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Aryl Ethers from Arenediazonium Tetrafluoroborate Salts: from Neat Reactions to Solvent-mediated Effects*

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A general procedure for the synthesis of various aryl ethers via the thermal decomposition of benzenediazonium tetrafluoroborate salts is described. Studies performed in neat alcohol at 60°C gave aryl ethers in yields ranging from 0–73%. Upon completion of a series of reactions, the effect of solvent was explored to expand rhe scope and relevance of this procedure. It was found that even solvents that are traditionally non-nucleophilic gave rise to products including bi-aryls and N-aryl acetamides. The utilization of an ionic liquid, 1-butyl-4-methylpyridinium tetrafluoroborate, resulted in yields comparable to reactions performed in neat alcoholic solvents.

INDEX DESCRIPTORS: synthesis, undergraduate research, benzenediazonium salts, aryl ether, aryl cation.

The use of arenediazonium salts in organic synthesis is a venerable art with a myriad of examples. The first reaction of this type involved the displacement of the diazonium group with iodide to yield the corresponding iodoarene. (Griess 1864) The reactions of these systems usually can fall into one of four mechanistic categories, although sometimes the lines are blurred. One process utilizes a free-radical mechanism derived from homolytic cleavage of the carbon-nitrogen bond on the salt. (Galli 1988) Two of the more recognized reactions that proceed via this pathway are the Sandmeyer (Sandmeyer 1884) and Meerwein (Meerwein, et. al. 1939) reactions. A number of electrophilic processes also exist and have been used to prepare a vast array of azo compounds when the terminal nitrogen is the site of electrophilic attack. Compounds that are prepared by this method are typically used as dyes and, when properly functionalized, as pH indicators. The lability of the carbon-nitrogen bond has also opened up a class of reactions involving the use of transition metals. Examples of this are the preparation of mixed anhydrides (Kikukawa, Kono, et. al. 1981) and the arylation of olefins (Kikukawa, Maemura, et. al. 1981) using palladium (0).

The system studied in this paper follows the final mechanistic class of reactions which involve heterolytic cleavage of the carbon-nitrogen bond. These processes have been shown to proceed through an intermediate approximating a very unstable aryl cation. To date, numerous reactions using this pathway have been performed as a class of nucleophilic aromatic substitution reactions. One well known example of this type of reaction is the Schiemann reaction (Balz, et. al. 1927; Swain, Rogers 1975) which, at elevated temperatures, is used to prepare aryl fluorides. Additionally, solvolysis reactions performed neat with water, acetic acid, trifluoromethyl sulfonic acid, thiols, and a few select alcohols have been performed to yield phenols (Lewis 1958), acetates (Haller, et. al. 1933), triflates (Yoneda, et. al. 1991), thioethers (Abeywickrema, et. al. 1986) and ethers, which are looked at below, respectively.

In our study, we want to develop a broad methodology for the formation of aryl ethers through thermal decomposition of arenediazonium salts. Though the conversion of an arenediazonium salt to a phenol in water proceeds quite readily, viable examples of their reaction with corresponding alcohols are not abundant. In our literature search, the examples we found dealt primarily with the mechanistic aspects of this reaction and not methodology. In most cases, only very polar alcohols were utilized with one exception where amyl and isoamyl alcohols were employed (Waring and Abrams, 1941). In one example, methanol was reacted at room temperature for two days with benzenediazonium tetrafluoroborate to give anisole with a trace of fluorobenzene. (Swain, Sheats, et. al 1975) Another study looked at two polyfluorinated alcohols, 2,2,2-trifluoroethanol and 1,1,1,3,3,3-Hexafluoro-2-propanol, and formed their corresponding aryl ethers in low to moderate yields by heating at reflux in neat solvent with an arendiazonium tetrafluoroborate salt. (Gasper, et. al. 1995) More recently, the thermal decomposition rates for arenediazonium tetrafluoroborate salts have been investigated in a number of solvents including water, ethanol and perfluorinated alcohols at room temperature. (Canning, et. al. 1999)

The most elaborate work done with aryl ethers was carried out in the 1950's by DeTar and coworkers (DeTar and Turetzky 1955, DeTar and Turetzky 1956, DeTar and Kosuge 1958). In this work, methanol was reacted with a variety of arenediazonium salts. They found that two reaction pathways were observed, S_N1 or reduction, depending on the substrate and reaction conditions. Results from our work correspond to and expand upon these observations.

Typically, aryl ethers are formed via alkylation of phenolate anions akin to the classical Williamson ether synthesis. Many variations of this protocol exist ranging from Mitsunobu-like conditions (Lepore, et. al. 2003) to fluorous-phase techniques. (Jana, et. al. 2003) While this pathway is quite attractive, limitations are seen when using electrophiles that are not primary due to competitive elimination (E2) pathways. Many of the more contemporary syntheses of aryl ethers involve the use of catalytic

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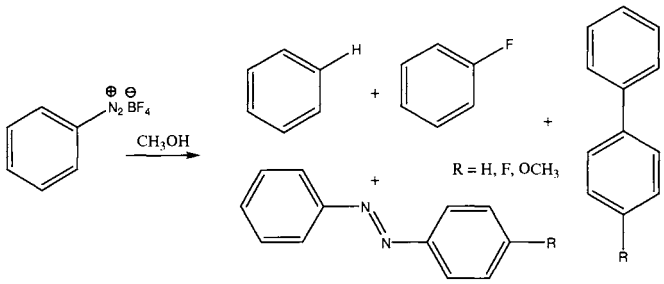


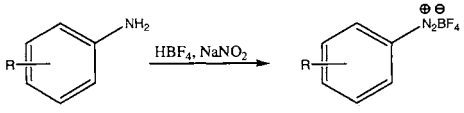
Scheme 1. Possible side products for the thermal decomposition of an arenediazonium salt in methanol.

metals including copper (Wolter, et. al. 2002; Manbeck, et. al. 2005) and palladium. (Anderson, et. al. 2006; Parrish, et. al. 2001) While these methods allow for the synthesis of substituted ethers, most require temperatures at or exceeding 100°C in addition to varying amounts of catalyst (up to10%). Because our proposed method is an umpolung to the Williamson method, and milder than the transition metal catalyzed procedures, we feel this work could complement these existing protocols. An added impetus for the development of this methodology is to exude control over a classical reaction that is riddled with possible side-products. A list of some of the possible side products are shown in Scheme 1.

RESULTS AND DISCUSSION

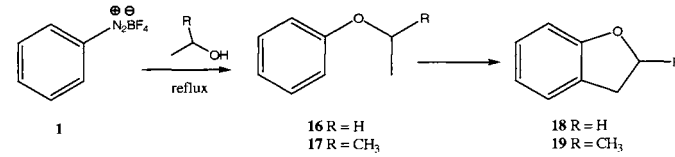
The first step in our work was the generation of a good cross section of arenediazonium salts. Though a variety of counter-anions were explored including chloride, sulfamate, hexafluorophosphate and hexafluorosilicate, we chose tetrafluoroborate salts due to their ease in preparation and isolation coupled with fairly long shelf life when stored cold under an inert atmosphere. Using literature procedures, (Dunker, et. al. 1936) we prepared a number of salts as shown (Scheme 2). As can be seen, we chose a number of 3- and 4- substituted amines with varying electronics. At this stage we wanted to limit 2-substituted amines in all but a few cases as they are isoelectronic to 4-substitution and we wanted to limit variables concerning sterics. For each of the resultant salts ^{1}H NMR data in D_2O corresponded to literature values.

With salts in hand, we wanted to find a generalized procedure for the synthesis of aryl ethers performed in neat alcohol solvents. To accomplish this, we first had to find an appropriate temperature at which the reactions would proceed in a realistic time frame. Using the work of Swain (Swain, et. al. 1975) as a starting point, we noted that two days reaction time in the most polar of solvents would not extrapolate to a general method. Therefore we decided to use refluxing temperatures as a starting



1 R = H (77%)
2 R = 2-CH_3 (30%)
3 R = 2-Cl (78%)
4 R = 3-Ac (93%)
5 R = 3-Br (58%)
6 R = 3-CH_3 (62%)
7 R = 3-Cl (95%)
8 R = 3-NO_2 (75%)
9 R = 3-OCH_3 (54%)
10 R = 3-Br (90%)
11 R = 4-CH_3 (59%)
12 R = 4-Cl (74%)
13 R = 4-NO_2 (90%)
14 R = 4-OCH_3 (55%)

Scheme 2. Preparation of aryldiazonium tetrafluoroborate salts.



Scheme 3. Formation of coumaran, 18, and 2-methyl coumaran, 19.

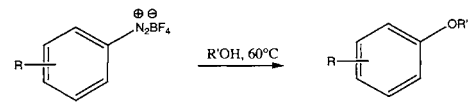
point. Reaction with methanol proceeded as expected to give anisole, 15, in up to 24% yield. While it was found that reactions done at these elevated temperatures led to our desired ethers, some interesting side products were observed when the benzenediazonium salt was heated with both ethanol and isopropanol. Reactions done in these media gave rise to annulated coumaran derivatives 18 and 19. These products are hypothesized to form subsequent to aryl ether formation in up to 20% of the total isolated product. The pathway which led to these side products (Scheme 3) likely proceeded through a free-radical mechanism.

It should be noted that when 2-methyl-2-propanol was used as the reaction medium we did not observe the formation of a corresponding dimethylcoumaran. Instead, phenol was the only observed product. This is likely due to acid-catalyzed ether cleavage, a process not uncommon for *t*-butyl ethers. To test this assumption, we carried out a control reaction where 2-methylpropyl phenyl ether was heated at reflux with one equivalent of HBF_4. As expected, the sole product was phenol.

The above observations led us to use a lower temperature in hopes that these undesired side reactions will no longer be an issue. The base temperature chosen for this work was 60°C to closely correspond with the boiling point of methanol. It was determined quickly that reactions done at this temperature limited all of the alternate pathways described above. All of the reactions were done at 0.5M concentration in neat alcohol at 60°C for the parent and derivative substrates unless otherwise noted (Scheme 4). The results are shown in Table 1.

As can be gleaned from Table 1, this reaction carried out with a variety of salts and low molecular weight alcohols led to the isolation of between 0% and 73% of the desired ether. For the parent substrate, isolated yields increased with the molecular weight of the alcohol. We attribute this observation to the fact that the parent ethers are much more volatile than their derivatives and some of the product was lost when dried under vacuum. It should also be noted that for the formation of **20** at these lowered temperatures, the elimination pathway previously observed to form phenol was inhibited.

Initially, we looked at 2- and 4-substituted arenediazonium salts to probe the electronic effects of this reaction (as 2-substituted systems also have steric concerns, we focused our attention on 4-substitution). In our first sequence of reactions, we noted that diazonium salt **13**, containing a NO_2 group in the *para* position, led to the isolation of only nitrobenzene in fairly good yields. This effect was also seen for **10**, but only when large, less polar alcohols were used. The reductive pathway in the presence of alcohols is well known, (Kornblum, et. al. 1944) it is



Scheme 4. Synthesis of aryl ethers from arenediazonium tetrafluoroborate salts.

Table 1. Results for aryl ether forming reactions.

Salt	R	Alcohol	Ether	Yield%	Notes	Salt	R	Alcohol	Ether	Yield%	Notes
1	H	MeOH	15	24		8	3-NO_2	MeOH	45	3	63% nitrobenzene
		EtOH	16	39				EtOH	46	0	91% nitrobenzene
		i-PrOH	17	32				i-PrOH	47	0	80% nitrobenzene
		t-BuOH	20	50	No phenol			t-BuOH	48	0	15% nitrobenzene
2	2-CH_3	MeOH	21	27		9	3-OCH_3	MeOH	49	73	
		EtOH	22	21				EtOH	50	53	
		i-PrOH	23	20				i-PrOH	51	58	
		t-BuOH	24	16				t-BuOH	52	0	31% 3-methoxyphenol
3	2-Cl	MeOH	25	0	37% chlorobenzene	10	4-Br	MeOH	53	65	
		EtOH	26	0	45% chlorobenzene			EtOH	54	trace	81% bromobenzene
		i-PrOH	27	0	38% chlorobenzene			i-PrOH	55	trace	92% bromobenzene
		t-BuOH	28	0	20% chlorobenzene			t-BuOH	56	trace	
4	3-Ac	MeOH	29	30		11	4-CH_3	MeOH	57	30	
		EtOH	30	26				EtOH	58	28	
		i-PrOH	31	trace	52% acetophenone			i-PrOH	59	12	
		t-BuOH	32	26	56% acetophenone			t-BuOH	60	0	
5	3-Br	MeOH	33	22		12	4-Cl	MeOH	61	31	
		EtOH	34	21				EtOH	62	0	
		i-PrOH	35	19				i-PrOH	63	1	
		t-BuOH	36	0				t-BuOH	64	3	
6	3-CH_3	MeOH	37	45		13	4-NO_2	MeOH	65	11	37% nitrobenzene
		EtOH	38	46				EtOH	66	0	56% nitrobenzene
		i-PrOH	39	41				i-PrOH	67	0	59% nitrobenzene
		t-BuOH	40	38				t-BuOH	68	0	1% nitrophenol
7	3-Cl	MeOH	41	4	16% chlorobenzene	14	4-OCH_3	MeOH	69	4	
		EtOH	42	10				EtOH	70	0	
		i-PrOH	43	24				i-PrOH	71	0	
		t-BuOH	44	0				t-BuOH	72	0	

clearly the major pathway for these substrates. This is likely due to the innate instability of the aryl cation possessing a strongly electron-withdrawing group, which would inhibit the substitution pathway.

On the other end of the spectrum, diazonium salt 14 contained a *para*-methoxy group and proved to be the most difficult substrate to analyze. This reaction appeared to proceed rather quickly as judged by dissolution of the salt. This is expected due to the postulated quinone-like intermediate. (Burnett, et. al. 1951) Despite the apparent stability of the intermediate, we were only able to isolate very small yields of the desired product. Additionally, we were unable to isolate any side products as there was merely residue present after work up.

We also tested five salts 2,3,5, 8 and 10 with moderate electronic effects containing *ortho*-methyl, *ortho*-chloro, *para*-methyl, *para*-chloro and *para*-bromo groups, respectively. With the exception of 3 and the aforementioned 10 with bulkier alcohols, the reactivity of these substrates were more akin to the parent substrate (1) and, in most cases, gave reasonable yields of their corresponding ether. In contrast to the parent substrate, the yields decreased with increasing molecular weight of the alcohol.

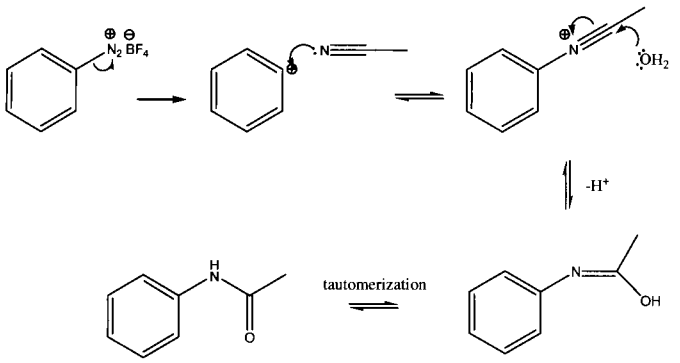
While a good variety of products were seen for *para*-substituted salts, we expected *meta*-substitution to have a muted effect as it lacks direct π-electronic connectivity. This expectation was generally observed for reactions carried out with diazonium salts 4–9. For salts 6 (*meta*-methyl) and 9 (*meta*-methoxy) relatively high yields were observed in most cases. In fact, the highest yield, 73%, was achieved for the reaction of 9 in methanol. One notable exception was the reaction of 3 with 2-methyl-2-propanol in which we observed the subsequent elimination leading to 3-methoxyphenol, 39. Results for salts 5 and 7 gave low to moderate yields ranging from 10–24% of total isolated yields with the exception of reactions run in *t*-butanol which gave no product in both instances.

The final diazonium salts looked at in this study were 4 and 8, where there was a strong deactivating group *meta* to the diazo group. Results for these substrates mirrored those seen for their *para* substituted congeners with reduction being the primary reactive pathway. Nitrobenzene was isolated in yields of up to 91% for this system.

Solvent effects

While this method works as a general procedure for the synthesis of aryl ethers with moderate electronic effects, it also possesses some clear limitations. The most obvious detraction from this method is that relatively large quantities of alcohol are needed for the reaction to proceed. This is prohibitive in that only short-chain ethers are accessible as the reaction is contingent upon using a liquid phase alcohol at 60°C. This also limits the use of more expensive liquid alcohols such as those possessing a stereogenic center. This reaction also suffers an inhibitive effect with increasing molecular weight of the alcohol due to the polarity necessary to generate and stabilize an intermediate aryl cation. Less obvious effects also exist, such as the reductive capacity of alcohols towards arenediazonium salts.

To help increase yields, the second phase of this project was to find a solvent suitable for this reaction to expand the breadth of this methodology to include higher molecular weight and more expensive alcohol precursors. Appropriate alternative solvents



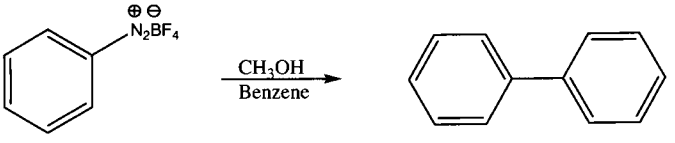
Scheme 5. Proposed mechanism for acetanilide formation.

could also assist in the inhibition of many of the side reactions observed during this study.

In choosing a suitable medium for this reaction, we desired a solvent that was both polar and non-nucleophilic. We began by looking at a number of traditional solvents such as N,N-dimethylformamide (DMF), dichloromethane (DCM), and chloroform, which all resulted in a complex mixture from which we could not isolate any desired product. Interestingly, when acetonitrile was used as the solvent, we were able to characterize and isolate a product. In the case for the parent diazonium salt, we were able to isolate a substantial amount of product which turned out to be acetanilide, 73. This observation suggests that acetonitrile is sufficiently nucleophilic to react under these conditions. We propose a mechanism for this transformation (Scheme 5) where water is added during workup. It is worth noting that repeating this procedure without additional alcohol resulted in up to 42% yield of 73.

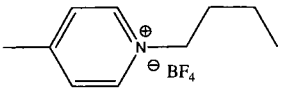
While this result was rather surprising, a reaction of this type is not without precedent. It has been shown that carbon monoxide can be used as a nucleophile, albeit at 320 atm., to yield a corresponding benzoate ester in the presence of alcohol (Bergstrom, et. al. 1976) in an analogous fashion to what we observed for acetonitrile. The initial charged intermediate is susceptible to attack by water, which gives acetanilide after tautmomerization. It was also found that this product was not entirely novel as it was observed as a very minor side product in some work exploring palladium-catalyzed processes with arene-diazonium salts. (Nagira, et. al. 1980)

The realization that polar solvents with extremely muted nucleophilicity are able to react led us to look at a few less polar examples. When the use of benzene was employed, we were again surprised to find that the major component of our reaction was a result of nucleophilic attack of the solvent. In this case, biphenyl, 74, was produced in up to 9% from the reaction of 1 with methanol in the presence of benzene in what can best be described as a non-alkali version of the Gomberg-Bachmann reaction



1 74

Scheme 6. Synthesis of biphenyl from parent salt in benzene.



75

Fig. 1. 1-Butyl-4-methylpyridinium tetrafluoroborate.

(Gomberg, et. al. 1924) (Scheme 6). Reactions attempted with more electron deficient arenes such as nitrobenzene, chlorobenzene and 1,2,4-trichlorobenzene led complex mixtures that were not purified.

With a good portion of traditional solvents exhausted, we decided to take a cue from green chemistry techniques which use polar and non-reactive solvents as a recyclable media. Two such systems that are often employed are perfluorinated hydrocarbons and ionic liquids. (Lancaster 2002) In both cases, the media are very non-nucleophilic as well as polar. In addition, they often form their own phase which makes isolation easier.

The first solvent used was perfluorinated methylcyclohexane, which was chosen for having a boiling point near 60°C. Unfortunately, the salt was extremely insoluble in this medium at both room temperature and elevated temperatures. The reaction did proceed as the reagents floated to the surface of the solvent, but only in 7% yield. The degree of insolubility led us to consider ionic liquids as a more appropriate choice.

Ionic liquids are typically made from an organic salt coupled with a large anion to prevent packing. With tetrafluoroborate being one of the more common anions, the logical synergistic choice was an ionic liquid with this counteranion. Considering that tetrafluoroboric acid is generated in the process of this reaction, we felt that a pyridinium salt would prove to be the most appropriate organic cation for this reaction. It is safe to assume that a pyridinium salt is sufficiently deactivated as to prevent side reactions. Based on availability, 1-butyl-4-methyl-pyridinium tetrafluoroborate, 75 was chosen as the ionic liquid (Figure 1).

Though this solvent is rather expensive, its use led to a 21% yield of 15 while only using 5-fold excess of methanol. This compares quite favorably with the typical 0.5M suspension (50-fold excess), which yields merely 24% percent of 15 under similar conditions. This result also suggests that more complex alcohols may prove viable as this method is optimized.

CONCLUSION

In conclusion, a general procedure for the synthesis of small chain aromatic ethers was developed. This method proves to work in low to moderate yields for arenes possessing substituents ranging from weakly electron withdrawing to moderately electron donating. The result with an ionic liquid is promising as a means to make a more general method for increasingly complex alcohols. Procedures to both produce and clean an optimal ionic liquid solvent are currently being explored. This will allow us to recycle the reaction media as we look towards more green synthetic methods. Additionally, as the solvent mediated method becomes increasingly developed; we will study both the amine forming and arene-arene coupling pathways in more detail.

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EXPERIMENTAL DETAILS

All reagents and solvents were used as purchased from Sigma-Aldrich or Fisher Scientific. Chromatography was performed using silica gel (Aldrich, 70–230 mesh, 60Å). Polymer-backed thin layer chromatography plates purchased from Aldrich with UV indicator were used. All ^{1}H NMR were run on a Brüker Biospin at 300MHz. All diazonium tetrafluoroborate salts were prepared using published methods and were analyzed by ^{1}H NMR in D_2O for purity. In all cases, spectra were in accordance with published data. For aryl ethers, ^{1}H NMR and, if necessary, ^{13}C NMR spectra were compared to published values as indicated, with a majority of them available from commercial sources.

General Procedure for the Synthesis of Aryl Ethers in Neat Alcohol

A 0.5 M slurry of arenediazonium tetrafluoroborate salt (20 mmol) in alcohol (40mL) was prepared and heated with stirring at 60°C for 3–36 h in an oil bath. The completion of the reaction was noted by complete dissolution of the arendiazonium salt. The reaction was cooled to room temperature and placed in a separatory funnel with dichloromethane (50mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 50mL). The organic phase was dried (Na_2SO_4), filtered, and the solvent was removed *via* rotary evaporation. Flash chromatography was performed using a hexanes:ethyl acetate mixture as the eluent. Pure aryl ether was collected, typically as a colorless to pale yellow oil and characterized in comparison to known spectral data.

Methoxybenzene (15).

Methanol (40 mL) and 1 (3.741 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 15 (0.511 g, 4.72 mmol, 24%) was collected as a colorless oil.

Ethoxybenzene (16).

Ethanol (40 mL) and 1 (3.741 g, 20.00 mmol) were reacted for 22 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 16 (0.955 g, 7.81 mmol, 39%) was collected as a pale yellow oil.

(1-Methylethoxy)-benzene (17). (Vogel 1959)

2-Propanol (40 mL) and 1 (3.741 g, 20.00 mmol) were reacted for 3 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 17 (0.865 g, 6.35 mmol, 32%) was collected as a pale yellow oil.

(1,2-Dimethylethoxy)-benzene (20). (Leupold, et. al. 1971)

2-Methyl-2-propanol (40 mL) and 1 (3.741 g, 20.00 mmol) were reacted for 10 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 20 (1.507 g, 10.03 mmol, 50%) was collected as a yellow oil.

1-Methoxy-2-methylbenzene (21).

Methanol (20 mL) and 2 (2.06 g, 10.00 mmol) were reacted for 15 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 21 (0.331 g, 2.71 mmol, 21%) was collected as a colorless oil.

1-Ethoxy-2-methylbenzene (22). (Cook, et. al. 1974)

Ethanol (20 mL) and 2 (2.06 g, 10.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 22 (0.283 g, 2.08 mmol, 21%) was collected as a yellow oil.

1-(Methylethoxy)-2-methylbenzene (23).

2-Propanol (20 mL) and 2 (2.06 g, 10.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 23 (0.298 g, 1.98 mmol, 20%) was collected as a pale yellow oil.

1-(1,1-Dimethylethoxy)-2-methylbenzene (24).

2-Propanol (20 mL) and 2 (2.06 g, 10.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 24 (0.260 g, 1.59 mmol, 16%) was collected as a dark yellow oil.

1-Chloro-2-methoxybenzene (25).

Methanol (20 mL) and 3 (2.264 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, chlorobenzene (0.410 g, 3.64 mmol, 37%) was collected as a yellow oil. No notable amount of 25 was observed.

1-Chloro-2-ethoxybenzene (26).

Ethanol (20 mL) and 3 (2.264 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, chlorobenzene (0.504 g, 4.48 mmol, 45%) was collected as a yellow oil. No notable amount of 26 was observed.

1-Chloro-2-(methylethoxy)-benzene (27).

2-Propanol (20 mL) and 3 (2.264 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, chlorobenzene (0.430 g, 3.82 mmol, 38%) was collected as a yellow oil. No notable amount of 27 was observed.

1-Chloro-2-(1,1-dimethylethoxy)-benzene (28).

2,2-Dimethylethanol (20 mL) and 3 (2.264 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, chlorobenzene (0.221 g, 1.96 mmol, 20%) was collected as a yellow oil. No notable amount of 28 was observed.

1-(3-Methoxyphenyl)-ethanone (29).

Methanol (20 mL) and 4 (2.34 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 7:3 hexanes:ethyl acetate, 29 (0.446 g, 2.97 mmol, 30%) was collected as a yellow oil.

1-(3-ethoxyphenyl)-ethanone (30). (Hirao et. al 1991)

Ethanol (20 mL) and 4 (2.34 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 7:3 hexanes:ethyl acetate, 30 (0.428 g, 2.61 mmol, 26%) was collected as a dark yellow oil.

1-(3-(1-Methylethoxy)-phenyl)-ethanone (31).

2-Propanol (20 mL) and 4 (2.34 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 7:3 hexanes:ethyl acetate, acetophenone 31 (0.620 g, 5.16 mmol, 52%) containing < 5% of 31 was collected as a yellow oil.

1-(3-(1,1-Dimethylethoxy)-phenyl)-ethanone (32). (Bernstein, et. al. 1996)

2-Propanol (20 mL) and 4 (2.34 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatog-

raphy with a solution of 7:3 hexanes:ethyl acetate, acetophenone (0.672 g, 5.59 mmol, 56%) and 32 (0.468 g, 2.61 mmol, 26%) were collected as yellow oils.

1-Bromo-3-methoxybenzene (33).

Methanol (20 mL) and 5 (2.71 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, 33 (0.412 g, 2.21 mmol, 22%) was collected as a dark yellow oil.

1-Bromo-3-ethoxybenzene (34).

Ethanol (20 mL) and 5 (2.71 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, 34 (0.440 g, 2.18 mmol, 21%) was collected as a yellow oil.

1-Bromo-3-(methylethoxy)-benzene (35).

2-Propanol (20 mL) and 5 (2.264 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, 35 (0.417 g, 1.94 mmol, 19%) was collected as a light yellow oil.

1-Bromo-3-(1,1-dimethylethoxy)-benzene (36).

2,2-Dimethylethanol (20 mL) and 5 (2.264 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, no notable amount of 36 or any side products were observed.

1-Methoxy-3-methylbenzene (37).

Methanol (40 mL) and 6 (4.12 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 37 (1.110 g, 9.08 mmol, 45%) was collected as a colorless oil.

1-Ethoxy-3-methylbenzene (38). (Cook, et. al. 1974)

Ethanol (40 mL) and 6 (4.12 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 38 (1.255 g, 9.22 mmol, 46%) was collected as a yellow oil.

1-(Methylethoxy)-3-methylbenzene (39). (Cook, et. al. 1974)

2-Propanol (40 mL) and 6 (4.12 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 39 (1.235 g, 8.22 mmol, 41%) was collected as a yellow oil.

1-(1,1-Dimethylethoxy)-2-methylbenzene (40).

2-Methyl-2-propanol (40 mL) and 6 (4.12 g, 20.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, 40 (1.247 g, 7.59 mmol, 38%) was collected as a yellow oil.

1-Chloro-3-methoxybenzene (41).

Methanol (40 mL) and 7 (4.528 g, 20.00 mmol) were reacted for 19 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl Acetate, chlorobenzene[33] (0.353 g, 3.15 mmol, 16%) was collected as a clear liquid. The next band yielded 41 (0.111 g, 0.78 mmol, 4%) as a faintly yellow oil.

1-Chloro-3-ethoxybenzene (42). (Brönstrup, et. al. 2000)

Ethanol (40 mL) and 7 (4.528 g, 20.00 mmol) were reacted for 23 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl Acetate, 42 (0.300 g, 1.91 mmol, 10%) was collected as a pale yellow oil.

1-Chloro-3-(1-methylethoxy)-benzene (43). (Cook, et. al. 1974)

2-Propanol (40 mL) and 7 (4.528 g, 20.00 mmol) were reacted for 23 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 43 (0.816 g, 4.78 mmol, 24%) was collected as a pale yellow oil.

1-Chloro-3-(1,1-dimethylethoxy)-benzene (44).

2-Methyl-2-propanol (40 mL) and 7 (4.528 g, 20.00 mmol) were reacted for 23 h as described above. Only a trace quantity of a highly colored material was recovered. No isolable compounds were noted.

1-Methoxy-3-nitrobenzene (45).

Methanol (40 mL) and 8 (4.742 g, 20.00 mmol) were reacted for 22 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, nitrobenzene[28] (1.549 g, 12.58 mmol, 63%) was collected as a pale yellow oil. This was followed by 45 (0.076g, 0.50mmol, 3%) collected as a pale yellow oil.

1-Ethoxy-3-nitrobenzene (46).

Ethanol (40 mL) and 8 (4.742 g, 20.00 mmol) were reacted for 22 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, nitrobenzene (2.502 g, 18.29 mmol, 91%) was collected as a pale yellow oil. No notable amount of 15 was observed.

1-(1-Methylethoxy)-3-nitrobenzene (47).

2-Propanol (40 mL) and 8 (4.742 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, nitrobenzene (1.965 g, 15.96 mmol, 80%) was collected as a pale yellow oil. No notable amount of 47 was observed.

1-(1-Methylethoxy)-3-nitrobenzene (48).

2-Methyl-2-propanol (40 mL) and 8 (4.742 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, nitrobenzene (0.370 g, 3.01 mmol, 15%) was collected as a pale yellow oil. No notable amount of 48 was observed.

1,3-Dimethoxybenzene (49).

Methanol (40 mL) and 9 (4.441 g, 20.00 mmol) were reacted for 26 h as described above. Following workup and chromatography with a solution of 20:1 pentane:ether, 49 (2.022 g, 14.64 mmol, 73%) was collected as a colorless oil.

1-Ethoxy-3-methoxybenzene (50). (Siegman, et. al. 1982)

Ethanol (40 mL) and 9 (4.441 g, 20.00 mmol) were reacted for 22 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 50 (1.623 g, 10.67 mmol, 53%) was collected as a pale yellow oil.

1-(1-Methylethoxy)-3-methoxybenzene (51). (Siegman, et. al. 1982)

2-Propanol (40 mL) and 9 (4.441 g, 20.00 mmol) were reacted for 22 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 51 (1.939 g, 11.67 mmol, 58%) was collected as a pale yellow oil.

1-(1,1-Dimethylethoxy)-3-methoxybenzene (52). (Siegman, et. al. 1982)

2-Methyl-2-propanol (40 mL) and 9 (4.441 g, 20.00 mmol) were reacted for 22 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 3-methoxyphenol, 73, (0.759 g, 6.12 mmol, 31%) was collected as a pale yellow oil. No direct detection of 52 was made at any stage.

1-Bromo-3-methoxybenzene (53).

Methanol (20 mL) and 10 (2.13 g, 8.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, 33 (0.969 g, 5.18 mmol, 65%) was collected as a pale yellow oil.

1-Bromo-3-ethoxybenzene (54).

Ethanol (20 mL) and 10 (2.13 g, 8.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, bromobenzene (1.015 g, 6.46 mmol, 82%) was collected as a yellow oil.

1-Bromo-3-(methylethoxy)-benzene (55).

2-Propanol (20 mL) and 10 (2.13 g, 8.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, bromo-

benzene (1.152 g, 7.33 mmol, 92%) was collected as a light yellow oil.

1-Bromo-3-(1,1-dimethylethoxy)-benzene (56).

2,2-Dimethylethanol (20 mL) and 10 (2.264 g, 10.00 mmol) were reacted for 18 h as described above. Following workup and chromatography with a solution of 19:1 hexanes:ethyl acetate, no notable amount of 56 or any side products were observed.

1-Methoxy-4-methylbenzene (57).

Methanol (40 mL) and 11 (4.126 g, 20.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 57 (0.735 g, 6.01 mmol, 30%) was collected as a pale yellow oil.

1-Ethoxy-4-methylbenzene (58). (Seshadri, et. al. 1972)

Ethanol (40 mL) and 11 (4.126 g, 20.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 58 (0.765 g, 5.62 mmol, 28%) was collected as a pale yellow oil.

1-(Methylethoxy)-4-methylbenzene (59). (Williams, et. al. 1977)

2-Propanol (40 mL) and 11 (4.126 g, 20.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 59 (0.373 g, 2.48 mmol, 12%) was collected as a pale yellow oil.

1-(Methylethoxy)-4-methylbenzene (60).

2-Propanol (40 mL) and 11 (4.126 g, 20.00 mmol) were reacted for 36 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, we were unable to isolate 60 or any side products.

1-Chloro-4-methoxybenzene (61).

Methanol (40 mL) and 12 (4.528 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 61 (0.885 g, 6.20 mmol, 31%) was collected as a pale yellow oil.

1-Chloro-4-ethoxybenzene (62).

Ethanol (40 mL) and 12 (4.528 g, 20.00 mmol) were reacted for 23 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, we were unable to isolate 62 or any side products.

1-Chloro-4-(1-methylethoxy)-benzene (63). (Hirano, et. al. 1997)

2-Propanol (40 mL) and 12 (4.528 g, 20.00 mmol) were reacted for 23 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 63 (0.048 g, 0.28 mmol, 1%) was collected as a pale yellow residue.

1-Chloro-4-(1,1-dimethylethoxy)-benzene (64). (Hirano, et. al. 1997)

2-Methyl-2-propanol (40 mL) and 12 (4.528 g, 20.00 mmol) were reacted for 23 h as described above. Following workup and chromatography with a solution of 49:1 hexanes:ethyl acetate, 64 (0.117 g, 0.64 mmol, 3%) was collected as a pale yellow residue.

1-Methoxy-4-nitrobenzene (65).

Methanol (40 mL) and 13 (4.742 g, 20.00 mmol) were reacted for 21 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, nitrobenzene[28] (0.918 g, 7.46 mmol, 37%) was collected as a yellow oil. The second fraction produced 65 (0.336 g, 2.19 mmol, 11%) as a yellow oil.

1-Ethoxy-4-nitrobenzene (66).

Ethanol (40 mL) and 13 (4.742 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 99:1 hexanes:ethyl acetate, nitrobenzene (1.372 g, 11.14 mmol, 56%) was collected as a yellow oil. No notable amount of 66 was observed.

1-(1-Methylethoxy)-4-nitrobenzene (67).

2-Propanol (40 mL) and 13 (4.742 g, 20.00 mmol) were reacted for 10 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, nitrobenzene (1.460 g, 11.85 mmol, 59%) was collected as a yellow oil. No notable amount of 67 was observed.

1-(1,1-Dimethylethoxy)-4-nitrobenzene (68).

2-Propanol (40 mL) and 13 (4.742 g, 20.00 mmol) were reacted for 10 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, nitrophenol (0.018 g, 0.13 mmol, 1%) was collected as a residue. No notable amount of 68 was observed.

1,4-Dimethoxybenzene (69).

Methanol (40 mL) and 14 (4.441 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, 69 (0.116 g, 0.84 mmol, 4%) was collected as a clear oil.

1,4-Dimethoxybenzene (70).

Methanol (40 mL) and 14 (4.441 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, we were unable to isolate 70 or any side products.

1,4-Dimethoxybenzene (71).

Methanol (40 mL) and 14 (4.441 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, we were unable to isolate 71 or any side products.

1,4-Dimethoxybenzene (72).

Methanol (40 mL) and 14 (4.441 g, 20.00 mmol) were reacted for 24 h as described above. Following workup and chromatography with a solution of 20:1 hexanes:ethyl acetate, we were unable to isolate 72 or any side products.

N-Phenylacetamide (73).

Acetonitrile (40 mL) and 1 (2.542 g, 13.60 mmol) were added to a 100 mL round bottom flask with a stir bar and the slurry was allowed to stir at ambient temperature for 48 h. The reaction was added to a separatory funnel along with dichloromethane (50 mL). The organic phase was washed with $NaHCO_3$ (2 × 50 mL). The organic extract was then dried (Na_2SO_4), filtered, and the solvent was removed via rotary evaporation. The crude yellow solid was then purified by chromatography using 9:1 hexanes:ethyl acetate to yield 73 (0.775 g, 5.73 mmol, 42%) as a yellow solid.

Biphenyl (74).

Benzene (40 mL) and 1 (3.741g, 20.00 mmol) were added to a 100 mL round bottom flask with a stir bar and the slurry was allowed to stir at room temperature for 18h, followed by heating at reflux for 2 h. The reaction was added to a separatory funnel along with dichloromethane (50 mL). The organic phase was washed with $NaHCO_3$ (2 × 50 mL). The organic extract was then dried (Na_2SO_4), filtered, and the solvent was removed via rotary evaporation. The crude product was then purified by chromatography using 9:1 hexanes:ethyl acetate to yield 74 (0.274 g, 1.78 mmol, 9%) as a white solid.

Methoxybenzene (15)

1,1,2,2,3,3,4,4,5,5,6-undecafluoro-6-(trifluoromethyl)cyclohexane (10 mL), methanol (1 mL) and 1 (0.935 g, 5.00 mmol) were added to a 50 mL round bottom flask with a stir bar. It was noted that the salt did not dissolve in the perfluorinated solvent, even at elevated temperatures. The solution was heated at 60°C for 18h. Ethyl acetate (15 mL) was added to the reaction flask and the fluorous layer was removed. The organic layer was then washed with saturated $NaHCO_3$ (2 × 10 mL). The organic extract was then dried (Na_2SO_4), filtered, and the solvent was removed via rotary evaporation. The crude

product was then purified by chromatography using 49:1 hexanes:ethyl acetate to yield 15 (0.036 g, 0.33 mmol, 7%) as a clear residue.

Methoxybenzene (15)

Methanol (0.5 mL), 42 (5.00 g) and 1 (0.467 g, 2.50 mmol) were added to a round bottom flask (50 mL) and stirred at 60°C for 18 h. Ethyl acetate (20 mL) was added to the reaction flask and it was washed with water (2 × 30mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed by rotary evaporation. The crude product was then purified by chromatography using 49:1 hexanes:ethyl acetate to yield 15 (0.056 g, 0.52 mmol, 21%) as a clear residue.