

The impact of earth-abundant metals as a replacement for Pd in cross coupling reactions

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Abstract. Substitution of one metal catalyst for another is not straightforward as simply justifying this change based on the availability and/or cost of the metals. A life cycle-like assessment was performed leading to the conclusion that the commonly held view that use of earth-abundant metals (and in this case study, Ni) are replacements for palladium most notably in cross coupling reactions, and Suzuki-Miyaura couplings, in particular, is an incomplete analysis of the entire picture. This notion can be misleading, and unfortunately derives nowadays mainly from the standpoint of cost, and to some degree, the relative natural abundance and mining impact of each metal. However, a more realistic appreciation emerges when several additional reaction parameters involved in the couplings are considered. Such an analysis unequivocally points to the major impact on climate change brought about by use of organic solvents, while the metals actually play subordinate roles in terms of CO₂-release into the environment. Clearly, this study reveals that several factors contribute in various ways to the overall carbon footprint. Hence, a far more detailed analysis is required than that typically being utilized!

Introduction

In reading any paper these days in most journals containing transition metal-mediated synthetic organic chemistry claiming to reduce our dependence on “precious metal catalysis”; ...well, as a search using SciFinder indicates, this is really about palladium; not platinum; not gold; palladium. So, once the introductory comments along these lines are made,¹ what’s to be expected? The answer is almost always the same: given the occurrence and relative amounts of Pd involved, the chemistry community is too dependent upon palladium for metal-catalyzed couplings due to its limited availability. Hence, one usually interprets this to mean, in either the short² or long term,³ that Pd must be replaced with “earth-abundant” metals such as Ni, Cu, and Co. Additional justification for switching to a base metal then shifts to the one parameter with which virtually all users can identify: cost. And what is cited as proof that switching to earth-abundant metal catalysis makes unequivocal economic sense? Answer: catalog pricing, showing how much less costly each of these base metals is compared with palladium.⁴ And while there are many exciting scientific advances emerging from development of new methodologies employing base metals, this buy in by the community that cost, natural abundance, and occasionally the pollution originating from mining and refining, rather than just the pure science associated with each metal is so pervasive that it has led to a long and (seemingly) impressive list of “supporting evidence”, further advancing these concepts. Thus, in addition to the many individual papers continuously promoting this notion,¹ there are now thematic issues noting collaborations highlighting earth-abundant

metal usage (complete with tabular surveys comparing costs).⁵ These “short cuts” taken over the years have led to conclusions that may well be misguided, as documented herein, surrounding use of earth-abundant metals. Also, part of this equation may well be a reflection of an overall deficiency in our ability to accurately measure the environmental impact of such widespread processes, potentially pointing to severe deficiencies in education in these particular aspects of green and sustainable chemistry found among the next generation of “up-and-coming” chemists.

What is driving this international interest?⁶ Could it really be just on the basis of the up-front cost differentials between Pd salts and those of cheaper metals? Is the available evidence overwhelming such that the move away from palladium is truly compelling, whether focusing on cost, relative abundance, or environmental issues such as sustainability? Direct comparisons along the lines shown in Figure 1 would, in fact, lead to this conclusion. But these numbers reflect a 1:1 relationship in terms of all reaction parameters. For example, if a Ni-catalyzed reaction requires 5 mol % catalyst, then 5 mol % Pd is the comparison amount being used. The same is true with organic solvents: those used for Ni are those being used for Pd catalysis. How much stock can be placed in these numbers? Does any process chemist making anything at scale use as much Pd as is typically needed with Ni? The answers to these questions are, or should be, obvious. In other words, is it possible that most of the discussion surrounding replacement of palladium in synthesis by earth-abundant metals for environmental reasons is actually misleading, and maybe improperly stated in terms of the bigger picture? There are those who have already started to ask the same question.⁷ So, is earth-abundant metal chemistry the path forward to a greener future? The numbers populating Figure 1 would appear to say so; the footprint for Pd, according to indicators used from the European Footprint (EF) model,⁸ is orders of magnitude greater than for Ni. But wait; is this conclusion the same after examining the many other variables associated with using each metal?

material	acidification ^a	climate change ^b (100 years)	ecotoxicity ^c (freshwater)	energy resources ^d (non-renewable)	eutrophication ^e (freshwater)	eutrophication ^f (marine)	eutrophication ^g (terrestrial)	human toxicity ^h (carcinogenic)
Ni	2.00	17.53	399.60	263.45	0.002	0.033	0.370	0.00000004
Pd	2277.66	11289.38	229970.45	168374.58	1.133	55.861	832.288	0.00000688
material	ionizing radiation ⁱ	land use ^j	material resources ^k	ozone depletion ^l (100 years)	particulate matter ^m	photochem. ozone formation ⁿ	water use ^o	human toxicity ^p (non-carcinogenic)
Ni	2.10	123.14	0.002	0.00000035	0.00000310	0.240	75.36	0.00000056
Pd	238.71	90,607.85	0.758	0.00010410	0.00296518	303.801	3025.49	0.00032414

^a EF v3.1 no LT; mol H⁺ eq. ^b EF v3.1 no LT; kg CO₂ eq. ^c EF v3.1 no LT. ^d EF v3.1 no LT, kg U235 eq. ^e EF v3.1 no LT, Pt. ^f EF v3.1 no LT, kg Sb eq. ^g EF v3.1 no LT, kg CFC-11 eq. ^h EF v3.1 no LT, disease incidence. ⁱ EF v3.1 no LT, kg NMVOC eq. ^j EF v3.1 no LT, m3 deprived. ^k EF v3.1 no LT, CTUh. ^l EF v3.1 no LT, kg CFC-11 eq. ^m EF v3.1 no LT, disease incidence. ⁿ EF v3.1 no LT, kg NMVOC eq. ^o EF v3.1 no LT, m3 deprived. ^p EF v3.1 no LT, CTUh.

Figure 1. Direct, 1:1 comparison of environmental indicators for the production of 1 kg of virgin (*i.e.*, freshly mined, from ore) Ni and Pd.⁹

Firstly, what needs to be appreciated is that any discussion involving both platinum group metals (PGMs) and base metals has many variables that the chemistry community today is starting to appreciate to a greater extent. In the past, due to the availability of limited data, consideration of variables such as price, natural abundance, and access (*i.e.*, the impact of mining) on the relative footprint associated with each metal unequivocally led to the conclusion that base metal usage is highly preferred. However, an

accurate, full picture did not emerge until recently when additional, important data are taken into account. For example, use of lower loadings of Pd catalysts can reduce environmental differences between metals, and while this analysis still favors base metals, different recovery techniques might come into play. Secondly, as will be shown, use of different reaction media can be a major determining factor.

To address conflicting arguments of availability, cost, environmental issues, endangered status, etc.; that is, to get at the reality of earth-abundant metal usage in organic synthesis, it seems timely to do an analysis that *focuses on as many reaction parameters* involved with transition metal catalysis as is feasible. In other words, factors that are not normally considered in the analysis, including, *e.g.*, solvent purchase and its more costly disposal as waste. What about the actual amounts of metal needed, and the associated ligands that might require research time and effort to find and/or optimize when using Ni? Is it important to determine residual metal content in the products, especially regarding drugs that the regulatory authorities require be removed (taking valuable time and adding cost, not to mention generation of more waste) to meet their stringent standards?⁹ These, and several other factors (*e.g.*, energy demands, as in typically higher reaction temperatures using Ni; functional group tolerance,¹⁰ etc.) are rarely part of the calculus leading to a conclusion as to which type of catalysis should actually be pursued. The effects of these parameters on climate change loom large, and cannot be ignored. Hence, these parameters can play important roles and suggest that an innate discrimination against Pd in their absence may lead to an inaccurate conclusion.

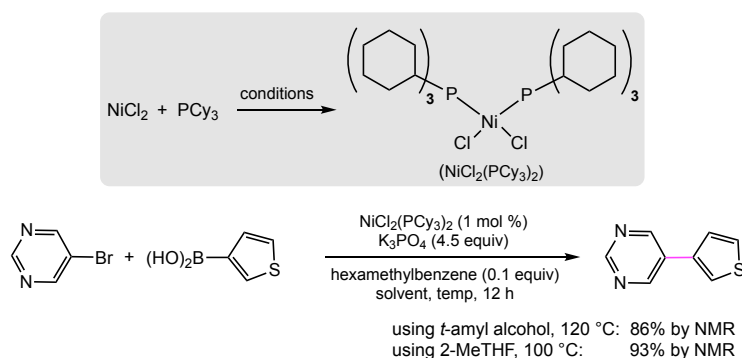
As a community, we have started to appreciate the value of utilizing, when possible, more extensive metrics associated with environmental issues. A life cycle assessment (LCA), while more time-consuming and costly, is recognized as the premier approach to evaluating the “greenness” of any process.¹¹ And while this may, today, be a reasonable approach mainly in industrial circles, nonetheless, an LCA is rapidly becoming the gold standard going forward. Nothing approaching this type of fact-finding mission yet exists for earth-abundant metal usage, at least to our knowledge. Therefore, it is the intention of this *Perspective* to provide more insight behind this alternative, base metal approach to Group 10 metal-catalyzed cross coupling chemistry. Isn't it time to find out whether using base metal catalysis as practiced today and encouraged for tomorrow makes sense? Should we be investing time and resources in alternative options to palladium? The conclusions that come forth from unbiased calculations is that the use of earth abundant (and also endangered)¹² metals in place of existing cross coupling technologies that rely on lower loadings of palladium in alternative reaction media is NOT inevitably the best solution; not in terms of cost, nor in terms of the environment and overall impact on sustainability, and certainly not in terms of climate change.¹³ Hence, use of Ni, in particular, while representative of earth-abundant metals, is not necessarily the best pathway for catalysis of cross couplings over palladium, either now or in the future.

The data

Two literature reports focused on the most common, by far, Group 10 metal-catalyzed reaction in the pharmaceutical industry were used to illustrate the point: a Suzuki-Miyaura cross coupling catalyzed by Ni and Pd, leading to the same product. Earth-abundant metal catalysis continues to be developed in this direction, with nickel leading the move away from use of palladium. Other metals have made an appearance, such as cobalt¹⁴ and more recently, Fe,¹⁵ but these reports are relatively few in number and

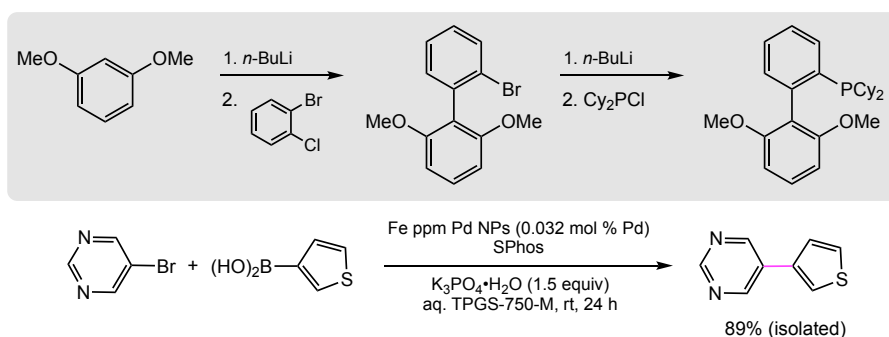
do not in any way change the outcome of this study. The model reaction associated with the paper appearing in *Organic Letters* on this topic is representative of this goal (Scheme 1).¹⁶ In this example, the mass balance for preparation of the catalyst, the substrates, and the Suzuki-Miyaura reaction are all considered. The other reaction, also representative of an alternative technology relying on well-established ligated Pd catalysis derives from a study appearing in *Science*,¹⁷ where ppm levels of palladium catalysis are employed in the same couplings (Scheme 2). Here, the mass balance for the preparation of the surfactant, the SPhos ligand, the substrates, and the coupling reaction itself are all evaluated. These published literature (unoptimized) procedures indicate that in order to prepare 1 kg of heterobiaryl product using each process as described, 18.9 g of NiCl₂ are needed at a cost of \$17.40, while 0.50 g of Pd(OAc)₂ need be invested costing \$36.50. As will be shown, however, that while these numbers reflect what is surely anticipated (*i.e.*, that using Ni is far less costly than is Pd), the more meaningful reaction parameter is that water (and not organic solvent) serves as the reaction medium.¹⁸ Couplings in water, where both the reaction partners and ligated catalysts are insoluble, is enabled by

Scheme 1. Reaction taken from the paper in *Organic Letters*¹⁶



the (representative) designer surfactant TPGS-750-M present at the two-weight percent level (*i.e.*, 20 mgs/mL of water).¹⁹ Nonetheless, as the data unequivocally confirm, factors such as use of a surfactant and many others, *including the choice of metal*, are of little-to-no consequence in terms of impact on cost, and notably, climate change and sustainability, and in general, the overall analysis (*vide infra*).

Scheme 2. Suzuki-Miyaura coupling using ppm Pd taken from the paper in *Science*¹⁷



Cost

While nickel is much more “earth-abundant” relative to palladium,²⁰ its price in any catalog and at any quantity should not even be a consideration in any analysis of its present or future prospects for replacing palladium as the premier PGM for catalysis in organic synthesis. Use of a Ni(II) salt (quantity-wise) represents an extremely small component of the overall picture (Figure 2), which is also the case for catalytic amounts of Pd(II)(OAc)₂. While it is correct to state that the relative cost of Pd can be much greater than that of Ni,²¹ in terms of all the parameters involved in converting reaction partners to a targeted product, both are insignificant. This remains true even when the amount of Pd catalyst is increased by a factor of ten; that is, to (unsustainable) loadings characteristic of many currently used couplings which, on occasion, may even be stoichiometric in palladium.²² Instead, what should be the focus of attention is the role that solvents play in determining overall cost and, notably, other categories of true consequence, such as toxicity, ionizing radiation, impact on ozone and water resources, and acidification, and most notably, their impact on climate change. That is, the total environmental footprint of both processes, rather than the footprint of metal usage alone, is significant by comparison (*vide infra*; Figure 3).

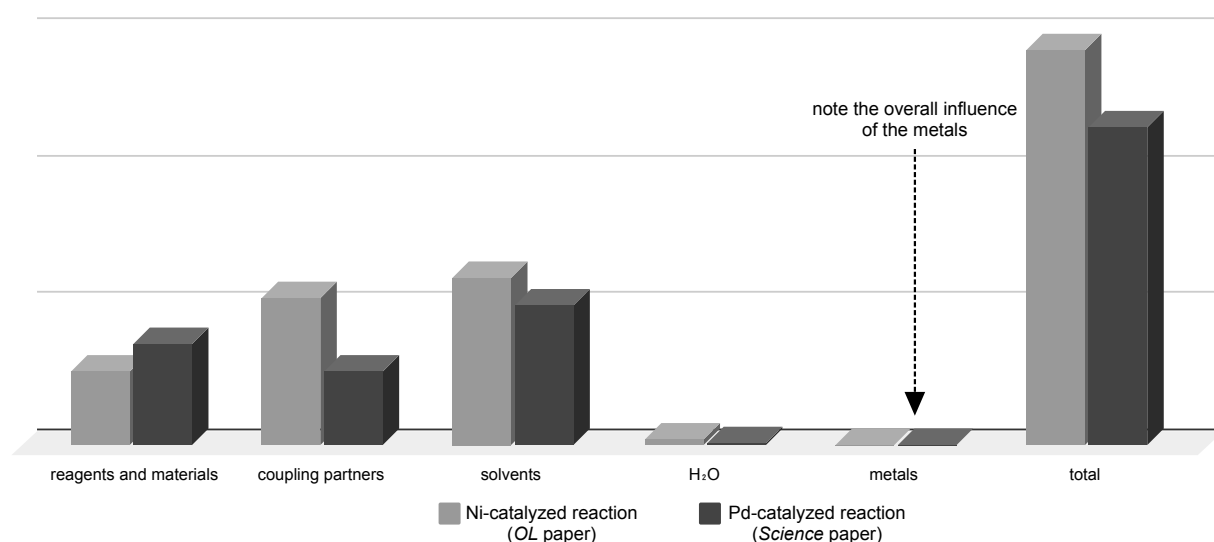


Figure 2. Relative costs associated with the numerous parameters involved for Suzuki-Miyaura couplings

The numbers in Figure 3 (which have varying units and hence, cannot be directly compared, column-to-column) do point out that for the processes involved, where post-reaction handling and waste treatment are (assumed) to be the same (extraction, purification via column chromatography, and incineration), palladium has, in fact, a slightly higher footprint than does nickel if treated individually. Looking at the entire process for each reaction, however, where organic solvent usage is higher, as is substrate usage in Ni catalysis, the micellar catalysis approach in water is roughly 45-50% “greener” in terms of the total carbon footprint.

	acidification ^a	climate change ^b (prod. + market)	climate change ^c (incineration)	climate change ^d (total)	ecotoxicity ^e (freshwater)	energy resources ^f (non-renewable)
Ni (paper in <i>OL</i>)	0.02	0.15	0.0375	0.19	3.40	2.24
Pd (paper in <i>Science</i>)	0.48	2.37	0.0010	2.37	48.29	35.36
^a EF v3.1 no LT; mol H+ eq. ^b EF v3.1 no LT; GWP100 years, kg CO ₂ eq. ^c EF v3.1 no LT; GWP100 years, kg CO ₂ eq. ^d EF v3.1 no LT; GWP100 years, kg CO ₂ eq. ^e EF v3.1 no LT, MJ eq.						

	eutrophication ^a (freshwater)	eutrophication ^b (marine)	eutrophication ^c (terrestrial)	human toxicity ^d (carcinogenic)	human toxicity ^e (non-carcinogenic)	ionizing radiation ^f
Ni (paper in <i>OL</i>)	0.0000	0.0003	0.0032	0.000000003	0.0000000047	0.02
Pd (paper in <i>Science</i>)	0.0002	0.0117	0.1748	0.000000014	0.0000000681	0.05
^a EF v3.1 no LT, kg P eq. ^b EF v3.1 no LT, kg N eq. ^c EF v3.1 no LT; molc N eq. ^{d,e} EF v3.1 no LT; CTUh. ^f EF v3.1 no LT; kg U235 eq.						

	land use ^a	material resources ^b (minerals, metals)	ozone depletion ^c (ODP100 years)	particulate matter ^d	Photochem. ozone formation ^e	water use ^f
Ni (paper in <i>OL</i>)	1.05	0.00002	0.0000000029	0.0000000264	0.0020	0.64
Pd (paper in <i>Science</i>)	19.03	0.00016	0.0000000219	0.0000006227	0.0638	0.64
^a EF v3.1 no LT, Pt. ^b EF v3.1 no LT, kg Sb eq. ^c EF v3.1 no LT; kg CFC-11 eq. ^d EF v3.1 no LT; disease incidence. ^e EF v3.1 no LT; kg NMVOC eq. ^f EF v3.1 no LT; m3 deprived.						

	acidification ^a	climate change ^b (prod. + market)	climate change ^c (incineration)	climate change ^d (total)	ecotoxicity ^e (freshwater)	energy resources ^f (non-renewable)
Ni (paper in <i>OL</i>)	9.40	1314.68	1011.22	2325.90	13,919.81	28,346.61
Pd (paper in <i>Science</i>)	5.96	821.06	733.03	1554.09	9239.08	18,249.63
^a EF v3.1 no LT; mol H+ eq. ^b EF v3.1 no LT; GWP100 years, kg CO ₂ eq. ^c EF v3.1 no LT; GWP100 years, kg CO ₂ eq. ^d EF v3.1 no LT; GWP100 years, kg CO ₂ eq. ^e EF v3.1 no LT, MJ eq.						

	eutrophication ^a (freshwater)	eutrophication ^b (marine)	eutrophication ^c (terrestrial)	human toxicity ^d (carcinogenic)	human toxicity ^e (non-carcinogenic)	ionizing radiation ^f
Ni (paper in <i>OL</i>)	0.22	1.44	14.29	0.00000075	0.00003	27.51
Pd (paper in <i>Science</i>)	0.11	0.88	9.09	0.00000046	0.00002	15.50
^a EF v3.1 no LT, kg P eq. ^b EF v3.1 no LT, kg N eq. ^c EF v3.1 no LT; molc N eq. ^{d,e} EF v3.1 no LT; CTUh. ^f EF v3.1 no LT; kg U235 eq.						

	land use ^a	material resources ^b (minerals, metals)	ozone depletion ^c (ODP100 years)	particulate matter ^d	Photochem. ozone formation ^e	water use ^f
Ni (paper in <i>OL</i>)	4921.12	0.02790	0.00012	0.00008	6.38	1403.95
Pd (paper in <i>Science</i>)	2886.66	0.01412	0.00051	0.00005	4.21	739.83
^a EF v3.1 no LT, Pt. ^b EF v3.1 no LT, kg Sb eq. ^c EF v3.1 no LT; kg CFC-11 eq. ^d EF v3.1 no LT; disease incidence. ^e EF v3.1 no LT; kg NMVOC eq. ^f EF v3.1 no LT; m3 deprived.						

Figure 3. Environmental footprint for just metal usage (top), and for the entire process (bottom). All indicators other than climate change represent the environmental burdens of material production (and market distribution). Climate change contains an additional indicator for waste treatment (incineration).

These numbers get even more lopsided against use of base metal catalysis when the details associated with using water as the gross reaction medium are considered. For Group 10 metal-catalyzed couplings leading to products that are usually solids (as routinely observed in the pharmaceutical industry), these are water-insoluble and hence, as noted previously,²³ participate in molecule-by-molecule exchange between micellar arrays. This occurs through the water, and in finding themselves, leads to precipitation. In other words, a “recrystallization” takes place automatically, in which case the “workup” oftentimes involves nothing more than a filtration. While this difference in purification is obvious (*i.e.*, no extraction and/or chromatography is needed), just what such a cost savings might be will vary and *is not included in this analysis*. Nonetheless, this will add further to the baseline differential in terms of total carbon footprint, already at *ca.* 45-50%.

The energy invested per reaction is yet another reaction variable that has not been included in the tabular survey illustrated in Figures 1-3. In the given example relying on aqueous micellar catalysis (Scheme 2) the implication is that couplings are taking place at much higher concentrations that exist within the inner micellar cores,²⁴ whereas traditional bond formations in organic solvents are impractical under these conditions (*i.e.*, reactions cannot be stirred). This leads to milder reactions conditions, and aside from the obvious lower reaction temperatures and hence, less energy being invested, another important outgrowth is the impact of temperature on the resulting impurity profile. Cleaner reactions characteristic of chemistry in water translates as well into a time savings associated with product isolation/purification, which can also lead to benefits on total solvent use and overall cost. The savings in time, energy investment, and use of resources for product cleanup are also not quantified herein.

And what about residual metals in the product of a Ni- or Pd-catalyzed coupling? All regulatory authorities make it very clear that only 20 and 10 ppm / day / dose is allowable for Ni and Pd, respectively.²⁵ Using 1-5 mole percent nickel virtually guarantees that cleanup to remove residual nickel will be needed should a cross coupling of this type *en route* to an API be used at a later stage of its synthesis. On the other hand, with lower Pd loadings associated with couplings run in water, levels of Pd found in an API are independent of when in the sequence the coupling is performed, since the products having residual levels of Pd above the FDA allowance are very rare.²⁶ This consideration undoubtedly adds even more cost to the bottom line when using an earth-abundant metal as catalyst.

And how are safety issues to be quantified? Flammable and toxic organic solvents are typically stored in large holding tanks on a manufacturing site. This raises questions as to, *e.g.*, governmental imposed limits placed on infrastructure, which might then dictate exactly where, how, and to what extent a target compound (*i.e.*, quantity) can be made at a given location. Efficiency, and thus, economics are likely to be impacted if such restrictions exist (*i.e.*, the economy of scale may be limited).

Then there is the question regarding waste generation and disposal. The rules that exist in any location throughout the world vary, and could certainly place additional limitations on production. Using aqueous media may ease many of these concerns, but each situation is likely to be unique. Nonetheless, what is clear from this analysis is that chemistry in water *vs.* use of petroleum-based *organic* solvents (or solvents obtained from any source, including renewables) is the key factor that determines the impact of the catalysis on climate change, and to a much lower extent the choice of metal, earth-abundant or otherwise. Water-based chemistry offers, in contrast, a high potential in this regard as already

demonstrated at Novartis.²⁷ Hence, the baseline differential of 45-50% is likely to be even greater when, on a case-by-case basis, all of these additional factors are considered. Indeed, a more likely number is far north of 50%.

Climate change & sustainability

A closer look at the data in Figure 3 (bottom) reveals that the total impact on climate change associated with the two processes is far from equal. The value for the Ni-catalyzed reaction stands at *ca.* 2326 kg CO₂/kg product, while that for the Pd-catalyzed coupling is roughly 1554 kg CO₂/kg product. By contrast, the corresponding data associated with the metal-only footprint (Figure 3, top) is 0.19 kg CO₂/kg product for Ni *versus* 2.4 for Pd. *These values, again, illustrate the relatively small, almost trivial overall impact associated with the choice of metal selected for catalysis.* Looking at the other environmental indicators outlined, each with its unique physical unit, it becomes clear that the different categories cannot be compared with each other. To understand each category's impact and to get a single score for the process' "greenness", the results in each category can be normalized and then weighted to afford unitless values generating a single numerical score (Figure 4).

impact category	normalization	weighting
climate change	0.00013240	21.06
ozone depletion	19.10000000	6.31
ionizing radiation	0.00023700	5.01
photochemical ozone formation	0.02447000	4.78
particulate matter	1680.00000	8.96
human toxicity; non-cancer	7768.00000	1.84
human toxicity; cancer	57961.00000	2.13
acidification	0.01800000	6.20
eutrophication; freshwater	0.62230000	2.80
eutrophication; marine	0.05116000	2.96
eutrophication; terrestrial	0.00565800	3.71
ecotoxicity; freshwater	0.00001763	1.92
land use	0.00000122	7.94
water use	0.00008719	8.51
resource use; fossils	0.00001538	8.32
resource use; mineral & metals	15.72000000	7.55

Figure 4. Normalization²⁸ and weighting²⁹ for the factors impacted by a metal-catalyzed coupling

Applying these factors to the initial analysis that led to the data provided in Figure 3 now leads to comparison values for the two methodologies (*i.e.*, using Ni catalysis, as in the *OL* paper,¹⁶ and the ppm Pd-catalyzed technology in water, as described in the *Science* paper),¹⁷ shown in Figure 5. The impact associated with each factor leads to the stand-alone conclusion: *climate change is the most important outcome, and substantially so.* It is followed by resource use, fossils, then metals and minerals, and then by particulate matter formation. The sum total of all factors points to the net differential between the two synthetic approaches: 19.48 Eco-Points for Ni catalysis vs. 12.09 using Pd,³⁰ or a *>60% change against using Ni.* Moreover, as noted above, these numbers represent a minimum differential, since several parameters are not easily included.

impact category	reaction in organic solvent (Ni)	reaction in aq. micellar media (Pd)
climate change	6.48	4.33
ozone depletion	0.02	0.06
ionizing radiation	0.03	0.02
photochemical ozone formation	0.75	0.49
particulate matter	1.20	0.81
human toxicity; non-cancer	0.45	0.24
human toxicity; cancer	0.09	0.06
acidification	1.05	0.67
eutrophication; freshwater	0.39	0.19
eutrophication; marine	0.22	0.13
eutrophication; terrestrial	0.30	0.19
ecotoxicity; freshwater	0.47	0.31
land use	0.05	0.03
water use	1.04	0.55
resource use; fossils	3.63	2.34
resource use; mineral & metals	3.31	1.68
SUMMARY	19.48	12.09

Figure 5. Relative weighting of factors involved in both Ni- and Pd-catalyzed Suzuki-Miyaura couplings

Conclusions

This discussion hopefully convinces the reader that the overall picture being put forth encouraging a switch to earth-abundant metals, and nickel, in particular, as a replacement for palladium *in cross-couplings*, and perhaps other types of processes, is not necessarily valid from an environmental perspective (as summarized in the spider diagram; Figure 6, which is representative of a relative comparison). Using straightforward analyses that include the many reaction variables and environmental issues involved clearly indicate that cost considerations, natural abundance, and/or the argument focused on the environmental impact of metal mining used so frequently in many contexts cannot be substantiated; that is, they are not the key factors, not today nor tomorrow. Of course, it must also be appreciated that not all Ni-based catalysis is aimed at this one goal; rather, there is a growing number of outstanding Ni-catalyzed technologies being developed for other purposes (*e.g.*, photocatalysis, C_{sp^3} - C_{sp^3} couplings, asymmetric synthesis, biocatalysis, etc.) many of which are not amenable for palladium catalysis.³¹ Hence, the overall conclusion might be that *Ni or other non-noble catalysis (such as that based on Cu, or Co, etc.) for cross-coupling chemistry is better regarded as complementary to, and not a replacement for, Pd.*³² Clearly, a more careful and extensive rather than superficial analysis including data-based environmental indicators and additional factors such as the sustainable development goals (SDGs),³³ along with health and safety concerns, must be taken into account prior to drawing conclusions. This recently developed tool for such an analysis at Novartis has helped in providing additional insight regarding various processes, while increasing opportunities for steering chemistry in even more impactful directions based on the use of better and broader environmental metrics being applied to this and other important topics. It is hoped, therefore, that this contribution will trigger additional efforts that reflect greater accuracy, practicality, and hence, more

extensive adoption in future experimental studies by the chemistry community. Indeed, looking to the future, where climate change is especially in focus, we may have no choice!

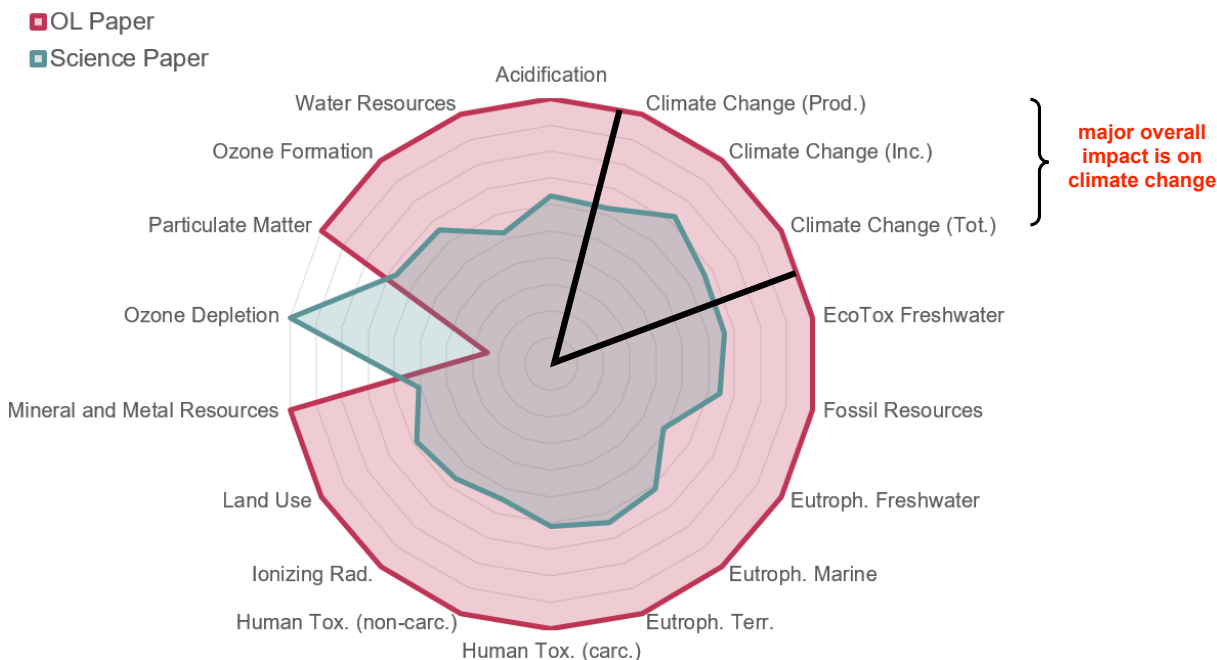


Fig. 6. Pictorial summary of the overall environmental impact of Ni (in red) vs. Pd (in green)

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