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Dialkyl Ether Formation via Nickel-Catalyzed Cross Coupling of Acetals and Aryl Iodides**

Kevin M. Arendt and Prof. Abigail G. Doyle

Department of Chemistry, Princeton University 120 Washington Road Princeton, NJ 08544

Abigail G. Doyle: agdoyle@princeton.edu

Abstract

A new substrate class for Ni-catalyzed C(sp³) cross-coupling reactions is reported. We show that α -oxy radicals generated from abundant and stable benzylic acetals, TMSCl, and a mild reductant can participate in chemoselective cross coupling with aryl iodides and a vinyl triflate using a 2,6-bis(*N*-pyrazolyl)pyridine (bpp)-ligated Ni catalyst. The mild, base-free conditions are tolerant of a variety of functional groups on both partners; as such, the reaction represents an attractive C–C bond-forming approach to dialkyl ether synthesis. Characterization of a (bpp)NiCl complex relevant to the proposed catalytic cycle is also described.

Keywords

cross-coupling; nickel; radicals; dialkyl ethers; CO bond activation

Over the past decade, tremendous advances have been made in the field of nickel-catalyzed cross coupling,^[1] including the development of stereoconvergent alkyl cross-coupling reactions^[2] and chemoselective cross-electrophile couplings.^[3] These two synthetic methods have recently been the subject of mechanistic studies,^[4] which have revealed a pathway that involves a radical-chain mechanism. Specifically, Weix and Fu concluded that oxidative addition of an organic halide to Ni(I) can occur via a bimetallic mechanism wherein a Ni(II) halide and transient organic radical are produced; this organic radical is subsequently captured by another Ni(II) species to furnish a Ni(III) intermediate primed for C–C bond formation (Figure 1A). This ability to engage highly reactive organic radicals in cross-coupling reactions presents exciting new possibilities for organic synthesis, especially if alternative mechanisms can be exploited for radical generation.

The Weix group recently reported a nickel/titanium catalyst system for mild and regioselective arylation of epoxides with aryl halides; this system demonstrated that radical generation and Ni-catalyzed coupling can be accomplished by two different catalysts.^[5] Our group, in collaboration with the MacMillan laboratory, subsequently described a platform

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Correspondence to: Abigail G. Doyle, agdoyle@princeton.edu.

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wherein a photoredox catalyst was able to supply radical partners to a nickel-catalyzed coupling reaction.^[6] This approach enabled α -amino C–CO₂H and C–H bonds to serve as handles for C(sp³)–C bond formation. In a concurrent study, the Molander group was able to overcome limitations inherent to transmetalation with C(sp³) organoboron reagents by generating radicals from these reaction partners utilizing a related photoredox/nickel catalysis approach.^[7]

In an effort to advance the synthetic scope of alkyl cross-coupling reactions further, we questioned what alternative radical-generating processes might be coupled with the Ni machinery. It is known that the combination of a Lewis acid and reductant can generate α -oxy radicals from acetals.^[8] We envisioned that successful coupling of these radicals with aryl and heteroaryl halides would deliver an attractive C–C bond-forming synthesis of dialkylethers (Figure 1B). Furthermore, the transformation would enable the use of simple, abundant, and stable acetals as handles for coupling reactions.

Dialkylethers are prevalent in pharmaceuticals and biologically active compounds.^[9] However, approaches to their synthesis typically rely upon C(sp³)–O bond formation (e.g. Williamson ether synthesis) and remain limited due to requirements for strong base, high temperature, and/or unhindered substrates.^[10] There are fewer examples of C–C bond-forming approaches to dialkyl ethers, and these often rely on the intrinsic reactivity of the electrophilic or nucleophilic reaction partner.^[11] C(sp³)–C bond-forming reactions that feature the modularity of a cross-coupling reaction but are applicable to heteroatom-containing, pharmaceutically relevant structures like ethers are rare in the field. The Bode group has reported Lewis-acid catalyzed additions of Ar–BF₃K salts to acetals; however, the conditions are restricted to primary C(sp³)–C bond formation.^[12] The Molander group has shown that α -oxy BF₃K salts couple efficiently with aryl chlorides under palladium catalysis; however, these nucleophiles are not readily available and the conditions for cross coupling require high temperature and strong base.^[13] Thus, we recognized that a Ni-catalyzed approach from readily available acetals and aryl halides could offer unprecedented mildness and generality for the preparation of this structural motif.^[14]

As shown in Figure 1C, we envisioned a catalytic cycle initiated by oxidative addition of Ni(0) **I** into an aryl halide. The resulting Ni(II) intermediate **II** would intercept an α -oxy radical **V** generated from acetal **III**, a Lewis acid, and reductant such as Zn ($E_{1/2}^{\text{red}} = -1.0\text{V}$ vs SCE in MeCN), delivering Ni(III) adduct **VI**. Subsequent reductive elimination would afford dialkylether **VIII**, releasing Ni(I) species **VII**. Completion of the catalytic cycle requires turnover of the Ni catalyst by a reductant to regenerate Ni(0) **I** ($E_{1/2}^{\text{red}}[\text{Ni}^{\text{II}}/\text{Ni}^0] = -1.2\text{V}$ vs SCE in DMF).^{[15],[16]}

We began our investigations by exploring the coupling of benzaldehyde dimethylacetal with iodobenzene using TMSCl as Lewis acid and Zn as reductant (Table 1).^[18] In the absence of a Ni catalyst, the acetal converts to a mixture of *rac*- and *meso*-pinacol dimers **B**, presumably via α -oxy radical **V** (entry 2). Indeed, trapping experiments using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) deliver 77% yield of the TEMPO adduct, also supporting the intermediacy of **V** and its formation using Zn as reductant.^[17] With a catalytic amount of nickel and 3 equiv TMSCl, cross coupling to form the desired ether **A**

was observed. However, the selectivity for the desired dialkylether **A** varied significantly depending on the identity of the ligand on Ni. Phosphine and amine ligands commonly employed in cross coupling were not efficient in the reaction (entries 6–11). After extensive ligand evaluation, it was found that highest cross-selectivity could be achieved using the tridentate amine ligand 2,6-bis(*N*-pyrazolyl)pyridine (bpp), which delivered the desired cross-coupled product in 91% yield (entry 1).

The bpp ligand has seen limited application in other Ni-catalyzed cross-coupling reactions.^[19] As such, we sought to elucidate the structure and properties of a bpp-ligated Ni species relevant to the catalytic reaction. Based on our proposed mechanism, we chose to prepare the Ni(I) chloride complex **1** (structure **VII** in Figure 1C). Comproportionation of Ni(cod)₂ and NiCl₂·DME in the presence of 2 equiv of bpp provided the monomeric chloride complex **1** as dark green crystals (Figure 2A). Importantly, complex **1** is catalytically competent, delivering dialkyl ether **1** in 64% yield under standard conditions. A single crystal X-ray diffraction study established that **1** adopts a slightly distorted octahedral geometry in the solid state and associates as a μ -chloride dimer upon recrystallization from ethanol (Figure 2B).^[20] Complex **1** exhibits an axial EPR signal with $g_{||} = 2.262$ and $g_{\perp} = 2.070$, consistent with its formulation as a d⁹ Ni(I) complex, rather than as a d⁸ Ni(II) species with the radical residing in the bpp ligand (Figure 2C). Computational experiments confirm that the unpaired spin is localized exclusively on nickel in a d_{x²-y²} orbital.^[17] These features are remarkably similar to those of (terpy)NiBr and (terpy)NiCl, as reported by Vicic^[21] and Wiegardt^[22] respectively, with the exception that the terpy complexes are monomeric and square planar in the solid state. The redox potential of (bpp)NiCl ($E^{\text{red}}_{1/2} = -0.8\text{V}$ vs SCE in MeCN) is also within 200mV of those for (terpy)Ni(I) halides.^[23] Taken together, these data do not provide an obvious parameter to discriminate the selectivity observed between bpp and terpy in this chemistry. Since the ligands themselves have more distinct redox potentials (terpy: $E^{\text{red}}_{1/2} = -2.2\text{V}$ vs SCE in MeCN; bpp: $E^{\text{red}}_{1/2} = -0.9\text{V}$ vs SCE in MeCN), it is possible that the reaction selectivity arises at stages in the catalytic cycle wherein oxidation/reduction of Ni is ligand-based.

With optimized conditions in hand, we next explored the generality of the transformation. High cross-selectivity was observed with a variety of aryl iodides (Table 2). Substitution around the aromatic ring was well tolerated, though *ortho*-tolyl iodide suffered from rapid formation of 2,2'-bitolyl (**3–5**). Both electron-rich (**7**) and electron-poor (**9**) aryl iodides coupled with equal levels of efficiency.^[24] This represents a significant advance as methods to form alkyl ethers via oxocarbenium ions typically rely on the inherent reactivity of the nucleophile and are thus limited to electron-rich coupling partners.^[11a,b] Nitrogen-containing heterocycles that are common in pharmaceuticals undergo reaction in good yield (**12** and **13**). Protic as well as Lewis basic functionality is tolerated (**14** and **15**) and in the case of carbonyl-containing aryl iodides, no evidence of products arising from ketyl formation are observed even in the presence of excess Lewis acid and reductant. Finally, we were able to extend the scope to vinyl substrates: a cyclohexenyl vinyl triflate reacts with good efficiency to provide the desired allylic ether (**16**).

Several of the trends observed with the aryl iodides were recapitulated with the acetals (Table 3). Substituents that are able to coordinate to the metal are well tolerated at the *ortho*

position whereas simple alkyl groups decrease the efficiency of the reaction (**17** versus **5**). When more than one halide is present, the cross coupling proceeds selectively at the aryl iodide (**22**). Lewis basic functionality is tolerated (**21**). Electron- rich (**10**), -neutral (**4**), and - poor (**23**) acetals perform well under these conditions. Recently, the MacMillan laboratory has reported a powerful photoredox/organocatalysis approach to form similar product types;^[11c,d] this method, however, is limited to easily reduced, electron-deficient aryl nitrile coupling partners. The current strategy allows us to bring together two carbon fragments independent of their electronic nature. Furthermore, although Ni-catalyzed C–O coupling of benzylic ethers is well- known,^[25] we have not observed the products arising from subsequent arylation of the benzylic ether products in Tables 2 and 3.

Pleasingly other types of benzylic acetals can be used to arrive at structurally distinct products (Figure 3). Phthalan-derived acetal **25** undergoes coupling with iodobenzene to generate isobenzofuran **26**, the core of a number of SSRI pharmaceuticals.^[9d,e] Cross coupling of dioxolane **27** furnishes ether **28** possessing an ethoxy alcohol tether that could be easily elaborated to motifs found in numerous bioactive compounds.^[9b] The ethoxy alcohol handle can also serve as a traceless directing group for an additional round of Ni-catalyzed cross coupling, ultimately affording tri- or di-arylalkanes, valuable pharmacophores in their own right.^[26] These results highlight opportunities to apply this C(sp³) coupling reaction to late-stage diversification of bioactive compounds. While exo- and endocyclic acetals are competent reaction partners, acyclic acetals other than dimethyl acetals have thus far proven unreactive under the outlined coupling conditions.

In conclusion we have demonstrated that bench stable and abundant benzylic acetals participate in formal C(sp³)–O cross coupling with aryl iodides in the presence of a Ni catalyst, Lewis acid, and reductant. This mild and functional group tolerant C–C bond-forming approach to dialkylethers provides access to a variety of acyclic and cyclic products in good yields with high chemoselectivity. We have shown that an α -oxy radical is generated under the reaction conditions and propose that this radical intercepts a (bpy)nickel complex to selectively generate the cross-coupled product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A. Weix and Fu: bimetallic oxidative addition between Ni(I) and alkyl halides. **B. Proposed C(sp³) cross coupling with acetals via an α -oxy radical.** **C. Proposed mechanism for acetal coupling with aryl halides**

Figure 1.
Ni-catalyzed C(sp³) cross coupling with radicals.

Figure 2.

(A) Comproportionation to form $\text{bpp}(\text{Ni})\text{Cl}$ **1**. (B) ORTEP diagram of dimeric **1** shown at 30% probability ellipsoids; H atoms omitted for clarity (except for ethanol O–H atoms). Selected bond lengths (Å): Ni–Cl1 2.333; Ni–Cl2 2.484; Ni–N3 2.012; Ni–N1 2.009; Ni–O1 2.078.. Selected bond angles (deg): N3–Ni–Cl 173.8; N5–Ni–Cl 101.3; N1–Ni–N5 154.9. (C) X-band EPR spectrum of **1** frozen in MeCN glass at 10K. Black line: experimental spectrum, red line: simulation using Easyspin. Parameters: microwave frequency 9.3742949 GHz; microwave power 2.0 mW; modulation amplitude 0.1 mT/100 kHz.

Figure 3.
Access to dialkyl ether-containing bioactive molecules

Table 1

Reaction Optimization Studies.^[a]

entry	deviation from std. conditions	A [%]	B [%]	C [%]
1	none	91	3	3
2	no NiCl ₂ ·DME	0	13	0
3	no Zn ⁰	0	0	0
4	no TMSCl	0	0	25
5	1 equiv PhI	55	2	2
6	PPh ₃ instead of bpp ^[b]	5	30	35
7	dppbz instead of bpp	4	28	10
8	bpy instead of bpp	38	10	31
9	terpy instead of bpp	10	11	35
10	Ph-Box instead of bpp	2	39	0
11	Ph-PyBox instead of bpp	0	27	38
12	Mn ⁰ instead of Zn ⁰	23	15	35

^[a] Determined by GC using dodecane as a quantitative internal standard.^[b] 20 mol% ligand loading. bpp = 2,6-bis(*N*-pyrazoyl)pyridine.

Table 2

Scope of Aryl Iodides.^[a]

2 91% yield	3 71% yield
4 82% yield	5 9% yield
6 85% yield
7 77% yield	8 50% yield^[b]
9 89% yield^[b]	10 80% yield
	11 78% yield
12 60% yield	13 44% yield
14 65% yield^[b]	15 60% yield
	16 60% yield^[c]

^[a] Isolated yields (0.50 mmol).^[b] 4.0 equiv. NaBF₄ added.^[c] Vinyl triflate was employed.

Table 3

Scope of Acetals.^[a]

 17 83% yield	 5 10% yield
 3 84% yield	 18 54% yield
 19 79% yield	 4 86% yield
 20 78% yield	 21 64% yield
 22 49% yield	 23 64% yield ^[b-d]
 24 59% yield	 10 73% yield

^[a] Isolated yields (0.50 mmol scale).^[b] 4.0 equiv. NaBF₄ added.^[c] Reaction run at 60 °C.^[d] *p*-Iodoanisole was employed as the coupling partner.