Pergamon

Tetrahedron 57 (2001) 5683–5705

TETRAHEDRON

Tetrahedron report number 573

Arylation with organolead and organobismuth reagents

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Received 12 March 2001

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1. Introduction

Formation of an sp_2–sp_3 bond through a direct arylation protocol traditionally has not been a key synthetic strategy in the formation of complex organic molecules. However, recent advances in this area, particularly in the use of organolead and organobismuth reagents, are poised to change this state of affairs. More than 10 years have passed since the former editor of this journal undertook a review of arylation reactions;[1] a new look at this area of research is in order. This review is focused specifically on the arylation reactions of organolead and organobismuth reagents and the newer developments in the field. The discussion of organolead reagents will include *C*-and *N*-arylations, while the organobismuth section will cover *C*-, *N*- and *O*-arylations. Both reagents require copper catalysis for arylation on nitrogen. Similar oxygen arylations with bismuth also require copper catalysis. A small segment on palladium-catalyzed arylations with aryllead reagents and arylbismuth(III) reagents is also included.

These reactions occur through a mechanism that has been termed 'ligand coupling'. The mechanism will not be a focus of this review and the reader is directed to an excellent monograph on the subject.[2] Although there is a good deal of mechanistic understanding, more work is necessary to define the limits of reactivity of these aryl cation equivalents. Operationally, both aryllead and arylbismuth compounds react under extremely mild conditions and afford high yields of desired product.

2. Organolead chemistry

No discussion of organolead reagents is complete without acknowledgment of the seminal contributions of Professor John T. Pinhey.[3] His many review articles[4–6] and original contributions have proven fertile ground for the ideas of those who continue in the field. He has shown that aryllead tricarboxylates react with phenols, β-dicarbonyls, α-cyano

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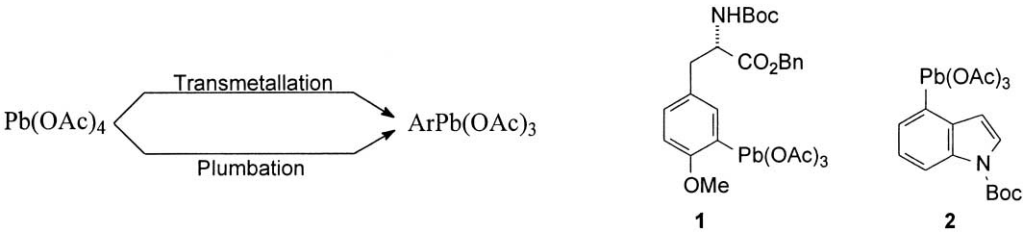
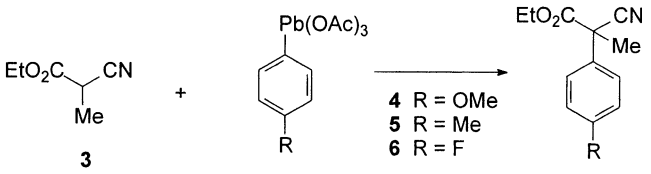
PII: S0040-4020(01)00385-4



Scheme 1.



Scheme 2.

esters, enamines, nitroalkanes, and other carbon acids to produce *C*-arylation products in high yield. The standard reaction conditions outlined by Pinhey employ 3 equiv. of pyridine to 1 equiv. of the lead reagent. Reactions are performed at 40–60°C in chloroform. In accord with the proposed mechanism, these reactions show no indication of proceeding through radical intermediates.[7] Of special importance to the synthetic organic chemist involved in total synthesis, these reactions afford excellent yields in the formation of quaternary centers in the arylation reaction with a suitably substituted starting material. The preparation of such highly substituted carbon centers has been a focus of the community for some time.[8]

2.1. Formation of organolead reagents

Two general routes, transmetallation and direct plumbation (Scheme 1), can be employed in the preparation of organolead reagents. The transmetallation methodology is the more general of the two and allows for greater variation in substituents on the aromatic ring. As such, it is the more useful methodology for the preparation of complex substrates for use in total synthesis ventures. Tyrosine-derived reagent **1**[9] and indole **2**[10] are examples of more sophisticated synthetic intermediates from this laboratory. Other groups have developed diverse organolead reagents for the synthesis of the flavonoid family of natural products.[11] The metal–lead exchange is normally accomplished with tin[12] or boron[13] and catalytic amounts of mercury(II) salts. Another, less common method employs diarylmercury.[14] Direct plumbation (bottom pathway, Scheme 1) is used to prepare a limited number of aryllead tricarboxylates.[15] It is traditionally restricted to electron-rich aromatics.

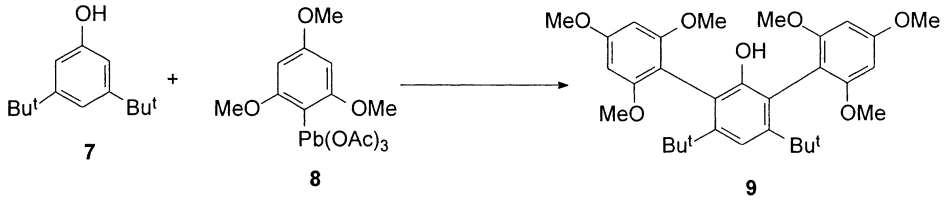
2.2. *C*-Arylation with organolead reagents

Ethyl α-cyanoacetate does not react with aryllead triacetates under standard conditions, but α-substituted derivatives do react cleanly (Scheme 2). Modest to good yields of arylated products are obtained. These reactions have been subjected to various aromatic amine bases in an effort to increase the yield. For the reaction of *p*-methoxyphenyllead triacetate (**4**) with cyano ester **3**, 4-dimethylaminopyridine (72%) was superior to either pyridine (49%) or 1,10-phenanthroline (68%). When the solvent system was changed from chloroform to dimethylsulfoxide (DMSO) the yield increased slightly to 78% with no base necessary. It was speculated that DMSO acts as a ligand for the lead in this reaction, in much the same way pyridine does under the standard conditions. However, the origin of the reactivity in the absence of base remains obscure and more work is needed to understand the generality of these reaction conditions. With *p*-tolyllead triacetate (**5**) and *p*-fluorophenyllead triacetate (**6**) the yields in DMSO were 81 and 74%, respectively. Note the excellent yields obtained from both electron-rich and electron-poor aromatic rings.[16]

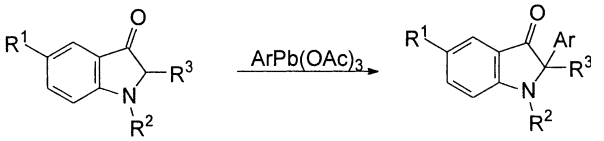
In a reaction designed 'to test the limits' of arylation with organolead reagents, Barton and co-workers successfully coupled 3,5-di-*tert*-butylphenol (**7**) with 2,4,6-trimethoxyphenyllead triacetate (**8**) (Scheme 3).[17] Use of 3 equiv. of lead reagent and 10 equiv. of pyridine provided an 87% yield of diarylated product **9** along with 10% mono-arylated product. The authors used these results to gain insight into the mechanism of this phenol arylation in comparison with similar organobismuth reactions.

Heterocyclic systems have been used extensively as substrates for organolead arylation reactions. For example, a variety of dihydroindoles were arylated with electron-rich aryllead(IV) reagents.[18] The arylation event can take place with the unprotected indole amine present (Scheme 4, entries 1 and 2).

Like the dihydroindoles shown in Scheme 4, benzofurans can be arylated as their corresponding β-ketoesters (Scheme 5).[19] Compound **10** was arylated in 85% yield



Scheme 3.



$R_1 = R_2 = H$; $R_3 = CO_2Me$; Ar = *p*-MeO-C_6H_4, 98%
$R_1 = R_2 = H$; $R_3 = CO_2Me$; Ar = 2,4-MeO-C_6H_4, 68%
$R_1 = OMe$; $R_2 = COMe$; $R_3 = H$; Ar = 2,4-MeO-C_6H_4, 81%
$R_1 = H$; $R_2 = SO_2Ph$; $R_3 = H$; Ar = 2,4-MeO-C_6H_4, 60%

Scheme 4.

with **8** under standard conditions. Compound **11** was converted to the natural product nor-neolignan.

Arylation of 5-oxazolone **12** with aryllead triacetates and subsequent hydrolysis and decarboxylation affords arylglycines in high yield (81–93%, Scheme 6), either as the ester or free acid depending on the hydrolysis conditions.[20] Once again, yields are uniformly high for both electron-rich and electron-poor aromatic rings, leading to a wide variety of arylglycine derivatives. In addition, in situ formation of the aryllead reagent from lead(IV) acetate and the desired arylboronic acid simplifies the process to a one-pot procedure. In this case, care must be taken to destroy any unreacted lead(IV) acetate with a small amount of formic acid.[21] Enzymatic resolution of **13** affords optically active D- and L-arylglycines with ee's in the >90%.[20,22]

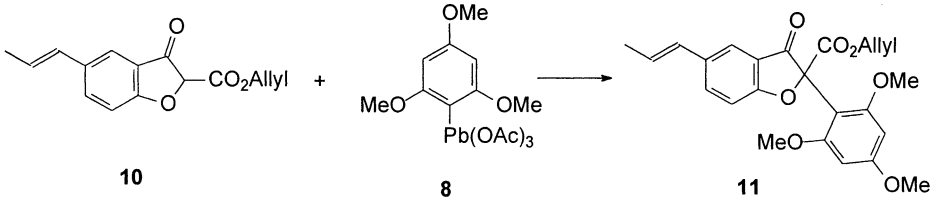
2.2.1. Total synthesis with organolead reagents. It comes as no surprise that, given the extensive body of fundamental work on aryllead(IV) reagents, there should be an increase of planned total synthesis ventures employing these reagents. The ease of preparation of highly functionalized aryllead compounds, the ability of these compounds to form C–C bonds, particularly quaternary centers, in high yield, and the extremely mild reaction conditions suggest many uses in contemporary organic synthesis.

Efforts in this laboratory toward the synthesis of the marine natural product diazonamide A have focused on the central quaternary center at C10.[9] In early studies (Scheme 7) it was shown that the coupling of benzofuranone **14** with tyrosine derivative **1** under standard conditions provided 78% isolated yield of desired product **15**. Unfortunately, compound **15** could not be elaborated effectively. More recently, sodium salt **16** has been shown to react with **1** in $CHCl_3$ solution with no added pyridine to afford **17** as a single isomer in an unoptimized yield of 40%.[23] Presumably the absolute stereochemistry [at C29, diazonamide numbering system], which is derived from the amino acid serine, directs the reaction to afford only one compound.

Efforts in this laboratory directed at *N*-methylwelwitindolinone C isothiocyanate, a multidrug resistance reversal agent (Scheme 8), led to the reaction of the indole-derived lead reagent **2** with β-keto ester **18**. This reaction proceeds in excellent yield (98%) and diastereoselectivity (>30:1) to afford product **19**.[10] A more detailed discussion of the diastereoselectivity of aryllead(IV) reagents is presented in Section 2.2.2.

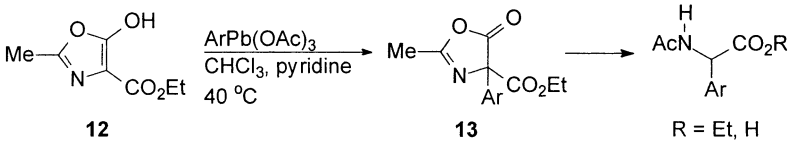
Finet and co-workers have focused on the compact array of aromatic rings found in flavonoids, isoflavonoids[24,25] and neoflavonoids,[26,27] which makes this class of compounds ideal targets for organolead chemistry development. Beyond the standard activating groups such as β-ketoesters and β-ketosulfones, the use of β-ketosulfides has proven quite successful, as shown below (Scheme 9). Reaction of β-ketosulfide **20** with electron-rich aryllead **21** affords desired coupled product **22** in 64% yield.[11,28] A similar coupling was employed in the synthesis of the natural 3-aryl-4-hydroxycoumarins robustin and isorobustin.[29,30] Greatest success in the synthesis of compounds in these classes of natural products was achieved when electron-rich lead reagents were employed.[24–28] Diastereoselectivity in the coupling reactions of **20** has been observed but never rigorously determined.[31] The success of these transformations illustrates the lower oxidation potential of aryllead(IV) reagents as compared to lead(IV) acetate, which would certainly be expected to react with the sulfide functionality.

In the total synthesis of (±)-sesamin, a diarylation of compound **23**, containing two β-ketoester functionalities, was accomplished in 72% yield with aryllead reagent **24** (Scheme 10).[32] Compound **25** was further elaborated to obtain the natural product. Similarly, other organolead reagents were employed with compound **23** to obtained (±)-eudesmin and (±)-yangambin.[33] In this case, the



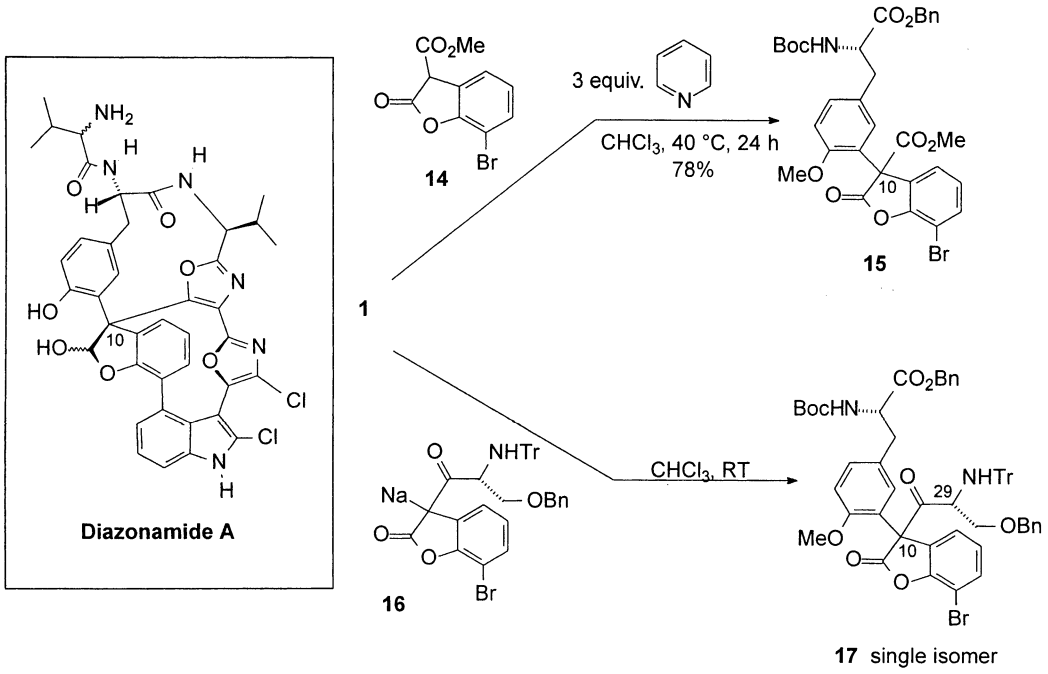
10 **8** **11**

Scheme 5.

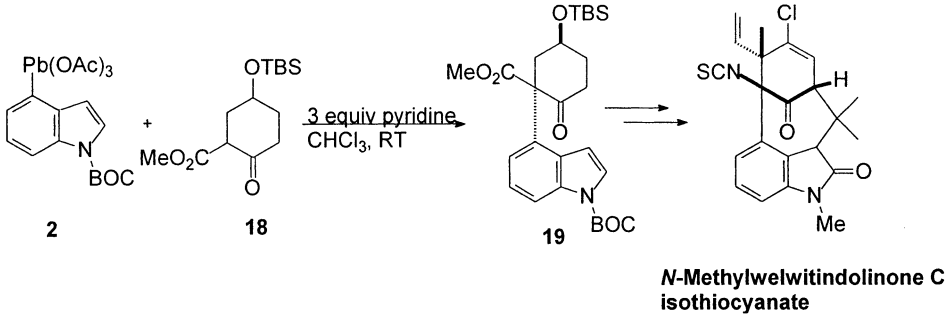


12 **13** R = Et, H

Scheme 6.



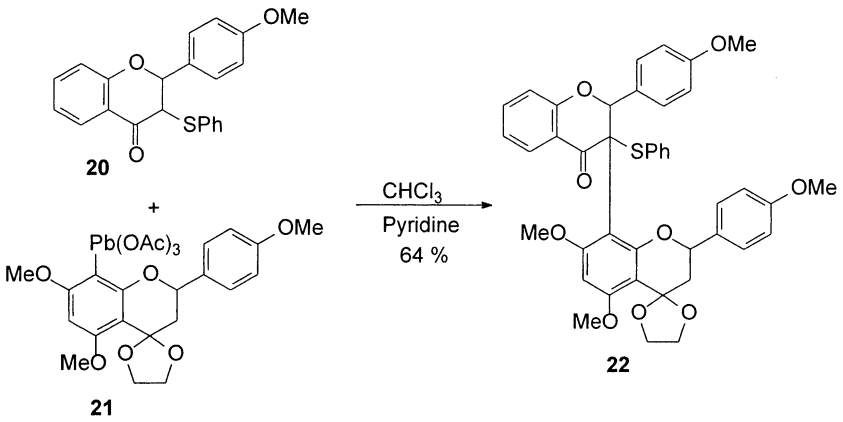
Scheme 7.



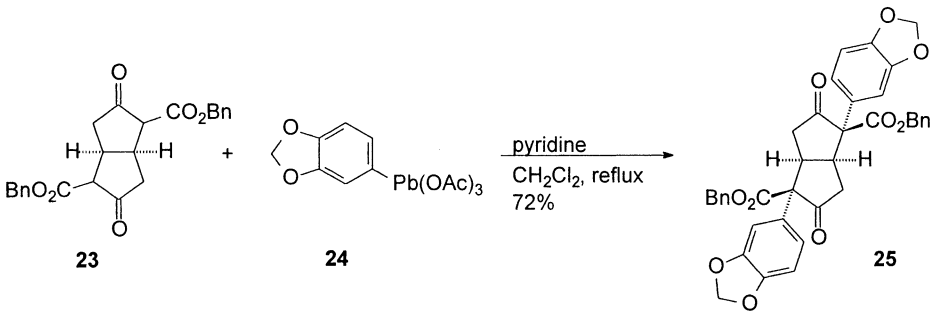
Scheme 8.

diastereoselectivity is dictated by the inherent bias of the bicyclo[3.3.0]octane ring system.

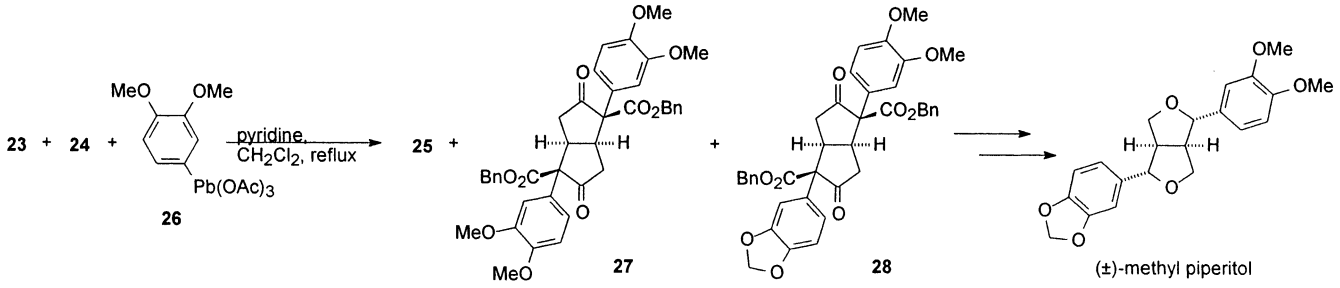
An interesting example of differential reactivity in aryllead reagents is disclosed in the synthesis of (±)-methyl piperitol (Scheme 11).[34] A one-pot treatment of compound **23** with two different organolead reagents (**24** and **26**) afforded a mixture of the two expected symmetric compounds **25** and **27** as well as unsymmetrical material **28**. With 1.1 equiv. of each lead reagent the ratio of products was 0.46:0.72:1.0, indicating the greater reactivity of lead reagent **26**. The ratio changed to 0.43:0.49:1.0 when



Scheme 9.



Scheme 10.



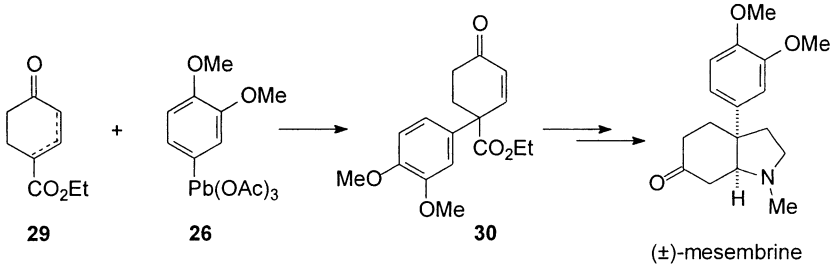
Scheme 11.

0.86 equiv. of **26** and 1.33 equiv. of **24** were used. Compound **28** was isolated in 33% overall yield and further elaborated to obtain (±)-methyl piperitol. Although this reaction displays only modest selectivity, it is interesting to speculate on the possibility of much larger differential reactivity between aryllead(IV) reagents modulated by more substantial differences in the electronic nature of the aryl groups (both **24** and **26** are electron-rich) and/or the ligands (carboxylate groups, solvent) bound to the lead itself.

For a formal synthesis of (±)-mesembrine, vinylogous β-ketoester **29** was arylated with 3,4-dimethoxyphenyllead triacetate (**26**) in good yield to provide compound **30** (Scheme 12),[35] which was further elaborated to the natural product. Replacement of ethyl ester **29** with the corresponding methyl ester increased the yield of coupled product significantly.

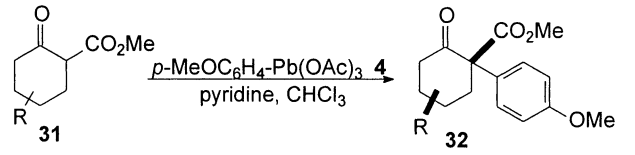
2.2.2. Diastereoselective reactions. The stereochemistry of aryllead reactions has not been extensively investigated. Pinhey et al. have reported diastereoselectivity for the arylation of two compounds,[36] and Moloney et al. have done the same for a single compound.[37] This laboratory has reported on the diastereoselectivity in the reaction of 5-substituted methyl 2-oxo-1-cyclohexanecarboxylates (**31a–d**, Table 1) with 1.1 equiv. of *p*-methoxyphenyllead triacetate (**4**).[38] Selectivities range from poor for ketal **32d** to excellent for protected alcohol **32c**. Increasing the lead reagent to 1.4 equiv. results in isolated yields of over 90% in all cases. Indeed, the crude reaction mixtures are quite clean, with only recovered starting material and desired product obtained. The extraordinary selectivity of the silyl protection group compared to the more bulky *tert*-butyl group (compare entry b with c in Table 1) was unexpected. In addition, this effect is consistently observed with other silyl protection groups and with other aryllead(IV) reagents in reactions with **31c**, as shown in Scheme 8.[10]

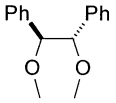
Table 1 also shows the results obtained when the 3-, 4-, 5-, and 6-methyl derivatives of methyl 2-oxo-1-cyclohexanecarboxylates are employed as substrates. The selectivities ranged from moderate to excellent, with the 3-methyl derivative giving the best selectivity (entry **32e**). The yield of this reaction was poor, however, with no recovered starting material. As this is the only reaction in which no starting material is recovered, it is suggested that this lone example of poor mass recovery of a room temperature



Scheme 12.

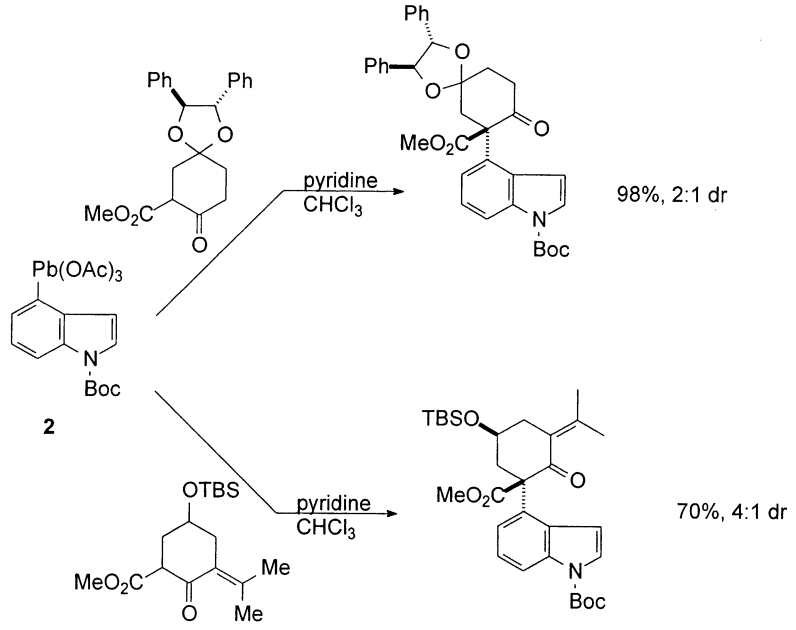
Table 1. Arylation results for substituted β-ketoesters



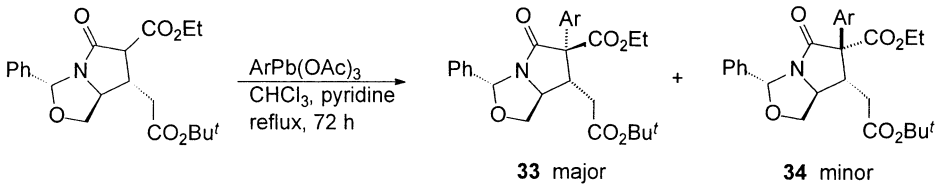
Entry	*R*	% yield **32**	Diastereomer ratio
a	5-Me	74	7:1
b	5-*tert*-butyl	66	9:1
c	5-OTBDMS	74	20:1
d		73	3:2
e	3-Me	16	15:1
f	4-Me	65	3:1
g	6-Me	23	9:2

reaction is due to overoxidation at the C3 center, with concomitant formation of water-soluble compounds. There is ample evidence for α-acetoxylation in aryllead reactions, although no direct evidence of this was obtained in the arylation of **31**. This side reaction may originate from an increase in the acidity of the C3 proton due to complexation of the β-ketoester functionality with a lead species functioning as a Lewis acid. The high diastereoselectivity may also arise through this mechanism; that is, by an equilibration of the final product under the reaction conditions. Alternatively, one diastereomer could be more rapidly oxidized, resulting in a significant increase in the relative amount of the least reactive isomer. These details must await further mechanistic studies. By contrast, the yield of product **32g** is low, but starting material makes up the remainder of material isolated. This low yield is most likely attributed to enhanced steric interactions in that system.

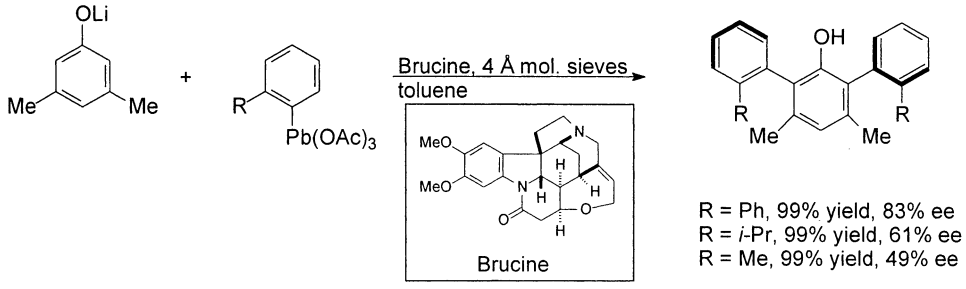
As part of our total synthesis venture of the marine cytotoxic compound *N*-methylwelwitindolinone C isothiocyanate (Scheme 8), the reaction of 4-indolyllead triacetate was explored with a number of β-ketoesters (Scheme 13).[39] As previously shown, silyl protection of the 5-hydroxycyclohexanone system (Scheme 8) led to excellent selectivity. Other silyl protection schemes were also very successful, while other protection groups for the hydroxyl functionality (e.g., acetyl, pivalyl) gave poor selectivity (reactions not shown). The introduction of an exocyclic double bond in anticipation of closing the 7-membered ring of the target compound also precipitated a drop in selectivity. Generally speaking, these results are accommodated by the accepted mechanism for addition to a stabilized enolate of the type derived from deprotonation of a β-ketoester.[40] The enhanced selectivities exhibited by silyl protection groups are still under investigation, although the results may be explained by the preference of the $OSiR_3$ functionality to occupy the axial orientation.[41]



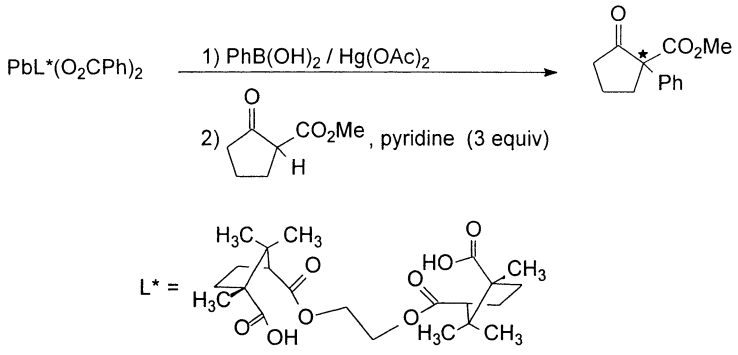
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

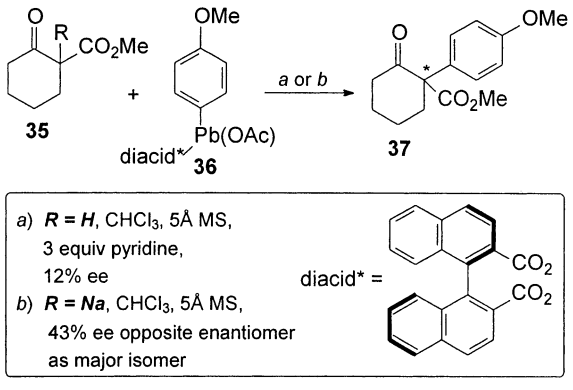
Moloney and co-workers have studied the arylation of constrained glutamate analogs (Scheme 14). In these systems the diastereoselectivities were not great, varying from 2.4:1 (**33**:**34**) with phenyllead triacetate to 1.7:1 for *o*-methoxyphenyllead triacetate.[37] In a later paper,[42] the diastereoselectivity increased to 4:1 for *m*-methoxyphenyllead triacetate (**33**:**34**). Overall, these reactions proved more challenging, requiring higher reaction temperatures and longer reaction times than is normally needed. The reactions could be accomplished with in situ generation of the organolead species from the corresponding boronic acid.

2.2.3. Enantioselective reactions. The challenges of asymmetric synthesis have been at the forefront of synthetic organic chemistry research for more than two decades, and many elegant examples of success in this area have been noted. It is not surprising, therefore, that organolead reagents, which excel at the formation of quaternary centers, would be the subject of studies aimed at the production of enantiomerically enriched material.

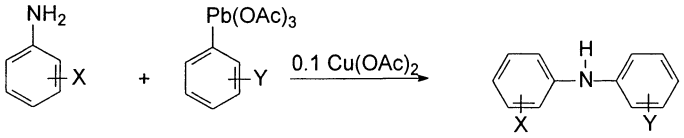
There is only one reported example of enantioselective couplings of organolead reagents with phenols, which provide access to triaryl compounds with axial chirality (Scheme 15).[43] The reaction conditions are unusual in a number of ways. Toluene is preferred as solvent over chloroform, and the reactions are best performed at low temperature (−20 to −40°C). It was found that the preformed lithium phenoxide was far superior to the free phenol in these reactions, and the addition of 4 Å molecular sieves was crucial to success. An array of enantiomerically pure nitrogen bases were tested as additives in place of the standard pyridine, and the alkaloid brucine provided the highest yields and enantiomeric excess (ee). Six equiv. of the alkaloid afforded the best results, although the authors showed that catalytic amounts of brucine (0.2 equiv.) could be used with no loss in enantiomeric excess. However, the isolated yield under these conditions was lower. For the reaction shown in Scheme 15, ee's are good to very good, and can be increased by recrystallization of the product. Diastereoselectivity (*dl*:meso) is uniformly high. With some reaction partners mono-arylation product is a significant portion of the final mixture.

Two groups have explored the asymmetric coupling of aryllead(IV) reagents with β-ketoesters by replacement of one or more of the labile acetate ligands with enantiomerically pure carboxylic acids.

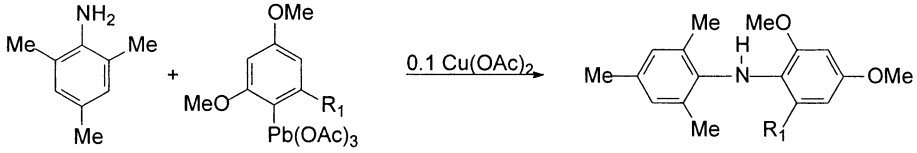
Moloney and co-workers employed camphoric anhydride to develop a series of enantiomerically pure diacid derivatives, only one of which is shown in Scheme 16.[44] The formation



Scheme 17.



Scheme 18.



38 **39** R_1 = H; **7** R_1 = OMe

38 + **39** 74 %; **38** + **7** 18 %

Scheme 19.

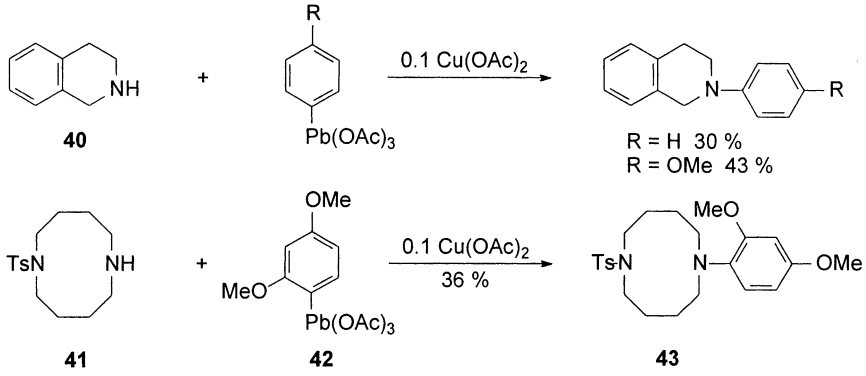
of novel aryllead(IV) reagents proceeded from lead(IV) acetate through a ligand exchange process.[45,46] In a one-pot, two-step process, in situ generation of phenyllead tricarboxylate is followed by the addition of a nucleophile along with pyridine (3 equiv.). Unfortunately, the asymmetric induction was very low for this reaction. The best enantiomeric excess obtained was 10% with a 69% chemical yield (Scheme 16).[47,48]

In this laboratory, preliminary work on enantioselective arylation reactions with aryllead(IV) tricarboxylates began with the recognition of the many contributions of the binaphthalene system to enantioselective transformations (Scheme 17).[49] In particular, analysis of the solid state structure of *p*-methoxyphenyllead triacetate **4**[50] indicated that enantiomerically pure 1,1′-binaphthyl-2,2′-dicarboxylic acid should be geometrically capable of replacing two of the three acetate ligands. Indeed, mixing of **4** with an equiv. amount of the binaphthalene derivative afforded a material consistent with the structure of **36**. Treatment of **36** with cyclohexanone **35** (*R*=H) in the presence of 3 equiv. of pyridine in $CHCl_3$ containing 5 Å molecular sieves afforded a 70% yield of desired product **37**. Recovered starting material accounted for the remaining organic material (≥95% mass recovery based on initial β-ketoester). Recovery of 1,1′-binaphthyl-2,2′-dicarboxylic acid was in the 85–90% range. Analysis employing both enantiomerically pure shift reagent $Eu(tfc)_3$ and enantiomerically pure stationary phase HPLC indicated approximately 12% enantiomeric excess (ee) was obtained, in accord with the results of Moloney. However, when the reaction was performed with **36** and the sodium salt of **35** (*R*=Na, prepared from NaH) in the absence of pyridine but otherwise under identical conditions, a 64% chemical yield of desired product **37** exhibiting 43% ee enriched in the opposite enantiomer from the pyridine experiment was obtained.[49]

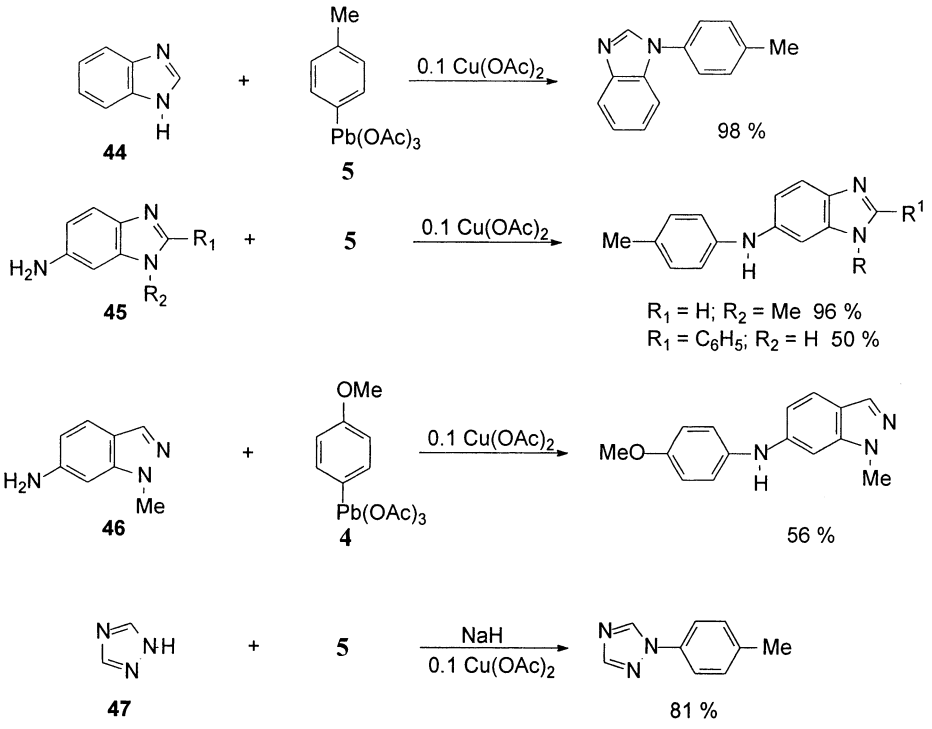
Clearly, much more work in this area is needed. The dramatic differences between the salt-free/pyridine and the preformed salt/pyridine-free conditions are worthy of close scrutiny, as is the use of molecular sieves. These are complex issues, since it is clear that pyridine enters the lead coordination sphere and effects changes in the redox potential, and the resultant chemistry, of the system.[51]

2.3. *N*-Arylation with organolead reagents

In a series of papers, Barton and co-workers showed that aniline derivatives could be *N*-arylated with aryllead triacetates via copper catalysis (Scheme 18).[52–54] The reactions occurred in CH_2Cl_2 with 10 mol% copper(II) acetate. *p*-Nitroanilines could not be arylated with this procedure.[54] On the other hand, significant steric hindrance on the aniline appeared to be tolerated. For example, mesitylamine **38** was reacted with a series of aryllead



Scheme 20.

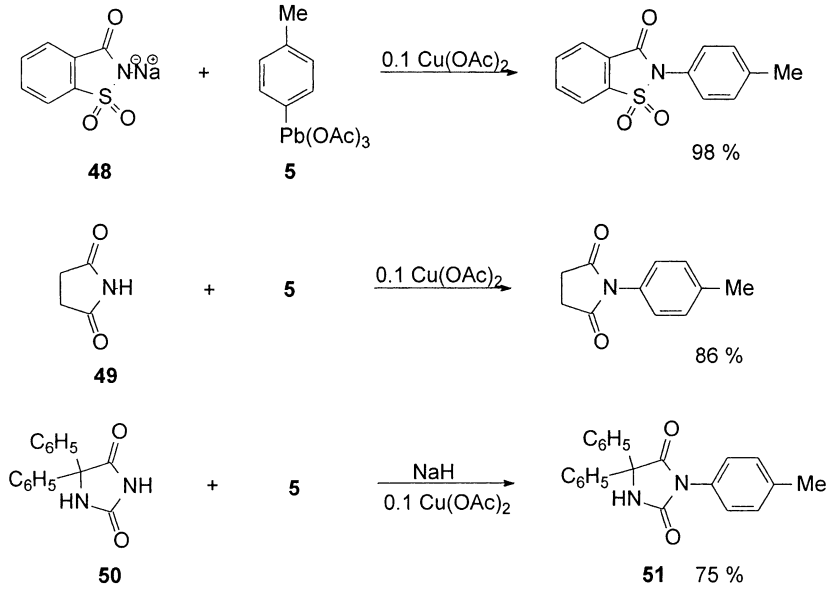


Scheme 21.

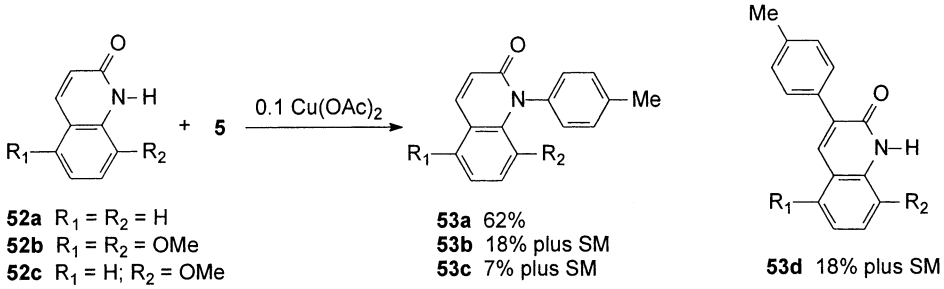
triacetates; two examples are shown in Scheme 19. With 2,4-dimethoxyphenyllead reagent **39** the coupled yield was a respectable 74%. However, only an 18% yield was recorded in the reaction of **38** with 2,4,6-trimethoxylead triacetate **7**.[52]

Aliphatic amines can be *N*-arylated in modest yields as shown in Scheme 20.[52,53,55] 1,2,3,4-Tetrahydroisoquinoline **40** was arylated with phenyllead triacetate in 30% yield[53] and with *p*-methoxyphenyllead triacetate in 43% yield.[52] Monotosyl 1,6-diazacyclodecane **41** was arylated with 2,4-dimethoxyphenyllead triacetate **42** in 36% yield by slow addition of the lead reagent.[55]

Azoles are excellent partners for this arylation technology (Scheme 21).[56,57] Benzimidazole **44** was arylated in 98% yield with lead reagent **5**. Heteroaromatic derivatives **45** and **46** were arylated in good to excellent yield on the aniline nitrogen.[58,59] In a key experiment, chemoselectivity was observed for amino-benzimidazole derivative **45**



Scheme 22.



Scheme 23.

(R_2=H). Only the aniline functionality was arylated in 50% yield.[57] Amino-benzopyrazole **46** was arylated with *p*-methoxyphenyllead triacetate **4** in 56% yield.[59]

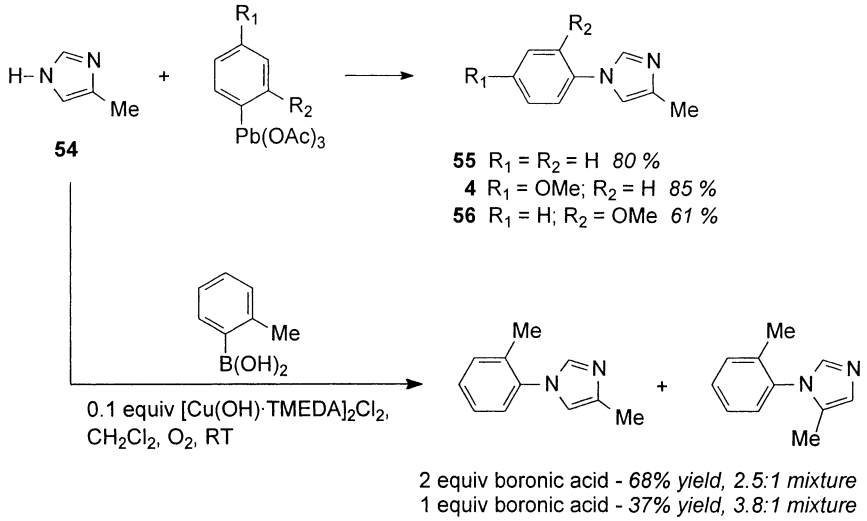
Imidazole, 3-methylindole and various triazoles were also arylated in high yields.[57] 1,2,4-triazole **47** was arylated at the 1-position with a slight excess of sodium hydride in 81% yield.[57] Without the sodium hydride, a mixture of arylated products was isolated in very low yield.

A wide variety of amides react with aryllead(IV) reagents via copper(II) catalysis. These include simple amides as well as more complex systems such as sulfonamides (**48**), imides (**49**), and hydantoins (**50**) (Scheme 22). Yields are good to excellent, with simple amides requiring more vigorous conditions that can lead to diarylation. Prior sodium salt formation has proven advantageous in many circumstances.[60,61]

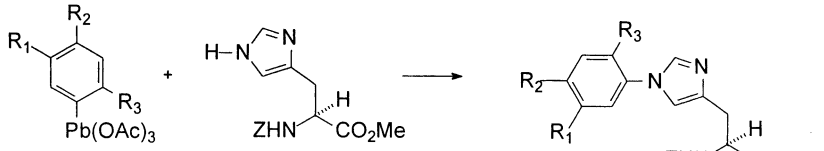
1,2-Dihydroquinolin-2-one **52a** (R=R^1=H) reacted with *p*-tolyllead triacetate **5** and copper(II) acetate to afford the coupled material **53a** in 62% yield (Scheme 23).[62] With methyl ethers (R_1, R_2=OMe, **52b**) yields dropped to 18% of the desired product with a large amount of recovered starting material. 8-Methoxycarbostyril **52c** affords some desired *N*-aryl material, but the majority of product was *C*-arylated compound **53d**. Without the copper catalyst, only *C*-coupled material was isolated.[62]

Work in this laboratory has focused on the regiocontrol of the *N*-arylation reaction with organolead reagents (Scheme 24).[63] The reaction between 4-methylimidazole **54** and phenyllead triacetate could, in principle, afford either or both *N*-aryl imidazole. In the event, exclusive formation of the *N*-1 arylation product **55** was observed with a yield of 80%. When the lead reagent was changed to a more electron-rich system, such as **4** and **56**, no change in selectivity was observed. The yields of these coupling reactions were 85 and 61% for the isolation of the respective *N*-1 aryl product. At the present time the origin of the lower yield for the *ortho*-substituted lead reagent **56** is unknown. Two possible explanations for these lower yields are the bulkiness of the *ortho*-group or the poor transfer of the aryl group from lead to copper. A single crystal X-ray structure of *o*-methoxylphenyllead triacetate shows the oxygen atom of the methoxy group in close proximity to the lead atom with weak donation of electron density.[64] This extra electron density stabilizes the organolead reagent, which could slow the transfer of the aromatic group to copper.

It is instructive to compare these results with other recent methods of imidazole arylation,[65,66] particularly the work of Collman.[67] As seen in Scheme 24, the use of the copper catalyst Cu(OH)Cl·TMEDA allows the coupling of 4(5)-methylimidazole with boronic acids under mild conditions. While not identical to the reactions performed in this laboratory, the reactions are similar enough for comparison. Both

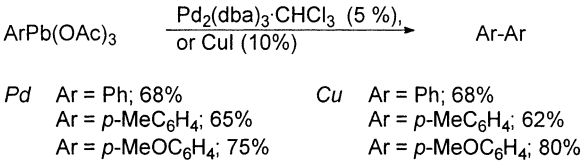


Scheme 24.



4 $R_1 = R_3 = H$; $R_2 = OMe$ 68 %
58 $R_1 = R_2 = H$; $R_3 = OMe$ 48 %
59 $R_1 = R_2 = H$; $R_3 = O$-allyl 49 %
60 $R_1 = (S)\text{-}CH_2C(H)(NHBoc)CO_2Bn$; $R_2 = H$; $R_3 = OMe$ 48%

Scheme 25.



Scheme 26.

reactions are run at room temperature in chlorocarbon solvent. However, for optimal yield the Collman procedure requires 2 equiv. of boronic acid to 1 equiv. of imidazole, and affords a 2.5:1 mixture of regioisomers. When a 1:1 ratio of reactants is employed, the yield suffers (37%) while the ratio of products improves (3.8:1). Thus, it would appear that, provided the in situ generation of the corresponding aryllead(IV) reagent affords the same general result as the preformed aryllead reagent does, the simple expedient of adding lead(IV) acetate to the boronic acid to form the aryllead(IV) reagent would increase the isolated yield of the major isomer greatly while decreasing the need for an extra equivalent of the organometallic agent.

The mildness of these reaction conditions suggested that coupling reactions with more sensitive residues, such as amino acids, would be possible. In particular, the active site ligand of cytochrome *c* oxidase possesses an unusual side chain coupled amino acid that is formed from the linkage of a histidine with a tyrosine residue.[68] Thus, histidine, with suitable protection, was chosen as the imidazole fragment in the coupling reaction, with the goal of assessing the level of regiocontrol and chiral center integrity attendant in this copper-catalyzed procedure (Scheme 25). As the histidine partner we chose Z-His-OMe (**57**). The coupling of **57** with **4** provided the desired product as a single *N*-1 isomer in 68% yield. The desired *ortho* phenol substituent was introduced with the coupling of **57** to **58** and **59** in 48 and 49% yields, respectively. Finally, the target dipeptide was obtained in 48% isolated yield as a single isomer through the reaction of organolead reagent **60**,[9] derived from L-tyrosine, with **57**. To our knowledge, this is the first coupling of amino acids mediated by lead reagents. Proton and carbon NMR for this coupling reaction detected no racemization.

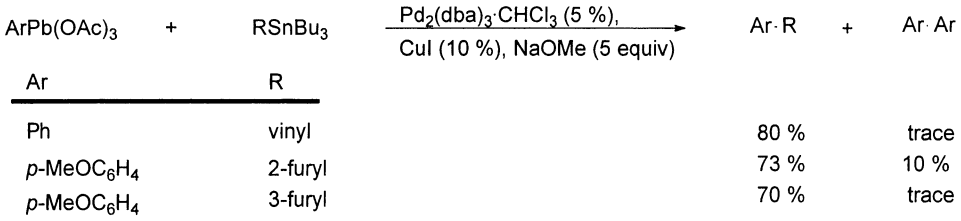
2.4. Palladium cross-coupling with organolead reagents

Palladium-catalyzed reactions are among the most powerful and versatile of synthetic transformations. The most successful synthetic precursors to aryllead(IV) reagents are arylstannanes and arylboronic acids, both of which are key components in cross-coupling reactions catalyzed by palladium. It is not surprising, therefore, that researchers have investigated the use of aryllead reagents in palladium-catalyzed transformations.

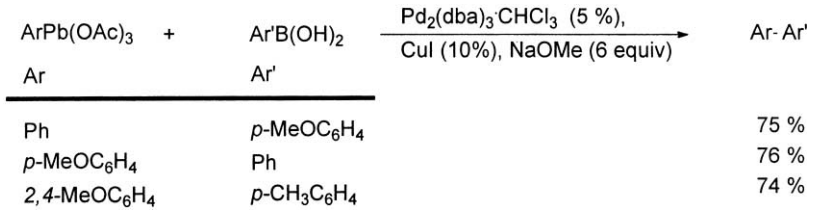
Initially, Kang and co-workers explored homocoupling catalyzed by either palladium or copper sources (Scheme 26).[69] Yields were good with either metal catalyst, although differences were noted both in the solvent and in the amount of catalyst employed. Both reactions proceeded at room temperature.

Stille-type reactions, normally taking place between organostannanes and aryl halides or triflates, were shown to proceed with organolead reagents. These reactions were accomplished with palladium and copper(I) iodide as co-catalysts.[70] The researchers believe that the copper slows the competing homocoupling reaction. In addition, 5 equiv. of sodium methoxide were essential. Phenyllead triacetate coupled with vinyl tributylstannane in 80% yield with trace amounts of homocoupling (Scheme 27). Similarly, *p*-methoxyphenyllead triacetate was coupled with 2- and 3-furyl tributyltin in 73 and 70% yield, respectively.

Suzuki-type reactions also are possible with aryllead



Scheme 27.

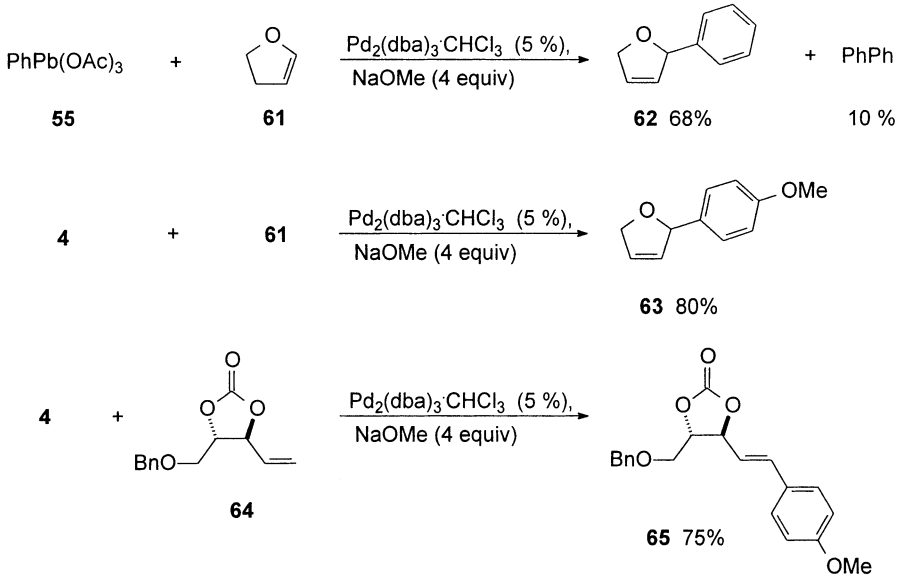


Scheme 28.

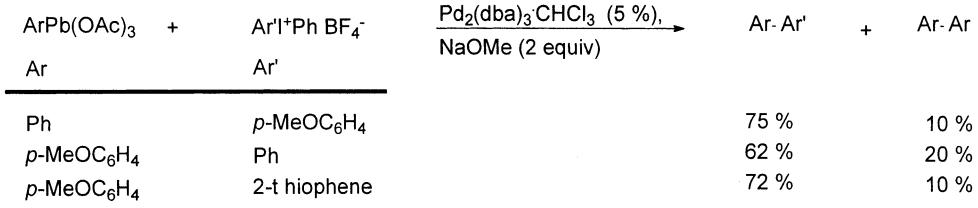
reagents (Scheme 28).[71] As in the previous scheme, there is a need for a mixed catalyst system. In addition, 6 equiv. of base are needed. The cross coupling yielded products in the 70% range. The generality of the procedure with regard to the electronic nature of the coupling partners was demonstrated by the reactions of phenyllead triacetate with *p*-methoxyphenylboronic (75%) in comparison with the reaction of *p*-methoxyphenyllead triacetate with phenylboronic acid (76%) to obtain the same product.

Coupling between an aryllead(IV) reagent and an olefin catalyzed by palladium (Heck-type reaction) was realized recently (Scheme 29).[72] As in the previous scheme, NaOMe must be added to achieve success. Phenyllead triacetate **55** was coupled with 2,3-dihydrofuran **61** in 68% yield to provide the 2-phenyl-2,5-dihydrofuran **62** with 10% homocoupling. With *p*-methoxyphenyllead triacetate **4** the yield was 80% for **63** with no homodimer seen. Compound **4** was coupled with a vinyl cyclic carbonate **64** in 75% yield without opening of the cyclic carbonate in product **65**. These reaction conditions are slightly different from the Suzuki and Stille type coupling with organolead reagents, in that these couplings do not need the copper(I) iodide co-catalyst. The authors speculate that the active aryllead reagent in the transformations requiring methoxide is $RPb(OMe)_3$ or one of the possible acetate/methoxide mixed ligand species $RPb(OMe)_x(OAc)_y$. Given the other examples of unique reactivity arising from ligand exchange in organolead reagents, further research in this area is essential.

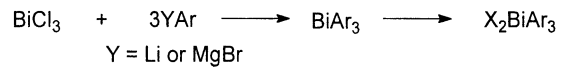
Finally, cross-coupling reactions between iodonium salts and organolead reagents via palladium catalysis has been explored (Scheme 30).[73] These reactions required 2 equiv. of base. Homocoupling of the lead reagent could not be completely suppressed, and the yields reported were moderate.



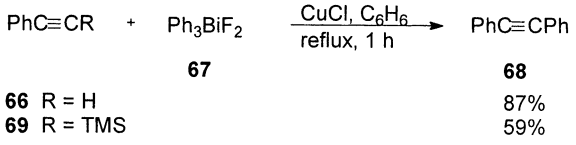
Scheme 29.



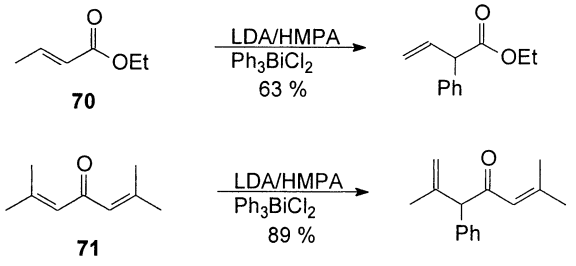
Scheme 30.



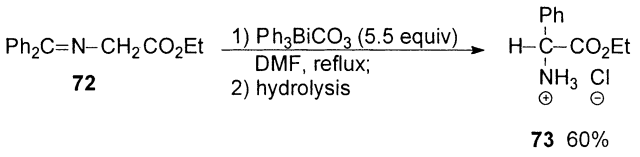
Scheme 31.



Scheme 32.



Scheme 33.



Scheme 34.

3. Organobismuth chemistry

The area of organobismuth chemistry encompasses two oxidation states, bismuth(III) and bismuth(V), and selectivity in arylation reactions is dependent on the oxidation state. Organobismuth reactions have been well reviewed.[1,2,74–76] This review will concentrate on newer selective arylations at carbon, nitrogen, or oxygen centers.

3.1. Formation of organobismuth reagents

The synthesis of pentavalent and trivalent bismuth reagents is straightforward. The most general approach to triarylbismuth reagents starts with bismuth trichloride and either aryllithiums or aryl Grignards (Scheme 31). The triarylbismuth is oxidized to the pentavalent bismuth. There are a variety of ways to accomplish this step.[77] Some new methods use sodium perborate in acetic acid[78] or iodobenzene diacetate[79] to make triarylbismuth diacetate.

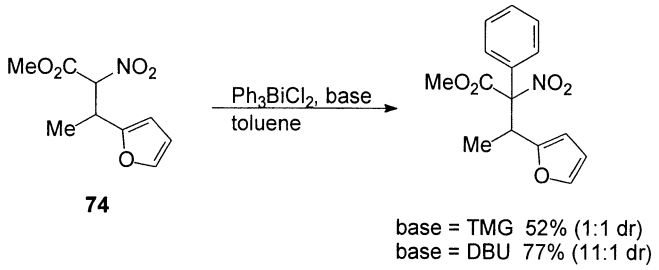
Two limitations to this technology are quickly apparent. First, the necessity of using aryllithium or arylmagnesium halide reagents severely limits the presence of other functionality in the molecule. The preparation of a bismuth reagent corresponding to **1** would be impossible by this route. Second, the bismuth reagents consist of three identical aryl groups, only one of which is reactive. Such a loss of material, particularly if the aryl group is itself the product of a synthetic series, could not be viewed as economical. Given the unique reactivity of organobismuth reagents, both of these limitations need to be addressed.

3.2. *C*-Arylations

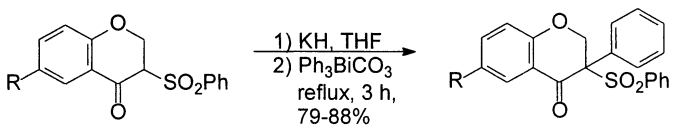
The arylation of phenylacetylene **66** by triphenylbismuth difluoride **67** proceeds in high yield to afford the coupled material **68** (Scheme 32).[80] The reaction also occurs in moderate yield when TMS-substituted **69** is used. Very little homocoupling is seen at benzene reflux. However, increasing the reaction temperature (toluene reflux) results in lower yield and up to 9% homocoupling product.

Treatment of α,β-unsaturated ketones with LDA/HMPA and triphenylbismuth dichloride provided regioselective α-phenylation with deconjugation of the olefin (Scheme 33).[81] Ethyl crotonate **70** was coupled in 63% yield. Phorone **71** was monoarylated with 1 equiv. of both base and bismuth reagent in 89% yield with >95:5 ratio of mono to diarylated product.

Monoarylation of glycine derivative **72** occurred with 5.5 equiv. of triphenylbismuth carbonate, followed by



Scheme 35.



Scheme 36.

hydrolysis to afford the racemic phenylalanine hydrochloride salt **73** in 60% overall yield (Scheme 34).[82] This selective monoarylation is interesting since the initial product formed has a more acidic proton than the starting material.

In an effort to develop nitroacetate as a template for unusual amino acid synthesis, Montgomery and co-workers reacted **74** with Ph_3BiCl_2 (Scheme 35).[83] The reaction proceeded in 52% yield with tetramethylguanidine (TMG) as base, and afforded a 1:1 mixture of diastereomers. By contrast, the selectivity increased to 11:1 and the yield increased to 77% when diazabicycloundecene (DBU) was employed. Reduction of the nitro group to the corresponding amine completes the synthesis.

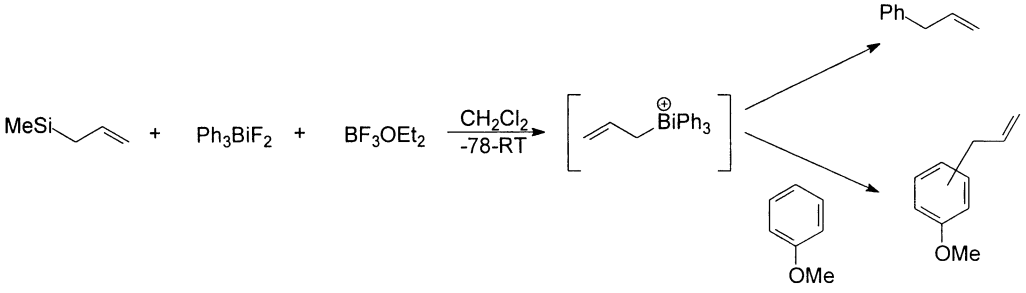
The preparation of a common intermediate for the synthesis of isoflavanones and isoflavones has been reported using pentavalent bismuth reagents (Scheme 36).[84] The yields were in the 80% range for a variety of couplings.

Allylsilanes can be used to directly allylate an arene ring (Scheme 37).[85] The authors provide evidence for the allylbismuthonium intermediate shown in the brackets. Furthermore, this species acts as an electrophilic allyl transfer agent. When substituted arylbismuth reagents are used, a mixture of *ortho, para* and *meta*-substituted products is obtained with the major product always arriving *ipso* to the bismuth-carbon bond. Mixtures also occur when an external nucleophile is employed, as exemplified by anisole in Scheme 37.

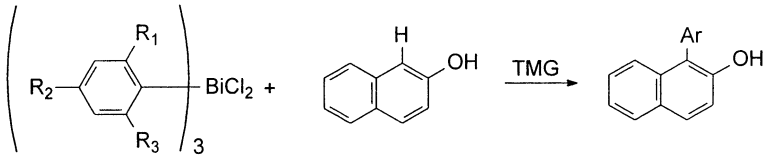
Finet and co-workers undertook a large study of steric effects in the reactions of arylbismuth reagents (Scheme 38).[86] As expected, yields drop for both the direct *C*-arylation and the copper-catalyzed reactions that afford *O*- and *N*-arylation products when steric bulk is extreme. For example, reaction of Ph_3BiCl_2 with 2-naphthol affords the expected 1-phenyl product in 90% yield after 4.5 h at RT, whereas trimesityl bismuth dichloride requires extended reaction time at elevated temperatures to obtain a 61% yield of product. A related arylation with $BiNp_3Cl_2$ (Np=naphthyl) on 3,5-di-*tert*-butylphenol afforded only the chiral form of the corresponding 2,5-dinaphthyl product.[87]

3.3. *O*-Arylations

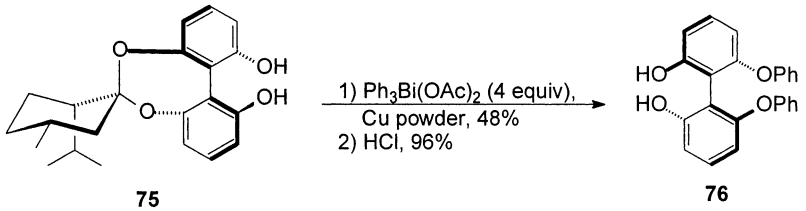
Harada, Oku, and co-workers explored the enantioselective acetalization of 2,2′,6,6′-biphenyltetrol as a route to novel biaryl catalysts. By reacting the tetrol with enantiomerically pure menthone, ketal **75** was obtained as the major product with good selectivity. The diphenylation of **75** with 4 equiv. of triphenylbismuth diacetate and 1.3 equiv. of copper powder provided the protected diphenyl product in 48% yield (Scheme 39).[88] This was followed by hydrolysis of



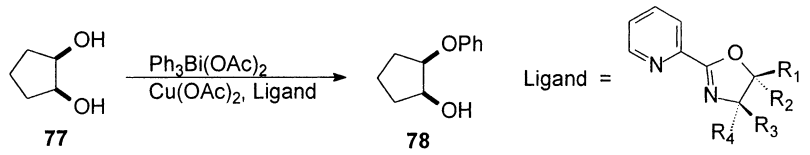
Scheme 37.



Scheme 38.



Scheme 39.

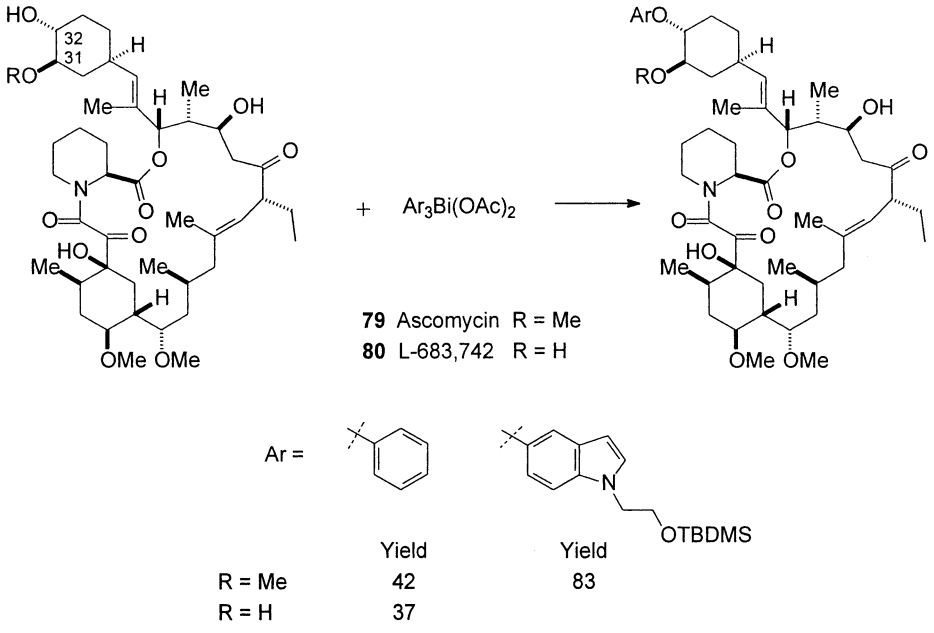


Scheme 40.

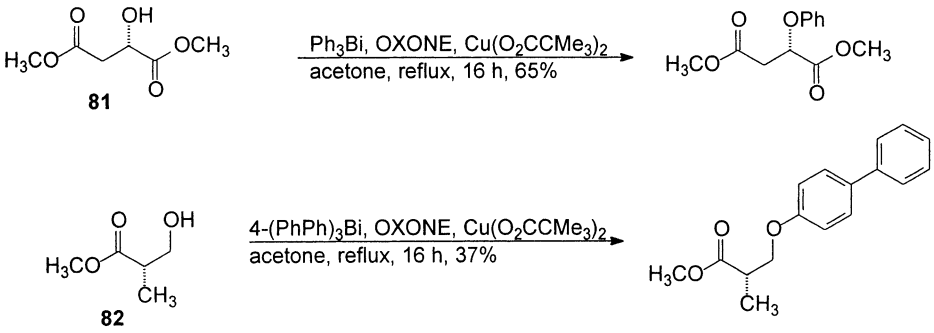
the chiral auxiliary to furnish optically active **76** in 96% enantiomeric excess.

Enantioselective *O*-phenylation reactions were carried out by copper catalysis with optically active ligands (Scheme 40).[89] The best enantiomeric excess was 50% for the reaction of *meso* diol **77** with the ligand derived from valine (R_1=R_2=R_3=H; R_4=isopropyl) to afford **78**. The yield for these reactions was in the 50% range for a variety of substrates. Lower ee's were produced for larger cyclic and acyclic compounds.

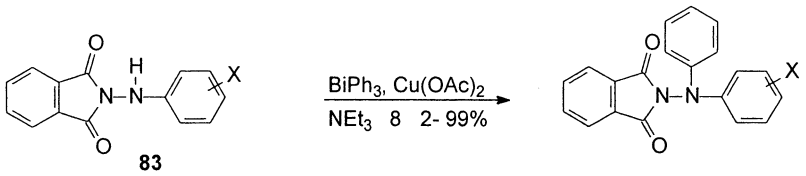
The power and flexibility of this methodology is aptly demonstrated by two contributions from medicinal chemistry groups. In an effort to define a novel immunosuppressant with a more 'promising biological profile,' researchers at Merck explored *O*-arylation of both ascomycin (**79**, *R*=Me) and L-683,742 (**80**, *R*=H) with a variety of bismuth reagents (Scheme 41).[90] Aryl groups with electron-withdrawing and electron-donating groups were incorporated into the study. The yields of these coupled products ranged from poor to excellent depending on the bismuth reagents. When compound **80** was reacted with triphenylbismuth diacetate and catalytic copper a 1:1 mixture of *C*-31 and the desired *C*-32 phenyl ethers was obtained. Coupling of the bismuthane prepared from the indole fragment shown in Scheme 41 with **79** was accomplished in excellent yield and on large scale. Removal of the silyl protection group afforded L-732,531, the desired target.



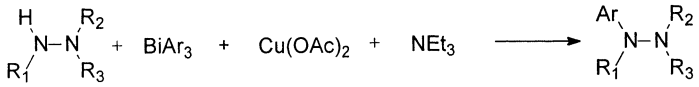
Scheme 41.



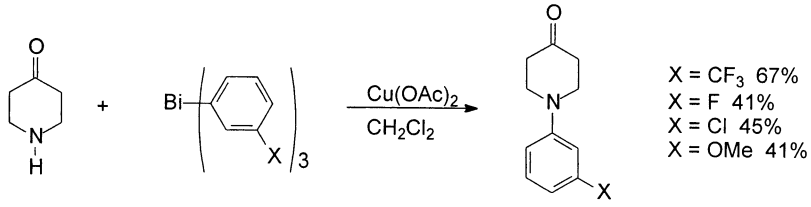
Scheme 42.



Scheme 43.



Scheme 44.

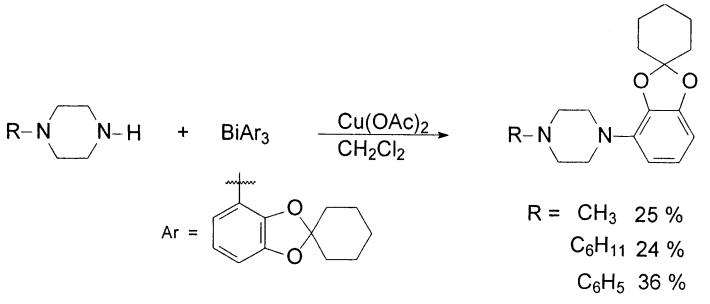


Scheme 45.

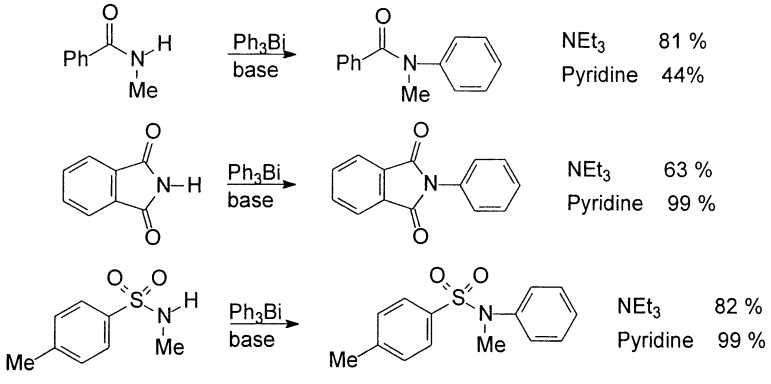
In situ generation of a pentavalent bismuth reagent and direct aryl transfer was accomplished in a one-pot protocol with OXONE™ as the oxidant and copper(II) pivalate (Scheme 42).[91] These changes in procedure increased the yield for the coupling products from zero to modest. Secondary alcohol **81** was *O*-phenylated in 65% yield. Using primary alcohol **82** the *O*-coupling proceeded in 37% yield.

3.4. *N*-Arylation with triarylbismuth

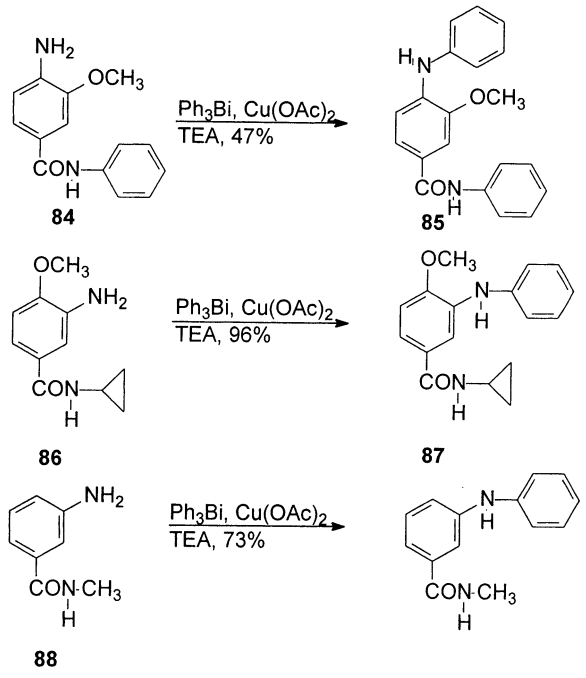
N-Arylaminophthalimide **83** is arylated with stoichiometric amounts of copper(II) acetate, triethylamine and triphenylbismuth (Scheme 43).[92] Other bismuth reagents also were employed. With 2 equiv. of bismuth reagent the yields were excellent.



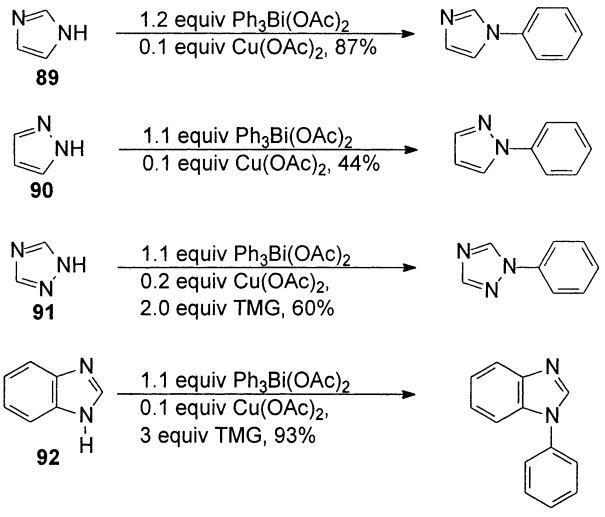
Scheme 46.



Scheme 47.



Scheme 48.



Scheme 49.

Triarylbismuthanes arylated triprotected hydrazines in excellent yields (Scheme 44) with copper(II) acetate.[93] A variety of compounds were investigated.

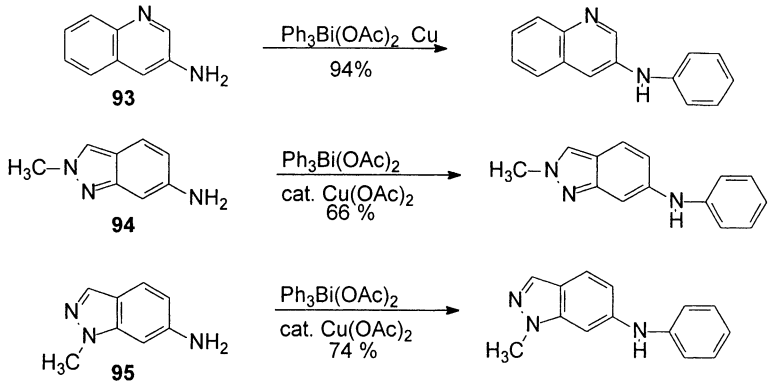
4-Piperidone was arylated with a variety of *meta*-substituted triarylbismuth reagents and copper acetate in moderate to good yields (Scheme 45).[94] Other piperidines were arylated using this procedure, as was a substituted piperidine.[95] Similarly, substituted piperazines were *N*-arylated.[96] With 1-substituted piperazine the yield of coupled material were in the 20–30% range (Scheme 46).

Chan reported the arylation of amides, imides, ureas, carbamates, sulfonamides and aniline with triphenylbismuth, copper(II) acetate, and an amine promoter.[97] It was found that triethylamine was a better promoter for amides, whereas pyridine was efficient at the arylations of the more acidic imides and sulfonamides. Shown in Scheme 47 is a small portion of the many reactions that were reported. Yields were excellent in all coupling reactions.

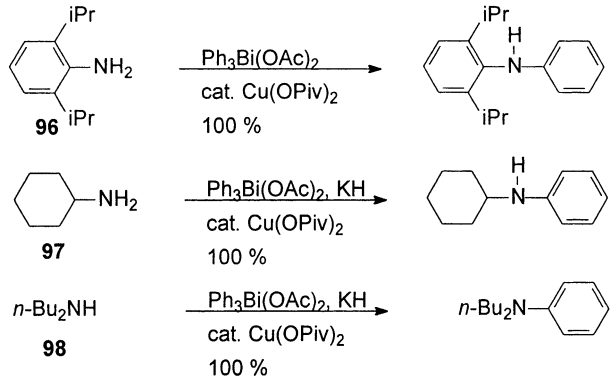
Selective *N*-arylation of aminobenzanilides was recently reported.[98] As expected, the arylation event occurs on the primary amino end rather than the secondary amide end. In fact, there is some competition between a primary amide and a primary aromatic amine under the reaction conditions. A wide assortment of substituted anilines are tolerated, whereas the bismuth reagents are relatively simple in structure and functionality. For the most part, yields are quite good (Scheme 48). The reaction of aminobenzanilides **84** with triphenylbismuth provides 47% of *N*-aryl **85**. With the cyclopropylamide **86** the yield of **87** was 96% without ring opening. Methylamide **88** was phenylated in 73%.

3.4.1. *N*-Arylation with pentavalentbismuth. Imidazole and other heteroarenes were *N*-arylated in moderate to excellent yield with triphenylbismuth diacetate and catalytic amounts of copper acetate (Scheme 49).[99] Imidazole **89** was phenylated in 87% yield with pentavalent bismuth. Pyrazole **90** and triazole **91** were arylated in more modest yields. Benzoimidazole **92** coupled in 93% yield in the presence of 3 equiv. of TMG. No experiments to probe the regiochemistry of the reaction of substituted heteroaromatic systems with bismuth reagents have been reported.

More elaborate heteroaromatic systems have also been studied. The coupling of aminoquinoline **93** and



Scheme 50.

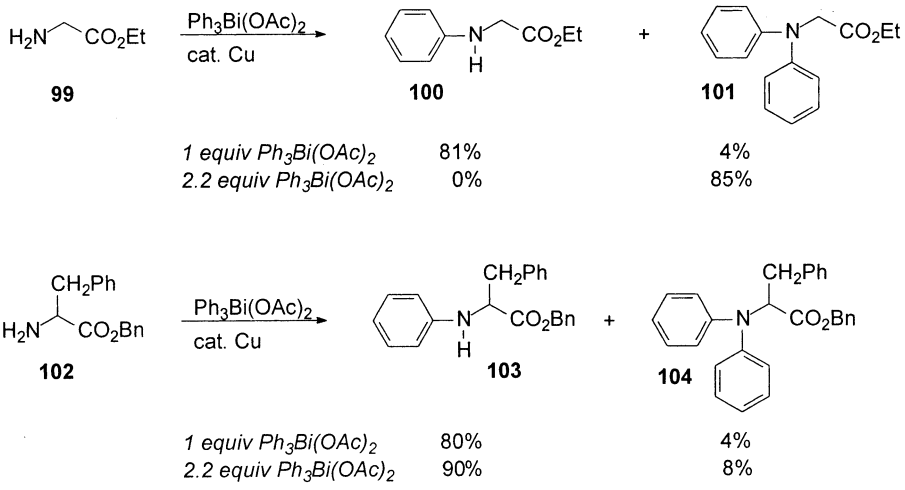


Scheme 51.

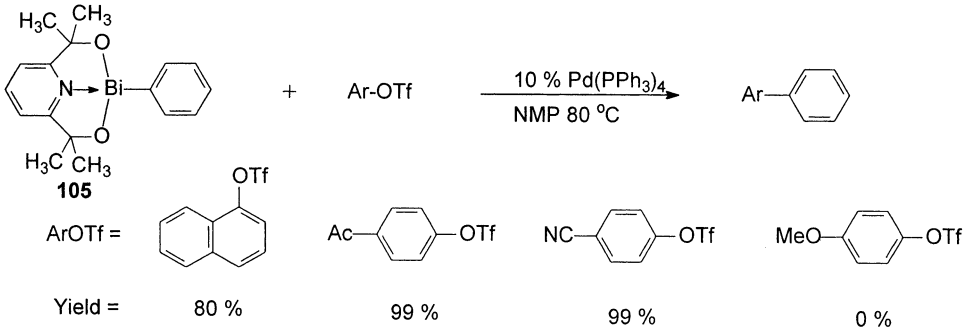
triphenylbismuth diacetate occurred in excellent yield with metallic copper (Scheme 50).[100] The arylations of aminoindazoles **94** and **95** were also completed with triphenylbismuth diacetate and catalytic amounts of copper acetate.[101] A similar arylation let to the preparation of a novel cyclopropapyrroloindole (CPI) derivative for cytotoxicity evaluation.[102]

As already discussed in ether formation (Scheme 42), changing the catalyst from copper diacetate to copper(II) pivalate increased the yield and decreased the overall reaction time for the phenylation of aliphatic and aromatic amines (Scheme 51).[103] 2,6-Diisopropylaniline **96** was quantitatively phenylated in 5 min with triphenylbismuth diacetate and catalytic copper pivalate. Similarly, primary amine **97** was arylated quantitatively with potassium hydride and the copper catalyst. Without the hydride source the yield was 66%. Secondary amine **98** was also phenylated quantitatively. Note that there is some ambiguity concerning the exact identity of the copper ligands during the course of the reaction, since acetic acid is liberated and could exchange with pivalate.

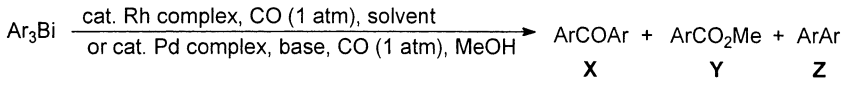
Amino acids derivatives could be *N*-arylated as either the free amino esters or as the amino ester salt (Scheme 52), although the amino acid salts gave only poor to modest yields.[104] When glycine ethyl ester **99** (free amine) was subjected to 1.0 equiv. of bismuth reagent the yield of product **100** was 81% with 4% diarylated product **101**. With 2.2 equiv. of organobismuth reagent the yield of **101** was 85% with no detection of **100**. In contrast, diarylation of amino acids with substitution on the α-carbon is far more difficult. Arylation of phenylalanine benzyl ester **102** with 1.0 equiv. of bismuth reagent afforded an 80% yield of monoaryl phenylalanine **103**. Increasing the equivalents of arylation reagent to 2.2 increased the yield of **103** to 90% with only 8% of diaryl phenylalanine **104**. Other researchers have employed two step protocols to produce the diarylation product.[105] The authors provide no proof of absolute stereochemical purity, although specific rotations are given for the



Scheme 52.



Scheme 53.



Scheme 54.

Table 2. Reactions with $[RhCl(CO)_2]_2$

AR	Solvent	*X*	*Y*	*Z*
Ph	MeCN	71	0	5
	MeOH	73	26	0
4-MeC_6H_4	MeCN	72	0	15
	MeOH	68	17	0
4-$MeOC_6H_4$	MeCN	49	0	trace
	MeOH	11	19	0
4-ClC_6H_4	MeCN	69	0	trace
	MeOH	76	22	0

Table 3. Reactions with $Pd(OAc)_2$

AR	Solvent	*X*	*Y*	*Z*
Ph	MeOH	0	0	92
	MeOH/K_2CO_3	0	64	22
4-MeC_6H_4	MeOH	0	0	99
	MeOH/K_2CO_3	0	67	24
4-$MeOC_6H_4$	MeOH	0	0	94
	MeOH/K_2CO_3	0	22	5
4-ClC_6H_4	MeOH	0	0	92
	MeOH/K_2CO_3	0	60	33

products. Cycopropyl amino acids are arylated without problem.[106]

3.5. Cross-couplings with organobismuth reagents

Allyl and propargyl halides couple with Ar_3Bi under palladium catalysis. Yields are very good for allyl bromide with most bismuth reagents, although when Ar=*p*-chlorophenyl a significant amount of biaryl material is isolated. Propargyl bromides afford aryl allenes.[107]

Venkatraman and Li have documented the formal conjugate addition of a phenyl group from Ph_3Bi with α,β-unsaturated carbonyl compounds under rhodium catalysis in water. No inert atmosphere is necessary. This 'green' chemistry affords good yields for disubstituted olefins activated with ketones or esters. Additional olefin substitution affords no useful yield of product, and aldehydes, nitriles, and carboxylic acids are not tolerated.[108]

A palladium catalyzed cross-coupling reaction between organobismuth alkoxide **105** and aryl triflates has been achieved with excellent yields (Scheme 53).[109] Electron-poor aryl triflates afford the best results; no reaction occurred with 4-methoxyphenyltriflate. Yields were very low with triphenylbismuth. Other ligands were tried without success.

Uemura and co-workers have shown that formation of benzophenone derivatives is achieved with a rhodium catalyst in acetonitrile and 1 atmosphere of carbon monoxide (Scheme 54, Table 2).[110] Switching solvents to methanol affords both benzophenone derivatives and formation of methyl benzoates.[111] Using palladium diacetate in methanol with potassium carbonate leads to formation of methyl benzoates (major) and biaryl homocoupling products (minor) (Table 3).[111] Without potassium carbonate, only biaryl product is formed in excellent yield.[112]

4. Conclusions

Organolead and organobismuth reagents have proven versatility in arylation reactions. The last decade has seen these agents move from the realm of a curiosity explored by a few laboratories to the stable of reliable synthetic methodologies. The reactions involving these main group metal reagents are very mild and tolerant of many other functionalities.

Each metal offers the researcher a set of strengths and weaknesses. Lead offers excellent synthetic methods to structurally diverse reagents. Only one aryl group/metal means the economy of coupling with regard to the aryl cation equivalent is good. On the negative side is the known toxicity of lead and the need for stoichiometric amounts of the metal. These two issues are intimately associated. Lead toxicity is no greater than that of many other metals used in organic synthesis, but these other metals are employed in catalytic amounts and are, therefore, tolerated by the community. We[38] and others[113] have shown that the standard workup methods are adequate to ensure only background levels of lead remain in the product. Clearly, the ability to perform the same transformations under catalytic lead conditions would be a major step toward general recognition and adoption of this methodology. In this regard, the position of aryllead(IV) coupling reactions is similar to that of osmylation reactions prior to the discovery of effective in situ oxidants for the spent osmium, allowing catalytic use of the metal. Currently there is little work being done in this area. Moloney has explored the use of electrochemical methods to effect reoxidation of Pb(II) to Pb(IV),[114] but much more needs to be done, particularly if large scale chemistry is ever to be contemplated. Additional studies are also needed on the details of the mechanism and the variations in reaction yield and stereochemistry with preformed salts versus carbon acid/pyridine mixtures. Indeed, the ability to knowledgeably modify ligands to obtain a certain type of reactivity is not available at the present time. This is hampered by the lability of carboxylate ligands, which undergo intermolecular exchange rapidly.[115]

By contrast, arylations with bismuth reagents do not engender a toxicity problem, and medicinal chemistry applications have recently been disclosed. But even these researchers recognize the limitations in a reagent in which two out of three aryl groups are not transferred to product. In addition, limitations in the method of synthesis of the reagents limit the functionality on one of the two organic

groups in the coupling event. Reagents such as **105** offer the possibility to design organobismuth reagents that economically incorporate only one aryl group, which is transferred efficiently. Fedorov and Finet have recently added to this literature with a study of biphenyl-2,2′-ylenebismuth derivatives in which the biphenyl ligand does not undergo the ligand transfer reaction.[116] Less is known about the stereochemistry of organobismuth reagent addition reactions than the corresponding organolead reagents, and more work needs to be accomplished in this area, including the design of enantiospecific reagents.

Overall, the future is bright for these organometallic reagents, and we look forward to the progress that will be made before the next review on arylation chemistry in this journal.

Acknowledgements

We wish to thank the American Chemical Society–Petroleum Research Fund (32051-AC1), the American Cancer Society (RPG-93-017-06-CDD), and the California Cancer Research Program (1II0129) for support of our work on organolead(IV) reagents. In addition, we gratefully acknowledge a Roche Biosciences (Palo Alto, CA) Fellowship in Synthetic Organic Chemistry for G. I. E. We wish to give a heartfelt thanks to Professor Jean-Pierre Finet (Université de Marseille) and Dr Mark G. Moloney (University of Oxford) for their comments on our manuscript. Both were generous with their time and energy in sharing with us their experience and knowledge on the title subject.

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Biographical sketch

Greg Elliott received a BS degree in chemistry from Colorado State University in 1996. He then returned to his home state of California to obtain a PhD degree from the University of California, Santa Cruz under the guidance of Professor Joseph Konopelski. His thesis is on organolead reagents and their synthetic applications. While at Santa Cruz, Greg received the first Roche Biosciences Award in Synthetic Organic Chemistry. He is currently a postdoctoral fellow with Professor Dale Boger at the Scripps Research Institute.

Joe Konopelski was born in Reading, PA. He did his undergraduate and masters degrees at The Johns Hopkins University in Baltimore, MD, and his PhD degree with Professor Carl Djerassi at Stanford University. Post-doctoral work in Strasbourg, France (with Professor Jean-Marie Lehn) and Philadelphia, PA (with Professor Amos B. Smith, III) preceded his move to the University of California in Santa Cruz. He is currently Professor of Chemistry and will assume the Chairmanship of the Department of Chemistry and Biochemistry on July 1, 2001.