JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Communication

C(sp^2)−H Hydroxylation via Catalytic 1,4-Ni Migration with N_2O

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Cite This: J. Am. Chem. Soc. 2023, 145, 17564−17569
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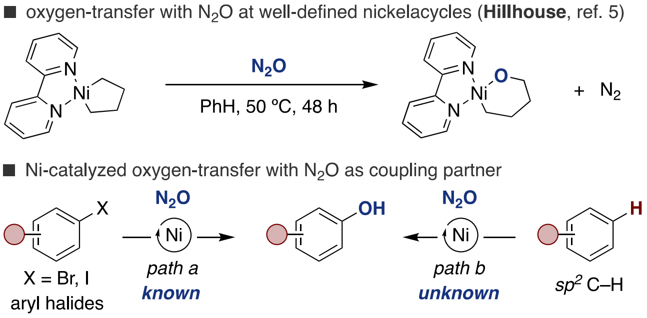
ABSTRACT: Herein, we report a Ni-catalyzed C(sp^2)−H hydroxylation of aryl bromides with N_2O as an oxygen-atom donor. The reaction is enabled by a 1,4-Ni translocation that results in *ipso/ortho* difunctionalized products. Regioselectivity and stereocontrol are dictated by a judicious choice of the ligand backbone, thus giving access to either carbonyl or phenol derivatives and offering an opportunity to repurpose hazardous substances en route to valuable oxygen-containing building blocks.

Nitrous oxide (N_2O) ranks as the third most emitted greenhouse gas and is currently the largest ozone-depleting substance emitted through human activities, with an atmospheric lifetime of 116 ± 9 years.[1] Not surprisingly, chemists have recently been challenged to repurpose N_2O en route to added-value chemicals by means of catalytic transformations.[2] Among various scenarios,[3] the utilization of N_2O as an oxygen-transfer reagent is particularly attractive given that N_2 is released as a benign byproduct. While the poor σ-donor and π-acceptor properties of N_2O might constitute a drawback when combined with transition metals,[4] seminal stoichiometric work by Hillhouse (Scheme 1, top) set the basis for designing catalytic oxygen-transfer events.[5] Despite the elegant advances realized, particularly from Cornella (path a) that showed the viability for enabling *ipso* oxygen-transfer reactions with aryl iodides as substrates,[6] a catalytic oxygen transfer at sp^2 C−H sites still constitutes an uncharted cartography in both the N_2O and C−H functionalization arenas (path b).[7]

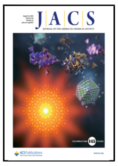
Scheme 1. Oxygen-Transfer Reactions with N_2O and Ni



As part of our ongoing interest in the catalytic valorization of greenhouse gases[8] and the ability of nickel catalysts to enable translocation events at previously unfunctionalized C−H reaction sites,[9] we wondered whether it would be possible to design an oxygen-transfer event at sp^2 C−H linkages with N_2O and readily available aryl bromides via 1,4-Ni translocation.[10] At the outset of our investigations, however, it was unclear whether such a strategy could be designed given (a) the low binding affinity of N_2O to transition metals,[4] (b) the proclivity of alkynes to promote multiple insertion events at C−Ni linkages,[11] (c) the likelihood of promoting homodimerization pathways of either alkynes or aryl halides, and (d) the subtleties required for effecting a 1,4-Ni translocation prior to N_2O insertion. If successful, however, we anticipated that such a strategy might constitute a worthwhile endeavor for chemical invention, offering an unrecognized opportunity to promote oxygen transfer at previously unfunctionalized sp^2 C−H sites with N_2O as a coupling partner. In addition, such a technique would also constitute a new entry point to promote the *ipso/ortho*-difunctionalization of aryl halides by incorporating both C(sp^2)−C(sp^2) and C(sp^2)−O linkages in a concerted, site-selective manner with readily available precursors. Herein, we report the successful realization of this goal, resulting in a regiodivergent strategy that promotes oxygen transfer at either vinyl or aryl sp^2 C−H sites with an excellent site-selectivity profile from simple and commercially available building blocks (Scheme 2).

We began our study by evaluating the reactivity of 1-bromo-4-(trifluoromethyl) benzene (**1a**) with 1-phenyl propyne (**2a**) under an N_2O atmosphere (2 bar). The choice of **1a** was not arbitrary, as it allows the identification of byproducts arising from N_2O insertion prior to 1,4-Ni shift or parasitic homodimerization events via ^{19}F NMR spectroscopy. After considerable optimization (Table 1),[12] a combination of $NiBr_2\cdot$diglyme (10 mol %), **L1** (20 mol %), and Mn (3.0 equiv) in DMA at 50 °C afforded the best results, giving rise to **3a** in 80% assay yield with a >20:1 *E/Z* ratio and an exquisite 40:1 (**3a**:**4a**) selectivity pattern (entry 1). Under these reaction conditions, it is worth noting that not even traces of 4-(trifluoromethyl) phenol arising from N_2O insertion at the initial aryl sp^2 C−Ni bond were found in the crude mixtures.[6a] As anticipated, a subtle interplay of electronic and steric effects

Received: July 3, 2023
Published: August 2, 2023



https://doi.org/10.1021/jacs.3c07018
J. Am. Chem. Soc. 2023, 145, 17564−17569

Scheme 2. sp^2 C−H Hydroxylation with N_2O via a 1,4-Ni Shift

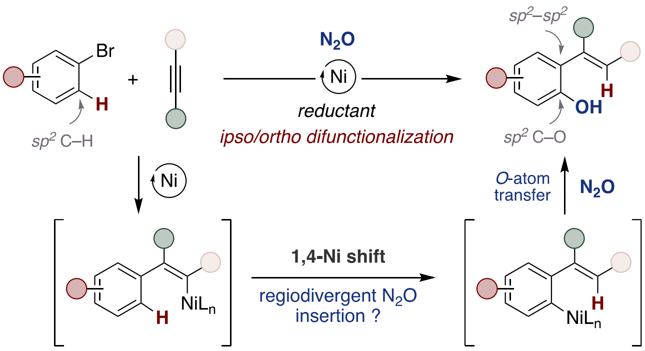
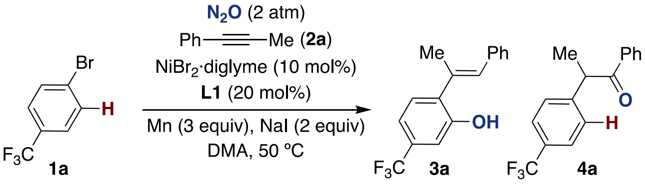
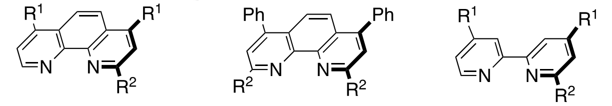


Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	**3a** (%)[b]	*E/Z*	**4a** (%)[b]
1	*none*	*80 (79[c])*	*>20:1(12:1)*	*2*
2	**L2** instead of **L1**	74	>20:1	3
3	**L3** instead of **L1**	68	>20:1	3
4	**L4** instead of **L1**	0	–	18
5	**L5** instead of **L1**	30	>20:1	0
6	**L6** instead of **L1**	67	>20:1	3
7	**L7** instead of **L1**	0	–	18
8	Zn instead of Mn	49	>20:1	3
9	NiI_2 instead of $NiBbr_2$·diglyme	51	>20:1	13
10	DMF instead of DMA	66	>20:1	7
11	N_2O (1 atm)	58	>20:1	7
12	no Ni, Mn or N_2O	0	–	0



L1 (R^1 = Ph; R^2 = *n*Bu)
L2 (R^1 = H; R^2 = *n*Bu)
L3 (R^1 = Ph; R^2 = Me)

L4 (R^2 = H)
L5 (R^2 = Me)

L6 (R^1 = H; R^2 = Me)
L7 (R^1 = CO_2Me, R^2 = H)

[a]Conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), $NiBr_2$·diglyme (10 mol %), **L1** (20 mol %), Mn (0.60 mmol), and DMA [0.2 M] at 50 °C under N_2O (2 atm) for 48 h. [b]^{1}H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield.

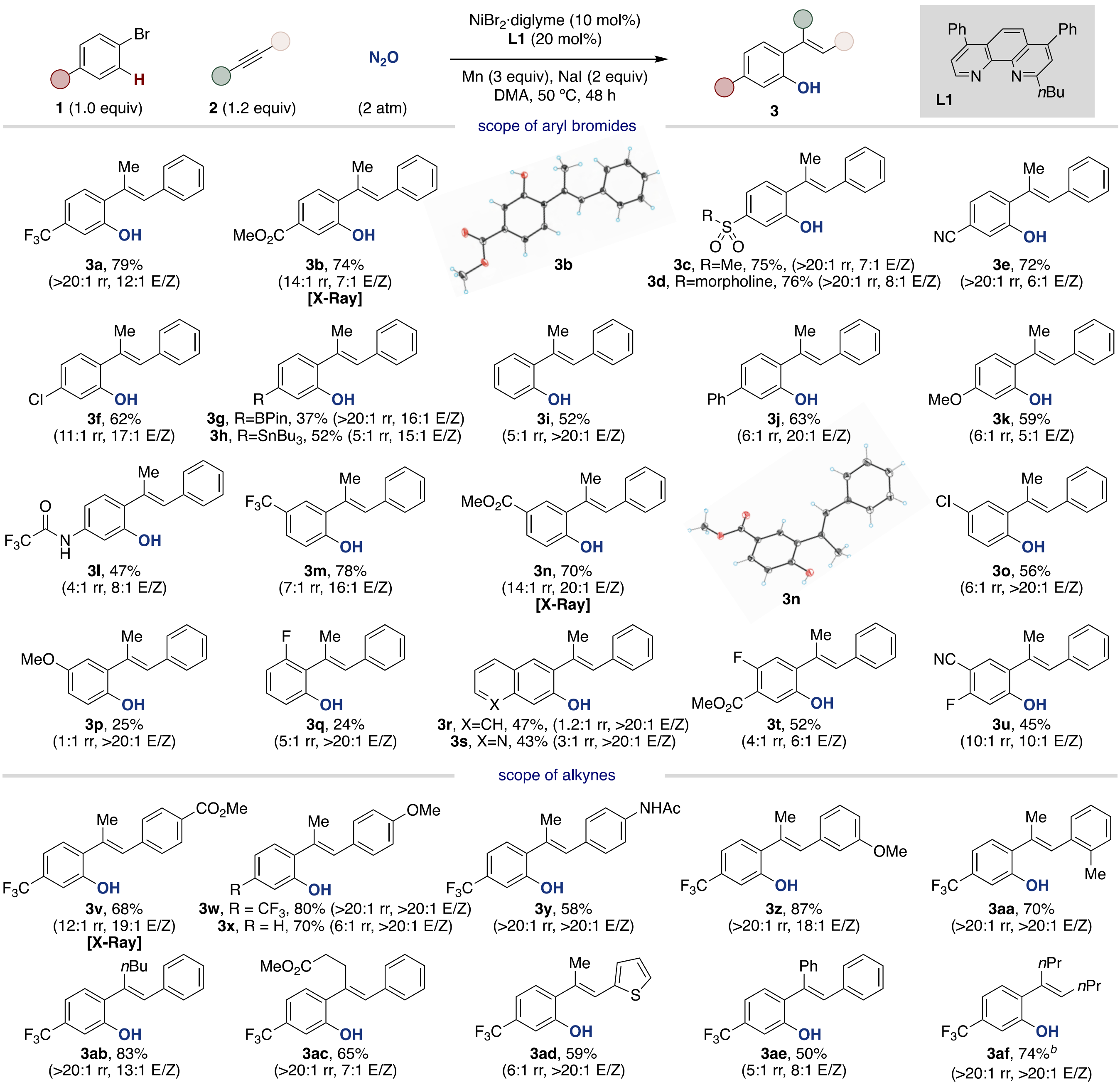
at the ligand backbone is critical for success. While similar yields were found for **L2** or **L3**, the lack of substituents adjacent to the nitrogen atom (**L4**) or the inclusion of substituents at both C2 and C9 (**L5**) had a deleterious effect on reactivity and site selectivity (entries 2–5). A similar trend was observed for otherwise related 2,2′-bipyridines **L6** and **L7** (entries 6 and 7). Strikingly, a close inspection of Table 1 revealed that both **L4** and **L7** delivered exclusively **4a**, albeit in low yields, thus suggesting the possibility for developing a regiodivergent oxygen-transfer scenario (entries 4 and 7). On the other hand, the utilization of reductants or nickel precatalysts other than Mn or $NiBr_2$·diglyme led to lower yields and selectivities (entries 8–11). Control experiments revealed that all of the reaction parameters were critical for success (entry 12).

With the optimized conditions in hand, we next examined the generality of our protocol. As is evident from the results compiled in Table 2, the catalytic oxygen-transfer event via 1,4-Ni translocation with N_2O could be performed independently of whether electron-rich or electron-poor aryl bromides were utilized as substrates, giving rise to the desired phenol derivatives in good yields (**3a**–**3e**). Interestingly, the presence of additional halogen atoms (**3f**) or organometallic partners (**3g**–**3h**) did not interfere with productive oxygen transfer at the *ortho* sp^2 C–H site, leaving ample room for derivatization via conventional cross-coupling reactions.[11] Although **3i**–**3l** were obtained in good yields and excellent stereochemistry, a non-negligible erosion in regioselectivity was observed, thus evidencing the subtle electronic interplay dictating the targeted 1,4-Ni migration. This observation is also illustrated by the different reactivities found for *meta*- substituted aryl bromides. While good yields and selectivities were found with electron-withdrawing backbones (**3m**–**3o**), the inclusion of electron-donating moieties (**3p**) or *π*-extended systems (**3r**) had a deleterious effect on regioselectivity.[13] While one might argue that the inclusion of *meta*- substituents might compromise the site-selective functionalization at different sp^2 C–H bonds, this was not the case, and **3m**–**3p** were all obtained with an exclusive 1,3,4-substitution pattern. Albeit in lower yields, 1-bromo-2-fluorobenzene (**1q**) could be employed as a substrate, resulting in the 1,2,3-functionalized phenol derivative **3q**.[12] The presence of heterocycles with nitrogen donors did not interfere with productive oxygen transfer via 1,4-Ni translocation, delivering the targeted phenol with C–O bond formation occurring exclusively at C7 (**3s**). Finally, a selection of aryl bromides decorated with fluorine atoms (**1t**, **1u**) delivered the corresponding phenol derivatives **3t** and **3u** with an exclusively 1,2,4,5-tetrasubstitution pattern, thus arguing against the intervention of concerted-metalation deprotonation pathways.[14,15]

Encouraged by our initial findings, we focused our attention on evaluating the influence of the alkyne counterpart on both the reactivity and selectivity (Table 2). As shown, similar yields and selectivities were found independently on the electronics at the alkyne terminus. Among these, the combination of an electron-rich alkyne with an electron-deficient aryl bromide was particularly efficient, leading to an exquisite regio- and stereoselective oxygen-transfer event with N_2O at the sp^2 C–H bond (**3w**, **3y**). Likewise, the utilization of *meta*- or *ortho*-substituted alkynes resulted in **3z** and **3aa** with high regiocontrol. The latter is particularly illustrative given the erosion in yield found when the oxygen-transfer event is attempted with *meta*-substituted aryl bromides (**3m**–**3p**). Equally interesting was the ability to incorporate longer alkyl chains (**3ab**, **3ac**) or sulfur-containing heteroaromatics (**3ad**) at the alkyne terminus without significant erosion in yield or selectivity. Furthermore, the successful preparation of **3ae** and **3af** stands as a testament to the generality of our oxygen-transfer reaction with diaryl- or dialkyl-substituted olefins, delivering the targeted phenols in high regio- and stereo-selectivity.

As judged by the data provided in Table 1 (entries 4 and 7), the lack of substituents adjacent to the nitrogen atom in both the 1,10-phenanthroline and 2,2′-bipyridine ligand series under otherwise identical reaction conditions resulted in a selectivity switch. In these cases, the oxygen-transfer reaction occurred via

Table 2. C(sp^2)−H Hydroxylation of Aryl Bromides with N_2O via Catalytic 1,4-Ni Migration[a,b]



[a]Conditions: **1** (0.20 mmol), **2** (0.24 mmol), $NiBr_2$·diglyme (10 mol %), **L1** (20 mol %), Mn (0.60 mmol), NaI (0.40 mmol), and DMA [0.2 M] at 50 °C under N_2O (2 atm) for 48 h. Isolated yields, average of two independent runs; *E*/*Z* corresponds to the isolated *E*/*Z* stereoisomeric ratio; rr corresponds to the regioisomeric ratio of **3** vs **4** by ^{1}H NMR analysis of the crude. [b]**3af**: 4-Octyne (2.0 equiv).

a formal 1,2-carboalkoxylation, leading to the exclusive formation of **4a** arising from a N_2O transfer at the vinyl sp^2 C−Ni bond prior to 1,4-Ni translocation. This result is particularly noteworthy, as it advocates the notion that the 1,4-Ni shift could be controlled by the nature of the ligand backbone, resulting in a regiodivergent scenario for accessing oxygen-containing compounds. After some optimization,[12] **L7** turned out to be the most competent ligand for enabling the 1,2-carboalkoxylation event with N_2O as the oxygen-transfer reagent, leading to the corresponding ketone derivatives with exquisite site-selectivity (Table 3). Albeit in moderate yields, a diverse range of aryl ketones displaying different electronic effects at the arene backbone could be obtained with high regiocontrol. Overall, these results should be assessed against the challenge that is addressed, suggesting that the development of regiodivergent oxygen-transfer reactions might constitute a new gateway for rapidly and reliably accessing valuable oxygen-containing products with N_2O as the coupling partner.

Although unraveling the mechanistic underpinnings of this reaction should await further investigations, we decided to gather indirect evidence about the mechanism of the reaction by studying the reaction of **1x-*d*$_5$** with N_2O under our Ni/**L1** regime (Scheme 3, top). As anticipated, full deuterium

https://doi.org/10.1021/jacs.3c07018
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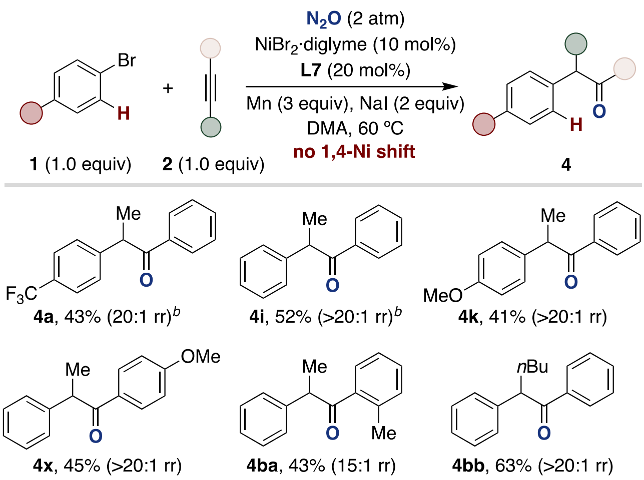
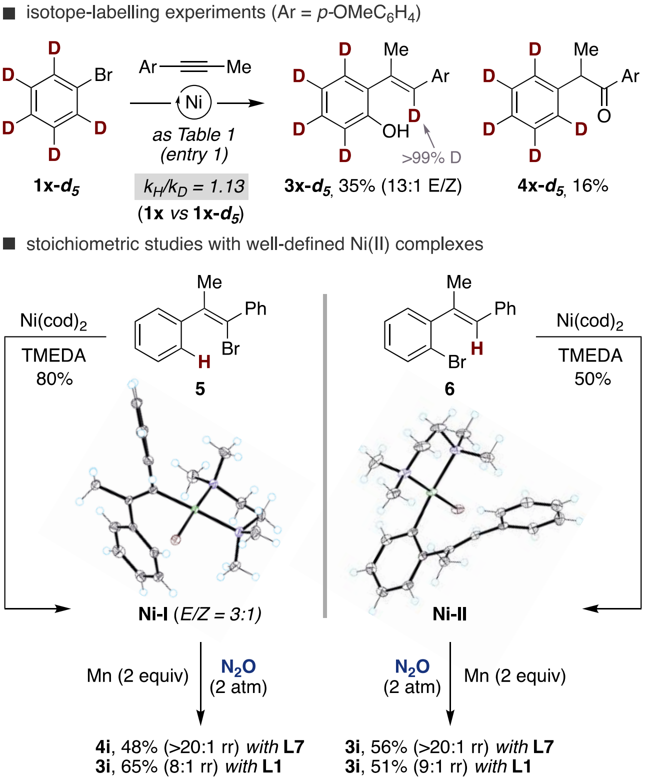
Table 3. Oxygen Transfer via 1,2-Carboalkoxylation[a,b]



[a]Conditions: **1** (0.20 mmol), **2** (0.20 mmol), $NiBr_2$·diglyme (10 mol %), **L7** (20 mol %), Mn (0.60 mmol), NaI (0.40 mmol), and DMA [0.2 M] at 60 °C under N_2O (2 atm) for 48 h. Isolated yields, average of two independent runs; rr = regioisomeric ratio of **4** vs **3** by ^1H NMR analysis of the crude. [b]**1a** (1.20 equiv).

Scheme 3. Preliminary Mechanistic Studies



incorporation was observed at the vinyl position (>99% D) in **3x-d_5**. In addition, no significant intermolecular kinetic isotope effect was observed in the competitive reaction of **1x** and **1x-d_5** (k_H/k_D= 1.13).[12] This result suggests that the 1,4-Ni translocation at the arene sp^2 C−H bond might not be rate-determining.[16] Aiming at gaining a deeper understanding of whether the key 1,4-Ni shift and/or N_2O insertion was catalyzed by either Ni(I) or Ni(II) centers, we turned our attention to investigate the reactivity of some of the putative reaction intermediates. To this end, we prepared **Ni−I** and **Ni−II** complexes by simple exposure of **5** or **6** to Ni(cod)$_2$ and TMEDA as ligands (Scheme 3, bottom).[17] As expected, X-ray crystallography evidenced a canonical square-planar geometry for both complexes. Although **Ni−I** rapidly undergoes *E*/*Z*-isomerization in solution,[18] oxygen transfer from N_2O cleanly delivered **3i** or **4i** in the presence of Mn with either **L1** or **L7**. Notably, these reactions occurred *only* in the presence of **L1**/**L7**, thus showing the importance of 1,10-phenanthroline or the 2,2′-bipyridine backbone on reactivity. More interestingly, **Ni−II** gave rise to **3i** regardless of whether **L1** or **L7** was utilized as a ligand in the presence of Mn. Altogether, these results suggest that (a) 1,4-Ni translocation is uniquely enabled by a Ni/**L1** regime, whereas (b) N_2O insertion can be effected at the targeted sp^2 C−Ni bond with both **L1** or **L7**. While 1,4-Ni shifts have been proposed to operate via Ni(II) species,[9c,d] the experiments compiled in Scheme 3 suggest the intermediacy of Ni(I) species prior to reaction with N_2O.[19,20] While the latter can be obtained via single-electron transfer with Mn as a reductant, our available data does not allow us to rule out the intervention of comproportionation events as a means to access Ni(I) complexes.[21]

In summary, we report the means to enable the C(sp^2)−H hydroxylation of aryl bromides via a 1,4-Ni shift with N_2O as an oxygen-atom transfer reagent, resulting in a formal *ipso*/*ortho*-difunctionalization event that forges C(sp^2)−C(sp^2) and C(sp^2)−O linkages in a tandem fashion. Good yields and excellent regio- and stereoselectivities are obtained regardless of whether electron-rich or electron-poor arenes are utilized. A judicious choice of ligand allows for dictating the selectivity of the process, resulting in regiodivergent scenarios en route to either phenols or ketones. Further studies into the exploitation of N_2O as an oxygen-transfer reagent are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c07018.

Experimental procedures and spectral and crystallographic data (PDF)

Accession Codes

CCDC 2277931−2277935 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank ICIQ, FEDER/MCI PID2021-123801NB-I00, and MCI/AIE (Severo Ochoa Excellence Accreditation 2002-2023, CEX2019-000925-S) for financial support. J.R. and H.Z. thank the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement 101105032 (CARBO-CHAIN) and China Scholarship Council (CSC) for a predoctoral fellowship. We sincerely thank Prof. Josep Cornella (MPI) for insightful suggestions and comments.

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