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CgPhen-DalPhos Enables the Nickel-Catalyzed *O*-Arylation of Tertiary Alcohols with (Hetero)Aryl Electrophiles

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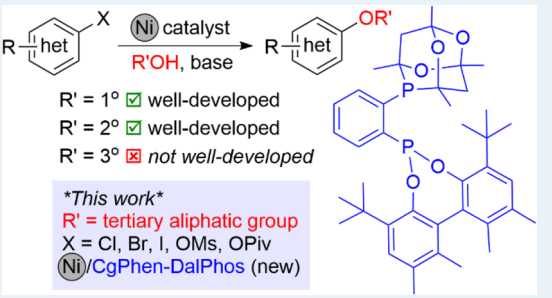
ABSTRACT: While the Ni-catalyzed cross-coupling of primary or secondary aliphatic alcohols and (hetero)aryl electrophiles is known, related cross-couplings involving tertiary aliphatic alcohols, with a broad scope, are challenging. Herein we disclose that a Ni^{II} precatalyst featuring the ligand CgPhen-DalPhos is unusual in its ability to promote the C−O cross-coupling of tertiary aliphatic alcohols with (hetero)aryl halides (Cl, Br, and I) or phenol derivatives (OMs and OPiv). An exploration of substrate scope and competition experiments help to shed light on the capabilities and reactivity preferences of this catalyst system.



KEYWORDS: *nickel, cross-coupling, tertiary alcohol, ligand design, phosphaadamantane*

The ubiquity of the C(sp^2)−O−C(sp^3) motif in active pharmaceutical ingredients, agrochemicals, and other biologically active compounds provides motivation for developing effective methods for the construction of such linkages.[1] When the reactant sp^3-carbon features a primary or secondary substitution, Williamson ether synthesis,[2] Mitsunobu chemistry,[3] and nucleophilic aromatic substitution (S_NAr)[4] provide suitably efficient routes to the desired alkyl (hetero)aryl ether. Metal-catalyzed C−O cross-coupling offers a complementary route to such ethers.[5] Particularly useful Pd[6] and base-metal (i.e., Cu[7] and Ni[8]) catalysts were reported recently for the cross-coupling of primary or secondary aliphatic alcohols and (hetero)aryl chloride or phenol derivatives, which are collectively the most inexpensive and widely available classes of commercial (hetero)aryl electrophiles.[9]

In contrast, synthetic options are more limited regarding the preparation of tertiary-alkyl (hetero)aryl ethers given that the aforementioned nonmetal-catalyzed methods (i.e., Williamson, Mitsunobu, and S_NAr) are often less effective when tertiary alkyl halides or alcohols are involved.[10,11] Within the domain of metal-catalyzed cross-coupling, only Pd-based *O*-arylation methods for the conversion of tertiary aliphatic alcohols to tertiary-alkyl (hetero)aryl ethers have been reasonably well-developed.[12] Such transformations were identified early in the field as being more straightforward than cross-couplings of primary or secondary aliphatic alcohols given that tertiary aliphatic alcohols are not prone to the β-hydride elimination processes.

Notwithstanding the utility of the aforementioned Pd-catalyzed C−O cross-couplings that lead to tertiary-alkyl (hetero)aryl ethers, there is fundamental interest in the development of efficient base-metal catalysis as an alternative to methods involving precious metals, both from a cost and sustainability point of view and because such catalysts might offer new or improved reactivity.[13] While some Ni catalysts that are capable of effecting C−O cross-couplings of primary or secondary aliphatic alcohols with (hetero)aryl chlorides have emerged,[8,14] negligible progress has been made in developing the Ni-catalyzed *O*-arylation of tertiary aliphatic alcohols after the initial report by Mann and Hartwig;[12c] in this 1997 study, only two unique *tert*-butyl aryl ethers were prepared from electron-poor aryl halides and NaO*t*Bu by the use of $Ni(COD)_2$ (15 mol %)/DPPF (30 mol %) catalyst mixtures (Figure 1).[15] As such, the development of synthetically useful Ni-catalyzed C−O cross-coupling routes to tertiary-alkyl (hetero)aryl ethers with useful scopes represents an important unmet reactivity challenge. We sought to address this deficit both from the perspective of fundamental base-metal catalyst development and, given the current interest in the incorporation of tertiary hydrocarbon groups (e.g., 1-adamantyl[16,17]) into biologically active compounds, to beneficially alter lipophilicity, absorption, metabolism, and other properties. Herein we report that the new ligand CgPhen-DalPhos is particularly effective in enabling such Ni-catalyzed C−O cross-couplings with useful scope (X = Cl, Br, I, OMs, and OPiv; Figure 1).

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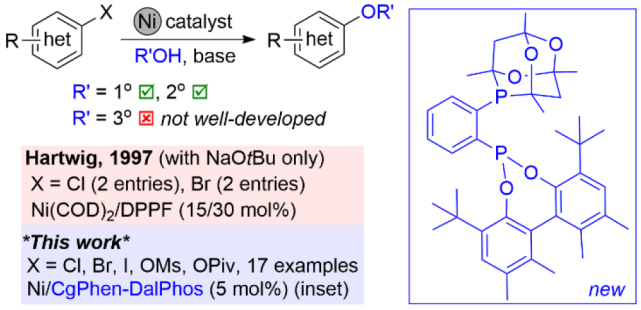
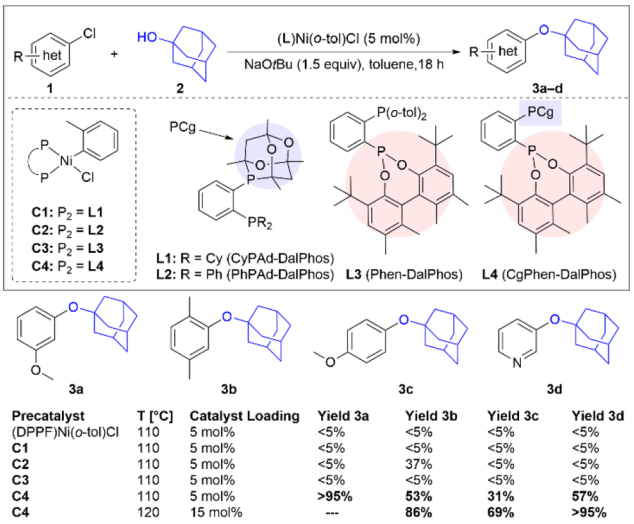


Figure 1. Nickel-catalyzed C−O cross-coupling of aliphatic alcohols (R′OH) with (hetero)aryl electrophiles.



Precatalyst	T [°C]	Catalyst Loading	Yield 3a	Yield 3b	Yield 3c	Yield 3d
(DPPF)Ni(o-tol)Cl	110	5 mol%	<5%	<5%	<5%	<5%
C1	110	5 mol%	<5%	<5%	<5%	<5%
C2	110	5 mol%	<5%	37%	<5%	<5%
C3	110	5 mol%	<5%	<5%	<5%	<5%
C4	110	5 mol%	>95%	53%	31%	57%
C4	120	15 mol%	---	86%	69%	>95%

Figure 2. Precatalyst screen for the Ni-catalyzed C−O cross-coupling of 1-adamantanol (**2**, 3.0 equiv), which leads to **3a**−**d**. Reactions were conducted at the 0.12 mmol scale (aryl halide, 0.12 M in toluene). Reported GC yields were determined based on response-factor calibrated GC data using authentic material, with the remaining mass balance corresponding to the unreacted starting material.

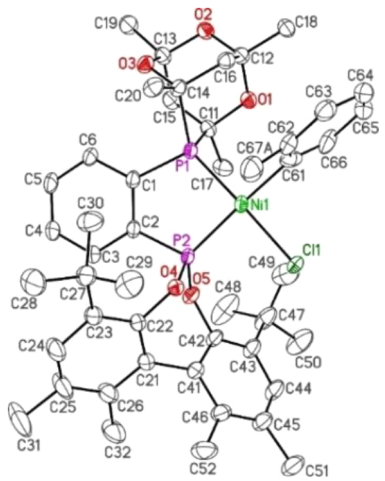


Figure 3. Crystallographically determined structure of **C4** shown with 30% displacement ellipsoids. Hydrogen atoms were removed for clarity. Selected interatomic distances (Å) and angles (°) are as follows: Ni1−P1, 2.1812(8); Ni1−P2 2.1406(9); Ni1−C61 1.9366(17); Ni1−Cl1 2.259(7); Cl1−Ni1−P2 89.2(2); Cl1−Ni1−C61 87.2(2); P1−Ni1−P2 87.34(3); P1−Ni1−C61 97.36(7).

Inspired by reactivity advances in Pd cross-coupling catalysis that have been enabled via ancillary ligand design,[18] one aspect of our research program is focused on the development of new ancillary ligand classes that reliably promote otherwise challenging Ni-catalyzed C(sp^2)−N or C(sp^2)−O cross-coupling chemistry. We envisioned that bulky and relatively electron-poor bisphosphine ligands might afford useful catalytic performance by discouraging both (bisphosphine)$_2$Ni^0 formation and comproportionation to give (bisphosphine)Ni^I species while also promoting product-forming C(sp^2)−N or C(sp^2)−O bond-reductive elimination.[19] On the basis of this strategy, we developed a family of "DalPhos" ligands that featured either phosphaadamantane (PCg, as found in PAd-DalPhos[20] and variants CyPAd-DalPhos (**L1**) and PhPAd-DalPhos (**L2**)) or bulky phosphonite (e.g., Phen-DalPhos (**L3**)[21]) donor groups. These ligands (Figure 2) have advanced the state of the art in a range of Ni-catalyzed C(sp^2)−N and C(sp^2)−O cross-coupling applications.[8a,21,22]

Building on this success, we turned our attention to identifying an effective Ni catalyst for the C−O cross-coupling of tertiary aliphatic alcohols with (hetero)aryl chlorides by conducting screening experiments. Electron-poor, *ortho*-substituted, electron-rich, and heteroaryl chloride test electrophiles were employed with 1-adamantanol as the nucleophile at practical loadings (5 mol % Ni), leading to **3a**−**d** (Figure 2). (**L**)Ni(*o*-tol)Cl precatalysts[23] were selected given their efficacy and ease-of-handling. While cross-couplings of NaO*t*Bu with a pair of electron-poor (i.e., activated) aryl chlorides that employed air- and temperature-sensitive Ni(COD)$_2$ (15 mol %)/DPPF (30 mol %) mixtures were described by Mann and Hartwig,[12c] under our screening conditions the use of (DPPF)Ni(*o*-tol)Cl[24] (5 mol %) afforded negligible conversions of **1** and **2**. Similarly, while (**L**)Ni(*o*-tol)Cl (**C1**, **L** = CyPAd-DalPhos **L1**,[8a] and **C2**, **L** = PhPAd-DalPhos **L2**[22e]) precatalysts proved effective in enabling otherwise challenging Ni-catalyzed C−O cross-couplings of primary and secondary aliphatic alcohols or sterically hindered nitrogen nucleophiles in past work, neither precatalyst proved suitable for cross-couplings of **1** and **2** despite the relationship of these nucleophiles with tertiary aliphatic alcohols. These observations highlight the apparent challenge of employing tertiary aliphatic alcohols as cross-coupling partners in Ni-catalyzed C−O cross-couplings, in contrast to the preferred nature of these substrates in analogous Pd catalysis (vide supra). Only in the specific case of **C2** leading to **3b** was the modest conversion to the product detected (37%). Similarly poor catalytic performance was observed when using the Phen-DalPhos precatalyst **C3**[21] (Figure 2).

Contemporaneous with our unsuccessful attempts to apply **DPPF**, **L1**, **L2**, and **L3** in the Ni-catalyzed *O*-arylation of tertiary aliphatic alcohols (Figure 2), we developed a new ligand, CgPhen-DalPhos (**L4**), which paired the PCg donor fragment found in **L1** and **L2** with the bulky phosphonite donor group found in **L3**. The new ligand **L4** was prepared via the lithiation of *rac*-8-(2-bromophenyl)-PCg with *n*-BuLi, followed by quenching with the chlorophosphonite derived from commercially available *rac*-5,5′,6,6′-tetramethyl-3,3′-di-*tert*-butyl-1,1′-biphenyl-2,2′-diol. The presence of chiral (racemic) PCg and phosphonite groups in **L4** gives rise to a mixture of two diastereomers (~5:1 ratio based on NMR data). In turn, the precatalyst (**L4**)Ni(*o*-tol)Cl (**C4**) was prepared; X-ray diffraction analysis of a sample of **C4**

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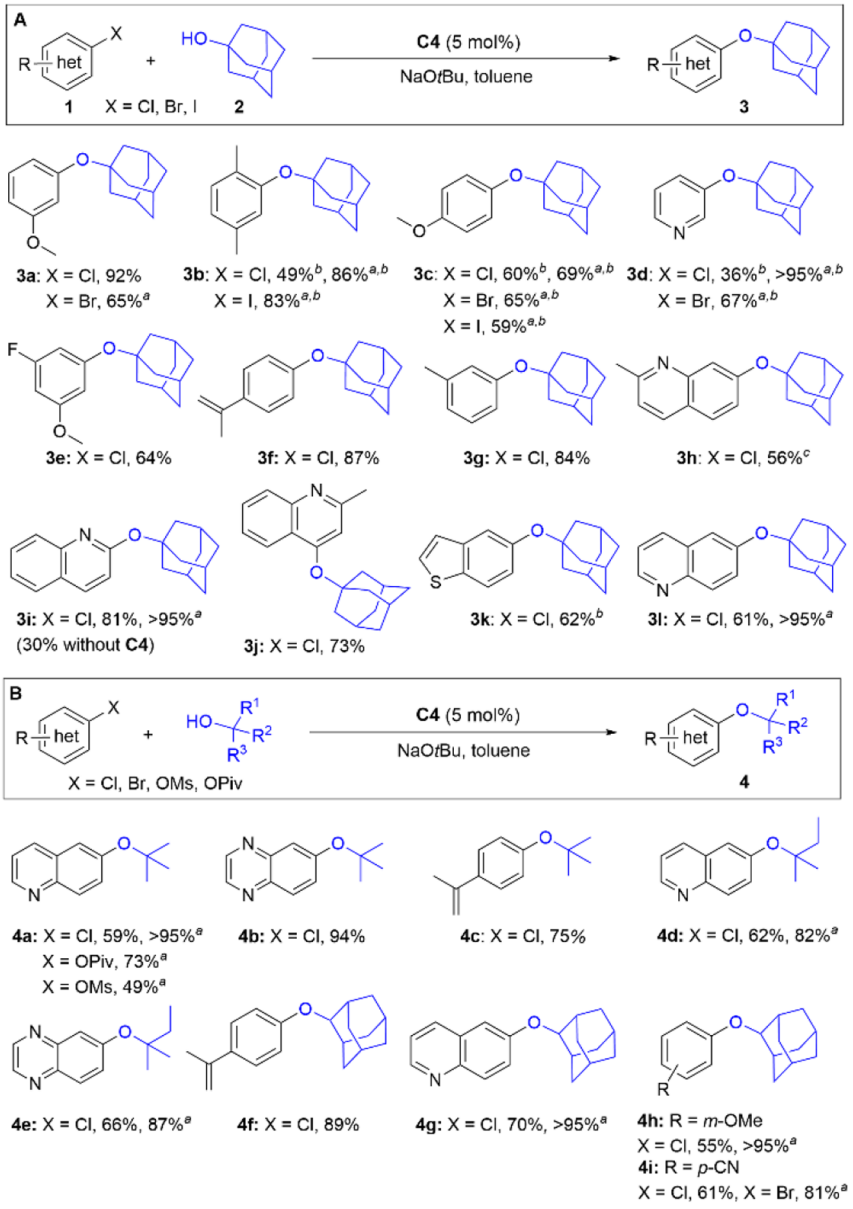

Figure 4. Scope of the Ni-catalyzed C−O cross-coupling using **C4**. Unless otherwise indicated, isolated yields are reported from reactions conducted at 110 °C on a 0.48 mmol scale (aryl halide, 0.12 M in toluene) with NaO*t*Bu (1.5 equiv) and alcohol (3.0 equiv) for 18 h (unoptimized). [a]Yield determined on the basis of response-factor-calibrated GC data using authentic material; differences between the GC and isolated yields arise from issues related to chromatographic purification (see the Supporting Information). [b]Using **C4** (15 mol %) at 120 °C. [c]Using NaO(1-Ad) (1.5 equiv) in place of NaO*t*Bu without added 1-adamantanol.

confirmed the ligand connectivity and revealed a coordination environment in this sample with *trans*-disposed halide and PCg groups (Figure 3).[25] Precatalyst **C4** performed remarkably well when deployed in the aforementioned test cross-couplings, leading to **3a−d** and affording appreciable conversion to the product in each case (Figure 2). Efforts to apply other commercially available bases (e.g., LiO*t*Bu, Cs_2CO_3, K_2CO_3, K_3PO_4, or LiHMDS) under these conditions to lead to **3a** proved unsuccessful (see Table S1), and toluene was found to be the optimal solvent among those surveyed (see Table S2). In the case of the more challenging cross-couplings featured in our screening protocol (e.g., leading to **3b−d**), higher catalyst loadings and reaction temperatures gave rise to improved product yields with **C4** (Figure 2).

Given the prima facie similarity in structure between the 1-adamantoxy and *tert*-butoxy fragments, our observed selectivity for the turnover of 1-adamantanol in the presence of potentially contending NaO*t*Bu, beyond the 2:1 ratio of these reagents used in our test reactions that led to **3a−d** (Figure 2), was surprising. While Arnett and Small[26] presented estimated pK_a (DMSO, 25 °C) values for 1-adamantanol (29.2) and *tert*-BuOH (29.4) that do not vary significantly, Bordwell and co-workers[27] reported a divergent estimate of the *tert*-BuOH pK_a (32.2) and note that the medium can influence the acidity order for aliphatic alcohols. This potential pK_a span leaves open the possibility that there *may* exist a sufficient difference in acidity between these tertiary aliphatic alcohols to rationalize the preferential deprotonation and transmetalation involving 1-adamantanol. Moreover, steric analyses by

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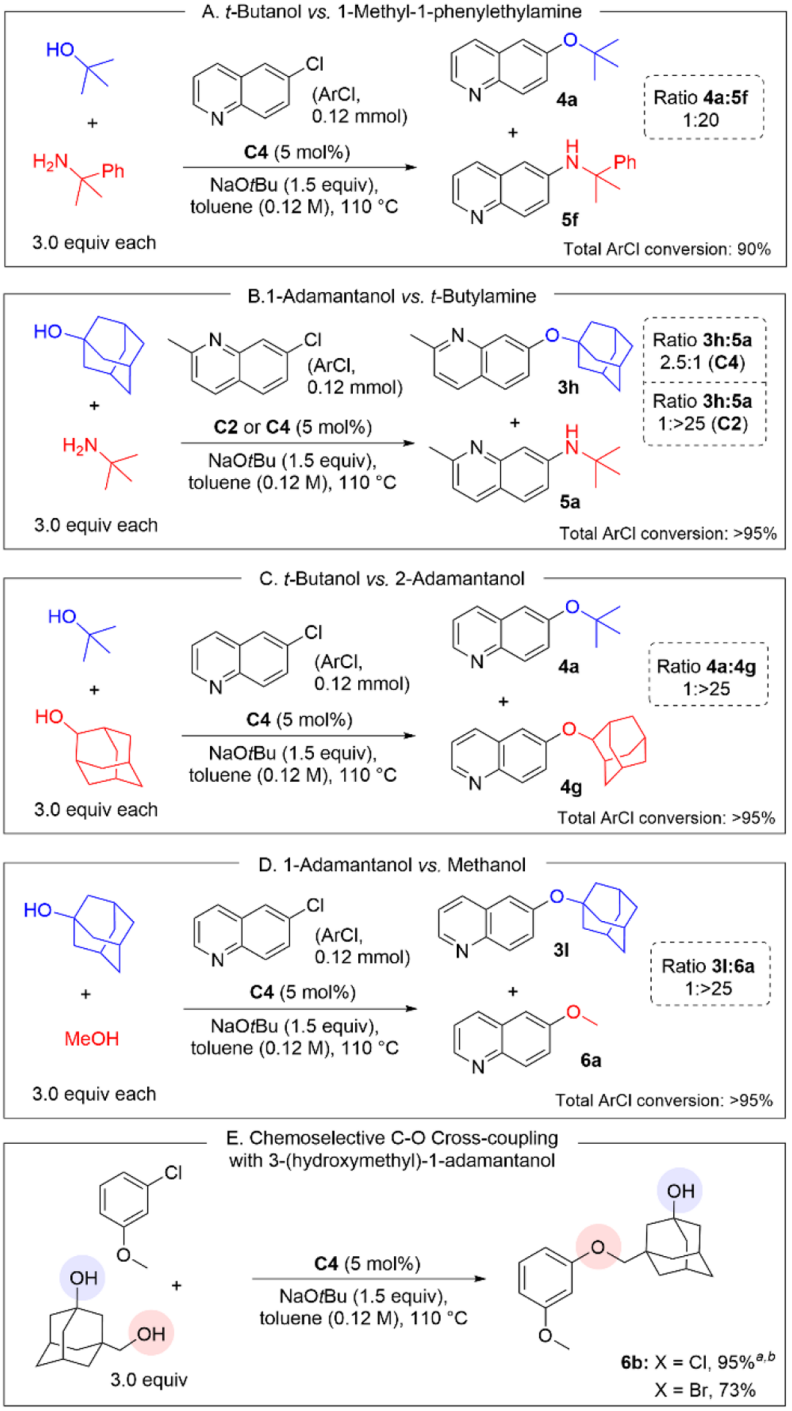

Figure 5. Competition cross-coupling experiments. Unless otherwise indicated, reported yields were determined from reactions conducted on a 0.12 mmol scale (aryl halide, 0.12 M in toluene, 18 h, unoptimized) on the basis of response-factor-calibrated GC data using authentic material. [a]Reaction conducted on a 0.48 mmol scale in aryl halide. [b]Isolated yield.

Charton[28] and a study of hindered C−C bond rotation by Lomas and Dubbois[29] support the view that the 1-adamantyl group is larger than the *tert*-butyl group. In a possible Curtin−Hammett scenario where the C−O bond-reductive elimination is rate-limiting and the exchange between (**L4**)Ni(aryl)(OR) and HOR′ species (R= *tert*-butyl, R′ = 1-adamantyl) is facile, steric effects may lead to a lower C−O bond reductive elimination barrier from (**L4**)Ni(aryl)(OR′) versus that from (**L4**)Ni(aryl)(OR), which is in keeping with the observed preferential turnover of 1-adamantanol. However, in the absence of definitive mechanistic data, the step(s) that may be selectivity-determining in the catalytic reactions disclosed herein remains uncertain.

The utility of **C4** in promoting the test C−O cross-couplings in Figure 2 prompted us to explore the reaction scope (Figure 4). The synthetically useful conversion to **3a**−**d** involving (hetero)aryl chloride test electrophiles was similarly achieved using bromide or iodide reaction partners (Figure 4A). Aryl chloride substrates featuring fluoro, methoxy, alkenyl, and methyl substitutions also performed well under our conditions

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(**3e**−**g**), as did heteroaryl chloride electrophiles based on quinaldine, quinoline, and benzothiophene core structures (**3h**−**l**). Conversely, no conversion was achieved in reactions that employed 2-chloroanisole, 2-chlorobenzotrifluoride, or 6-chloroindole. Control experiments confirmed that the uncatalyzed background reactivity (e.g., S_NAr) contributes negligibly to the observed yields herein, except for the formation of **3i** where a 30% conversion to product was observed in the absence of **C4**.

The feasibility of employing *tert*-butanol and *tert*-amyl alcohol, as well as the bulky secondary substrate 2-adamantanol, in Ni-catalyzed C−O cross-couplings with (hetero)aryl electrophiles (Cl, Br, OMs, and OPiv) using **C4** was also demonstrated, leading to **4a**−**i** (Figure 4B). In this chemistry, quinoline and quinoxaline heteroaryl electrophiles, as well as aryl chlorides featuring alkenyl, nitrile, and methoxy substitutions, proved to be effective reaction partners. Although not the primary focus of the present study, **C4** can also be employed successfully in conceptually related C−N cross-couplings involving bulky alkylamines (including 1-adamantylamine, *t*-butylamine, and cumylamine) in combination with (hetero)aryl chlorides (90−110 °C, leading to **5a**−**f**; Scheme S1).

Competition experiments were conducted to establish the preferred reactivity of **C4** (Figure 5) in terms of C−O versus C−N cross-couplings of comparably sized nucleophiles as well as C−O cross-couplings of aliphatic alcohols that differ in size. While **C4** proved to be capable of effecting both C−N and C−O cross-coupling involving sterically demanding aliphatic nucleophiles (vide supra), a clear preference for cumylamine to give **5f** over *tert*-butanol to give **4a** (20:1) was observed in competitions involving 6-chloroquinoline (Figure 5A). This is in keeping with the common trend of C−N cross-coupling being favored over analogous C−O cross-couplings, as is reflected in the preference of **C1** for the cross-coupling of octylamine over a structurally related primary aliphatic alcohol.[8a] Conversely, when the contending nucleophiles 1-adamantanol and *tert*-butylamine were explored in cross-couplings of 7-chlorquinaldine that led to **3h** and **5a**, respectively, **C4** exhibited a preference for C−O cross-coupling (2.5:1), while **C2** displayed a clear selectivity for C−N cross-coupling (Figure 5B). These observations underscore that **C4** is well-matched to the C−O cross-coupling of tertiary aliphatic alcohols relative to **C1** or **C2**, especially when the 1-adamantanol nucleophile is involved. In a competition between *tert*-butanol and 2-adamantanol when **C4** and 6-chloroquinoline were employed, which led to **4a** and **4g**, respectively, a clear selectivity for the secondary alcohol was observed (Figure 5C). Similarly, methanol outpaced 1-adamantanol as a nucleophile in the formation of **6a** over **3l** (Figure 5D). These latter two observations establish that while **C4** can promote the C−O cross-coupling of tertiary aliphatic alcohols as demonstrated in this report, primary and secondary aliphatic alcohols are preferred substrates. On this basis, we anticipated that it should be possible to selectively *O*-arylate the primary aliphatic position in 3-(hydroxymethyl)-1-adamantanol; this indeed proved to be the case when 3-X-anisole electrophiles were used (X = Cl or Br), leading to the formation of **6b** (Figure 5E).

In summary, a Ni precatalyst featuring the new ligand CgPhen-DalPhos enables the C−O cross-coupling of tertiary aliphatic alcohols and (hetero)aryl electrophiles, with a substrate scope that has not previously been demonstrated by any base-metal catalyst system. Competition experiments highlight important selectivity differences between Ni catalysts supported by this new ligand and other DalPhos ligands (e.g., PhPAd-DalPhos), thereby suggesting that CgPhen-DalPhos may offer unique catalytic performance in other sought-after cross-couplings. Future work will involve exploring the mechanism of these and related Ni-catalyzed transformations to gain insights into the role of the ligand structure in enabling transformations of the type presented herein.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c03010.

Synthetic protocols and product characterization data, including NMR spectra (PDF)

X-ray crystallographic data (CIF)

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Notes

The authors declare the following competing financial interest(s): Dalhousie University has filed patents on the DalPhos ancillary ligands and derived nickel pre-catalysts used in this work, from which royalty payments may be derived.

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