Catalytic synthesis of phenols with nitrous oxide

The development of catalytic chemical processes that enable the revalorization of nitrous oxide (N\textsubscript{2}O) is an attractive strategy to alleviate the environmental threat posed by its emissions\textsuperscript{1}–\textsuperscript{6}. Traditionally, N\textsubscript{2}O has been considered an inert molecule, intractable for organic chemists as an oxidant or O-atom transfer reagent, owing to the harsh conditions required for its activation (>150 °C, 50–200 bar)\textsuperscript{7}–\textsuperscript{11}. Here we report an insertion of N\textsubscript{2}O into a Ni-C bond under mild conditions (room temperature, 1.5–2 bar N\textsubscript{2}O), thus delivering valuable phenols and releasing benign N\textsubscript{2}. This fundamentally distinct organometallic C-O bond-forming step differs from the current strategies based on reductive elimination and enables an alternative catalytic approach for the conversion of aryl halides to phenols. The process was rendered catalytic by means of a bipyridine-based ligands for the Ni centre. The method is robust, mild and highly selective, able to accommodate base-sensitive functionalities as well as permitting phenol synthesis from densely functionalized aryl halides. Although this protocol does not provide a solution to the mitigation of N\textsubscript{2}O emissions, it represents a reactivity blueprint for the mild revalorization of abundant N\textsubscript{2}O as an O source.

The increasing emission of greenhouse gases represents a global environmental threat, and strategies to address this issue have been the focus of intense research in recent times\textsuperscript{12}. From the sustainability point of view, the development of chemical processes that extend beyond the traditional degradations and repurpose such gaseous by-products as useful synthons to produce valuable chemical feedstocks is highly desirable. Whereas the revalorization of CO\textsubscript{2} or CH\textsubscript{4} by-products as useful synthons to produce valuable chemical feedstocks is highly desirable. Nevertheless, the activation of N\textsubscript{2}O to form C-O bonds is highly desirable. Whereas the revalorization of CO\textsubscript{2} or CH\textsubscript{4} by-products as useful synthons to produce valuable chemical feedstocks is highly desirable.
formation of N₂ (Fig. 1b, right). In contrast to the traditional synthesis of phenols, after C‒O bond formation the oxidation state of the metal centre remains intact, thus requiring an external reductant to close the cycle. To orchestrate this reductive process, we focused our attention on Ni and its demonstrated ability to manoeuvre between different oxidation states through single-electron transfer. Here we demonstrate that a mechanistically guided approach for the activation of N₂O with organometallic complexes results in the development of a mild and selective catalytic synthesis of high-value phenols from aryl halides using N₂O as an electrophilic O source. The mild conditions (25 °C and 1.5–2 atm) allow the accommodation of a variety of functional groups, including base-sensitive moieties, thus providing an orthogonal strategy to the current technologies (Fig. 1c).

To investigate the feasibility of the M‒C(sp²) oxidation, we drew inspiration from previous work, in which N₂O was demonstrated to react with certain phosphine–Ni(II) complexes. To this end, we synthesized the product of oxidative addition 4, and studied its reactivity with N₂O (Fig. 2a). As expected, 4 rapidly decomposes mainly towards homocoupling (5) when dissolved in DMA under argon, with only traces of protodemetalation (6) detected (path a). This reactivity is exacerbated by the presence of reducing agents such as Zn (path b). Yet, when the argon atmosphere is replaced by N₂O, the bright red colour of the solution of 4 remains, thus pointing towards a slower decomposition rate. After acidic workup, a 15% yield of phenol 7 is observed. However, when the same reaction is performed in the presence of a reducing agent, substantially higher yields of 7 were observed, with a 73% yield obtained when a combination of Zn and NaI was used (path d). These results point to the feasibility of developing a reductive catalytic protocol based on Ni catalysis using aryl halide precursors. From our extensive ligand survey, it was evident that tridentate nitrogenated ligands with the general pattern of 2-substituted bipyridine were crucial to obtain catalytic activity, with terpyridine (L₈) and 6-pyrazolyl-2,2'-bipyridine (L₅₀) affording the highest yields of 9 (Fig. 2b and Supplementary Information). Analysis
of the R group revealed three key features of the ligand for catalytic activity: replacing the N atom with C–H or S prevents catalytic activity; derivatives such as CF₃ (31), aryl (26), and nitrile (22–23) posed no difficulty for the C–O bond formation. Electron-donating substituents such as alkyl (25), aryl (26), or even methoxy and thiomethyl (27 and 28) delivered phenol in good yields. Moreover, a fluorene derivative (29) featuring benzylic C–H bonds was also amenable for phenol synthesis, albeit in 38% yield. A classical feature of reductive couplings is that steric hindrance at the ortho position can impede reactivity. Indeed, C–O bond formation from indanone (31) and 1-chloro-2-iodobenzene (30) derivatives afforded slightly diminished yields. In contrast to 30, 32 was

---

**Table 1**

| Reductant | Yield of 7 |
|-----------|------------|
| Zn (0.0 equiv.) | 55% |
| Mn (0.8 equiv.) | 52% |
| TDAE (2.0 equiv.) | 50% |

---

**Fig. 2 | Initial discovery, ligand optimization and potential intermediates.**

*a* Stoichiometric reactivity using bipyridine-supported Ni(II) oxidative addition complexes. conv., conversion; equiv., equivalents. *b* Key electronic and structural features of the ligand in the catalytic synthesis of phenols from aryl halides and N₂O. Details on the complete optimization of the reaction conditions can be found in the Supplementary Information. *c* Using 2 atm of N₂O. *d* With 5 mol% extra L₅₀. *e* Yields using NiBr₂(glyme).
obtained in 79% yield, illustrating a possible beneficial chelating effect of the ortho OMe and the Ni centre. A silylated benzylic alcohol (33) or a diethylphosphonate (34) were also tolerated in this protocol. Heterocycles such as indole (35), quinoline (36), carbazole (37) or dibenzothiophene (38) also afforded the corresponding phenol in good yields. Substrates prone to rapid oxidation after C–O bond formation could be further functionalized in situ, as exemplified by the 68% yield obtained for the pivaloyl derivative 39. An iodide derivative of the biologically active agent clofibrate could be converted to phenol 40 in 78% yield despite the presence of a tertiary α-oxy ester. This protocol does not require the use of nucleophilic alkoxy surrogates, and hence base-sensitive functionalities such as esters or sensitive amides, can be tolerated. An example of this chemoselectivity is observed in the derivatization of a substrate containing pinacol boronate. In this case, phenol 41 was still obtained in 56% yield, thus providing an orthogonal tool to classical oxidation. The observation of 7% yield of sulfoxide in the reaction of 28 (ref. 40), and the low yield obtained for fluorenol 29, suggest that the oxy-insertion step lies towards the oxo/oxyl–pathway in the continuum postulated for OMBV-type reactions. N₂ was detected using a gas chromatography–thermal conductivity detector in the headspace after the reaction had finished for 7, 9, 18, 25 and 34 (Fig. 3). When the oxygen on the solvent was labelled ([18O]DMF, 25% 18O), no 18O was incorporated in 9. On the other hand, when N₁⁵N₁⁸O was used (ca. 23% 18O), 22% ± 1 of the O in 9 was labelled (Supplementary Information). Together, these data point to N₂O as the source of O.

The same optimized reaction conditions for aryl iodides permitted C–O bond formation of more accessible and commercially available aryl bromides. Yet, electron-withdrawing substituents were required to allow C(sp²)–Br cleavage to occur. In this sense, phenols bearing CF₃ (7), Ac (20) and CN (22) in the para position, as well as paraben (21), could be obtained in high yields (Fig. 4a). Medicinally relevant phthalides such as phthalic anhydride, also smoothly converted to the phenol (42), thus providing a method to synthesize this building block with three fewer steps compared with the reported method⁴¹. Phenols derived from π-extended or conjugated systems such as naphthoate 43 or cinnamate 44 were also obtained in 63% and 78% yields, respectively. In contrast to current light-mediated processes, no isomerization of the double bond in 44 was observed⁴⁵. Finally, another base-sensitive group such as the aryl

---

**Article**

**Fig. 3** | Revalorization of N₂O as O source in the catalytic synthesis of phenols. Scope of aryl iodides. [N₂], N₂ detected by a gas chromatography–thermal conductivity detector at the end of the reaction. Ally yields are of isolated pure material. Yield in brackets: 1H NMR yield calculated using dibromomethane as an internal standard. incorp., incorporated. See the Supplementary Information for details of the procedures. *Use of L18 as the ligand instead of L50. †Owing to the rapid oxidation of the free alcohol, 39 was obtained after quenching with Piv₂O.
methyl sulfone could be tolerated and the corresponding phenol 45 was obtained in 82% yield. Heterocyclic bromides are not compatible with the current protocol.

Complex aryl halides functionalized with sensitive moieties were then tested. For example, an empagliflozin derivative, which contains a plethora of weak C–H bonds prone to HAT, was smoothly converted...
to the corresponding phenol (46) in excellent yield (Fig. 4b). An ester derivative of the natural product eugenol afforded the desired phenol (47) in an 84% yield, highlighting the high chemoselectivity of this process over alternative oxidation through metal–oxygen pathways. Despite the triphasic nature of the protocol, synthesis of 47 could be scaled up to 5 mmol with only a slight reduction in the yield (66%). Substrates containing saturated N-heterocycles such as piperazine 48, azetidine 49, pyrrolidinone (anilcatem intermediate) 50 and nortropinine derivative 51 are well tolerated. The requirement of an electron-withdrawing group to activate the aryl bromide can be turned into a synthetic advantage, thus permitting regioselective control on the activated aryl bromide (52, 78%). Finally, a derivative ezetimibe, the drug used to treat high blood cholesterol, could be smoothly converted into the corresponding phenol (53), without altering the chiral and unprotected secondary alcohol, the ester and the strained β-lactam. Similar chemoselectivity can be observed in the conversion of paroxetine derivative 54. Finally, Fig. 4c illustrates a proof-of-concept of the potential for the revalorization of greenhouse gases for organic synthesis. It is now possible to combine N₂O and CO₂ revalorization strategies and obtain metaxolone (59), in which 66% of the oxygen atoms originate from waste gaseous feedstock. A more striking example is illustrated in the synthesis of bazedoxifene (68), a drug candidate against breast and pancreatic cancer. The three phenolic building blocks could be rapidly obtained from the parent halides in good yields (64–66). Subsequent Fischer-indole synthesis allows access to indole 67, enabling the synthesis of bazedoxifene (68) with all 0 atoms originating from N₂O (refs. 43–44). Whereas a 42% yield could be obtained for precursor 63 with 1 mol% catalyst loading, a <10% yield of 14 was observed with the same catalyst loading, with substantial protoiodolation of the parent iodide 61, which highlights the subtle differences between aryliodides and aryl bromides in this system.

Conclusions

Through a distinct fundamental organometallic step, a catalytic protocol for the revalorization of N₂O as a green, mild and chemoselective O-atom insertion reagent for organic synthesis has been unlocked. Mechanistically guided insights into the reactivity of N₂O with Ni complexes point to formally low-valent Ni(II)-aryl permitting the O insertion in an efficient manner. The inert N₂O molecule succumbs to activation under mild conditions for the selective synthesis of phenols from aryl halides. The catalytic system features an electronically asymmetric tridentate bipyridine-based ligand (LS0) for the Ni centre, which enables selective C-O bond formation. The reported conditions are simple and robust, allowing phenol formation in densely functionalized molecules. Whereas other catalytic protocols capitalize on nucleophilic HO–counterparts, this method represents a unique example of catalytic C–O bond formation with an electrophilic O-atom source, which in turn can accommodate base-sensitive functionalities. Furthermore, this protocol demonstrates the feasibility of accessing relevant drugs for which N₂O is the sole source of oxygen atoms.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-022-04516-4.
39. Figg, T. M. & Cundari, T. R. Mechanistic study of oxygen insertion into nickel-carbon bonds with nitrous oxide. Organometallics 31, 4998–5004 (2012).
40. Liang, Y. et al. Electrochemically induced nickel catalysis for oxygenation reactions with water. Nat. Catal. 4, 116–123 (2021).
41. Walsh, S. et al. Inhibitors of the renal outer medullary potassium channel. Patent WO2013039802 (A1) (2013).
42. Del Vecchio, A. et al. Audisio, carbon isotope labeling of carbamates by late-stage \(^{13C}\) and \(^{14C}\)carbon dioxide incorporation. Chem. Commun. 56, 11677–11680 (2020).
43. Soliev, P. N., Sherman, D. K., Novikov, R. A., Levina, E. A. & Kochetkov, S. N. Hydrazo coupling: the efficient transition-metal-free C–H functionalization of 8-hydroxyquinoline and phenol through base catalysis. Green Chem. 21, 6381–6389 (2019).
44. Kelly, P. M. et al. Synthesis, antiproliferative and pro-apoptotic activity of 2-phenylindoles. Bioorg. Med. Chem. 24, 4075–4099 (2016).
45. Wang, C., Sun, H., Fang, Y. & Huang, Y. General and efficient synthesis of indoles through triazene-directed C–H annulation. Angew. Chem. Int. Ed. 52, 5795–5798 (2013).
46. Hwang, S. G. et al. Methods of preparing bazedoxifene. Patent KR201895239 (A) (2018).

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022, corrected publication 2022
Data availability
Details on the procedures, optimization, characterization and mechanisms, including spectra of new compounds and compounds made using the reported method, are available in the Supplementary Information. Crystallographic data for compound 10 can be obtained free of charge from www.ccdc.cam.ac.uk under reference number 2114695.

Acknowledgements Financial support for this work was provided by Max-Planck-Gesellschaft, Max-Planck-Institut für Kohlenforschung, Fonds der Chemischen Industrie (FCI/VCI), the Swiss National Science Foundation (Early Mobility Postdoctoral Fellowship (grant number 184406), 2019-2021) (F.L.V.) and Universidad de Oviedo-Banco Santander (Mobility Fellowship S.G.-P.). We thank A. Fürstner for discussions and generous support. We also thank the members of the analytical department at MPI-Kohlenforschung for support in the characterization of compounds.

Author contributions J.C. and F.L.V. conceived the idea. F.L.V. designed the approach, optimized the process, performed the experiments, analysed the experimental data and prepared the Supplementary Information. S.G.-P. helped in the initial stages of the catalysis optimization. A.M.C. performed ligand syntheses and contributed in mechanistic studies. S.N. carried out the reactions with labelled compounds, and aided in the scope, scalability and limitations of the reported protocol. E.J.R. carried out EPR measurements and analysis. J.B. helped in the scale up of the optimized ligand and in starting materials syntheses for the scope. The manuscript was written by F.L.V. and J.C. The project was directed by J.C.

Funding Open access funding provided by Max Planck Society.

Competing interests Max-Planck-Institut für Kohlenforschung has filed a patent (EP21202763.8) on the procedure described in this article.

Additional information Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41586-022-04516-4.

Correspondence and requests for materials should be addressed to Josep Cornella.

Peer review information Nature thanks the anonymous reviewers for their contribution to the peer review of this work.

Reprints and permissions information is available at http://www.nature.com/reprints.