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Nickel-Catalyzed Reductive Alkylation of Heteroaryl Imines

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This paper is dedicated in memory of our colleague and friend Prof. Robert H. Grubbs.

[‡] These authors contributed equally to this work.

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Abstract: The preparation of heterobenzylic amines by a Ni-catalyzed reductive cross-coupling between heteroaryl imines and C(sp³) electrophiles 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 Ni center. The resulting bis(2-imino)heterocyclic-Ni complexes can engage in alkylation reactions with a variety of C(sp³) electrophiles, giving heterobenzylic amine products in good yields.

Introduction

Benzylic amines are common substructures in a variety of natural products, agrochemicals, and pharmaceuticals. 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 and Pfizer’s commercial anticancer agent Glasdegib (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; however, pre-generation of sensitive and reactive organometallic reagents and use of activated imine derivatives 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 benzylic amines, chemists have explored complimentary single electron reactions of imines, including the 1,2-addition of organic radicals to imines and the reductive alkylation of imines via α-amino radicals. These reactions often exhibit improved functional group tolerance by avoiding the use of organometallic reagents; however, they typically require activated imine derivatives (e.g. sulfimyl imines, N-arylimines, oximes, hydrazones, or phosphoryl imines) to stabilize the resulting N-centered radicals or facilitate imine reduction. As part of our efforts to broaden the scope of electrophiles for cross-electrophile coupling, we became interested in a mechanistically distinct transition metal-catalyzed reductive alkylation of heterocyclic imines that leverages the...
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Our investigations commenced with the coupling between \((E)\)-N-isopropyl-1-(pyridin-2-yl)methanamine (1a) and benzyl bromide (2a) in the presence of Mn\(\text{II}\) as a stoichiometric reductant, NMP as the solvent, and TMSCl as an additive. Product 3a was formed in varying yields for a series of metal dihalide salts (Table 1, entries 1–6). Of the metals evaluated, NiCl\(_2\)·dme was found to be optimal, providing 3a in 87% yield (Table 1, entry 1). Interestingly, when TMSCI is used, the reaction proceeds in the absence of exogenous catalyst (Table 1, entry 7). It is likely that the combination of Mn\(\text{II}\) and TMSCI generates MnCl\(_2\), which was previously shown by Wieghardt\(^\text{12}\) to form a redox-active complex with a similar heteroaryl imine. Use of MnCl\(_2\) gives no improvement over just Mn\(\text{II}\) and provides 3a in lower yield than NiCl\(_2\)·dme (entry 6).\(^{13,14,15}\) When TMSCI was omitted from the reaction, 3a was formed in only 39% yield (entry 9). Protic additives such as hexafluoroisopropanol (HFIP) (entry 10) and AcOH (entry 11) were also beneficial, but inferior to TMSCI.\(^{16}\)

Table 1. Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>M catalyst</th>
<th>deviation from standard conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl(_2)·dme</td>
<td>none</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>CrCl(_2)</td>
<td>none</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>FeBr(_2)</td>
<td>none</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl(_2)</td>
<td>none</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>CoCl(_2)</td>
<td>none</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>MnCl(_2)</td>
<td>none</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>none</td>
<td>none</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>no TMSCI</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>NiCl(_2)·dme</td>
<td>no TMSCI</td>
<td>39</td>
</tr>
<tr>
<td>10</td>
<td>NiCl(_2)·dme</td>
<td>NMP/HFIP (4:1), no TMSCI</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>NiCl(_2)·dme</td>
<td>AcOH (1 eq), no TMSCI</td>
<td>69</td>
</tr>
<tr>
<td>12</td>
<td>NiCl(_2)·dme</td>
<td>Zn(_2) (\text{II}) (2 eq), no Mn(\text{II})</td>
<td>45</td>
</tr>
<tr>
<td>13</td>
<td>NiCl(_2)·dme</td>
<td>TDAE (1.5 eq), no Mn(\text{II})</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>NiCl(_2)·dme</td>
<td>1 mol % catalyst</td>
<td>83</td>
</tr>
<tr>
<td>15</td>
<td>NiCl(_2)·dme</td>
<td>0.1 mol % catalyst</td>
<td>62</td>
</tr>
<tr>
<td>16(\text{c}d)</td>
<td>NiCl(_2)·dme</td>
<td>Zn anode, RVC cathode, TBAPF(_6) (1 eq), 20 mA, no Mn(\text{II}) or TMSCI</td>
<td>76</td>
</tr>
<tr>
<td>17(\text{c}d)</td>
<td>MnCl(_2)</td>
<td>Zn anode, RVC cathode, TBAPF(_6) (1 eq), 20 mA, no Mn(\text{II}) or TMSCI</td>
<td>23</td>
</tr>
</tbody>
</table>

\(^{\text{c}}\)Reactions conducted under inert atmosphere on 0.3 mmol scale. \(^{\text{d}}\)Determined by \(^1\)H NMR versus an internal standard: \(^1\)H, 2.2 mmol scale. \(^{\ast}\)1.5 eq of 2a.

Results and Discussion

...continued...

...previous text...

redox-noninnocence of 2-iminoheterocycles as ligands on first-row transition metals. This strategy allows for the mild activation of imines for single electron alkylation and provides direct access to N-alkyl heterobenzyl amines by the equivalent of a C\(\text{sp}^3\)–C\(\text{sp}^3\) coupling reaction. In this report, we describe the development of this method, which provides access to a variety of heterobenzyl N-alkylamines in good yields.

Conjugated nitrogen ligands such as diiminopyridines, \(\alpha\)-diimines, and bi- and terpyridines can be electronically noninnocent: their \(\tau\)-systems are able to accept one or two electrons when bound to first-row transition metals.\(^{11}\) For example, spectroscopic, electrochemical, and computational investigations conducted by Wieghardt and coworkers demonstrated that low-valent Cr, Mn, Fe, Co, Ni, and Zn bis-(2-imino)pyridine complexes possess ligand-centered radicals (Figure 2a).\(^{12}\) Although the alkylation of ligand backbones has been observed previously,\(^{13}\) this reactivity has not been leveraged for a catalytic cross-coupling.

We hypothesized that these redox-active complexes could be considered persistent \(\alpha\)-amino radicals, which might react with alkyl radicals to give metal-coordinated imine alkylation products (Figure 2b, I to II). This process could be rendered catalytic if 1) the alkylated product-metal complex II could activate a C\(\text{sp}^3\) electrophile to generate an alkyl radical, 2) the product could be liberated from complex III by exchange with imine 1, and 3) the bis-(2-iminoheterocycle)M\(_2\)X\(_2\) complex IV could be reduced by a terminal reductant to regenerate the low-valent complex I. We envisioned that turnover might be facilitated by a Brønsted acid (H–X) or electrophilic reagent (E–X) able to sequester the anionic nitrogen of III.

...previous text...
Scheme 1. Substrate Scope

Reactions were conducted under inert atmosphere on 0.3 mmol scale with isolated yields reported as average of 2 runs. *1.0 mmol scale. †50% yield of homocoupling product 1a.

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Alternative reductants such as Zn\(^6\) and tetrakis(N,N-dimethylamino)ethylene (TDAE) did not perform as well as Mn\(^0\) (entries 12–13). The catalyst loading could be dropped to 1 mol % with only a small decrease in yield (entry 14); however, lowering the catalyst loading to 0.1 mol % significantly reduced the yield and showed no improvement over the background Mn-mediated reaction (entry 15 vs. entry 7). To investigate the reaction in the absence of Mn\(^0\), a constant current electrolysis protocol was employed for both Ni and Mn salts. The Ni-catalyzed electrolysis provided 3a in good yield (entry 16) while the Mn-catalyzed reaction provided drastically lower yield of 3a (entry 17). Although the reaction could be performed with just Mn\(^0\), the addition of NiCl\(_2\)-dme resulted in higher yields of the imine alkylation product. As a result, the conditions from entry 1 were used to evaluate the scope of the reaction using Mn\(^0\) as the terminal reductant.

The scope of the heteroaryl imine coupling partner was investigated using benzyl bromide as the electrophile (Scheme 1). Sterically diverse N-substitution on the imine was well tolerated, affording the products containing Bu, Pr, and tBu groups in high yields (3a–3c). Imines bearing cyclopropyl and cyclobutyl groups, two interestingly popular fragments in drug development,\(^1\) 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 and 3m), possibly because the substituent hinders coordination of the imine to the Ni-catalyst. In general, substrates bearing electron withdrawing groups at the 5-position gave lower yields of the product. 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. Ortho-substituted benzylic bromides 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, X = Cl 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 reaction yield is influenced by the identity of both the imine and the alkyl electrophile. N-Bu imine 1b could be coupled with cyclohexyl iodide and cyclohexyl bromide to furnish 4i in 57% yield and 32% yield, respectively. Coupling of the N-Pr imine (1a) with cyclohexyl iodide gave 4m in 45% yield; however, it was accompanied by 50% yield of the imine homocoupling product 1a'.\(^{18,19}\) In contrast, use of the corresponding N-hydroxyphenylhydrazide (NHP) ester\(^20\) gave 4m in 41% yield but with minimal formation of 1a'. Reaction of 1a or 1b with pyranyl and piperdinylic electrophiles furnished products 4n–4q in modest to good yields. Taken together, these scope studies demonstrate a generally high tolerance for nitrite, ketone, ester, and halide functional groups, which are often incompatible with organomagnesium and organolithium reagents.

Given that deleterious imine homodimerization was observed in some reactions when Mn\(^2\) was used as a reductant (Table S1), we sought to drive the reaction electrochemically to eliminate the need for Mn\(^2\). Moreover, an electroreductive system removes the mechanistic ambiguity about the identity of the active catalyst (Ni vs. Mn). Under constant current electrolysis using reticulated vitreous carbon (RVC) foam as the cathode and Zn\(^0\) metal as a sacrificial anode, alkylation of 1a with 2a proceeded smoothly (Scheme 2). We were pleased to find that several substrates that gave low yields under the Mn\(^0\) conditions performed better under the electroreductive conditions. For example, when 1a was coupled with iodocyclohexane under standard conditions, product 4m was formed in 45% yield and was accompanied by 50% yield (Figure S2) of imine dimer 1a' (see Scheme 1). Under the electroreductive conditions, 4m was produced in 59% yield on a 1.2 mmol scale; no 1a' was observed. Alkylation products from primary (4s, 4v, and 4w) and tertiary (4u) iodides, could also be formed in good yield under the electroreductive conditions (Scheme 2). Both reactions proceeded in <20% yield when Mn\(^0\) was used as a reductant.

Since the electroreductive coupling demonstrates that Ni salts can catalyze the alkylation of 2-iminopyridines, we carried out a series of mechanistic experiments studying the Ni system. Initial mechanistic investigations focused on the substrate-catalyst complexes proposed to be key catalytic intermediates (Scheme 3). Non-chelating substrates like benzaldehyde-derived imine 5 and isomeric pyridyl imine 6 failed to couple under standard conditions, demonstrating the importance of forming a bidentate...
substrate-metal complex (Scheme 3a). Bis(2-iminopyridine)-Ni complex 9 was prepared by the addition of imine 1a (2.0 equiv) to Ni(cod)2 (1.0 equiv).12 Subsequent addition of benzyl bromide provided 3a in 53% yield, providing support for reduced Ni complex 9 as a competent species in the catalytic cycle (Scheme 3b).

We sought to investigate the redox properties of (1a)2NiCl2 (10) to confirm that reduction to the low-valent complex 9 is possible under the reaction conditions. Using cyclic voltammetry (CV), the reduction potential of free 1a was compared to the reduction potentials of corresponding in situ generated complexes (1a)2NiCl2 (10) and (1a)2MnCl2 (11) (Figure 3a). Complex 11 (E1/2 = −1.82 V vs. Fc/Fc in NMP) is more challenging to reduce than Ni complex 10 (E1/2 = −1.43 V vs. Fc/Fc in NMP). The free imine 1a has a reduction potential (E1/2) of −2.65 V vs. Fc/Fc in NMP, which is significantly more negative than that of either complex 10 or 11. Complexation of 1a with a non-redox-active Lewis acid such as MgBr does not significantly change the potential of imine reduction (E1/2 = −2.55 V vs. Fc/Fc in NMP) (Figure 3a). The significant anodic shift of the reduction potentials and the increased reversibility of the redox events demonstrate that imine coordination to Ni and Mn facilitates reduction and stabilizes the ligand-centered radicals. We note that reduction of 10 is 420 mV more anodic than 11 indicating the formation of proposed intermediate I (Figure 2b) is more thermodynamically favorable, which may correlate with the improved product yields when catalytic Ni is included.

It was unclear from the CV alone whether the observed reduction of (1a)2NiCl2 (10) corresponded to a one-electron or a two-electron process.24 To investigate the identity of the species generated upon reduction, UV/Vis spectrophotometric analysis of 10 was performed at varying potentials (Figure S24). At −1.4 V vs. Fc/Fc, a species develops with a UV/Vis spectrum that is consistent with that of an independently prepared sample of (1a)Ni (9) (Figure 3b). Alternatively, mixing 1 equiv each of 9 and 10 results in comproportionation to the Ni2 complex; this species has a different spectroscopic profile, and consistent with Wieghardt’s prior studies,15 computational and EPR studies suggest that this complex does not have any significant radical character on the ligand backbone (Figure S3). These experiments suggest that at potentials accessible under the catalytic reaction conditions, complex 10 undergoes two electron reduction to generate 9.25,26

To probe whether reductively generated 9 can react with alkyl electrophiles, CVs of complex 10 in the presence of benzyl chloride were acquired. Scanning in the negative direction, the CV of a mixture of 10 (1 equiv) and benzyl chloride (100 equiv) shows a cathodic shift and increase in peak current relative to complex 10 alone (Figure 3c). The cathodic shift indicates that, upon reduction, complex 10 does not react with benzyl chloride through a simple EC mechanism, but instead through a mechanism that likely involves intermediate chemical steps such as loss of chloride ligands. Kinetic analysis of the reaction with benzyl chloride reveals a second order rate constant k = 1.8 × 10−1 M−1 s−1 (Supporting Information section 6.3).27 Addition of AcOH (150 equiv) and additional 1a (50 equiv) results in a catalytic wave (Figure 3c) that is not observed in the absence of BnCl or excess 1a (Figure S13). AcOH was used for these studies because it was found to give reasonable alkylation yields (Table 1, entry 11) and had greater stability than TMSCl in the electrochemical cell.

In agreement with Wieghardt and coworkers,12 computational studies suggest that the electronic structure of the formally Ni0 complex 9 is best described as a NiII center with antiferromagnetically coupled ligand-based radicals. DFT calculations of 9 at the B3LYP/def2-TZVP level of theory show the broken symmetry solution BS(2,2) being lower in energy than the closed-shell or high spin solutions (Scheme 3c).21,22 A qualitative molecular orbital diagram of the magnetic orbitals reveals seven orbitals with significant d contribution (Figure S30). Upon closer examination of the electronic structure, there are two ligand-based SOMOs as the imine π* orbitals (Scheme 3d). Using the Yamaguchi equation, the spin-spin coupling constant (J) between the metal-based SOMOs and the ligand-based SOMOs was calculated to be J = −777 cm−1.23 These data support our hypothesis that the ligand non-innocence of reduced catalyst-substrate complexes such as 9 allows for facile access to persistent α-amino radical intermediates (Figure 2b).

Scheme 3. Investigation of Ni–substrate complexes. *Spin density plot of 9 with Loewdin spin population values for atoms with significant radical character. Qualitative MO diagram of BS(2,2) 9 and corresponding magnetic orbitals with corresponding spatial overlap (S) for orbitals with S < 0.999.
Conclusion

In conclusion, the Ni-catalyzed reductive cross-coupling of (2-imino)heterocycles with C(sp³) 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 imine coupling partners. Mechanistic studies support the formation of low-valent bis(2-imino)pyridine-Ni complexes as persistent ligand-centered radical species that can react with alkyl electrophiles and be leveraged for catalytic C–C bond formation.

Acknowledgements

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Keywords: cross-coupling • electrochemistry • imines • nickel-catalysis • alkylation
Entry for the Table of Contents

A Ni-catalyzed reductive cross-coupling of heteroaromatic imines with C(sp²) esters for the preparation of heterobenzyl amines is reported. Mechanistic studies are consistent with the imine substrate acting as a redox-active ligand upon coordination to a low-valent Ni center.

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[Diagram of Ni-catalyzed cross-coupling reaction]

+ abundant alkyl electrophiles + mild conditions

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