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Nickel- vs Palladium-Catalyzed Synthesis of Protected Phenols from Aryl Halides

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We report the nickel-catalyzed formation of alkyl and silyl ethers from aryl halides in one step. These ethers can act as precursors to phenols by reaction with Brønsted or Lewis acids or with fluoride. A combination of Ni(COD)$_2$ and DPPF mediates the formation of *tert*-butyl aryl, methyl aryl, and *tert*-butyldimethyl silyl aryl ethers efficiently from aryl halides and sodium alkoxides or sodium siloxides under mild reaction conditions. Reactions to form the *tert*-butyl aryl ethers mediated by nickel complexes have lower turnover numbers than the analogous palladium-catalyzed reactions. However, reactions to form methyl aryl ethers show higher yields when catalyzed by a combination of Ni(COD)$_2$ and BINAP than when catalyzed by BINAP or DPPF and palladium catalyst precursors. Similarly, the formation of silyl aryl ethers occurs in higher yields and under milder conditions when catalyzed by a combination Ni(COD)$_2$ and DPPF than when catalyzed by palladium complexes. We also report improved yields from our previous results for the palladium-catalyzed conversion of aryl halides to *tert*-butyl aryl ethers.

Introduction

Phenols are widespread in nature and are common in synthetic chemistry. New mild methods for their synthesis would, therefore, be valuable. Aryl halides would be suitable precursors to phenols if mild methods for nucleophilic aromatic substitution could be found.[1] Reactions that convert aryl halides to phenols in the absence of a catalyst require strongly basic conditions, high temperatures, and elevated pressures. For example, in industry, chlorobenzene is hydrolyzed by 10−20% NaOH(aq) at 350−400 °C under pressure.[2]

The phenolic hydroxyl group is common in natural products. Protection of the hydroxyl functionality becomes necessary in order to prevent reaction with oxidizing agents and electrophiles in the course of multistep synthesis. Many methods are available for protecting phenols, and ethers are a widely used mask.[3] Thus, new methods for the formation of phenols as readily cleavable silyl or alkyl ethers would be valuable.

The synthesis of phenols as protected alkyl aryl ethers under mild conditions from the direct reaction between aryl halides and alkoxides is limited to reactions of aryl halides with strong electron-withdrawing substituents.[1] Copper salts can mediate the formation of alkyl aryl ethers from aryl halides,[4−8] but these reactions usually require prolonged heating in strongly basic solutions and in solvents such as DMF that are difficult to remove. Improved copper-catalyzed processes have made this method more practical, but strongly basic conditions are still required.[9,10]

We recently reported the palladium-catalyzed intermolecular conversion of aryl bromides to phenols by substitution of *tert*-butoxide, followed by deprotection under acidic conditions.[11,12] The formation of alkyl aryl ether most likely occurs by reductive elimination from the palladium alkoxide complex we had isolated. We have investigated the scope of this chemistry using nickel complexes as catalysts because (1) nickel alkoxide complexes are known,[13−16] (2) first-row transition metals are often more reactive than second-row metals, (3) nickel complexes are known to catalyze cross-coupling processes through mechanisms not likely to occur with palladium complexes,[17,18] and (4) nickel is less expensive than palladium.

We now report a new mild method for the efficient conversion of aryl halides to phenols protected as alkyl or silyl aryl ethers in one step catalyzed by nickel phosphine complexes.[19] The ethers formed by this method are *tert*-butyl aryl ethers, methyl aryl ethers, and *tert*-butyldimethylsilyl aryl ethers that can all be conveniently deprotected to form phenols. We have found that Ni(COD)$_2$ and a chelating phosphine catalyze the formation of methyl aryl ethers and silyl aryl ethers in better

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[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1997.

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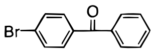
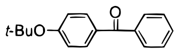
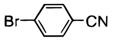
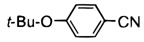
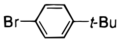
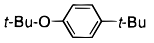
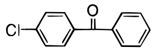
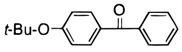
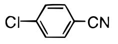
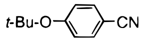
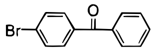
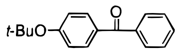
Table 1. Formation of *tert*-Butyl Aryl Ethers from Aryl Halides Catalyzed by 15 mol % Ni(COD)$_2$ and 30 mol % Ligand

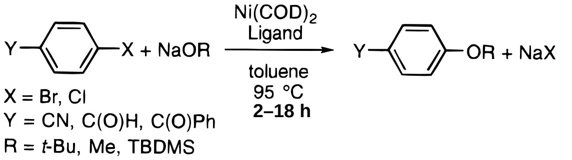
	ligand	aryl halide	product	yield
1	DPPF			$63^{a,b}$
2	DPPF			90^{c}, $58^{a,b}$
3	DPPF			< 1^{c}
4	DPPF			69^{a}
5	DPPF			70^{c}
6	DPPE			$90^{a,b}$

[a] Yield is based on isolated, purified products. [b] Isolated yield is the average of two runs. [c] Yield is determined by GC from an average of two or more runs with respect to an internal standard.

yields and under milder conditions than several palladium complexes (COD = cyclooctadiene). In the context of ether formation, a survey of nickel catalysts, a comparison with the Pd-catalyzed system, and a brief comparison between DPPF and Tol-BINAP (DPPF = 1,1′-bis(diphenylphosphino)ferrocene, Tol-BINAP = 2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl) ligands are presented.

Results and Discussion

Reactions of aryl halides and sodium alkoxides and sodium siloxides catalyzed by a combination of nickel catalyst precursor and chelating ligand provide alkyl aryl ethers or silyl aryl ethers in high yields for electron deficient aryl halides. The overall reaction is shown in eq 1. The experimental procedure for the generation of

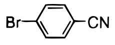
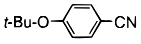
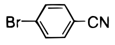
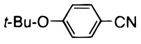
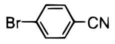
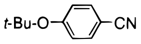
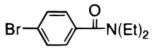
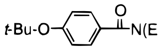
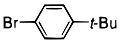
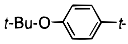
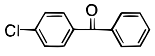
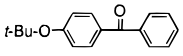
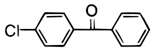
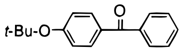
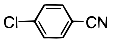
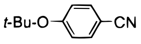


(Eq. 1)

protected phenols from aryl halides by a nickel catalyst simply involved heating a mixture of aryl halide (1 equiv), sodium alkoxide or sodium siloxide (1.2 equiv), DPPF ligand (15−30%), and Ni(COD)$_2$ (10−15%) in toluene or a mixture of methanol and toluene for 2−18 h at 95 °C. Absorption of the crude mixture onto silica gel followed by flash chromatography afforded the pure isolated alkyl ethers. Isolation of the silyl ethers by column chromatography on silica gel led to a small amount of deprotected phenol. The major side product observed in each reaction by GC/MS was the dehalogenated arene. No *tert*-butyl aryl ether or silyl aryl ether was formed in toluene solvent in the absence of the nickel catalyst or ligand as detected by GC analysis. Similarly, less than 5% of methyl aryl ether was detected by GC/MS when methanol or a mixture of methanol and toluene were used as solvent in the absence of Ni(COD)$_2$ or DPPF.

Formation of *tert*-Butyl Aryl Ethers with Nickel and Palladium Catalysts. Table 1 shows our results for the formation of *tert*-butyl aryl ethers from aryl halides catalyzed by Ni(COD)$_2$ and DPPF. Sodium counterion proved critical. Reactions with potassium *tert*-butoxide or lithium *tert*-butoxide, Ni(COD)$_2$, DPPF, and aryl halide afforded no significant amounts of ether. Like the reactions catalyzed by DPPF-ligated palladium complexes, complexes generated from the Ni(COD)$_2$ precursor mediated the formation of *tert*-butyl aryl ethers from electron deficient aryl halides. Less than 1% ether was observed by GC when electron neutral or electron rich aryl halides were used. In these reactions, the dehalogenated arene was the major product after prolonged heating. In addition to aryl bromides, Ni(COD)$_2$ and DPPF also catalyzed the conversion of electron deficient aryl chlorides to alkyl aryl ethers in good yields.[20]

Table 2. Formation of *t*-Butyl Aryl Ethers from Aryl Halides Catalyzed by DPPF and Palladium Precatalysts[a]

	pre-catalyst	aryl halide	product	yield
1	Pd(DBA)$_2$			98^{b}
2	Pd(OAc)$_2$			100^{b}, $92^{c,d}$
3	Pd(PPh$_3$)$_4$			91
4	Pd(DBA)$_2$			56^{c}
5	Pd(OAc)$_2$			**$38^{b,e}$**
6	Pd(DBA)$_2$			84^{c}
7	Pd(OAc)$_2$			89^{c}
8	Pd(DBA)$_2$			84^{b}

[a] 10 % mol pre-catalyst and 20 % mol DPPF were used in these reactions. [b] Yield is determined by GC with respect to an internal standard. [c] Yield is based on isolated, purified product. [d] Isolated yield is the average of two runs. [e] 5 % mol pre-catalyst and 6 % mol were used in these reactions.

We briefly invested the combination of Ni(COD)$_2$ and chelating ligands other than DPPF for the formation of *tert*-butyl aryl ethers. Ni(COD)$_2$ and DPPE (1,2-bis-(diphenylphosphino)ethane) catalyzed the formation of (4-*tert*-butoxyphenyl)phenylmethanone in better yield than Ni(COD)$_2$ and DPPF, but this catalyst system was not effective for the arylation of alkoxides using other aryl halides. In general, the yields for formation of *tert*-butyl aryl ether were higher for reactions involving DPPF than those involving DPPE, but the optimal metal and ligand appears to depend on the specific substrates.

Results from palladium-catalyzed conversion of aryl halides to *tert*-butyl aryl ethers are outlined in Table 2 for comparison with Ni-catalyzed systems (Table 1).[21] Pd catalysts mediated the conversion of aryl halides to *tert*-butyl aryl ethers with higher yields than Ni catalysts. Reactions that were complete using 3% palladium catalyst required 15% nickel catalyst for complete consumption of aryl halide. Reactions using 3% palladium catalyst were complete in 5 h at 95 °C while reactions with 10% palladium catalyst were complete in just 1 h at the same temperature. The yields and selectivities for reactions containing either 3% or 10% palladium catalyst were similar to each other, and reaction yields were independent of whether 1 or 2 equiv of DPPF ligand per Pd were used. The yields were the same for reactions containing either 1 or 2 equiv of alkoxide.

In addition to results presented in communication form previously, we found that bromobenzamides underwent formation of aryl ethers. This type of aryl halide is important for solid phase applications, since amides commonly link substrates to the support. Further, a combination of DPPF and Pd(OAc)$_2$ catalyzed the formation of *tert*-butyl aryl ethers with electron neutral aryl

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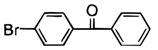
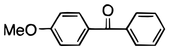
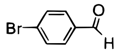
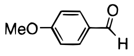
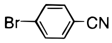
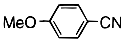
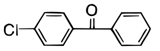
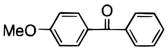
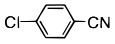
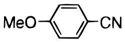
(20) The first Pd-catalyzed amination of aryl chlorides was recently published. Beller, M.; Riermeier, T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073−2079.

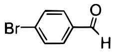
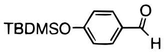
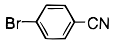
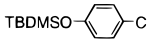
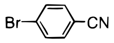
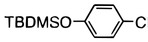
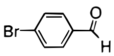
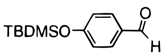
(21) We have previously reported the Pd-mediated formation of *tert*-butyl aryl ethers, ref 11. The yields in Table 2 are higher than those published in ref 11 simply due to improved isolation techniques.

Table 3. DPPF/Ni(COD)$_2$-Catalyzed Conversion of Aryl Halides to Methyl Aryl Ethers[a]

	aryl halide	product	yield
1			76[b]
2			55[b,c,e]
3			58[d]
4			81[b]
5			53[d]

[a] 15 % mol Ni(COD)$_2$ and 30 % mol DPPF were used in these reactions. [b] Yield is based on isolated, pure material. [c] Isolated yield is the average of two runs. [d] Yield is determined by GC from an average of two or more runs with respect to an internal standard. [e] 2 % of methyl 4-bromobenzoate was detected by GC and GC/MS analysis.

Table 4. Ni(COD)$_2$ and Pd(DBA)$_2$-Catalyzed Formation of *tert*-Butyldimethylsilyl Ethers from Aryl Halides Using DPPF as Ligand

	catalyst	aryl halide	product	temp (°C)[a]	yield[b]
1	15 % Ni(COD)$_2$			95	98
2	15 % Ni(COD)$_2$			95	96, 67[c,d]
3	10 % Pd(DBA)$_2$			120	49[e]
4	10 % Pd(DBA)$_2$			120	76

[a] Unless otherwise stated, reactions were complete in 2 h. [b] Yield is determined by GC from an average of two or more runs with respect to an internal standard. [c] Isolated yield from an average of 2 runs. [d] 12 % of the deprotected 4-cyanophenol was isolated. [e] Incomplete consumption of aryl halide was observed after heating 2 h. Heating the reaction for 5 h resulted in a 58 % yield with complete consumption of aryl halide.

halides at temperatures that are slightly higher than those used for reactions of electron poor aryl halides, but the yields were modest and slightly lower than those obtained previously with Tol-BINAP as ligand.[12] Surprisingly, both Pd(DBA)$_2$ (DBA = dibenzylideneacetone) and Pd(OAc)$_2$ catalyzed the conversion of some aryl chlorides to aryl ethers in good yields at 95 °C.[20] Control experiments with aryl chlorides performed simultaneously in the presence and absence of metal and ligand showed that formation of ether required the palladium catalyst in these solvent systems.

Formation of Methyl Aryl Ethers. In combination with DPPF, the nickel catalyst precursor Ni(COD)$_2$ was superior to the three palladium catalyst precursors Pd(DBA)$_2$, Pd(OAc)$_2$, and Pd(PPh$_3$)$_4$ for formation of methyl aryl ethers from aryl halides. The results for nickel-catalyzed formation of methyl aryl ethers are summarized in Table 3. The nickel-catalyzed formation of alkyl aryl ethers from NaOMe occurred in much higher yields than those catalyzed by palladium complexes. The yields of methyl aryl ether from reactions catalyzed by palladium and DPPF were less than 25% when monitored by GC, and these reactions were not pursued. The dehalogenated arene was the major product formed in the reactions catalyzed by DPPF and the palladium catalyst precursors.[22] As was the case for reactions that formed *tert*-butyl aryl ethers, reactions catalyzed by Ni(COD)$_2$ and DPPF that formed methyl aryl ethers in the presence of sodium methoxide were limited to electron deficient aryl halides. The major side product was the dehalogenated arene.

Due to the insolubility of the sodium methoxide, these reactions were conducted in the presence of methanol. Reactions conducted in pure methanol or in a 1:1 mixture of methanol and toluene gave similar yields, but reactions with a smaller amount of methanol resulted in incomplete consumption of aryl halide and increased amounts of arene product. The methanol was used directly from a commercial source, suggesting that careful elimination of water and air is not necessary for this chemistry to occur.

Uncatalyzed formation of methyl aryl ethers using 4-bromobenzonitrile were studied in various solvents in order to compare these reactions to those catalyzed by nickel complexes in a combination of untreated methanol and toluene. Reactions conducted in methanol solvent in the absence of metal or ligand resulted in only 5% yield of the methyl aryl ether when heated for 48 h at 95 °C. Analogous reactions conducted in anhydrous NMP solvent resulted in the formation of the methyl aryl ether in 95% yield by GC after heating for 17 h at 55 °C. The uncatalyzed arylation of alcohols and the need for anhydrous solvents in these uncatalyzed reactions has been discussed recently.[12] Thus, the nickel-catalyzed reactions allow for the conversion of electron deficient aryl halides to methyl aryl ethers in volatile, nonpolar solvents.

Formation of Silyl Aryl Ethers. We also investigated the use of sodium siloxides in the nickel-mediated formation of silyl aryl ethers from aryl halides. Reactions of aryl halide and sodium trimethylsiloxide, sodium triethylsiloxide, or sodium triphenylsiloxide catalyzed by a combination of Ni(COD)$_2$ and DPPF did not form silyl aryl ether. However, excellent yields of *tert*-butyldimethylsilyl aryl ether were observed by GC for the reaction of sodium *tert*-butyldimethylsiloxide (NaOTBDMS) and electron deficient aryl halides catalyzed by Ni(COD)$_2$ and DPPF (Table 4). Attempts to isolate the *tert*-butyldimethylsilyl aryl ethers by column chromatography resulted in some hydrolysis of the silyl ether to generate phenol. Thus, we report yields determined by GC for all of the reactions of NaOTBDMS. Nevertheless, isolated yields were high. An average isolated yield for the reaction between NaOTBDMS and bromobenzonitrile was 67% (12% of the deprotected phenol was also isolated).

In addition to the combination of Ni(COD)$_2$ and DPPF, the combination of DPPF and Pd(DBA)$_2$ also mediated the formation of silyl aryl ethers. However, yields for the reactions catalyzed by Ni(COD)$_2$ and DPPF were higher, and the nickel-catalyzed reactions occurred at lower temperatures and in shorter reaction times. For example, Ni(COD)$_2$ and DPPF mediated the formation of silyl aryl ethers in greater than 95% yield at 95 °C in 2 h, but less than 10% of the silyl ether was observed under these conditions when a combination of DPPF and Pd(DBA)$_2$ were used as the catalyst. Instead, the palladium-catalyzed formation of silyl aryl ethers in 2 h required heating at 120 °C. Reaction temperature proved important to the reaction yield, since prolonged heating of the silyl aryl ether product resulted in its slow decomposition. Thus, nickel catalysts are not only better than palladium catalysts for formation of methyl aryl ethers from aryl halides but also for the analogous formation of silyl aryl ethers.

Survey of Nickel Precursors. A survey of several potential nickel catalyst precursors showed that Ni(COD)$_2$ was superior to other Ni(0) sources and to L$_2$Ni(II) complexes. Three Ni(0) catalyst precursors, Ni(COD)$_2$, Ni(CO)$_2$(PPh$_3$)$_2$, and Ni(PPh$_3$)$_4$, were heated in the presence of DPPF, sodium alkoxide, and aryl halide. The

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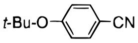
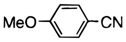
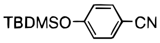
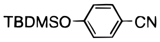
(22) Helquist, P.; Zask, A. *J. Org. Chem.* **1978**, *1978*, 1619−20.

Table 5. Comparison of Tol-BINAP and DPPF with $Ni(COD)_2$ and $Pd(DBA)_2$ Catalyzed Formation of Alkyl and Silyl Ethers

	catalyst	NaOR	product	GC yield[a]	
				Tol-BINAP	DPPF
1	12 % - 15 % $Ni(COD)_2$	NaO-*t*-Bu	 *t*-Bu-O–C₆H₄–CN	38[b,c]	84
2	11 % - 15 % $Ni(COD)_2$	NaOMe	 MeO–C₆H₄–CN	84	58
3	15 % $Ni(COD)_2$	NaOTBDMS	 TBDMSO–C₆H₄–CN	75[b,d]	96
4	10 % $Pd(DBA)_2$	NaOTBDMS	 TBDMSO–C₆H₄–CN	75[e]	49[b,e,f]

[a] Yields were determined by GC from an average of two or more runs with respect to an internal standard. Unless otherwise stated, yields were obtained after heating the reactions for 2 h at 95 °C. [b] Incomplete consumption of aryl halide was observed after 2 h. [c] Reactions were complete after 5 h, giving a 45 % yield for an average of two runs. [d] After heating the reactions for 5 h, the reaction gave a 59 % yield for an average of two runs. The decrease in yield is due to decomposition of the silyl aryl ether upon prolonged heating. [e] Reactions were heated at 120 °C for 2 h. [f] Reaction was complete after 5 h, giving a 58 % for an average of two runs.

reaction containing $Ni(COD)_2$ showed the fastest rate and best selectivity for converting 4-bromobenzophenone to (4-*tert*-butoxyphenyl)phenylmethanone. In 12 h at 95 °C, the ratio of aryl halide:arene:ether determined by GC were 0:1:11 for reactions involving $Ni(COD)_2$, 2:1:3 for those involving $Ni(CO)_2(PPh_3)_2$, and 13:3:1 for those involving $Ni(PPh_3)_4$.

A combination of the five Ni(II) catalyst precursors, $Ni(PPh_3)_2Cl_2$, $Ni(DPPF)Cl_2$, $Ni(DPPP)Cl_2$ (DPPP = 1,3-bis(diphenylphosphino)propane)), $Ni(acac)_2{\cdot}10H_2O$, and $Ni(OAc)_2{\cdot}4H_2O$, and DPPF (or DPPP in the case of $Ni(DPPP)Cl_2$), were tested in similar fashion for reaction of 4-bromobenzophenone with NaO-*t*-Bu. Reactions involving $Ni(DPPF)Cl_2$, $Ni(DPPP)Cl_2$, $Ni(acac)_2{\cdot}10H_2O$, and $Ni(OAc)_2{\cdot}4H_2O$ produced less than 5% aryl ether, as determined by GC, and left a majority of the starting aryl halide unreacted after the solution was heated for 12 h at 95 °C. A combination of 15% $Ni(PPh_3)_2Cl_2$ and 30% DPPF converted half of the aryl halide to ether after the solution was heated for 2 h at 95 °C, and no further reaction occurred after an additional 12 h. Reactions employing 5% $Ni(COD)_2$ and 10% ligand did not completely consume the aryl halide after 20 h at 95 °C. There was no significant difference in selectivity or yield in reactions containing 10% or 15% nickel precatalyst although the reactions with 15% $Ni(COD)_2$ were faster. Again, the reaction yields for formation of *tert*-butyl and silyl aryl ethers were not dependent on whether a 1:1 or 2:1 ratio of ligand to catalyst was used. However, a 2:1 ratio of ligand to $Ni(COD)_2$ gave higher yields than a 1:1 ratio for formation of methyl aryl ethers.[23]

Comparison of DPPF and Tol-BINAP: Optimized Catalysts for Formation of *tert*-Butyl, Methyl, and Silyl Aryl Ethers. Table 5 shows the results for a brief comparison of the reactions involving Tol-BINAP and DPPF in conjunction with $Ni(COD)_2$ as catalyst for formation of alkyl and silyl ethers. Buchwald recently published the use of Tol-BINAP or BINAP and $Pd_2(DBA)_3$ for the synthesis of aryl ethers,[12] oxygen-containing heterocycles,[24] aminopyridines,[25] and aryl amines.[26] For the nickel-catalyzed formation of *tert*-butyl aryl ethers, reactions involving a combination of $Ni(COD)_2$ and DPPF gave higher yields of *tert*-butyl ether than did reactions involving Tol-BINAP. Thus, the optimal nickel-containing catalyst at this time for formation of *tert*-butyl aryl ethers is a combination of DPPF and $Ni(COD)_2$. However, turnover numbers in the nickel-catalyzed formation of *tert*-butyl aryl ethers are lower than those for analogous reactions catalyzed by palladium complexes. Thus, palladium complexes are preferred over nickel systems for formation of *tert*-butyl aryl ethers.

As stated above, the formation of methyl and silyl aryl ethers occurs in higher yields for nickel catalysts than for palladium catalysts. The formation of methyl aryl ethers occurred in higher yields when catalyzed by the combination of $Ni(COD)_2$ and Tol-BINAP than when catalyzed by the combination of DPPF and $Ni(COD)_2$. Thus, the most effective group 8 catalyst for formation of methyl aryl ethers from aryl halides at this time is a combination of BINAP and $Ni(COD)_2$.

At this time, the most effective catalyst for formation of *tert*-butyldimethyl silyl ethers from aryl halides is DPPF and $Ni(COD)_2$. The more hindered NaOTBDMS appeared to require a sterically less demanding ligand. Reactions between aryl halides and this siloxide catalyzed by $Ni(COD)_2$ and Tol-BINAP required longer reaction times and afforded lower yields of *tert*-butyldimethylsilyl ether than did reactions with $Ni(COD)_2$ and DPPF. Similar rates and yields for the formation of silyl aryl ether were observed in reactions with Tol-BINAP or DPPF and $Pd(DBA)_2$, but these reactions occurred in lower yields than those catalyzed by DPPF and $Ni(COD)_2$.

Conclusion

In short, we have shown that $Ni(COD)_2$ can catalyze the formation of both alkyl and silyl aryl ethers with electron deficient aryl halides in arene solvents or a mixture of arene and alcohol. For the formation of methyl and silyl aryl ethers, the yields of the nickel-catalyzed chemistry are higher than those for analogous reactions catalyzed by DPPF and Tol-BINAP-ligated palladium. Our results show that the selection of catalyst for a specific set of reagents may require one to test a variety of metal ligand systems until the mechanistic aspects of both palladium- and nickel-catalyzed etherations is better understood. We plan to pursue mechanistic studies as a means to address these issues of catalyst choice.

Experimental Section

General Methods. All reagents were weighed in a drybox under N_2. Reagent weights have errors of ±0.2 mg using a microbalance and antistatic bar. Unless otherwise stated, all solvents were dried with sodium metal and benzophenone prior to use. Aryl halides and sodium alkoxides were used as obtained from commercial suppliers without further purification. GC yields were calculated with respect to the response factors of trimethoxybenzene or naphthalene as internal standards.

General Procedure for the Isolation of Alkyl and Silyl Aryl Ethers: (4-*tert*-Butoxyphenyl)phenylmethanone (1) from 4-Bromobenzophenone (2) Catalyzed by $Ni(COD)_2$ and DPPF. To a screw capped vial were added 17.0 mg of $Ni(COD)_2$ (0.0618 mmol), 68.5 mg of DPPF (0.124 mmol), 44.0 mg of sodium *tert*-butoxide (0.458 mmol), and 100.3 mg of 4-bromobenzophenone (0.3843 mmol). To this solid mixture was added 4 mL of toluene. The vial was capped under N_2 and heated in an oil bath at 95 °C for 18 h. After being cooled to room temperature, the crude mixture was adsorbed onto silica gel and the product was isolated in 67% yield by column chromatography eluting with 30:1 hexanes/ethyl ether to

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(23) The yields in Tables 1−2 and 4−5 were conducted using a 2:1 ratio of ligand to catalyst but it was discovered later that a 1:1 ratio of ligand to catalyst gave similar yields by GC.

(24) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333−10334.

(25) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240−7241.

(26) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.

produce a pale yellow liquid: ^{1}H NMR (CDCl$_3$) δ 1.44 (s, 9H), 7.05 (d, J = 8.6 Hz, 2H), 7.52 (m, 3H), 7.77 (d, J = 8.6 Hz, 4H); ^{13}C NMR (CDCl$_3$) δ 28.9, 79.6, 122.2, 128.2, 129.8, 131.69, 131.72, 132.0, 138.1, 160.0, 195.8; MS m/z 254; HRMS calcd for $C_{17}H_{18}O_2$ 254.1307, found 254.1307.

(4-*tert*-Butoxyphenyl)phenylmethanone (1) from 4-Chlorobenzophenone (3) Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 95 °C for 10 h gave a 69% yield of the product after silica gel chromatography eluting with 30:1 pentane/ethyl ether.

1 from 2 Catalyzed by Ni(COD)$_2$ and DPPE. Reaction at 95 °C for 14 h gave 93% yield of the product after silica gel chromatography eluting with 30:1 hexanes/ethyl ether.

4-Methoxybenzophenone (4) from 2 Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 80 °C for 16 h gave 76% yield of the product after silica gel chromatography eluting with 30:1 pentane/ethyl ether. The spectroscopic data of the product were identical to those of commercial material (Aldrich).

4 from 3 Catalyzed by Ni(COD)$_2$ and DPPF. Reaction in a mixture of methanol/toluene (2 mL/2 mL) at 105 °C for 12 h gave an 81% yield of the product after silica gel chromatography eluting with 30:1 pentane/ethyl ether.

***p*-Anisaldehyde (5) from 4-Bromobenzaldehyde (6) Catalyzed by Ni(COD)$_2$ and DPPF.** Reaction in a mixture of methanol/toluene (1 mL/3 mL) at 70 °C for 2 h gave a 61% yield of the product after silica gel chromatography eluting with 30:1 hexanes/ethyl acetate. The spectroscopic data of the product were identical to commercial material (Aldrich).

4-(*tert*-Butyldimethylsiloxy)benzonitrile (7) from 8 Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 95 °C for 2 h gave a 69% yield of the product[27] after silica gel chromatography eluting with 30:1 hexanes/ethyl ether: ^{1}H NMR (CDCl$_3$) δ 0.20 (s, 6H), 0.95 (s, 9H), 6.86 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ −0.43, 18.3, 25.6, 104.7, 119.3, 121.0, 124.1, 159.8. After subsequent elution with 1:1 hexanes/ether, 4-cyanophenol was isolated in 12% yield.

4-*tert*-Butoxybenzonitrile (9) from 4-Bromobenzonitrile (8) Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 100 °C for 17 h gave 59% yield of the product after silica gel chromatography eluting with 20:1 hexanes/ethyl acetate.

9 from 8 Catalyzed by Pd(OAc)$_2$ and DPPF. Reaction at 120 °C for 12 h gave a 94% yield of the light yellow product after silica gel chromatography eluting with 30:1 hexanes/ethyl ether: ^{1}H NMR (CDCl$_3$) δ 1.41 (s, 9H), 7.03 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 28.8, 80.2, 105.7, 119.1, 123.0, 133.4, 159.9; MS m/z 175; HRMS calcd for $C_{11}H_{13}NO$ 175.0997, found 175.0998.

1 from 3 Catalyzed by Pd(OAc)$_2$ and DPPF. Reaction at 95 °C for 12 h gave an 89% yield of the product after silica gel chromatography eluting with 30:1 hexanes/ethyl ether.

1 from 3 Catalyzed by Pd(DBA)$_2$ and DPPF. Reaction at 110 °C for 36 h gave an 84% yield of the product after silica gel chromatography eluting with 30:1 pentane/ethyl ether.

N1,N1-Diethyl-4-*tert*-butoxybenzamide from N1,N1-Diethyl-4-bromobenzamide Catalyzed by Pd(DBA)$_2$ and DPPF. Reaction at 120 °C for 13 h gave a 56% yield of the product after silica gel chromatography eluting with 3:5 hexanes/ethyl acetate. Anal. Calcd for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.45; H, 9.22; N, 5.48.

General Procedure for Obtaining the GC Yield for the Formation of Alkyl and Silyl Aryl Ethers. 1 from 2 Catalyzed by Ni(COD)$_2$ and DPPF. To a screw capped vial were added 2.2 mg of Ni(COD)$_2$ (0.0080 mmol), 9.6 mg of DPPF (0.017 mmol), 8.0 mg of sodium *tert*-butoxide (0.083 mmol), 10.0 mg of 4-bromobenzophenone (0.038 mmol), and 9.3 mg (0.055 mmol) of trimethoxybenzene. To this solid mixture was added 1.6 mL of toluene. The vial was capped under N$_2$ and heated in an oil bath at 95 °C for 2 h. After the solution was cooled to room temperature, 0.5 μL of the crude reaction was injected into the GC. The GC yield of the product was 89% after correcting for the response factor of the product with respect to the trimethoxybenzene internal standard. The response factor was obtained from isolated, purified product. All GC yields reported in the tables are an average of two or more runs.

9 from 4-Chlorobenzonitrile (10) Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 95 °C for 17 h gave the product in 72% yield as determined by GC analysis.

4-Methoxybenzonitrile (11) from 8 Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 95 °C for 1.7 h gave the product in 59% yield and benzonitrile in a 40% yield as determined by GC analysis. The response factor of the product was determined from material obtained from Aldrich.

11 from 10 Catalyzed by Ni(COD)$_2$ and DPPF. Reaction in methanol at 95 °C for 2 h gave the product in 48% yield determined by GC analysis.

4-(*tert*-Butyldimethylsiloxy)benzaldehyde (12) from 6 Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 95 °C for 2.8 h gave the product in a 100% yield by GC analysis. The response factor of the product was obtained from the isolated material. The spectroscopic data of the product were identical to that reported previously.[28]

7 from 8 Catalyzed by Ni(COD)$_2$ and DPPF. Reaction at 95 °C for 2.7 h gave the product in 97% yield as determined by GC analysis.

12 from 6 Catalyzed by Pd(DBA)$_2$ and DPPF. Reaction at 120 °C for 2.3 h gave the product in 79% yield as determined by GC analysis.

7 from 8 Catalyzed by Pd(DBA)$_2$ and DPPF. Reaction at 120 °C for 2 h gave the product in a 47% yield with 13% of the aryl halide remaining as determined by GC analysis. Complete reaction occurred after the solution was heated for 5 h, and the yield of the product after this time was 59% as determined by GC analysis.

9 from 8 Catalyzed by Pd(PPh$_3$)$_4$ and DPPF. Reaction at 95 °C for 2 h gave the product in 91% yield as determined by GC analysis.

9 from 8 Catalyzed by Pd(DBA)$_2$ and DPPF. Reaction at 95 °C for 2 h gave the product in 98% yield as determined by GC analysis.

9 from 8 Catalyzed by Pd(OAc)$_2$ and DPPF. Reaction at 95 °C for 2 h gave the product in 100% yield as determined by GC analysis.

13 from 14 Catalyzed by Pd(OAc)$_2$ and DPPF. Reaction at 100 °C for 35 h gave the product in 38% yield as determined by GC analysis.

9 from 10 Catalyzed by Pd(DBA)$_2$ and DPPF. Reaction at 95 °C for 17 h gave the product in 82% yield by GC analysis.

9 from 8 Catalyzed by Ni(COD)$_2$ and Tol-BINAP. Reaction at 95 °C for 2 h gave the product in 40% yield as determined by GC analysis with 31% of the starting aryl halide remaining. After being heated for 5 h, the reaction gave the product in 47% yield by GC analysis with 17% of the starting aryl halide remaining.

11 from 8 Catalyzed by Ni(COD)$_2$ and Tol-BINAP. Reaction at 95 °C for 2 h gave the product in 91% yield as determined by GC analysis.

7 from 8 Catalyzed by Ni(COD)$_2$ and Tol-BINAP. Reaction at 95 °C for 2 h gave the product in 76% yield determined by GC with 17% of the starting halide remaining. After being heated for 5 h, the reaction gave the product in 59% yield by GC analysis with 6% of the starting aryl halide remaining. The decrease in yield is due to decomposition of the product upon prolonged heating.

7 from 8 Catalyzed by Pd(DBA)$_2$ and Tol-BINAP. Reaction at 120 °C for 2 h gave the product in 85% yield as determined by GC analysis.

General Procedure for the Formation of Sodium Siloxides. A slight excess of silanol was added dropwise to a pentane solution of freshly cut sodium metal. The reaction was stirred for 12 h at room temperature at which time all the sodium metal was consumed. The remaining pentane mixture was evaporated to dryness, and the resultant white

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[27] Saunders, D. G. *Synthesis* **1988**, *5*, 377−379.

[28] Swenton, J. S.; Carpenter, K.; Chen, Y.; Kerns, M. L. *J. Org. Chem.* **1993**, *58*, 3308−3316.

product was rinsed twice with pentane to remove the excess silanol. The white product was dried under vacuum for 12 h.

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Note Added in Proof: Concurrent work on nickel-catalyzed amination recently appeared: Wolf, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058.

Supporting Information Available: Full experimental details with quantities of reagents employed (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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