METHOD of the week

Palladium Scavengers

The SARLAH Group

Background:

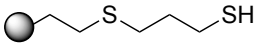
- Palladium-catalyzed cross-coupling reactions are used extensively
- In the pharmaceutical industry, strict regulatory limits have motivated the development of methods for metal scavenging
- Recovery of palladium can mitigate its high cost, limited supply, and environmental impact

Review: Economidou, M. *Org. Process Res. Dev.* **2023**, *27* (9), 1585–1615. https://doi.org/10.1021/acs.oprd.3c00210

Adsorption:

- Adsorption refers to the adhesion of particles onto a surface called the adsorbent
- Treatment of organic solutions with solid adsorbents (e.g. silica gels, resins, and activated carbon) allows filtration of the metal to give product-rich liquors
- Benefits: inexpensive, Limitations: formation of new impurities during treatment, leaching of impurities from the adsorbent, and yield losses

Functionalized Silicas-



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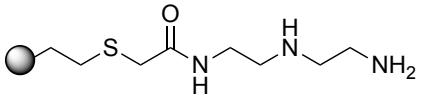

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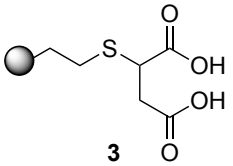

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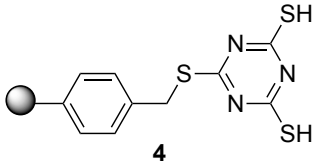

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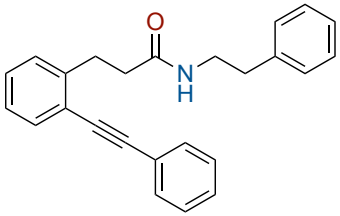
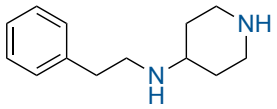
Activated Carbons-

- Darco KB-B
- Ecosorb C-941

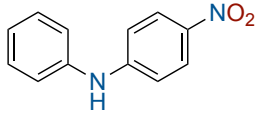
Functional Group Tolerance-



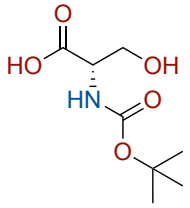
Initial: 700 ppm Pd
After treatment: 5 ppm Pd



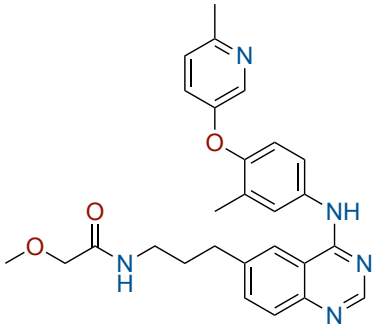
Initial: 1000 ppm Pd
After treatment: 7 ppm Pd



Initial: 30 ppm Pd
After Treatment: <1 ppm Pd

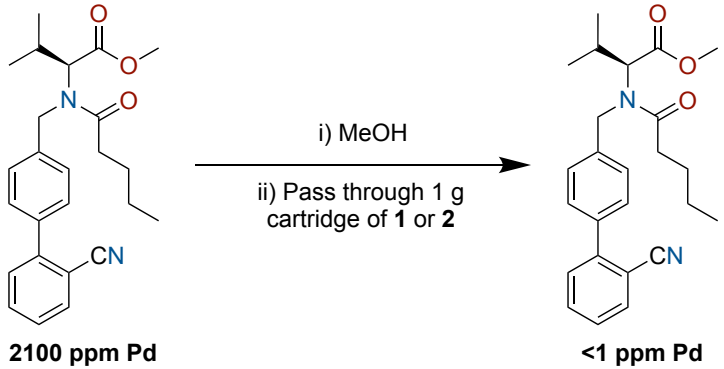


Initial: 300 ppm Pd
After treatment: <1 ppm Pd



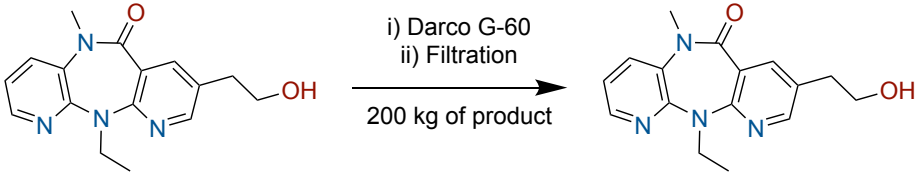
Initial: 307 ppm Pd
After treatment: 4.8 ppm Pd

Galaffu, N.*Org. Process Res. Dev.* **2007**, *11* (3), 406–413. https://doi.org/10.1021/op7000172



2100 ppm Pd **<1 ppm Pd**

Galaffu, N.*Org. Process Res. Dev.* **2007**, *11* (3), 406–413. https://doi.org/10.1021/op7000172



100 ppm Pd **<3 ppm Pd**

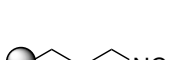
Chekal, B. *Org. Process Res. Dev.* **2015**, *19* (12), 1944–1953. https://doi.org/10.1021/op500412a

Palladium Scavengers

Isocyanides:

- First reported for the removal of ruthenium
- Operates by formation of an isocyanide insertion complex
- Homogenous scavenger **6** requires chromatography while silica-supported **5** does not

Common Scavengers-



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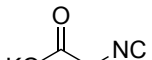

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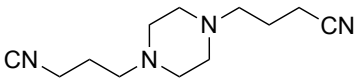

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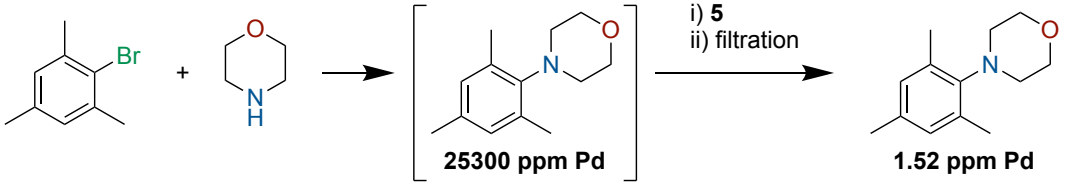
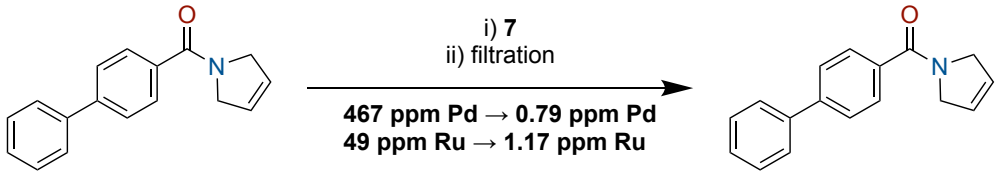




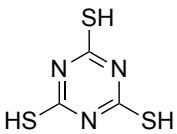
French, J. M. *Adv. Synth. Catal.* **2015**, *357* (2–3), 361–365. https://doi.org/10.1002/adsc.201400754

Extraction/Precipitation:

- Extraction involves chelation of palladium with a hydrophilic species to achieve transfer to the aqueous phase
- Precipitation involves formation of an insoluble metal complex allowing removal via filtration

Common Agents-

- Sodium bisulfite
- Trimercaptotriazines, e.g. TMT (**8**)
- L-Cysteine (**9**) and *N*-acetyl cysteine (**10**)
- Dithiocarbamates (DTCs), e.g. sodium dimethyl dithiocarbamate (**11**)



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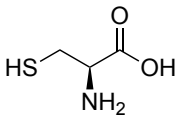

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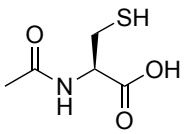

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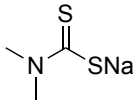

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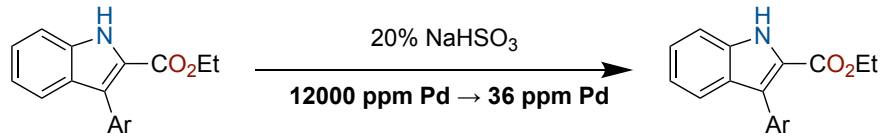
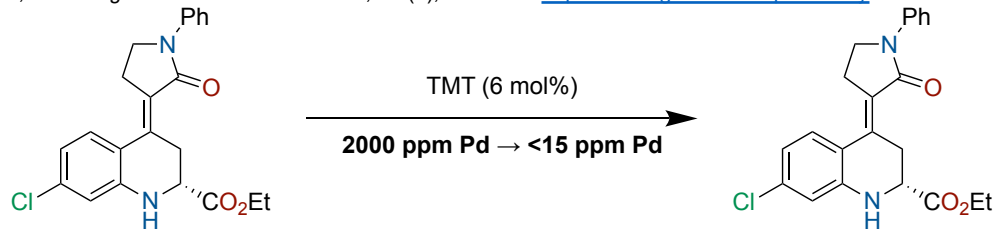
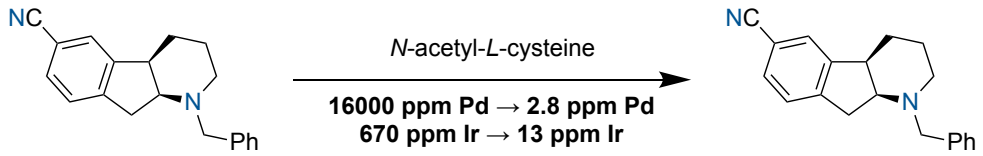


Bullock, K. M. *Org. Process Res. Dev.* **2008**, *12* (5), 896–899. https://doi.org/10.1021/op800064y



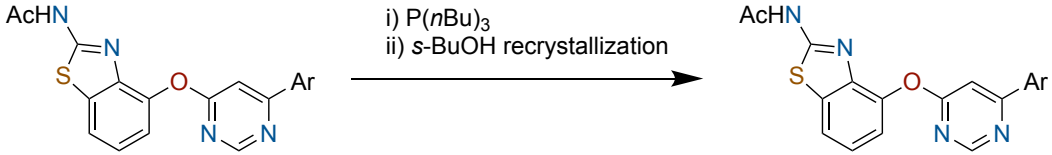
Banks, A. *Org. Process Res. Dev.* **2009**, *13* (6), 1130–1140. https://pubs.acs.org/doi/10.1021/op9001824



Qu, B. *Org. Process Res. Dev.* **2022**, *26* (3), 963–975. https://doi.org/10.1021/acs.oprd.1c00290

Crystallization:

- Crystallization is typically less efficient in the presence of metals
- Additives, including P(*n*Bu)$_3$, *N*-acetyl cysteine, L-cysteine, and xanthates, are often necessary



Larsen, R. D. *J. Org. Chem.* **1994**, *59* (21), 6391–6394. https://doi.org/10.1021/jo00100a048 **<10 ppm Pd**