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Recent Advances in Diaryl Ether Synthesis

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1. Introduction

The recent publication of several total syntheses of vancomycin aglycon has further focused attention on the importance of new technology for the construction of the diaryl ether unit.[1–6] While the impressive routes to vancomycin discussed in these accounts rely on intramolecular macrocyclization strategies, these same research groups have also worked to develop novel intermolecular approaches for diaryl ether synthesis. A large group of methods for the synthesis of diaryl ethers continues to be developed by other groups searching for new routes to a wide range of biologically active compounds. This Report will concentrate mostly on both inter- and intramolecular methodology developments since the publication of Zhu's review of S_NAr-based macrocyclization strategies for the synthesis of diaryl ether-containing natural products.[7]

2. Variations on the Ullmann Ether Synthesis

The classical Ullmann ether synthesis remains an important tool in diaryl ether synthesis. Despite limitations under the original conditions, such as elevated reaction temperatures, formidable purification problems, generally low yields, and the use of stoichiometric quantities of copper, recent work has revitalized this method considerably.

2.1. Intermolecular Ullmann ether syntheses

A procedure developed by Smith[8] involving the use of catalytic copper(I) iodide and ultrasound gives better yields of diaryl ethers at lower temperatures than the traditional Ullmann procedure (Scheme 1). The use of 2 equiv. of the

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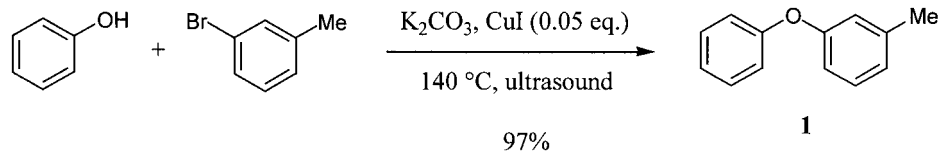
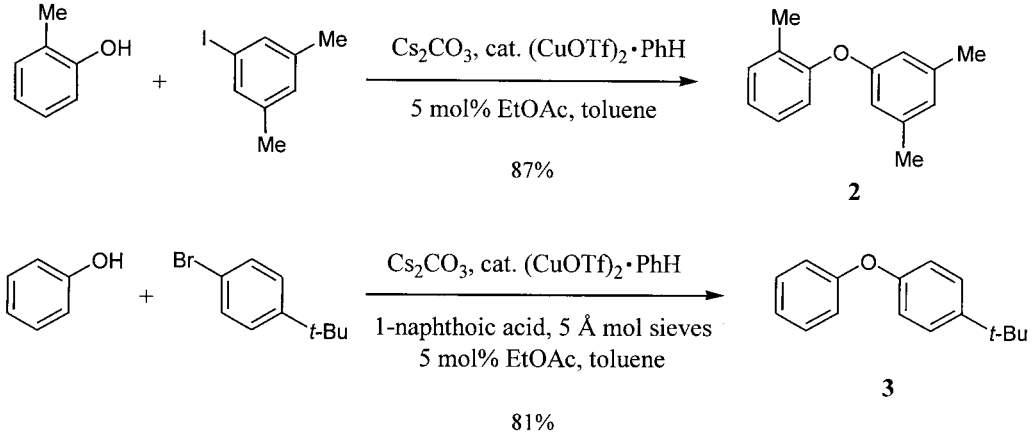


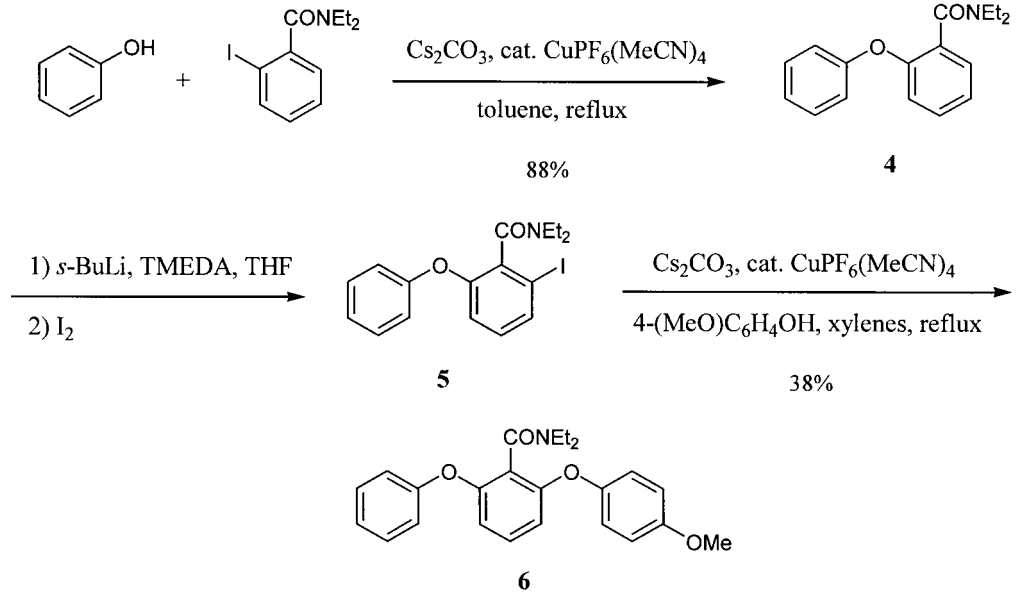
Scheme 1.



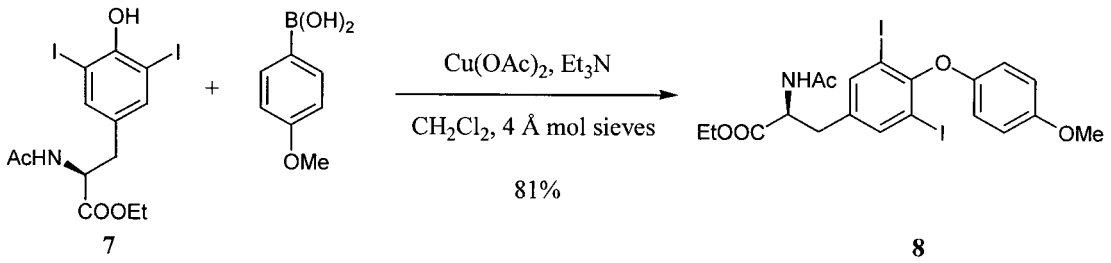
Scheme 2.

phenol in conjunction with sonication gave diaryl ethers in yields generally greater than the corresponding classical Ullmann conditions. These reactions were conducted in the absence of solvent and the authors speculate that the role of sonication was primarily to break up particles of the base and catalyst. A procedure has been developed by Buchwald[9] that utilizes cesium carbonate as the base along with a catalytic amount of $(CuOTf)_2$-benzene complex, together with the optional addition of stoichiometric quantities of a carboxylic acid (Scheme 2). Cesium carbonate was shown to be the optimal base in this system and allows the use of a non-polar solvent (toluene) at reduced reaction temperatures. Addition of a carboxylic acid and molecular sieves was effective in promoting couplings of specific phenols devoid of electron donating groups to unactivated aryl halides (e.g., the formation of **3**).

A recently published variation on this procedure by Snieckus details use of catalytic $CuPF_6(MeCN)_4$ in place of $(CuOTf)_2$-benzene to facilitate coupling of phenols to *o*-halo tertiary and secondary benzamides and sulfonamides.[10] The resulting diaryl ethers may then be submitted to directed ortho metalation, halogenation, and an additional Ullmann ether operation to produce Ar–O–Ar′–O–Ar″ units (Scheme 3). Such units are a core component of vancomycin architecture. The use of $CuPF_6(MeCN)_4$ is described



Scheme 3.



Scheme 4.

as more convenient than $(CuOTf)_2$-benzene as the latter catalyst is more air sensitive. Aryl boronic acids, normally associated with the Suzuki biaryl synthesis, have been coupled to phenols by Chan[11] and Evans[12] in a copper-mediated synthesis of diaryl ethers. Like the original Ullmann conditions, stoichiometric quantities of copper(II) acetate are used. However, the reaction is run at room temperature, tolerates a wide variety of substituents on both fragments, and proceeds in generally high yields. Evans has used this procedure to construct diaryl ether **8**, an intermediate in the synthesis of L-thyroxine, by coupling phenol **7** with *p*-methoxyphenylboronic acid (Scheme 4).

One of the most interesting recent developments in Ullmann methodology was reported by Nicolaou.[13] A dihaloaromatic unit substituted with a triazene group proved to be a suitable electrophilic component in a tandem phenolic addition catalyzed by copper(I) bromide (Scheme 5). Interestingly, additions to these di-*ortho*-halogenated aromatic triazenes proceeded more efficiently than to the corresponding mono-halo derivatives. As mentioned above, Ar–O–Ar′–O–Ar″ units such as **6** and **10** are important scaffolds for the synthesis of vancomycin, and indeed represent the linear COD and DOE diaryl ether fragments.

2.2. Intramolecular Ullmann macrocyclizations

An intramolecular version of the triazene-based synthesis of diaryl ethers has been successfully exploited by the Nicolaou group in the total synthesis of vancomycin. Model systems of the DOE[13] and COD[14] ring systems of vancomycin were first constructed via macrocyclization of acyclic precursors. For the actual synthesis of vancomycin aglycon, intermediate **11** was subjected to the standard triazene macrocyclization conditions to give a 1:1 mixture of atropisomers **12ab** in 60% yield (Scheme 6).[3] Establishment of the stereochemical outcome of this cyclization was ascertained by use of COSY and NOESY NMR analysis. Elaboration of the correct atropisomer **12a** to **13** was followed by a second triazene macrocylization resulting in a 1:3 mixture of atropisomers **14ab**. These were equilibrated thermally to provide a 1:1 mixture that was separated by chromatography to give pure **14a**,[4] which was subsequently progressed to vancomycin aglycon.[5]

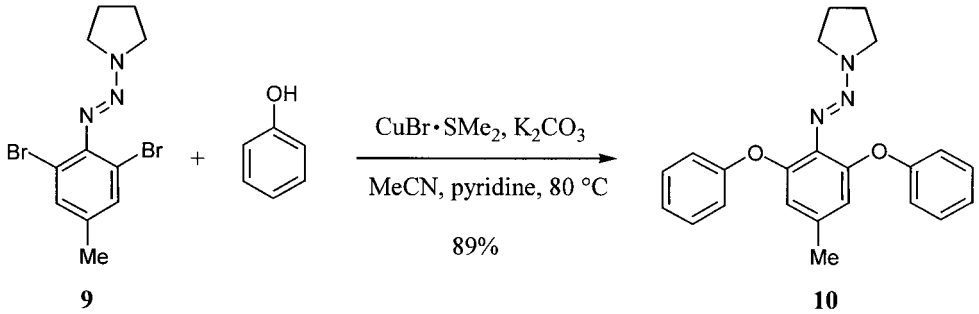
In addition to the triazene variation, the standard Ullmann ether synthesis has been recently used in construction of a macrocyclic natural product. Cyclization of **15** with copper(II) bromide led to a low yield of **16**, an intermediate in the synthesis of the diarylheptanoid acerogenin C (Scheme 7).[15] This cyclization reaction was successful after attempts to close the ring system with the diaryl ether in place proved futile.

3. S_NAr-Based Addition Reactions

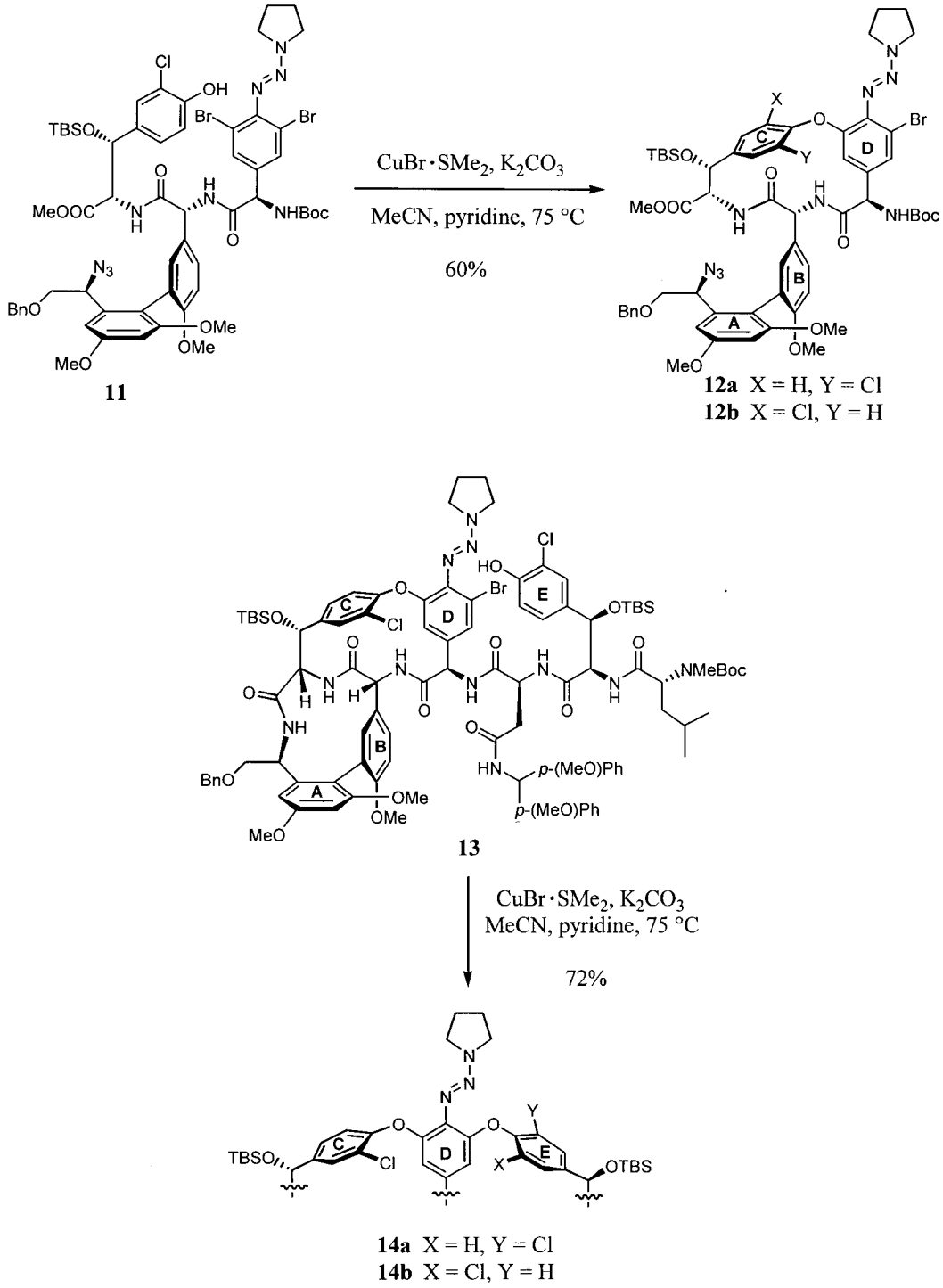
By far the method of diaryl ether synthesis generating the most intense recent study is the S_NAr addition reaction. While the direct nucleophilic coupling of phenols to electron-deficient aryl frameworks has been known for some time, synthetic interest in diaryl ether-containing natural products such as vancomycin, piperazinomycin, and the combretastatins has stimulated new extensions of this classic method.

3.1. Standard intermolecular S_NAr additions

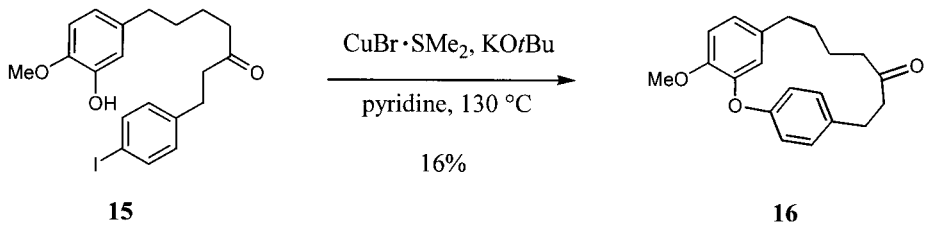
In our own laboratory potassium fluoride-alumina has been shown to be an effective mediator of the S_NAr addition of phenols to electron-deficient aryl halides in the presence of 18-crown-6.[16,17] Electronically favorable substitution patterns may be addressed using halo-substituted benzonitriles or nitrobenzenes in refluxing acetonitrile. Even the sterically crowded nucleophile 2-*tert*-butylphenol, usually uncooperative under normal Ullmann conditions, added



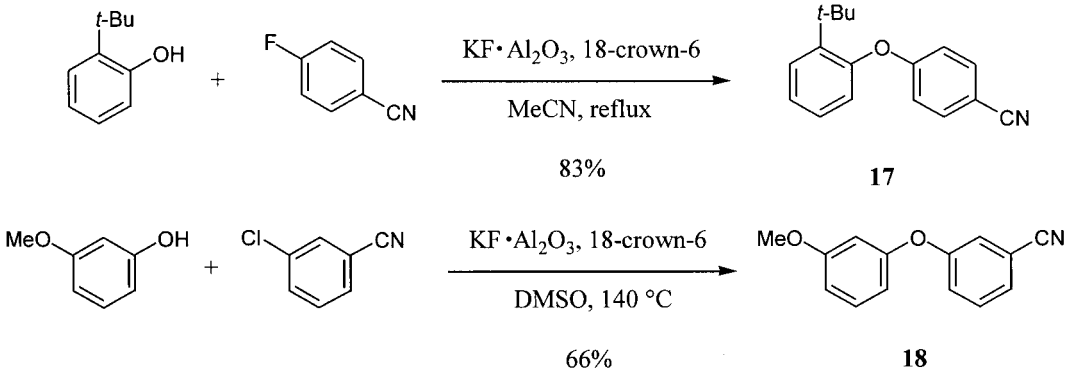
Scheme 5.



Scheme 6.



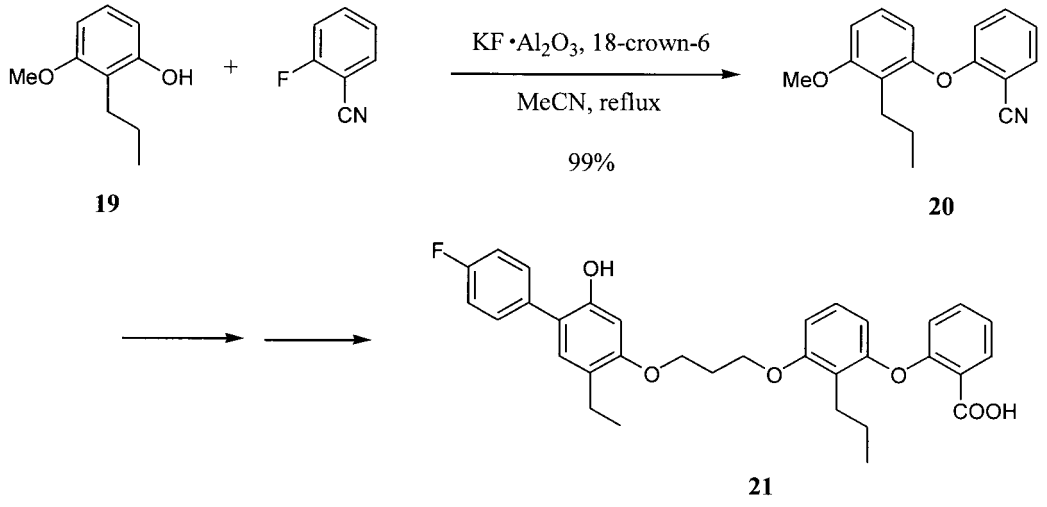
Scheme 7.



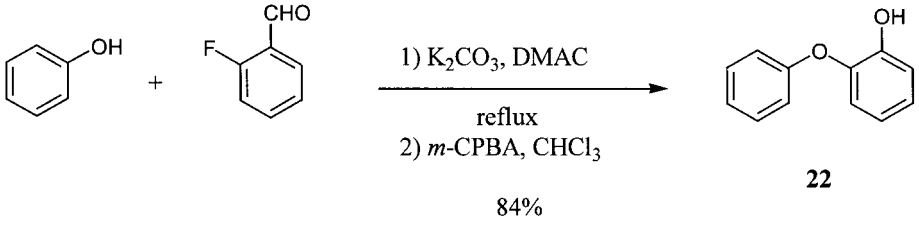
Scheme 8.

smoothly to 4-fluorobenzonitrile to give diaryl ether **17** (Scheme 8). It was discovered that the utility of the method could be significantly extended by conducting the reaction in DMSO at higher temperatures. Thus, diaryl ether **18** was produced by the coupling of 3-methoxyphenol to 3-chlorobenzonitrile in acceptable yield, an example of an electronically unfavorable process seldom observed using conventional S_NAr methodology. When using the DMSO protocol, other electron-withdrawing groups on the electrophile may be used in place on nitrile or nitro, such as aldehyde, acetate, ester, and amide. We have employed the method to make the critical diaryl ether fragment **20** (Scheme 9),[18] a component of **21**, the potent LTB_4 receptor antagonist LY293111.[19]

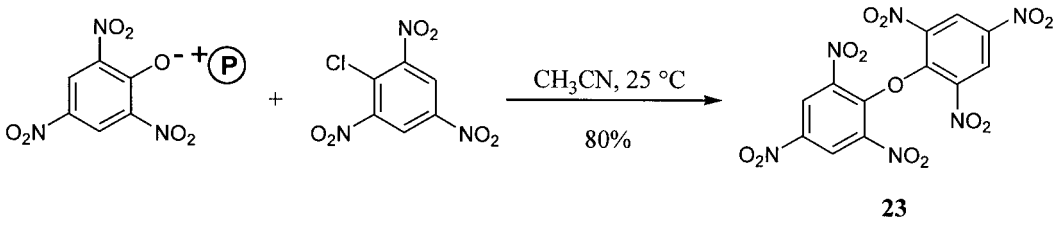
A three-step process has been developed that effectively constitutes an umpolung synthon approach to the synthesis of 2-aryloxyphenols (Scheme 10).[20] This involves the use of potassium carbonate to mediate the addition of phenols to 2-fluorobenzaldehyde, followed by a Baeyer–Villiger oxidation to provide 2-aryloxyphenols in high yields. A more recently developed S_NAr method consists of the addition of polymer-supported phenoxide ions to highly electron-deficient aryl halides under mild conditions (Scheme 11).[21] The method works well even with highly electron-deficient phenols. Products such as the polynitrated diaryl ether **23** may prove useful as heat resistant explosives.



Scheme 9.

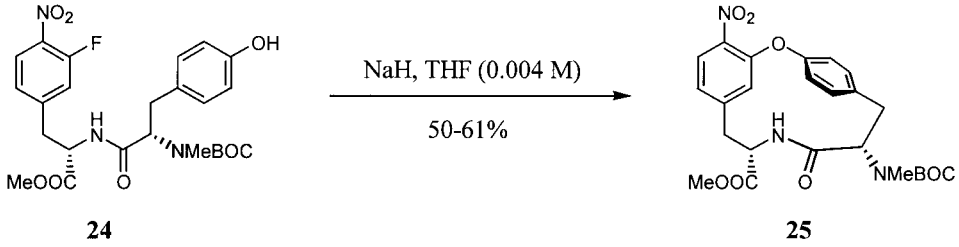


Scheme 10.



23

Scheme 11.



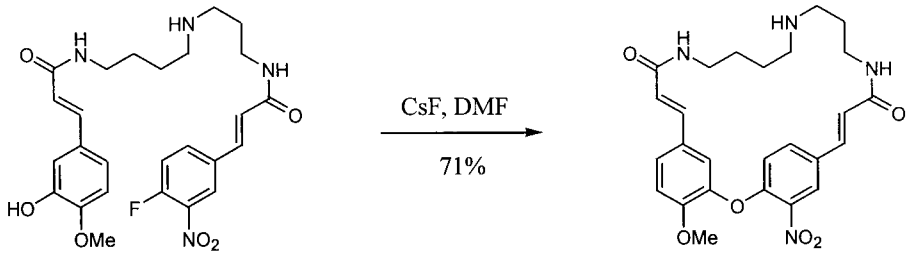
24 25

Scheme 12.

3.2. Standard intramolecular S_NAr macrocyclizations

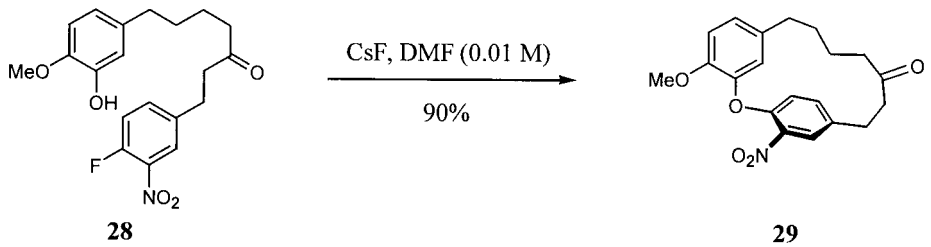
The intramolecular S_NAr macrocyclization strategy has become the preeminent method for construction of vancomycin and related cyclic peptides.[7] An example from the Boger group illustrates the facile nature of the macrocyclization operation. Compound **24** was successfully cyclized to the 14-membered macrocycle **25** using relatively mild conditions at moderate dilution (Scheme 12).[22] The final configurations of the 9-substituted ester and 12-substituted amino functionalities were highly dependent on the diastereomeric nature of the acyclic precursor **24** and on the base used to initiate ring closure. Compound **25** represents an important fragment of the antitumor agents deoxybouvardin and RA-VII. Larger macrocycles have also been efficiently constructed, including compound **27**, a derivative of the naturally occurring 24-membered polyamine lactam alkaloid cadabicine (Scheme 13).[23] In this example, 3 equiv. of cesium fluoride were used to effect ring closure.

Returning to the acerogenin-type diarylheptanoids (vide supra), Zhu used the same cesium fluoride conditions to cyclize **28** to **29** in 90% yield (Scheme 14),[24] a considerable improvement over the intramolecular Ullmann cyclization of **15** discussed above. Macrocycle **29**, an intermediate for the synthesis of acerogenins C and A, was isolated as the single atropisomer indicated. Execution of the reaction at higher concentrations led to progressively lower yields. Roussi has used the S_NAr method for construction of



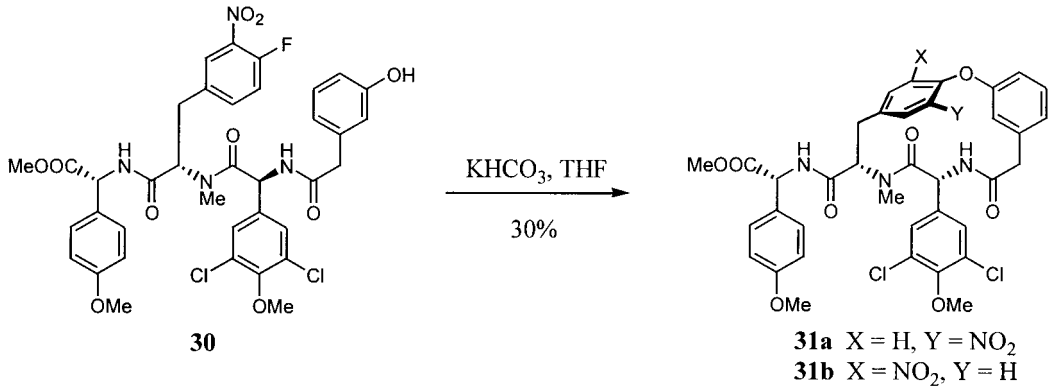
26 27

Scheme 13.



28 29

Scheme 14.

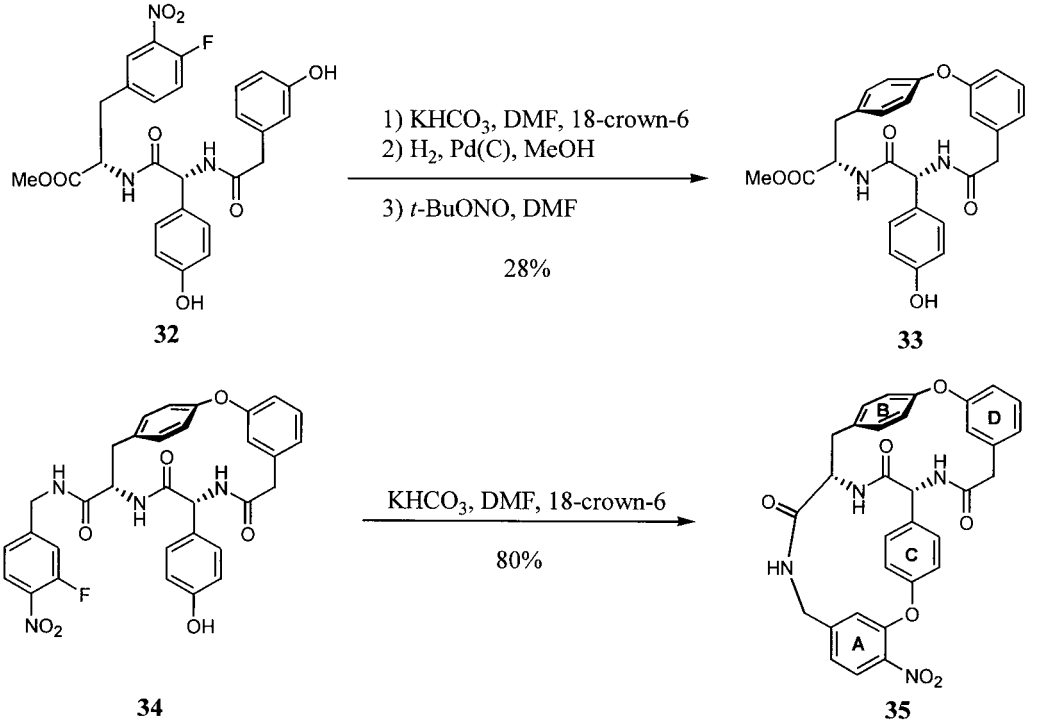


Scheme 15.

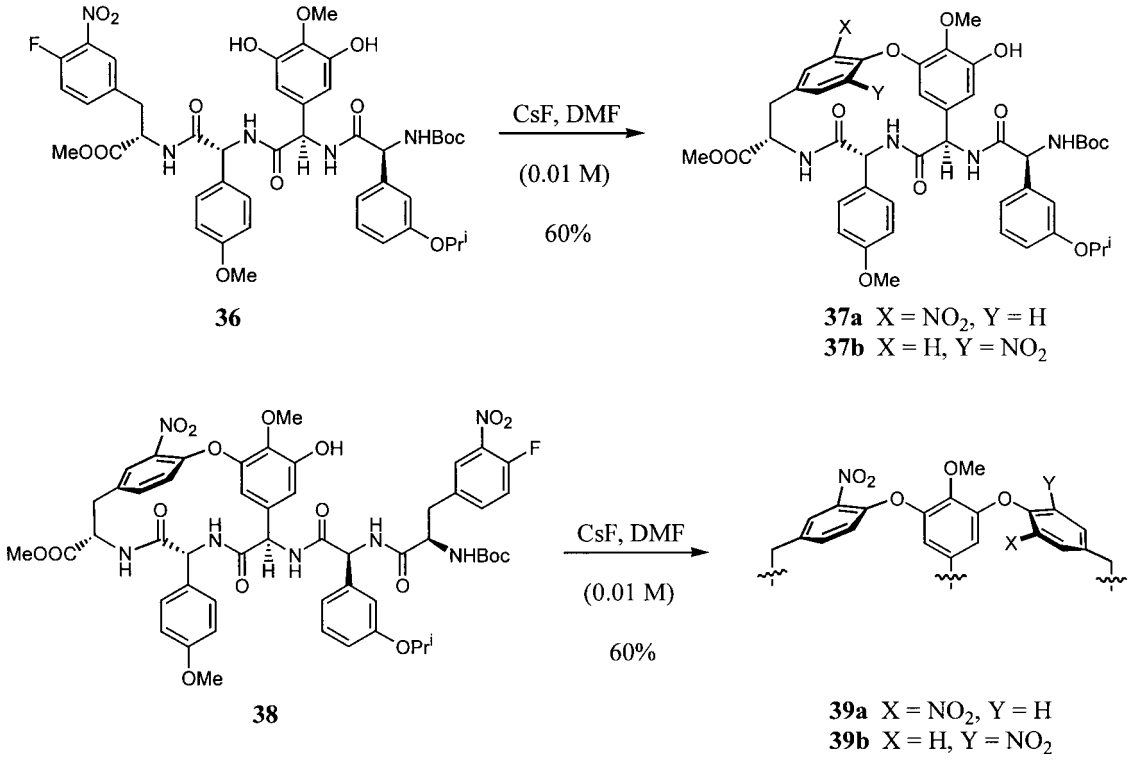
model systems related to chloropeptin I and II. Cyclization of peptide **30** provided a 2:1 mixture of **31ab**, wherein the (*S*)-3,5-dichloro-4-methoxyglycine residue has racemized under the reaction conditions (Scheme 15).[25] In a similar strategy, compound **32** was cyclized to a mixture of atropisomers that was subsequently reduced via two further operations to macrocycle **33** (Scheme 16). This compound was efficiently elaborated to **34**, which was subjected to another S_NAr procedure to produce **35**, a model representative of the AOCBOD ring system of the antiviral/antibacterial agents kistamicins A and B.[26,27]

Zhu has used the cesium fluoride S_NAr method for the synthesis of a model of the CODOEFOG ring system of teicoplanin, a tetracyclic glycopeptide related to vancomycin, but of greater complexity.[28] Cyclization of **36** gave a 1:1 mixture of the 16-membered macrocyclic atropisomers **37ab**, while elaboration of **37a** to **38** and subsequent treatment with cesium fluoride provided the CODOE ring system **39ab**, again as a 1:1 mixture of atropisomers, in good yield (Scheme 17). Synthesis of the FOG fragment required conversion of the correct isomer **39a** to intermediate **40**, which was then subjected to a third S_NAr macrocyclization procedure to give the full CODOEFOG ring system **41** in 45–50% yield (Scheme 18). A similar strategy has also been used by both Rao[29] and Zhu[30] in construction of intermediates for the synthesis of vancomycin, and by Evans[31] for the synthesis of orienticin C (des-dichloro analogue of vancomycin).

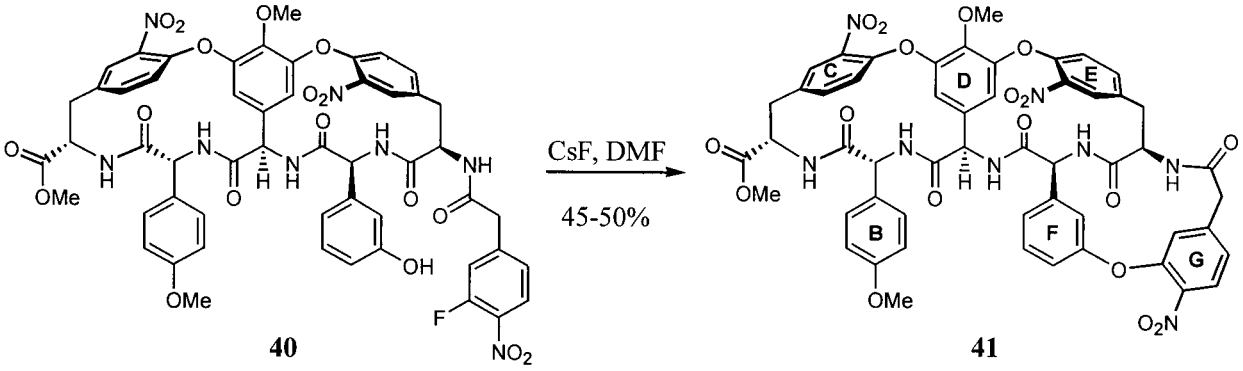
For the total synthesis of vancomycin aglycon, the Evans group effectively used the nitro group of the S_NAr electrophilic component to direct the cyclization of intermediate **42** to give atropisomer **43** with 5:1 diastereoselectivity (Scheme 19).[1] Although requiring an extended reaction time, cyclization of the des-chloro analogue of **42** exhibited



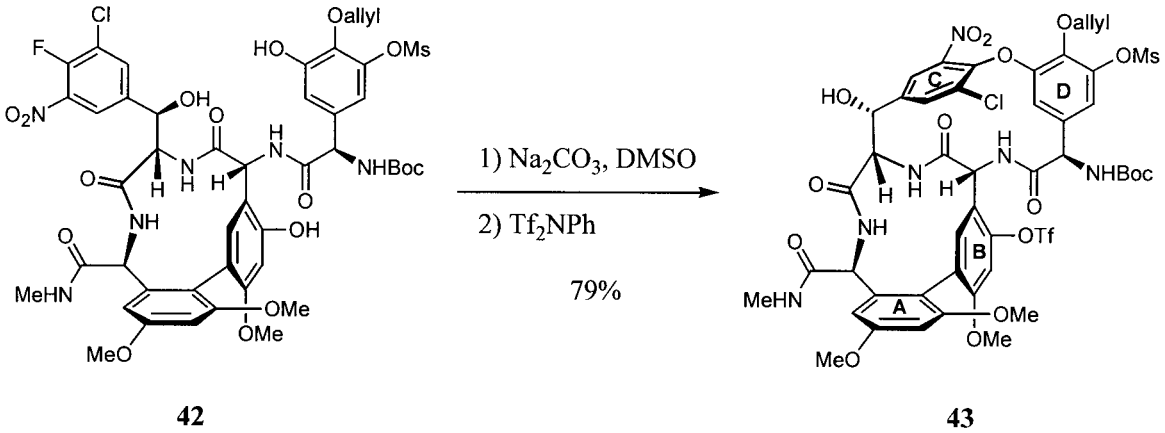
Scheme 16.



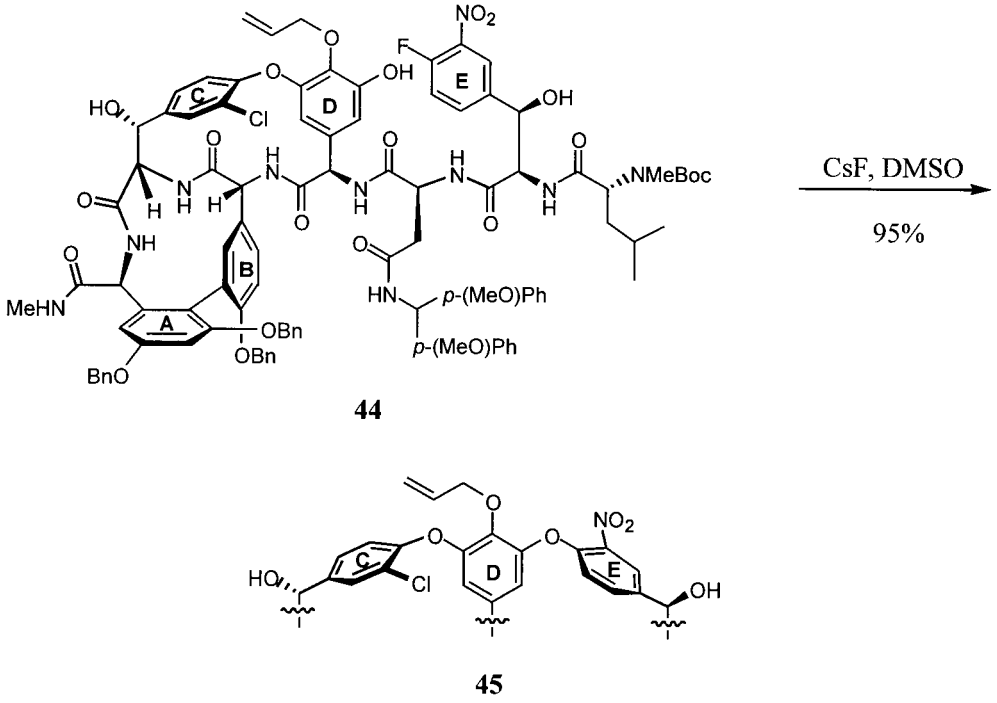
Scheme 17.



Scheme 18.



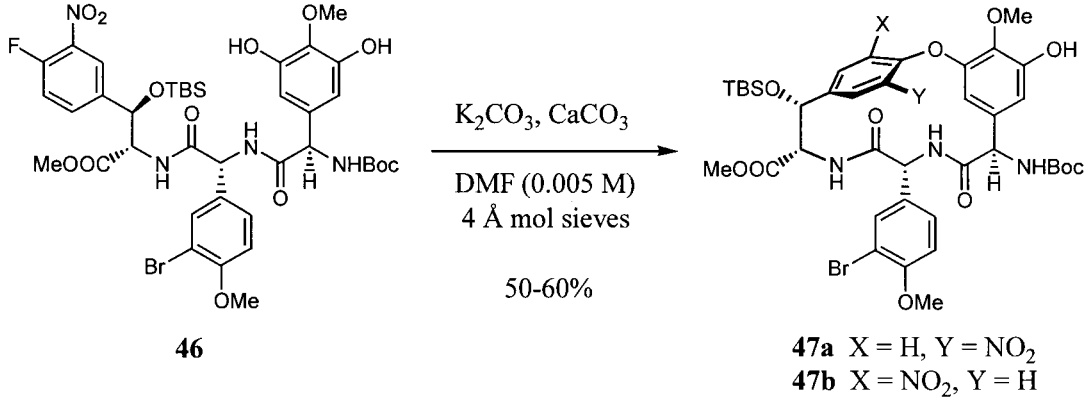
Scheme 19.



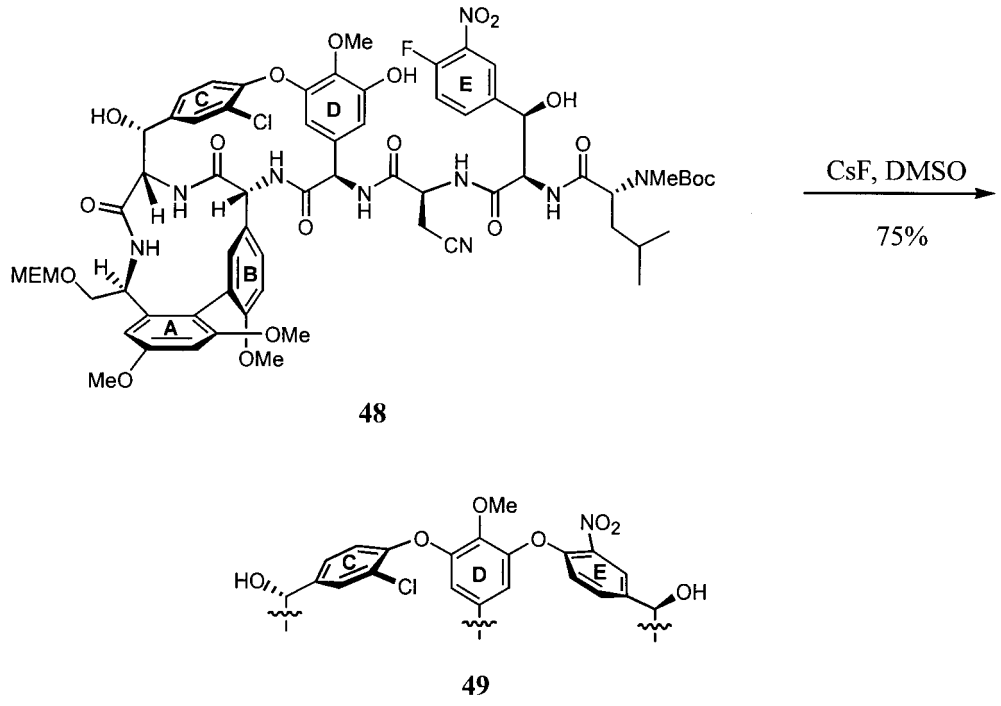
Scheme 20.

the same stereochemical bias, but provided a compound devoid of the correct functionalization required for vancomycin. The cyclization of **42** was found to be so facile that it could even be conducted in the absence of base. Assemblage of DOE ring precursor **44** was followed by the second key intramolecular S_NAr step utilizing cesium fluoride/DMSO rather than sodium carbonate/DMSO. Diastereoselectivity in the formation of **45** was again 5:1 in favor of the E-ring *exo*-nitro atropisomer as depicted (Scheme 20). Conversion of **45** to vancomycin aglycon was accomplished in a further seven steps. Interestingly, the kinetic bias producing the desired atropisomers apparently originates with the AB biaryl framework. Incorporation of the AB fragment early in the synthesis is therefore a key feature of the Evans approach.[2]

Recently, the Boger group[6] has disclosed a completed synthesis of vancomycin aglycon that also relies on a fluoronitroaryl-based S_NAr strategy similar to Zhu's approach to teicoplanin. For construction of the COD ring, the optimal conditions for the cyclization of **46** were found to include a mixture of potassium carbonate and calcium carbonate, which maintained the integrity of the TBS protecting group (Scheme 21).[32] The 1:1 mixture of atropisomers produced (**47ab**) could be separated and the undesired isomer **47b** subjected to thermal equilibration under precise conditions to give a second 1:1 mixture of **47ab**, thus providing a recycling system for enrichment of the desired isomer **47a**.[33] Interestingly, it was also found that cyclization of **46** using the standard cesium fluoride/DMSO protocol failed to provide clean conversion to **47**. Formation of the DOE ring was initiated after incorporation of the AB biaryl ether loop. Thus compound **48** was cyclized using cesium fluoride/DMSO (the potassium carbonate/calcium carbonate method was also investigated on the TBS-protected analogue of diol **48**)[34] to provide the completed



Scheme 21.



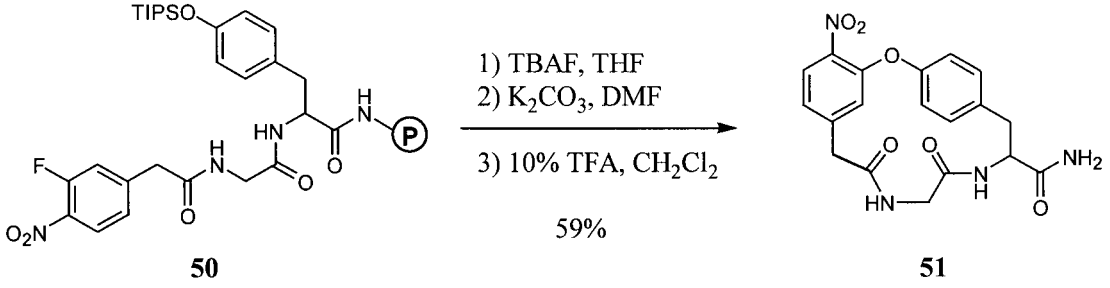
48

49

Scheme 22.

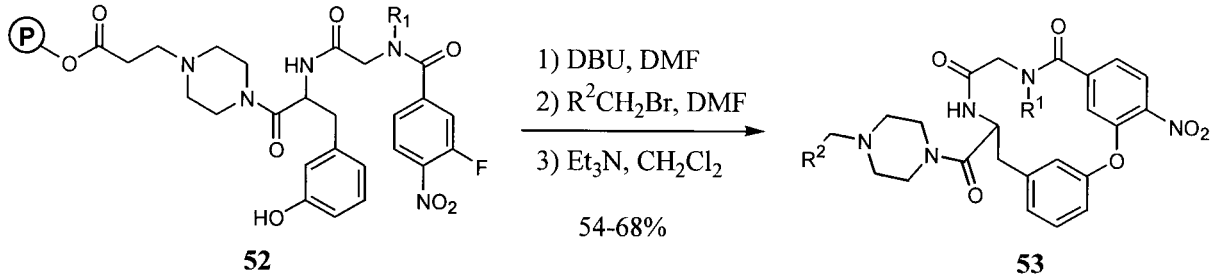
vancomycin skeleton **49** in 75% yield and in a 6:1 ratio of atropisomers (Scheme 22). Conversion of **49** to the target natural product required seven further steps.[6,35]

As with intermolecular S_NAr reactions (vide supra), the use of solid-phase synthesis has also been explored relative to intramolecular S_NAr reactions. A method for the synthesis of derivatives related to the OF-4949 class of antitumor agents has been developed involving fluoronitroaryl-containing macrocyclic precursors bound to Rink's amide resin. Intermediate **50** was cyclized and de-coupled from the resin to provide the macrocycle **51** in good yield (Scheme 23).[36] The use of cesium fluoride/DMF was less efficient, providing 16-membered macrocycle **51** in only 25% yield. The potassium carbonate/DMF method has been successfully applied to 17-membered macrocycles related to OF-4949 as well. A solid-phase approach to 14-membered macrocycles has also been developed as illustrated by the cyclization of resin-bound intermediates of type **52** (Scheme 24).[37] In this case, the initial macrocycle is quaternized with



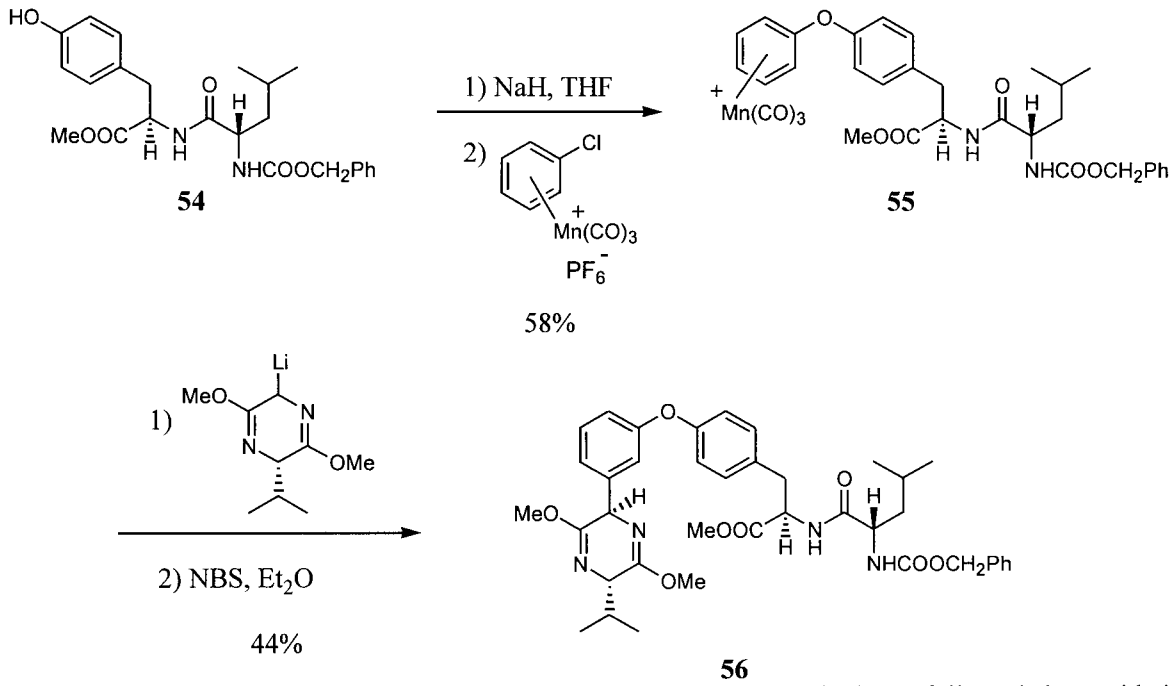
50 51

Scheme 23.



52 53

Scheme 24.

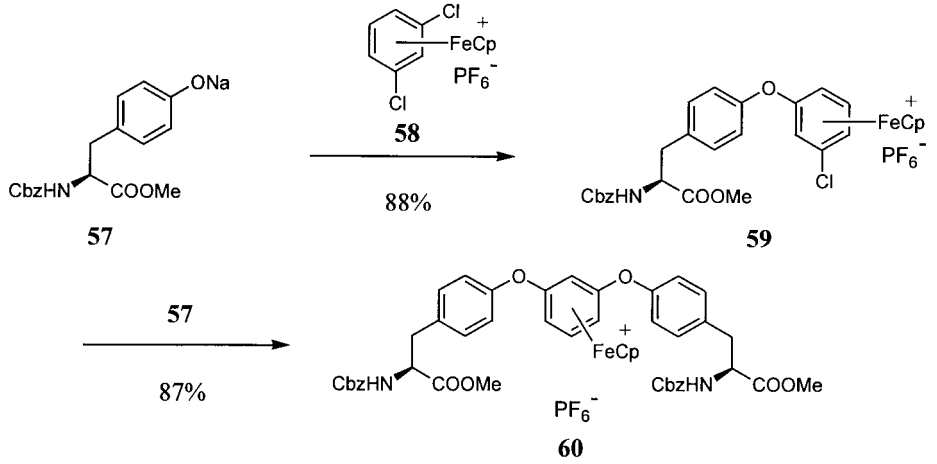


Scheme 25.

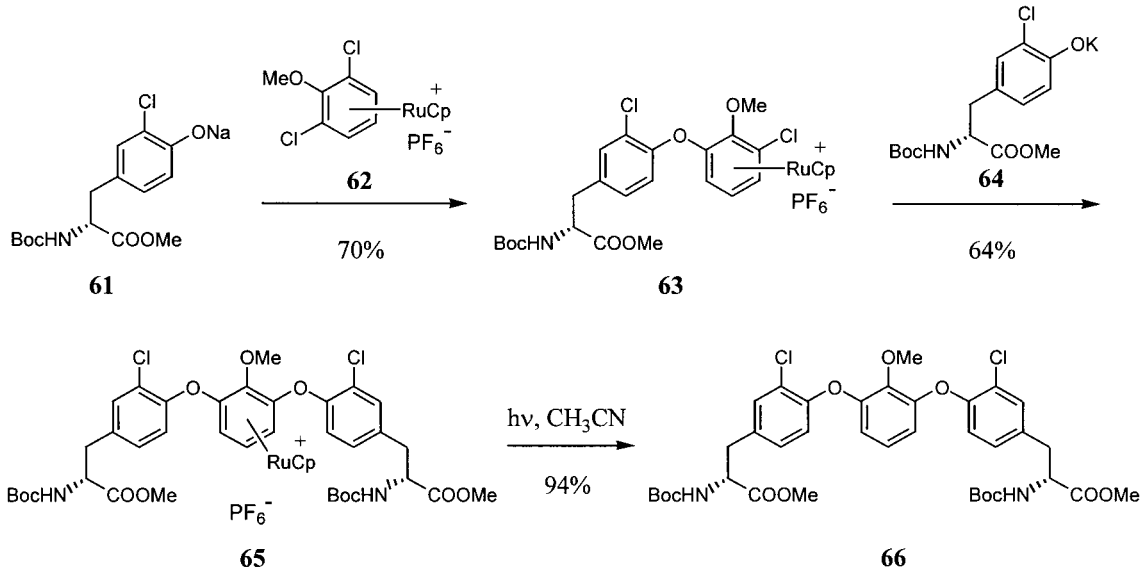
a benzyl bromide prior to base-mediated de-coupling from the polymer. Attempted cyclization of **52** with potassium carbonate/18-crown-6 in DMF failed to provide the target products, again illustrating the specific nature of the base/solvent system required for a given S_NAr macrocyclization strategy.

3.3. Intermolecular S_NAr additions to metal-arene complexes

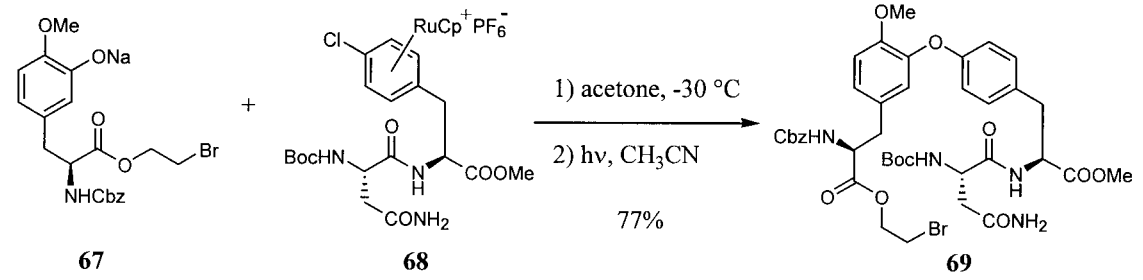
This interesting area has been developed in part to address the need of a mild method of diaryl ether formation applicable in the presence of sensitive functionality associated with the synthesis of the cyclic peptide class of natural products. Original work by Pearson established that arene-manganese complexes represent promising electrophilic platforms in the S_NAr process. Treatment of phenol **54** with a manganese complex derived from chlorobenzene provided compound **55** (Scheme 25).[38] This complex could be further elaborated by the addition of Schöllkopf's chiral glycine enolate equivalent, followed by oxidative demetallation with NBS, to provide peptide **56**, a system related to the DOE portion of vancomycin. Because of the limitations imposed by the use of arene-manganese complexes, including difficulty in forming complexes from the dichlorobenzene systems needed for vancomycin, iron and ruthenium complexes were investigated. In general, iron cyclopentadienyl complexes such as **58** could be reacted with nucleophiles in two sequential operations to provide Ar–O–Ar′–O–Ar″ units such as **60** (Scheme 26).[39] Nucleophilic addition to complexes such as **59** was not limited to sodium phenoxides, as stabilized enolates such as malonate also added smoothly. The use of the more expensive ruthenium cyclopentadienyl



Scheme 26.



Scheme 27.



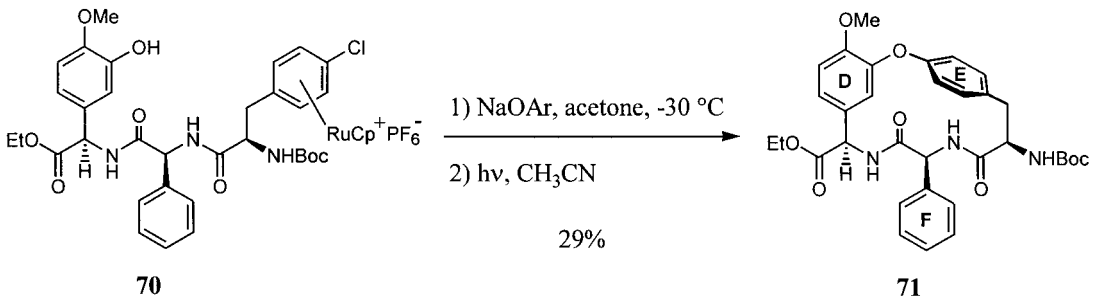
Scheme 28.

complexes proved less suitable than the iron counterparts in these reactions. However, the sodium salt of tyrosine derivative **61** could be added to the analogous ruthenium complex **62** to provide **63**, which was in turn coupled to the potassium salt **64** resulting in formation of **65** (Scheme 27).[40] Demetallation of this intermediate provided the triaryloxy compound **66**, a fully chlorinated model for the synthesis of vancomycin.

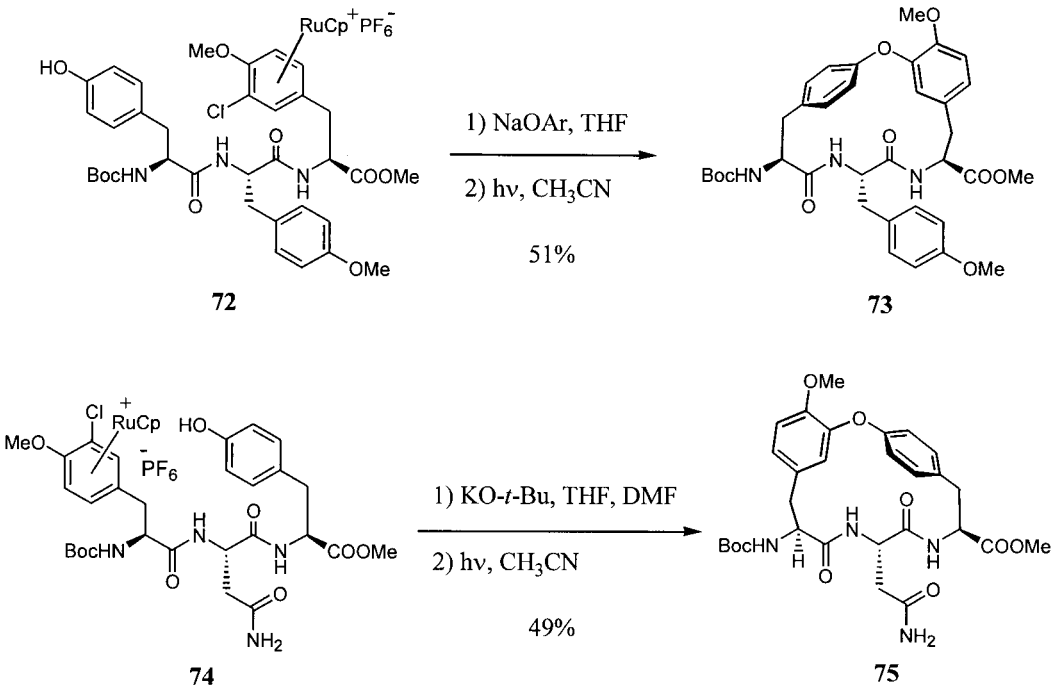
A formal total synthesis of OF-4949 III has also been achieved through the coupling of phenoxide **67** to ruthenium cyclopentadienyl complex **68**, which led to advanced intermediate **69** after demetallation via infrared irradiation (Scheme 28).[41] Completion of the natural product was realized after an additional 3-step sequence involving protecting group removal and lactamization.

3.4. Intramolecular macrocyclizations via S_NAr additions to metal-arene complexes

Application of ruthenium cyclopentadienyl complexes to the synthesis of diaryl ethers through macrocyclization has proven to be a process equally as effective as the intermolecular examples discussed above. Pearson has synthesized the 16-membered DOE ring system of teicoplanin through cyclization of complex **70** mediated by treatment with sodium 2,6-di-*tert*-butylphenoxide in acetone followed by demetallation (Scheme 29).[42] A key feature of this process is



Scheme 29.



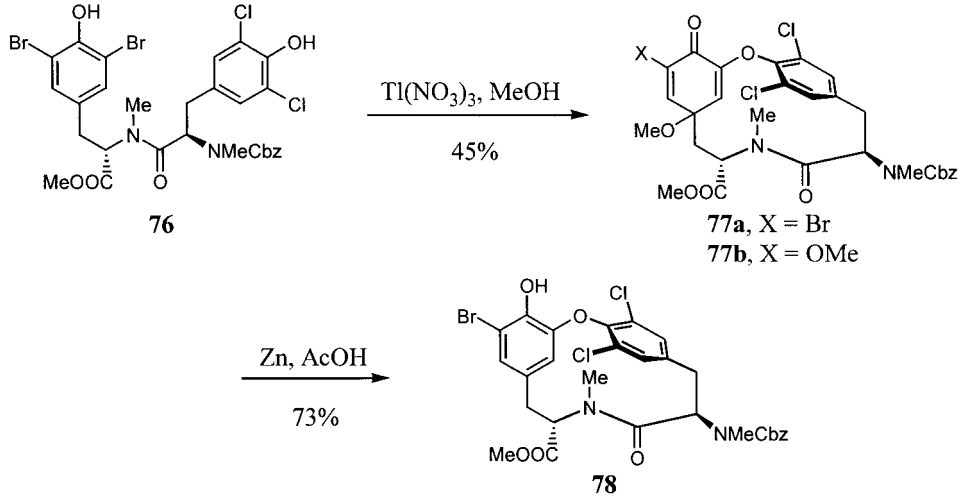
Scheme 30.

recovery of the stoichiometric quantities of ruthenium used as $[CpRu(CH_3CN)_3]PF_6$, which may be recycled to form additional complexes.

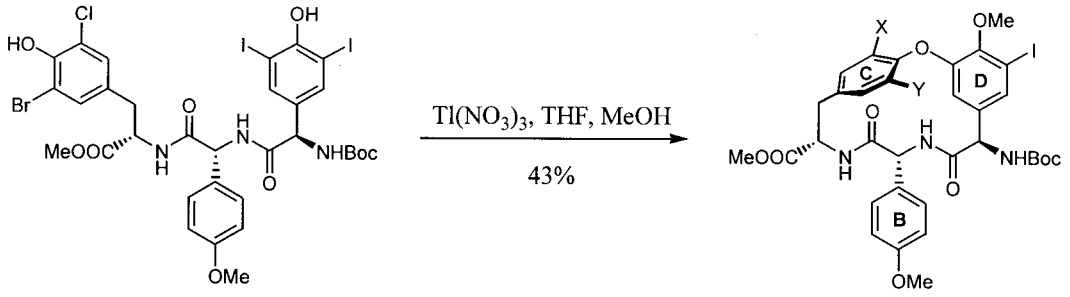
For the synthesis of the cyclic diaryl ether peptide protease inhibitors K-13 and OF-4949 III, Rich developed the cyclization of ruthenium-arene complexes to construct 17-membered ring systems. Using the sodium 2,6-di-*tert*-butylphenoxide method, complex **72** was cyclized and demetallated to provide **73**, an advanced intermediate in the synthesis of ACE inhibitor K-13 (Scheme 30).[43,44] Alternatively, potassium *tert*-butoxide-induced cyclization of **74** led to macrocycle **75**, an intermediate for the synthesis of OF-4949 III. Application of the sodium 2,6-di-*tert*-butylphenoxide conditions to complex **74** provided **75** in only 24% overall yield.

4. Thallium(III)-Mediated Intramolecular Oxidative Macrocyclizations

The quest for the total synthesis of vancomycin aglycon has featured the use of one other method for diaryl ether formation. Thallium(III)-mediated oxidation of halophenolic systems had previously been employed by Inoue for the synthesis of bicyclic hexapeptides RA-VII and deoxybouvardin.[45,46] The method was recently applied to the synthesis of 14-membered macrocycle **78** (Scheme 31).[47] Treatment of bis-phenol **76** with thallium(III) nitrate in methanol resulted in the formation of **77ab** as a 1:3 mixture of products. Bromide **77a** was converted to diaryl ether **78**, a compound possessing the *N,N′*-dimethylcycloisodityrosine skeleton. While the overall yield of **78** is low in this example, it illustrates the feasibility of macrocyclizing



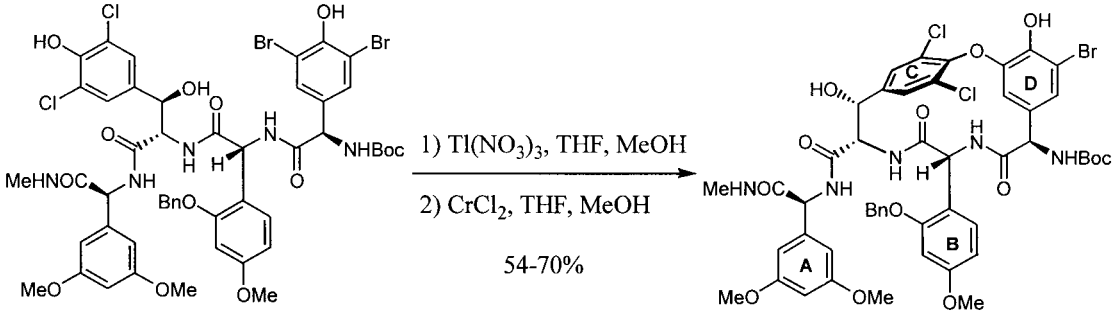
Scheme 31.



79

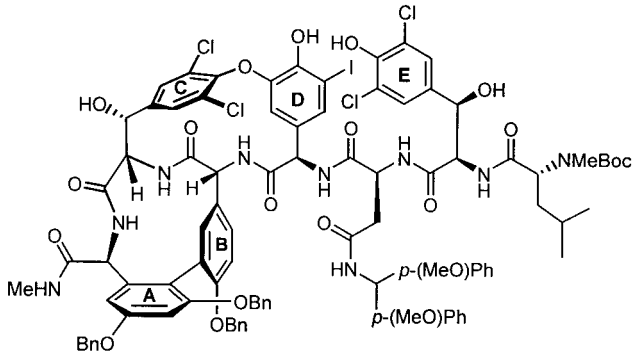
80a, X = Br, Y = Cl
80b, X = Cl, Y = Br

Scheme 32.



81 **82**

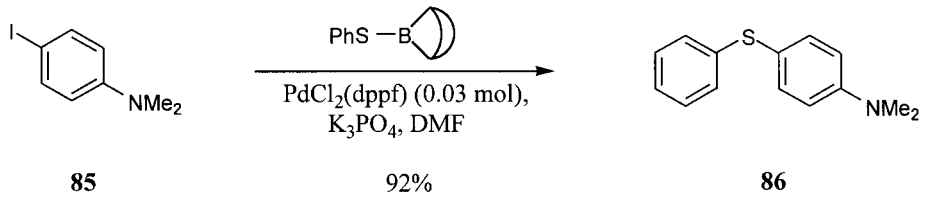
Scheme 33.



83

84

Scheme 34.



85 92% **86**

Scheme 35.

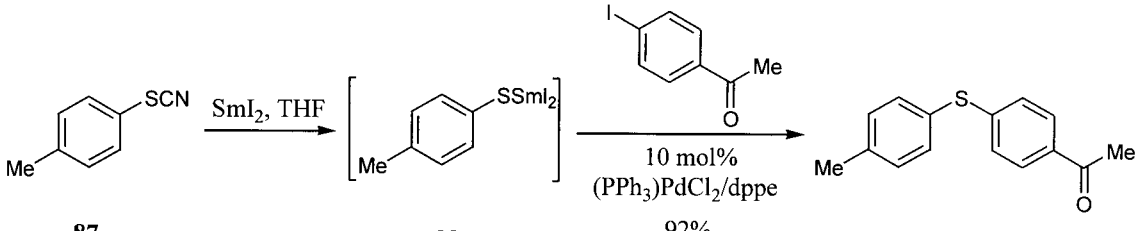
peptide platforms comprised of mixed halogenated tyrosine derivatives. In an application designed to access the COD ring system of vancomycin, bis-phenol **79** was treated with thallium(III) nitrate to give **80ab** as an unspecified mixture of atropisomers (Scheme 32),[48] a transformation that apparently proceeds without a reduction step. As with the example above, the methodology requires phenols with halogens substituted at both *ortho* positions, although in the case of Scheme 32 each halogen on the C-ring of **79** is different.

For the synthesis of orienticin C aglycon, Evans used a thallium(III)-mediated strategy for constructing the COD ring system as illustrated in Scheme 33 (**81** to **82**).[49] While use of this oxidative macrocyclization strategy for assemblage of the COD ring proved facile, application to advanced intermediate **83** provided cyclized tetrachlorinated derivative **84** in low yield accompanied by significant formation of byproducts (Scheme 34).[31] At this stage the Evans group examined alternate methodology for closure of the DOE ring system of orienticin C, eventually settling on the fluoronitroaryl S_NAr macrocyclization strategy described above. Interestingly, incorporation of the AB biaryl system was detrimental to DOE ring closure via the thallium(III) method,[50] in direct contrast to the fluoronitroaryl S_NAr methodology as applied to vancomycin (vide supra).

5. Palladium-Catalyzed Syntheses of Diaryl Ethers

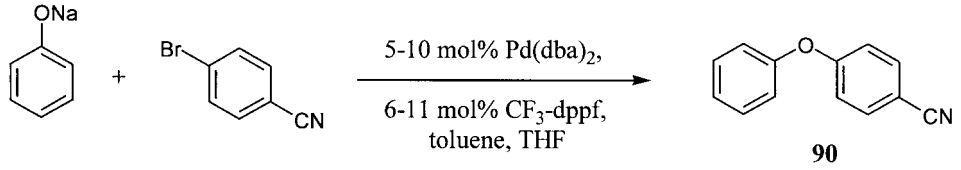
Palladium has recently been used to catalyze the synthesis of both diaryl ethers and thioethers. In an example of the latter case, it was found that 9-thiophenoxy-9-borabicyclo[3.3.1]nonane (prepared by the dehydrogenative condensation of 9-BBN with thiophenol) could be cross-coupled to aryl iodides catalyzed by a palladium complex in the presence of base (e.g., Scheme 35).[51] The conditions are also applicable to the synthesis of alkyl aryl sulfides. Samarium thiolates derived from aryl thiocyanates have also been employed in combination with palladium catalysis for the synthesis of diaryl thioethers under relatively mild conditions (Scheme 36).[52] A survey of several different palladium and nickel catalysts revealed that the use of 1,2-bis(diphenylphosphino)ethane (dppe) and triphenylphosphine ligands together with palladium(II) chloride provided for optimal catalysis. Aryl iodides were generally preferred over bromides in the coupling reaction.

For diaryl ether formation, Hartwig has used a combination



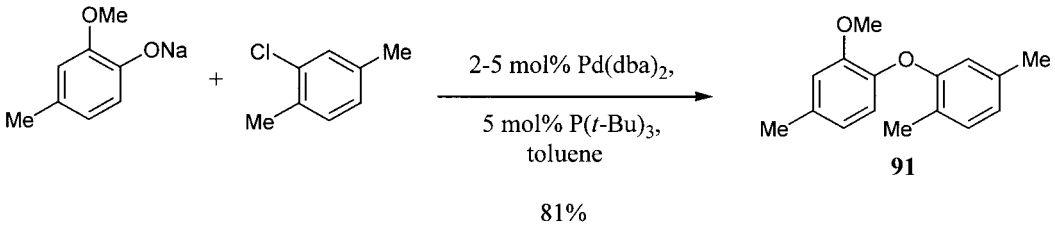
87 **88** 92% **89**

Scheme 36.

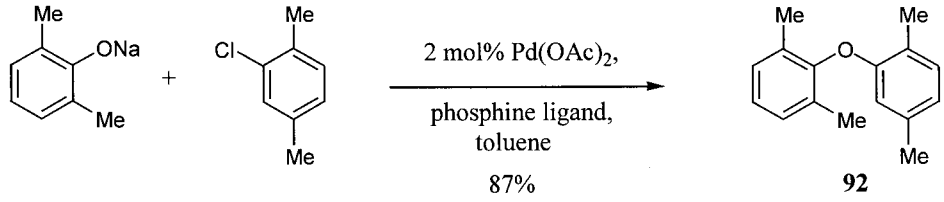


74% **90**

Scheme 37.



Scheme 38.



Scheme 39.

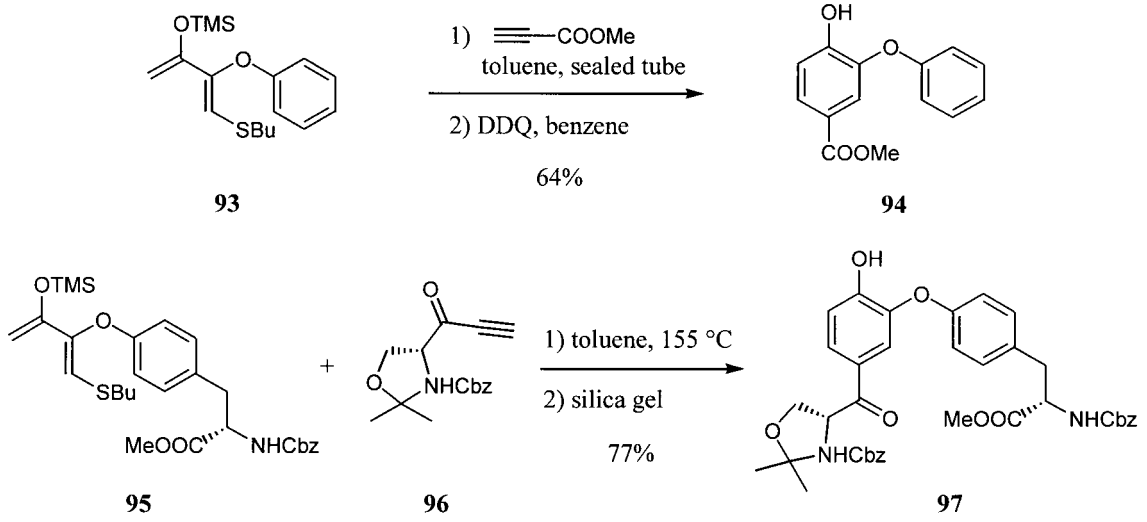
of palladium catalysts featuring dibenzylideneacetone (dba) and 1,1′-di[bis(4-(trifluoromethyl)phenyl)phosphino]ferrocene (CF_3-dppf) ligands to effect coupling of electron deficient aryl bromides with phenoxides (Scheme 37).[53] This process may be viewed as complimentary to standard S_NAr additions where fluoride is the usual leaving group present in the electrophile. A further evolution of this methodology allows for coupling of unactivated aryl chlorides and bromides to phenoxides through the addition of a ferrocenyldi-*tert*-butylphosphine complex or tri-*tert*-butylphosphine as a co-ligand (Scheme 38).[54] Yields were similar with each ligand when relatively hindered aryl halides were employed, but better yields were observed on non-hindered electrophiles using the ferrocene complex. Similar aryl phosphine ligands, notably 2-(*N*,*N*-dimethylamino)-2′-(di-*tert*-butylphosphino)-1,1′-binaphthyl have been developed by Buchwald that also allow coupling of hindered phenoxides to hindered aryl chlorides (Scheme 39).[55]

6. Cycloaddition Reactions

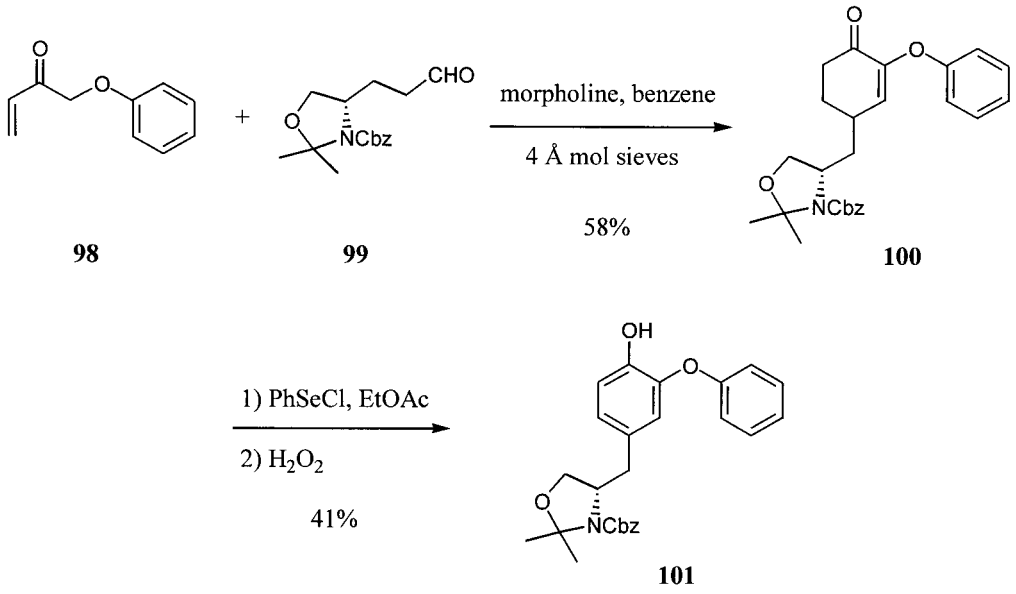
While not a subject of intense investigation, the strategy of building one ring of a diaryl ether sub-unit through a cycloaddition reaction has been explored. Such an approach may be useful in certain situations where the functionality present is intolerant to the usual coupling methods.

6.1. Diels–Alder cycloadditions

Application of the Diels–Alder reaction to the cycloaddition of aryloxy-substituted 1,3-butadienes with acetylenic electrophiles, followed by aromatization, gives fuctionalized diaryl ethers in good yields. For example, diene **93** was condensed with methyl propiolate and the resulting cycloadduct oxidized with DDQ to provide diaryl ether **94** in 64% yield (Scheme 40). More elaborate fuctionalization is also tolerated under the reaction conditions, as is demonstrated



Scheme 40.



Scheme 41.

by the condensation of diene **95** with dienophile **96** to give isodityrosine derivative **97**, which was isolated after silica gel chromatography without the additional DDQ oxidation step.[56]

6.2. Robinson annulations

Another isodityrosine model system has recently been constructed through use of the classic Robinson annulation reaction. In a one-pot reaction vinyl ketone **98** was condensed with aldehyde **99** to give the Robinson product **100** (Scheme 41).[57] After several attempts at oxidation of **100** to the corresponding diaryl ether using oxidants such as $CuBr_2$/LiBr or $Mn(OAc)_3$, it was found that treatment with PhSeCl in refluxing ethyl acetate followed by in situ oxidation/elimination of the resulting aryl selenide with hydrogen peroxide provided **101** in acceptable yield.

6.3. Fischer chromium carbene-mediated benzannulations

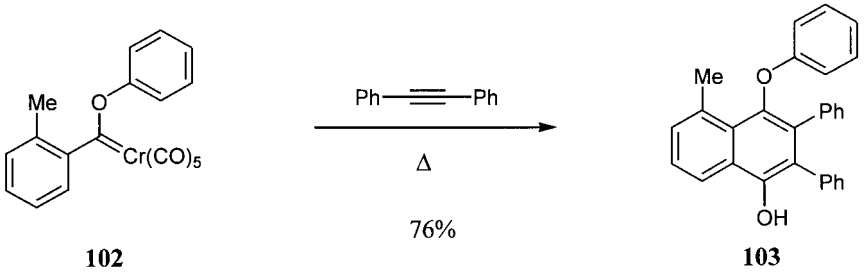
A recent report describes a Dötz-type benzannulation reaction involving the cycloaddition of Fischer chromium carbenes to alkynes leading to highly substituted diaryl ethers.[58] The chromium carbenes, e.g. **102** (Scheme 42), may be prepared from chromium hexacarbonyl, aryllithiums, and phenoxides via a modification of the original Fischer procedure. These are heated with mono- or di-substituted alkynes to effect a formal [3+2+1] cycloaddition to provide diaryl ethers (e.g. **103**) in moderate to good yields. The use of ultrasonic irradiation is reported to give significantly improved yields and shorter reaction times. The resulting regiochemistry of **103** is in agreement with the accepted mechanism of the Dötz benzannulation, which involves the cyclization and aromatization of a vinyl ketene formed through CO insertion into an intermediate vinyl carbene complex.

7. Miscellaneous Methods

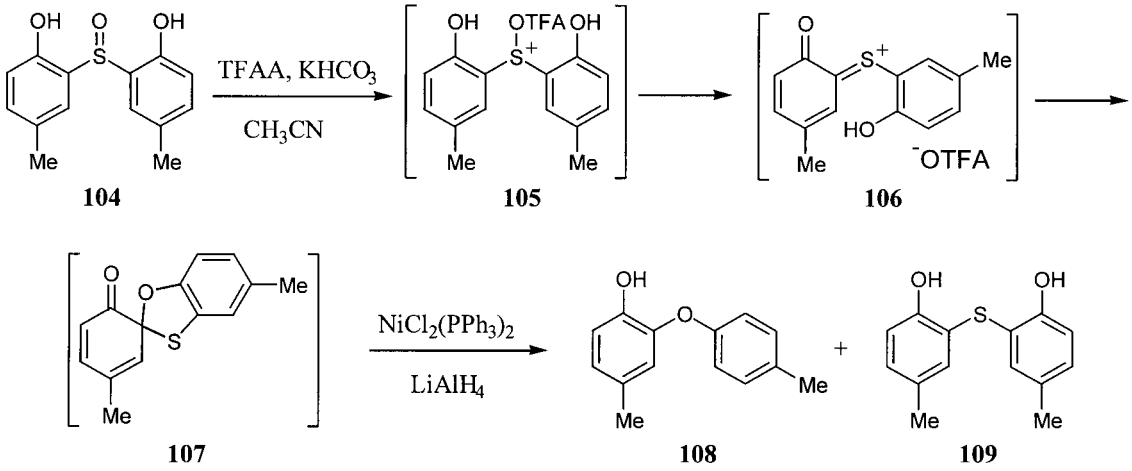
A number of other interesting methods have been developed to construct the diaryl ether unit which do not readily fit into the categories discussed thus far. Most of these are directed at natural product synthesis.

7.1. Pummerer-type rearrangements

An elaborate two-step process has been described by Jung that involves the intramolecular trapping of an α-keto-sulfonium salt derived from a Pummerer rearrangement of a symmetrical *o*-hydroxyaryl sulfoxide. In this process, sulfoxide **104** is treated with trifluoroacetic anhydride to initiate a Pummerer sequence progressing through intermediate **105** to the α-ketosulfonium salt **106**. This species undergoes intramolecular attack by the phenolic oxygen to the



Scheme 42.

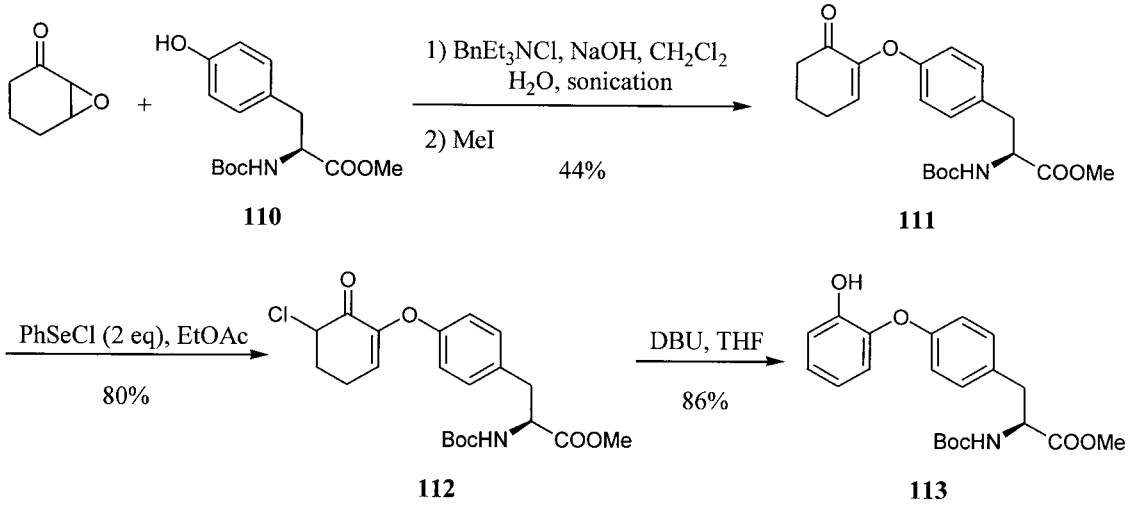


Scheme 43.

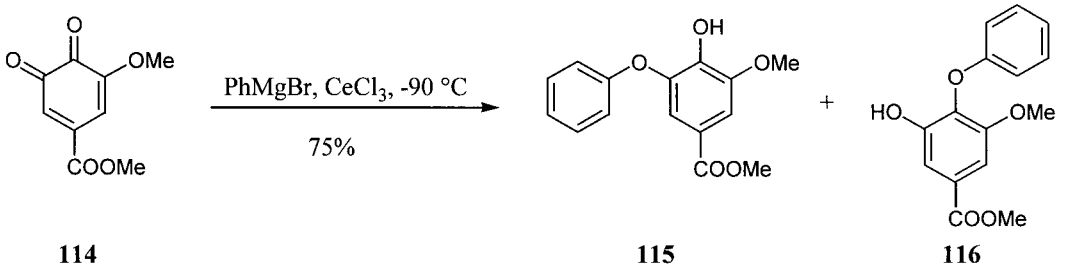
proposed intermediate spirocycle **107**, which may be reduced via a desulfurization reagent to give a mixture of diaryl ether **108** (38% yield) and **109** (56% yield, Scheme 43).[59,60]

7.2. Additions to cyclohexenone oxide

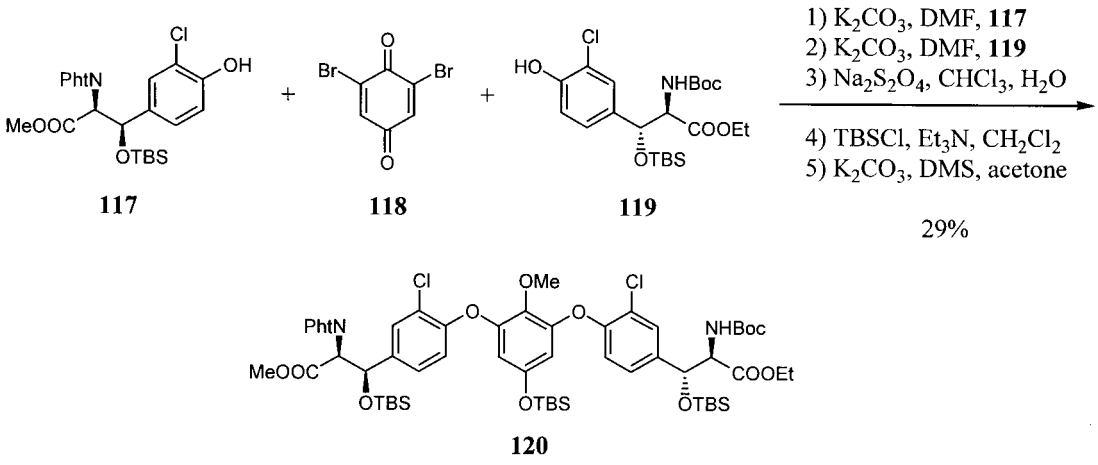
While the Pummerer route described above does not represent a very efficient route to diaryl ethers, Jung has also developed a second sequence involving the addition of phenols to cyclohexenone oxide in an approach similar to the intermolecular S_NAr strategy.[61] In a particular application, diaryl ether **113**, an intermediate in the synthesis of (*S*,*S*)-isodityrosine, was constructed beginning with the base-catalyzed addition of phenol **110** to cyclohexenone oxide followed by re-esterification to provide enone **111**. Attempts to introduce a phenyl selenide group adjacent to the ketone using 2 equiv. of PhSeCl actually led to the chloride **112** instead, which was conveniently dehydrohalogenated to the diaryl ether in good yield (Scheme 44).[60]



Scheme 44.



Scheme 45.



Scheme 46.

7.3. Additions to quinones

An unusual quinonoid carbonyl addition reaction has been reported to produce diaryl ethers. In this example, treatment of quinone **114** with an aryl Grignard reagent catalyzed by cerium or copper resulted in a heterophilic addition to the carbonyl oxygen atoms rather that the usual conjugate addition. The resulting diaryl ethers **115/116** were isolated in an approximately 5:1 ratio (Scheme 45).[62] Lower yields were observed when higher reaction temperatures were used.

Finally, Rao has reported a bis-addition to a quinone in the synthesis of vancomycinic acid, effectively the CODOE Ar–O–Ar′–O–Ar″ sequence of vancomycin. Sequential addition of **117** and **119** to quinone **118** was followed by oxidation and differential alcohol protection to provide the CODOE system **120** (Scheme 46).[63,64]

Although conversion of **120** to vancomycinic acid required a number of further transformations, this efficient construction of the basic Ar–O–Ar′–O–Ar″ backbone of vancomycin illustrates the potential of the quinone methodology.

8. Summary

Undoubtedly development of new methods for the synthesis of diaryl ethers and refinement of existing protocols are on the horizon. With the first complete syntheses of vancomycin recently accomplished, attention will now shift to vancomycin analogues that may solve the pressing problem of antibiotic-resistant pathogens. This area, together with interest in diaryl ether natural products that have evaded total synthesis to date, will insure continued evolution of new diaryl ether methodology.

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Biographical Sketch

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