



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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Remaining years until depletion of known reserves (based on current rate of extraction)																					
<div style="display: flex; justify-content: space-around;"> <div style="background-color: red; color: white; padding: 2px;">0-50 years</div> <div style="background-color: orange; color: white; padding: 2px;">50-100 years</div> <div style="background-color: yellow; color: black; padding: 2px;">100-500 years</div> </div>																					
1 H 1.00794																	2 He 4.002602				
3 Li 6.941	4 Be 9.012182															5 B 10.811	6 C 12.0107	7 N 14.00674	8 O 15.9994	9 F 18.99840	10 Ne 20.1797
11 Na 22.98977	12 Mg 24.3050															13 Al 26.98153	14 Si 28.0855	15 P 30.97376	16 S 32.066	17 Cl 35.4527	18 Ar 39.948
19 K 39.0983	20 Ca 40.078	21 Sc 44.95591	22 Ti 47.867	23 V 50.9415	24 Cr 51.9961	25 Mn 54.93804	26 Fe 55.845	27 Co 58.93320	28 Ni 58.6934	29 Cu 63.546	30 Zn 65.38	31 Ga 69.723	32 Ge 72.61	33 As 74.92160	34 Se 78.96	35 Br 79.904	36 Kr 83.80				
37 Rb 85.4678	38 Sr 87.62	39 Y 88.905	40 Zr 91.224	41 Nb 92.90638	42 Mo 95.94	43 Tc (98)	44 Ru 101.07	45 Rh 101.0668	46 Pd 106.42	47 Ag 107.8682	48 Cd 112.411	49 In 114.818	50 Sn 118.710	51 Sb 121.757	52 Te 127.60	53 I 126.9044	54 Xe 131.29				
55 Cs 132.9054	56 Ba 137.327	57 La* 138.9055	58 Hf 178.49	59 Ta 180.9479	60 W 183.84	61 Re 186.207	62 Os 190.23	63 Ir 192.222	64 Pt 195.078	65 Au 196.9665	66 Hg 200.59	67 Tl 204.3871	68 Pb 207.2	69 Bi 208.9804	70 Po (209)	71 At (210)	72 Rn (222)				
87 Fr (223)	88 Ra 226.025	89 Ac‡ (227)	90 Rf (257)	91 Db (260)	92 Sg (263)	93 Bh (262)	94 Hs (265)	95 Mt (266)	96 Ds (271)	97 Rg (272)	98 Uub (285)	99 Uut (284)	100 Uuq (289)	101 Uup (288)	102 Lv (292)	103 Uus (292)	104 Uuo (222)				
Lanthanides*																					
58 Ce 140.9077	59 Pr 144.24	60 Nd (145)	61 Pm 150.36	62 Sm 151.964	63 Eu 157.25	64 Gd 158.9253	65 Tb 158.9253	66 Dy 162.50	67 Ho 164.9303	68 Er 167.26	69 Tm 168.9342	70 Yb 173.04	71 Lu 174.967								
Actinides‡																					
90 Th 232.0381	91 Pa 231.0289	92 U 238.0289	93 Np (237)	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (262)								

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

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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]

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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–heteroatom bond formation.

1. J. Maes, E. Mitchell and B. 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*, 2016.
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

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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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2. J. Maes, E. Mitchell and B. 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*, 2016.

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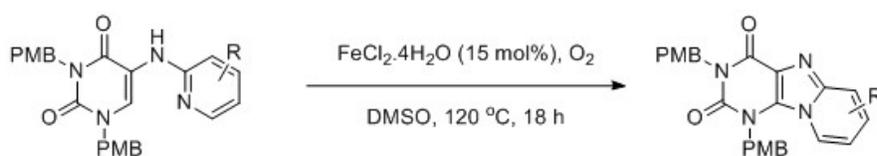
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CHEM21 case study: Base metal catalysed C-H Amination

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[1,2e]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]



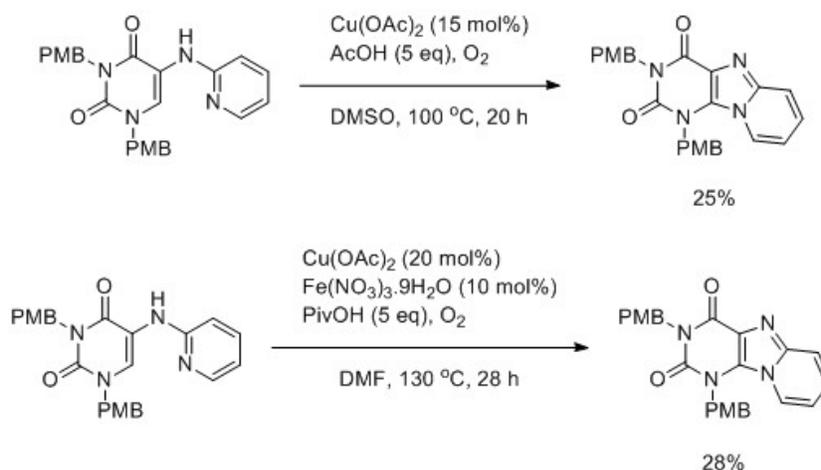
Scheme 1: Iron catalysed C-H amination for the formation of C8-N9 purines (Maes et al., 2013 ^[14])

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Intermolecular copper-mediated direct amination of aromatics with amidines involving C(sp²)-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 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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