidant and the substrate **1a** established conditions under

***Table 1:*** Intermolecular regioselective diamination of (*Z*)-β-methylstyrene (**1a**): optimization.




| Entry | Variation | Yield [%][a] |
|---|---|---|
| 1[c] | single-step procedure, 2.5 equiv **1a** | 20[b] |
| 2[c] | 2.5 equiv **1a** | 48[b] |
| 3 | 2.5 equiv **1a** | 85[b] |
| 4 | 1.1 equiv $PhI(OPiv)_2$ | 20 |
| 5 | 1.5 equiv $PhI(OPiv)_2$ | 60 |
| 6 | none | 93 |
| 7 | 5 mol% $[PdCl_2(NCPh)_2]$ | 99 |
| 8 | 3 mol% $[PdCl_2(NCPh)_2]$ | 99 |
| 9 | 2 mol% $[PdCl_2(NCPh)_2]$ | 80 |
| 10 | 1 mol% $[PdCl_2(NCPh)_2]$ | 74 |
| 11 | distilled **1a** | 74 |

[a] Yield of isolated product after column chromatography. [b] Yield based on phthalimide. [c] With $[PdCl_2(NCMe)_2]$ instead of $[PdCl_2(NCPh)_2]$.

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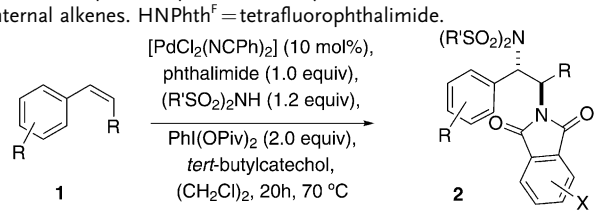
which the alkene served as limiting agent and the product **2a** was isolated in 93% yield (Table 1, entries 4–6). It is interesting to note that higher yields were obtained at lower catalyst loadings, and quantitative yields resulted from reactions with 5 and 3 mol% palladium, (Table 1, entries 7 and 8). Excellent results were still obtained even with catalyst loadings of 1–2 mol% (Table 1, entries 9 and 10). An important observation was made for a reaction using freshly distilled alkene **1a**, where a significant drop in yield was obtained (Table 1, entry 11). Commercial (*Z*)-β-methylstyrene contains *tert*-butylcatechol as a stabilizer, which suppresses polymerization under the present reaction temperature. A control experiment revealed that in the presence of trace amounts of palladium, freshly distilled alkene **1a** polymerizes readily within a short period of time.

Under the optimized conditions, a number of (*Z*)-β-alkylstyrenes could be transformed into the corresponding diamination products (Table 2). These reactions all proceed with complete chemo-, regio-, and diastereoselectivity. The successful combination of phthalimide with bistosylimide as well as with bisphenylsulfonimide and mesyltosylimide (HNMsTs) as the second nitrogen source was demonstrated with the standard substrate alkene **1a** (Table 2, entries 1–3). Likewise, the reaction tolerates the more acidic tetrafluorophthalimide in place of phthalimide (Table 2, entry 4), demonstrating that the combination of the nitrogen sources can be varied on a case-by-case basis. This variety of different nucleophiles is without precedence for palladium-catalyzed intermolecular reactions. In addition, the reaction can be conveniently conducted on a larger scale: the diamination of **1a** with phthalimide and bistosylimide was conducted on a 17 mmol scale to provide the corresponding isolated product **2a** in a yield of 9 g (91%). This is the currently largest scale preparative $Pd^{II/IV}$-catalyzed reaction (Table 2, entry 1).

In additional examples the substituted β-methylstyrenes **1b** and **1c** yield the expected products **2e** and **2f** (Table 2, entries 5 and 6). The variety of nitrogen sources was again demonstrated for the example of the cinnamyl methyl ether (**1d**) and the four products **2g**–**2j** were obtained in 60–84% yield (Table 2, entries 7–10). These results are superior to those previously recorded for the aminoacetoxylation of **1d**, which required an excess of alkene.[10] Different substituents

***Table 2:*** Scope of the palladium-catalyzed intermolecular diamination of internal alkenes. $HNPhth^F$ = tetrafluorophthalimide.

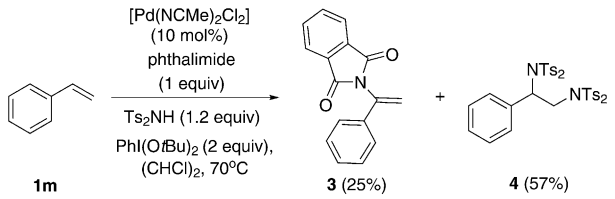



| Entry | Alkene | Nitrogen sources | Product | Yield [%][a] |
|---|---|---|---|---|
| 1[b] | **1a** | HNPhth, $HNTs_2$ | **2a** | 91 |
| 2 | **1a** | HNPhth, $HN(SO_2Ph)_2$ | **2b** | 90 |
| 3 | **1a** | HNPhth, HNMsTs | **2c** | 88 |
| 4 | **1a** | $HNPhth^F$, $HNTs_2$ | **2d** | 90 |
| 5 | **1b** | HNPhth, $HNTs_2$ | **2e** | 52 |
| 6 | **1c** | HNPhth, $HNTs_2$ | **2f** | 50 |
| 7 | **1d** | HNPhth, $HNTs_2$ | **2g** | 65 |
| 8 | **1d** | HNPhth, $HN(SO_2Ph)_2$ | **2h** | 60 |
| 9 | **1d** | HNPhth, $HNMs_2$ | **2i** | 84 |
| 10 | **1d** | HNPhth, $HNMs_2$ | **2j** | 70 |
| 11 | **1e** | HNPhth, $HNTs_2$ | **2k** | 60 |
| 12 | **1f** | HNPhth, $HNTs_2$ | **2l** | 62 |
| 13 | **1g** | HNPhth, $HNTs_2$ | **2m** | 57 |
| 14 | **1h** | HNPhth, $HNTs_2$ | **2n** | 50 |
| 15 | **1i** | HNPhth, $HNTs_2$ | **2o** | 60 |
| 16 | **1j** | HNPhth, $HNTs_2$ | **2p** | 66 |
| 17 | **1k** | HNPhth, $HNTs_2$ | **2q** | 52 |
| 18 | **1l** | HNPhth, $HNTs_2$ | **2r** | 40 |

[a] Yield of isolated product after column chromatography. [b] Reaction on 17 mmol scale.

at the arene core were investigated with alkenes **1e–1k** (Table 2, entries 11–17). These reactions proceed with acceptable yields and with the expected complete regio- and diastereoselectivities. The reaction of the corresponding derivative with 4-methoxy substituent was a notable exception, leading to complete degradation under the reaction conditions.[16] Finally, the cyclopentyl derivative **1l** gives a lower yield, which may be the consequence of steric hindrance of the aminopalladation. The constitution and configuration of the products was supported by X-ray single-crystal analyses for the three compounds **2a**,**d**,**i**,[17] and all three products show identical relative configuration (*unlike* for **2a**,**d**, *like* for **2i**).[18]

It is interesting that the described reaction conditions do not apply to styrene (**1m**). The corresponding attempt resulted in a product mixture and only phthaloyleneamide **3**[19] and diamine **4** could be isolated (Scheme 1); the latter

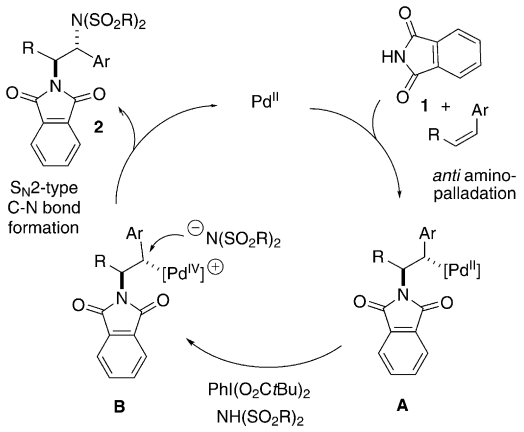



***Scheme 1.*** Reaction of styrene.

results from the uncatalyzed reaction of the iodine(III) reagent itself.[20] Since products of this type are not formed in the reactions of the internal alkenes **1a–l**, this result also demonstrates that in these cases the palladium catalysis from Table 2 is kinetically superior to the metal-free iodine(III)-promoted reaction.[20]

The above-mentioned observation that catalyst loadings of 3–5 mol% provide better results than 10 mol% can be explained by the fact that for **1a** in the presence of a higher catalyst loading an alternative isomerization to (*E*)-β-methylstyrene becomes competitive.[12] The latter isomer is indeed not oxidized under the present conditions as confirmed by a competition experiment. When a 1:1-mixture of (*E*)- and (*Z*)-β-methylstyrene was submitted to reaction under standard conditions, selective diamination of only the *Z* isomer was observed. This result should be the consequence of the more difficult coordination of the sterically more demanding *E* isomer to the palladium catalyst.

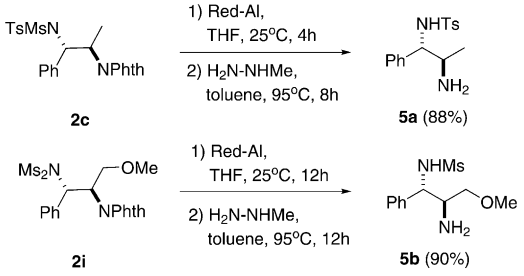
An extensive mechanistic investigation of the reaction is still lacking. Based on the observed coherent stereochemistry of the products, a preliminary mechanistic interpretation is possible based on the geometry of the alkene substrate. We currently prefer the catalytic cycle depicted in Scheme 2. Because of the observed dependence of the reaction on the *E*/*Z* geometry of the alkene, the initial step should consist of coordination of the alkene to the palladium catalyst. The subsequent aminopalladation through nucleophilic addition of phthalimide should then proceed with *trans* stereochemistry. This step also establishes the regioselectivity of the reaction, which is determined through the preferential positioning of palladium in the benzylic position.[21,22] The




***Scheme 2.*** Proposed catalytic cycle.

resulting σ-alkylpalladium complex **A** undergoes rapid, irreversible oxidation to the palladium(IV) intermediate **B**, which engages in the formation of the second C–N bond under net inversion of configuration at the stereogenic benzylic position. This step regenerates the original palladium(II) catalyst. An analogous sequence was recently verified mechanistically for related primary σ-benzylpalladium(IV) intermediates and bissulfonimide as the nucleophile[23] and for the present case this would provide the correct diastereomeric diamination product **2**.[24] It is noteworthy that this postulated sequence is largely identical to the mechanistic conclusions by Bäckvall from work on a related stoichiometric transformation dating back to the 1970s.[25]

The presence of the phthalimide group permits the facile transformation of the generated products. Two representative reactions leading to monosulfonylated diamines **5a,b** are depicted in Scheme 3. Thanks to their broad range of applications, monosulfonylated diamines constitute a privi-




***Scheme 3.*** Monosulfonylated diamines from products **2c**,**i**. Red-Al = $Na[AlH_2(OC_2H_4OCH_3)_2]$.

leged class of ligands,[26] which has now been made available for the first time through a novel sequence of alkene oxidation followed by transformation of the substituents at the nitrogen atoms.

We have discovered a general palladium(II/IV)-catalyzed difunctionalization reaction of internal alkenes under intermolecular conditions. This diamination reaction proceeds with complete chemo-, regio-, and diastereoselectivity and without the assistance of directing groups. The reaction

conditions are robust and the process can be readily conducted on a larger scale.

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