Late-Stage C(sp^2)–C(sp^3) Diversification via Nickel Oxidative Addition Complexes

Carlota Odena,[†¶§] Tomás G. Santiago,[†§] María Lourdes Linares,[&§] Nahury Castellanos-Blanco,[†] Ryan T. McGuire,[†] Belén Chaves-Arquero,[&] Jose Manuel Alonso,[&] Alejandro Diéguez-Vázquez,[#] Eric Tan,[#] Jesús Alcázar,[&] Peter Buijnsters,[#] Santiago Cañellas,*[&] and Ruben Martin*[†£]

[†] Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, 43007 Tarragona, Spain

[¶] Universitat Rovira i Virgili, Departament de Química Orgànica, c/Marcel·lí Domingo, 1, 43007 Tarragona, Spain

[£] ICREA, Passeig Lluís Companys, 23, 08010, Barcelona, Spain

[&] Janssen-Cilag, S.A., a Johnson & Johnson company, C/ Jarama 75A, Toledo, Spain

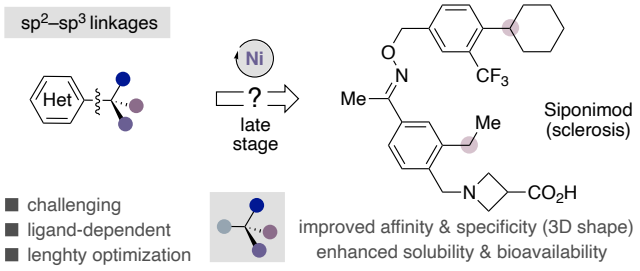
[#] Janssen Pharmaceutica NV, a Johnson & Johnson company, Turnhoutseweg 30, 2340, Beerse, Belgium

Supporting Information Placeholder

ABSTRACT: Herein, we describe nickel oxidative addition complexes (Ni-OACs) of drug-like molecules as a platform to rapidly generate lead candidates with enhanced C(sp^3) fraction. The potential of Ni-OACs to access new chemical space has not only been assessed in C(sp^2)–C(sp^3) couplings but also in additional bond-formations without recourse to specialized ligands and with improved generality when compared to Ni-catalyzed reactions. The development of an automated diversification process further illustrates the robustness of Ni-OACs, thus offering a new gateway to expedite the design-make-test-analyze (DMTA) cycle in drug discovery.

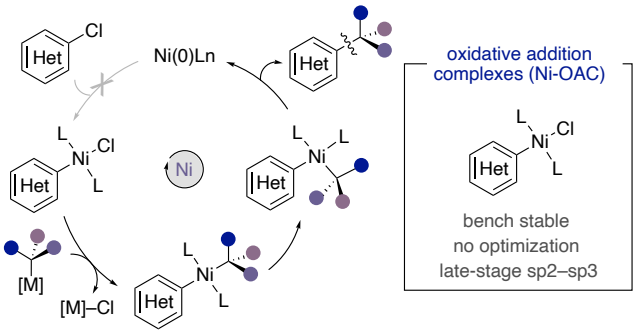
The high attrition rates of small molecules make early phases of drug discovery via conventional multistep sequences time-consuming, resource intensive and expensive.[1] These problems might be alleviated by new techniques that rapidly and reliably incorporate sp^3 hybridized carbons – molecular fragments that improve several molecular attributes that contribute to clinical success[2] – at late-stages in advanced intermediates, thus accelerating structure-activity relationship (SAR) explorations[3] while increasing the likelihood of compounds entering clinical trials and being approved for medicinal use.

Scheme 1. C(sp^2)–C(sp^3) Linkages in Medicinal Chemistry.



Recently, nickel catalysis has offered new vistas for forging C(sp^2)–C(sp^3) architectures via one- or two-electron manifolds.[4] However, the majority of active molecules in medicinal chemistry contain nitrogen, sulfur or oxygen atoms that might bind the nickel center.[2,5] Indeed, specialized tailor-made ligands, high-throughput experimentation campaigns and/or several rounds of optimization are oftentimes required to enable Ni-catalyzed cross-couplings (Scheme 1).[4] In practice, such vulnerabilities contribute to the perception that new Ni-mediated approaches might be necessary for *de novo* synthesis or late-stage functionalization with drug-like molecules.

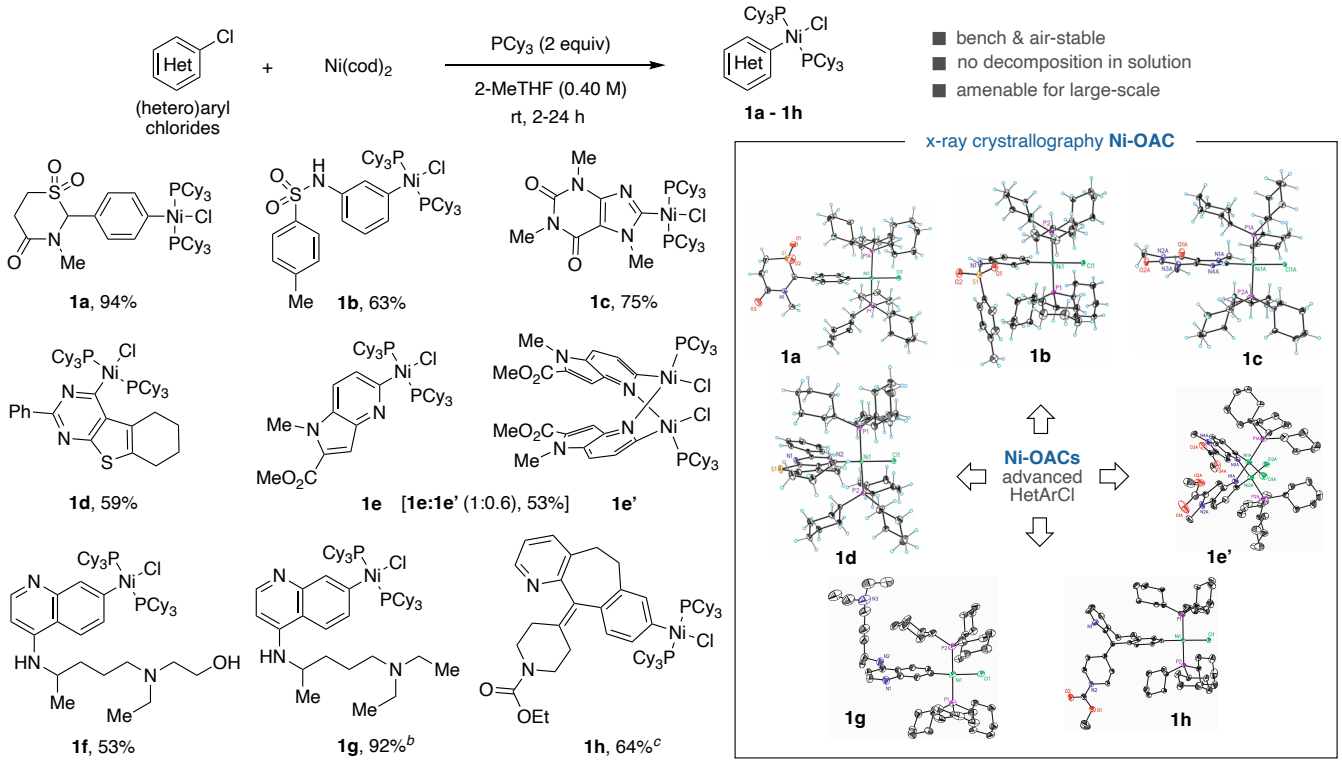
Scheme 2. Ni-OAC For C(sp^2)–C(sp^3) Diversification.



There is ample consensus that a subtle balance of all individual steps within the catalytic cycle is critical for success.[4,6] Among these, catalyst (pre)activation and oxidative addition are key for success given that such reactions precede bond-formation (Scheme 2). Consequently, we envisioned that stoichiometric nickel oxidative addition complexes (Ni-OAC) could rapidly and reliably access molecular diversity with drug-like scaffolds, as (a) parasitic bimolecular pathways commonly present in Ni-catalyzed reactions would be minimized,[7] (b) we might

obviate the need for optimizing the nickel catalyst and ligand,[4] while avoiding the prerequisite for catalyst turnover. Given the propensity of Ni complexes to operate via one- or two-electron manifolds,[4] we anticipate Ni-OACs might constitute an alternative to two-electron Pd-based processes for C-N or sp^2–sp^2 couplings[8] by rapidly accessing analogues with increased fraction of sp^3 hybridized carbons as well as new chemical space that would be difficult to access otherwise. In addition, such a technique might facilitate the likelihood that reactions might occur in advanced synthetic intermediates, thus accelerating structure-activity relationship (SAR) studies while lowering the overall costs that are typically associated with conventional synthetic sequences and/or lengthy optimization campaigns in the early phases of drug discovery.[1] Herein, we report the realization of this goal, culminating in a broadly applicable platform – even in the context of an automated diversification approach in continuous flow[9] – that might expedite the access to lead candidates.

Scheme 3. **Preparation of Ni-OACs from Advanced (Het)ArCl**.[a]



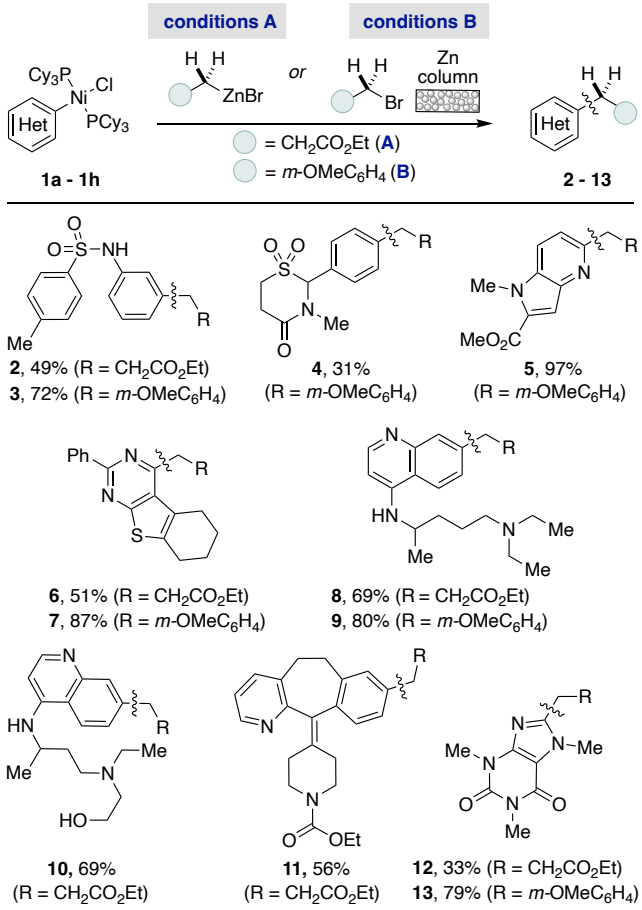
[a] (Het)ArCl (1.0-1.30 equiv), $Ni(cod)_2$ (1.0 equiv), PCy_3 (2.0 equiv), 2-MeTHF (0.40 M), rt, 2-24 h; **1a-1g**: Isolated yields, average of two runs. [b] 1.64 mmol scale. [c] (Het)ArCl (0.5 equiv), $Ni(cod)_2$ (1.0 equiv), PCy_3 (1.6 equiv), THF (0.018 M), rt, 12 h. X-ray crystal structures of **1a-1h** (thermal ellipsoids at the 50% probability level). Hydrogen atoms have been omitted for clarity.

We began our study by accessing Ni-OAC from antimalarial drug chloroquine (Scheme 3).[10] Its choice was not arbitrary, as chloroquine possesses structural features that might be problematic in classical catalytic cross-couplings, such as the presence of both tertiary and secondary amines that possess hydrogen bond-donors or acceptors, a coordinating 4-aminopyridine moiety and a non-activated heteroaryl chloride.[4,5] Notably, exposure of chloroquine to $Ni(cod)_2$ and PCy_3 in 2-MeTHF at rt followed by simple filtration cleanly delivered **1g** in 70% yield. The robustness of the protocol was assessed in a gram-scale, obtaining **1g** in an improved 92% yield. The stability of **1g** is illustrated by the lack of apparent decomposition or loss of purity under air after 3 months, as judged by NMR spectroscopy. This protocol was then applied to a series of advanced heteroaryl chlorides possessing nitrogen binding sites. As shown in Scheme 3, the synthesis of Ni-OACs could be accomplished by utilizing chlormezanone (**1a**), sulfonamides (**1b**), hydroxychloroquine (**1f**) or loratadine (**1h**) with equal ease. The presence of nitrogen-containing heterocycles in the vicinity resulted in either mononuclear Ni-OAC **1c** or **1d** possessing caffeine or pyrimidine backbones, or dinuclear complexes (**1e'**) containing pyrrolo[3,2-*b*]-pyridine cores. The structure of the latter was univocally determined by X-ray crystallography. At present, we believe the formation of either mononuclear or dinuclear complexes might be dictated by the geometry and solubility of Ni-OAC.[11]

Prompted by the modularity and chemoselectivity of organozinc reagents,[12] we wondered whether these reagents could be employed as coupling partners with Ni-OACs **1a-h** to forge advanced C(sp^2)–C(sp^3) architectures (Scheme 4).[13] Indeed, this turned out to be the case and coupling of Ni-OAC **1g** with commercially available (3-ethoxy-3-oxopropyl)zinc(II) bromide proceeded at rt in 1:1 THF/DMA, giving rise to **8** in 69% yield. These results were benchmarked by exposure of chloroquine under previously reported Ni-catalyzed cross-couplings of alkyl organozinc reagents with aryl halides with

DPEPhos, PPh_3 or terpyridine ligands, among others, resulting in traces of **8**.[14,15] This observation stands as a testament to the impact that Ni-OACs might have for generating molecular complexity in medicinal chemistry when promoting late-stage diversification. Then, we tested the generality of our approach on a diverse set of Ni-OACs with (3-ethoxy-3-oxopropyl)zinc(II) bromide. As expected, the catalytic performance provided lower yields, if any, of products.[14] In contrast, the Ni-OACs either used as isolated solids (**1a**-**1g**) or generated *in situ* (**1h**) resulted in the targeted C(sp^2)–C(sp^3) linkages in synthetically-useful yields (Scheme 4).

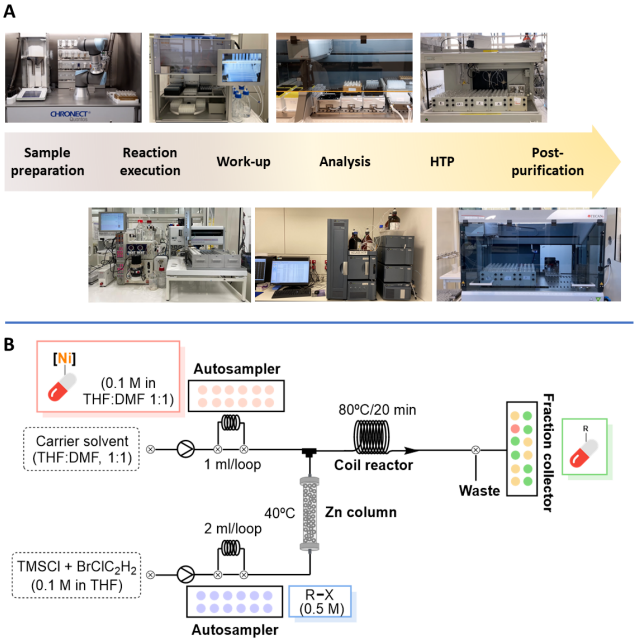
Scheme 4. C(sp^2)–C(sp^3) Architectures via Ni-OAC.[a,b]



[a] Conditions A: **1a-h** (0.10 mmol), (3-ethoxy-3-oxopropyl)zinc(II) bromide (3.0 equiv), THF/DMA 1:1 (0.13 M), rt, 14 h; Isolated yields, average of two independent runs. [b] Conditions B: **1a-g** (0.10 mmol), 1-(bromomethyl)-3-methoxybenzene (4.0 equiv.) previously passed through a Zn column at 40 ºC, THF, 70 ºC, 12 h; Purification via normal phase chromatography.

Given the paucity of commercially available organozinc reagents, their propensity to decompose in solution after prolonged reaction times,[12,13f,16] and the good solubility observed for Ni-OACs **1a-g** in common organic solvents (Scheme 3), we wondered whether we could implement an automated diversification approach in continuous flow.[16] If successful, such a technique would not only enable a faster and reliable access to C(sp^2)–C(sp^3) linkages, but would also broaden the chemical space accessible through this approach. To this end, we designed an activated packed-bed reactor containing Zn metal that generated organozincs *in situ* from alkyl halides prior to coupling with **1a-g**. As a proof-of-concept, (3-methoxybenzyl)zinc(II) bromide was generated from 1-(bromomethyl)-3-methoxybenzene, and reacted with **1a-e** and **1g** (Scheme 4). Convinced about the relevance of our platform for drug discovery campaigns, we then focused our attention on building up a library synthesis with **1g** as a surrogate of a drug-like scaffold. To this end, the library synthesis was carried out using Janssen's modular automation platform including sample preparation (Quantos Chronect), reaction execution (Vapourtec), scavenging (Extrahera), liquid-liquid extraction (Tecan), purification and analysis (Waters) and post-purification workflows (Tecan) with minimal, if any, human intervention (Scheme 5).[16d-e]

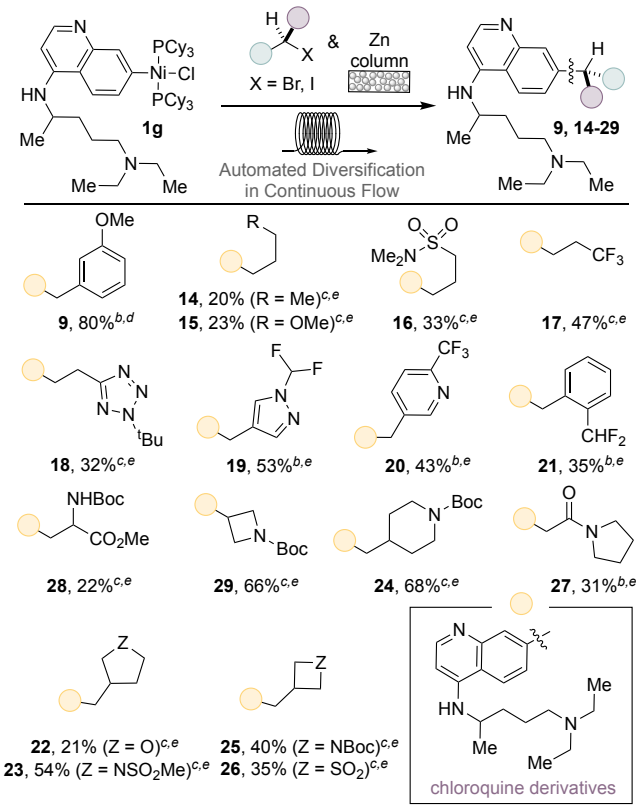
Scheme 5. End-to-End Automated (Continuous) Workflow.



It is worth noting that the alkyl halides utilized in our continuous flow automated process possess moieties typically utilized in SAR explorations of early drug discovery programs[16d,18,19] such as ethers (**9**, **15**, **22**), sulfonamides (**16**, **23**), fluorine atoms (**17**, **19**, **20**, **21**), amides (**27**), azetidines (**25**, **29**), piperidines (**24**), sulfones (**26**), nitrogen-containing heterocycles (**18**, **19**, **20**) or amino-acid derivatives (**28**) (Scheme 6). While moderate yields were obtained in some cases, automated protocols prioritize speed, throughput and quality for obtaining sufficient quantities for biological testing while minimizing human intervention. This has been demonstrated by performing head-to-head comparison of standard purification techniques with automated reverse-phase HPLC showing significantly increased isolated yields.[14] The results of Schemes 4 and 6 demonstrate that a single set of reaction conditions can be applied across a diverse set of nucleophiles and advanced intermediates without re-optimization. This is noteworthy given that Ni-catalyzed reactions

oftentimes require lengthy optimizations of the reaction parameters, including ligands or nickel precatalysts.[4] Therefore, a protocol based on Ni-OACs holds promise for accessing complex architectures in sufficient quantities for biological testing.

Scheme 6. Automated Diversification in Continuous Flow.[a]

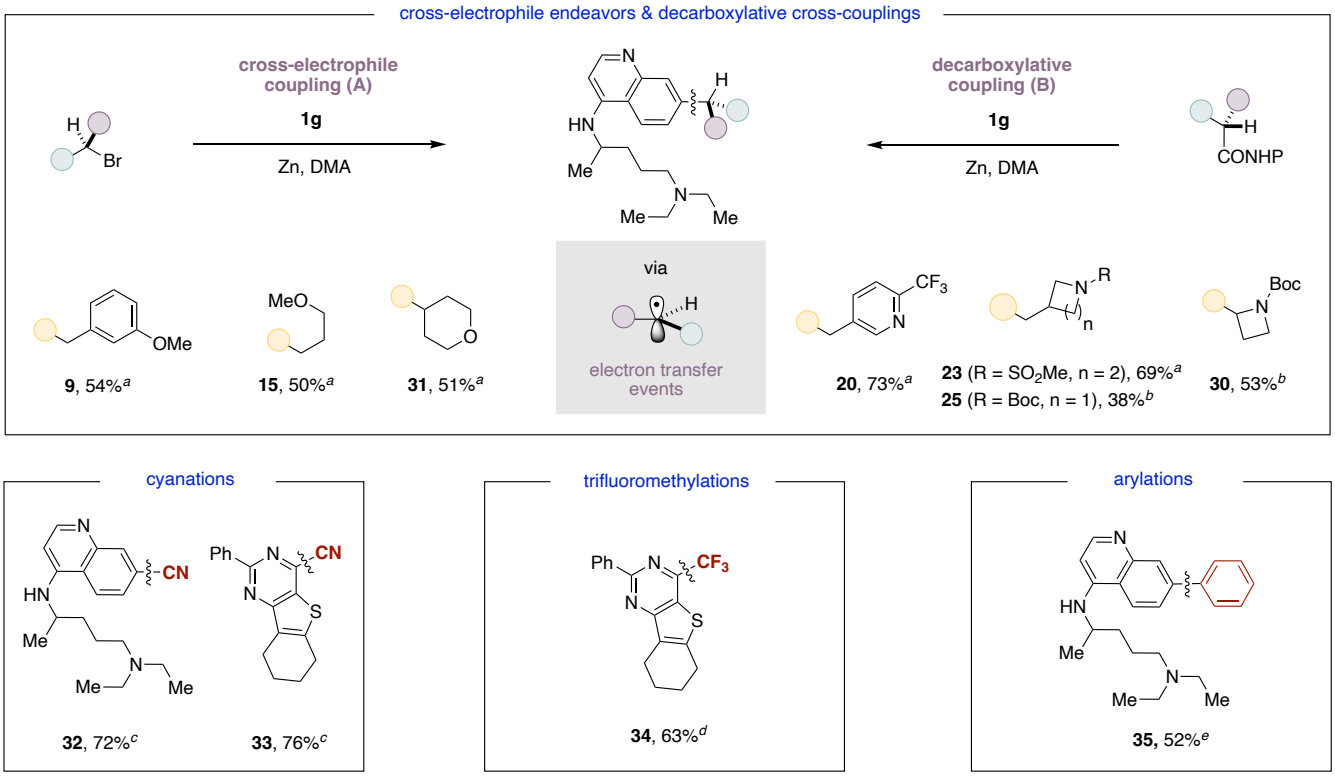


[a] Conditions: organozinc precursor (10.0 equiv), flow through activated Zn column at 40 ºC before mixing with **1g** (0.10 mmol) in THF/DMF 1:1 (0.10 M) at 80 ºC for 20 min. [b] X = Br. [c] X = I. [d] Purification via normal phase chromatography. [e] Purification via automated reverse-phase HPLC.

Complementary techniques that allow for a broad and efficient exploration of chemical space are critical in medicinal chemistry programs.[19] Thus, we turned our attention to study the viability of conducting decarboxylative couplings of chloroquine-Ni-OAC (**1g**) by employing primary or secondary redox-active NHP-esters derived from simple carboxylic acids.[20] As shown in Scheme 7, compounds bearing azetidines (**23** or **30**) could be obtained in synthetically useful yields. These results should be assessed against the challenge that is addressed, as structures of type **30** are currently beyond reach in Negishi-type cross-couplings.[21] Given the paucity of these structures in classical cross-couplings, the ability to access these scaffolds show the potential that Ni-OACs might have in modern decarboxylative couplings. Prompted by the popularity of cross-electrophile couplings for accessing C(sp^2)–C(sp^3) architectures,[4i,22] we turned our attention to study the viability of utilizing Ni-OACs for these purposes. As shown in Scheme 7, Ni-OAC **1g** reacted smoothly with a diverse set of activated or unactivated primary or secondary alkyl bromides with Zn as reductant, thus obviating the need for well-defined organozincs or redox-active esters. Furthermore, this approach was found to be particularly suited for substrates prone to parasitic β-hydride elimination such as **15**. Particularly important is the preparation of **30** and **31**, compounds that were obtained in traces, if any, under the protocol shown in Scheme 6,[14] thus constituting a testament to the flexibility that one-electron endeavors based on Ni-OAC might have in drug discovery.

While one might argue that the cost of stoichiometric amounts of metals might hamper the utility in medicinal chemistry, it is worth mentioning that the cost of one equivalent of nickel and ligand on a drug discovery scale is much lower than that of a densely functionalized drug-like scaffold.[23,24] Given that the majority of Ni-catalyzed cross-electrophile couplings or decarboxylation events require nitrogen-containing ligands, we believe our results suggest that Ni-OACs containing phosphine-type ligands might offer an operationally-simple platform for the rapid and reliable diversification of pharmaceutically-relevant scaffolds by allowing couplings that are challenging to conduct in a catalytic manner. Specifically, we found that our C(sp^2)–C(sp^3) bond-forming events could be extended to cyanations, trifluoromethylations or Suzuki-Miyaura arylations by exposing the corresponding Ni-OAC to either CuCN, $Zn(CF_3)(DMPU)_2$ or $PhB(OH)_2$ under mild conditions, resulting in the formation of **32-35** (Scheme 7, *bottom*). In contrast to conventional Ni-catalyzed cross-couplings, these transformations do not require the inclusion of a particular ligand for the reactions to occur. This observation cannot be underestimated, as the ability to reliably access molecular diversity from a common reaction intermediate without the need for optimization offers an untapped potential in medicinal chemistry settings, allowing for the rapid exploration of potential drug-type candidates.

Scheme 7. Ni-OACs in Alternate Bond-Forming Reactions.



[a] **1g** (0.1 mmol), alkylBr (0.15 mmol), Zn dust (0.2 mmol), $MgCl_2$ (0.115 mmol) and pyridine (0.2 mmol) in DMA (1 mL) at 80 ºC for 1 h; Purification via automated reverse-phase HPLC. [b] **1g** (0.053 mmol), redox active ester (0.13 mmol) and Zn dust (0.21 mmol) in DMA (0.2 mL) at 60 ºC for 16 h; Purification via automated reverse-phase HPLC. NHP = *N*-hydroxyphthalimide. [c] **1g** or **1d** (0.053 mmol) and CuCN (0.13 mmol) in ACN (0.5 mL) at 70 ºC for 16 h; Purification via automated reverse-phase HPLC. [d] **1d** (0.054 mmol), $Zn(CF_3)_2(DMPU)_2$ (0.11 mmol) and CuI (5.4 umol) in DMF (0.5 mL) at 70 ºC for 16 h; Purification via automated reverse-phase HPLC. [e] **1g** (0.05 mmol), $PhB(OH)_2$ (0.15 mmol) and K_3PO_4 (0.15 mmol) in THF (1 mL) at rt for 16 h.

In summary, this work suggests that Ni-OACs might offer a new entry point in late-stage diversification from advanced intermediates.[25] Reactions with bench-stable Ni-OACs can be applied in an automated diversification approach, and are characterized by their simplicity and broad utility across a variety of counterparts without recourse to specialized ligands or lengthy optimizations, thus expediting the access to lead candidates in drug discovery campaigns. Given that Ni-OACs can be utilized in six different cross-couplings, our results hold promise to accelerate SAR explorations in medicinal chemistry in the early phases of drug discovery, thus impacting the cost, resources and time investments required to advance drug candidates to clinical trials. Further studies into the exploitation of Ni-OACs are currently underway.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectral and crystallographic data (PDF)

Data for **1a** (CCDC-2311601) (CIF)
Data for **1b**(CCDC-2311602) (CIF)
Data for **1c** (CCDC-2311603) (CIF)
Data for **1d** (CCDC-2311604) (CIF)
Data for **1e'** (CCDC-2311605) (CIF)
Data for **1g** (CCDC-2311606) (CIF)
Data for **1h** (CCDC-2311607) (CIF)

AUTHOR INFORMATION

Corresponding Author

* rmartinromo@iciq.es
* SCanella@its.jnj.com

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Author Contribution

§ C. O., T. G. S. and M. L. L. contributed equally to the work.

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REFERENCES

1. (a) Magano, J.; Dunetz, J. R. Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals. *Chem. Rev.* **2011**, *111*, 2177–2250. (b) Jia, C.-Y.; Li, J.-Y.; Hao, G.-F.; Yang, G.-F. A drug-likeness toolbox facilitates ADMET study in drug discovery. *Drug Discov. Today* **2020**, *25*, 248–258.

2. (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25. (b) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752–6756. (c) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. What Do Medicinal Chemists Actually Make? A 50-Year Retrospective. *J. Med. Chem.* **2011**, *54*, 6405–6416. (d) Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515–519. (e) Meyers, J.; Carter, M.; Mok, N. Y.; Brown, N. On the origins of three-dimensionality in drug molecules. *Future Med. Chem.* **2016**, *8*, 1753–1767. (f) Talele, T. T. Opportunities for tapping into three-dimensional chemical space through a quaternary carbon. *J. Med. Chem.* **2020**, *63*, 13291–13315.

3. (a) McKinney, J. D.; Richard, A.; Waller, C.; Newman, M. C.; Gerberick, F. The Practice of Structure Activity Relationships (SAR) in Toxicology. *Toxicol. Sci.* **2000**, *56*, 8–17. (b) Tong, W.; Welsh, W. J.; Shi, L.; Fang, H.; Perkins, R. Structure-Activity Relationship Approaches and Applications. *Environ. Toxicol. Chem.* **2003**, *22*, 1680–1695.

4. For selected reviews on Ni-catalyzed transformations: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent Advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299–309. (b) Ananikov, V. P. Nickel: The "Spirited Horse" of Transition Metal Catalysis. *ACS Catal.* **2015**, *5*, 1964–1971. (c) Hazari, N.; Melvin, P. R.; Beromi, M. M. Well-defined nickel and palladium precatalysts for cross-coupling. *Nat. Chem. Rev.* **2017**, *1*, 25. (d) Janssen-Müller, D.; Sahoo, B.; Sun, S.-Z.; Martin, R. Tackling Remote sp^3 C–H Functionalization via Ni-Catalyzed "chain-walking" Reactions. *Isr. J. Chem.* **2019**, *59*, 1–13. (e) Campeau, L. C.; Hazari, N. Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future. *Organometallics* **2019**, *38*, 3–35. (f) Shrikant, M. K.; Chatani, N. Nickel-Catalyzed C–H Functionalization Using a Non-directed Strategy. *Chem* **2020**, *6*, 1056–1081. (g) Diccianni, J.; Lin, Q.; Diao, T. Mechanisms of Nickel-Catalyzed Coupling Reactions and Applications in Alkene Functionalization. *Acc. Chem. Res.* **2020**, *53*, 906–919. (h) Derosa, J.; Apolinar, O.; Kang, T.; Tran, V. T.; Engle, K. M. Recent developments in nickel-catalyzed intermolecular dicarbonfunctionalization of alkenes. *Chem. Sci.* **2020**, *11*, 4287–4296. (i) Yi, L.; Ji, T.; Chen, K.-Q.; Chen, X.-Y.; Rueping, M. Nickel-Catalyzed Reductive Cross-Couplings: New Opportunities for Carbon–Carbon Bond Formations through Photochemistry and Electrochemistry. *CCS Chem.* **2022**, *4*, 9–30. (j) Chan. A-Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath. C. P.; MacMillan, D. W. C. Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1485–1542.

5. (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57,* 10257–10274. (b) Jampilek, J. Heterocycles in medicinal chemistry. *Molecules* **2019**, *24*, 3839–3842. (c) Bhutani, P.; Joshi, G.; Raja, N.; Bachhav, N.; Rajanna, P. K.; Bhutani, H.; Paul, A. T.; Kumar, R. U.S. FDA Approved Drugs from 2015–June 2020: A Perspective. *J. Med. Chem.* **2021**, *64*, 2339–2381.

6. Diederich, F.; Meijere, A., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004.

7. For selected examples on bimolecular reactions of nickel complexes: (a) Xu, H.; Diccianni, J. B.; Katigbak, J.; Hu, C.; Zhang, Y.; Diao, T. Bimetallic C–C Bond-Forming Reductive Elimination from Nickel. *J. Am. Chem. Soc.* **2016**, *138*, 4779–4786. (b) Diccianni, J.; Diao, T. Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions. *Trends Chem.* **2019**, *1*, 830–844. (c) Mohadjer Beromi, M.; Brudvig, G. W.; Hazari, N.; Lant, H. M. C.; Mercado, B. Q. Synthesis and Reactivity of Paramagnetic Nickel Polypyridyl Complexes Relevant to $C(sp^2)$–$C(sp^3)$ Coupling Reactions. *Angew. Chem. Int. Ed.* **2019**, *58*, 6094–6098. (d) Day, C. S.; Renteria-Gómez, A.; Ton, S. J.; Gogoi, R.; Gutierrez, O.; Martin, R. Elucidating electron-transfer events in polypyridine nickel complexes for reductive coupling reactions. *Nat. Catal.* **2023**, *6*, 244–253. (e) Day, C. S.; Martin, R. Comproportionation and disproportionation in nickel and copper complexes. *Chem. Soc. Rev.* **2023**, *52*, 6601–6616.

8. (a) Uehling, M. R.; King, R. P.; Krska, S. W.; Cernak, T.; Buchwald, S. L. Pharmaceutical diversification via palladium oxidative addition complexes. *Science* **2019**, *363*, 405–408. (b) King, R. P.; Krska, S. W.; Buchwald, S. L. A Ligand Exchange Process for the Diversification of Palladium Oxidative Addition Complexes. *Org. Lett.* **2021**, *23*, 6030–6034.

9. (a) Schneider, G. Automating drug discovery. *Nat. Rev. Drug Discov.* **2018**, *17*, 97–113. (b) Farrant, E. Automation of Synthesis in Medicinal Chemistry: Progress and Challenges. *ACS Med. Chem. Lett.* **2020**, *11*, 1506–1513. (c) Wang, Z.; Zhao, W.; Hao, G.-F.; Song, B.-A. Automated synthesis: current platforms and further needs. *Drug Discov. Today* **2020**, *25*, *11*, 2006–2011. (d) Breen, C. P.; Nambiar, A. M. K.; Jamison, T. F.; Jensen, K. F. Ready, Set, Flow! Automated Continuous Synthesis and Optimization. *Trends Chem.* **2021**, *3*, *5*, 373–386. (e) MacLeod, B. P. Flexible automation accelerates materials discovery. *Nat. Mater.* **2022**, *21*, 722–726. (f) Pijper, B.; Abdiaj, I.; Leonori, D.; Alcázar, J. Development of an Automated Platform for $C(sp^3)$–$C(sp^3)$ Bond Formation via XAT Chemistry. *ChemCatChem*, **2023**, *15*, *4*, e202201289. (g) El-khawaldeh, R.; Hein, J. E. Balancing act: when to flex and when to stay fixed. *Trends Chem.* **2023**. DOI: 10.1016/j.trechm.2023.10.008. (h) Pijper, B.; Martín, R.; Huertas-Alonso, A. J.; Linares, M. L.; López, E.; Llaveria, J.; Díaz-Ortiz, A.; Dixon, D. J.; de la Hoz, A.; Alcázar, J. Fully Automated Flow Protocol for $C(sp^3)$–$C(sp^3)$ Bond Formation from Tertiary Amides and Alkyl Halides. *Org. Lett.* **2023**. DOI: 10.1021/acs.orglett.3c01390.

10. (a) Sullivan, D. J.; Gluzman, I. Y.; Russell, D. G.; Goldberg, D. E. On the Molecular Mechanism of Chloroquine's Antimalarial Action. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 11865–11870. (b) Freedman, D. O. Clinical Practice. Malaria Prevention in Short-Term Travelers. *N. Engl. J. Med.* **2008**, *359*, 603–612. (c) Plantone, D.; Koudriavtseva, T. Current and Future Use of Chloroquine and Hydroxychloroquine in Infectious, Immune, Neoplastic and Neurological Diseases: A Mini-Review. *Clin. Drug. Investig.* **2018**, *38*, 653–671. (d) Park, T. Y.; Jang, Y.; Kim, W.; Shin, J.; Toh, H. T.; Kim, C. H.; Yoon, H. S.; Leblanc, P.; Kim, K. S. Chloroquine Modulates Inflammatory Autoimmune Responses Through Nurr1 in Autoimmune Diseases. *Sci Rep.* **2019**, *9*, 15559.

11. For selected examples on multinuclear nickel complexes of (hetero)aryl chlorides, see: (a) Isobe, K.; Nakamura, Y.;

Kawaguchi, S. Organonickel(II) Complexes Containing Carbon-bonded Heterocycles as a Ligand. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 139–145. (b) Bennett, M. A.; Hockless, D. C. R.; Wenger, E. Preparation of (*ortho*-halogeno)-η^1-pyridylnickel(II) complexes, precursors for the generation of pyridyne-nickel(0) complexes. *Polyhedron* **1995**, *14*, 2637–2645. (c) Rull, S., G.; Funes-Ardoiz, I.; Maya, C.; Maseras, F.; Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C. Elucidating the Mechanism of Aryl Aminations Mediated by NHC-Supported Nickel Complexes: Evidence for a Nonradical Ni(0)/Ni(II) Pathway. *ACS Catal.* **2018**, *8*, 3733–3742.

12. Selected reviews on Ni-catalyzed Negishi-type cross-coupling reactions: (a) Knochel, P.; Jones, P.; Langer, F. Organozinc chemistry: an overview and general experimental guidelines, in *Organozinc reagents: A practical approach.* Eds., Oxford University Press, Oxford, 1999, pp 1-21. (b) Phapale, V. B.; Cárdenas, D. J. Nickel-catalysed Negishi cross-coupling reactions: scope and mechanisms. *Chem. Soc. Rev.* **2009**, *38*, 1598–1607. (c) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. Recent Developments in Negishi Cross-Coupling Reactions. *ACS Catal.* **2016**, *6*, 1540–1552.

13. Selected examples of Ni-catalyzed Negishi cross-coupling C(sp^2)–C(sp^3) bond-forming reactions: (a) Giovannini, R.; Knochel, P. Ni(II)-Catalyzed Cross-Coupling between Polyfunctional Arylzinc Derivatives and Primary Alkyl Iodides. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187. (b) Jensen, A. E.; Dohle, W.; Knochel, P. Improved Nickel-Catalyzed Cross-Coupling Reaction Conditions between *ortho*-Substituted Aryl Iodides/Nonaflates and Alkylzinc Iodides in Solution and in the Solid-Phase. *Tetrahedron* **2000**, *56*, 4197–4201. (c) Huo, S. Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents from Unactivated Alkyl Bromides and Chlorides. *Org. Lett.* **2003**, *5*, 423–425. (d) Walters, I. A. S. A convenient one-pot Negishi coupling of amino-heteroaryl chlorides and alkyl bromides. *Tetrahedron Lett.* **2006**, *47*, 341–344. (e) Melzig, L.; Gavryushin, A.; Knochel, P. Direct Aminoalkylation of Arenes and Hetarenes via Ni-Catalyzed Negishi Cross-Coupling Reactions. *Org. Lett.* **2007**, *9*, 5529–5532. (f) Phapale, V. B.; Guisán-Ceinos, M.; Bañuel, E.; Cárdenas, D. J. Nickel-Catalyzed Cross-Coupling of Alkyl Zinc Halides for the Formation of C(sp^2)–C(sp^3) Bonds: Scope and Mechanism. *Chem. Eur. J.* **2009**, *15*, 12681–12688. (g) Liang, Y.; Fu, G. C. Stereoconvergent Negishi Arylations of Racemic Secondary Alkyl Electrophiles: Differentiating between a CF_3 and an Alkyl Group. *J. Am. Chem. Soc.* **2015**, *137*, 9523–9526. (h) Abdiaj, I.; Fontana, A.; Gómez, M. V.; de la Hoz, A.; Alcázar, J. Visible-Light-Induced Nickel-Catalyzed Negishi Cross-Couplings by Exogenous-Photosensitizer-Free Photocatalysis *Angew. Chem. Int. Ed.* **2018**, *57*, 8473–7477.

14. For details, see Supporting information.

15. We also found that Ni-OAC **1g** outperforms analogous Pd complexes prepared by exposing chloroquine to neophyl palladacycles described by Buchwald (ref. 8a) and Cámpora (see Supporting Information) with PCy_3 or *t*BuXPhos, either in a stoichiometric or catalytic manner. In all cases, little amounts of **8**, if any, were found in the crude mixtures. See ref. 14.

16. For examples on Negishi cross-couplings in flow and Automated synthesis using Janssen's modular platform, see: (a) Egle, B.; de Muñoz, J. M.; Alonso, N.; Borggraeve, W. M. D.; de la Hoz, A.; Díaz-Ortiz, A.; Alcázar, J. First Example of Alkyl-Aryl Negishi Cross-Coupling in Flow: Mild, Efficient and Clean Introduction of Functionalized Alkyl Groups. *J. Flow Chem.* **2014**, *4*, 22–25. (b) Alonso, N.; Miller, L. Z.; Muñoz, J. M.; Alcázar, J.; McQuade, D. T. Continuous synthesis of organozinc halides coupled to Negishi reactions. *Adv. Synth. Catal.* **2014**, *356*, 3737–3741. (c) Abdiaj, I.; Horn, C. R.; Alcazar, J. Scalability of Visible-Light-Induced Nickel Negishi Reactions: A Combination of Flow Photochemistry, Use of Solid Reagents, and In-Line NMR Monitoring. *J. Org. Chem.* **2019**, *84*, 4748–4753. (d) Abdiaj, I.; Cañellas, S.; Dieguez, A.; Linares, M. L.; Pijper, B.; Fontana, Al; Rodríguez, R.; Trabanco, A.; Palao, E.; Alcázar, J. End-to-End Automated Synthesis of C(sp^3)-Enriched Drug-Like Molecules via Negishi Coupling and Novel, Automated Liquid-Liquid Extraction. *J. Med. Chem.* **2023**, *66*, 716–732. (e) Alonso, M.; Cañellas, S.; Delgado, F.; Serrano, M.; Diéguez-Vázquez, A.; Gómez, J. E. Accelerated Synthesis of Bicyclo[1.1.1]pentylamines: A High-Throughput Approach. *Org. Lett.* **2023**, *25*, 771–776.

17. Wang, G.; Ang, H .T.; Dubbaka, S. R.; O'Neill, P.; Wu, J. Multi-step Automated Synthesis of Pharmaceuticals. *Trend. Chem.* **2023**, https://doi.org/10.1016/j.trechm.2023.03.008.

18. Wang, Y.; Haight, I.; Gupta, R.; Vasudevan, A. What is in Our Kit? An Analysis of Building Blocks Used in Medicinal Chemistry Parallel Libraries. *J. Med. Chem.* **2021**, *64*, 17115–17122.

19. (a) Rombouts, F. J. R.; Tresadern, G.; Buijnsters, P.; Langlois, X.; Tovar, F.; Steinbrecher, T. B.; Vanhoof, G.; Somers, M.; Andres, J. I.; Trabanco, A. A. -I.; Trabanco, A. A. Pyrido[4,3-e][1,2,4]triazolo[4,3-a]pyrazines as selective, brain penetrant phosphodiesterase 2 (PDE2A) inhibitors. *ACS Med. Chem. Lett.* **2015**, *6*, 282–286. (b) Dombrowski, A. W.; Gesmundo, N. J.; Aguirre, A. L.; Sarris, K. A.; Young, J. M.; Bogdan, A. R.; Martin, M. C.; Gedeon, S.; Wang, Y. Expanding the Medicinal Chemist Toolbox: Comparing Seven C(sp^2)–C(sp^3) Cross-Coupling Methods by Library Synthesis. *ACS Med. Chem. Lett.* **2020**, *11*, *4*, 597–604. (c) Liu, W.; Mulhearn, J.; Hao, B.; Cañellas, S.; Last, S.; Gómez, J. E.; Jones, A.; De Vera, A.; Kumar, K.; Rodríguez, R.; Van Eynde, L.; Strambeanu, I. I.; Wolkenberg, S. E. Enabling Deoxygenative C(sp^2)-C(sp^3) Cross-Coupling for Parallel Medicinal Chemistry. *ACS Med. Chem. Lett.* **2023**, *14*, *6*, 853–859.

20. For selected references, see: (a) Okada, K.; Okamoto, K.; Oda, M. A new and practical method of decarboxylation: photosensitized decarboxylation of *N*-acyloxyphthalimides via electron-transfer mechanism. *J. Am. Chem. Soc.* **1988**, *110*, 8736–8738. (b) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. Practical Ni-catalyzed aryl-alkyl cross-coupling of secondary redox-active esters. *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177. (c) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. Decarboxylative cross-electrophile coupling of *N*-hydroxyphthalimide esters with aryl iodides. *J. Am. Chem. Soc.* **2016**, *138*, 5016–5019. (d) Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S. Nickel-Catalyzed Cross-Coupling of Redox-Active Esters with Boronic Acids. *Angew. Chem. Int. Ed.* **2016**, *55*, 9676–9679.

21. For an illustrative example, see: Kennedy, A. R.; Klett, J.; Mulvey, R. E.; Wright, D. S. Synergic Sedation of Sensitive Anions: Alkali-Mediated Zincation of Cyclic Ethers and Ethene. *Science* **2009**, *326*, *5953*, 706–708.

22. (a) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159. (b) Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*, 4793–4798. (c) Moragas, T.; Correa, A.; Martin, R. Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-Type Compounds. *Chem. Eur. J.* **2014**, *20*, 8242–8258. (d) Knappke, C. E. I.; Grupe, S.; Gärtner, D. Corpet, M.; Gosmini, C.; von Wangelin, A. J. Reductive Cross-Coupling Reactions between

Two Electrophiles. *Chem. Eur. J.* **2014**, *20*, 6828–6842. (e) Weix, D. J. Methods and mechanisms for cross-electrophile coupling of Csp^2 halides with alkyl electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767–1775. (f) Richmond, E.; Moran, J. Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents. *Synthesis* **2018**, *50*, 499–513. (g) Liu, J.; Ye, Y.; Sessler, J. L.; Gong, H. Cross-Electrophile Couplings of Activated and Sterically Hindered Halides and Alcohol Derivatives. *Acc. Chem. Res.* **2020**, *53*, 1833–1845. (h) Tortajada, A.; Börjesson, M.; Martin, R. Nickel-Catalyzed Reductive Carboxylation and Amidation Reactions. *Acc. Chem. Res.* **2021**, *54*, 3941–3952.

23. An illustrative example of this observation can be visualized by the cost of Loratadine in Sigma-Aldrich (4290 €/mmol) when compared to $Ni(cod)_2$ (20 €/mmol) and PCy_3 (8 €/mmol).

24. The presence of metal-related species were easily and effectively removed utilizing automated scavenging protocols in a Biotage Extrahera. Metal content (Ni and Zn) was analyzed by ICP-OES in one of the final products, obtaining 7 and 16 ug/g respectively, which corresponds to >99.99% metal scavenging. See ref. 14.

25. This contribution was deposited in ChemRxiv (10.26434/chemrxiv-2023-v6r13). While this contribution was being revised, an elegant contribution by Sevov described organonickel complexes for sp^2–sp^3 bond-formations: Dinh, L. P.; Starbuck, H. F.; Hamby, T. B.; LaLama, M. J.; He, C. Q.; Kalyani, D.; Sevov, C. S. Persistent organonickel complexes as general platforms for Csp^2–Csp^3 coupling reactions. *Nat. Chem.* **2024**, https://doi.org/10.1038/s41557-024-01528-7.