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LETTERS

The Heck reaction in the presence of molecular oxygen

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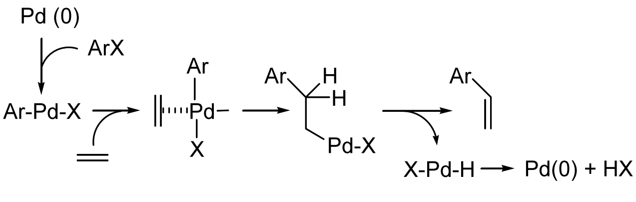
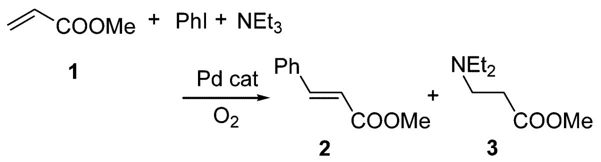
Abstract—Palladium-catalyzed reaction of $CH_2{=}C(R)COOMe$ (R = H or CH_2OH) with PhI in the presence of NEt_3 under O_2 induces the oxidative dealkylation of NEt_3, affording either methyl 3-diethylaminopropionate (**3**) or methyl (*Z*)-2-benzyl-3-(*N*,*N*′-diethylamino)propenate (**6**), in case of R = H or R = CH_2OH, respectively. © 2002 Elsevier Science Ltd. All rights reserved.

Coupling reaction of aromatic halides (ArX) with alkenes by using palladium catalysts (Heck reaction) is one of representative reactions in organic chemistry of palladium.[1] The reaction proceeds via pathways shown in Scheme 1, and after completion of the arylation, the resulting X–Pd–H decomposes to Pd(0) and HX. The HX formed is scavenged by bases such as tertiary amines (NR_3). In order to protect Pd(0) formed against O_2, the Heck reaction is usually performed under Ar or N_2. However, if O_2 reacts with either X–Pd–H or Pd(0) to generate X–Pd–OOH species,[2] it could serve as an oxidant in the reaction. Described herein is the first observation of such a case, where the presence of O_2 induces an oxidative dealkylation of NR_3, resulting in alternation of product composition in the Heck reaction.[3] This finding is important as a fundamental experimental fact in the Heck reaction.



Scheme 1.

When the reaction of methyl acrylate (**1**) and iodobenzene (PhI) with NEt_3 was carried out under O_2 (Table 1), methyl 3-diethylaminopropionate (**3**) was formed along with the usual arylation product **2** (Scheme 2). This result shows that NEt_3 is oxidatively dealkylated to give $NHEt_2$ which adds to **1**. Under an inert atmosphere (Ar), only the arylation product **2** is formed (entry 3 in Table 1). For the present reaction, palladium(II) complex such as $PdCl_2(MeCN)_2$ is allowable as the catalyst (entries 2–3), because palladium(II) reacts with tertiary amines to form Pd(0).[4]



Scheme 2.

The arylation of methyl (α-hydroxymethyl)acrylate (**4**) with PhI in the presence of NEt_3 under Ar (Table 2) gave aldehyde **5**,[5,6] as shown in Scheme 3. By contrast,

Table 1. Arylation of **1** with PhI and NEt_3 under O_2 or Ar[a]

Entry	Catalyst	Atmosphere	**2** (%)[b]	**3** (%)[c]
1	$Pd(PPh_3)_4$	O_2	96	27
2	$PdCl_2(MeCN)_2$	O_2	96	26
3	$PdCl_2(MeCN)_2$	Ar	96	–

[a] The reaction was performed by using **1** (4 mmol), PhI (1 mmol), NEt_3 (4 mmol) and palladium catalyst (0.05 mmol) in DMF (4.3 mL) at 75°C for 24 h.

[b] Yield based on PhI was determined by NMR.

[c] Yield (NMR) based on NEt_3.

Keywords: amination; Heck reaction; oxidation; oxygen; palladium.

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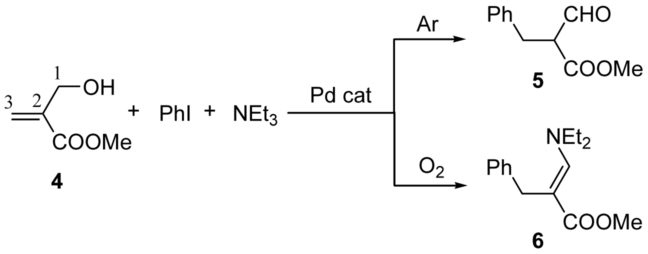


Scheme 3.

Table 2. Arylation of **4** with PhI and NEt_3 under O_2 or Ar[a]

Entry	Catalyst	Atmosphere	Reaction time (h)	Enamine **6** (%)[b]
1	$Pd(PPh_3)_4$	O_2	8	34
2	$Pd(OAc)_2$	O_2	5	51 (49)[c]
3	$PdCl_2(MeCN)_2$	O_2	6	57
4	$PdCl_2(MeCN)_2$	Ar	6	–[d]

[a] The reaction was performed by using **4** (2 mmol), PhI (2.2 mmol), NEt_3 (4 mmol) and palladium catalysts (0.1 mmol) in DMF (10 mL) at 80°C.

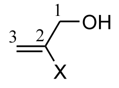
[b] Yield based on **4** was determined by NMR.

[c] In air for 32 h.

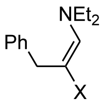
[d] Aldehyde **5** is formed in 62% yield based on **4**.

the use of O_2 altered the product composition, resulting in enamine **6**[7,8] as the sole product (entries 1–3). The aldehyde **5** arises from the arylation at C(3)=C(2) in **4** followed by Pd–H elimination from C(1) bearing OH group. The enamine **6** is derived from **5** and $NHEt_2$, showing that the oxidative dealkylation of NEt_3 again takes place. The enamine formation appears to be general with aryl iodides (ArI). As shown in Table 3, the formation of enamines is facilitated by electron-withdrawing substituent on ArI (entry 3), whereas it is retarded by electron-donating groups (entries 4–6).

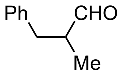
Allylic substrate **7a** or **7b** bearing an electron-withdrawing substituent at C(2) similarly reacts with NEt_3 to give the corresponding enamine **8** (X = MeCO) (38%) or **9** (X = CN) (39%), respectively, under the conditions described in Table 1 (entry 2). However, β-methallyl alcohol **7c** affords only aldehyde **10** (31%), indicating that the enamine formation is required for the activation of aldehyde by electron-withdrawing group.



7a: X=MeCO
7b: X=CN
7c: X=Me



8: X=MeCO
9: X=CN



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The participation of O_2 in the present reaction is demonstrated by the formation of cyclohexanone from cyclohexyldimethylamine ($NCyMe_2$) (Scheme 4). The yield of cyclohexanone (22%) is nearly the same as that (19%) of enamine **11** bearing *N*,*N*-dimethyl group. This means that the $NHMe_2$ formed reacts almost quantitatively with aldehyde **5** to give **11**.

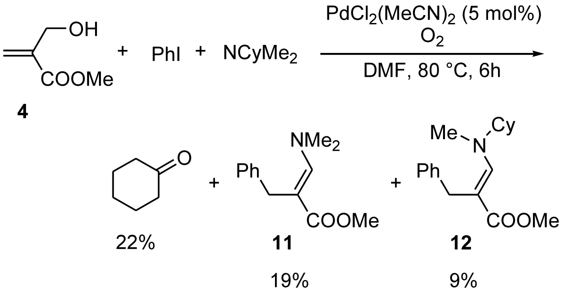
Table 3. Arylation of **4** with ArI and NEt_3 under O_2[a]

Entry	Ar	Reaction time (h)	Enamine[b] (%)[c]
1	C_6H_5	6	57
2	Naph	6	62
3	*p*-Cl-C_6H_4	3	62
4	*p*-MeO-C_6H_4	6	41
5	*p*-MeO-C_6H_4	24	59
6	*p*-Me-C_6H_4	24	49

[a] The reaction was performed by using **4** (2 mmol), ArI (2.2 mmol), NEt_3 (4 mmol) and $PdCl_2(MeCN)_2$ (0.1 mmol) in DMF (10 mL) at 80°C.

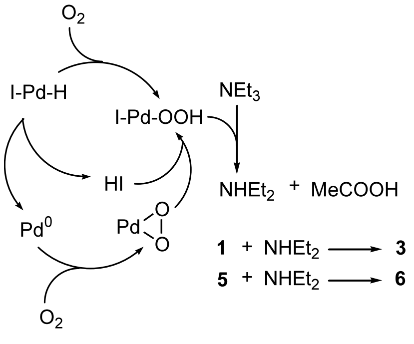
[b] The structure of enamine formed corresponds to **6** in Scheme 3.

[c] Yield based on **4** was determined by NMR.



Scheme 4.

Although the dealkylation process is not clear in detail, it could be induced by I–Pd–OOH species,[2] which is derived either from I–Pd–H and O_2 or via peroxopalladium(II) formed by Pd(0) and O_2. The conceptual pathway for NEt_3 is illustrated in Scheme 5. The Et group removed from NEt_3 must be transformed into MeCOOH via MeCHO, because ~1.1 mol of O_2 uptake is observed for the production of 1 mole of **3** or **6**; that is, nearly two O atoms of O_2 are consumed for the present reaction. The $NHEt_2$ formed further reacts with either alkene **1** or aldehyde **5** to give diethylaminopropionate **3** or enamine **6**, respectively. An iminium salt, which is produced from NEt_3 and Pd(II),[4,9] is probably involved in the dealkylation.



Scheme 5.

In summary, we have found that the Heck reaction in the presence of O_2 is accompanied by an oxidative dealkylation of tertiary amines usually employed as the acid scavenger. The catalysis for arylation is operative even in the presence of O_2. Although the present study has not focused on the synthetic utility, our finding may provide a cue for the nature of Pd–H species.

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6. Into a mixture of $PdCl_2(MeCN)_2$ (12.9 mg, 0.05 mmol), PhI (225 mg, 1.1 mmol) and NEt_3 (202 mg, 2.0 mmol) in DMF (5 mL) was added **4** (116 mg, 1.0 mmol). After the solution was stirred under argon at 80°C for 6 h, the resulting mixture was diluted with Et_2O and washed with brine. The organic layer was dried over anhydrous Na_2SO_4. Filtration followed by evaporation of the solvent gave oily material (297 mg) containing **5** in 62% NMR yield. The product **5** was purified by a short column chromatography of SiO_2. Compound **5** is in keto-enol equilibrium. ^{1}H NMR (270 MHz, $CDCl_3$): δ (*keto form*) 9.74 (d, $J=1.9$ Hz, 1H, C*H*O), 7.23 (m, 5H, C_6H_5), 3.72 (s, 3H, CO_2CH_3), 3.65 (ddd, $J=7.8$, 6.7, 1.9 Hz, 1H, C*H*-CHO), 3.22 (d, $J=6.7$ Hz, 1H, $C_6H_5CH_2$), 3.20 (d, $J=7.8$ Hz, 1H, $C_6H_5CH_2$); δ (*enol form*) 11.47 (d, $J=12.7$ Hz, 1H, CHO*H*), 7.23 (m, 5H, C_6H_5), 7.04 (dt, $J=12.7$, 0.9 Hz, 1H, C*H*OH), 3.72 (s, 3H, CO_2CH_3), 3.41 (broad s, 2H, $C_6H_5CH_2$); ^{13}C NMR (68 MHz, $CDCl_3$): δ 196.1, 172.5, 161.9, 140.0, 137.4, 128.8, 128.7, 128.4, 128.3, 126,9, 126.2, 104.4, 60.2, 52.4, 51.5, 33.1, 32.2; IR (neat): ν 3400 (O-H), 2950, 1725 (C=O), 1670, 1610, 1495, 1445, 1395 (C-H), 1335 (O-H), 1210, 1200, 1175 (C-O), 1095, 825 (C=CH), 750 (Ph-), 700 (Ph-), 475 cm^{-1}, MS (70 eV): *m/z* 192 (M^+), 163 (M^+–CHO), 104 ($PhCH_2CH$-), 91 ($PhCH_2$-).
7. The configuration of enamine **6** is determined to be *E* by nuclear Overhauser effect (NOE) in NMR.
8. The reaction was performed under oxygen (balloon) by using **4** (232 mg, 2.0 mmol), PhI (448 mg, 0.25 mL, 2.2 mmol), NEt_3 (404 mg, 0.56 mL, 4.0 mmol) and $PdCl_2(MeCN)_2$ (26.0 mg, 0.1 mmol) in DMF (10 mL). After the solution was stirred at 80°C for 6 h, usual work-up gave oily material (550 mg) containing **6** in 57% NMR yield. The product **6** was purified by a short column chromatography of Al_2O_3 (12 g). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.62 (s, 1H, C=C*H*-N), 7.19 (m, 5H, C_6H_5-), 3.78 (s, 2H, C_6H_5-CH_2), 3.65 (s, 3H, $COOCH_3$), 3.18 (q, $J=7.2$ Hz, 4H, NCH_2CH_3), 1.12 (t, $J=7.2$ Hz, 6H, NCH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$): δ 171.6 (*C*=O), 148.3 (C=*C*HN), 142.6 (C_6H_5-), 128.2 (C_6H_5-), 127.5 (C_6H_5-), 125.5 (C_6H_5-), 93.0 (*C*-$COOCH_3$), 51.0 (OCH_3), 47.0 (N-CH_2-), 30.9 (C_6H_5-CH_2), 14.8 (NCH_2CH_3); IR (neat): ν 2975, 2945, 1680 (C=O), 1615 (C=C), 1495, 1450, 1430, 1380, 1360, 1345, 1315, 1260, 1135, 1085 (C-O-C), 735 (Ph-), 700 (Ph-), 480 cm^{-1}; MS (70 eV): *m/z* 247 (M^+), 232 (M^+–Me), 218 (M^+–Et), 156 (M^+–$PhCH_2$), 131 ($PhCH_2CCO$-), 115 ($PhCH_2CC$-); HRMS calcd for $C_{15}H_{21}NO_2$ 247.1572. Found: 247.1613.
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