Faraday Discussions

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Manipulate – techniques to manipulate the surroundings of a synthetic catalyst to control activity and selectivity: general discussion

Torsten Beweries, Michael R. Buchmeiser, Neil R. Champness, Miquel Costas, Anne Duhme-Klair, Jorge Echeverría, Odile Eisenstein, Calum T. J. Ferguson, Joe C. Goodall, Rafael Gramage-Doria, Matthew Gyton, Rens Ham, Sonja Herres-Pawlis, Chloe L. Johnson, Pierre Kennepohl, Bartosz Lewandowski, Pim R. Linnebank, Stuart A. Macgregor, Kamran T. Mahmudov, Eva Meeus, Miquel Navarro, Pinkie Ntola, Tatjana N. Parac-Vogt, Robin N. Perutz, Albert Poater, David C. Powers, Sonja Pullen, Paul R. Raithby, Joost N. H. Reek, Thomas R. Ward, Andrew S. Weller and Helma Wennemers

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Eva Meeus opened discussion of the paper by Helma Wennemers: I was wondering whether you could “revert” this process? More specifically, can you equip your peptide-based template to enable length-controlled scissions of oligomers to facilitate, for example, monomer recycling?

Helma Wennemers answered: Yes, this idea should work with proper design and possibly allow for the development of a “polymer degrader”.

Michael R. Buchmeiser asked: Since two asymmetric carbons are generated per repeat unit, have you thought about trying to make tactic polymers?

Helma Wennemers responded: Of course. We are working on enhancing the stereoselectivity by varying the stereochemistry at C^{γ}, the attachment sites of the binding/activating groups, or installing chiral moieties, *e.g.* amino acids, at these sites, or both.

Kamran T. Mahmudov enquired: You have modified the catalyst system with a thiourea moiety. Why did you attach this moiety, and what are the advantages? What is the role of the $-CF_3$ groups?

Helma Wennemers replied: Thiourea is a good H-bonding group and a common activator for electrophiles in organocatalysis. The electron-withdrawing CF_3-group enhances H-bonding and thus activation.

Kamran T. Mahmudov asked: Have you tried to control the oligomerisation *via* noncovalent interactions?

Helma Wennemers responded: Non-covalent interactions do control the oligomerization.

Miquel Navarro opened discussion of the paper by Sonja Herres-Pawlis: I am very curious about complex **C6** in your work (**https://doi.org/10.1039/d2fd00162d**). Have you found evidence that this is the right structure, a copper(I) complex without the chloride, namely a naked copper(I)? Are you sure you do not have any sort of Cu–Ag multimetallic species?

Sonja Herres-Pawlis answered: We were not successful in crystallizing it but we see it in electron spray ionization (ESI) mass spectra as “naked species”. Moreover, this species can also be generated with $TlPF_6$ instead of $AgPF_6$ or $AgSbF_6$ with the exact same reactivity.

Odile Eisenstein asked: Cu(I) has a very sensitive coordination sphere. Even if the metal is globally tetracoordinated, one of the bonds is often weaker so that the coordination is between trigonal and tetrahedral. Does the reaction of hydroxylation require the de-coordination of one of the ligands to proceed?

Sonja Herres-Pawlis replied: In computational studies, we observed that the interaction with the third (mostly weaker) donor is weakened but not completely lost in order to host the substrate near the copper ions.

Kamran T. Mahmudov enquired: Which types of noncovalent interactions did you observe in the crystal structure of the copper–peroxide complex?

Sonja Herres-Pawlis answered: The Cu–O and the Cu–N bonds are dative bonds with partly covalent character. Moreover, we observe dozens of van der Waals contacts between the ligands in the crystals.

Kamran T. Mahmudov asked: What is the O–O distance in this peroxide complex? Is it a covalent bond?

Sonja Herres-Pawlis responded: Yes, this is a covalent bond with a length of 1.45–1.55 Å, depending on the solvent and packing effects.

Kamran T. Mahmudov opened discussion of the paper by David C. Powers: What types of noncovalent interactions do you see between the metal–organic frameworks (MOFs) and the catalyst?

David C. Powers replied: The basis of the disparate kinetic isotope effects observed in the most microporous materials is confinement effects, which are presumably mediated by van der Waals interactions between encapsulated solvent molecules. We envision the toluene that is confined within the pores to behave as though it is frozen (positionally confined) despite the amination chemistry proceeding at 100 °C. This vision further supports the contention that significant tunneling, promoted by transition state preorganization, is responsible for the large intramolecular k_H/k_D values observed in the microporous materials.

Neil R. Champness questioned: You said that it is difficult to make isoreticular structures with the Ru paddlewheel systems, this is surprising, do you know why this is the case?

David C. Powers responded: We don't have any specific insights into this question beyond the typical challenges encountered with accessing crystalline materials comprised of 2nd and 3rd row late metal ions. These ions often display slow ligand exchange kinetics that mandate exceedingly high temperature to access M–L reversibility, which is needed for crystallization. We have been working on metallopolymerization strategies to access crystalline materials with Ru_2 sites (or generic slow-exchanging metal ions) but these efforts have not yet resulted in reticular families of materials of the sort that you propose. See, for example, ref. 1.

1 W.-Y. Gao, A. Sur, C.-H. Wang, G. R. Lorzing, A. M. Antonio, G. A. Taggart, A. A. Ezazi, N. Bhuvanesh, E. D. Bloch and D. C. Powers, *Angew. Chem., Int. Ed.*, 2020, **59**, 10878–10883.

Neil R. Champness enquired: In order to make more crystalline samples for the Ru paddlewheel MOFs, have you tried using modulators, or perhaps doping a Cu analogue with Ru sites?

David C. Powers replied: Yes, we have pursued strategies akin to the suggestion. Essentially we prepare MOF monomers in which a carboxylate-supported Ru_2 complex is decorated with peripheral carboxylate substituents. Mechanochemical polymerization of these molecules with $Cu_2(OAc)_4$ has provided access to porous crystalline materials.[1] Unfortunately, materials available by these methods have not been compatible with the azide chemistry that we utilize to prepare nitride precursors and thus we have not been able to apply these bespoke materials for the specific amination chemistry discussed in the current paper (**https://doi.org/10.1039/d2fd00167e**).

1 W.-Y. Gao, A. Sur, C.-H. Wang, G. R. Lorzing, A. M. Antonio, G. A. Taggart, A. A. Ezazi, N. Bhuvanesh, E. D. Bloch and D. C. Powers, *Angew. Chem., Int. Ed.*, 2020, **59**, 10878–10883.

Rafael Gramage-Doria said: I have a question regarding the stability of your system. Do you observe amination in the aromatic or in the benzylic positions from your carboxylate derivatives?

David C. Powers answered: We observe only the benzylic amination products. This was initially surprising to us given the facility of $C(sp^2)$ amination from related systems reported by Berry *et al.*[1] Based on the computational results we report in the manuscript (**https://doi.org/10.1039/d2fd00167e**), however, the observed selectivity is unsurprising. The carboxylate-supported Ru_2 complex effects amination *via* an H-atom abstraction, radical rebound mechanism. Accordingly, the weakest C–H bond is the most prone to cleavage.

1 J. S. Pap, S. DeBeer George and J. F. Berry, *Angew. Chem., Int. Ed.*, 2008, **47**, 10102–10105.

Albert Poater asked: What would happen if you thermalise the molecule instead of using light?

David C. Powers responded: The nitrogen-atom transfer that we describe is promoted thermally. In contrast, we have not observed analogous photochemistry from either the Ru-HKUST-1 or from molecular tetracarboxylate-bridged diruthenium complexes.

Sonja Pullen enquired: What is the particle size of the MOFs you used? How many metal sites are accessible and thus participate in the nitrogen-atom transfer reaction?

David C. Powers responded: The experiments that we describe are single turnover reactions in which the substrate is pre-introduced into the porous material. As such, all Ru_2 sites are solvated with toluene before the thermolysis, which is reflected in 30–50% yield based on Ru_2 sites. Without presoaking of the material, no products of C–H amination are obtained.

Sonja Pullen asked: Would it be possible to tune the particle size of the MOFs and thus accessibility of active sites? Along the same lines, would it be possible to use a larger linkers in order to increase pore-size?

David C. Powers replied: Regarding the particle size question, the experiments that we describe are single turnover reactions in which the substrate is pre-introduced into the porous material. As such, all Ru_2 sites are solvated with toluene before the thermolysis, which is reflected in 30–50% based on Ru_2 sites. Without presoaking of the material.

Sonja Pullen opened discussion of the paper by Sonja Herres-Pawlis: You mentioned that you can recycle 58% of the ligand after catalysis. Did you observe any oxidation of the ethylene bridge in the remainder? If oxidation of the ligand is a degradation pathway, how would you modify the bridge in order to prevent this?

Sonja Herres-Pawlis responded: We observed oxidation of the *tert*-butyl groups since they are in the ideal position for an attack from the peroxide unit. This is under further investigation.

Chloe L. Johnson asked: The naked Cu complex is also very interesting; what other substrates have you tried to bind?

Sonja Herres-Pawlis replied: (a) CO (works but not interesting); (b) iminoiodinanes in order to obtain nitrenes, see ref. 1. They display highly interesting reactivity in catalytic nitrene transfer and amination.

1 J. Moegling, A. Hoffmann, F. Thomas, N. Orth, P. Liebhäuser, U. Herber, R. Rampmaier, J. Stanek, G. Fink, I. Ivanović-Burmazović and S. Herres-Pawlis, *Angew. Chem., Int. Ed.*, 2018, **57**, 9154–9159.

Andrew S. Weller enquired: Have you considered using David Powers' chemistry in the solid state, using the O_2 complexes in the single crystal form for onward reactivity?

Sonja Herres-Pawlis responded: Great idea, not yet. This is our first complex to be stable for so long in the form of crystals.

Miquel Costas continued discussion of the paper by Helma Wennemers: Is there anything known about the status of the catalyst during the catalytic reactions? Is the rate determining step of the reaction known? Why are then the reactions slow?

Helma Wennemers replied: Organocatalytic reactions are typically slow and often require catalyst loadings of 10–30 mol%. Extrapolating from related Michael- and aldol-type reactions with malonic acid half thioesters (MAHTs) (*e.g.* ref. 1 and 2), the C–C bond formation precedes the decarboxylation, which is irreversible.

1 J. Lubkoll and H. Wennemers, *Angew. Chem., Int. Ed.*, 2007, **46**, 6841.
2 J. Saadi and H. Wennemers, *Nat. Chem.*, 2016, **8**, 276.

Calum T. J. Ferguson questioned: It is a very interesting system that you have developed but I am wondering why you can form a small amount of oligomers that are larger than the pore size. Does the template move along the growing oligomeric chain?

Helma Wennemers responded: Yes, the template could move along the growing oligomeric chain. Alternatively, the minor quantity of longer oligomers could arise from non-templated catalysis.

Andrew S. Weller asked: Do you see zero order kinetics for catalytic turnover?

Helma Wennemers replied: We have so far not carried out kinetic studies since the reaction rate of the oligomerization is slow (days rather than hours).

Rens Ham enquired: You mention that your system takes inspiration from RNA polymerase. The RNA contains four different monomers. Would it be possible to use different propagators in your system to mimic the biological activity and form block or alternating co-polymers?

Helma Wennemers responded: That is challenging, but yes, we would love to develop a system that uses multiple building blocks.

Joost N. H. Reek asked: It is interesting to see that the results look promising when using a single linear polyproline template (instead of the macrocycle template), although it works not perfectly yet. The equilibria between substrate and product binding are crucial, both the thermodynamics as well as the kinetics. Have you considered attaching the template to a support and trying these reactions in a flow reaction set up? This may provide additional parameters to control the reaction outcome, and also may be practical for optimisation.

Helma Wennemers answered: This is an interesting idea. Immobilization will add another level of complexity but could be interesting.

Anne Duhme-Klair enquired: Since you have significant binding affinity, could you monitor the binding events by using circular dichroism spectroscopy? Is the structure of the template and hence its CD signature affected significantly? Could the targeted oligomeric product be synthesised and altered chemically to study and optimise, *e.g.*, its solubility and spectroscopic properties?

Helma Wennemers replied: Very good question. The CD spectrum of the macrocyclic catalyst does not change significantly upon addition of the oligomer. We prepared the oligomer(s) also in a stepwise manner. That synthesis takes longer and provides the oligomer in lower yield compared to the templated catalysis. Thus, yes, it is possible to prepare a modified oligomer. Installing a better chromophore in the monomer and, thus, oligomer could, indeed, be a good method for analysis by CD spectroscopy.

Joost N. H. Reek continued discussion of the paper by David C. Powers: You have used the MOF approach to achieve site isolation of your reactive catalysts to prevent side reactions and decomposition. The diffusion of substrates can limit the reaction which you have studied in more detail. Have you considered making monomeric complexes that are site isolated by encapsulation in molecular cages, which can operate in solution and therefore have no limitation in diffusion?

David C. Powers answered: Yes, we are actively working on such strategies. The challenges that need to be addressed are (i) the propensity for intramolecular C–H functionalization when ligand-borne C–H bonds are accessible to the reactive metal nitride intermediates needed for amination chemistry, and (ii) the aggregation of Ru_2 azide sites *via* azide-bridged $–Ru_2–N_3–Ru_2–$ chains which limits solubility. The reported MOF platform nicely addresses both of these challenges and thus supports intermolecular nitrogen-atom transfer (NAT) chemistry. Molecular or supramolecular systems may also be able to address both of these challenges, but we do not yet have such systems.

Robin N. Perutz asked: I am unclear about the modelling of the kinetic isotope effect: are you modelling the tunnelling or the over-the-hill kinetic isotope effect?

David C. Powers responded: The isotope effects were calculated for the over-the-hill pathway. The similarity of the isotope effect calculated and that observed for the mesoporous limit of our Ru_2 materials suggests that tunneling is not a significant contributor to amination in those materials. In the more microporous materials, we speculate that tunneling may play an important role. The experimental work, including variable temperature isotope effect studies, that we used to support this hypothesis is detailed in ref. 1.

1 C.-H. Wang, W.-Y. Gao and D. C. Powers, *J. Am. Chem. Soc.*, 2019, **141**, 19203–19207.

Joe C. Goodall enquired: You mentioned in the paper (**https://doi.org/10.1039/d2fd00167e**) that the nitrene complex is transient and not observed in any of the reactions. What decomposition products do you obtain if you thermolyse or photolyse in the absence of reactive substrates such as toluene?

David C. Powers answered: This is an important unresolved question. We have tried to thermolyze our Ru_2N_3-based materials in the presence of less reactive solvents, such as pentane or benzene, in an effort to observe the putative nitride intermediates. These experiments have neither provided amination products nor provided compelling spectroscopic data (*i.e.* Raman spectroscopy) for the presence of the nitride. In molecular systems, for example, $Ru_2(OBz)_4(N_3)$, indirect evidence for the intermediacy of a reactive nitride was obtained by isotope labeling studies which suggested facile nitride dimerization pathways. In the materials we report, presumably site isolation prevents dimerization.

Andrew S. Weller asked: Do you see the same isotope effects using gas-phase NMR and substrates?

David C. Powers responded: This is a great idea – a way to look at the isotope effect in a lower density environment in which the materials are not fully solvated. We will look into this.

Pierre Kennepohl continued discussion of the paper by Sonja Herres-Pawlis: Dan Stack[1] and Bill Tolman[2,3] showed a number of years ago that the Cu_2O_2 core in synthetic models for hemocyanins and tyrosinases are very sensitive to solvent effects – mostly because of the highly asymmetric charge distribution between the Cu(II) metal centres and the peroxide dianion. The peroxide bonding pocket in complex **P** *seems* (at first glance) to be reasonably well protected from solvent, both due to the bulky terminal *tert*-butyl groups and the bridge but it's not clear how flexible the overall pocket would be. Is it known how sensitive this particular model is to solvent effects?

1 L. M. Mirica, X. Ottenwaelder and T. D. P. Stack, *Chem. Rev.*, 2004, **104**, 1013–1046, DOI: **10.1021/cr020632z**.
2 E. A. Lewis and W. B. Tolman, *Chem. Rev.*, 2004, **104**, 1047–1076, DOI: **10.1021/cr020633r**.
3 C. E. Elwell, N. L. Gagnon, B. D. Neisen, D. Dhar, A. D. Spaeth, G. M. Yee and W. B. Tolman, *Chem. Rev.*, 2017, **117**, 2059–2107, DOI: **10.1021/acs.chemrev.6b00636**.

Sonja Herres-Pawlis replied: This species is especially sensitive to solvents during formation: this means that for the precursor we have to avoid MeCN or DMF, only small amounts of THF, DCM and $CHCl_3$ are better. But when the peroxo is formed, even some drops of water are tolerated and other solvents such as more THF or DMF.

Stuart A. Macgregor asked: The ethylene linker in complex **P** appears to pull the N_3 tripodal units together with consequences for the coordination geometry at Cu. The other systems (**C1–4**) discussed in your paper (**https://doi.org/10.1039/d2fd00162d**) appear more flexible in this regard. How does the coordination geometry at Cu affect the binding of the peroxide ligand and does this correlate with spectroscopic properties and maybe reactivity? Might there be a role for non-covalent (dispersive) interactions in controlling the orientation of the tripodal ligands that feature bulky groups? I am thinking of the important role of bulky substituents in conferring stability on bulky hexaarylethanes, as discussed by Grimme *et al.*[1]

[1] S. Grimme and P. R. Schreiner, *Angew. Chem., Int. Ed.*, 2011, **50**, 12639.

Sonja Herres-Pawlis answered: The ethylene linker is rather unconstrained when you look at the structure in 3D. Remarkably, with a propylene linker the whole system has to twist and we could not observe a peroxide species. So, propylene is too long for the stabilisation of the peroxide species. What we also know from similar ligands is that when no *tert*-butyl groups are there, we observe no peroxide species. And when phenyl rings are there, for only few seconds, a peroxide species is visible which is not fully formed.

Miquel Costas continued discussion of the paper by David C. Powers: Have you looked at the lifetime of your radical, if it collapses fast? Could you investigate a chiral substrate such as monodeuterated ethylbenzene?

David C. Powers answered: We have not but this would be a nice way to evaluate the hypothesis for significant tunneling during the C–H amination in our most microporous materials. We have proposed that the intramolecular KIE decreases with increasing mesoporosity as a result of less efficient transition state preorganization. Observation of increased scrambling as a function of mesoporosity would provide complementary data to this effect.

Anne Duhme-Klair enquired: In terms of by-product formation associated with the radical rebound mechanism, is there an observable difference between the lattice-isolated catalysts in the MOF and the corresponding free molecular catalysts in solution?

David C. Powers responded: Yes, in the lattice-isolated experiments, we see benzylamine, which we attribute to NAT chemistry from a transient nitride intermediate. In solution-phase experiments with molecular site mimics of the Ru_2 active sites, we have never seen products of NAT. The only products that we have been able to observe in solution-phase experiments are N_2 and Ru_2[II,II] complexes. We believe these products arise from nitride dimerization which prevents intermolecular NAT to organic substrates.

Tatjana N. Parac-Vogt asked: MOFs: have you measured N_2 adsorption isotherms? How clogged are the MOFs before and after reaction?

David C. Powers answered: Yes, we have extensively measured adsorption isotherms. The mesoporous materials used in the experiment to evaluate the impact of mobility on the intra- and intermolecular kinetic isotope effects (KIEs) were evaluated by N_2 isotherm analysis. Materials were categorized as a function of the fraction of the total surface area comprised of mesopores *versus* micropores.

Relatedly, materials were also characterized by gas adsorption before and after nitrogen-atom transfer (NAT). Assuming materials were activated similarly, the porosity was not significantly changed by NAT.

Tatjana N. Parac-Vogt enquired: Number of defects in the structure?

David C. Powers responded: We have not done anything to specifically characterize the number of defects in the materials presented beyond what was done by Fischer *et al.*, who originally disclosed the strategy for introducing material mesoporosity that we used.[1,2] In our work, we characterize materials by PXRD to show that the crystal structure is conserved across varying mesoporosities and by gas adsorption to determine the fraction of total surface area that arises from mesopores.

1 Z. Fang, J. P. Dürholt, M. Kauer, W. Zhang, C. Lochenie, B. Jee, B. Albada, N. Metzler-Nolte, A. Pöppl, B. Weber, M. Muhler, Y. Wang, R. Schmid and R. A. Fischer, *J. Am. Chem. Soc.*, 2014, **136**, 9627–9636.
2 O. Kozachuk, I. Luz, F. X. Llabrés i Xamena, H. Noei, M. Kauer, H. B. Albada, E. D. Bloch, B. Marler, Y. Wang, M. Muhler and R. A. Fischer, *Angew. Chem., Int. Ed.*, 2014, **53**, 7058–7062.

Tatjana N. Parac-Vogt continued discussion of the paper by Helma Wennemers: In the system, the template limits the size of the substrate. How flexible is the template and the substrate size in the system?

Helma Wennemers answered: Oligoprolines adopt a polyproline II (PPII) helix already at a length of 6 proline residues. These peptides have been coined as “molecular rulers” since they are significantly more rigid compared to most other peptides.[1] For a study on the flexibility of oligoprolines of different lengths using EPR spectroscopy, see ref. 2. Within the macrocyclic template, the rigidity is further enhanced due to the macrocycle.

1 L. Stryer and R. P. Haugland, *Proc. Natl. Acad. Sci. U. S. A.*, 1967, **58**, 719–726.
2 L. Garbuio, B. Lewandowski, P. Wilhelm, L. Ziegler, M. Yulikov, H. Wennemers and G. Jeschke, *Chem.–Eur. J.*, 2015, **21**, 10747–10753.

Pinkie Ntola communicated: Could you elaborate a bit on the process followed to identify or select a suitable template for length control?

Helma Wennemers communicated in reply: A rigid macrocyclic template, bearing two different types of functional groups for substrate binding and activation at defined positions and at distances that match the distance of the reactive groups on the bifunctional template; solubility; synthetic accessibility.

Matthew Gyton opened discussion of the paper by Pim R. Linnebank: What is the logic for using the difference in the carbon shift as a descriptor of polarisation instead of other direct metrics like the C–H coupling constant?

Pim R. Linnebank replied: We were inspired by a Sigman paper[1] in which he reports regioselective transformations of a redox relay Heck reaction and shows that he was able to predict the outcome with reasonable accuracy. Moreover a paper that I refer to also uses this approach in the hydroformylation reaction.[2] Using a CH coupling constant is something we haven't considered and possibly could also be used as a predictive descriptor.

1 T. S. Mei, E. W. Werner, A. J. Burckle and M. S. Sigman, *J. Am. Chem. Soc.*, 2013, **135**, 6830–6833, DOI: **10.1021/ja402916z**.

2 Z. Yu, M. S. Eno, A. H. Annis and J. P. Morken, *Org. Lett.*, 2015, **17**, 3264–3267, DOI: **10.1021/acs.orglett.5b01421**.

Stuart A. Macgregor asked: In standard hydroformylation (*e.g.* with $Rh(H)(CO)(PPh_3)_3$ as catalyst) selectivity is governed by steric bulk around the Rh centre. Less sterically encumbered primary alkyls are favoured over secondary alkyls leading to high linear : branched ratios. In many cases the descriptors used in your paper (**https://doi.org/10.1039/d3fd00023k**) generally reflect electronic factors. However, I wonder if the use of these remote tetraphenylporphyrin (TPP) units may have the effect of moving the steric bulk further away from the metal centre – towards the secondary coordination sphere – and so then may play a role in the change in regioselectivity that you observe? *i.e.* the bulky secondary alkyl intermediates are now being favoured on steric grounds with there being more room nearer to the metal?

Pim R. Linnebank answered: It might. So the hydroformylation system goes from a biscoordinated catalytic species for the non-encapsulated catalyst to a monophosphine coordinated species in the encapsulated system. However, we do find a strong correlation between the alkene polarization parameter and the regioisomeric outcome. So polarization is definitely relevant. This is very hard to separate, since the cage enforces monophosphine coordination, whereas you would get bisphosphine and non-ligated rhodium if you added only a little rhodium under catalytic conditions. However, I found the same linear over branched ratios for all disubstituted alkylalkenes, which are vinylcyclohexane, vinylcyclopentane, vinylcyclooctane and 3-methylhex-1-ene for the non-coordinated catalyst, whereas the steric bulk is different. It also makes sense that the hydride, which you can view as an H^-, would migrate to the most electron deficient carbon atom in the selectivity determining step.

Stuart A. Macgregor enquired: How do your substrates behave under normal hydroformylation conditions (*i.e.* with $Rh(H)(CO)(PPh_3)_3$ as catalyst)?

Pim R. Linnebank responded: Alkylalkenes generally give the linear product. This varies between substrates, but substrates such as 1-octene give a linear : branched ratio of 3 : 1. For disubstituted alkylalkenes, the linear over branched ratio is 6 : 1 and based on the strong correlation between alkene polarization and regioselectivity this is cause by the electron-rich nature of the alkene. For electron poorer alkenes, we get a regioselectivity of about 1 : 1 for the most electron-poor alkenes such as allylpentafluorobenzene. I should note that there are only 3 known catalysts that give the branched product for terminal alkylalkenes of which this encapsulated catalyst is the first one reported, despite many efforts also by our group trying to find such catalysts.

Michael R. Buchmeiser opened discussion of the paper by Rafael Gramage-Doria: 10 mol% catalyst is quite high; what is the active species? Could it be forming nanoparticles coordinated to the pyridine moiety?

Rafael Gramage-Doria replied: We also observe the supramolecular effect at 5 mol% but to a lesser extent. By NMR and HRMS we observe that pyridine binds to the molecular recognition site while palladium binds to the peripheral nitrile groups. In a previous publication, we performed several control experiments that indicate no formation of nanoparticles under our reaction conditions.[1]

[1] P. Zardi, T. Roisnel and R. Gramage-Doria, *Chem.–Eur. J.*, 2019, **25**, 627, DOI: **10.1002/chem.201804543**.

Michael R. Buchmeiser questioned: The average TON is 8; may the reason that you don't see nanoparticles be that their concentration is so low because the catalyst loading is so high? Maybe you would see them if you used a lower catalyst loading (*e.g.* 0.01 mol%) and longer reaction times, eventually resulting in larger nanoparticles that further agglomerate and precipitate?

Rafael Gramage-Doria answered: The reactions conducted in lower catalyst loadings (0.01 mol%) and longer reaction times (24 h) are unproductive so far. Our conditions using toluene solvent are probably not well adapted to the formation of palladium nanoparticles, which are actually known to readily form with DMF solvent for example.

Bartosz Lewandowski asked: Olefins bearing aryl substituents seem to perform particularly well as substrates in the reaction; is there a possibility for additional π–π interactions between the substrate and your catalyst that could explain this observation?

Rafael Gramage-Doria replied: So far, we do not have experimental evidence for π–π interactions between the substrate and this supramolecular catalyst. In fact, I do not see how eventual π–π interactions may occur between the substrate and the catalyst unless some type of dimers or higher aggregates form between palladium and two or more ligands.

Eva Meeus requested: Your catalyst has two vacant sites for the pyridine-based substrate to ‘coordinate’. Can you comment on this? (Does ‘coordination’ of one substrate affect coordination of the other substrate? Can two substrates ‘coordinate’ simultaneously? Does it affect the catalysis in some way?)

Rafael Gramage-Doria responded: In theory, there is only one substrate binding at a time to the molecular recognition site of the catalyst. This binding can be on one face or on the other face. Actually, this is a dynamic system, so the substrate is binding and unbinding all time on both faces in a fast manner. Because the catalyst contains four peripheral nitrile groups that have free rotation around the porphyrin backbone, we are rather convinced that there is little influence regarding a specific site-binding. In the future, we could explore the design of a supramolecular catalyst in which one side is blocked so it could eventually increase the effective molarity on the other side.

Bartosz Lewandowski opened discussion of the paper by Sonja Pullen: When you use bromobenzaldehyde as the substrate in the dehalogenation reaction you see less decomposition, but the substrate doesn't seem to bind to your perylene diimide (PDI) macrocycle so what could be the reason behind the lower degree of decomposition?

Sonja Pullen replied: For both benzaldehyde as well as the other two dehalogenation products, light-promoted dimerization is likely the ‘decomposition pathway’. Since substrates **4** and **5** in the paper (**https://doi.org/10.1039/d2fd00179a**) already show a high degree of unsensitized reactivity, the degree of decomposition should be higher for the respective products as well. Our hypothesis is thus that decomposition/dimerization is not directly affected by the nature of catalyst.

Bartosz Lewandowski queried: Could it be that the PDI monomer facilitates the side reaction(s) and the macrocycle does not?

Sonja Pullen answered: Thank you for this very good question. We do not have a definite answer yet to this question, but our hypothesis is that for the PDI monomer, the dehalogenation reaction proceeds significantly faster, and therefore more benzaldehyde **3b** is generated early on which can dimerize under reductive conditions.

Calum T. J. Ferguson asked: How do you know that the reaction is happening inside the cavity and not just on the surface? Is hydrophobicity a driving force behind this? You have a hydrophobic pocket and a hydrophobic substrate.

Sonja Pullen replied: It was indeed the goal to provide a binding site for substrates in the cavity, in order to influence reactivity by the cavity. Since the binding constants are only moderate for substrates **4** and **5**, and since we observe already a high degree of background-reaction, at this moment we do not have strong evidence for that the reaction takes place only in the cavity.

We are currently modifying the supramolecular catalyst, in order to provide a stronger binding site and will then reinvestigate.

Helma Wennemers questioned: Are you sure about the role of binding inside the cavity for catalysis? How about taking a mixture of different π-systems to study which of those compounds binds into the cavity? This approach could help to understand (a) selective binding and (b) the role of binding for compound conversion? You might consider MS analysis as a tool to analyze host–guest formation.

Sonja Pullen responded: Thank you for these very interesting suggestions! I especially like the idea to perform competitive binding studies with different substrates. In order to have a larger variety of substrates and respective binding strength, we will also have to test the system in different solvents like CH_3CN and

DCM, where stronger binding is observed, for instance, for pyrene. For the flat aromatic substrates **4** and **5**, we see significantly stronger binding in the cavity of the dimer as compared with the single PDI. Therefore, we would argue that we have a sort of cooperative binding in between the two PDIs, since binding to the outside of the square and thus only to one PDI would be less strong, and thus less likely.

Kamran T. Mahmudov continued discussion of the paper by Pim R. Linnebank: Changing substrate to regulate selectivity is a good approach; what type of noncovalent interaction is in this work?

Pim R. Linnebank replied: Many different ones. However mainly weak noncovalent interactions together with steric hindrance regulate the regioselectivity. It is however very difficult to predict and understand which interactions does what, since you have many relevant transition states that contribute to the formation of both the linear and the branched product.

Kamran T. Mahmudov asked: Are C–H$\cdots\pi$ interactions relevant to the system?

Pim R. Linnebank answered: Yes they are and in many ways. First of all the capsule is likely held together in part by CH$\cdots\pi$ interactions. Furthermore, the substrates should all display such interactions with the aromatic planes of the walls of the cage. The strength and exact form obviously varies between substrates, which makes predictive models very challenging.

Kamran T. Mahmudov continued discussion of the paper by Rafael Gramage-Doria: How do you prove that your Zn$\cdots$N interaction is an interaction and not a covalent bond? Is it a spodium bond?

Rafael Gramage-Doria replied: It is a dative coordinating bond. However, because of the nature of the system, this interaction is reversible. We prefer to term it a supramolecular interaction since the binding of zinc–porphyrins to pyridines is well known since the early years of supramolecular chemistry.

Odile Eisenstein commented: The interaction of the pyridine derivative and the Zn raises an interesting question. This is in principle a classic donor (pyridine)–acceptor (Zn) interaction, which is a dative bond. If this bond is weak because the Zn–N distance is long, does this change the nature of the bond? In my opinion, if the Zn–N distance is long, it just becomes a weak dative bond. Noncovalent interactions are of a different nature. It won't be dominated by a single term but it will result from the interplay of Pauli, electron-transfer, polarization and dispersion as mentioned in the earlier discussion around the halogen bond.

Rafael Gramage-Doria responded: I totally agree with this comment.

Robin N. Perutz enquired: You showed the variable temperature NMR spectra but didn't analyse them for us; what is the equilibrium constant for binding the pyridine to the zinc porphyrin at room temperature and what is it at 130 °C? The room temperature value for such binding constants is usually of the order of 1000.

Rafael Gramage-Doria answered: At room temperature the binding of 3-bromopyridine to our supramolecular ligand containing a zinc–porphyrin in the molecular recognition site is 8.4×10^3,[1] but we did not consider to study such binding at 130 °C.

1 P. Zardi, T. Roisnel and R. Gramage-Doria, *Chem.–Eur. J.*, 2019, **25**, 627–634.

Robin N. Perutz said: Could you do a van't Hoff plot over a limited temperature range and extrapolate from that to 130 °C?

Rafael Gramage-Doria responded: This is a superb suggestion that we will definitely explore.

Tatjana N. Parac-Vogt asked: What is the effect of temperature on your system? The NMR shows that at higher temperatures the process becomes very dynamic.

Rafael Gramage-Doria answered: Yes, proton NMR at high temperature does show that the supramolecular substrate-to-ligand assembly is rather dynamic. The proton signals from the 3-bromopyridine substrate are still up-field shifted at values similar to those observed at room temperature. In the future we should study this association constant at high temperatures. We still believe that this dynamic nature is not a problem but a benefit in order to get turnover numbers during the catalysis as the substrates and the products may likely have similar affinity for the molecular recognition site in the supramolecular catalyst. Finding the right balance between thermodynamics and kinetics is clearly a challenge in supramolecular catalysis to get systems with higher performances.

Tatjana N. Parac-Vogt continued discussion of the paper by Sonja Pullen: Looking at your system, you use 1 : 1 stoichiometry, but there are multiple binding sites. Could you get substrates binding to different sites?

Sonja Pullen replied: In comparison with free PDI, the binding of the flat aromatic substrates is significantly enhanced, which indicates that strong binding is facilitated only when the substrate is “sandwiched” between two PDI units. We therefore expect that binding of the substrate outside the cavity at only one PDI ligand is disfavored and can thus be neglected.

Tatjana N. Parac-Vogt said: Could you potentially use isothermal titration calorimetry in order to determine this?

Sonja Pullen responded: Yes, in principle we could also use isothermal titration calorimetry (ITC) in order to determine the binding constants.

Sonja Herres-Pawlis continued discussion of the paper by Pim R. Linnebank: What is the advantage of Voronoi deformation density (VDD) charges over natural bond orbital (NBO) charges in this study? Suggestion: perhaps the use of Fukui functions can also help to find a correlation.

Pim R. Linnebank answered: We have considered NBO charges, however the predictive value was lower than with VDD charges. Fukui functions we haven't considered, but could do in the future.

Thomas R. Ward asked: Sigman methodology[1] has attracted a lot of attention, but in homogeneous catalysis. Has this been applied to enzymes where second coordination is important?

[1] M. S. Sigman, K. C. Harper, E. N. Bess and A. Milo, The Development of Multidimensional Analysis Tools for Asymmetric Catalysis and Beyond, *Acc. Chem. Res.*, 2016, **49**, 1292–1301, DOI: 10.1021/acs.accounts.6b00194.

Pim R. Linnebank replied: I have not found any reports that use such an approach for enzymes. In our report (https://doi.org/10.1039/d3fd00023k) we use several substrates and just 2 catalysts. So I do think that our approach of investigating multiple substrates is not very suited to enzymes that have a narrow substrate scope. However, the use of a multiparameter approach to predict the selectivity of multiple catalysts could be used for enzymatic catalysts in theory. However the current approach of using computational studies for predicting the selectivity could benefit and such formulas could be instructive in showing what factors affect the catalytic outcomes.

Thomas R. Ward said: Abigail Doyle recently published[1] a machine learning approach for non-linear systems (*i.e.* Bayesian optimization), could that be used to better describe these weak interactions?

[1] B. J. Shields, J. Stevens, J. Li, M. Parasram, F. Damani, J. I. Martinez Alvarado, J. M. Janey, R. P. Adams and A. G. Doyle, Bayesian reaction optimization as a tool for chemical synthesis, *Nature*, 2021, **590**, 89–96, DOI: 10.1038/s41586-021-03213-y.

Pim R. Linnebank responded: Potentially yes! We will consider this paper to see if it is applicable for our system.

Neil R. Champness continued discussion of the paper by Sonja Pullen: How important is the rigidity of your system? By making the system rigid you are restricting the interactions that the guests will have with it. If rigidity is important then have you considered MOFs?

Sonja Pullen replied: Thank you for this very interesting question. Indeed, fixing the two PDI units *via* metal-coordination adds a certain degree of rigidity, and the distance between the two PDI units is determined by the second ligand. In our system, with terephthalate as the second ligand, the distance between the two PDIs is ideal to facilitate binding of flat aromatic guests between the two PDIs. For guest binding, rigidity certainly plays a role, as the size and shape of the binding pocket determines binding properties of the system.

MOFs are certainly interesting to look into as well. In principle, our PDI dimer can serve as a model system for PDI-based MOFs.

Kamran T. Mahmudov asked: Why did you use bromine and not, for example, chlorine? Is there halogen bonding between the substrate and catalyst?

Sonja Pullen answered: Reductive dehalogenation proceeds *via* single electron transfer from $PDI^{\bullet-}$ to the aryl halide, generating an aryl radical. The reduction potential for chloro-substituted substrates is significantly higher, therefore we started out with bromo-substrates, which are easier to be reduced. In future, we might look into other substrates. We do not have any evidence for halogen bonding between substrate and catalyst.

Kamran T. Mahmudov enquired: Did you try to isolate your transition state experimentally and potentially obtain a solid-state structure/crystal analysis?

Sonja Pullen replied: To the best of my knowledge, transition states cannot be isolated/crystallized, you probably mean the isolation of intermediate species? We are currently focusing our studies on the host–guest chemistry and on the mechanism in solution, as this is most representative for conditions used in catalysis.

Jorge Echeverría opened a general discussion: Regarding the comments made by Kamran on the nature of the N···Zn bonds in Rafael's systems, my question is: do we really need a bond name for any group of the Periodic Table?

The use of terms such as “spodium bond” might be confusing, because under this name we can find a square-planar Zn complex, as in the present case, a tetrahedral Cd compound or a linear dicoordinated Hg system acting as the Lewis acid. Considering that the origin of the interaction is different for each of these three cases, the name “spodium bond” is not informative at all since it just says that there is a group 12 atom involved. On the other hand, there are interactions involving transition metals from different groups that can be rationalized within the same framework. This might be an unpopular opinion but I really think that we should tend to generalize rather than to give particular names to interactions.

Odile Eisenstein responded: I tend to agree with the fact that it is not such a good idea to give a bond name for any group of the Periodic Table. However, it still helps to communicate. I like the following example. Hydrogen bond was universally accepted and is even defined by IUPAC. In this case the donor of electron was an oxygen or a nitrogen. When the donor of electron was found to be a hydrogen itself (often a metal hydride), the need for a new name appeared obvious because the “old” hydrogen bond was too strongly associated with oxygen or nitrogen. The name of *cis*-interaction appeared (ref. 1 and references therein) but the name of dihydrogen bond proposed by Crabtree was later accepted because it can appear with diverse geometries.[2] This was a clear case. It could be less so in other situations.

1 L. S. van der Sluys, *et al.*, *J. Am. Chem. Soc.*, 1990, **112**, 4831–4841.
2 R. H. Crabtree, *et al.*, *Acc. Chem. Res.*, 1996, **29**, 348–354.

Kamran T. Mahmudov replied: In Rafael's systems there is no X-ray structure, but you can analyse experimental Zn···N interactions in similar systems, for example, in NEPWOU (see CCDC). Is Zn1···N3 2.695 Å in NEPWOU a covalent/coordination bond? In fact, the Zn(1)···N(3) 2.695 Å distance is significantly longer than the sum of covalent radii of the interacting atoms (Σr_{cov} (Zn···N) = 1.93 Å), it means that there is no covalent bond. Both Zn(1)···N(3) (2.695 Å, Σr_{vdW} (Zn···N) = 2.94 Å) distance and the ∠N(3)–Zn(1)···N(3B) (180.00°) angle are in agreement with the strength and directionality terms of a spodium bond.[1]

Regarding, intermolecular interactions in Zn, Cd or Hg complexes, it is not necessary to call those interactions as "spodium bonds", but we must analyse each, and give priority to experimental data that proves a "spodium bond" or covalent/coordination bond. We should also remember that there is a π–hole version of the spodium bond. We should use a name for each interaction in order to understand the crucial role of covalent or noncovalent bonds in synthetic chemistry.

1 A. Bauzá, I. Alkorta, J. Elguero, T. J. Mooibroek and A. Frontera, *Angew. Chem., Int. Ed.*, 2020, **59**, 17482–17487.

Odile Eisenstein said: The nature of bonds has been the topic of considerable discussions and this is not a fully settled matter even if considerable work has been done on the topic. See for instance the books edited by Gernot Frenking and Sason Shaik.[1,2] The non-covalent interactions suffer from the same difficulty and in addition they take many forms. Should the difficulty in understanding the non-covalent interaction stop us using the words? Could it not be useful to communicate even if one does not fully understand it?

1 *The Chemical Bond: Fundamental Aspects of Chemical Bonding*, ed. G. Frenking and S. Shaik, Wiley, 2014.
2 *The Chemical Bond: Chemical Bonding Across the Periodic Table*, ed. G. Frenking and S. Shaik, Wiley, 2014.

Pierre Kennepohl responded: I completely agree. Ultimately, we need terminology and definitions in order to communicate. The biggest barriers in science tend to be that different scientific communities use different words/terms to describe the same (or similar) things. The added difficulty is that there are necessarily limitations to such definitions – and that we need to be constantly always aware of those limitations. With regards to this particular situation, the term "non-covalent interactions" is easily (and often) misinterpreted as meaning that such interactions are characterized by not having any covalent contributions. That is clearly incorrect for many such interactions. One can still wonder how much covalent character is "acceptable" when calling something non-covalent.

Paul R. Raithby added: I agree.

Andrew S. Weller asked: What would you call a 3-centre 2-electron bond? Dative, covalent, non-covalent?

Odile Eisenstein replied: I would call it a 3-centre 2-electron bond! This would be the name given by the NBO analysis. It could be dative and it could have a certain degree of covalency depending on how the electrons are shared between the three centers. The most frequent case is probably represented by a bond with two electrons in interaction with an empty orbital. Typically H_3^+, an occupied π or sigma bond in interaction with a Lewis acid (H^+, the empty orbital of BF_3), and also weaker bonding interaction like an agostic interaction, a sigma bond complex *etc.* These cases are better thought of as dative bonds rather than covalent bonds. They would not be viewed as representative of non-covalent interactions. However, very weak interactions between a bond and a weak acceptor orbital are at the limit between dative and non-covalent. The frontier is not so well defined.

Odile Eisenstein commented: It is not easy to give names to bonds. In fact, now there is the covalent bond, the ionic bond and the charge-shift bonds.[1] The latter can be found in highly varying systems, inside molecules and even in non-covalent interactions between molecules. There is probably a continuum between all types of bonds with fuzzy frontiers between them. It is of great interest to understand better what is behind the various bonds. This could require more work. In the mean time, it is probably useful to use their names to communicate. We should however be aware that naming a bond does not mean that one fully understands what is behind it.

1 S. Shaik *et al.*, *Angew Chem., Int. Ed.*, 2020, **59**, 984.

Pierre Kennepohl responded: It is worth noting that the perceived “importance” of a particular contribution to a bond/interaction will depend on what is expected of that bond. For example, if the most important concern is the energetics of the interaction (*i.e.* how strongly is something bound) then from a practical standpoint, it ultimately doesn't really matter that much where that stabilization is coming from – as long as you know how strong it is overall. On the other hand, if a particular interaction is important because it is being used to modulate magnetic or electronic properties (for example: to accelerate electron transfer[1,2]), then the nature of the interaction (more specifically how covalent it is) can become critical.

1 F. G. L. Parlane, C. Mustoe, C. W. Kellett, S. J. Simon, W. B. Swords, G. J. Meyer, P. Kennepohl and C. P. Berlinguette, *Nat. Commun.*, 2017, **8**, 1761, DOI: 10.1038/s41467-017-01726-7.
2 C. W. Kellett, P. Kennepohl and C. P. Berlinguette, *Nat. Commun.*, 2020, **11**, 3310, DOI: 10.1038/s41467-020-17122-7.

Kamran T. Mahmudov responded: The chemical bonds are not limited to covalent bonds, ionic bonds and the charge-shift bonds, in fact, the hydrogen bond,[1] the halogen bond[2] and the chalcogen bond[3] have already been recognized by IUPAC.

The authors of these recommendations are well known by theoretical and experimental researchers working in noncovalent chemistry. The charge-shift bonds have not yet been recognized by IUPAC. Should we follow IUPAC? Or the charge-shift bonds?

For information: ref. 4–7 are additional references on σ–hole interactions.

1 E. Arunan, G. R. Desiraju, R. A. Klein, J. Sadlej, S. Scheiner, I. Alkorta, D. C. Clary, R. H. Crabtree, J. J. Dannenberg, P. Hobza, H. G. Kjaergaard, A. C. Legon, B. Mennucci and D. J. Nesbitt, *Pure Appl. Chem.*, 2011, **83**, 1637–1641.
2 G. R. Desiraju, P. S. Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati and K. Rissanen, *Pure Appl. Chem.*, 2013, **85**, 1711–1713.
3 C. B. Aakeroy, D. L. Bryce, G. R. Desiraju, A. Frontera, A. C. Legon, F. Nicotra, K. Rissanen, S. Scheiner, G. Terraneo, P. Metrangolo and G. Resnati, *Pure Appl. Chem.*, 2019, **91**, 1889–1892.
4 P. Politzer, J. S. Murray and T. Clark, *Phys. Chem. Chem. Phys.*, 2013, **15**, 11178–11189.
5 P. Politzer, J. S. Murray and T. Clark, *Phys. Chem. Chem. Phys.*, 2010, **12**, 7748–7757.
6 P. Politzer, J. S. Murray, T. Clark and G. Resnati, *Phys. Chem. Chem. Phys.*, 2017, **19**, 32166–32178.
7 J. S. Murray, P. Lane and P. Politzer, *Int. J. Quantum Chem.*, 2007, **107**, 2286–2292.

Robin N. Perutz replied: The dominant element in halogen bonds is iodine with a few examples from bromine. The dominant elements for chalcogen bonds are selenium and tellurium. The names derive in part from the order of their discovery and investigation. In a more general sense, we see this type of bonding with heavy main group elements with principal quantum number 4, 5 and 6. However, a general name has not emerged.

Paul R. Raithby responded: I completely agree. The standard single-crystal X-ray experiment (not those using a Hirshfeld atom refinement (HAR) analysis) provides only the centres of electron density and allows for the distances between those centres to be measured. It says nothing about the nature of the intramolecular or intermolecular bonding between these centres which is decided upon by the current bonding theories developed by chemists. It is highly likely that there is a continuum of bonding types between atoms.

Jorge Echeverría replied: I completely agree with you in the vision of the chemical bond as a continuum and, of course, there is nothing inherently wrong with giving names to bonds. However, we must be coherent and stick to general

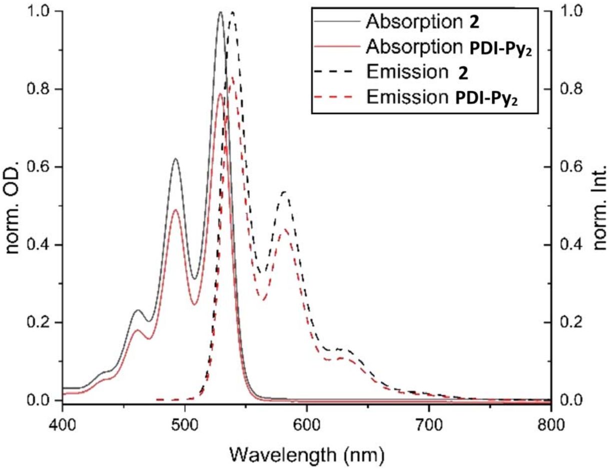

Fig. 1 Molar absorptivity for PDI dimer **2** (3.33 μM in DMF) and single **PDI-Py$_2$** ligand (6.66 μM). Spectrum is normalized with respect to **2**.

definitions while trying to maximize the information that a bond name gives about a particular interaction. That is why, in my opinion, the idea of putting interaction names based on the periodic group of the atom acting as the Lewis acid must be questioned. While hydrogen or halogen bonds refer to very specific bonding situations that also have historical connotations, one should be more careful when dealing with transition metals in which different orbitals come into play.

Pierre Kennepohl continued discussion of the paper by Sonja Pullen: You mention that only a minor energy shift is observed in the electronic absorption (UV/vis) spectra in the PDI-Py_2 dimer (**2**) relative to the parent PDI monomer (**1**), but how different are the intensities (molar absorptivities) between these species?

Sonja Pullen answered: The molar absorptivity for the PDI dimer **2** (at concentration of 3.33 μM in DMF) indeed appears slightly higher in comparison with single PDI (6.66 μM), see Fig. 1 here where the spectrum is normalized with respect to **2**, and the small difference in absorption is shown. We are currently investigating the electronic absorption spectra at higher concentrations (0.42 mM, as used in catalysis), and the difference in molar absorption is even more dominant, which needs further investigation.

Pierre Kennepohl asked: Are there any changes in the visible spectra when substrates bind into the cavity of the PDI-Py_2 dimer (**2**)?

Sonja Pullen replied: In initial studies which were conducted at lower concentration as compared with ^{1}H-NMR titrations and catalysis (3.33 μM *vs.* 0.42 mM) due to high molar absorptivity of dimer **2**, we have not observed a significant change in the UV-vis spectra when substrates are added. We are currently investigating the substrate binding at higher concentrations.

Joost N. H. Reek continued discussion of the paper by Rafael Gramage-Doria: The selectivity obtained at 130 °C is surprising and perhaps a bit counter-intuitive considering the expected lower affinity of the pyridine for the zinc atom at these high temperatures. The question is how this can be explained by looking at the proposed mechanistic scheme. You could assume that pre-organisation plays a role, leading to high local concentration of the substrate, but given the lower binding constant this may be unlikely. A second effect that may be anticipated is that the C–Br bond is activated for oxidative addition by pyridine coordination to the zinc, giving faster reactions. What is your view on this and do you have any evidence for either one of the explanations?

Rafael Gramage-Doria answered: In the past we performed some molecular modelling in which the electrostatic potential map around the C–Br bond does not change significantly when binding to simple ZnTPP.[1] Anyway, we may have a closer look for the current system.

[1] P. Zardi, T. Roisnel and R. Gramage-Doria, *Chem.–Eur. J.*, 2019, **25**, 627–634.

Joost N. H. Reek enquired: Could it be that the *meta*-bromopyridyl substrate binds in a ditopic fashion with an interaction between the pyridine and Zn, and an additional interaction between the Br atom and the nitrile? This latter interaction also may activate the C–Br bond for oxidative additions. (See also the paper of Pierre Kennepohl (**https://doi.org/10.1039/d2fd00140c**)).

Rafael Gramage-Doria responded: This is a very nice suggestion and we could study it in detail in the future using different spectroscopic techniques.

Joost N. H. Reek asked: Following up on the previous two questions, did you perform the reaction in the dark to exclude reaction pathways that are initiated by photo-activation (see also the paper of Pullen (**https://doi.org/10.1039/d2fd00179a**) for example)?

Rafael Gramage-Doria replied: This is an interesting point. We did not perform the reactions in the dark so far. We should further evaluate this as well as the eventual formation of radical-like species that may form since the porphyrin ligand could act as a chromophore.

Rens Ham enquired: Your system contains four cyano groups that could potentially bind four different palladium sites. Do you know how many of these sites are occupied by palladium? And if there were more than one, could it be possible that the bromopyridine is coordinating the excess palladium site(s) instead of the zinc porphyrin motif?

Rafael Gramage-Doria answered: In the past[1] we performed extensive NMR and HRMS studies that support the binding of, at least, one palladium to a nitrile group from the supramolecular ligand **L**. However, we cannot rule out other possibilities as you mention.

Regarding the second question, if the bromopyridine is coordinating the excess palladium site(s) instead of the zinc porphyrin motif an increased reactivity would have been observed with a supramolecular ligand lacking the zinc centre. This corresponds to $\mathbf{H_2L}$ from Table 1 in the paper (**https://doi.org/10.1039/d2fd00165a**) that leads to lower activity when compared to the supramolecular ligand **L** containing the zinc centre.

1 P. Zardi, T. Roisnel and R. Gramage-Doria, *Chem.–Eur. J.*, 2019, **25**, 627–634.

Miquel Costas asked: Have you considered designing your system to accommodate the organometallic intermediate? Can you potentially catch the first reaction intermediate?

Rafael Gramage-Doria replied: We tried to catch the first intermediate resulting from oxidative addition at palladium but we did not succeed so far. Perhaps we can try it with the more reactive pyridyl iodide under milder conditions.

Robin N. Perutz continued discussion of the paper by Pim R. Linnebank: Natalie Fey has analysed the effect of ligands; she uses a lot of parameters and draws a map with principal component analysis; the map shows the regions where the ligand does what you want, and the regions where it doesn't.[1] Could you do something similar for substrates? You won't necessarily recover a rational explanation but you can make predictions on this basis. A further comment: the intensity of the C–C stretch may be determined by vibrational mixing and I don't see the relevance of that.

1 D. J. Durand and N. Fey, *Acc. Chem. Res.*, 2021, **54**(4), 837.

Pim R. Linnebank answered: This is indeed an interesting approach that we haven't considered in this contribution. However we will look into it further.

Miquel Costas asked: At which point in your analysis do you think you need to separate the substrates according to their structures to try to fit a model to them? Maybe you can use just aromatic or just aliphatic substrates since the selectivity deciding parameters may be different?

Pim R. Linnebank replied: This is indeed what we did in the final section in which allylbenzene type substrates were treated as a subset of 21 different substrates and were used as the data set instead of the entire data set of 41 substrates. This indeed leads to an interesting correlation of $R^2 = 0.36$ when the alkene, the C=C stretch and the average charge on the two *meta* carbon atoms on the aryl ring were used as descriptors. This can also point towards a weak interaction between the aromatic plane of the cage and the aryl ring of the allylbenzene derivative. It is a compromise in which you would ideally have a single formula for all the substrates, but that is not feasible and you have to be pragmatic. For this allylbenzene set, it was feasible since the subset is relatively uniform and large. However, this may be harder and less robust if smaller subsets are used.

Stuart A. Macgregor said: Some of the systems discussed in this session are complex and elegantly engineered to realise improvements in either reaction yields or regioselectivity. However, the observed changes (*e.g.* a 3-fold increase in a yield; a 2 : 1 *vs.* a 7 : 1 regioselectivity) in fact correspond to very small differentials in an activation barrier, of the order of 1 kcal mol^{-1}. It is likely to be very challenging to rationalise this behaviour and even more so to then find descriptors that capture the performance of these systems.

Pim R. Linnebank responded: This is indeed true and very subtle changes will affect the regioisomeric ratios, so success is definitely not guaranteed. However, for the non-encapsulated catalyst we are able to predict this and for small data sets we do find correlations which do predict and point towards certain interactions that are relevant for the regioisomeric outcome. So it is still worthwhile to put in effort in trying to predict the overall regioisomeric outcome. However, this is a compromise which revolves around trying to predict and understand the outcome of a reaction and just trying the reaction yourself. Which is essentially what I did in my first effort in which I ordered 41 substrates and investigated the regioisomeric outcomes experimentally.

Torsten Beweries communicated about the paper by Rafael Gramage-Doria: Was the reaction tested for homogeneity? Reaction monitoring using *in situ* ^{1}H

NMR or GC analysis (probably better) would be most appropriate to check for induction periods/sigmoidal profiles.

Rafael Gramage-Doria communicated in reply: The reaction was not tested for homogeneity, but we plan to perform mercury tests and other ones. The reaction conditions we are using (toluene solvent and anhydrous conditions) are, in principle, rather compatible for a homogeneous regime. A preliminary kinetic study (shown in the supplementary information of the paper (**https://doi.org/10.1039/d2fd00165a**)) with reaction monitoring using *in situ* GC analysis shows no induction period nor sigmoidal profiles.

Torsten Beweries communicated: An additional NMR binding study of Zn + bromopyridine + Pd would be helpful to see whether the Pd can bind the Zn–bromoarene moiety.

Rafael Gramage-Doria communicated in reply: We have done this experiment in the past[1] at room temperature and there is a nice allosteric effect, in which the binding of nitrile to palladium increases qualitatively the binding of bromopyridine to the zinc–porphyrin site (up-field shifts). However, these experiments will have to be done at higher temperatures too.

1 P. Zardi, T. Roisnel and R. Gramage-Doria, *Chem.–Eur. J.*, 2019, **25**, 627–634.

Torsten Beweries communicated: How about product decoordination from the Zn–porphyrin moiety. A comparison of the binding affinity of substrate *vs.* product would be interesting.

Rafael Gramage-Doria communicated in reply: We did not measure the binding constant of the product towards the supramolecular ligand. Although we anticipate that it should be in the same order of magnitude as the substrate (8.4×10^3 M^{-1}).[1] However, during the catalytic reactions it could be possible that there is less affinity for the product than the substrate since the supramolecular palladium complex could provide additional steric shields. Reaction progress kinetic studies could be performed to unravel if there is product inhibition or not.

1 P. Zardi, T. Roisnel and R. Gramage-Doria, *Chem.–Eur. J.*, 2019, **25**, 627–634.

Conflicts of interest

There are no conflicts to declare.