New palladium-catalyzed aerobic oxidative cleavage and cyclization of *N*-aryl peptide derivatives

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Oxidative cleavage and cyclization cascades of *N*-aryl peptides have been achieved under palladium catalysis with air as the sole stoichiometric oxidant.

Catalytic oxidations certainly represent one of the most challenging developments in Pd chemistry.[1] The main studies in this field deal with alcohol oxidations[2] and oxidative couplings between substrates such as alkenes and various heteroatom[3] or carbon[4] nucleophiles. In opposition to classical non-oxidative cross-coupling reactions, these transformations often involve a Pd(II) salt. When a Pd(0) complex is generated in the catalytic cycle, an external oxidizing agent has to be added to the medium. Several suitable additives have been described: benzoquinone,[5] $CuCl_2$, $PhI(OAc)_2$,[6] peroxides.[7] In the context of environmentally friendly processes, molecular oxygen undoubtedly represents the best potential oxidant for organic compounds.[8] When oxygen is the sole stoichiometric oxidant, efficient conversions are usually obtained by the use of additives such as DMSO,[2a–d] pyridines,[2e–g] tertiary amines,[2h,i] or metal co-catalysts.[1,9]

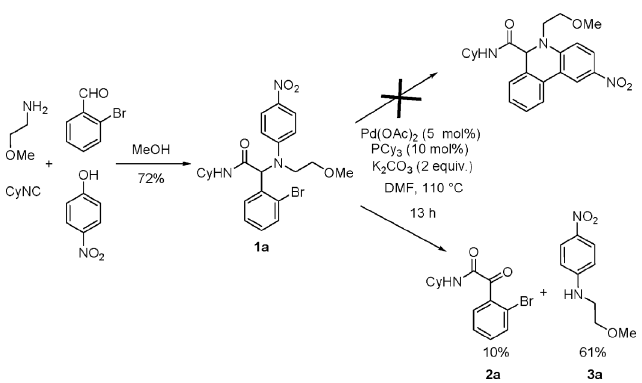
We recently disclosed a new 4-component coupling between an amine, a carbonyl compound, an isocyanide and a phenol (Ugi–Smiles reaction).[10] In an attempt to couple this new reaction with Heck type processes, we prepared the bromo compound **1a** and treated it with a catalytic amount of palladium in order to obtain phenanthridine derivatives. Surprisingly, when heated overnight in DMF with $Pd(OAc)_2$ (5 mol%), tricyclohexylphosphine (10 mol%) and potassium carbonate (2 equiv.), the α-ketoamide **2a** and the amine **3a** were obtained without any trace of the expected adduct (Scheme 1).

We surmised that the slow introduction of oxygen into the medium was responsible for such a cleavage and decided to study further this new Pd-catalyzed fragmentation. The reaction was indeed much faster when performed under air and without added phosphine. Various α-arylamino amides behave similarly, as shown in Table 1, except for alkyl derivatives such as **1b**, which does not react under the conditions (Table 1, entry 1). When *ortho*-nitro derivative **1i** was submitted to these conditions, the sole product we could isolate was the α-ketoamide **2i** (Table 1, entry 8).

Then we envisioned trapping the reactive intermediates with new carbon–carbon bond formation. There are relatively few successful cyclizations of stabilized carbanions onto alkenes due to the competition with simple oxidation. Recently, Widenhoefer *et al*. have reported several oxidative cyclizations of β-dicarbonyl derivatives on alkenes with Pd(II)/Cu(II) catalytic systems. However, this Pd(II)-promoted cyclization is restricted to alkenyl-1,3-diones.[9] The homoallylamine derivatives **1k**–**1n** were consequently prepared by a Staudinger–Ugi–Smiles sequence from the homoallylazide and the latter submitted to oxidative conditions. Instead of the former nitro aniline–α-ketoamide mixture, we were pleased to observe the formation of a polycyclic product **5k**–**5n** resulting from a new Pd cascade (Table 2).

The need for an acidic proton in the substrate (alkyl derivatives such as **1b** are not reactive under these conditions, see Table 1, entry 1) is probably associated with the formation of the palladium enolate **I**, which evolves into an iminium derivative **II**. This latter may be converted to the amide **2** by water or peroxides in the medium (Scheme 2). Alternatively, the enolate **I** can be trapped by a pendant olefin to form a Pd–alkyl species **III**, which further cyclizes onto the aromatic ring. In both processes, the generated Pd(0) is oxidized back to Pd(II) by the oxygen, as reported in similar palladium-catalyzed reactions.

Other possible mechanistic pathways involve radicals as classically described in Cu(I) chemistry.[13] Indeed, the α-ketoamide formation could result from the coupling of a peptidyl



Scheme 1 Pd-induced fragmentation of α-arylamino amide derivatives.

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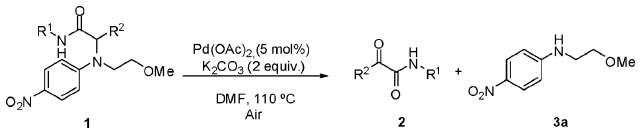
[b] *Noria Alta S/N, Facultad de Química, Guanajuato, Gto., México. E-mail: rociogm@quijote.ugto.mx; Fax: +(52) 47 37 32 00 06 ext 8111; Tel: +(52) 47 37 32 00 06 ext 8170*

Table 1 Pd-catalyzed oxidative cleavage[11]



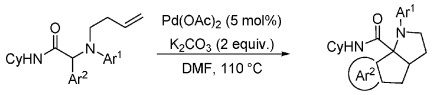
Entry		Starting material R^1	Starting material R^2	α-Ketoamide **2** (yield, %)	**3a** (%)	Time of reaction
1	**1b**	Cy	CH_3CH_2–	—	—	—
2	**1c**	Cy	Ph	**2c** (69)	80	3 h
3	**1d**	Cy	*o*-CH_3Ph	**2d** (61)	47	17 h
4	**1e**	Cy	*p*-CNPh	**2e** (48)	52	3 h
5	**1f**	Cy	*p*-OMePh	**2f** (52)	86	6 h
6	**1g**	Cy	*p*-BrPh	**2g** (47)	59	3 h
7	**1h**	Cy	Quinolin-3-yl	**2h** (42)	82	1.5 h
8	**1i**[a]	*p*-ClBn	Ph	**2i** (49)	—	3 h

[a] Performed with *o*-nitro substituted aniline.

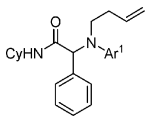
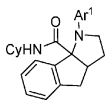
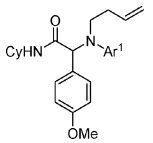
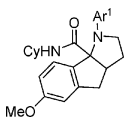
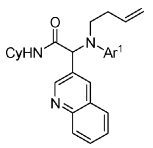
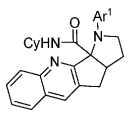
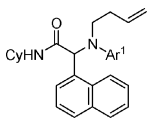
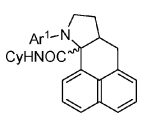
radical with oxygen.[14] The former radical could also be involved in a radical cascade forming the polycyclic product **5**.

In conclusion, we have disclosed some new oxidative palladium-catalyzed reactions with oxygen as the sole oxidant. The reactive intermediates form α-ketoamides or can undergo intramolecular cyclization to provide polycyclic derivatives in a palladium-catalyzed cascade reaction. The natures of

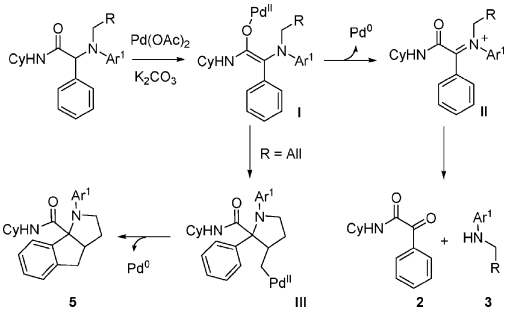
Table 2 Pd-catalyzed cyclizations[12]



Ar^1 = *p*-NO_2Ph
Ar^2= Ph, p-MeOPh, Quinolin-3-yl, Naphth-1-yl

Entry	Starting material	Cyclized product	Yield (%)
1	 **1k**	 **5k**	55
2	 **1l**	 **5l**	59
3	 **1m**	 **5m**	27
4	 **1n**	 **5n**	62[a]

[a] Isolated as a 2 : 1 mixture of diastereomers.



Scheme 2 Possible mechanisms.

the reactive intermediates are still under study in our research group.

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Notes and references

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8 These reactions are usually of poor efficiency when performed in air instead of an oxygen atmosphere.

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11 **For a typical experimental procedure: Ugi–Smiles procedure for 1c:** To a 2 M solution of the benzaldehyde (1 mmol) in methanol was added successively 1.0 equiv. of methoxyethylamine, 1.0 equiv. of cyclohexyl isocyanide and 1.0 equiv. of *para*-nitrophenol under inert atmosphere. The resulting mixture was stirred for 24 h at 60 °C. It was then concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate) to give the desired adduct **1c** as a yellow solid in an 87% yield. **Mp** 118.0–120.0 °C. **^{1}H NMR ($CDCl_3$; 400 MHz)** δ 8.18 (d, 2H, J = 9.4 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.41–7.35 (m, 3H), 7.26–7.24 (m, 2H), 6.81 (d, 2H, J = 9.4 Hz), 5.37 (s, 1H), 3.95–3.86 (m, 1H), 3.79–3.73 (m, 1H), 3.44–3.42 (m, 3H), 3.36 (s, 3H), 1.98–1.86 (m, 2H), 1.71–1.63 (m, 3H), 1.42–1.32 (m, 2H), 1.15–1.03 (m, 3H). **^{13}C NMR ($CDCl_3$; 100.6 MHz)** δ 169.6, 153.4, 139.3, 134.9, 129.8, 129.3, 128.9, 126.1, 113.5, 70.7, 69.5, 59.2, 48.8, 47.6, 33.6, 33.5, 25.9, 25.3. **IR** (thin film) 2929, 1643, 1594, 1315, 1104 cm^{-1}. **HRMS** calcd for $C_{23}H_{29}N_3O_4$ 411.2158; found 411.2152. **Oxidation procedure of 1c**: To a 0.2 M solution of the Ugi–Smiles adduct **1c** (1 mmol) in freshly distilled DMF were added 2 equiv. of K_2CO_3 and 5 mol% of $Pd(OAc)_2$. The resulting mixture was stirred at 110 °C for 3 h under air before being concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate) to give the α-ketoamide **2c** as white crystals in 69% yield and the corresponding aniline **3** as a yellow solid in 80% yield. **Spectroscopic data for 2c: mp** 112.0–113.1 °C. **^{1}H NMR ($CDCl_3$; 400 MHz)** δ 8.37 (d, 2H, J = 8.2 Hz), 7.66 (t, 1H, J = 7.4 Hz), 7.52 (t, 2H, J = 7.4 Hz), 6.98 (br s, 1 H), 3.94–3.85 (m, 1H), 2.04–1.87 (m, 4H, H_{Cy}), 1.49–1.38 (m, 2H), 1.34–1.23 (m, 4H). **^{13}C NMR ($CDCl_3$; 100.6 MHz)** δ 188.5, 161.2, 134.7, 133.8, 131.6, 128.8, 48.8, 33.1, 25.8, 25.2. **IR** (thin film) 3279, 2933, 2360, 1652, 1647 cm^{-1}. **Spectroscopic data for 3: mp** 87.2–88.7 °C. **^{1}H NMR ($CDCl_3$; 400 MHz)** δ 8.11 (d, 2H, J = 9.1 Hz), 6.57 (d, 2H, J = 9.1 Hz), 4.90 (br s, 1H), 3.65 (t, 2H, J = 5.3 Hz), 3.42 (s, 3H), 3.40 (q, 2H, J = 5.3 Hz). **^{13}C NMR ($CDCl_3$; 100.6 MHz)** δ 153.6, 138.6, 126.8, 111.6, 70.6, 59.3, 43.2. **IR** (thin film) 3331, 2937, 1589, 1276 cm^{-1}. **HRMS** calcd for $C_9H_{12}N_2O_3$ 196.0848; found 196.0839.

12 **For a typical experimental procedure: Staudinger–Ugi–Smiles procedure for 1k:** A mixture of the homoallyl bromide (1 mmol) and sodium azide (1 mmol) in DMSO (2 M) was stirred at 60 °C for 18 h under an inert atmosphere. Then were added, at room temperature, methanol (to reach a concentration of 1 M), the triphenylphosphine (1.2 mmol) and the aldehyde (1 mmol). The resulting mixture was stirred at 60 °C. After 15 h, were added the isocyanide (1 mmol) and nitrophenol (1 mmol). The resulting mixture was stirred at 60 °C for 5 days. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous $NaHCO_3$ solution (3×), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel (petroleum ether–ethyl acetate) to give the desired adduct **1k** as a yellow solid in 52% yield. **Mp** 149.7–151.1 °C. **^{1}H NMR ($CDCl_3$; 400 MHz)** δ 8.17 (d, 2H, J = 9.4 Hz), 7.43–7.41 (m, 3H), 7.35–7.32 (m, 2H), 6.77 (d, 2H, J = 9.4 Hz), 5.84 (br d, 1H, J = 8.3 Hz), 5.61 (ddt, 1H, J = 16.9, 10.4, 6.6 Hz), 5.41 (s, 1H, H_4), 5.02 (d, 1H, J = 10.4 Hz), 4.97 (dd, 1H, J = 16.9, 1.5 Hz), 3.92–3.84 (m, 1H, H_6), 3.46 (dt, 1H, J = 15.4, 6.1 Hz), 3.39 (dd, 1H, J = 16.9, 6.1 Hz), 2.39–2.31 (m, 1H), 2.01–1.84 (m, 3H), 1.71–1.52 (m, 2H), 1.42–1.28 (m, 2H), 1.17–1.00 (m, 3H). **^{13}C NMR ($CDCl_3$; 100.6 MHz)** δ 168.6, 153.4, 138.9, 135.0, 134.7, 129.8, 129.5, 129.3, 126.4, 117.8, 112.6, 68.4, 49.1, 48.6, 33.4, 33.2, 32.5, 25.7, 25.0. **IR** (thin film) 3270, 2934, 1653, 1317, 1111 cm^{-1}. **HRMS** calcd for $C_{24}H_{29}N_3O_3$ 407.2209; found 407.2240. **Cyclization procedure:** To a 0.2 M solution of the Ugi–Smiles adduct (1 mmol) in DMF were added successively 2 equiv. of K_2CO_3, 10 mol% of PCy_3 and 5 mol% of $Pd(OAc)_2$. The resulting mixture was stirred at 110 °C for 4 h under air before being concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate) to give the tricyclic compound **5k** as a yellow solid in 55% yield. **^{1}H NMR ($CDCl_3$; 400 MHz)** δ 8.15 (d, 2H, J = 9.4 Hz), 7.61 (d, 1H, J = 8.0 Hz), 7.38–7.31 (m, 2H), 7.25 (t, 1H, J = 8.0 Hz), 6.78 (d, 2H, J = 9.4 Hz), 5.58 (br d, 1H, J = 8.3 Hz), 3.87–3.78 (m, 1H), 3.74–3.70 (m, 2H), 3.37 (qd, 1H, J = 7.5, 2.3 Hz), 3.22 (dd, 1H, J = 16.2, 7.5 Hz), 2.86 (dd, 1H, J = 16.2, 2.3 Hz), 2.39–2.31 (m, 1H), 1.95–0.98 (m, 11H). **^{13}C NMR ($CDCl_3$; 100.6 MHz)** δ 170.7, 151.1, 144.1, 141.5, 138.1, 130.1, 128.1, 126.8, 126.2, 113.1, 82.6, 53.7, 51.1, 48.9, 35.4, 33.3, 33.1, 29.8, 25.7, 25.0. **IR** (thin film) 2929, 2858, 1658, 1599, 1304 cm^{-1}. **HRMS** calcd for $C_{24}H_{27}N_3O_3$ 405.2052; found 405.2057.

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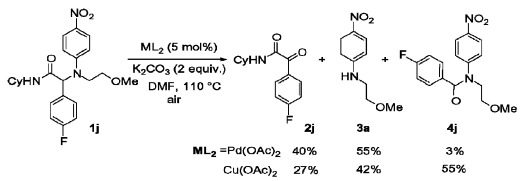
14 Further indication on the reaction mechanism was obtained by the following experiment. When the α-arylamino amide **1j** was treated with $Cu(OAc)_2$ instead of Pd(II), the amide **4j** was isolated as the major product, whereas it was obtained only as a trace under Pd catalysis (see image below). These results with copper are consistent with a radical mechanism involving the trapping of a peptidyl radical with oxygen. The fragmentation of the resulting hydroperoxide could then lead to **4j**.



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