Synthetic Methods

Deutsche Ausgabe: DOI: 10.1002/ange.201503936
Internationale Ausgabe: DOI: 10.1002/anie.201503936

Dialkyl Ether Formation by Nickel-Catalyzed Cross-Coupling of Acetals and Aryl Iodides[**]

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Abstract: *A new substrate class for nickel-catalyzed C(sp^3) cross-coupling reactions is reported. α-Oxy radicals generated from benzylic acetals, TMSCl, and a mild reductant can participate in chemoselective cross-coupling with aryl iodides using a 2,6-bis(N-pyrazolyl)pyridine (bpp)/Ni catalyst. The mild, base-free conditions are tolerant of a variety of functional groups on both partners, thus representing 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.*

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, the Weix and Fu groups concluded that oxidative addition of an organic halide to nickel(I) can occur by a bimetallic mechanism wherein a nickel(II) halide and transient organic radical are produced (Figure 1 a). This organic radical is subsequently captured by another nickel(II) species to furnish a nickel(III) intermediate primed for C–C bond formation. 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 nickel-catalyzed coupling can be accomplished by two different catalysts.[5] Our group, in collaboration with the MacMillan group, subsequently described a platform wherein a photoredox catalyst was able to supply radical partners to a nickel-catalyzed coupling reaction.[6] This approach enabled α-amino C–CO_2H and C–H bonds to serve as handles for C(sp^3)–C bond formation. In a concurrent study, the Molander group was able to overcome limitations inherent to transmetalation with C(sp^3) organoboron reagents by generating radicals from these reaction partners utilizing a related photoredox/nickel catalysis approach.[7]

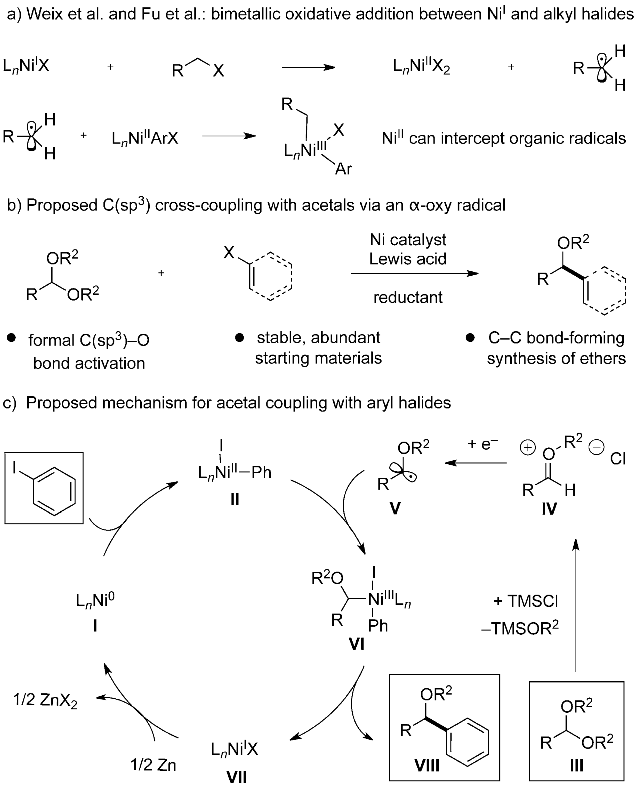

Figure 1. Nickel-catalyzed C(sp^3) cross-coupling with radicals. TMS = trimethylsilyl.

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 nickel 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 1 b). 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(sp^3)–O bond formation (e.g. Williamson ether synthesis) and remain limited because of the 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

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[**] Financial support from NIGMS (R01 GM100985) is gratefully acknowledged. We thank Brian Schaefer (Princeton University) for assistance with EPR and computational data, and Phillip D. Jeffrey (Princeton University) for X-ray structure determination.

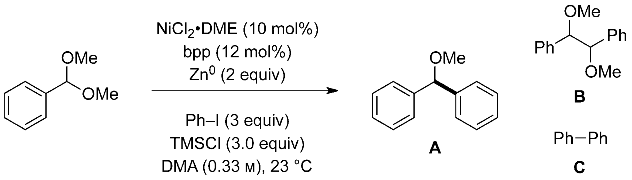
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503936.

rely on the intrinsic reactivity of the electrophilic or nucleophilic reaction partner.[11] C(sp^3)–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. Bode and co-workers have reported Lewis acid catalyzed additions of Ar-BF_3K salts to acetals.[12] However, the conditions are restricted to primary C(sp^3)–C bond formation. Molander and co-workers have shown that α-oxy BF_3K salts couple efficiently with aryl chlorides under palladium catalysis.[13] However, these nucleophiles are not readily available and the conditions for cross-coupling require high temperature and strong base. Thus, we recognized that a nickel-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 the acetal **III**, a Lewis acid, and reductant such as Zn ($E^{red}_{1/2} = -1.0$ V vs SCE in MeCN), delivering the Ni^{III} adduct **VI**. Subsequent reductive elimination would afford the dialkylether **VIII**, releasing the Ni^I species **VII**. Completion of the catalytic cycle requires turnover of the nickel catalyst by a reductant to regenerate **I** ($E^{red}_{1/2}[Ni^{II}/Ni^0] = -1.2$ V vs SCE in DMF).[15,16]

We began our investigations by exploring the coupling of benzaldehyde dimethylacetal with iodobenzene using TMSCl as a Lewis acid and Zn as a reductant (Table 1).[18] In the absence of a nickel catalyst, the acetal converts into a mixture of *rac*- and *meso*-pinacol dimers (**B**), presumably via the 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 a reductant.[17] With a catalytic amount of nickel and 3 equivalents TMSCl, cross-coupling to form the desired ether **A** was observed. However, the selectivity for **A** varied significantly depending on the identity of the ligand on nickel. 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).

Table 1: Reaction optimization studies.



Entry	Deviation from standard conditions	Yield [%][a] 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. Box = bis(oxazoline), DMA = *N*,*N*-dimethylacetamide, DME = dimethoxyethane.

The bpp ligand has seen limited application in other nickel-catalyzed cross-coupling reactions.[19] As such, we sought to elucidate the structure and properties of a bpp-ligated nickel species relevant to the catalytic reaction. Based on our proposed mechanism, we chose to prepare the nickel(I) chloride complex **1** (see **VII** in Figure 1c). Comproportionation of [Ni(cod)$_2$] and $NiCl_2$·DME in the presence of 2 equivalents of bpp provided the monomeric chloride complex **1** as dark green crystals (Figure 2a). Importantly, **1** is catalytically competent, thus delivering dialkyl ether **A** 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] The complex **1** exhibits an axial EPR signal with $g_{\parallel} = 2.262$ and $g_{\perp} = 2.070$, consistent with its formulation as a d^9 nickel(I) complex, rather than as a d^8 nickel(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 $d_{x^2-y^2}$ orbital.[17] These features are remarkably similar to those of [(terpy)NiBr] and [(terpy)NiCl], as reported by Vicic[21] and Wieghardt[22] respectively, with the exception that the terpy complexes are monomeric and square-planar in the solid state. The redox potential of [(bpp)NiCl] ($E^{red}_{1/2} = -0.8$ V vs. SCE in MeCN) is also within 200 mV 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: $E^{red}_{1/2} = -2.2$ V vs SCE in MeCN; bpp: $E^{red}_{1/2} = -0.9$ V vs SCE in MeCN), it is possible that the reaction selectivity arises at stages in the catalytic cycle wherein oxidation/reduction of nickel is ligand-based.

With optimized reaction 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 (**3**,**4**), though *ortho*-tolyl iodide (**5**) suffered from rapid formation of 2,2′-bitolyl. Both electron-rich (**7**) and electron-poor (**9**) aryl iodides coupled with equal levels of efficiency.[24] This reactivity 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, which are common in pharmaceuticals, undergo the 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

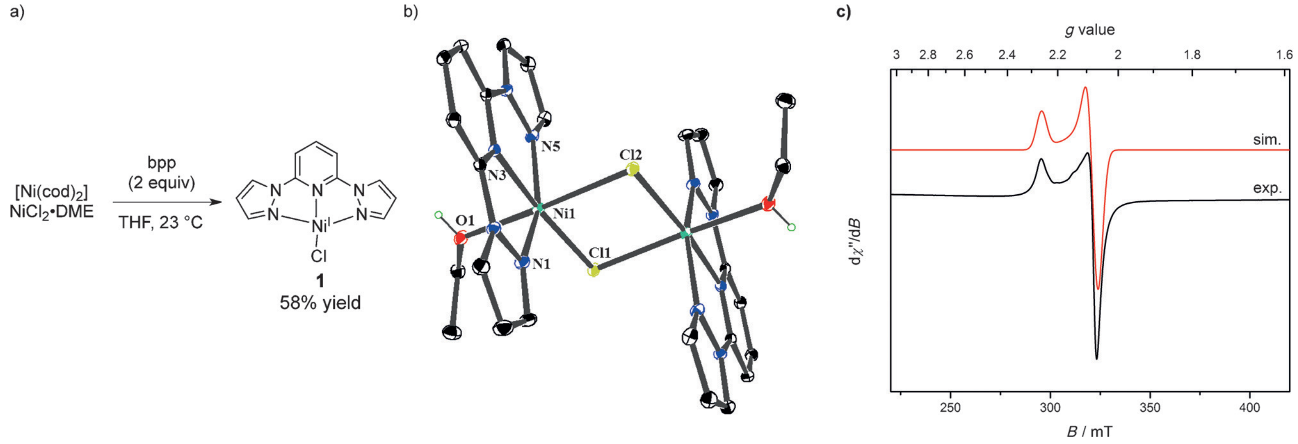
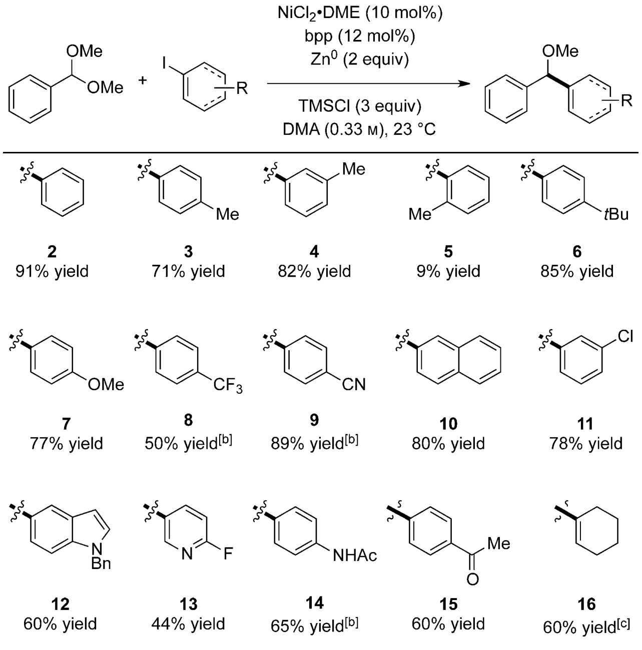


Figure 2. a) Comproportionation to form [bpp(Ni)Cl] (**1**). b) ORTEP diagram of dimeric **1**. Ellipsoids shown shown at 30% probability and H atoms omitted for clarity (except for ethanol O–H atoms). Selected bond lengths [Å]: Ni–Cl1 2.333; Ni–Cl2 2.484; Ni–N3 2.012; Ni–N1 2.009; Ni–O1 2.078. Selected 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 10 K. 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. cod = 1,5-cyclooctadiene, THF = tetrahydrofuran.

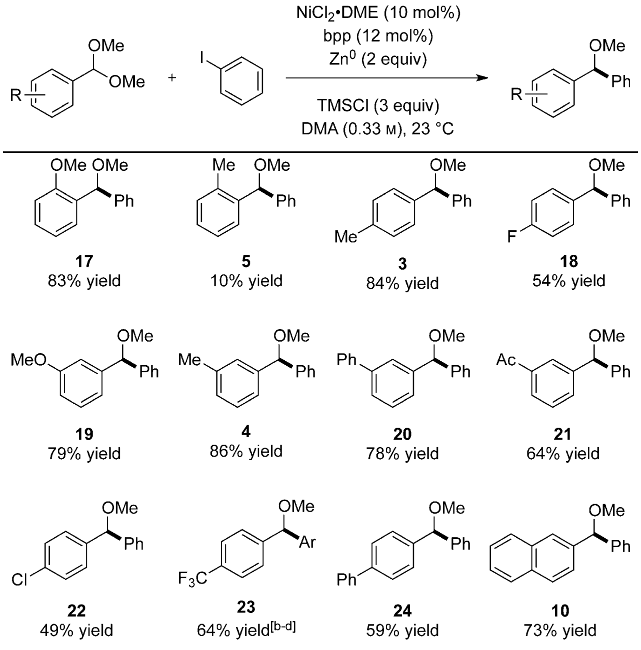
Table 2: Scope of aryl iodides.[a]



Compound	Yield
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] Yield is that of the isolated product (0.50 mmol). [b] 4.0 equiv NaBF$_4$ added. [c] Vinyl triflate was employed.

Table 3: Scope of acetals.[a]



Compound	Yield
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] Yield is that of the isolated product (0.50 mmol scale). [b] 4.0 equiv NaBF$_4$ added. [c] Reaction run at 60 °C. [d] *p*-Iodoanisole was employed as the coupling partner.

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**), electron-neutral (**4**), and electron-poor (**23**) acetals perform well under these reaction conditions. Recently, the MacMillan group 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 nickel-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 Table 2 and Table 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**, which represents the core of a number of SSRI pharmaceuticals.[9d,e] Cross-coupling of dioxolane **27** furnishes ether **28**, which possesses 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 nickel-catalyzed cross-coupling, ultimately affording tri- or diarylalkanes, which are valuable pharmacophores in their own right.[26] These results highlight opportunities to apply this C(sp^3) 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.

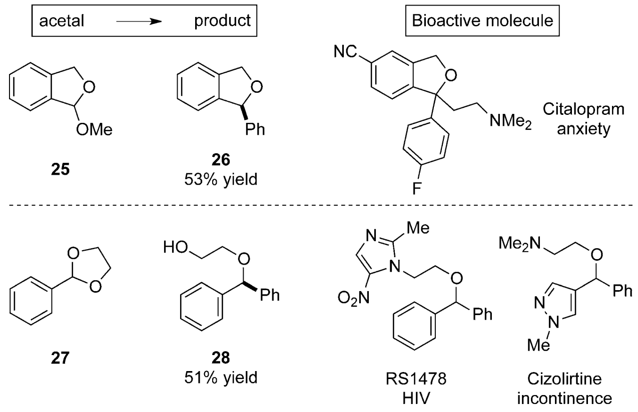


Figure 3. Access to dialkyl ether-containing bioactive molecules.

In conclusion we have demonstrated that bench-stable and abundant benzylic acetals participate in formal C(sp^3)−O cross-coupling with aryl iodides in the presence of a nickel catalyst, Lewis acid, and reductant. This mild and functional-group tolerant C−C bond-forming approach to dialkyethers provides access to a variety of acylic 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 [(bpp)nickel] complex to selectively generate the cross-coupled product.

Keywords: cross-coupling · ethers · nickel · radicals · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9876–9880
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1 does not produce the pinacol byproduct **B**. Trapping experiments with TEMPO, **A**, TMSCl, and **1** lead to bleaching of **1**. See Ref. [4,b] for a similar observation.

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Received: April 29, 2015