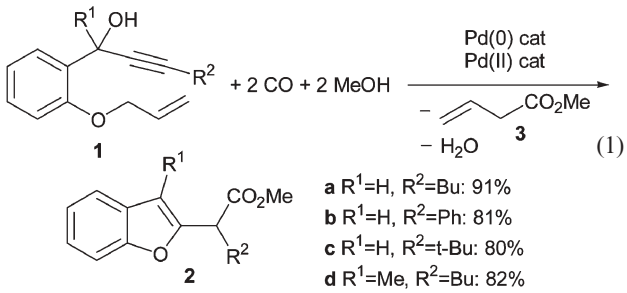
Sequential homobimetallic catalysis: an unprecedented tandem Pd(0)-catalysed deprotection – Pd(II)-catalysed heterocyclisation reaction leading to benzofurans

Bartolo Gabriele,*[a] Raffaella Mancuso,[b] Giuseppe Salerno[b] and Lucia Veltri[b]

Received (in Cambridge, UK) 31st August 2004, Accepted 4th October 2004
First published as an Advance Article on the web 12th November 2004
DOI: 10.1039/b413240h

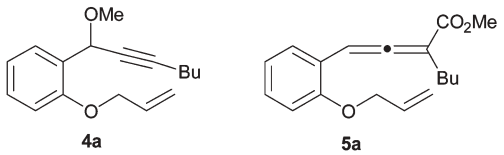
We report here the first example of "sequential homobimetallic catalysis": a transition metal catalyst with the metal in a certain oxidation state catalyses the deprotection of a functional group, which *in situ* undergoes a subsequent transformation catalysed by another complex of the same metal but in a different oxidation state.

We report here the first example of "sequential homobimetallic catalysis": a transition metal catalyst with the metal in a certain oxidation state catalyses the deprotection of a functional group, which *in situ* undergoes a subsequent transformation catalysed by another complex of the same metal but in a different oxidation state. The concept is illustrated by the tandem Pd(0)-catalysed carbonylative deallylation – Pd(II)-catalysed carbonylative cyclisation of 1-(2-allyloxyphenyl)-2-yn-1-ols **1**, leading to 2-benzofuran-2-ylacetic methyl esters **2** in high yields together with but-3-enoic acid methyl ester **3** as coproduct, according to Eqn. (1).[1]

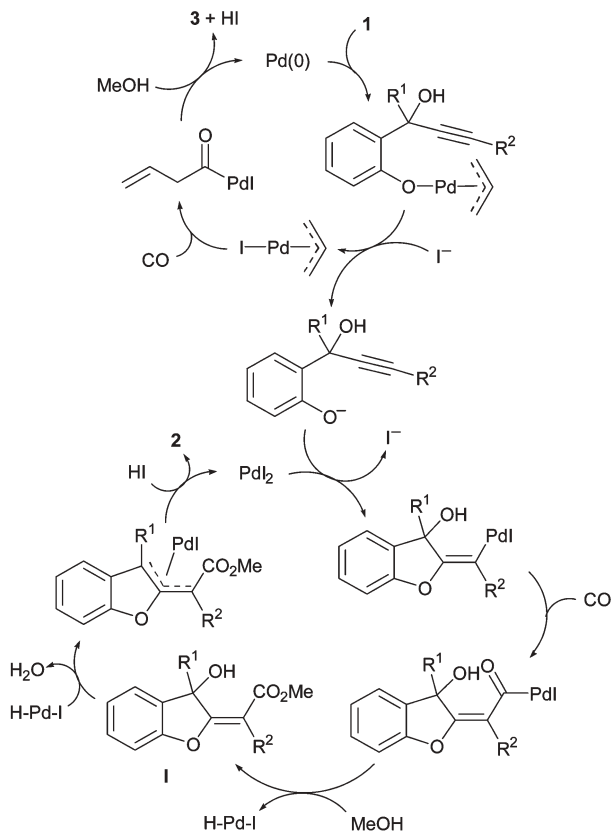


(1)

The first experiments were carried out with 1-(2-allyloxyphenyl) hept-2-yn-1-ol **1a** (R^1 = H, R^2 = Bu) at 100 °C and under 30 atm of CO, in anhydrous MeOH as the solvent and nucleophile, and in the presence of $Pd(PPh_3)_4$ (0.5 mol %) and PdI_2 (0.5 mol %) in conjunction with an excess of KI (100 equiv with respect to PdI_2)[2] as the catalytic systems. After 15 h, benzofuran-2-ylhexanoic acid methyl ester **2a** was obtained as the main reaction product (76% GLC yield), together with **3** (*ca.* 70%) and small amounts of 1-allyloxy-2-(1-methoxyhept-2-ynyl)benzene **4a** (6%, deriving from etherification of the alcoholic function of **1a**) and of 4-(2-allyloxyphenyl)-2-butylbuta-2,3-dienoic acid methyl ester **5a** (8%, from Tsuji-type carbonylation[3] of the propargylic function of **1a**).



The two sequential catalytic cycles leading to **2** and **3** are shown in Scheme 1 (unreactive ligands are omitted for clarity). The first cycle, catalysed by Pd(0), corresponds to the oxidative addition of the allyloxy moiety to Pd(0) followed by cleavage by iodide anions and allylic carbonylation,[4] with formation of **3** and 2-(1-hydroxyalk-2-ynyl)phenate. The latter then acts as *substrate* in the *second* catalytic cycle, catalysed by Pd(II): a 5-*exo*-*dig* type heterocyclisation occurs through nucleophilic attack by oxygen on



Scheme 1 Sequential homobimetallic catalysis leading to **2**.

*b.gabriele@unical.it

the triple bond activated by coordination to Pd(II) followed by methoxycarbonylation,[5] leading to intermediate **I** and H–Pd–I. Reduction of the allylic alcohol moiety of **I** then takes place by the reaction of **I** with H–Pd–I (with formation of a π-allyl complex and elimination of water),[6] followed by regiospecific protonolysis[7] with formation of **2** and regeneration of the Pd(II) catalyst.

Several experimental evidences support the validity of the proposed catalytic sequence. (a) First of all, the allenic derivative **5a** was not an intermediate in the formation of **2a**, since it was not converted into **2a** under the reaction conditions. This result rules out the possibility that carbonylation occurs first, followed by deallylative cyclisation. (b) Practically no deallylation occurred when the reaction was carried out under the same conditions reported above, but in the absence of $Pd(PPh_3)_4$: with 1 mol % of PdI_2 along with 100 equiv of KI and 4 equiv of PPh_3 in anhydrous MeOH, **2a** was formed in only 8% GLC yield, the main reaction product being **4a** (83% GLC yield; **5a** was also present in the reaction mixture in 2% yield). This result confirms the essential role played by Pd(0) in promoting the initial deallylation step. (c) When the reaction was carried out with $Pd(PPh_3)_4$ in the absence of the PdI_2–KI catalyst, only traces of **2a** were obtained. This result shows that no carbonylative cyclisation occurs in the absence of the Pd(II) catalyst.

Interestingly, we have found that a PPh_3-stabilized Pd(0) complex could be formed *in situ* directly from PdI_2 and PPh_3 working in MeOH in the presence of small amounts of H_2O. In fact, under these conditions, formation of an I–Pd–CO_2H species (from the reaction between PdI_2, CO and H_2O)[8] occurs, whose decarboxylation[9] affords H–Pd–I in equilibrium with Pd(0) and HI. Actually, the use of PdI_2 (1 mol %) in conjunction with 100 equiv of KI, 4 equiv of PPh_3 and 200 equiv of H_2O (at 100 °C and under 30 atm of CO, as in the previous experiments) led to even better results with respect to the PdI_2–KI–$Pd(PPh_3)_4$ system: after 15 h, **2a** was obtained as the sole product in 96% GLC yield [91% isolated, Eqn. (1); this result should be compared with the 76% GLC yield obtained above with the PdI_2–KI–$Pd(PPh_3)_4$ system]. The presence of PPh_3 was essential for the reaction, its function being to stabilize the Pd(0) species responsible for the initial deallylation. In fact, by carrying out the above reaction without PPh_3, the main reaction product was **4a** (85% GLC yield), benzofuran **2a** being formed in only 7% GLC yield along with small amounts of **5a** (2%). Under the same conditions optimized for the reaction of **1a**, other 1-(2-allyloxyphenyl)-2-yn-1-ols **1b–d** were easily converted, after 15–24 h, into the corresponding benzofuran-2-ylacetic esters **2b–d** in high isolated yields [80–82%, Eqn. (1)].† It is noteworthy that the reaction worked nicely even with a very bulky substituent on the triple bond, as in the case of **1c** (R^2 = t-Bu).

In conclusion, we have reported an unprecedented catalytic sequence involving two sequential catalytic cycles: in the first cycle, promoted by Pd(0), deprotection of a nucleophilic oxygen occurs, with formation of the substrate[1] undergoing the subsequent carbonylative heterocyclisation process, catalysed by Pd(II). From a synthetic point of view, the net transformation corresponds to the one-step, selective conversion of simple and readily available starting materials[10] into very important heterocyclic derivatives in high yields. Benzofurans are in fact a very important class of heterocycles, which display a wide range of biological activity.[11] In particular, benzofuranacetic derivatives are known to exhibit a peculiar and very interesting pesticidal, insecticidal, and acaricidal activity.[12]

Bartolo Gabriele,*[a] Raffaella Mancuso,[b] Giuseppe Salerno[b] and Lucia Veltri[b]

[a]*Dipartimento di Scienze Farmaceutiche, Università della Calabria, 87036, Arcavacata di Rende (CS), Italy. E-mail: b.gabriele@unical.it; Fax: 39 0984 492044; Tel: 39 0984 492813*

[b]*Dipartimento di Chimica, Università della Calabria, 87036, Arcavacata di Rende (CS), Italy*

Notes and references

† Representative experimental procedure for the synthesis of **2**: a 250 mL stainless steel autoclave was charged with PdI_2 (5.0 mg, $1.39 \cdot 10^{-2}$ mmol), KI (230 mg, 1.39 mmol), PPh_3 (14.6 mg, $5.57 \cdot 10^{-2}$ mmol) and a solution of **1** (1.40 mmol) in anhydrous MeOH (6.3 mL). Water (50 μL, 2.78 mmol) was then added, and the autoclave was sealed, purged at room temperature several times with CO with stirring (5 atm) and eventually pressurized at 30 atm. After stirring at 100 °C for 15 h (**1a–c**) or 24 h (**1d**), the autoclave was cooled and degassed. The solvent was evaporated and products were purified by column chromatography [SiO_2, 1 : 1 hexane–CH_2Cl_2 (**2a**), 8 : 2 hexane–acetone (**2b**), 8 : 2 hexane–AcOEt (**2c**), 9 : 1 hexane–AcOEt (**2d**)]. *Characterization data* for **2a** (315 mg, 91%, colourless oil): IR (film): ν = 1743, 1454, 1252, 1160, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.49 (m, 1 H), 7.47–7.42 (m, 1 H), 7.27–7.15 (m, 2 H), 6.59–6.58 (m, 1 H), 3.82 (t, J = 7.3 Hz, 1 H), 3.72 (s, 3 H), 2.18–1.93 (m, 2 H), 1.43–1.24 (m, 4 H), 0.89 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 155.3, 154.8, 128.4, 123.9, 122.7, 120.7, 111.1, 103.8, 52.3, 45.7, 30.6, 29.5, 22.4, 13.8; MS (EI, 70 eV): *m/z* (%): 246 (33) [M^+], 187 (36), 131 (100). For **2b** (303 mg, 81%, yellow oil): IR (film): ν = 1739, 1453 1253, 1156, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.26 (m, 7 H), 7.25–7.12 (m, 2 H), 6.57 (t, J = 1.0 Hz, 1 H), 5.14 (s, br, 1 H), 3.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 155.0, 154.6, 128.8, 128.7, 128.2, 128.0, 124.1, 123.6, 122.7, 120.9, 111.1, 105.2, 52.6, 51.7; MS (EI, 70 eV): *m/z* (%) 266 (20) [M^+], 207 (100), 178 (31). For **2c** (275 mg, 80%, pale yellow solid, mp 60–61 °C): IR (KBr): ν = 1733, 1456, 1243, 1205, 1150, 755, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.49 (m, 1 H), 7.46–7.41 (m, 1 H), 7.25–7.14 (m, 2 H), 6.74 (dd, J = 1.0 Hz, 0.3 Hz, 1 H), 3.73 (d, J = 0.3 Hz, 1 H), 3.69 (s, 3 H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 154.5, 153.9, 128.5, 123.7, 122.7, 120.7, 111.0, 105.5, 55.9, 51.7, 35.1, 28.0. MS (EI, 70 eV): *m/z* (%): 246 (11) [M^+], 190 (100), 158 (35). For **2d** (298 mg, 82%, pale yellow oil): IR (film): ν = 1743, 1455, 1255, 1246, 1167, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.40 (m, 2 H), 7.27–7.17 (m, 2 H), 3.84 (dd, J = 9.1 Hz, 6.6 Hz, 1 H), 3.68 (s, 3 H), 2.21 (s, 3 H), 2.23–1.96 (m, 2 H), 1.41–1.17 (m, 4 H), 0.87 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 154.1, 149.6, 130.0, 123.8, 122.2, 119.0, 112.2, 111.1, 52.2, 43.6, 29.7, 29.5, 22.4, 13.9, 7.9; MS (EI, 70 eV): *m/z* (%) 260 (23) [M^+], 201 (53), 145 (100). Elemental analyses were satisfactory.

1 2-(1-Hydroxyalk-2-ynyl)phenols, with the –OH group unprotected, could not be prepared and used directly as substrates because of their instability, according to the literature: D. Pflieger and B. Muckensturm, *Tetrahedron Lett.*, 1990, **31**, 2299.

2 The use of PdI_2 in conjunction with an excess of KI as the catalytic system for carbonylation reactions was disclosed by us several years ago: B. Gabriele, M. Costa, G. Salerno and G. P. Chiusoli, *Chem. Commun.*, 1992, 1007; B. Gabriele, M. Costa, G. Salerno and G. P. Chiusoli, *J. Chem. Soc., Perkin Trans. 1*, 1994, 83.

3 J. Tsuji and T. Mandai, *J. Organomet. Chem.*, 1993, **451**, 15 and references therein.

4 The Pd(0) catalysed substitutive carbonylation of allylic derivatives is a well-known reaction: J. Tsuji, *Palladium Reagents and Catalysts*, John Wiley & Sons, Chichester, 1995, pp. 340–345; T. Mandia, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley-InterScience, New York, 2002, **vol. 2**, pp. 2505–2508.

5 For very recent reviews and accounts on this kind of reactivity, see: B. Gabriele, G. Salerno, M. Costa and G. P. Chiusoli, *J. Organomet. Chem.*, 2003, **687**, 219; B. Gabriele, G. Salerno, M. Costa and G. P. Chiusoli, *Curr. Org. Chem.*, 2004, **8**, 919; F. Alonso, I. Beletskaya and

M. Yus, *Chem. Rev.*, 2004, **104**, 3079; S. A. Vizer, K. B. Yerzhanov, A. A. A. Al Quntar and V. M. Vembitsky, *Tetrahedron*, 2004, **60**, 5499.
6 The possibility of obtaining a π-allylpalladium complex directly from the reaction between an allyl alcohol and a palladium hydride species without any activator was disclosed by us some years ago: B. Gabriele, G. Salerno, M. Costa and G. P. Chiusoli, *J. Mol. Catal.*, 1996, **111**, 43. More recently, the formation of an allylpalladium intermediate from allyl alcohols and an hydridopalladium complex has been reported: F. Ozawa, T. Ishiyama, S. Yamamoto, S. Kawagishi and H. Murakami, *Organometallics*, 2004, **23**, 1698.
7 The possibility of reducing an allyl alcohol moiety through the reaction with an H–Pd–I species with formation of a π-allyl complex followed by protonolysis has been recently demonstrated by us: G. P. Chiusoli, M. Costa, L. Cucchia, B. Gabriele, G. Salerno and L. Veltri, *J. Mol. Catal. A: Chem.*, 2003, **687**, 219.
8 B. Gabriele, L. Veltri, G. Salerno, M. Costa and G. P. Chiusoli, *Eur. J. Org. Chem.*, 2003, 1722 and references therein.
9 Decarboxylation of X–Pd–CO_2H complexes to give X–Pd–H species is a well-known process: see, for example, references 6, 7 and R. Bertani, G. Cavinato, L. Toniolo and G. Vasapollo, *J. Mol. Catal.*, 1993, **84**, 165; V. V. Grushin, *Chem. Rev.*, 1996, **96**, 2011.
10 Substrates **1** were easily prepared in 86–92% overall isolated yields starting from commercially available 2-hydroxybenzaldehyde (R^1 = H) or 2′-hydroxyacetophenone (R^1 = Me) through allylation (as described by B. S. Orlek, P. G. Sammes and D. J. Weller, *Tetrahedron*, 1993, **49**, 8179) followed by Grignard reaction with $R^2C{\equiv}CMgBr$.
11 For some very recent examples, see: E. Tsuji, K. Ando, J. Kunitomo, M. Yamashita, S. Ohta, S. Kohno and Y. Ohishi, *Org. Biomol. Chem.*, 2003, **1**, 3139; K. Kawasaki, M. Masubuchi, K. Morikami, S. Sogabe, T. Aoyama, H. Ebiike, S. Niizuma, M. Hayase, T. Fujii, K. Sakata, H. Shindoh, Y. Shiratori, Y. Aoki, T. Ohtsuka and N. Shimma, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 87.
12 T. N. Wheeler (Union Carbide Corp., USA), US Pat. 4,431,650, 1977 (*Chem. Abstr.* 1984, **101**, 54903u).