Aerobic Oxidation

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Palladium-Catalyzed Intermolecular Aerobic Oxidative Amination of Terminal Alkenes: Efficient Synthesis of Linear Allylamine Derivatives**

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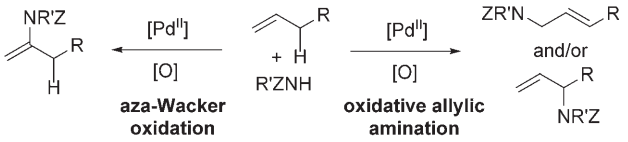
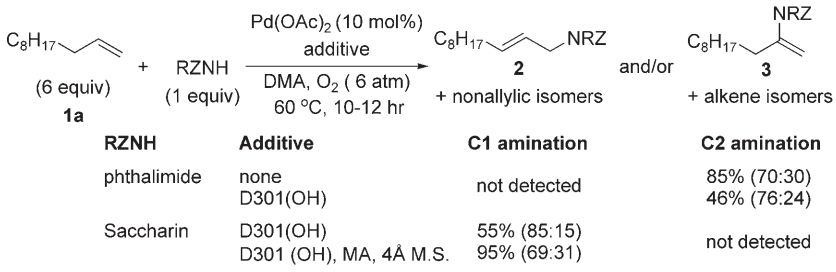
Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

The rich variety of nitrogen-containing molecules that occur as natural and synthetic products has inspired considerable interest in the development of new methods for their syntheses.[1] Among the strategies involving the direct amination of olefins by C–N bond formation,[2–3] the synthesis of amine derivatives by intermolecular dioxygen-coupled oxidative amination of olefins is particularly attractive.[4–6] Palladium-catalyzed methods for intermolecular aerobic oxidative amination of unactivated olefins, known as aza-Wacker reactions, have been recently reported to yield enamide derivatives (Scheme 1, left arrow).[2e,4,6] These reactions are proposed to proceed by Markovnikov aminopalladation of the alkene with subsequent β-hydride elimination, resulting in the functionalization of the olefin at the C2 position. Herein we describe a new method for intermolecular dioxygen-coupled oxidative amination of unactivated olefins under cocatalyst free reaction conditions, which affords linear allylic amine derivatives with high regioselectivity (Scheme 1, right arrow).[7–10] These reactions appear to proceed by allylic C–H activation and subsequent nucleophilic attack at the C1 position of an intermediate π-allylpalladium species.



Scheme 1. Possible pathways for Pd-mediated intermolecular oxidative anation of akenes.

We initiated the search for allylic amination reactions by examining the reaction of 1-undecene (**1a**) with nitrogen nucleophiles having an acidic NH group.[11] Dimethylacetamide (DMA) was selected as the solvent because it was shown to be the most effective solvent for aerobic allylic acetoxylation of alkenes.[7c] Treatment of phthalimide and **1a** with $Pd(OAc)_2$ under a dioxygen atmosphere (6 atm) in the presence or absence of the basic resin D301 (OH)[12] afforded oxidative amination products exclusively associated with aza-Wacker-type reactivity; the products were enimide **3** and various alkene isomers (Scheme 2). No allylic amination products were observed. The reaction of tosylamide and *N*-methyl tosylamide did not form any amination product. The use of saccharin as the nucleophile, however, resulted in highly regioselective linear (*E*)-allylic amination products (**2**) and the corresponding alkene isomers (Scheme 2). Optimal results were obtained when the reaction was performed in the presence of maleic anhydride (MA) and 4 Å molecular sieves (see the Supporting Information Table-S1 for details), which led to a 95% yield of the oxidative allylic amination product with respect to saccharin. Only linear amination products (C1 amination) were obtained; neither the enimide (C2 amination) nor the branched allylimide (C3 amination) was detected. The yield decreased to 78% under 1 atmosphere of dioxygen, and the use of *N*-methylpyrrolidinone (NMP) or *N*,*N*-dimethylformamide (DMF) instead of DMA, gave a slightly lower yield. A very low product yield (ca. 10%) was obtained with dimethylsulfoxide (DMSO) as the solvent.



Scheme 2. Pd-catalyzed the aerobic oxidative amination of 1-undecene (**1a**) with phthalimide and saccharin.

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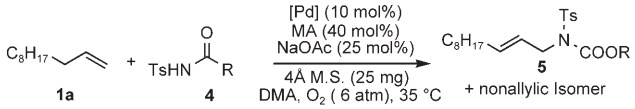
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

These results highlight the ability to achieve selective terminal functionalization of alkenes.

Reactions of saccharin with various terminal alkenes worked well (see the Supporting Information Table-S2 for additional examples), however, the difficulty of converting saccharin into useful amine analogs prompted us to investigate other nitrogen sources. Under mild reaction conditions, slightly modified from those identified with saccharin, 1-undecene (**1a**, 6 equiv) reacted with *O*-methyl-*N*-tosylcarbamate (**4a**, 1 equiv) to afford linear allylimide **5a** and its isomers[13] in 92% yield (Table 1, entry 1). A similar yield

Table 1: Reaction optimization for the palladium-catalyzed aerobic allylic amination of 1-undecene **1a**.[a]



1a 4 5

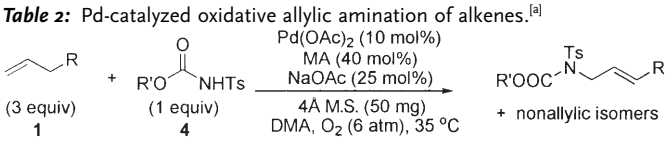
Entry	Catalyst	Imide **4**	**1a**:**4**	**5**	Yield [%][b]
1	$Pd(OAc)_2$	**4a** R = OMe	6:1	**5a**	92 (69:31)
2	$Pd(OAc)_2$		3:1		88 (64:36)
3[c]	$Pd(OAc)_2$		1:1.2		52 (65:35)
4[c,d]	$Pd(OAc)_2$		1:1.2		73 (72:28)
5	$PdCl_2$		3:1		57 (17:83)
6	$Pd(TFA)_2$		3:1		52 (56:44)
7	$Pd(OAc)_2$	**4b** R = O*t*Bu	3:1	**5b**	74(73:27)[e]
8	$Pd(OAc)_2$	**4c** R = OBn	3:1	**5c**	67(65:35)[e]
9	$Pd(OAc)_2$	**4d** R = CH_2CF_3	3:1	**5d**	32(62:38)[e] < 5[e]
10	$Pd(OAc)_2$	**4e** R = CH_3	3:1	**5e**	< 5[e]
11	$Pd(OAc)_2$	**4f** R = Bn	3:1	**5f**	< 5[e]
12	$Pd(OAc)_2$	**4g**[f]	3:1	**5g**	15[e]

[a] The reaction was conducted on a 0.1 mmol scale in 0.5 mL of DMA. [b] Yield determined by GC methods in which diphenyl ether was used as the internal standard. The data in parentheses is the ratio of allylimide and nonallylimide isomers. [c] NaOAc 50 mol%. [d] 20 mol% $Pd(OAc)_2$. [e] Yield determined by 1H NMR spectroscopy methods in which 1,3,5-trimethoxybenzene was used as the internal standard. [f] **4g** = $CF_3CH_2OSO_2NHCOOMe$. Ts = *p*-toluenesulfonyl.

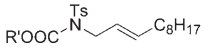
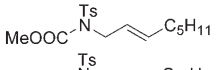
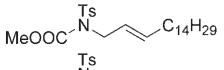
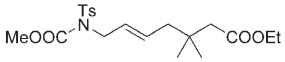
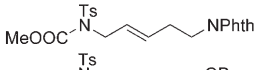
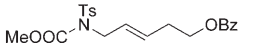
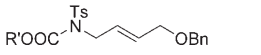
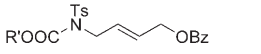
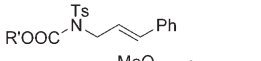
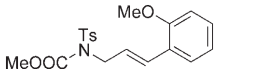
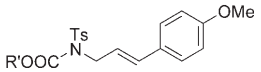
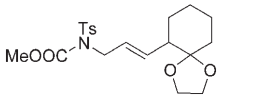
(88%) was obtained, even when the amount of **1a** was reduced to 3 equivalents (Table 1, entry 2). Allylimide **5a** was the predominant product isomer in all cases, except when $PdCl_2$ was used as the catalyst, in which case a complex mixture of alkene isomers resulted. The same products were obtained when alkene **1a** was used as the limiting reagent, albeit in somewhat reduced yield (52%, Table 1, entry 3). A higher chemical yield (73%) could be obtained with alkene **1a** as the limiting reagent if the $Pd(OAc)_2$ loading was increased to 20 mol% (Table 1, entry 4). $Pd(OAc)_2$ was a more effective catalyst than $Pd(O_2CCF_3)_2$ or $PdCl_2$ (Table 1, entries 5–6). Different nitrogen nucleophiles were examined under the optimized conditions, and both **4b** and **4c** showed good reactivity towards the formation of linear amination products **5b** and **5c**, respectively (Table 1, entries 7–8). The use of nucleophiles **4d** and **4g** resulted in lower yields (Table 1, entries 9 and 12), and **4e** and **4f** exhibited almost no reactivity (Table 1, entries 10–11).

We next explored the scope and the utility of this method with other unactivated alkenes. As summarized in Table 2, these reactions are operationally simple and tolerant of a wide

Table 2: Pd-catalyzed oxidative allylic amination of alkenes.[a]



(3 equiv) 1 (1 equiv) 4

Entry	Product		Yield [%][b]
1		**5a** R′ = Me	87 (70:30)
2[c]		**5a**	65 (71:29)
3		**5b** R′ = *t*Bu	69 (76:24)
4		**5c** R′ = Bn	63 (66:34)
5[c]		**5c**	61 (74:26)
6		**6**	75 (69:31)
7		**7**	74 (57:43)
8		**8**	63 (84:16)[e]
9[c,d]		**9**	81 (91:9)[e]
10		**10**	78 (92:8)[e]
11		**11a** R′ = Me	61
12		**11b** R′ = *t*Bu	83
13[c]		**11b**	80
14		**12a** R′ = Me	62
15		**12b** R′ = *t*Bu	65
16		**13a** R′ = Me	70
17		**13b** R′ = *t*Bu	62
18		**14**	75
19		**15a** R′ = Me	71
20		**15b** R′ = *t*Bu	67
21		**15c** R′ = Bn	80
22[c]		**15c**	64
23[c]		**16**	53

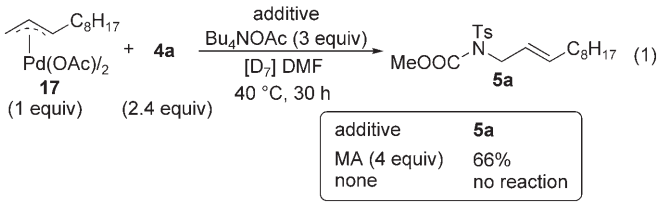
[a] The reaction was conducted on a 0.2 mmol scale in 0.8 mL of DMA. [b] Yield of isolated product; the data in parentheses is the ratio of the allylimide and the nonallylimide isomers. [c] Alkene was used as the limiting reagent: **1** (0.2 mmol, 1 equiv), **4** (0.25 mmol, 1.25 equiv), $Pd(OAc)_2$ (20 mol%), MA (40 mol%), NaOAc (50 mol%), 4 Å M.S. (50 mg), DMA (0.8 mL). [d] phthN = Phthalimidyl. [e] The nonallylic isomer is the homoallylic imide. Bn = benzyl; Bz = benzoyl.

range of functionalities. Terminal olefins featuring benzyl ether, methyl aryl ether, ester, phthalimidyl, and ketal functional groups underwent direct oxidative amination at the C1 position to generate the corresponding linear (*E*)-allylamine derivatives in preparatively useful yields. Olefins with long alkyl chains usually yielded a mixture of the linear allylimide and the corresponding alkene isomers (Table 2, entries 1–10). When homoallylic alcohol derivatives and allylarenes were employed, linear (*E*)-allylic imides were formed. Nonlinear (*Z*)-allylic imides were observed (Table 2, entries 11–22). We also examined the possibility of using

alkenes as the limiting reagent; when alkenes **1** (1 equiv) and nitrogen sources **4** (1.25 equiv) were treated with $Pd(OAc)_2$ (20 mol%) and NaOAc (50 mol%), the reactions afforded modest to good yields (Table 2, entries 2, 5, 9, 13, and 22–23).

The present oxidative amination procedure provides an effective route to *anti*-Markovnikov hydroamination products if the allylic (and isomeric) terminal amination products are reduced under standard alkene hydrogenation conditions (H_2, Pd/C; see the Supporting Infomation for details). The tosyl protecting groups of **5**–**16** are easily removed to provide linear allylcarbamates by treatment with magnesium in methanol under sonication.[14]

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 alternate possibility, *anti*-Markovnikov aminopalladation and then β-hydride elimination, seems less likely because intermolecular aza-Wacker reactions of terminal alkenes (Scheme 1) exhibit Markovnikov regioselectivity[6b,d] unless the alkene bears an electron-withdrawing group (e.g., styrenes[6a,c] or acrylates[5]). Experimental support for an allylic C–H activation mechanism was obtained by preparing π-allylpalladium complex **17**[15] and investigating its reactivity with imide **4a**. When the reaction was performed in the presence of MA (4 equiv) and a base (Bu_4NOAc, 3 equiv), linear allylimide **5a** was formed in 66% yield [Eq. (1)]. In the absence of MA, no reaction was observed. These results are consistent with a mechanism involving π-allylpalladium intermediates and suggest that maleic anhydride facilitates nucleophilic attack on the π-allylpalladium species.[16]



In conclusion, we have developed a novel method for the highly regioselective synthesis of linear (*E*)-allylimide from palladium-catalyzed oxidative amination of unactivated alkyl olefins, and the catalytic system allows an efficient dioxygen-coupled turnover without additional redox-active cocatalysts. Investigation of the reaction mechanism is in progress.

Experimental Section

Representative procedure: Alkene **1** (0.6 mmol), imide **4** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), maleic anhydride (0.08 mmol), NaOAc (0.05 mmol), and 4 Å molecular sieves (50 mg) were combined in a glass tube containing 0.8 mL of DMA. The reaction tubes, each with different alkene substrates, were placed into a nine-well parallel reactor mounted in a 300 mL Parr bomb and sealed. The whole system was purged with molecular oxygen ca. 10 times. Then the oxygen pressure was increased to 6 atm and the reactor was warmed to 35 °C. The reactions were stirred for 36 h. After the reactions were stopped, the reaction mixtures were concentrated in vacuo and the crude mixture was purified by column chromatography to afford allylic amination products.

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