NEW ORGANOMETALLIC APPROACHES TO HETEROCYCLES

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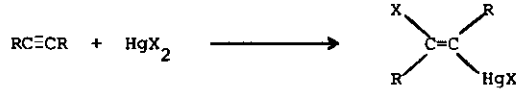
Abstract - The mercuration of acetylenes and subsequent palladium promoted reactions provides a new route to butenolides, furans, benzofurans, isocoumarins, and benzopyrones, while thallation-palladation of appropriately substituted arenes affords phthalides, 3,4-dihydroisocoumarins, aryl anhydrides and imides, and isocoumarins.

This review is dedicated to Professor Herbert C. Brown on the occasion of his 70th birthday. Few men have been more productive, dedicated, enthusiastic, and influential in the history of organic chemistry.

Some time ago we became interested in the possibility of using organomercurials in organic synthesis. Much of our early work involved new applications of vinylmercurials in organic synthesis.[1] During the course of that work, we have developed several novel new routes from acetylenes to heterocycles via intermediate organomercurials. More recently we have begun to explore possible applications of organothallium compounds in organic synthesis. In so doing, we have developed a number of simple, direct new routes from arenes to a wide variety of heterocycles. These approaches form the basis of the following review.

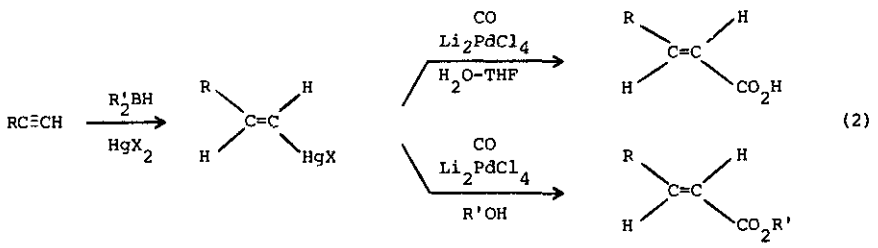
The addition of mercury salts to acetylenes is a well-known and rather general reaction (eq. 1).[2,3]



(1)

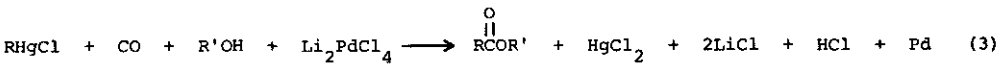
X = Cl, OAc, SCN

It provides a very convenient, stereospecific route to β-substituted vinylmercurials. Some time ago we observed that simple vinylmercurials derived from acetylenes via hydroboration-mercuration[4,5] could be readily carbonylated using Li_2PdCl_4, carbon monoxide and either aqueous or alcoholic solvent systems to provide α,β-unsaturated carboxylic acids or esters respectively (eq. 2).[6]



(2)

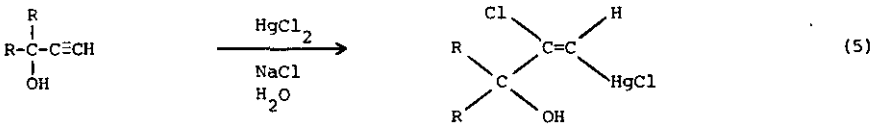
It is important to point out that these carbonylation reactions can be effected using only one atmosphere of carbon monoxide and temperatures at or below room temperature. Furthermore, the reaction becomes catalytic in palladium when 2 equivalents of anhydrous $CuCl_2$ are added to the reaction mixture. Both palladium chloride and palladium on charcoal appear to be equally effective as catalysts. The cupric chloride simply serves to reoxidize the palladium(O) formed upon carbonylation (eqs. 3,4). Encouraged by our results with simple vinylmercurials, we attempted to



(3)

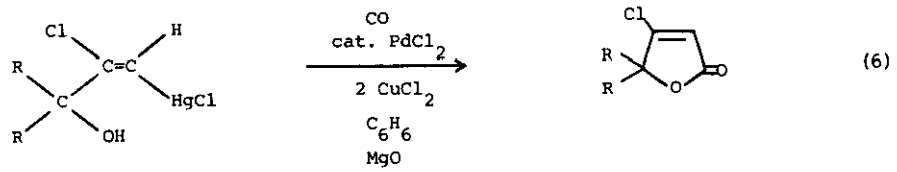
(4)

extend this reaction to the synthesis of heterocycles. Propargylic alcohols were known to readily add mercuric chloride trans to the triple bond to form stable vinylmercurials which precipitate from solution (eq. 5).[7] We have observed that this reaction works well for water soluble,



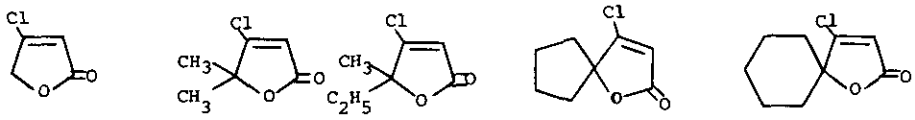
(5)

reasonably symmetrical, primary and tertiary alcohols, but other types of alcohols fail to precipitate the desired organomercurials.[8,9] Upon examining the carbonylation of these vinylmercurials, we found that best results were obtained using our earlier catalytic palladium procedure, but with benzene as a solvent and inorganic bases such as MgO or K_2CO_3 added. Under these conditions, near quantitative yields of the corresponding $\Delta^{\alpha,\beta}$-butenolides could be obtained (eq. 6).[8,9] The non-polar solvent appears to prevent direct $CuCl_2$ chlorination of the

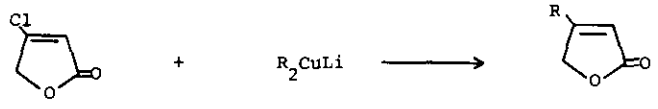


(6)

vinylmercurial and the inorganic bases help to remove the 1 equivalent of HCl generated upon lactone formation. Each of the following lactones has been prepared in this fashion.

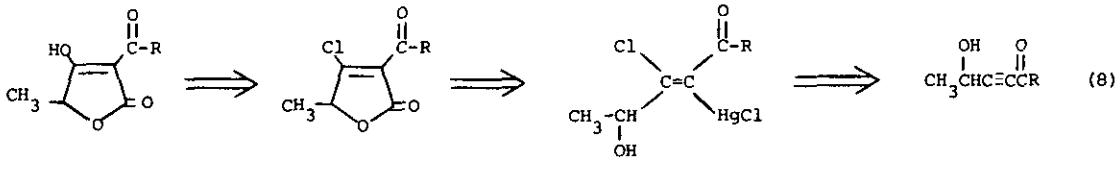


A brief study of the reaction of these chlorolactones with organocopper reagents indicated that the chlorine can be readily substituted, but the nature of the organocopper reagent and the reaction conditions are critical (eq. 7).[8]



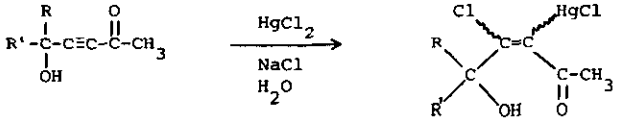
(7)

It was hoped that this approach to the butenolide ring system might be extended to the synthesis of α-acyltetronic acids, a class of compounds exhibiting some interesting antibiotic activity (eq. 8). Several keto acetylenic alcohols of the type required were prepared and their



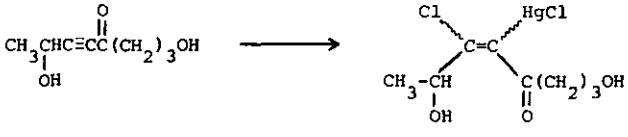
(8)

mercuration examined (eqs. 9,10).[10] In spite of the electron withdrawing carbonyl group, all



(9)

R	R	%
H	H	70
H	CH_3	100
CH_3	CH_3	100

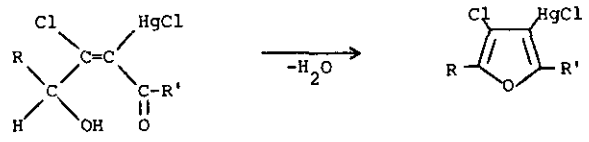


(10)

10%

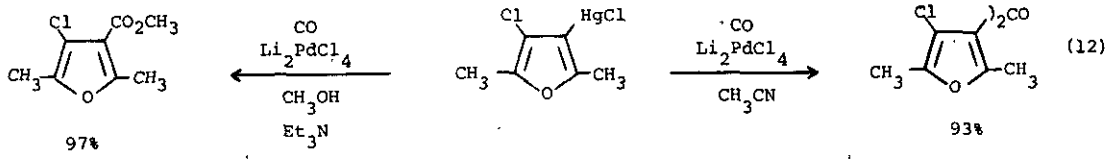
compounds underwent *smooth mercuration*, although the yield of the latter compound was low. Much to our surprise, however, attempted carbonylation of these compounds gave none of the anticipated butenolides.

After considerable work with these compounds, we have come to the conclusion that these vinylmercurials probably have the chlorine and chloromercuric groups cis to each other, not trans as expected. As evidence for this, these vinylmercurials are readily dehydrated to mercurated furans upon treatment with dilute HCl or on simple recrystallization (eq. 11). This provides a unique



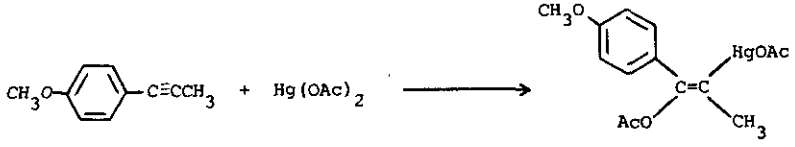
(11)

approach to 3-substituted furans, since the mercury can no doubt be readily substituted by a variety of substituents, as we will show later with analogous mercurated benzofurans. We have looked briefly at the carbonylation of these 3-furylmercurials and found that they can be converted in near quantitative yields to either the corresponding methyl esters or symmetrical ketones (eq. 12).[10]



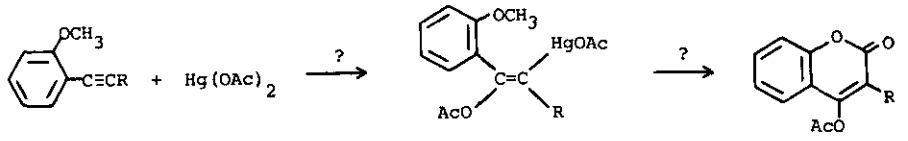
(12)

We have also examined the mercuration of arylacetylenes as a possible route to heterocyclic compounds. Since 1-*p*-anisyl-1-propyne[11] and other related acetylenes[12] are known to add mercuric acetate *stereo- and regioselectively* to give the corresponding vinylmercurials (eq. 13), we



(13)

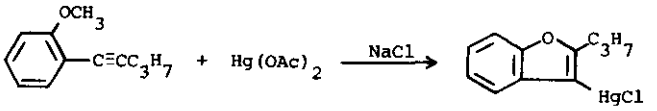
reasoned that the corresponding ortho substituted compound should behave similarly (eq. 14). Hopefully, subsequent carbonylation might generate the very important coumarin ring system. Once



(14)

again, however, the mercuration was observed to take an entirely different course, affording the

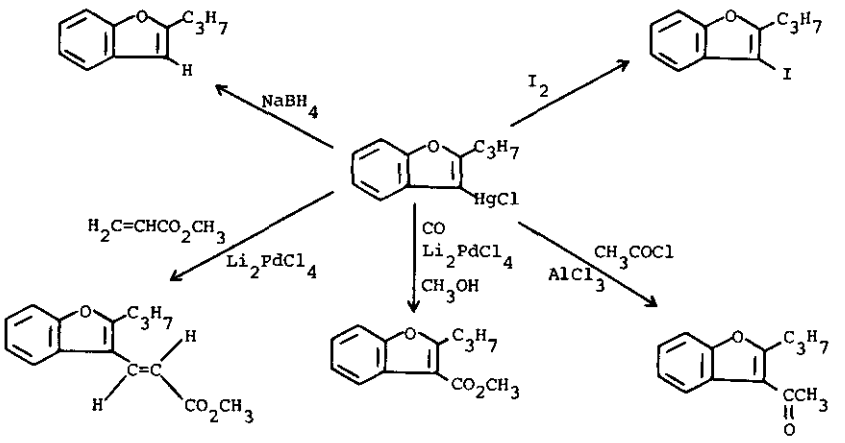
corresponding mercurated benzofuran instead (eq. 15).[13] Such compounds can prove quite valuable as intermediates in the synthesis of a wide variety of substituted benzofurans, as shown by each



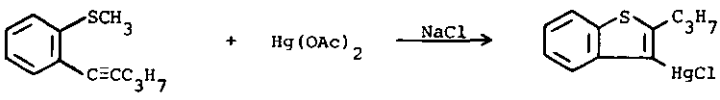
(15)

of the following transformations carried out in our laboratories (Scheme 1).

Scheme 1



This type of intramolecularly assisted mercuration is not limited to the benzofuran system, but works equally well in the preparation of mercurated benzothiophenes, isocoumarins and benzopyrones (eqs. 16-18).[13] We are presently examining the scope and generality of this type of reaction for the synthesis of a wide variety of heterocyclic systems.



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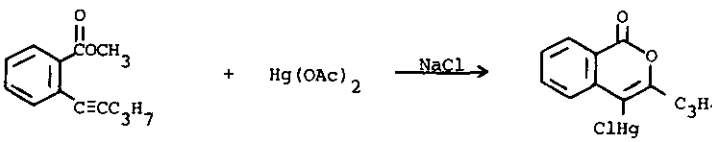

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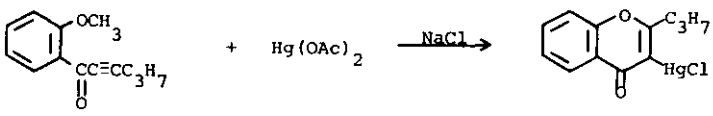
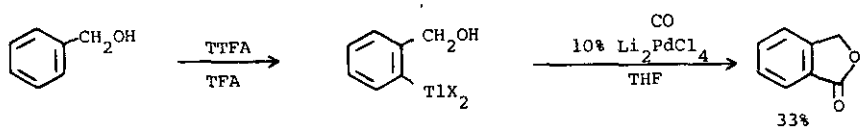


(18)

Another major area of recent interest in our group has been the use of organothallium compounds in organic synthesis. Taylor and McKillop have closely examined the electrophilic thallation of arenes using thallium tris(trifluoroacetate) (TTFA).[14,15] They report that certain functionally substituted arenes, such as benzyl alcohol, phenethyl alcohol, benzoic acid, benzamide, etc. undergo thallation to give an unusually high percentage of ortho substitution product (generally >90%). Apparently the heteroatom is coordinating to the thallium electrophile and directing attack on the ortho position.

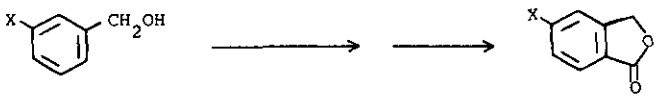
We have taken advantage of this ortho metallation reaction and subsequent transmetallation of thallium by palladium to generate arylpalladium intermediates which have proven quite useful in organic synthesis. For example, benzyl alcohol gives 99% ortho thallation.[14,15] Upon treatment with 10% Li_2PdCl_4 and 1 atmosphere of carbon monoxide in tetrahydrofuran (THF) solvent, one obtains the corresponding phthalide (eq. 19).[16] Note that this reaction is run in one pot and the



(19)

intermediate arylthallium compound is not isolated, but is treated directly with carbon monoxide and catalytic amounts of palladium(II). In these reactions the thallium(III) formed in the transmetallation step is apparently a sufficiently good reoxidant of palladium(0) to allow only catalytic amounts of palladium(II) to be used. The thallium presumably ends up as thallium(I) although that has not been proven.

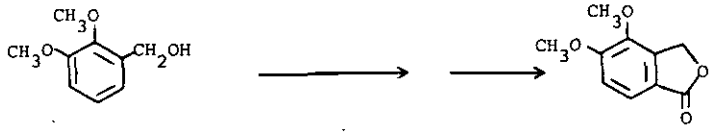
Unfortunately, the yield of phthalide from benzyl alcohol is not good. Difficulties are encountered in trying to run the thallation of this acid sensitive alcohol in strongly acidic trifluoroacetic acid (TFA). The corresponding trifluoroacetate ester is formed as a significant side-product. Substantial amounts of starting alcohol are also observed in many of our thallation reactions, indicating that thallation is incomplete. Fortunately, most naturally occurring phthalides possess groups such as OH and OCH_3 on the aromatic ring which tend to activate the ring towards electrophilic aromatic substitution. When such substituted benzylic alcohols are treated with TTFA in TFA and subsequently carbonylated, much better yields of phthalides are obtained (eqs. 20, 21). Note that in the two examples of equation 20 thallation-carbonylation of these meta-substituted alcohols gives exclusively the 5-substituted phthalides. It appears that the bulky thallium electrophile prefers not to substitute between the two groups (ortho to the substituent X). This regioselectivity nicely complements the previous work of others who report



X = CH_3O 89%

HO 95%

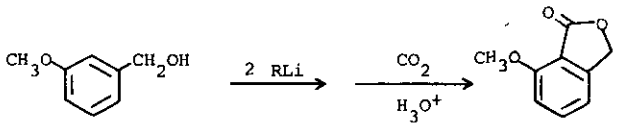
(20)



64%

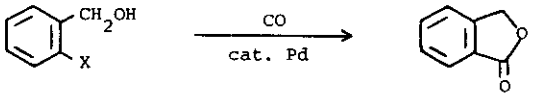
(21)

that this same m-methoxybenzyl alcohol can be lithiated and subsequently treated with carbon dioxide to give the 7-substituted product (eq. 22).[17] Our one-pot approach to phthalides also



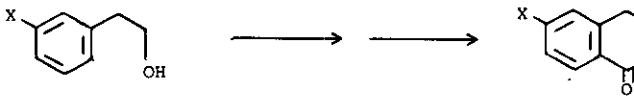
(22)

provides one of the most convenient routes to the naturally occurring lactone pseudomeconin (eq. 21). Recently, Stille[18] and Mori[19] have reported related phthalide syntheses starting with more difficultly obtainable aryl halides and using carbon monoxide and palladium catalysts (eq. 23).



(23)

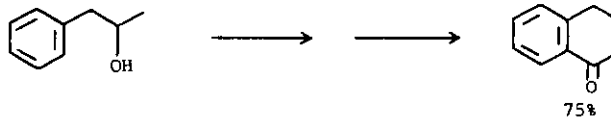
These thallation-carbonylation reactions are not restricted to the synthesis of phthalides. β-Phenethyl alcohols are known to undergo thallation primarily in the ortho position.[14,15] As before, subsequent carbonylation affords a highly convenient route to a variety of 3,4-dihydroisocoumarins (eqs. 24-26).[16] In general the yields in this system are higher, presumably due to



X = H 51%

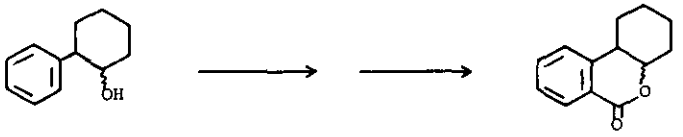
CH_3O 58%

(24)



75%

(25)



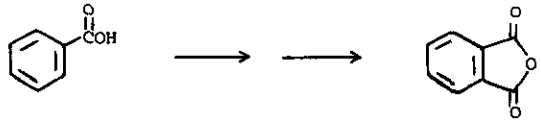
(26)

cis 88%

trans 77%

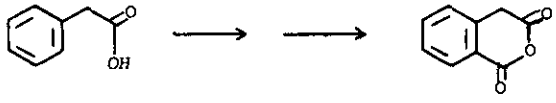
the decreased sensitivity of these alcohols to the acidic thallation conditions. Once again the meta-methoxy alcohol gives only the product of substitution para to the methoxy group.

The thallation-carbonylation route to aryl carbonyl compounds is not limited to the synthesis of lactones.[16] Deactivating, normally meta-directing groups such as the carboxylic acid group also direct thallation almost exclusively ortho.[14,15] Carbonylation affords phthalic anhydride (eq. 27). Phenylacetic acid reacts similarly (eq. 28). Benzophenone also gives a good yield of



(27)

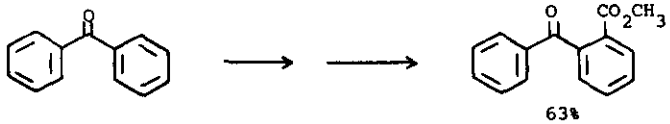
44%



(28)

46%

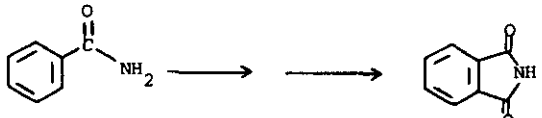
ortho substituted ester when the carbonylation is run in methanol (eq. 29). Such keto esters



(29)

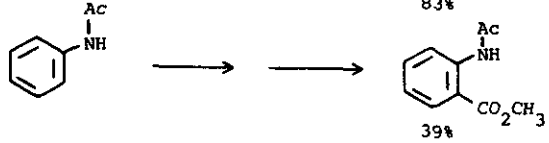
63%

have proven valuable as intermediates in the synthesis of anthraquinones. Amides also afford ortho carbonylated products by this sequence (eqs. 30,31). This latter product has previously



(30)

83%

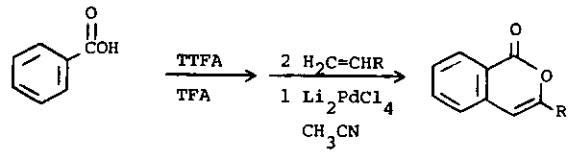


(31)

39%

proven useful in the synthesis of acetylanthranil and related heterocycles.

The ortho-thallated intermediates are not only useful as intermediates in the synthesis of aryl carbonyl compounds, but they can also be made to react with olefins in the presence of palladium salts to give a number of other heterocycles.[20] For example, thallation of benzoic acid followed by treatment with 2 equivalents of olefin and 1 equivalent of Li_2PdCl_4 affords a highly convenient route to the isocoumarin and phthalide ring systems (eqs. 32-34). This simple "one-



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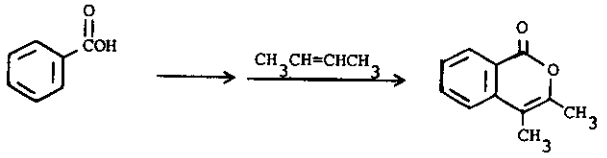

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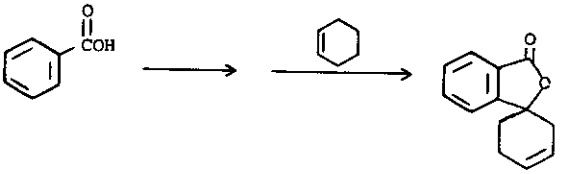
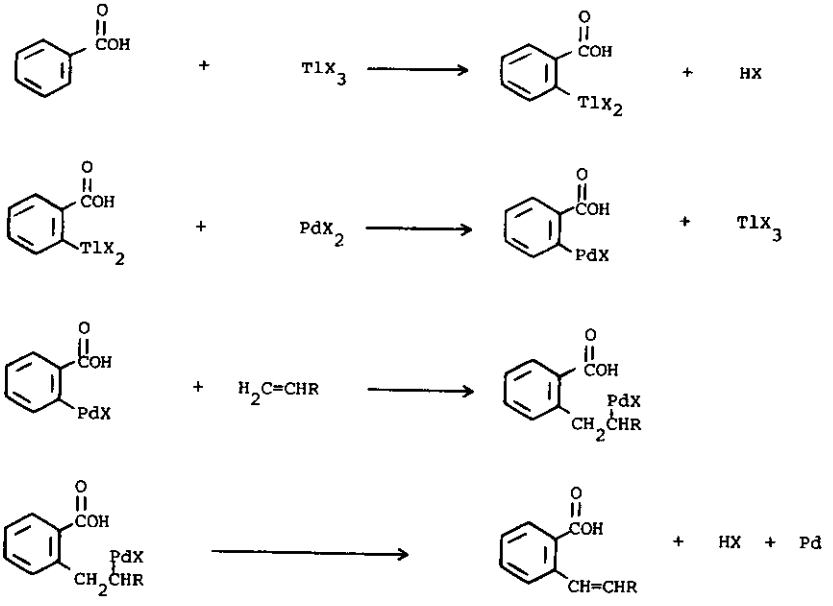
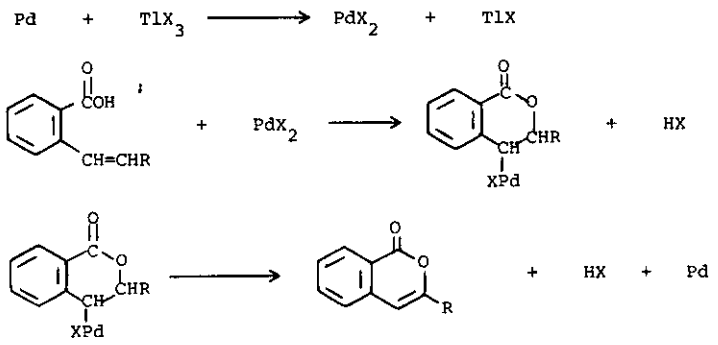


(34)

pot" reaction apparently proceeds by the following sequence of classical organometallic reactions, everyone of which has literature precedent (Scheme 2).

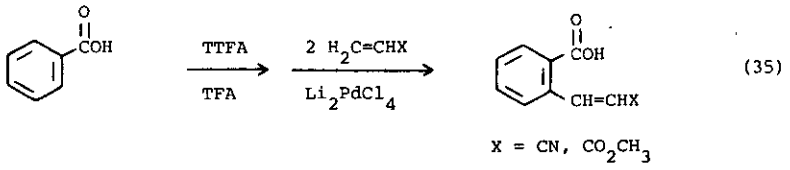
Scheme 2





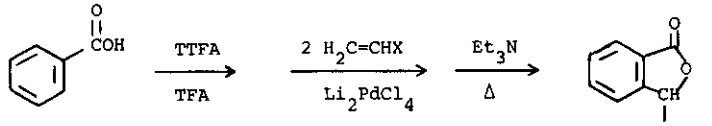
Note that once again palladium (II) is reduced during the reaction to palladium(0) and thallium (III) reoxidizes it. However, in this reaction palladium(II) is reduced a second time, necessitating a full equivalent of Li_2PdCl_4 to complete the reaction.

When electron deficient olefins such as acrylonitrile or methyl acrylate are employed, the reaction stops at the o-alkenylbenzoic acid stage (eq. 35). However, these compounds can be



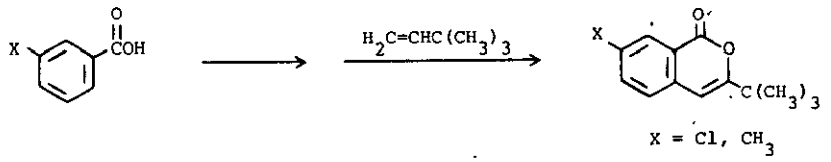
(35)

closed to the corresponding phthalides by simply adding triethylamine at the end of the reaction and refluxing (eq. 36).



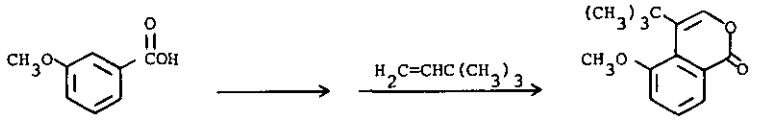
(36)

The regioselectivity of the thallation-olefination sequence with substituted benzoic acids is quite interesting. As seen previously in the carbonylation reactions, meta-chloro and meta-methyl groups direct thallation to the less hindered position, para to these substituents, the predominant product of thallation-olefination thus being the 7-substituted compounds (eq. 37).



(37)

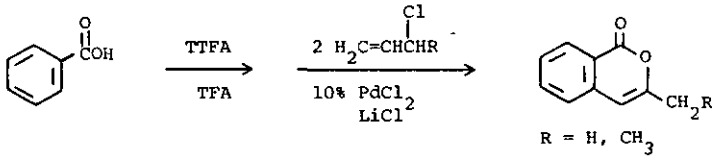
However, meta-methoxybenzoic acid behaves quite differently from the corresponding benzyl and β-phenethyl alcohols. In this case the predominant product is the 5-methoxy derivative (eq. 38).



(38)

Presumably, coordination by the methoxy group overcomes the steric preference for attack para to the methoxy group.

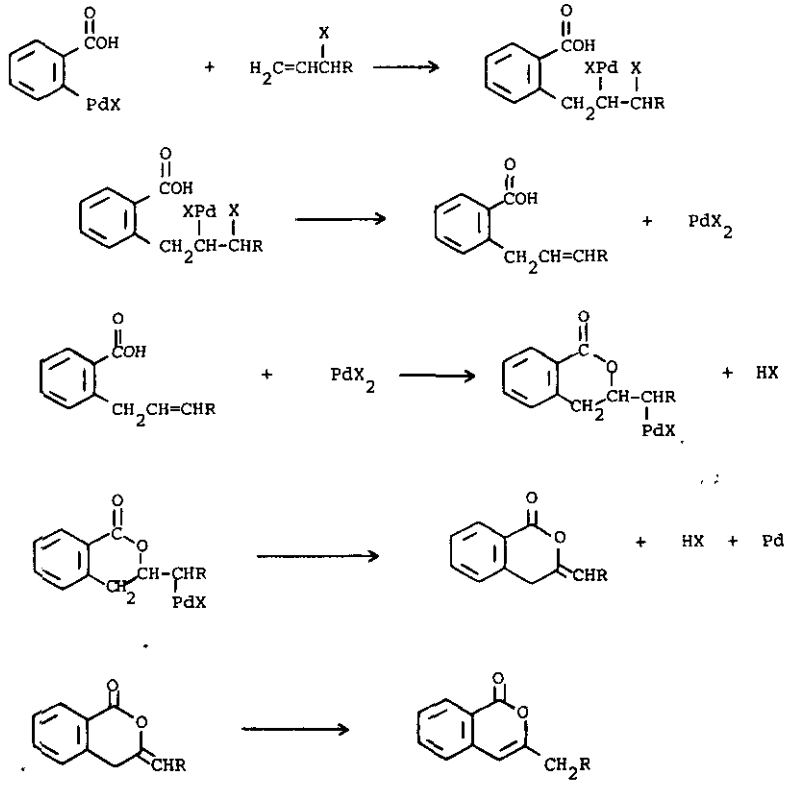
If one employs allylic chlorides in the thallation-olefination sequence, isocoumarins are again obtained, but only catalytic amounts of palladium chloride become necessary (eq. 39). These



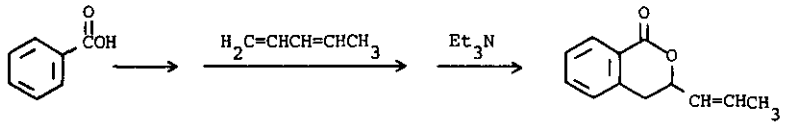
(39)

reactions no doubt proceed by a path similar to that described before, except that the initial arylpalladium intermediate undergoes allylation rather than vinylation (Scheme 3).

Scheme 3

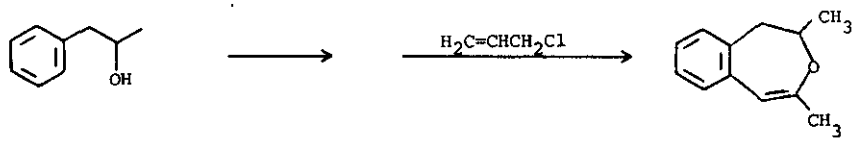


This reaction regenerates palladium(II) rather than reducing it to palladium(0) as in the vinylation reactions, and the overall process then requires only catalytic amounts of palladium chloride. The resulting ortho-allylbenzoic acids have been cyclized to isocoumarins previously by Hegedus using palladium(II) salts.[21] The cyclization presumably involves oxypalladation, palladium hydride elimination and palladium hydride promoted isomerization of the double bond. Our one-pot approach to isocoumarins is considerably shorter than the Hegedus approach which requires difficultly available ortho-halobenzoic acids as starting materials, introduces the ortho allylic group via air-sensitive, difficult-to-prepare π-allylnickel halides and requires palladium for cyclization in still a third reaction. These reactions can also be extended to 1,3-dienes which provide a convenient route to 3,4-dihydroisocoumarins (eq. 40). This reaction is quite interesting in that it can be carried out catalytically in palladium.

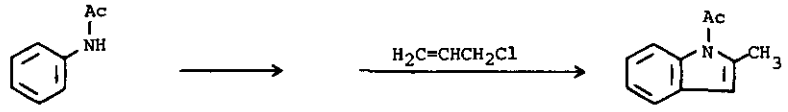


(40)

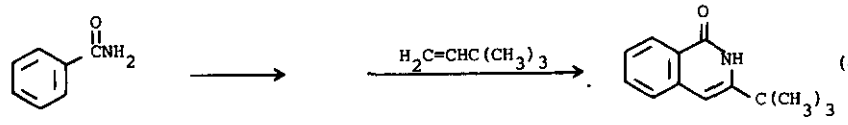
At present it appears that a number of other heterocyclic ring systems should also become readily available by our thallation-olefination methodology. Most promising are the following systems which have been shown to work, but which still require considerable work to improve the yields (eqs. 41-43).



(41)



(42)



(43)

In conclusion, organomercury and -thallium compounds are readily prepared from a variety of acetylenes and arenes containing heteroatoms. Taking advantage of the ease with which organopalladium compounds can be obtained from these heavy metal organometallics by simple transmetallation and the number of useful reactions organopalladium compounds are known to undergo,

we have developed a number of novel new routes to heterocyclic compounds. These approaches require only simple starting materials, generally proceed at or below room temperature, and appear to tolerate a wide variety of functional groups. Increasing application of these types of organometallic approaches to heterocyclic synthesis can be anticipated.

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