# Base metal catalysis

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Catalysis is one of the overarching principles of green chemistry that offers significant energy, environmental and economic savings. At present, 85% of chemical products worldwide, both bulk and fine chemicals are made *via* methods that use a metal catalyst; most of these processes use precious metals to perform the chemical transformation. However, the limited abundance of these metals poses a substantial threat to these industries, even those metals that are forecast to last for another 100 years (Figure 1) have various associated issues, such as the uncertain stability of their price based on the current rates of extraction. Furthermore, geopolitical uncertainty in areas that currently mine these metals, as well as potential market manipulation to limit the amount exported, can cause global shortages on the international markets.[1]

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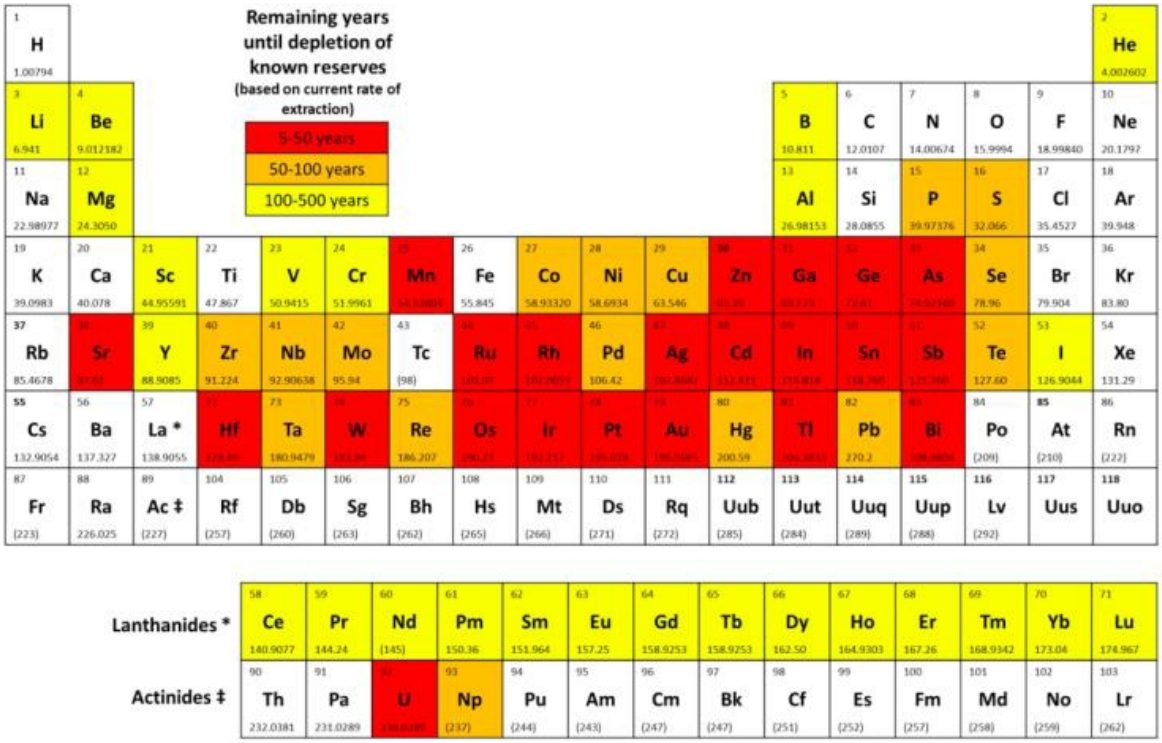


*Figure 1: **Periodic table displaying critical elements (Reproduced from A.Hunt [2] with permission from the Royal Society of Chemistry)***


1. J. Maes, E. A. Mitchell and B. U. W. Maes, Base Metals in Catalysis: From Zero to Hero, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 16, pp. 192-202.
2. A. Hunt, *Element Recovery and Sustainability*, Royal Society of Chemistry, Cambridge, UK, 2014.



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# Application of base metal catalysts



The industry has gone some way in mitigating the cost and scarcity of catalytic species based on rare metals, through the development of metal reclaiming processes. An alternative strategy to metal reclaiming processes is to shift away from the use of scarce metals to more earth abundant and cheaper base metal catalysts. The major advantages to the use of base metal catalysts, aside from the greater abundance and low cost, include the fact that base metals exhibit low toxicity and are also environmentally benign.[1]

The application of such metals in catalysis has crawled behind the huge advances made by precious metals however; there has been a renewed interest in the challenge in matching or outperforming the high activity and selectivity demonstrated by the platinum group metals, through investigating new ligands and reaction conditions that overcome the unpredictable nature of base metals.  First row transition metals are known to readily undergo one electron oxidation state changes, partake in uncontrolled reactions with elemental oxygen and display facile ligand redistribution. In contrast, precious metal catalysis has established a plethora of predictable chemistries based on two electron changes between oxidation states. Base metals such as cobalt, copper, nickel, iron among others are some of the most earth abundant and the nearly limitless supply of iron allows its use on vast reaction scales such as those of the Haber–Bosch ammonia synthesis.[2]

Cobalt, iron and nickel catalysts have been investigated in parallel with palladium catalysts for carbon-carbon bond formation and it has been found that when supported by the appropriate ligands, nickel and cobalt can enable efficient coupling reactions allowing the formal addition of carbon-hydrogen bonds in unsaturated systems. [2] Iminopyridine ligands have shown promise as privileged ligands in iron catalysis, and have been used in iron-catalysed methodologies for the production of olefin hydrogenation, carbon–carbon and carbon–hetroatom bond formation.

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2. P. Chirik and R. Morris, Getting Down to Earth: The Renaissance of Catalysis with Abundant Metals, *Acc. Chem. Res.*, 2015, 48, 2495-2495.

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# Use in the pharmaceutical industry



Within the pharmaceutical industry, precious metal based catalysts are predominantly used in cross-coupling reactions, with 17% of the transformations catalysed by palladium [1] (please see the introduction to C-H activation), other palladium catalysed transformations include hydrogenation/hydrogenolysis, Bn/CBz deprotection.

Given the prevalence of the use of precious metals in the synthesis of important molecules, finding alternative methods is not clear cut; as there are associated issues with the required selectivity, and the use of a different method would require complete or partial redesign of large scale processes. Moreover, small changes in a production process for pharmaceutically relevant molecules would require reopening of the associated registration files, which would incur further costs. In addition to the issue of the scarcity and cost of precious metals, the ligands associated with them in a given method can be more expensive per mole than the metal itself, and there are no means for their recovery. [2]

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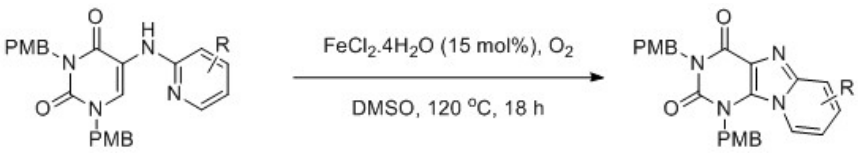
# CHEM21 case study: Base metal catalysed C-H Amination

This case study was provided by Prof. Bert Maes' ORSY team at the University of Stuttgart.

Purines and their derivatives exhibit a broad range of biological activity, making them important structural motifs in the pharmaceutical industry.[1][2][3] The development of efficient synthetic methods for the formation of purines is an active area of research; the main challenge to obtaining good purine based receptor (ant)agonists and enzyme inhibitors is overcoming the lack of selectivity for a particular enzyme. Modifying the substitution pattern and alterations on the purine core can both result in improved selectivity and increased reactivity. As such, synthetic approaches that construct new scaffolds based on purines that can be easily functionalised are important.

Interestingly, heteroarenes annulated to the C8-N9 unit of the purine core have received less interest than their C8-N7 counterparts,[4][5][6][7][8][9][10][11][12][13] despite being present in the structures of variety of pharmaceutical agents such as in phosphodiesterase type 5 (PED5) inhibitors.[12] However, current synthetic strategies to achieve such scaffolds do not allow for efficient post-modification of the pyrimidine substitution pattern.[14] Given the potential of such purine cores, CHEM21 researchers developed an efficient synthesis of substituted 1,3-bis(4-methoxybenzyl)pyrido[1,2*e*]purine-2,4(1*H*,3*H*)-diones based on an iron catalysed direct amination reaction on 5-(pyridin-2-ylamino)pyrimidine-2,4(1 *H*,3*H*)-diones, using oxygen as the oxidant in the process (**Scheme 1**). The products from this transformation would allow for further elaboration in a late stage synthesis.[14]




*Scheme 1*: ***Iron catalysed C-H amination for the formation of C8-N9 purines (Maes et al.,2013 [[14]])***

Intermolecular copper-mediated direct amination of aromatics with amidines involving C($sp^2$)-H using oxygen as an oxidant had been previously reported by both Buchwald[15] and Zhu,[16] however when these approaches were applied to the parent substrate, the

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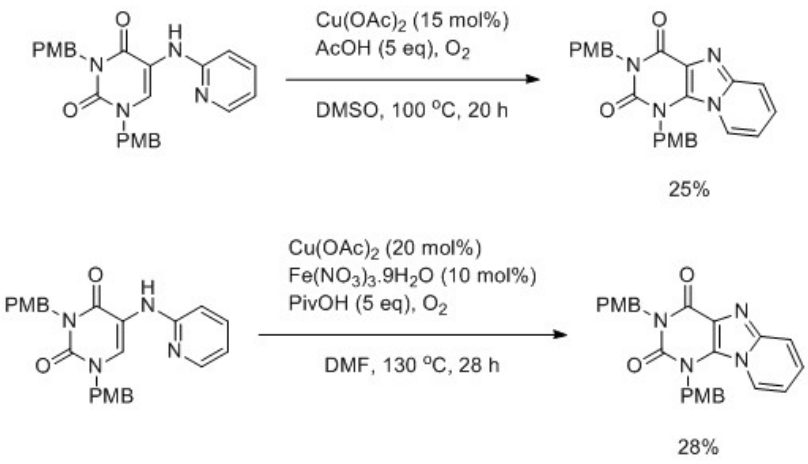
product was only achieved in 25 and 28% for the Buchwald and Zhu methods respectively (**Scheme 2**).[14] Given the low yields observed with the copper catalyst due to issues of selectivity, the CHEM21 researchers investigated the use of an iron based catalyst given its higher crustal abundance and much lower cost.[14]




*Scheme 2*: ***Buchwald and Zhu Copper catalysed C-H amination methods applied to the synthesis of C8-N9 purines (Maes et al.,2013 [14])***

The method developed by the CHEM21 researchers boasts of excellent functional group tolerance, and exhibited higher chemoselectivity than the copper catalysts especially with respect to substrates furnished with halogens, which would allow further functionalisation of the annulated ring post-synthesis.[14]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