METALLATION AND METAL-ASSISTED BOND FORMATION IN Π-ELECTRON DEFICIENT HETEROCYCLES

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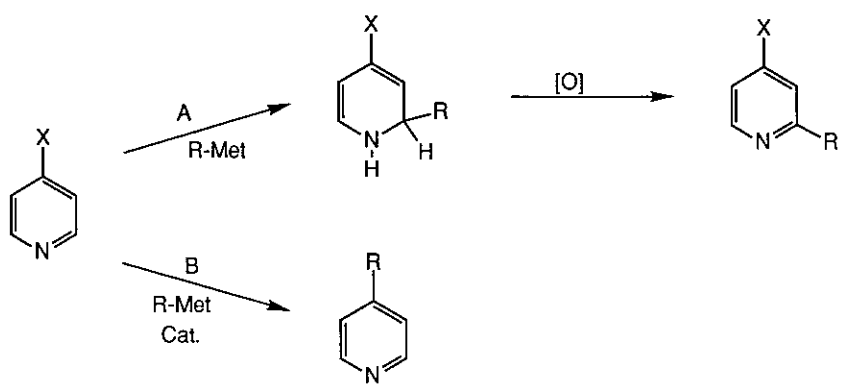
Abstract-Regiospecific C-C bond formation in electrophilic positions in π-electron deficient heteroarenes results from 1:1-adduct formation with organometallic reagents and dehydrogenation to heteroarenes. Cross-coupling between halogenoheteroarenes and organostannanes using Pd-catalysis introduces carbon substituents in a regio- or chemoselective manner; a Br- or I-substituent is replaced in any position, a Cl-substituent in an electrophilic position. Methods for the stannylation and palladation of pyrimidines are described. These metallopyrimidines are active in cross-coupling reactions. Pd(0,II)-catalysis has been used in the formation of the C-N bond by rearrangements of 2-propenyloxypyrimidines, and π-allylpalladium complexes in the direct N-alkylation. Preparation and reactions of pyrimidinylcerium dichlorides are discussed.

Carbon-carbon bond formation in π-electron deficient heteroaromatic systems can be achieved either by a two-step reaction which involves 1:1 adduct formation between the heterocycle and an organometallic reagent with a subsequent dehydrogenation (Method A), or by cross-coupling reactions (Method B).

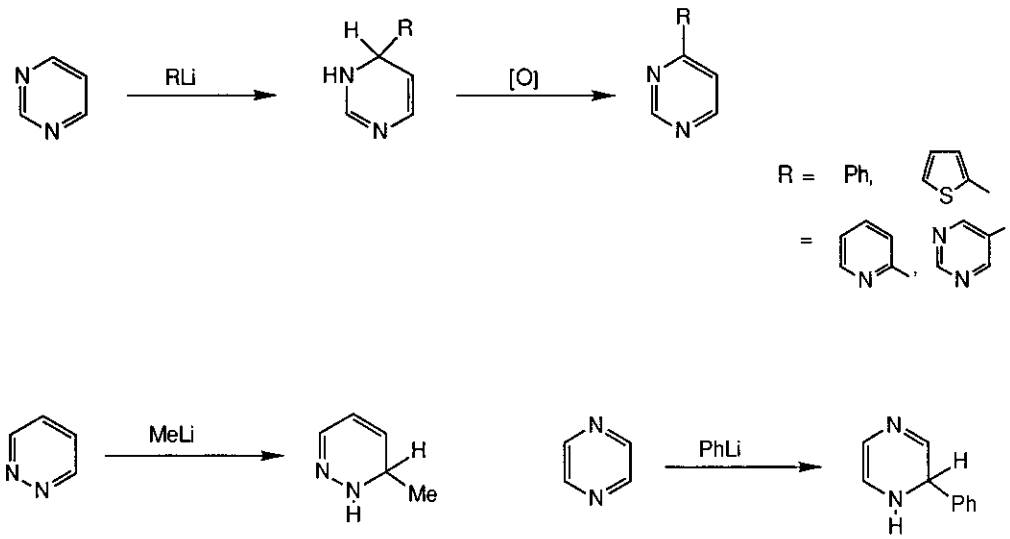


Scheme 1

Method A normally requires an activated position, polarized to an electrophilic center, for the carbon nucleophile to add. Bond formation by cross-coupling reactions does not require activated positions, and is therefore the more general approach. We have worked on both methods and our results are discussed in the above order (Scheme 1). The carbon-nitrogen bond formation studies were run on allylic reactants under the influence of palladium catalysis (Method C).

A.1. CARBON-CARBON BOND FORMATION BY 1:1-ADDUCT FORMATION

In a π-electron deficient heterocycle a carbon in an α– or γ-position to the annular heteroatom is partially positively charged. Pyridine constitutes the simplest system of this type, and is activated in the 2- and 4(6)-positions whereas the 3(5)-position is benzenoid in its properties. Early work on metallations of pyridines showed that the metallation and dihydropyridine formation were competing reactions, and the outcome was very much dependent on substituents in the pyridine and on the organometallic reagent. Pyridine itself adds organo-lithium and -magnesium reactants preferentially in the 2-position.



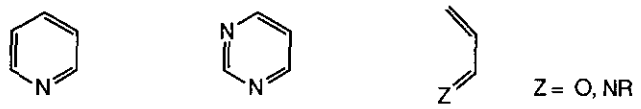
Scheme 2

The polarization and aromatic destabilization are increased in diazines which therefore will be more reactive than pyridine towards organometallic reagents (Scheme 2). Already in 1958 it was reported that pyrimidines form 4-adducts with phenyl- and 2-thienyllithium reagents at low temperature.[1] More

recently, the 4-regiochemistry has been confirmed in reactions of pyrimidine with 2-pyridinyllithium and 5-pyrimidinyllithium; the pyridine and pyrimidine lithiated species were prepared from the corresponding bromides and butyllithium at -50 and -100 °C, respectively. Either potassium permanganate or nitrobenzene was used for the dehydrogenation of the adducts to the 4-substituted heteroarenes.[2] The other diazines, pyridazine and pyrazine, form adducts with organolithium compounds in the same way.[3]

It has become clear that in many of its properties the π-electron deficient azine ring resembles the carbonyl group. The ready substitution of a halogen, an oxygen or sulfur substituent and sometimes an amino substituent in the heterocycle, is comparable to the reactions of an acid chloride, an ester and thiol ester, or an amide with nucleophiles. Ketones and aldehydes are reversibly solvated by covalent bond formation, and so are azines.[4]

Aldol reactions, which can be either acid or base catalyzed, are also expected to have its equivalents in the azine systems. Strongly nucleophilic reactants (phenol, anisole, pyrrole, and thiophene) have been added to 5-methylpyrimidine in the 4-position by acid catalysis alone. The dihydro product was dehydrogenated to the heteroaromatic 4-arylated or heteroarylated pyrimidine by potassium ferricyanide.[5]

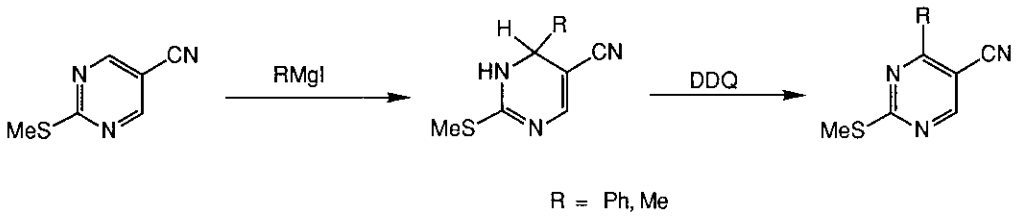


Scheme 3

Carbonyl derivatives add organometallic reagents resulting in carbon-carbon bond formation. The same behaviour is seen in azine systems. But the N(1)-C(4) part of the pyridine and the corresponding part of the pyrimidine system can also be regarded as possessing electronic properties similar to an α,β-unsaturated carbonyl system, or more closely to the corresponding α,β-unsaturated imines (Scheme 3). Both organolithium and organomagnesium compounds add to α,β-unsaturated imines, but the organolithium compounds show the greater tendency for 1,2-addition.[6] The regiochemistry in the addition of the lithiated species to pyridine and to the diazines, as reviewed above, corresponds to 1,2-conjugate addition.

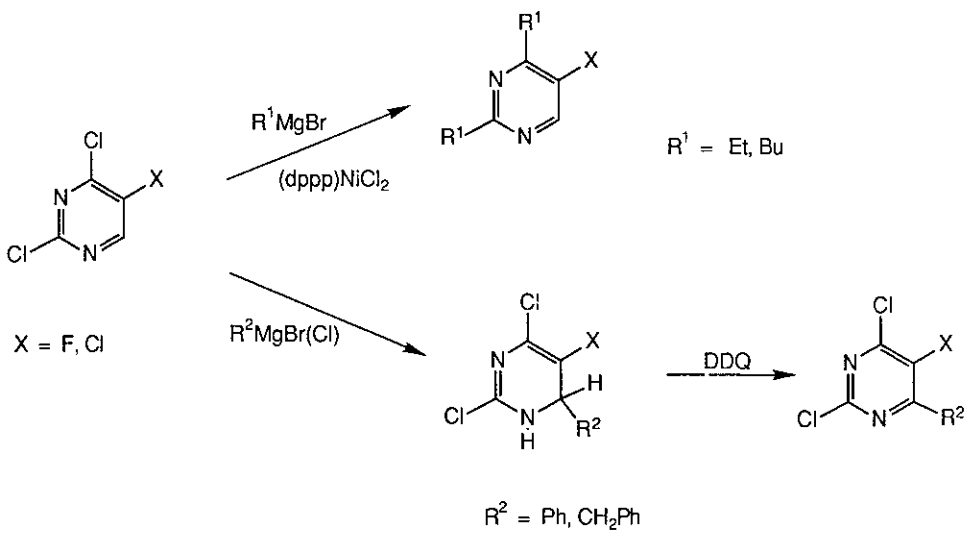
In a 5-cyanopyrimidine competition between addition to the ring system and addition to the cyano group might be expected (Scheme 4). In the reactions of methyl- and phenylmagnesium iodides with the 2-methylthio homologue, exclusive addition in the ring resulted. 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) was used for the dehydrogenation of the dihydro product to the 4-substituted heteroarene.[7]

Although the methylthio group sits in an activated, electrophilic pyrimidine 2-position, and is further



Scheme 4

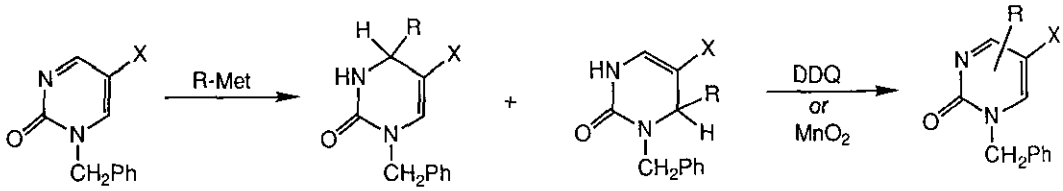
activated by the 5-cyano group, nucleophilic displacement was not seen (Scheme 4). In fact, substitution of thio groups by Grignard reagents requires the presence of a catalyst such as a Ni(II)-phosphine complex, e. g. in the 2-phenylation of 4,6-dimethyl-2-methylthiopyrimidine with phenylmagnesium bromide.[8] Halogen substituents can also be replaced by carbon substituents in Ni(II)-catalyzed coupling reactions as discussed below in more detail. Competition between cross-coupling and addition, however, may arise when there is a free, activated position in the heterocycle (Scheme 5). This was shown to be the case for



Scheme 5

2,4,5-trichloro- and 2,4-dichloro-5-fluoropyrimidines using bis(1,3-diphenylphosphinopropane)-nickel(II) chloride, (dppp)$NiCl_2$, as catalyst in the reaction with phenylmagesium bromide. The main product was the adduct with the new carbon-carbon bond in the 6-position. With benzylmagnesium chloride the product was also the adduct at C-6. With alkyl Grignard reagents under the same conditions, however, cross-coupling took place in the 2- and 4-position. DDQ oxidation of the adducts gave the fully substituted pyrimidines.[9,10] Exclusive cross-coupling, however, was seen with these substrates in their reactions with organostannanes under the influence of Pd(II)-catalysis,[11] which is discussed below.

1-Substituted 2(1H)-pyrimidinones are highly polarized molecules. 1-Alkyl-2(1H)-pyrimidinones have been claimed to react with regioselective carbon-carbon bond formation in the 4-position when treated with aryllithium and arylmagnesium reagents.[12] Even 5-phenyl derivatives react in the same way and give 4,5-diaryl derivatives.[13] On the other hand, when the alkyl substituent on the nitrogen is changed to a phenyl group, methyllithium gave the 3,4-adduct whereas methylmagnesium iodide gave the 3,6-adduct.[14] Adduct formation can occur even in methyl substituted positions. Thus 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone with methylmagnesium iodide afforded the 6,6-dimethyl adduct whereas methyllithium gave mainly the 4,4-dimethyl adduct. In the presence of phenyl substituents the regiochemistry is such as to give the adduct with the remaining double bond of the heterocycle in conjugation with the phenyl group.[14]

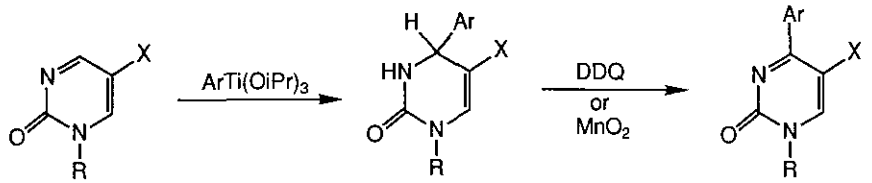


		Rel. % 3,4-dihydro isomer			
X=		H	Cl	Br	I
RMgI	Me	43	47	40	30
	Ph	10	10	37	
RLi	Me	100	72	64	
	Ph	86	75	75	
R_2CuLi	Me	62	60	66	44
	Ph	85	31	30	

Scheme 6

In 1-benzyl-2(1H)-pyrimidinones presumably the benzyl group exerts less steric hindrance than the phenyl group to attack in the 6-position (Scheme 6). The benzyl group is also less electron-withdrawing than the phenyl group, and hence the pyrimidine ring is less activated towards nucleophilic reactions. The halogens introduced into the 5-position will electronically activate the pyrimidine system, but on the other hand give rise to steric interference for reactions in the 4- or 6-position. The highest activation is therefore seen in the 5-fluoro- and the 5-chloro derivatives. The 5-iodo derivative was in most cases recovered. In their reactions with organolithium compounds, formation of the 3,4-dihydro isomer was favoured, and this isomer was the exclusive product from methyllithium in the reaction with the pyrimidinone without the 5-halogen substituent. Grignard reagents favoured formation of the 3,6-isomer. In the case of the organocuprate reagents the relative bulkiness of the reagents seems to be the major determinant for the regiochemistry. The reaction is chemoselective in that the 5-halogen atom was not involved in any coupling reaction.[15]

In order to improve on the regiochemistry in the adduct formation, we started a search for alternative organometallic reagents, and we have found that regiospecific 3,4-adduct formation can be achieved by the use of organotitanium compounds (Scheme 7). The application of organotitanium reagents for selective reactions in π-electron deficient heterocycles was suggested by the high chemoselectivity and regioselectivity established generally for these reagents in reactions with carbonyls, which is consistent with high sensitivity to steric and electronic effects.[16]



X = H, Cl, Br, I R = CH_2Ph, Me, CH_2OCH_2Ph, $CH_2SC_6H_4Cl$-p

Ar = Ph, C_6H_4OMe-p, C_6H_4Cl-p, C_6H_4OMe-p

Scheme 7

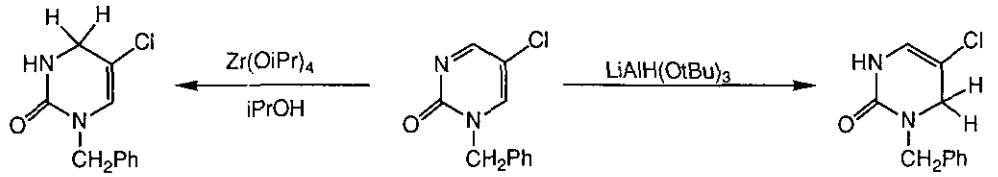
The aryltri-isopropoxytitanium reagent used was made from the corresponding aryllithium by metal-metal exchange. In reactions with the pyrimidinone only the 3,4-dihydro adduct was obtained. The nature of the 1- and 5-substituents in the pyrimidinone, or the presence of substituents in the aryl group of the titanium reagent, did not affect the course of the reaction.

To complete the sequence for aromatic substitution at C-4, the dihydro compounds were converted to the fully conjugated pyrimidinones by means of DDQ or activated manganese dioxide. The latter was the more potent reagent, and could be used if the yields from the DDQ reactions were unsatisfactory.

The regiospecificity observed in the adduct formation may, in part, be rationalized by steric repulsion between the 1-substituent and the bulky aryltri-isopropoxytitanium reagent which would be expected to favour bond formation at C-4 in preference to C-6. Alternatively, the formation of the 3,4-adduct can be regarded as a 1,2-conjugate addition as found for titanium reagents in reactions with α,β-unsaturated carbonyl compounds.[16,17]

Assuming partial localization of the double bonds in the ring of the 1-substituted pyrimidinone the N(3)-C(6) part of the pyrimidinone can be regarded as possessing electronic properties similar to an α,β-unsaturated carbonyl system, or more closely to α,β-unsaturated imines as discussed above for the parent ring structure. Hence carbon-carbon bond formation at C-6 corresponds to a 1,4-conjugate addition, comparable to the preference for this reaction site shown by Grignard reagents. Contrary to the expectations based on the above reasoning, this preference was not displayed by the corresponding organocopper reagents, which normally add 1,4 to α,β-unsaturated carbonyl systems. The findings, however, can possibly be rationalized by steric repulsion between the relatively large cuprate reagents and the pyrimidine 1-substituent. The organolithium reagents show a preference for carbon-carbon bond formation at C-4, which corresponds to 1,2-conjugate addition. For the understanding of the regiochemistry it may also be important that the reaction with lithium and magnesium derivatives and the cuprates are relatively fast and, in part, had to be run at low temperatures, whereas the reactions with the titanium reagents are relatively slow at ambient temperature.[18]

Regioselectivity in dihydro formation can also be achieved in reactions with metal hydrides (Scheme 8). With lithium tri-t-butoxyaluminium hydride, the 3,6- and 3,4-dihydro isomers are formed in the ratio 9:1, respectively, and the major isomer can be isolated in pure form. When the ring carries a substituent capable of conjugation, the dihydro product has its remaining double bond in conjugation with this substituent.[19]



Scheme 8

A method for the selective formation of the minor 3,4-dihydro isomer under the above reaction conditions, has been worked out by the use of a zirconate catalyzed Meerwein-Ponndorf-Verley reduction.[20] This reagent in isopropanol was tried because it was known that tetra-isopropoxyzirconium shows high functional group selectivity due to both steric and electronic effects.[21]

The reaction between the 2-pyrimidinone and tetra-isopropoxyzirconium in isopropanol is relatively slow (Scheme 8). The rate of the reaction is accelerated by an electron-withdrawing substituent in the pyrimidine 5-position. When the 4-position was blocked by a methoxycarbonyl group, there was no reduction. Tri-isopropoxyaluminium can also be used, but reacts less readily. Both tri-isopropoxyaluminium and tetra-isopropoxyzirconium give selective 1,2-reduction of α,β-unsaturated carbonyl compounds.[22] In the pyrimidinones, formation of the 3,4-dihydro adducts corresponds to 1,2-conjugate addition in the α,β-unsaturated imine model.

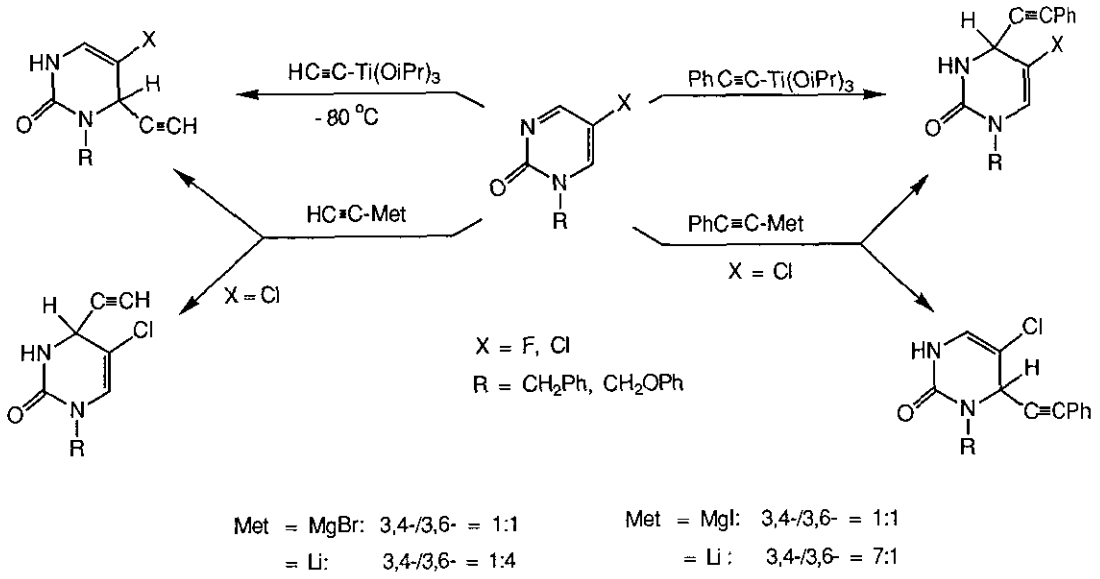
Ethynyl groups can be introduced into heteroarenes via ethynylmetals (Scheme 9). In the adduct formation between 1-substituted pyrimidinones and phenylethynyl-lithium and -magnesium both the 3,4- and 3,6-dihydro isomers were formed; with the lithium derivative the 3,4-dihydro isomer is slightly favoured.[23]

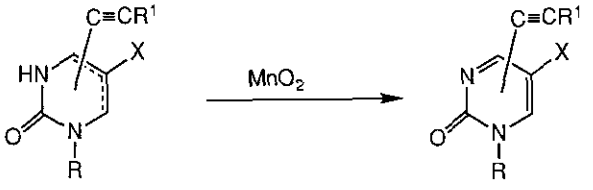
The regiochemical success with the titanium reagent, as discussed above, led to the preparation of phenylethynyltri-isopropoxytitanium and reactions with pyrimidinones (Scheme 9). The regiochemistry was the same; exclusive carbon-carbon bond formation at C-4. [23]

With the Grignard derivative of acetylene itself, a mixture of both dihydro isomers, ratio 1:1, was formed (Scheme 9). With ethynyllithium the 3,4- to 3,6-dihydro isomer ratio was 1:4. Before commencing studies with the titanium analogue, a method for its preparation had to be worked out. It has been found that ethynyltri-isopropoxytitanium can be generated by treatment of the lithium precursor with chlorotri-isopropoxytitanium at -80 ^{o}C. The carbon-carbon bond formation in the 1:1 adducts with the 2-pyrimidinones was at C-6 since the 3,6-dihydro isomer was obtained. It is noteworthy that the reactions of the phenylacetylene and the acetylene titanium derivatives resulted in reversed regiochemistry. The pyrimidinones in this study were substituted by a halogen in the 5-position; the chloro and fluoro derivatives readily formed adducts whereas the bromo derivative failed to react. The failure of the bromo derivative is probably caused by the bulkiness of the bromine, but also by the lower electronegativity of the bromine which leads to less activation of the pyrimidinone for adduct formation.[24]

The acetylene substituted dihydropyrimidines are chemically unstable, and attempts to effect dehydrogenation to the heteroarenes were unsuccessful. In retrospect, this is no surprise since we later learned, as discussed below, that the desired heteroaromatic acetylenic derivatives are unstable. The phenylacetylenic derivatives, however, can be dehydrogenated by activated manganese dioxide. The dehydrogenation of the 3,4-dihydro isomer is much faster than of the 3,6-dihydro isomer. This difference has been seen in all the 3,4- and 3,6-dihydro isomers which have been prepared, and can be rationalized

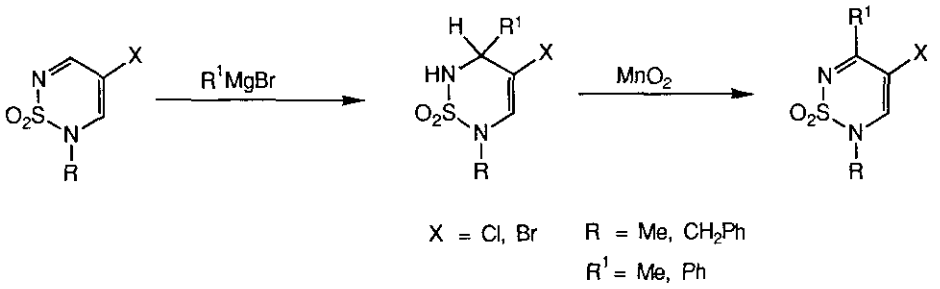
as due to different non-bonding interactions with the N-1 substituent.[24]





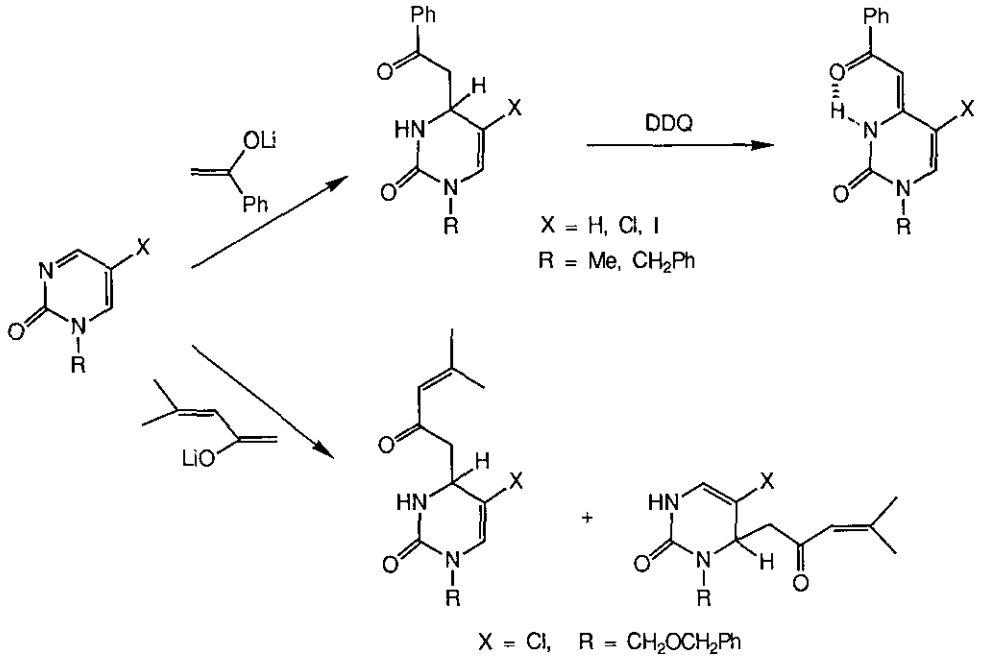
Scheme 9

Formation of adducts with organometallic reagents is a general property of π-electron deficient heteroaromatic systems, and is not restricted to the pyrimidine and pyridine systems discussed above. We have also studied some reactions in 1,2,6-thiadiazine 1,2-dioxides (Scheme 10). Grignard reagents react with 1,2,6-thiadiazine 1,1-dioxides to give exclusive carbon-carbon bond formation in the 5-position. The latter corresponds to the 4-position in the pyrimidinones. The reaction proceeds readily. It will be recalled that variable mixtures of the 3,4- and 3,6-dihydro isomers were formed in reactions between organomagnesium reagents and pyrimidinones. The regiochemistry observed in the thiadiazine system may be rationalized as due to the larger bulkiness of the SO_2 group compared to the CO group. The oxygen



Scheme 10

of the CO group lies in the plain of the ring whereas the oxygens in the SO_2 group lie below and above the ring plane. Interaction between the N-1 substituent and the oxygens may therefore result in stronger shielding of the 3-position in the thiadiazines than the shielding of the corresponding position (C-6) by the N-1 substituent in pyrimidinones. Electronic activation by a halogen in the 4-postion (benzenoid) seems to be a requirement for the reaction to proceed at a reasonable rate. The dehydrogenation to the fully conjugated heterocycle was effected by activated manganese dioxide.[25]

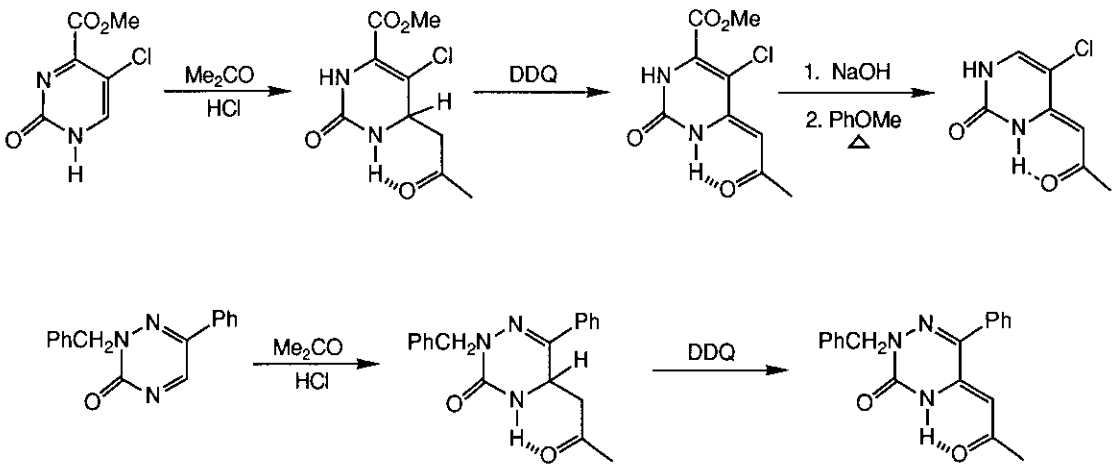


Scheme 11

The aldol reaction in carbonyl compounds has its equivalents in carbon-carbon bond forming reactions in π-electron deficient heteroarenes (Scheme 11). In the anion approach, the lithium enolate of acetophenone added rapidly to 1-substituted 2-pyrimidinones in ether type solvents. Only the 3,4-dihydro isomer was formed. The adducts are readily oxidized to the aromatic equivalents, either during the work up, or at will by DDQ. The product isolated, however, is the phenacylidene tautomer because of the extended conjugation with the carbonyl group. In the (Z)-configuration (X-ray analysis) hydrogen bonding results in the formation of a pseudo-ring.[19]

When the lithium enolate of mesityl oxide was generated in THF at -80 °C and treated with a 2-pyrimidinone, the 3,4- and 3,6-dihydro isomers were formed in the ratio 1:1 (Scheme 11). The use of the potassium enolate of mesityl oxide at higher temperatures was less satisfactory.[24]

Acid catalyzed adduct formation is demonstrated by the reaction between 2-pyrimidinones, activated by a 4-methoxycarbonyl group, and acetone. Under the influence of acid catalysis an acetonyl group is added in the 6-position (Scheme 12). Dehydrogenation was effected by DDQ.[26]



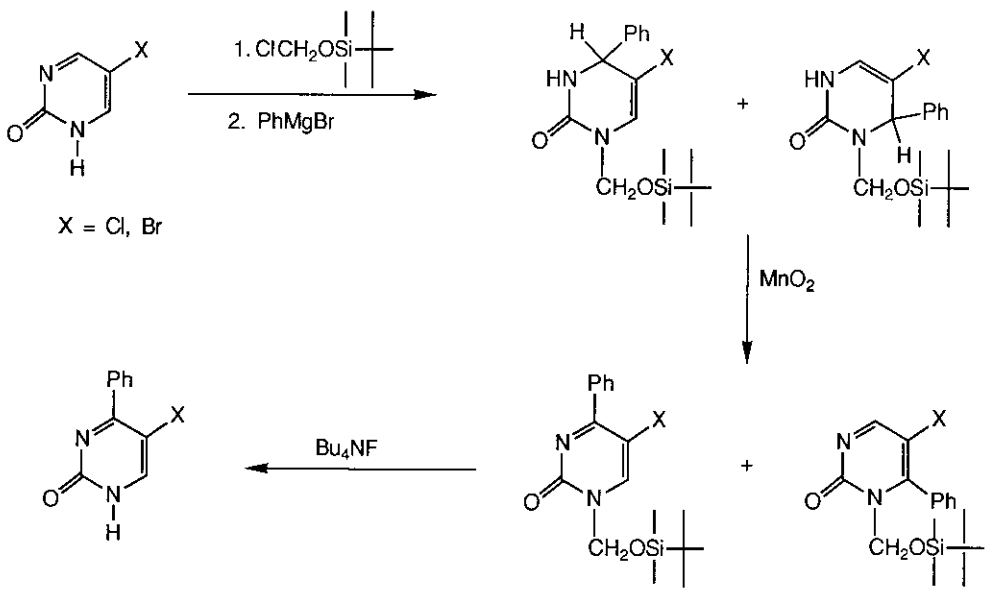
Scheme 12

Another example of acid catalyzed aldol type reaction is taken from the 1,2,3-triazin-3(2H)-one system (Scheme 12). The extra nitrogen introduced into the pyrimidine ring, so that it becomes a triazine, makes the new heterocycle more π-electron deficient than the pyrimidine system and promotes nucleophilic reactions. High reactity towards nucleophiles is seen in the 5-position, less in the 6-position. Under the influence of acid catalysis, acetone adds rapidly into the 5-position. Dehydrogenation by DDQ gave the tautomer with extended conjugation and the (Z)-configuration because of hydrogen bonding and pseudo-ring formation.[27]

Bromoacetic acid derivatives add to 2-pyrimidinone derivatives under the Reformatsky reaction

conditions. From 1-phenyl-2(1H)-pyrimidinone the 3,4- to 3,6-dihydro isomers were reported to be formed in the ratio 3:1.[28] According to our analogy, the product after oxidation corresponds by to a β-oxo ester, and would therefore not be expected to be extensively enolized; the enol form of the 4-isomer was not reported.[28]

For the addition of organometallic nucleophiles to 2-pyrimidinones the NH functionality must be blocked. For this purpose we have developed a protecting group which is stable to organometallic reagents (Scheme 13). In this case it is important that the protecting group can be removed without hydrogenolysis since the pyrimidinone is very sensitive to reducing conditions. The new reagent is α-chloromethyl t-butyldimethyl silyl ether which was reacted with O-silylated or O-stannylated pyrimidinones to form the N-alkylated product. Treatment of the latter with the organometallic reagent furnished the adduct. With phenylmagnesium bromide, a mixture of the 3,4- and 3,6-dihydro isomers was formed. The mixture was oxidized to the heteroaromatic product and treatment with a fluoride salt, which cleaved the oxygen-silicon bond, generated the phenylated pyrimidinone.[29]

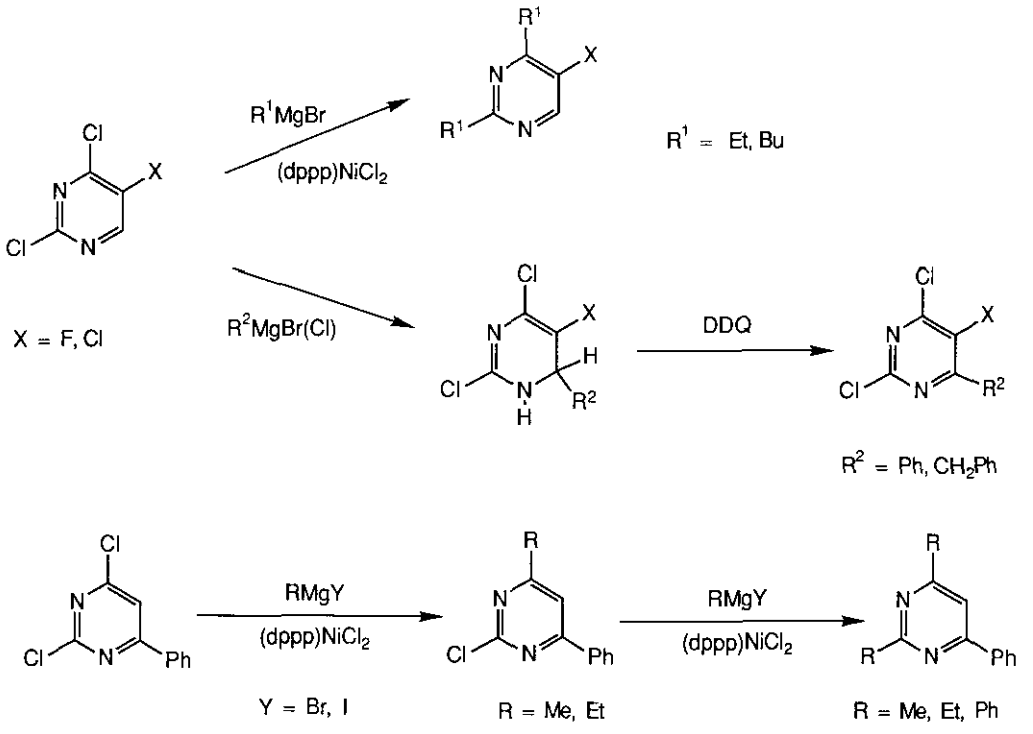


Scheme 13

B.1. CARBON-CARBON BOND FORMATION BY CROSS-COUPLING REACTIONS

Nucleophilic displacement of a halogen in a specially activated azine position can be effected using stabilized carbanion nucleophiles, an example being malonate type alkylations. This approach is in most cases inferior to the new coupling type reactions. Organocopper derivatives can be used in coupling

reactions, an example being the synthesis of 2-arylpyridines from 2-pyridinylcopper complexes.[30] Several reports describe nickel catalysis. Nickel complexes of type $NiCl_2L_2$ are used. Bidentate ligands are generally more active than monodentate ligands and 1,3-bis(diphenylphosphino)propane is frequently the ligand of choice. Cross-coupling in pyridines proceeds in all positions.[31] Similarly, methylation and phenylation occur in all the activated positions when 2,4,6-trichloropyrimidine is reacted with methyl- and phenylmagnesium reagents using (dppp)$NiCl_2$ catalysis.[32] In 2,4,5-trichloro- or 2,4-dichloro-5-fluoropyrimidine, however, which carries a halogen in the benzenoid 5-postion, only the halogens in the activated positions participate in coupling reactions (Scheme 14). In the reaction with phenylmagnesium bromide, however, the reaction takes another course in that adduct formation in the free, activated 6-position is favoured. The course of the reaction for the benzyl analogue was the same. With simple alkyl Grignard reagents, however, the major products were formed by coupling reactions. When all the activated positions are occupied, as in the case of 2,4-dichloro-6-phenylpyrimidine, exhaustive couplings take place; with alkyl reagents regioselective mono-coupling at C-4 can be achieved.[9,10]



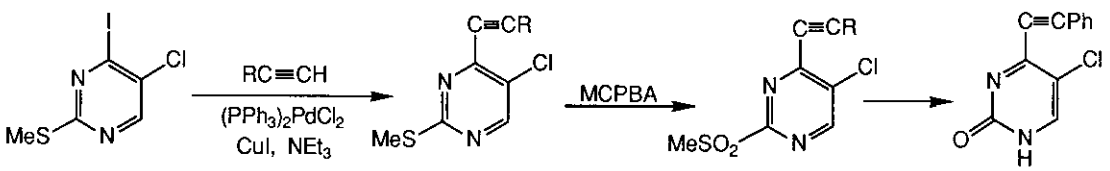
Scheme 14

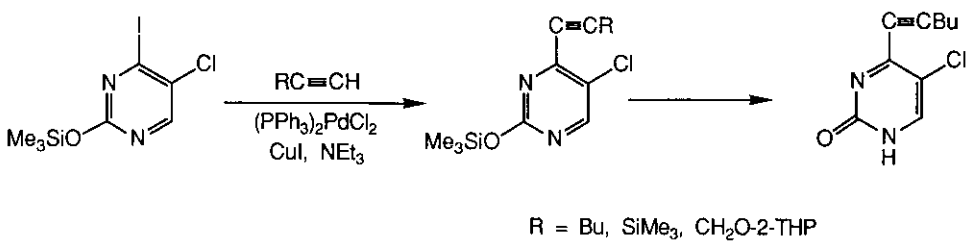
The replacement of a thio group with introduction of a carbon substituent from a Grignard reagent can be effected by Ni(II)-catalysis.[33] This reaction can be regarded as complimentary to the replacement of

halogeno groups by Pd-catalysis.

The chemoselectivity in palladium catalyzed reactions is outstanding, and most functional groups are compatible. Iodobenzene is readily coupled with terminal acetylenes using a Pd(0)-catalyst which is generated in situ from a bis(triphenylphosphine)palladium(II) chloride - copper(I) iodide complex in the presence of an amine. This coupling has been used in reactions between phenylacetylenes and bromo- or iodopyrimidines. In the electrophilic 2-position, the order of reactivity established was the I>Br>>Cl. In quinazoline, however, the 4-position is highly activated, and the chlorine in this position was readily replaced in the coupling reaction.[34] The 3-chloro substituent in 3-chloropyrazine N-oxides can also be replaced under similar conditions in reactions with terminal acetylenes.[35] In uracils the 1-butyne group has been substituted into the 5-position by reactions with the corresponding iodides.[36]

In our work we wished to introduce unsaturated carbon substituents into the 4-position of 5-chloro-2-methylthiopyrimidine; the coupling reactions were run on the 4-iodo derivative (Scheme 15). The couplings proceeded exclusively at C-4, and high yields were obtained for both terminal aryl- and alkylacetylenes. Acetylene itself in this reaction was protected by monosilylation because the free acetylene product is chemically unstable. The sulfide function in the coupling products could be oxidized and the sulfone was hydrolyzed to the lactam. Because of chemical instability of the final product under alkaline hydrolysis, only the phenylacetylenic pyrimidinone could be isolated. Coupling with the O-silylated lactam

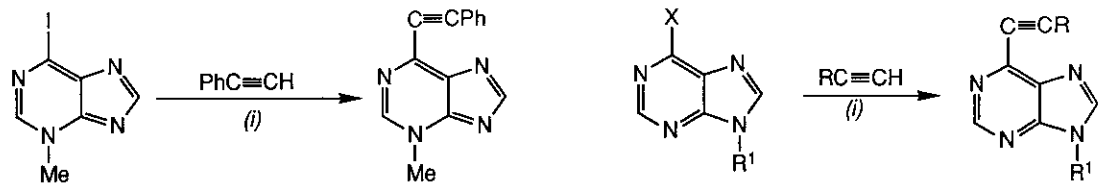




Scheme 15

also proceeded well under anhydrous conditions, but only the 4-phenyl- and 4-butylacetylenic derivatives were stable enough for isolation after hydrolytic cleavage of the silyl ether in aqueous dioxane.[37]

In purines substituted on N-9, a bromine or chlorine in the activated 6-position is replaced through carbon-carbon bond formation by alkyl- or arylacetylenes using the above conditions for the coupling.[38]
We find that the 4-iodo derivative of N-3 methylpurine readily undergoes this coupling reaction with phenylacetylene (Scheme 16).[39]

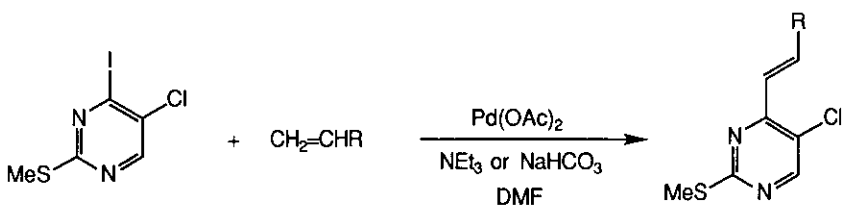


(i) = $PdCl_2(PPh_3)_2$, CuI, NEt_3
MeCN or DMSO

X = Cl, Br
R^1 = H, Alk, Ar, β-D-rib.
R = Alk, Ar

Scheme 16

Introduction of alkenyl substituents can be achieved under similar conditions (Scheme 17). The reactivty is lower than for the corresponding acetylenes.The coupling with styrene was best carried out using Pd(II) acetate and triethylamine, whereas coupling with methyl acrylate gave a better yield using Pd(II) acetate in



R = Ph, CO_2Me, Bu

Scheme 17

DMF, with sodium hydrogen carbonate as the base. The coupling was at C-4, and the product possessed the trans configuration. The reaction with 1-hexene was unsatisfactory, and it is concluded that the terminal alkenes have to be activated by electron-withdrawing or readily polarizable groups for the reaction to proceed well.[40]
This conclusion is in accord with experimental findings in related work.[41] The limitations imposed on the vinyl group for reaction to occur under these conditions, led us to look at transmetallation reactions. Several organometallic reagents are known to react with palladium(II)-complexes. The catalyst inserts

initially into a carbon-halogen bond and thereafter complexes with the organometallic reagent. Subsequent reductive elimination results in the formation of the new carbon-carbon bond. Organometallic reagents which are known to couple with palladium(II)-complexes in this manner include R-MgX, R-Li, R-Zn-, R-Al=, R-Zr≡, R-B=, R-Sn≡, R-Hg- and R-Cu.[42,43] These compounds differ, however, very much in availability, tolerance to functional groups, and the reaction conditions suitable for coupling to occur. Mercury derivatives are of importance because they are often available by simple electrophilic substitution reactions, at least in benzenoid positions, but their toxcicity is a great disadvantage.[44] Organozinc derivatives are particularly attractive reagents. Thus pyridinylzinc chlorides have been coupled with 6-halogenoquinolines using Pd(0)-catalysis.[45] Coupling can also be effected using oppositely polarized reactants such as in the reaction between 2-iodopyridine and trifluoroethenylzinc chloride, and the biheterocyclic syntheses from 2-bromopyridines and 1-methyl-2-pyrrolylzinc chloride.[46]

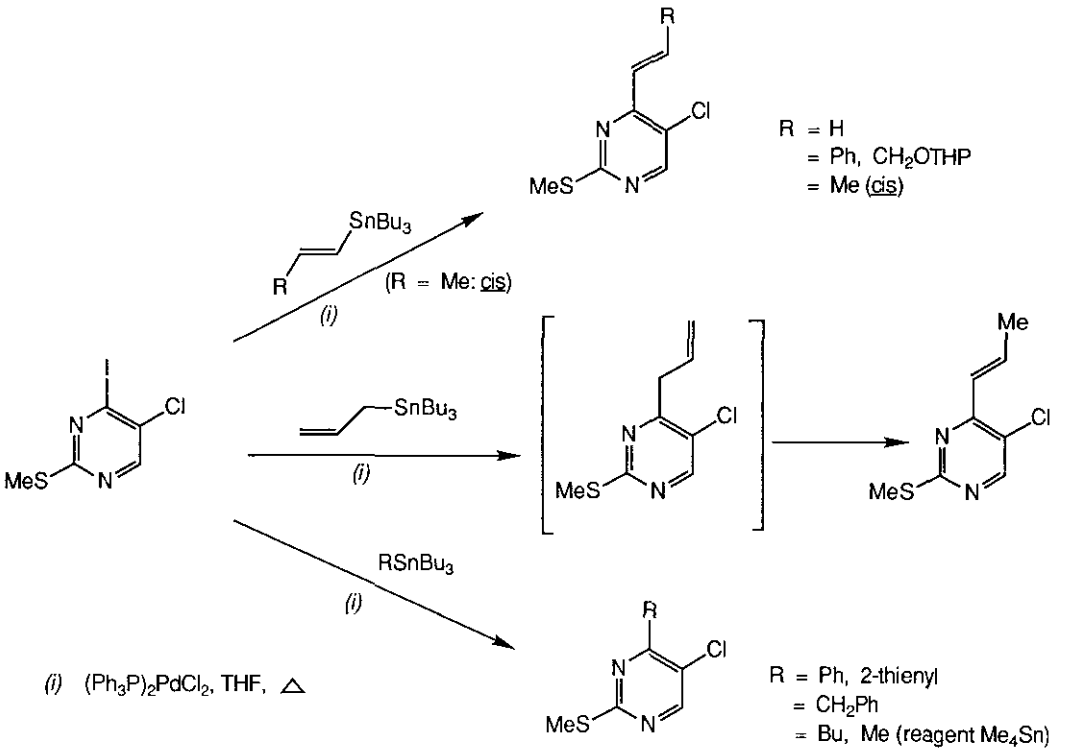
Boronic acid derivatives are useful reactants in Pd-catalyzed coupling reactions, as in the introduction of alkenyl and phenyl groups into pyridines,[47] and thienyl substituent into azines from thiopheneboronic acids.[48] But organotin compounds have over a very short period of time become the most important organometallic reagents in palladium catalyzed coupling reactions.[49]

Important for our decision to select organotin reagents for coupling reactions was the statement by Beletskaya back in 1983: " Since organic compounds of tin and mercury are readily available, do not react with oxygen and atmospheric moisture, are thermally stable and inert towards many functional groups, it is of considerable interest to employ them in organic synthesis. Their low reactivity is easily overcome with transition metal catalysis."[43]

Few examples of palladium-catalyzed coupling reactions between organotin compounds and heterocycles were known when our work was started,[50] and there was no mentioning of pyrimidines.

We started our work on a 4-iodopyrimidine (Scheme 18). The catalyst was bis(triphenylphosphine) palladium(II) chloride. The coupling with alkenes is stereospecific as in the case of aryl halides.[51] The reaction is not dependent on the presence of electron withdrawing substituents in the alkene. With propenyltributylstannane, however, there was a significant increase of the trans component, from 10% in the reagent to 20% in the product. This change could have been caused by palladium-induced isomerization, but more likely the isomerization has arisen because the methyl group in the initial coupling product is highly activated by homoconjugation with the π-electron deficient pyrimidine ring; deprotonation and subsequent protonation will favour formation of the trans isomer.

In order to compare the reactivities, an equimolar mixture of the 4-iodopyrimidine, iodobenzene and styryltributylstannane was allowed to react under the influence of the catalyst. Exclusive coupling between the 4-iodopyrimidine and the organotin reagent was seen. These findings agree with the report that the rate of the reaction between aryl bromides and vinyltin reagents is promoted by electron-withdrawing substituents in the aryl reactant.[52]

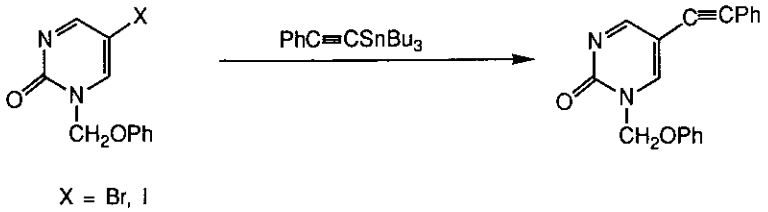


Scheme 18

The reactions with organostannanes proceed less readily when the metal is attached to sp^3-hybridized in contrast to sp^2-hybridized carbon. But alkylation by methyl and butyl groups could be effected from the corresponding tetraalkylstannanes under vigorous reaction conditions (Scheme 18). When the sp^3-carbon carries an activating group, the reaction is promoted. Thus the benzyl group in benzyltributylstannane is transferred in DMF. The product from the reaction of allyltributylstannane was trans-4-propenylpyrimidine.[40] Presumably the coupling with the allyl tin reagent occurs to give the 4-allylpyrimidine as the initial product by analogy to the formation of allylbenzenes in corresponding reactions between allyltributylstannane and aryl halides.[53] In the case of the pyrimidine derivative, however, the allylic carbon is highly activated by the π-electron deficient ring, resulting in deprotonation. Reprotonation will preferentially be on the terminal carbon, whereby the double bond becomes conjugated with the heteroaromatic system, with preference for the trans form. This seems the most plausible explanation, but does not rule out the possibility that palladium may be involved in the isomerization.[54]

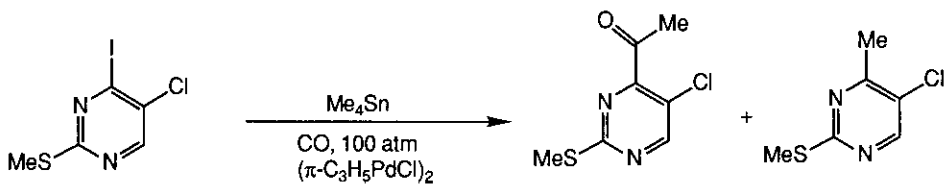
The introduction of alkynyl substituents by using alkynylstannanes as reactants and Pd(II)-catalysis seems superior to the method which involves Pd(0) and the alkyne itself, as discussed above. Reactions between

(phenylethynyl)tributylstannane and a 5-bromo- or 5- iodopyrimidine is shown (Scheme 19).[55]



Scheme 19

Introduction of acyl functions was attempted with tetramethylstannane using bis(π-allylpalladium chloride) in various solvents in an atmosphere of carbon monoxide (Scheme 20). The reaction was slow, even at 100 atm. pressure and at best the product was a 1:1 mixture of the 4-acyl and the 4-alkylated derivative. The latter is formed by competitive alkylation.[56] Iodoarenes, however, are readily acylated at 1 atm. pressure.[57] A convenient approach to acylations, however, has been found in the coupling reactions with stannylated enol ethers,[11] and is discussed below.

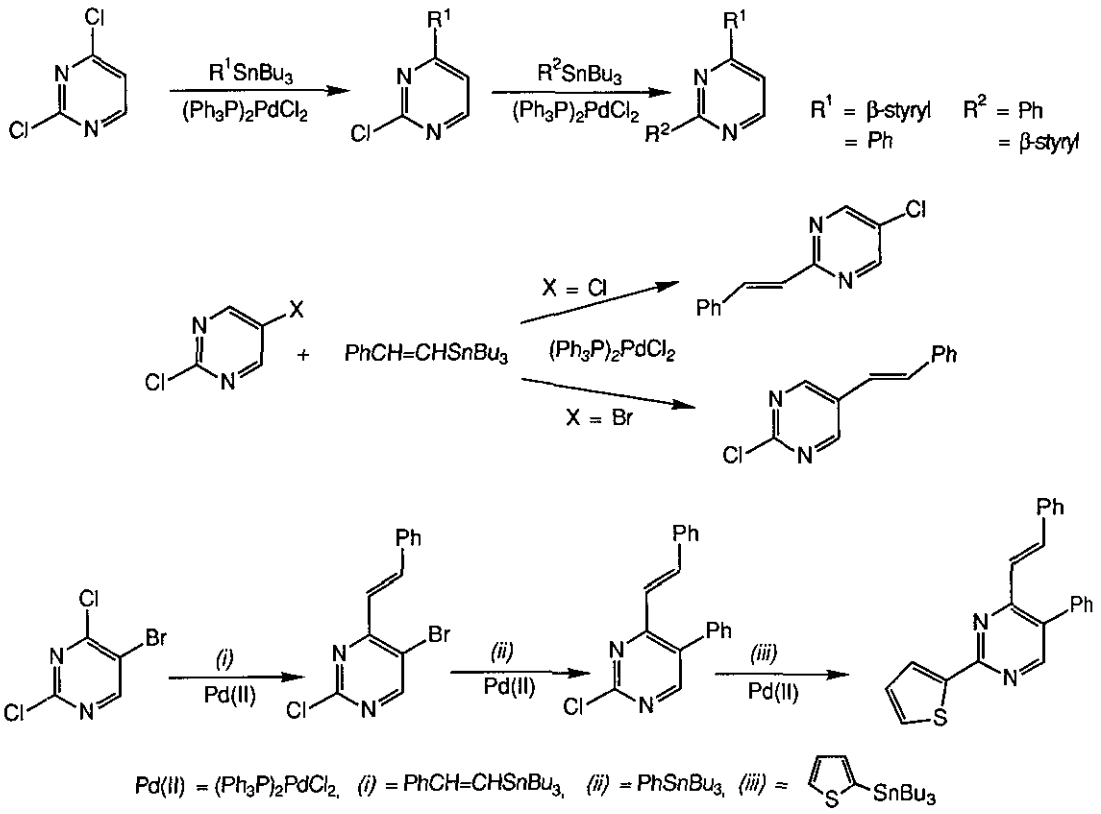


Scheme 20

In coupling ractions between aryl halides and organostannanes the arenes must generally be bromo or iodo derivatives for the coupling to occur; replacement of a chlorine substituent requires the presence of a strongly electron-withdrawing group.[49,52,58] In π-electron deficient heteroaromatic systems, chlorines are readily introduced into the activated positions by well established procedures. The corresponding bromo or iodo derivatives, however, are generally less readily available, and they are often prepared from the chlorides by halogen exchange reactions. This led us to investigate reactivities of chloropyrimidines towards palladium catalyzed cross-coupling reactions, and it has been found that chlorines in activated pyrimidine positions can be replaced by carbon substituents using organotin reagents and palladium catalysis. The importance of this methodology lies in that it opens up for ready introduction of carbon substituents into all π-electron deficient heteroaromatic systems where the corresponding chloro derivatives are readily available, two example being the biologically important purine and pteridine

systems. In many cases this methodology will obliterate cumbersome and often low yielding cyclisation reactions for the preparation of heterocycles carrying carbon substituents.

It should also be pointed out that the use of triflates of readily available hydroxy-azines may become of considerable importance. The triflates of phenols are becoming important intermediates for cross-coupling reactions,[59] and the triflate in the benzenoid 5-uracil position has been replaced with alkenyl substituents in Pd(II)-catalyzed coupling reactions.[60]



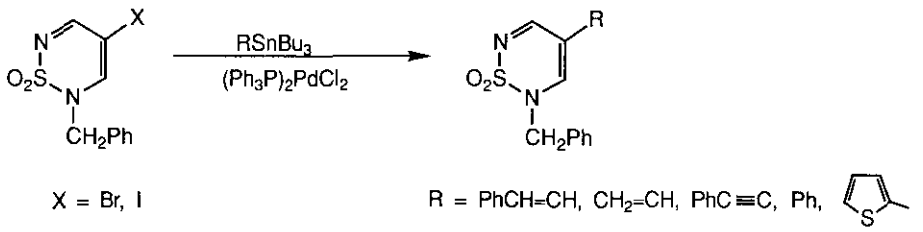
Scheme 21

The 4(6)-position in pyrimidine is more reactive than the 2-position, and regiospecific coupling results in the reaction between 2,4-dichloropyrimidine and β-styryl- or phenyltributylstannane; the carbon substituent is introduced into the 4-position (Scheme 21). The chlorine in the 2-position can subsequently be replaced. In stannylation reactions, however, regiospecific metallation takes place in the 2-position (see below). Subsequent coupling with an organohalide gives the isomer of the above direct coupling method. A bromine or iodine is required for coupling to take place in the benzenoid 5-position. Hence in 4,5-dichloropyrimidine coupling only occurs in the activated 4-position. This is also the position for the first attack in 2,4,5-trichloropyrimidine, and then in the 2-position. It will be recalled that the reaction of this

substrate with arylmagnesium reagents under Ni(II)-catalysis, took another course in that adduct formation occurred in the free 6-position. The reactivity difference between the 4-chloro and 5-bromo substituents in the coupling reaction is relatively small, but the 5-position is more reactive than the 2-position in the case of 5-bromo-2-chloropyrimidine. In reactions between 5-bromo-2,4-dichloropyrimidine and phenyltributylstannane, regioselectivity between the 4- and 5-positions was not achieved. With the more reactive styryl reagent and milder reaction conditions, however, regioselectivity was achieved.

To demonstrate the power of regioselectivity in these reactions, three different substituents were introduced into 5-bromo-2,4-dichloropyrimidine in a sequential and regioselective manner; initial styrylation in the 4-position, subsequent phenylation in the 5-position and finally thienylation in the 2-position.This reaction sequence corresponds to the reactivity order 4-Cl > 5-Br > 2-Cl.[11]

In the 1,2,6-thiadiazine system it will be recalled that carbon substituents were introduced into the 5-position via the adduct formation. In the benzenoid 4-position coupling reactions proceed readily with the 4-bromo or 4-iodo derivative under Pd(II)-catalysis (Scheme 22). Coupling with phenylacetylene failed using a Pd(II)-catalyst and a Cu(I) salt in a tertiary base. The reaction was successful in the pyrimidines, and the failure was apparently due to attack by the copper reagent on the thiadiazine ring system . The tributylstannyl derivative of phenylacetylene, however, underwent a smooth coupling reaction.[25]

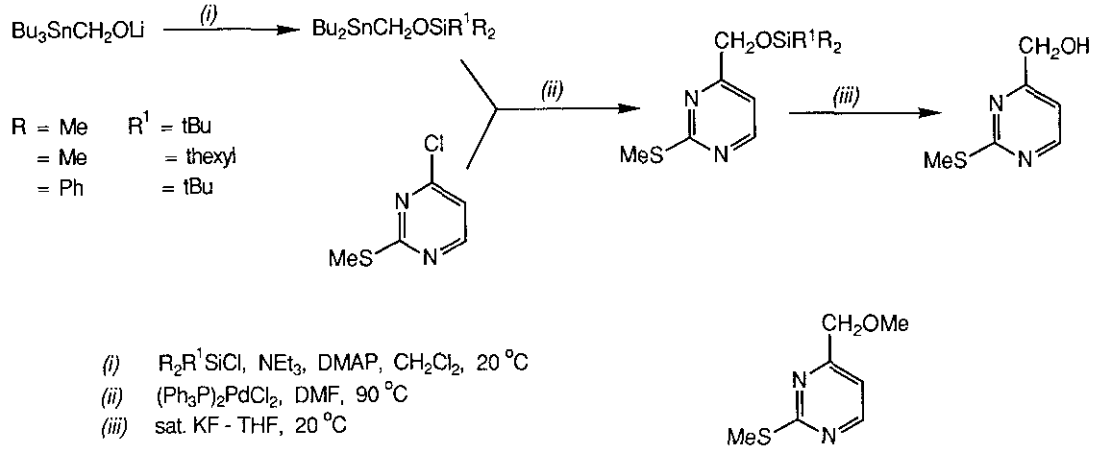


Scheme 22

Hydroxymethyl groups can be introduced by coupling reactions as shown (Scheme 23). Methods for the preparation of t-butyldimethylsilyl-, dimethylthexylsilyl- and t-butyldiphenylsilyloxymethyltributyl-stannanes have been worked out, and the silyl ether derivatives studied in the coupling reaction with pyrimidines. The coupling proceeds under Pd(II)-catalysis, but not with the use of Pd(0), the best catalyst being the bis(triphenylphosphine)palladium(II) chloride. The reaction is slow, however, because the group to be transferred is bonded to the tin through an sp^3-hybridized carbon.[61]

The methyl ether was similarly prepared. Bulky silyl groups were chosen for the protection of the hydroxyl group because of their high stability towards the reaction conditions, and their ability to withstand cleavage by an aqueous solution of fluoride ions. Aqueous fluorides are added at the end of the reaction in order to precipitate the stannyl halide coproduct as an insoluble stannyl fluoride. The silyl

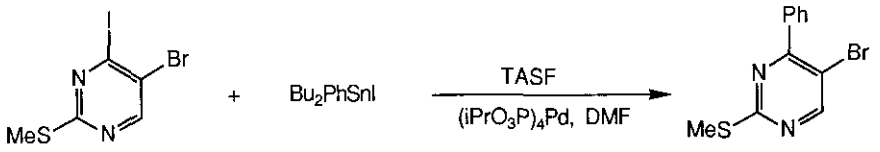
groups are readily cleaved, however, when a solution in THF is treated with tetrabutylammonium fluoride to yield the 4-hydroxmethylpyrimidine.[62]



Scheme 23

Cross-coupling reactions between organosilanes and organohalides in the presence of fluoride ions using the allylpalladium chloride dimer catalyst have recently been reported.[63] Tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) was a particular good source for fluoride ions in this reaction. One or two fluorines attached to the silicon of the silyl group accelerates the rate of the reaction.[63]

In cross-coupling reactions between distannanes and iodo- or bromopyrimidines, we have found the presence of fluoride ions essential for the palladium catalyzed reactions to proceed.[62,64] It is assumed that the fluoride ion adds on to the tin, weakens the tin-tin bond and increases the nucleophilicity of the reagent, and a stannyl group is transferred via palladium to the pyrimidine.

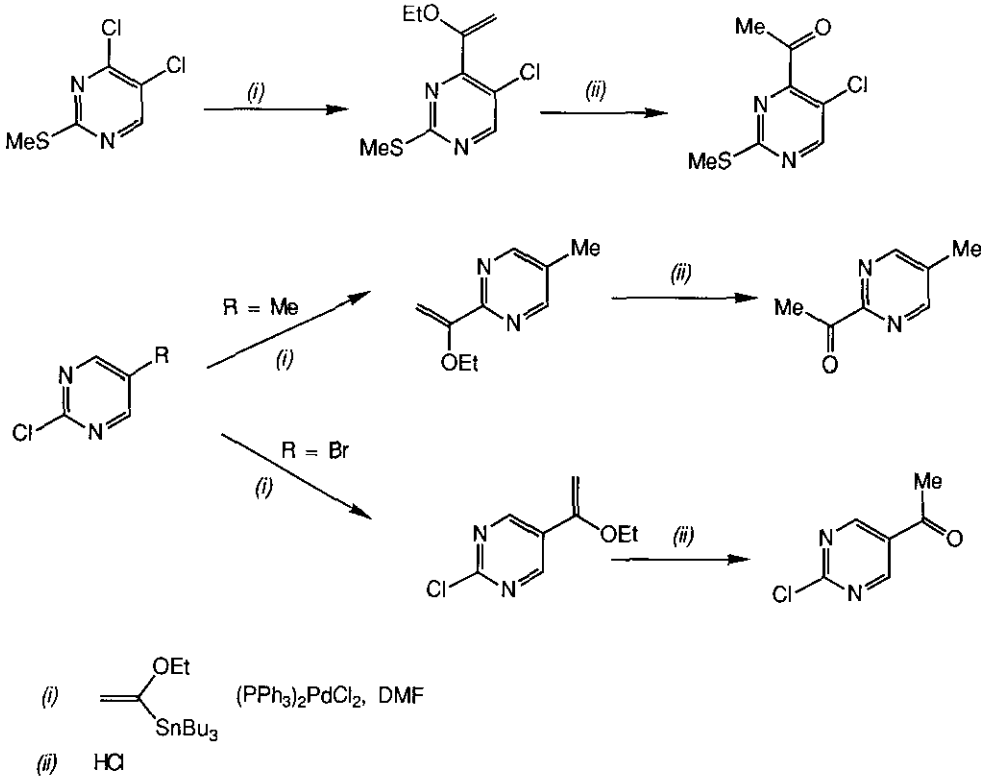


Scheme 24

A fluoride ion is also expected to add on to the tin in a stannyl group and to facilitate the transmetallation of an organic residue to the palladium catalyst. This pathway resembles the reactions with the silyl derivatives above. In the example shown (Scheme 24), dibutylphenylstannyl iodide was reacted with a 4-

iodopyrimidine, in the presence of TAFS as supplier of fluoride ions and tetrakis(triisopropyl phosphite)-palladium as catalyst. The phenyl group was transferred from the tin reagent to the pyrimidine. The stannyl fluoride is probably an intermediate since fluoride ions react readily with the other stannyl halides. Addition of a second fluoride ion leads to a negatively charged, reactive species. Accordingly, the reaction requires 1 -2 molar equivalents of fluoride ions.[65]

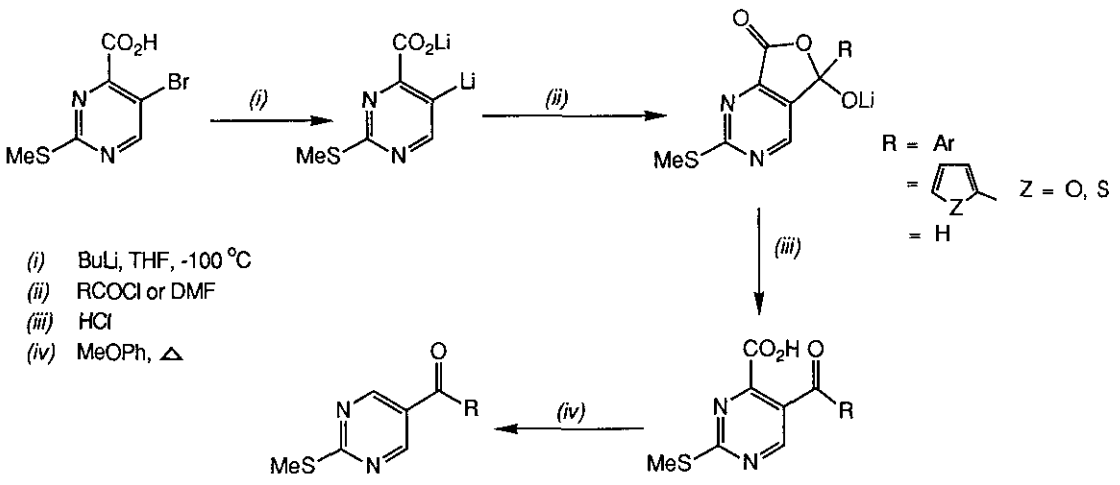
A convenient and general method for the introduction of acyl groups into any position in the heterocycle has been found in the coupling reaction with α-stannylated enol ethers (Scheme 25).[11] The reagents are available from enol ethers by α-lithiation and treatment with a trialkylstannyl chloride. The coupling reactions were run on derivatives which had either a chlorine in an activated position or a bromine in the benzenoid position. Mild acid hydrolysis of the α-pyrimidinyl enol ethers yields the acyl substituted pyrimidines.



Scheme 25

We have been especially interested in acylation in the pyrimidine 5-position and have also worked out some alternative methods for acylations (Scheme 26). Starting from a 2-substituted 5-bromopyrimidine-4-carboxylic acid, which is readily available by a cyclisation reaction, aroyl and heteraroyl groups, and

the formyl group, were introduced into the 5-position. The vicinal bromo acid is dilithiated at ca. -100 °C by butyllithium and treated with an acid chloride or DMF in the case of the formyl derivative. The reaction stops after the introduction of the carbonyl group because of complexation with the vicinal lithium carboxylate. The carbonyl group in the negatively charged complex is protected towards further reaction. Subsequently, the carboxyl group is removed by thermal decarboxylation, which proceeds with ease because the carboxyl group is situated in an activated ring position and is vicinal to the new carbonyl group.[66]



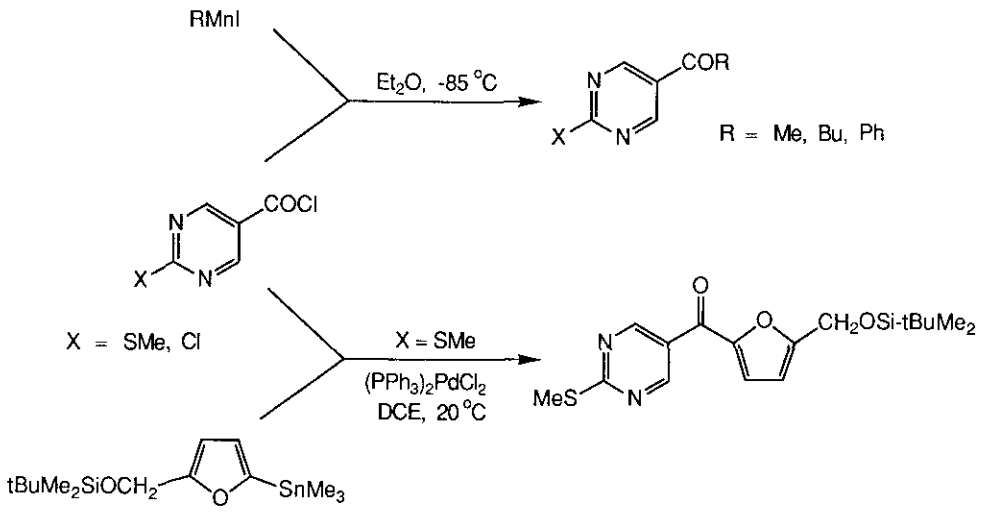
Scheme 26

The strongly basic conditions of this method, however, exclude the use of carboxylic acid chlorides containing an α-hydrogen. In our alternative method for the preparation of alkyl 5-pyrimidinyl ketones the acid chloride of the pyrimidine was reacted with alkylmanganese(II) iodide (Scheme 27).[67] The organomanganese reagent is of low basicity and is highly chemoselective.[68]

The organomanganese reagents were prepared by treating an organolithium compound with manganese(II) iodide. The coupling with the 5-pyrimidinecarbonyl chloride was run at -85 °C. Originally it was claimed that the organomanganese reagents with acid chlorides gave exclusively the corresponding ketone. In our reactions, however, the tertiary alcohol was formed as a minor component in the case of the smaller alkyl groups, especially the methyl group. Formation of the tertiary alcohol is ascribed to the electron-withdrawing effect of the pyrimidine ring which results in activation of the carbonyl group in the product first formed, and another nucleophile may add to this carbonyl group. This finding parallels the report that the activated oxo group in α-keto esters reacts with organomanganese reagents.[69]

A general and convenient method for ketone formation has been found in the reaction between a

pyrimidine-5-carbonyl chloride and an organostannane under the influence of Pd(II)-catalysis (Scheme 27).[70]



Scheme 27

B.2.1. METALLATION REACTIONS

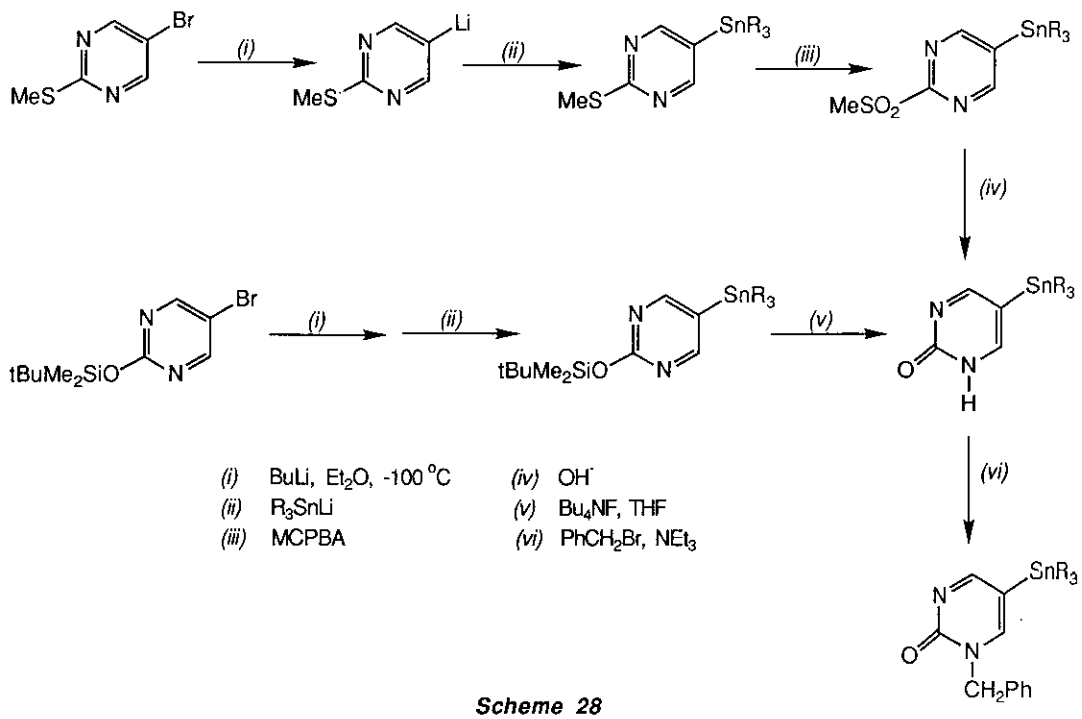
The polarity of the reagents used the above reactions for the formation of the carbon-carbon bond can also be reversed. This requires the presence of the π-electron deficient heterocycle as an organometallic derivative prior to the carbon-carbon bond forming reaction. Most of our efforts have been on working out routes for stannylation of pyrimidines, which are to be used in Pd-catalyzed coupling reactions. The stannylated pyrimidines have been found to be relatively stable compounds, and can be isolated and purified by conventional methods. Stannyl substituents in the benzenoid position are chemically most stable.

Stannylation is often effected by a transmetallation reaction between an organostannyl chloride and the appropriate lithiated species. This method can be used in the benzenoid 5-position in pyrimidines (Scheme 28). Cold-temperature lithiation, at ca. -95 °C, was used in order to avoid adduct formation between the lithium reagent and the pyrimidine in a free activated position, and the metal-metal exchange was effected by quenching the lithiated species with a trialkylstannyl chloride.[71,72]

2-Methylsulfonyl-5-stannylpyrimidines have been prepared by chemoselective oxidation of the stannylated sulfide (Scheme 28). Controlled alkaline hydrolysis yielded the corresponding 5-stannylated 2(1H)-pyrimidinones, which have also been prepared by initial lithiation and stannylation of a 5-bromo-

2(1H)-pyrimidinone which is protected on the oxygen as the dimethyl-t-butylsilyl ether derivative.[72] The large dimethyl-t-butylsilyl group was used for protection because the silyl group in the trimethylsilyl analogue is cleaved during lithiation.[73]

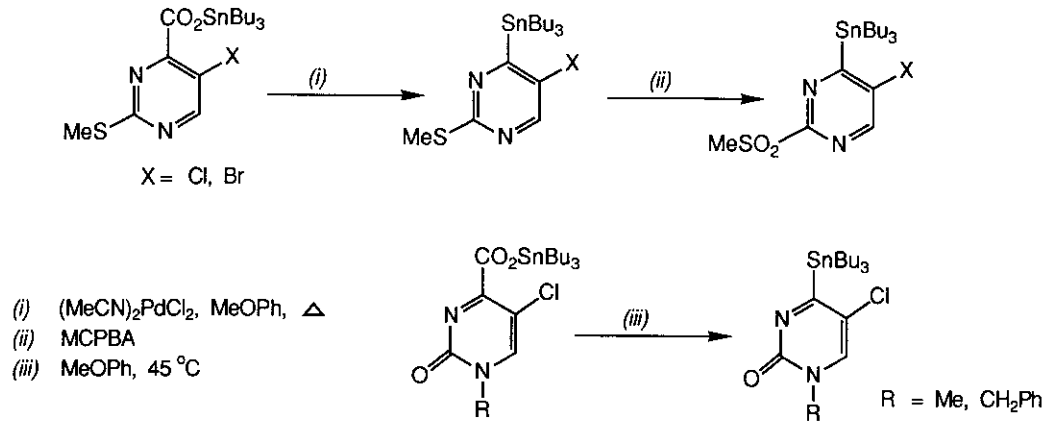
The 5-stannyl-2(1H)-pyrimidinones are subsequently prepared by chemoselective cleavage of the silyl group when treated with anhydrous tetrabutylammonium fluoride in THF. The stannylpyrimidinones can thereafter be N-alkylated and used in coupling reactions.[72]



Scheme 28

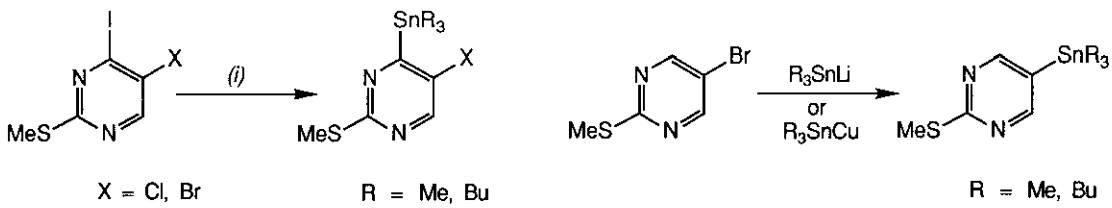
Lithiated derivatives suitable for transstannylation in the activated 2,4(6)-pyrimidine positions, however, are less readily available because of competitive nucleophilic reactions between the heterocycle and the lithium reagent, or between the heterocycle and its lithiated species acting as a nucleophile. We have found that stannylation in an activated position can be effected by decarboxylation of the corresponding stannyl carboxylate (Scheme 29).The trialkylstannyl 4-carboxylates were prepared from the carboxylic acid and bis(tributylstannyl) oxide. The stannylpyrimidine is formed by thermal decarboxylation. Free radical conditions, AIBN and illumination, had no significant influence on the yield. Pd-catalysis, in the cases studied, increased the stannylation substantially; the ester was heated in anisole in the presence of bis(acetonitrile)- or bis(triphenylphosphine)palladium(II) chloride. In highly activated systems, catalysis is not required. Thus N-1 alkylated 2-oxopyrimidine-4-carboxylic acid, which is sensitive to decarboxylation, as stannyl ester was decarboxylated in anisole alone at 45 °C to form the stannylated

pyrimidine (Scheme 29).[62]



Scheme 29

An iodo, but not a chloro substituent in the electrophilic 4-position in the pyrimidine can be substituted by a stannyl group (Scheme 30). Tributylstannyl-lithium, -sodium, and -copper were reacted with the pyrimidine at -78 °C. This reaction may not be a simple nucleophilic substitution,[74] however, since the



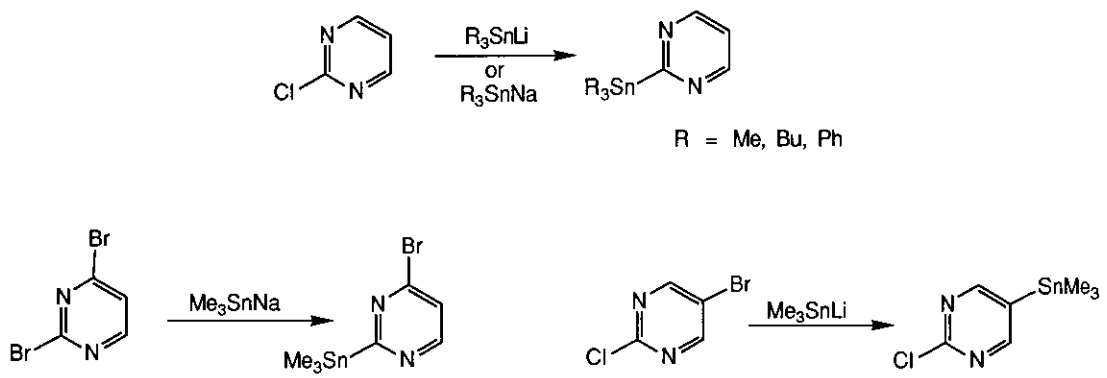
(i) a. Bu_3SnCu, THF, -78 °C to 20 °C
b. Me_3SnNa
c. Bu_3SnLi

Scheme 30

bromine in the benzenoid 5-position in the 5-bromo-2-methylthiopyrimidine isomer is readily displaced by a stannyl group in reactions with the trialkylstannylmetal reagents at -78 °C. Minor by-products are the corresponding hexaalkyldistannanes and the dehalogenated pyrimidine.[62,64]

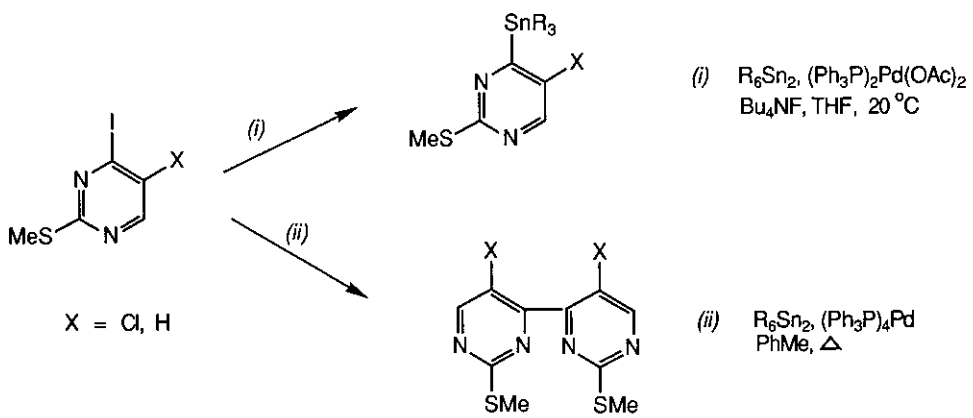
In the electrophilic pyrimidine 2-position a halogen can be substituted by trialkylstannyl anions (Scheme 31). In the 2,4-dibromopyrimidine regioselective substitution of the bromine in the 2-position is observed, and in 5-bromo-2-chloropyrimidine chemoselective metallation is in the 5-position with replacement of the bromine.[39] The relative reactivities observed strongly suggest that the metallation is not a simple

nucleophilic substitution.



Scheme 31

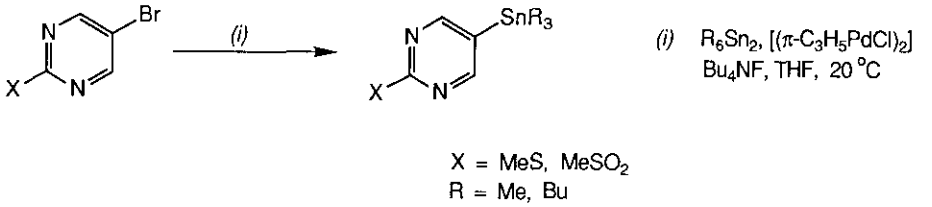
Palladium-catalyzed coupling of hexaalkyldistannane with aryl halides has been used to a limited extent in the preparation of arylstannanes, especially in the case of aryl substrates containing electron-withdrawing substituents.[75] In 4-iodopyrimidine stannylation can also be effected using hexaalkyldistannanes (Scheme 32). 1 - 2 molar equivalents of fluoride ions have to be present in the reaction mixture. Among the



Scheme 32

palladium catalysts tried, the best was bis(triphenylphosphine)palladium(II) acetate. The stannylation, however, could be accompanied by various amounts of bipyrimidine which is formed by reductive coupling, but under optimal conditions the reaction was clean. When the stannylation was tried using

Pd(0)-catalysis in the absence of fluoride ions, the product was the reductively coupled bipyrimidine.[62]
In the cross-coupling of the 5-bromopyrimidine with hexaalkyldistannanes the best catalyst was bis(π-allylpalladium chloride) , although bis(benzylideneacetone)palladium also gave reasonable yields of the 5-stannylated product, albeit more slowly (Scheme 33). Bis(triphenylphosphine)palladium(II) chloride, the catalyst used exclusively in the biheteroaryl syntheses described below, gave little or no product in the stannylation reaction. These results parallel the findings in stannylation reactions of aryl bromides.[76]
In the absence of halide ions the distannnanes did not undergo the coupling reaction. The reaction was slow with chloride ions present, but coupling occurred readily in the presence of at least one molar equivalent of fluoride ions.[64]

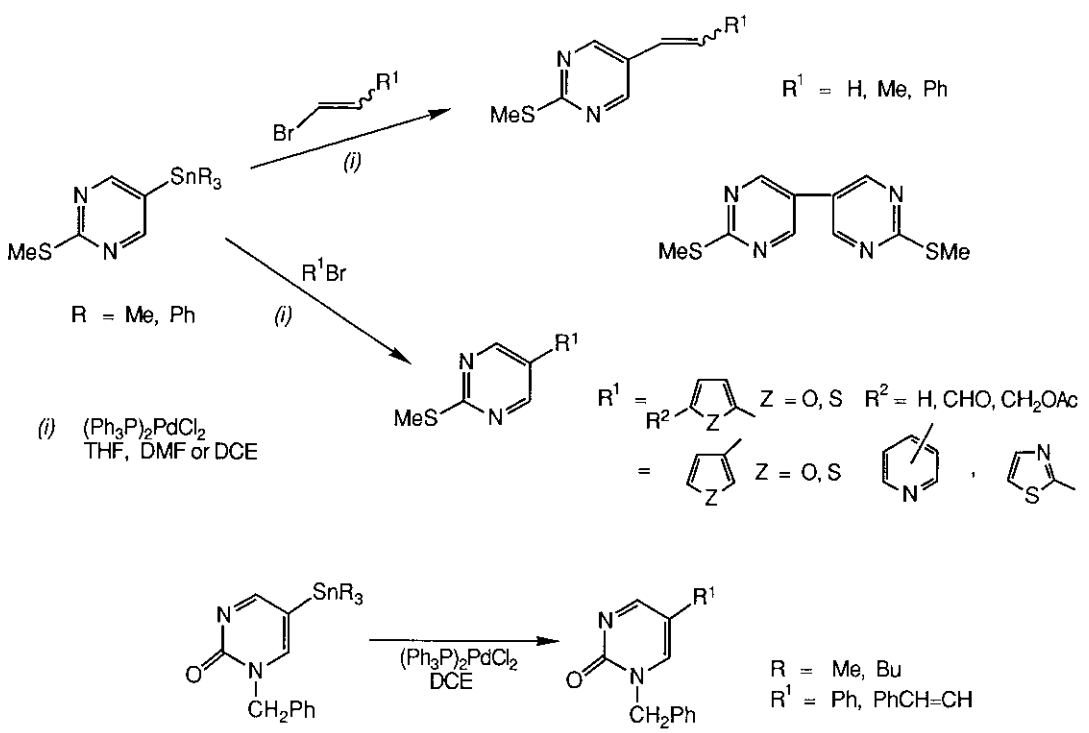


Scheme 33

The promoting effect of the fluoride ion has been ascribed to its great affinity for tin. It is assumed that the fluoride ion adds onto the tin in the distannane which results in a charged species with weakened tin-tin bond.[77]

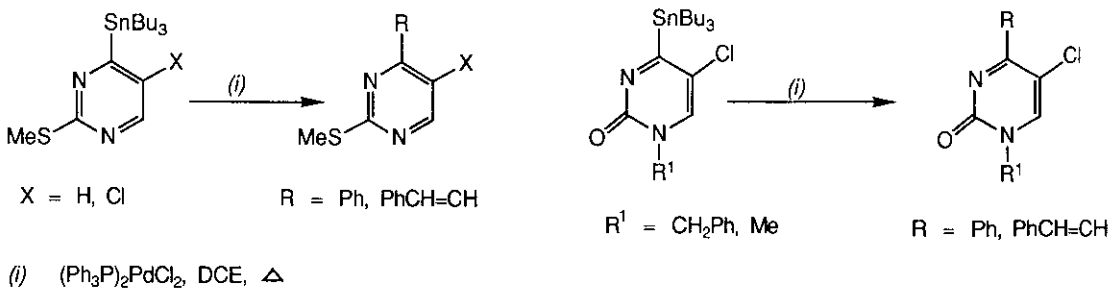
B.2.2. METALLATED HETEROCYCLES IN CROSS-COUPLING REACTIONS

Coupling between the pyrimidinylstannanes and bromo- or iodo-arenes, -heteroarenes and -alkenes, or acid chlorides proceeds readily with Pd(II)-catalysis to give the same products as those obtained in coupling reactions with the reversed polarized reagents, as discussed above (Scheme 34). The method of choice will depend on the relative availability, reactivity and stability of the reactants. Solvents may affect the course of the reaction. In 1,2-dichloroethane (DCE) the reaction between 2-methylthio-5-tributylstannylpyrimidine and β-bromostyrene or propenyl bromide, in the presence of bis(triphenylphosphine)palladium(II) chloride, gave the 5-alkenylpyrimidines in good yields, while in THF a mixture of the cross-coupled product and the bipyrimidine was obtained. The latter is formed by reductive homocoupling. With vinyl bromide only the homocoupled bipyrimidine was obtained in these reactions. The heterocoupled product, however, was available by the reversed procedure from the 5-bromopyrimidine and tributylvinylstannane.[71]



Scheme 34

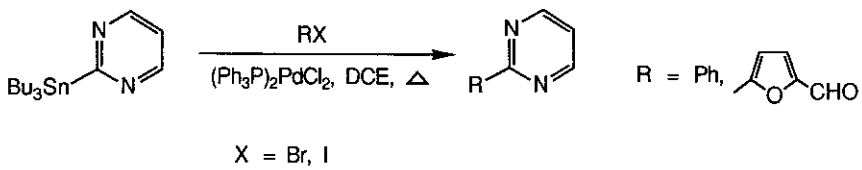
Cross-coupling with the formation of biheteroarenes from the isomeric bromofuranes, bromothiophenes, or their formyl homologues, and from bromopyridines go well. In the case of 2-bromopyridine DMF was the solvent.[64] 5-Stannylated 2-pyrimidinones are reactive and were coupled with β-bromostyrene and iodobenzene (Scheme 34).[72]



Scheme 35

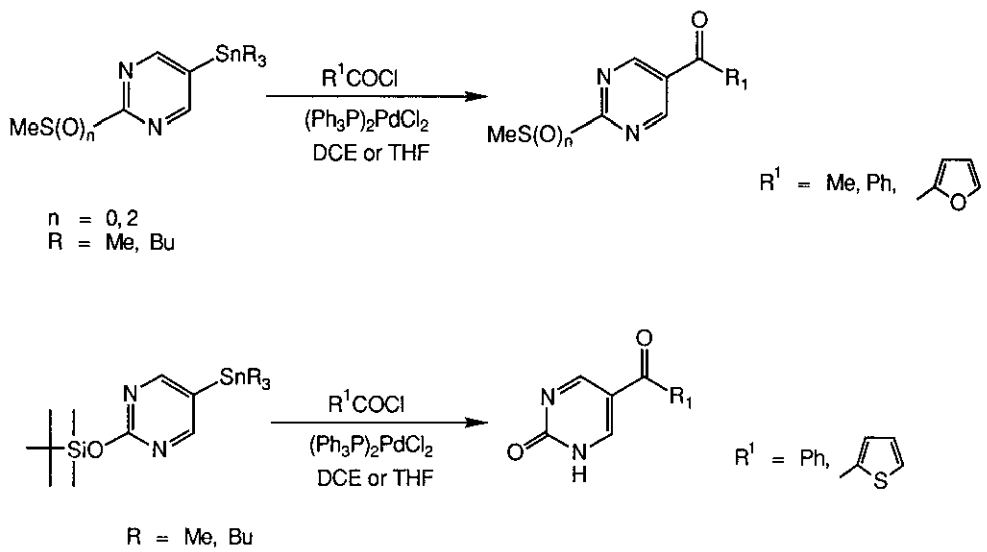
The coupling reactions between the 2-methylthio-4-stannylated pyrimidines and iodobenzene or β-bromostyrene were run in the same manner using the same Pd(II)-catalyst (Scheme 35). The 4-stannyl-2(1H)-pyrimidinones were also active in coupling reactions.[62]

Finally, it has been found that coupling can be achieved in the pyrimidine 2-position (Scheme 36). The reaction between 2-tributylstannylpyrimidine and arenes under the influence of Pd(II)-catalysis proceeds readily.[39]



Scheme 36

Ketones are also available by this route (Scheme 37). The 5-stannylated pyrimidines were reacted with acid chlorides under Pd-catalysis to yield alkyl and aryl ketones. In 2-pyrimidinone derivatives where the oxygen is protected as the dimethyl-t-butylsilyl ether, the silyl group was cleaved off in the coupling



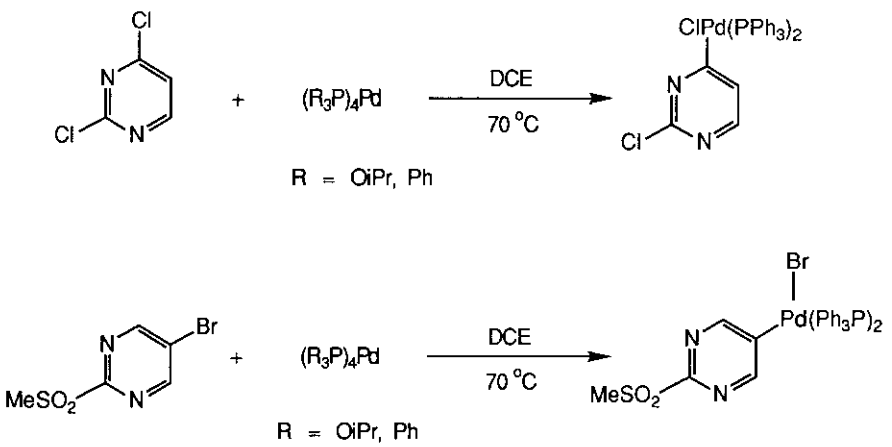
Scheme 37

reaction with acid chlorides. Presumably it is the stannyl chloride, which is generated during the coupling reaction, which leads to cleavage of the silyl-oxygen bond.

The 2-methylsulfonyl-5-trialkylstannylpyrimidines undergo the coupling reaction with acid chlorides

under fairly mild conditions; reflux in THF was used (Scheme 37). The relatively mild conditions suggest that the sulfonyl group exerts an activating effect with respect to the stannyl function. Controlled alkaline hydrolysis of the sulfone gave the 5-stannyl-2(1H)-pyrimidinone. The latter is highly reactive under the coupling reaction conditions. In the reactions with acid chlorides, however, the 5-acylated pyrimidinones first formed were involved in additional reactions to give unidentified product mixtures. The best route for the preparation of 5-acyl derivatives from a stannylated pyrimidine therefore appears to be hydrolysis of either the 2-acylated sulfone or the silyl ether, with subsequent N-alkylation. In most cases, however, the 5-acyl derivatives are more conveniently prepared by the alternative route, which has been discussed above, involving reactants of the reversed polarization.[72]

Our studies of metallation in pyrimidines have also been extended to include palladium derivatives since the latter may correspond to intermediates in the Pd-catalyzed cross-coupling reactions. Several organopalladium compounds containing α-carbon bonded aryl ligands have been described.[78] Corresponding complexes involving heteroarenes, however, have been much less investigated.[79] The complexes have generally been prepared by oxidative insertion by the Pd(0)-catalyst into the halogen-carbon bond in the heterocycle. In the reaction of 2-chloropyrimidine with tetrakis(triphenylphosphine)-palladium an excess of the former was used, and a mixture of the 1:1 complex and a binuclear complex was obtained.[80]

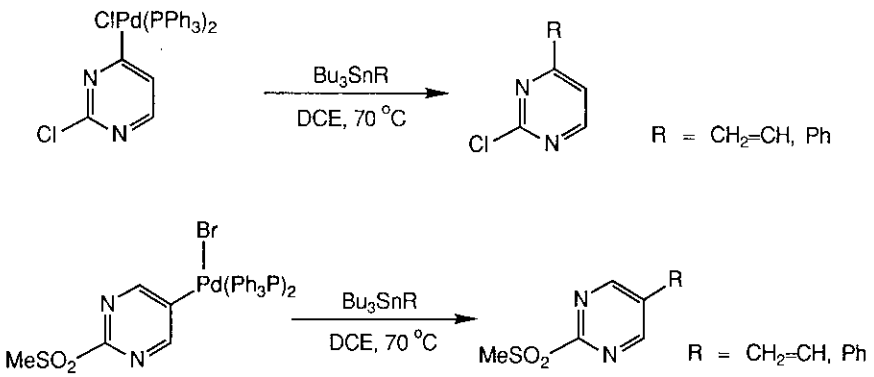


Scheme 38

In reactions between 2,4-dichloropyrimidine or 5-bromo-2-methylsulfonylpyrimidine and tetrakis(triphenylphosphine)- or tetrakis(triisopropyl phosphite)palladium, however, only the 1:1 insertion complex was obtained (Scheme 38). The reactions proceed well in 1,2-dichlorethane at 70 °C. These findings may be rationalized in terms of the relative basicities of the annular nitrogens. The basicity of the nitrogens in the pyrimidines which are substituted by two electronegative substituents, will be lower

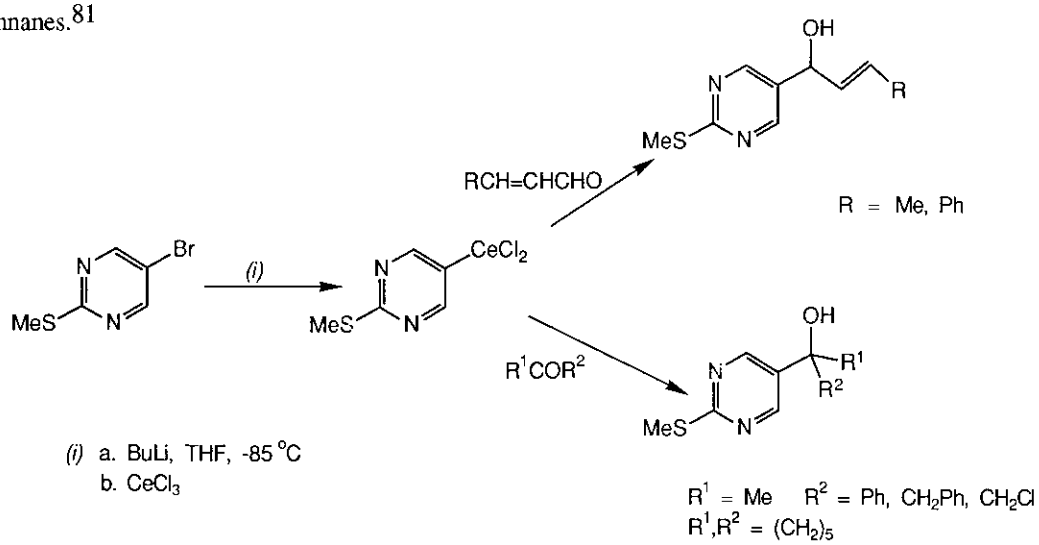
than in the monosubstituted derivative, and this will reduce the tendency for coordination between the nitrogen and the metal.[81]

The regioselectivity in the insertion reaction between the dichloropyrimidine and the Pd-catalyst is in accord with the 4-regiochemistry observed in the Pd-catalyzed coupling reactions between organostannanes and the chloropyrimidines,[11] as discussed above.



Scheme 39

The insertion complexes described have been isolated and purified by conventional methods. They react readily with organostannanes with carbon-carbon bond formation (Scheme 39). The insertion complexes may also serve as catalysts in coupling reactions between the respective pyrimidine precursor and stannanes.[81]



Scheme 40

In the search for other useful metallopyrimidines as intermediates for reactions leading to carbon-carbon bond formation, we were interested in exploring the potential of cerium(III) chlorides because of the recent reports that organocerium chlorides constitute a new class of promising organometallic reagents.[82] The 5-cerium derivatives were prepared by low-temperature metal-metal exchange using cerium trichloride and 5-lithiated pyrimidine (Scheme 40). In all of its reactions with aldehydes and ketones the 5-pyrimidinylcerium dichloride was superior to the corresponding lithium derivatives, and especially in reactions with enolizable aldehydes and ketones, and in the 1,2-addition to α,β-unsaturated carbonyls.[83] These results agree well with previous findings for other organocerium dichlorides in reactions with α,β-unsaturated carbonyls and enolizable carbonyls.[82]

C.1. CARBON-NITROGEN BOND FORMATION BY PALLADIUM CATALYSIS

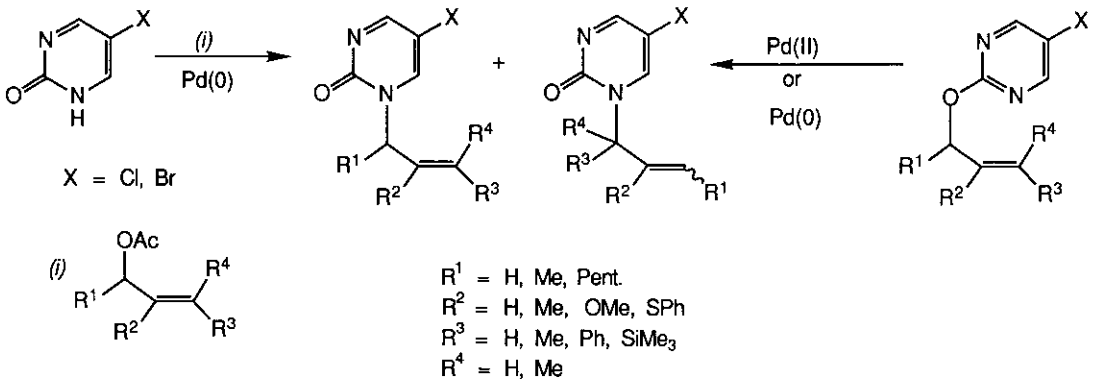
Substitution reactions of allylic compounds in the form of π-allylpalladium complexes with nucleophiles constitute a widely used synthetic method for alkylation, and we have adapted this method for the formation of carbon-nitrogen bond in the N-alkylation of 2(1H)-pyrimidinones. In our first example of this reaction 2-stannyloxypyrimidines were reacted with allyl acetate in the presence of a Pd(0)-catalyst to give the N-allyl derivative.[84]

In our further work, pyrimidinone anions were found to show high reactivity towards π-allylpalladium complexes (Scheme 41).[85] The reactions were run in dichloromethane at ambient temperature using Pd(0) generated in situ from palladium(II) acetate and triisopropyl phosphite. Substitution at the more substituted allylic carbon in the allylpalladium complex is favoured initially, but the reaction is reversible, and with time the less substituted isomer becomes the major product.

The simple N-allyl derivatives can also be obtained from 2-allyloxypyrimidines by allylic rearrangement under the influence of either Pd(0)- or Pd(II)-catalysis. No rearrangement was observed in the absence of a catalyst. In substituted allylic derivatives the product compositions from the use of the Pd(0)- and the Pd(II)-catalysts differ. Using Pd(II)-catalysis the Claisen rearrangement proceeds well for 2-(2-butenyloxy)pyrimidines (R^1=R^2=R^4=H, R^3=Me) but not for isomeric 2-(2-methylpropenyloxy)-pyrimidines (R^1=R^3=R^4=H, R^2=Me). The former has a methyl group in the γ-allylic position, the latter in the β-position. The 3,3-sigmatropic rearrangement also failed for other β-substituted derivatives in agreement with the generally poor rearrangement properties of β–substituted allylic ethers in the Claisen rearrangement. In the rearrangement of the γ,γ-dimethylallyl and γ-phenylallyl derivatives an equilibrium was set up between the allyloxy substrate and the two isomeric N-allyl rearangement products.

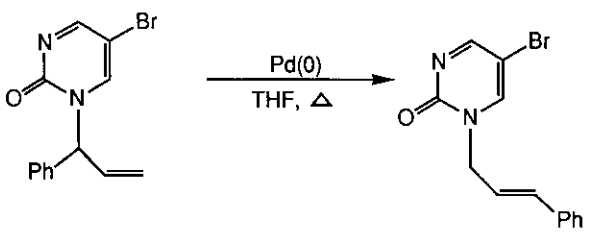
With Pd(0)-catalysis a π-allylpalladium complex similar to that formed in the reactions with allylic acetates might be an expected intermediate (Scheme 41). The relative yields of the rearranged products, however,

differed to some extent from the relative yields in the allylic acetate reactions. This may, in part, be due to the different conditions used in the two reactions; the rearrangement was run under essentially neutral conditions, whereas one mole equivalent of base was used in the reaction of the 5-halogeno-2-pyrimidinones with allylic acetates. The rearrangements proceed readily, and the relative yields of the rearranged products in the substituted allylic derivatives were markedly different from those in the Pd(II)-catalyzed reaction which show that the reactions proceed by different mechanisms. The 1,3-rearrangement dominates, except in the monosubstituted α-alkylallyl derivatives (R^1=Me or Pent, R^2=R^3=R^4=H), when the major product arises by the 3,3-rearrangement.



Scheme 41

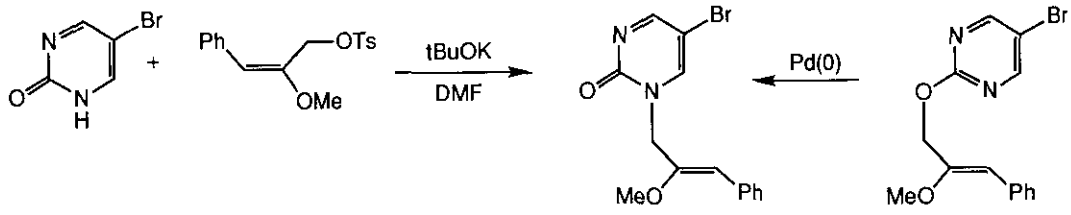
In the reaction of the 5-bromo-2-γ-methylallyloxypyrimidine (R^3=Me, R^1=R^2=R^4=H) the ratio of the 1,3- and 3,3-rearrangement product was close to 2:1, whereas the γ-phenyl analogue only gave the 1,3-rearrangement product. In the latter case it was shown by a stability study on the 1-α-phenylallylpyrimidinone (Scheme 42), which corresponds to the 3,3-rearrangement product, that on heating this isomer with Pd(0) in THF, which corresponds to the conditions used in the rearrangement reactions, gave the 1,3-product. Hence the former serves as an allylic substrate, in a reversible reaction which is thermodynamically controlled.



Scheme 42

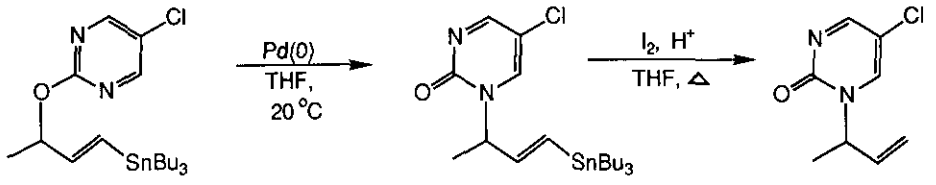
The yields in the Pd(0)-catalyzed 1,3-rearrangements are generally better than in the Pd(0)-catalyzed allylic acetate alkylations. In alkylation reactions with functionalized allylic systems, rearrangement of an allylic ether intermediate may be superior to direct alkylation reactions (Scheme 43). An example is given in the N-alkylation of 5-chloro-2(1H)-pyrimidinone with the unstable tosylate of 2-methoxy-3-phenyl-2-propen-1-ol which gave the product in 16% yield, whereas the corresponding allylic ether, which is readily available from the olate and the 2-chloropyrimidine, undergoes the 1,3-rearrangement under the influence of Pd(0)-catalysis to yield the N-alkylated product in 60% yield.

From this study it is seen that by suitable choices of substrate, the Pd(II)-catalyzed reaction can be used for attaching secondary or tertiary carbons to nitrogen, which is of some importance since direct alkylation becomes increasingly difficult as the number of substituents on the alkylating carbon increases.[85]



Scheme 43

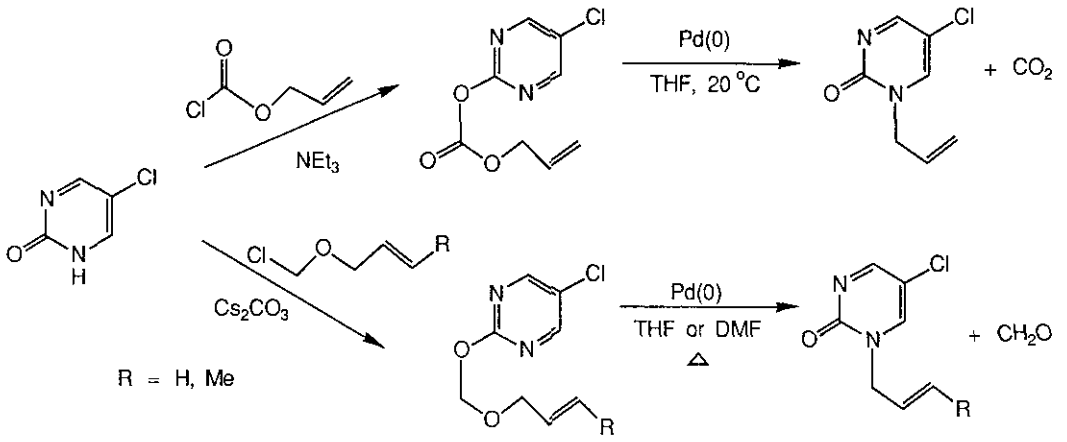
A γ-stannyl substituent in the allylic ether is not affected when Pd(0) is used to effect the 1,3-rearrangement (Scheme 44). The same product can be obtained, albeit in low yield, from Pd(0)-catalysis of the alkylation using the allylic acetate. Cleavage of the tin-carbon bond in the allyl derivative can be achieved in THF by treatment with iodine under acidic conditions.[86]



Scheme 44

It occurred to us that allylic rearrangements would seem likely to take place also from mixed allylic carbonates. The reaction shown was found to proceed readily at room temperature under the influence of Pd(0)-catalysis. No reaction took place in the absence of the catalyst. After a similar reasoning, we have also shown that mixed acetals with allylic alcohols can be used in Pd(0)-catalyzed rearrangements. In

contrast to the allylic carbonate, however, the allylic acetals require heating to effect the reaction.[86]



Scheme 45

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Received, 11th September, 1989