# Nickel-Catalyzed Reductive Alkylation of Heteroaryl Imines

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**ABSTRACT:** A Ni-catalyzed reductive cross-coupling of heteroaryl imines with C($sp^3$) electrophiles for the preparation of heterobenzylic amines is reported. This umpolung-type alkylation proceeds under mild conditions, avoids the pre-generation of organometallic reagents, and exhibits good functional group tolerance. Mechanistic studies are consistent with the imine substrate acting as a redox-active ligand upon coordination to a low-valent nickel center. The resulting Ni-bis(2-imino)heterocycle complexes can engage in alkylation reactions with a variety of C($sp^3$) electrophiles, giving the heterobenzylic amine products in good yields.

Benzylic amines are common substructures in a variety of natural products, agrochemicals, and pharmaceuticals.[1] In particular, heterobenzylic amines serve as important nitrogen-containing scaffolds in medicinal chemistry. Two representative examples are Gilead's Phase II/III HIV capsid inhibitor Lenacapavir[2] and Pfizer's commercial anticancer agent Glasdegib[3](Figure 1a). Due to broad interest in this structural motif, a variety of synthetic approaches to prepare benzylic amines have been developed. Of these methods, the 1,2-addition of organometallic reagents to imines is one of the most well-established;[4] however, pre-generation of sensitive and reactive organometallic reagents and use of activated imine derivatives (e.g. sulfinyl imines, *N*-arylimines, oximes, hydrazones, or phosphoryl imines) is typically required (Figure 1b). When simple *N*-alkylimines are employed, stoichiometric Lewis acid additives can be necessary to enhance the reactivity. Moreover, α-deprotonation of the imine substrate by the basic nucleophiles can be problematic.

In order to improve access to these structures, chemists have explored two complimentary reaction modes of imines: 1,2-addition of organic radicals to imines,[5,6,7] and the reductive alkylation of imines via α-amino radicals.[8] These reactions often exhibit improved functional group tolerance by avoiding the use of organometallic reagents. As part of our efforts to broaden the scope of electrophiles for Ni-catalyzed cross-electrophile coupling, we discovered a mechanistically distinct Ni-catalyzed reaction that enables the alkylation of heterocyclic imines.[9,10] This reaction leverages the redox non-innocence of 2-iminoheterocycles as ligands on Ni in order to generate α-amino radical intermediates that can engage in alkylation reactions. In this communication, we report the development of this method, which provides access to a variety of heterobenzylic amines in good yield under mild conditions (Figure 1c).

Conjugated nitrogen ligands such as diiminopyridines, α-diimines, and bi- and terpyridines can be electronically non-innocent: their π-systems are able to accept one or two electrons when bound to first row transition metals such as Fe, Co, and Ni.[11] For various organonickel complexes, the redox properties of these catalysts have been proposed to facilitate C–C bond forming and oxidation reactions.[12] Although the alkylation of imine ligand backbones by organometallic reagents has been described previously,[13] this reactivity has not been leveraged for a catalytic cross-coupling. We envisioned that in the presence of a terminal reductant, the radical character on the ligand could be harnessed in a metal-catalyzed umpolung alkylation of 2-iminoheteroarenes.

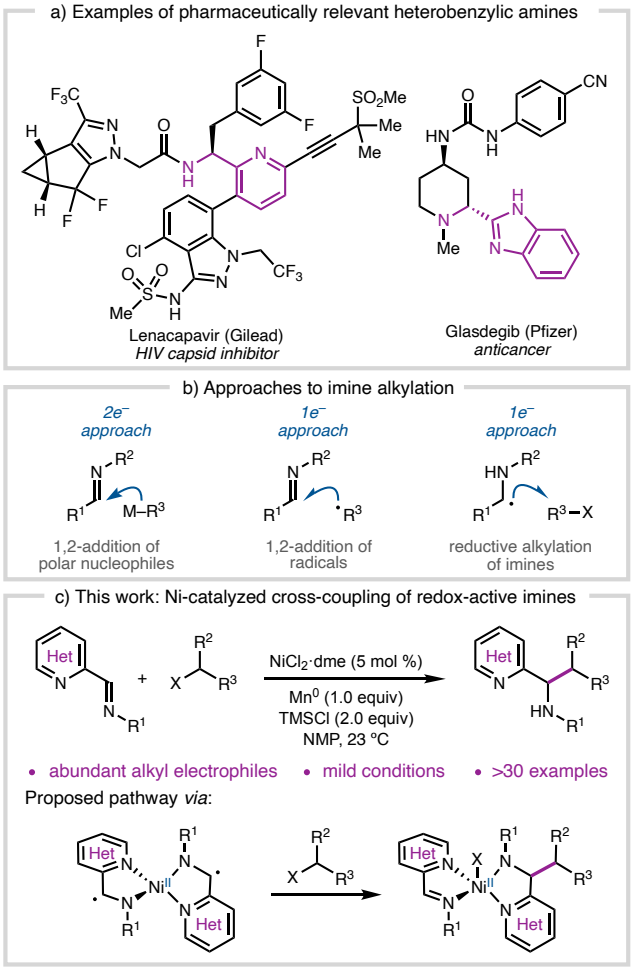
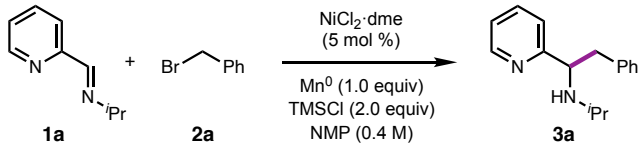



Figure 1. Context for development of Ni-catalyzed reductive imine alkylation.

**Table 1. Optimization of Reaction Conditions**[a]




| entry | deviation from standard conditions | yield (%)[b] |
|---|---|---|
| 1 | none | 87 |
| 2 | no TMSCl | 39 |
| 3 | NMP/HFIP (4:1), no TMSCl | 67 |
| 4 | AcOH (1.0 equiv) instead of TMSCl | 69 |
| 5 | $Zn^0$ (2.0 equiv) instead of $Mn^0$ | 45 |
| 6 | TDAE (1.5 equiv) instead of $Mn^0$ | 12 |
| 7 | benzyl chloride instead of **2a** | 88 |
| 8 | 1 mol % $NiCl_2$·dme | 83 |
| 9 | 0.1 mol % $NiCl_2$·dme | 62 |
| 10 | no $Mn^0$ or TMSCl | 0 |
| 11 | no $NiCl_2$·dme or TMSCl | 19 |
| 12 | no $NiCl_2$·dme | 66 |
| 13 | $MnCl_2$ (5 mol %) instead of $NiCl_2$·dme | 68 |
| 14 | $MnCl_2$ (5 mol %) instead of $NiCl_2$·dme, no TMSCl | 30 |
| 15 | $Ni(cod)_2$ (1.0 equiv), no $Mn^0$ or TMSCl | 24 |

[a]Reactions conducted under inert atmosphere on 0.3 mmol scale. [b]Determined by $^1$H NMR versus an internal standard.

Our investigations commenced with the coupling between (*E*)-*N*-isopropyl-1-(pyridin-2-yl)methanimine (**1a**) and benzyl bromide (**2a**). Use of $NiCl_2$·dme (5 mol %) as catalyst, $Mn^0$ as stoichiometric reductant, NMP as solvent, and TMSCl as additive was found to be optimal, furnishing the 1,2-addition product **3a** in 87% yield (Table 1, entry 1). When TMSCl was omitted from the reaction, **3a** was formed in only 39% yield (entry 2). It is hypothesized that TMSCl assists the turnover of the Ni catalyst by intercepting the initially formed anionic imine alkylation product. Protic additives, such as hexafluoroisopropanol (HFIP) (entry 3) and AcOH (entry 4) were also beneficial, but inferior to TMSCl. Alternative reductants, such as $Zn^0$ and tetrakis(*N,N*-dimethylamino)ethylene (TDAE), did not perform as well as $Mn^0$ (entries 5–6). Benzyl chloride was found to react just as well as **2a**, providing the identical product in 88% yield (entry 7). The catalyst loading could be dropped to 1 mol % with only a small decrease in yield (entry 8); however, further lowering the catalyst loading to 0.1 mol % significantly reduced the yield (entry 9).

A series of control experiments determined that no product formed in the absence of $Mn^0$ and TMSCl (entry 10). However, we were surprised to find that **3a** still forms with just $Mn^0$ (19% yield, entry 11). Moreover, when the reaction was carried out under otherwise identical conditions but without $NiCl_2$·dme, or using $MnCl_2$ instead of $NiCl_2$·dme, **3a** was obtained in 66% yield (entry 12) and 68% yield (entry 13), respectively. Use of $MnCl_2$ instead of $NiCl_2$·dme in the absence of TMSCl resulted in lower yield (entry 14). One possible explanation is that the combination of $Mn^0$ and TMSCl generates $MnCl_2$, which may also form a redox active complex with the coordinated heteroaryl imine.[14] A second explanation is that the $Mn^0$ source has trace Ni. Trace metal analysis by ICP-MS confirmed that the $Mn^0$ source contains 54 ppm total Ni species. However, this would represent a very low concentration of Ni catalyst (<0.005 mol %).[15] Use of $Ni(cod)_2$ (1.0 equiv) in place of $NiCl_2$·dme, in the absence of $Mn^0$ and TMSCl, furnished **3a** in 24% yield, confirming that Mn is not required for product formation (entry 15). Although use of $MnCl_2$ gives product, the combination of $NiCl_2$·dme/$Mn^0$/TMSCl consistently gave better yields in the imine alkylation. As a result, these conditions were used to evaluate the scope of the reaction.

With the optimized conditions in hand, the scope of the heteroaryl imine coupling partner was investigated (Scheme 1). Sterically diverse *N*-substitution on the imine was well tolerated, affording the products containing *n*-Bu, *i*-Pr, and *t*-Bu groups in high yields (**3a**–**3c**). Imines bearing cyclopropyl and cyclobutyl groups, two increasingly popular fragments in drug development,[16] provided the coupled products in 67% yield (**3d**) and 70% yield (**3e**), respectively. Use of the chiral imine derived from (*R*)-1-phenylethylamine gave product **3f** in good yield, albeit with poor diastereoselectivity. The use of a ketimine substrate did result in product formation (**3g**), however the yield was low, likely due to the increased steric hindrance at the site of C–C bond formation.

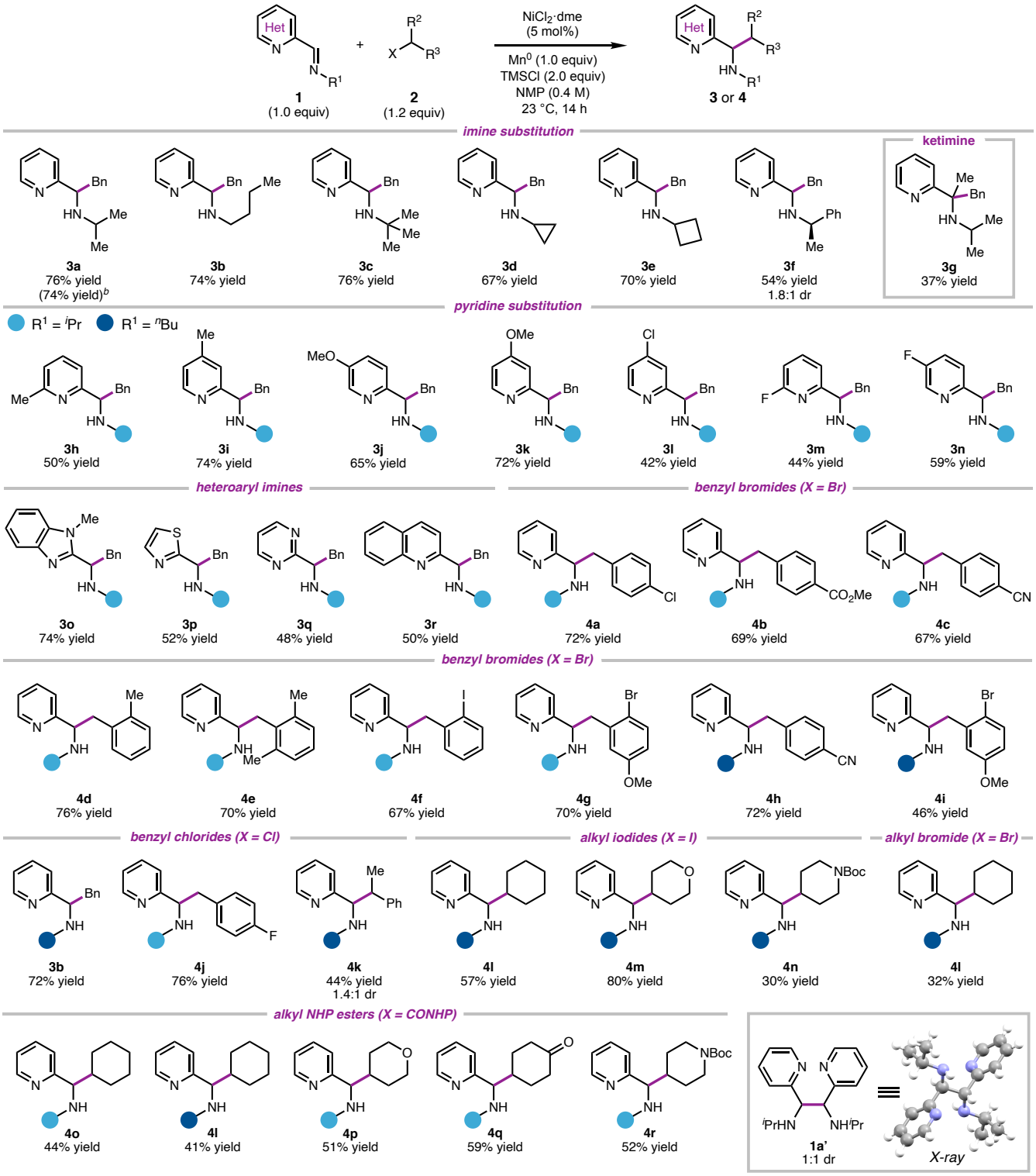
Electron donating substituents at the 4- and 5-position of the pyridine were tolerated, furnishing the desired products in generally good yields (**3i-3k**). Substitution at the 6-position afforded the products in lower yields (**3h**, **3m**, and **S3a**), possibly because the substituent hinders coordination of the imine to the Ni-catalyst. In general, substrates bearing electron withdrawing groups at the 5-position give lower yield of the product, possibly due to competitive over reduction.[17] In addition to 2-iminopyridines, several other heterocyclic imines can be employed, including the corresponding benzimidazole (**3o**), thiazole (**3p**), pyrimidine (**3q**), and quinoline (**3r**).

A range of substituted benzylic bromides could be coupled with imine **1a**. Benzylic bromides with *ortho* substitution coupled smoothly, affording products **4d**–**4g** in good yield. In addition, the reaction exhibits chemoselectivity for the benzylic halide in the presence of aryl iodides and bromides (**4f** and **4g**); these functionalities are frequently incompatible with standard organometallic reagents. Benzylic chlorides perform comparably under standard reaction conditions (**3b** and **4j**). A secondary benzylic chloride also underwent the alkylation, although in reduced yield and with poor diastereoselectivity (**4k**).

Non-benzylic alkyl halides were also investigated (Scheme 1), which revealed that the yield of the reaction is influenced by both the identity of the imine and the alkyl electrophile. Whereas efforts to couple cyclohexyl iodide with 2-iminopyridine **1a** gave significant quantities of the imine homocoupling product **1a'**,[18] the corresponding *sec*-alkyl *N*-hydroxyphthalimide (NHP) esters were competent coupling partners, giving the desired products in serviceable yields (**4o**–**4r**).[19] The less hindered *n*-Bu imine **1b** was less prone to homocoupling and could be coupled with cyclohexyl iodide and cyclohexyl bromide to furnish **4l** in 57% yield and 32% yield respectively. Reaction of **1b** with the corresponding heterocyclic halides furnished products **4m** and **4n** in modest to good yields but with excellent selectivity for the 1,2-addition product. For comparison, benzylic halides **4h** and **4i** and an NHP ester (**4l**, X = CONHP) that performed well with branched imine **1a** were coupled with imine **1b** to afford

products in comparable yields (Scheme 1). Taken together, these scope studies demonstrate a generally high tolerance for nitrile,

**Scheme 1. Substrate Scope**[a]




[a]Reactions conducted under inert atmosphere on 0.3 mmol scale with isolated yields reported as average of 2 runs. [b]1.0 mmol scale.

ketone, ester, and halide functional groups, which often are poorly tolerated under standard organometallic conditions.

Initial mechanistic investigations were focused on the role of Ni and Mn, given that productive reactivity is observed in the absence of Ni (Table 1, entries 11-14). When the reaction between **1a** and

cyclohexyl iodide was carried out electrochemically with a reticulated vitreous carbon foam (RVC) cathode and $Zn^0$ as a sacrificial anode, amine **4o** was isolated in 58% yield (Scheme 2a). Addition of imine **1a** (2.0 equiv) to $Ni(cod)_2$ (1.0 equiv) resulted in formation of a royal-purple colored complex presumed to be bis(2-iminopyridine) complex **5**; subsequent addition of benzyl bromide and TMSCl provided **3a** in 51% yield (Scheme 2b). Addition of pregenerated benzyl manganese chloride[20] **6** to imine **1a** in the absence of $NiCl_2$·dme failed to give imine alkylation product **3a**; when the same experiment was conducted in the presence of Ni, diamine **1a'** was produced 57% yield (Scheme 2c). Finally, the importance of forming a bidentate substrate-metal complex was confirmed by using benzaldehyde-derived imine **7** and isomeric pyridyl imine **8**, which both failed to undergo the coupling reaction under standard conditions (Scheme 2d). Taken together, these results demonstrate that Mn is not required for product formation and that Ni catalyzes the radical alkylation reaction through bidentate coordination to the imine substrate.

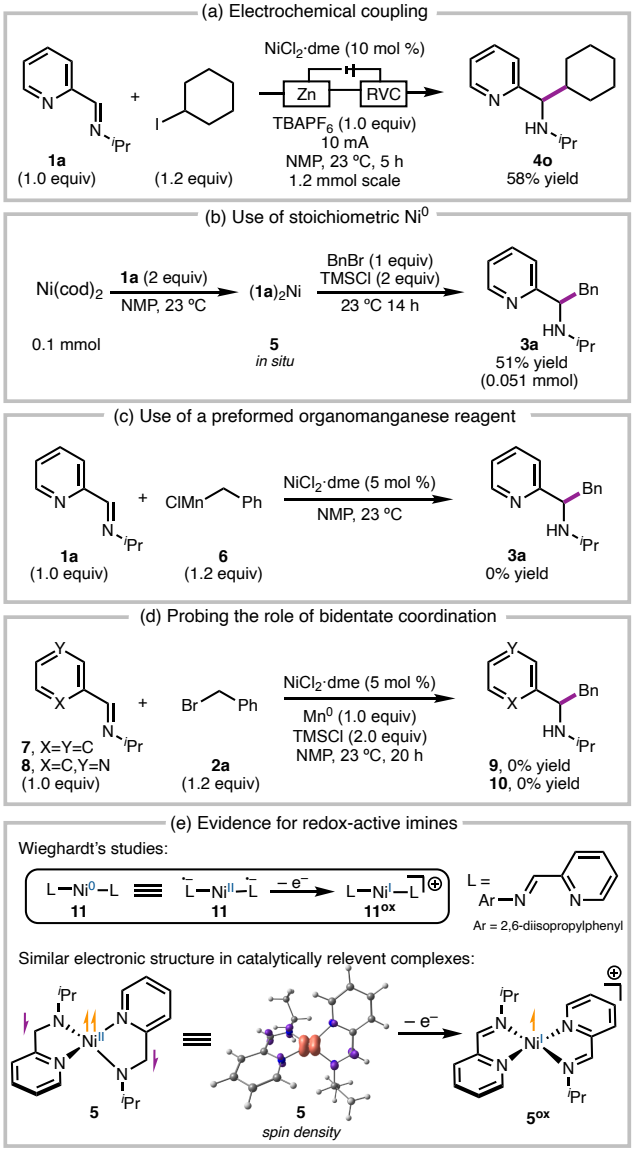



Figure 2. Mechanistic studies.

We next decided to investigate our hypothesis that these substrates are non-innocent ligands in reduced Ni complexes. Although redox-active 2-iminopyridines have not previously been leveraged for Ni-catalyzed cross-electrophile couplings, Wieghardt and others have characterized the redox properties and electronic structures of low-valent bis(2-imino)pyridine nickel complexes. In Wieghardt's studies, the electronic structure of the formally $Ni^0$ complex **11** can be best described as a $Ni^{II}$ with antiferromagnetically coupled ligand-based radicals localized on the imine carbons. Oxidation of this complex results in a $Ni^I$ complex $\mathbf{11^{ox}}$ with remarkable covalency between the metal-ligand $\pi$-system (Scheme 2e).[21] DFT[22] and EPR[23] on putative reaction intermediates derived from **1a** verified that the complex **5** [24] and $\mathbf{5^{ox}}$ has similar electronic properties to those (**11** and $\mathbf{11^{ox}}$) studied by Wieghardt (Figure 2e).[20a] We hypothesize the substrate's capacity to act as a redox-active ligand enables the activation of imines for alkyl radical addition under mild conditions through coordination to low-valent Ni.

From the calculated electronic structures and mechanistic experiments, a plausible mechanism is proposed in Scheme 2. Initial complexation of the bidentate 2-iminoheteroarene with the $Ni^{II}$-precatalyst is hypothesized to form complex **I**, which could undergo two electron reduction to yield intermediate **II**. Addition of the C($sp^3$) radical to **II** would give $Ni^I$ complex **III**, which can propagate the radical chain by single electron transfer (SET) to the electrophile while generating $Ni^{II}$ complex **IV**. With the assistance of *N*-silylation of the alkylated product, ligand exchange with the 2-iminoheteroarene could then regenerate complex **I**. We hypothesize the radical character localized on the imine carbon of nickel complex **II** facilitates the addition of an alkyl radical (Figure 2); however, alternative mechanisms involving radical addition to $(\mathbf{1a})_2Ni^I$ ($\mathbf{5^{ox}}$) cannot be ruled out at this time.

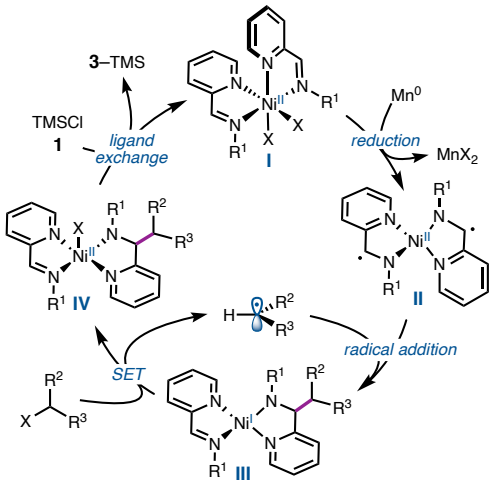



Figure 2. Proposed catalytic cycle.

In conclusion, the Ni-catalyzed reductive cross-coupling of redox-active imines with C($sp^3$) alkyl electrophiles has been reported. The reaction occurs under mild conditions and is tolerant of a variety of functional groups, including *N*- and *S*-heterocyclic coupling partners. Formation of low valent Ni-2-iminoheteroarene complexes provides a mild way to access intermediates primed for radical addition. Further mechanistic investigations into the nature of the exact mode of C($sp^2$) and C($sp^3$) electrophile activation as well as the role

of manganese salts formed during the reaction are the subject of ongoing research in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data ($^{1}H$ and $^{13}C$ NMR, HRMS, FTIR) for all new compounds (pdf). Computational coordinates statement?

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## REFERENCES


[1] (a) Lawrence, S. A. Amines: Synthesis, Properties, and Applications; Cambridge University Press: Cambridge, **2004**. (b) Lewis, J. R. Amaryllidaceae, *Sceletium*, imidazole, oxazole, thiazole, peptide and miscellaneous alkaloids. *Nat. Prod. Rep.* **2001**, 95. (c) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* **2006**, *4*, 2337. (d) Hill, R.; Yudin, A. K. Making carbon-nitrogen bonds in biological and chemical synthesis. *Nat. Chem. Biol.* **2006**, *2*, 284.

[2] Link, J. O.; Rhee, M. S.; Tse, W. C.; Zheng, J.; Somoza, J. R.; Rowe, W.; Begley, R.; Chiu, A.; Mulato, A.; Hansen, D.; Singer, E.; Tsai, L. K.; Bam, R. A.; Chou, C.-H.; Canales, E.; Brizgys, G.; Zhang, J. R.; Li, J.; Graupe, M.; Morganelli, P.; Liu, Q.; Wu, Q.; Halcomb, R. L.; Saito, R. D.; Schroeder, S. D.; Lazerwith, S. E.; Bondy, S.; Jin, D.; Hung, M.; Novikov, N.; Liu, X.; Villaseñor, A. G.; Cannizzaro, C. E.; Hu, E. Y.; Anderson, R. L.; Appleby, T. C.; Lu, B.; Mwangi, J.; Liclican, A.; Niedziela-Majka, A.; Papalia, G. A.; Wong, M. H.; Leavitt, S. A.; Xu, Y.; Koditek, D.; Stepan, G. J.; Yu, H.; Pagratis, N.; Clancy, S.; Ahmadyar, S.; Cai, T. Z.; Sellers, S.; Wolckenhauer, S. A.; Ling, J.; Callebaut, C.; Margot, N.; Ram, R. R.; Liu, Y.-P.; Hyland, R.; Sinclair, G. I.; Ruane, P. J.; Crofoot, G. E.; McDonald, C. K.; Brainard, D. M.; Lad, L.; Swaminathan, S.; Sundquist, W. I.; Sakowicz, R.; Chester, A. E.; Lee, W. E.; Daar, E. S.; Yant, S. R.; Cihlar, T. Clinical Targeting of HIV Capsid Protein with a Long-Acting Small Molecule. *Nature* **2020**, *584* (7822), 614–618.

[3] Munchhof, M. J.; Li, Q.; Shavnya, A.; Borzillo, G. V.; Boyden, T. L.; Jones, C. S.; LaGreca, S. D.; Martinez-Alsina, L.; Patel, N.; Pelletier, K.; Reiter, L. A.; Robbins, M. D.; Tkalcevic, G. T. Discovery of PF-04449913, a Potent and Orally Bioavailable Inhibitor of Smoothened. *ACS Med. Chem. Lett.* **2012**, *3*, 106.

[4] (a) Bloch, R. Additions of Organometallic Reagents to C=N Bonds: Reactivity and Selectivity. *Chem. Rev.* **1998**, *98*, 1407. (b) Marcantoni, E.; Petrini, M. Lewis acid promoted addition reactions of organometallic compounds. *Compr. Org. Synth.* **2014**, *1*, 344.

[5] Reviews on radical additions to imines under thermal conditions, see: (a) Friestad, G. K. Addition of Carbon-Centered Radicals to Imines and Related Compounds. *Tetrahedron* **2001**, *57* (26), 5461–5496. (b) Miyabe, H.; Yoshioka, E; Kohtani, S. Progress in intermolecular carbon radical addition to imine derivatives. *Curr. Org. Chem.* **2010**, *14*, 1254–1264. (c) Tauber, J., Imbri, D. & Opatz, T. Radical addition to iminium ions and cationic heterocycles. *Molecules,* **2014**, *19*, 16190–16222.

[6] Reviews on addition to imines under photoredox catalysis: (a) Cullen, S. T. J.; Friestad, G. K. Synthesis of Chiral Amines by C–C Bond Formation with Photoredox Catalysis. *Synthesis* **2021**, 53, A-W. (b) Zhao, J.-J.; Zhang, H.-H.; Yu, S. Enantioselective Radical Functionalization of Imines and Iminium Intermediates via Visible-Light Photoredox Catalysis. *Synthesis* **2021**, *53* (10), 1706–1718.

[7] For a recent method involving free radical addition to *N*-alkyliminium ions: Kumar, R.; Flodén, N. J.; Whitehurst, W. G.; Gaunt, M. J. A general carbonyl alkylative amination for tertiary amines. *Nature* **2020**, *581*, 415–420.

[8] For a review on the use of photoredox catalysis to generate α-amino radicals from imines, see: Leitch, J. A.; Rossolini, T.; Rogova, T.; Maitland, J. A. P.; Dixon, D. J. α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives. *ACS Catal.* **2020**, *10* (3), 2009–2025.

[9] For a complementary Ni-catalyzed imine alkylation, see: Heinz, C.; Lutz, J. P.; Simmons, E. M.; Miller, M. M.; Ewing, W. R.; Doyle, A. G. Ni-Catalyzed Carbon-Carbon Bond-Forming Reductive Amination. *J. Am. Chem. Soc.* **2018**, *140*, 2292.

[10] For a Ni-catalyzed addition of free radicals to glyoxylate-derived sulfinimines: Ni, S.; Garrido-Castro, A. F.; Merchant, R. R.; de Gruyter, J. N.; Schmitt, D. C.; Mousseau, J. J.; Gallego, G. M.; Yang, S.; Collins, M. R.; Qiao, J. X.; Yeung, K.-S.; Langley, D. R.; Poss, M. A.; Scola, P. M.; Qin, T.; Baran, P. S. A General Amino Acid Synthesis Enabled by Innate Radical Cross-Coupling. *Angew. Chem. Int. Ed.* **2018**, *57* (44), 14560–14565.

[11] (a) Jacquet, J.; Murr, M. D.-E.; Fensterbank, L. Metal-Promoted Coupling Reactions Implying Ligand-Based Redox Changes. *ChemCatChem* **2016**, *8*, 3310. (b) Luca, O. R.; Crabtree, R. H. Redox-active ligands in catalysis. *Chem. Soc. Rev.* **2013**, *42*, 1440. (c) Praneeth, V. K. K.; Ringenberg, M. R.; Ward, T. R. Redox-Active Ligands in Catalysis. *Angew. Chem. Int. Ed.* **2012**, *51*, 10228. (d) Lyaskovskyy, V.; de Bruin, B. Redox Non-Innocent Ligands: Versatile New Tools to Control Catalytic Reactions. *ACS Catal.* **2012**, *2*, 270. (e) Chirik, P. J.; Wieghardt, K. Radical ligands confer nobility on base-metal catalysts. *Science* **2010**, *327*, 794.

[12] (a) Kuang, Y.; Anthony, D.; Katigbak, J.; Marrucci, F.; Humagain, S.; Diao, T. Ni(I)-Catalyzed Reductive Cyclization of 1,6-Dienes: Mechanism-Controlled trans Selectivity. *Chem.* **2017**, *3*, 268. (b) Zhu, D.; Korobkov, I.; Gambarotta, S.; Budzelaar, P. H. M. Redox-Active Ligands and Organic Radical Chemistry. *Inorg. Chem.* **2011**, *50*, 9879. (c) Jones, G.

D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. Ligand Redox Effects in the Synthesis, Electronic Structure, and Reactivity of an Alkyl-Alkyl Cross-Coupling Catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 13175. (d) Dobrov, A.; Darvasiova, D.; Zalibera, M.; Bucinsky, L.; Puskarova, I.; Rapta, P.; Shova, S.; Dumitrescu, D.; Martins, L. M. D. R. S.; Pombeiro, A. J. L.; Arion, V. B. Nickel(II) Complexes with Redox Noninnocent Octaazamacrocycles as Catalysts in Oxidation Reactions. *Inorg. Chem.* **2019**, *58*, 11133.

[13] (a) Bailey, P. J.; Dick, C. M.; Fabre, S.; Parsons, S.; Yellowlees, L. J. Complexation of dimethylmagnesium with a-diimines; structural and EPR characterisation of single electron and alkyl transfer products. *Dalton Trans.* **2006**, 1602. (b) Riollet, V.; Copéret, C.; Bassed, J.-M.; Rousset, L.; Bouchu, D.; Grosvalet, L.; Perrin, M. Reaction of "$[Mn^{II}(CH_2tBu)_2)]$" with Bidentate Diimine Ligands: From Simple Base Adducts to C–C Activation of the Ligand. *Angew. Chem. Int. Ed.* **2002**, *41*, 3025. (c) Kaupp, M.; Stoll, H.; Preuss, H.; Kaim, W.; Stahl, T.; Van Koten, G.; Wissing, E.; Smeets, W. J. J.; Spek, A. L. Theoretical and Experimental Study of Diamagnetic and Paramagnetic Products from Thermal and Light-Induced Alkyl Transfer between Zinc and Magnesium Dialkyls and 1,4-Diaza-1,3-butadiene Substrates. *J. Am. Chem. Soc.* **1991**, *113*, 5606.

[14] (a) Solomon, M. B.; Chan, B.; Kubiak, C. P.; Jolliffe, K. A.; D'Alessandro, D. M. The spectroelectrochemical behavior of redox-active manganese salen complexes. *Dalton Trans.* **2019**, *48*, 3704. (b) Morrison, M. M.; Sawyer, D. T. Redox Chemistry of the Polyimine Complexes of Manganese(II), -(III), and (-IV) in Acetonitrile. *Inorg. Chem.* **1978**, *17*, 333. (c) Rao, J. M.; Hughes, M. C.; Macero, D. J. Redox Behavior of Aromatic Tridentate Imine Ligand Complexes of Manganese and Chromium. *Inorg. Chim. Acta* **1976**, *18*, 127.

[15] See Supporting Information, section 11 for ICP-MS sample preparation and calculations.

[16] Talele, T. T. The "Cyclopropyl Fragment" is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59*, 8712.

[17] See Supporting Information.

[18] Given the reactivity trends and literature precedent for aza-pinacol reactions we suspect that **1a'** forms when reduced Ni-$(imine)_2$ complex accumulates, either due to slow alkyl radical addition into a more sterically hindered imine or from the slower activation of alkyl radical precursors in the case of unstabilized alkyl iodides and bromides. For examples see: (a) Vanessa Faugeroux and Yves Genisson, "The Imino-pinacol Coupling Reaction", Current Organic Chemistry (2008) 12: 751. (b) Hulley, E. B.; Wolczanski, P. T.; Lobkovsky, E. B. Carbon–Carbon Bond Formation from Azaallyl and Imine Couplings about Metal–Metal Bonds. *J. Am. Chem. Soc.* **2011**, *133* (45), 18058–18061.

[19] (a) 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. J. Decarboxylative Cross-Electrophile Coupling of *N*-Hydroxyphthalimide Esters with Aryl Iodides. *J. Am. Chem. Soc.* **2016**, *138*, 5016. (b) Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E. Nickel-Catalyzed Enantioselective Cross-Coupling of *N*-Hydroxyphthalimide Esters with Vinyl Bromides. *Org. Lett.* **2017**, *19*, 2150. For a recent review Ni-catalyzed cross-couplings with NHP esters: Konev, M. O.; Jarvo, E. R. Decarboxylative Alkyl-Alkyl Cross-Coupling Reactions. *Angew. Chem. Int. Ed.* **2016**, *55*, 11340.

[20] Quinio, P.; Benischke, A. D.; Moyeux, A.; Cahiez, G.; Knochel, P. New Preparation of Benzylic Manganese Chlorides by the Direct Insertion of Magnesium into Benzylic Chlorides in the Presence of $MnCl_2$·2LiCl. *Synlett* **2015**, *26*, 514.

[21] For thorough investigations into first row transition metal bisiminopyridine complexes as well as closely related Nickel complexes see: (a) Lu, C. C.; Bill, E.; Weyhermüller, T.; Bothe, E.; Wieghardt, K. Neutral Bis(α-Iminopyridine)Metal Complexes of the First-Row Transition Ions (Cr, Mn, Fe, Co, Ni, Zn) and Their Monocationic Analogues: Mixed Valency Involving a Redox Noninnocent Ligand System. *J. Am. Chem. Soc.* **2008**, *130* (10), 3181–3197. (b) Lu, C. C.; Bill, E.; Weyhermüller, T.; Bothe, E.; Wieghardt, K. The Monoanionic π-Radical Redox State of α-Iminoketones in Bis(Ligand)Metal Complexes of Nickel and Cobalt. *Inorg. Chem.* **2007**, *46* (19), 7880–7889. (c) Mondal, A.; Weyhermüller, T.; Wieghardt, K. Redox-Noninnocence of N,N′-Bis(6-Methyl-2-Pyridylmethylene)Ethane-1,2-Diamine (L): Synthesis and Characterization of Diamagnetic [NiII2(L˙˙)2] and [ZnII2(L)Cl4]((L˙˙)2–π Diradical Dianion of L). *Chem. Commun.* **2009**, No. 40, 6098–6100. (d) Tsvetkov, N. P.; Chen, C.-H.; Andino, J. G.; Lord, R. L.; Pink, M.; Buell, R. W.; Caulton, K. G. Synthesis and Oxidative Reactivity of 2,2′-Pyridylpyrrolide Complexes of Ni(II). *Inorg. Chem.* **2013**, *52* (16), 9511–9521. (e)
Sengupta, D.; Ghosh, P.; Chatterjee, T.; Datta, H.; Paul, N. D.; Goswami, S. Ligand-Centered Redox in Nickel(II) Complexes of 2-(Arylazo)Pyridine and Isolation of 2-Pyridyl-Substituted Triaryl Hydrazines via Catalytic N-Arylation of Azo-Function. *Inorg. Chem.* **2014**, *53* (22), 12002–12013.

[22] DFT calculation performed using the ORCA software package at the B3LYP/def2-TZVP level of theory. See supporting information for optimization, frequency, broken symmetry, EPR, and property calculations.

[23] EPR studies on the $(\mathbf{1a})_2Ni^{I}$ show metal radical in agreement with data from Wieghardt and coworkers (ref 20a). See supporting information section 7 for more details.

[24] For complex **5** broken symmetry solution BS(2,2) was favored over the closed-shell and high spin solutions. Broken symmetry solutions are in agreement with the observations of Wieghardt and coworkers where ligand radicals are antiferromagnetically coupled to unpaired electrons on $Ni^{II}$ center. See Supporting Information for further details on the electronic structure of **5**.

TOC Graphic