Review Article

Metallation and Metal-Assisted Bond Formation in π-Electron Deficient Heterocycles

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Work is reviewed on the regio- and chemo-selective introduction of carbon substituents into π-electron deficient heterocycles. Halogeno and trifluoromethanesulfonyl derivatives have been coupled with organostannanes and organozinc reagents in Pd-mediated reactions. Acyl, aryl or heteroaryl, and unsaturated or saturated alkyl derivatives are formed. Organomanganese reagents are used in ketone syntheses. Methods for preparing metallopyrimidines, especially stannopyrimidines, are described. Palladized pyrimidines have been isolated. Stannopyrimidines are used in Pd-catalyzed coupling reactions. Pyrimidinylcerium derivatives are superior to lithio analogs in most reactions. Organometallics (Li, Mg, Cu) form C–C bonds by 1:1-adduct formation in an activated, vacant electrophilic position, and the products are aromatized by oxidation. Organotitanium reagents show high regioselectivity. Tetraisopropoxyzirconium is used for regioselective dihydro formation. N–C bonds are formed by Pd(0)-catalyzed allylation reactions. Stereo- and regio-specific syntheses of carbonucleosides from pyrimidines and purines are described. The regiochemistry in Pd(0, II)-catalyzed allylic rearrangements from *O* to *N* in 2-pyrimidinones depends on the oxidation state of the palladium and on the nature of substituents. Pyrimidinyl allylic carbonates rearrange with loss of CO_2. The regiochemistry in the *N*-allyl substituent may change because the allylation is reversible. Allylic rearrangement has been used in the preparation of a carbocyclic uridine analog.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Carbon substituents can be attached onto annular carbon in π-electron deficient heterocycles either by a metal–complex mediated cross-coupling reaction, or by a two-step reaction which involves 1:1-adduct formation with an organometallic reagent, and subsequent dehydrogenation. On the annular nitrogen, carbon substituents have traditionally been attached by simple alkylation reactions. Herein we discuss metal-catalyzed allylation reactions. The work will be reviewed in the following order:

A. Carbon–carbon bond formation by:
   1. Cross-coupling reactions:
      a. Halogeno or trifluoromethanesulfonyl substituted heterocycles.
      b. Metallated heterocycles.
   2. Covalent 1:1-adduct formation with organometallic reagents.

B. Carbon–nitrogen bond formation by Pd-catalysis.

A. Carbon–Carbon Bond Formation.

A.1.a. Cross-coupling reactions from halogeno or trifluoromethanesulfonyl substituted heterocycles: Carbon substituents from stabilized carbanions such as a malonate, can be introduced into an electrophilic azine position which is substituted by a halogen or a group with leaving properties suitable for nucleophilic substitution. The modern coupling methods mediated by transition metals have dramatically changed the ease and opportunities for the introduction of carbon substituents. Organocopper reactions are useful.[1] Nickel-catalysis is especially useful for the replacement of a thio group with a carbon substituent from a Grignard reagent.[2]

Cross-coupling reactions in pyridine proceed in all positions using Ni-catalysis.[3] Exhaustive methylation or phenylation results when 2,4,6-trichloropyrimidine is reacted with methyl- or phenyl-magnesium reagents using [1,3-bis(diphenylphosphino)propane]nickel(II) dichloride, (dppp)$NiCl_2$, as catalyst.[4] The 5-halogeno substituent in 2,4,5-trichloro- or 2,4-dichloro-5-fluoropyrimidine (**1**) resists the coupling reaction with alkyl-

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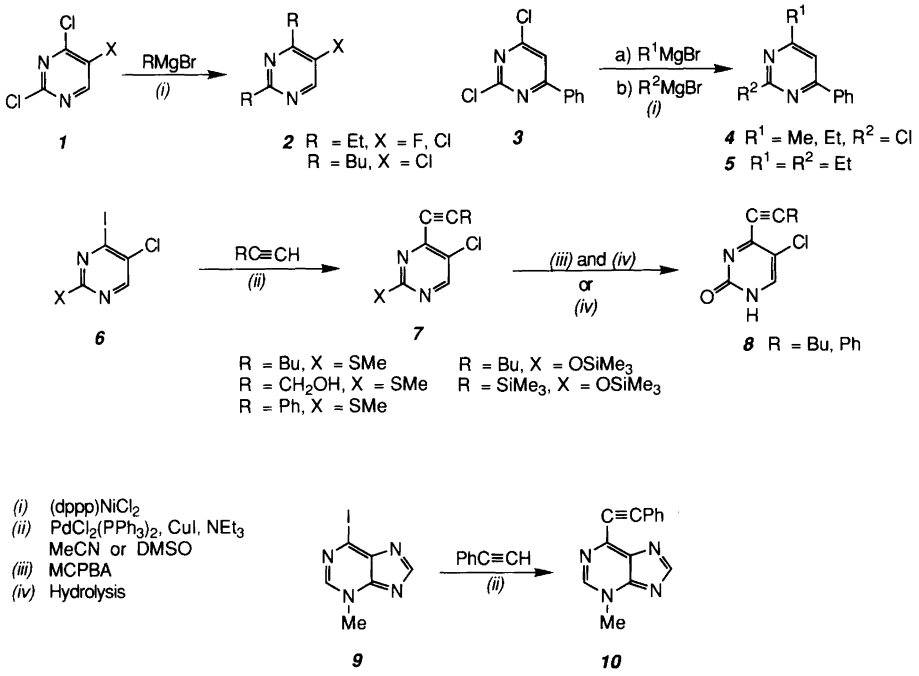


Scheme 1.

magnesium reagents. Adduct formation in the vacant electrophilic 6-position is the faster reaction (*vide infra*) with phenyl- and benzyl-magnesium reagents.[5,6] 2,4-Dichloro-6-phenylpyrimidine, which has all the electrophilic positions occupied, can be coupled exhaustively.[5,6] A chlorine in the 4-position is more reactive than one in the 2-position as regards nucleophilic substitution reactions. Sequential substitution (**4**, **5**) can be effected as in the case of Pd-catalysis (*vide infra*).

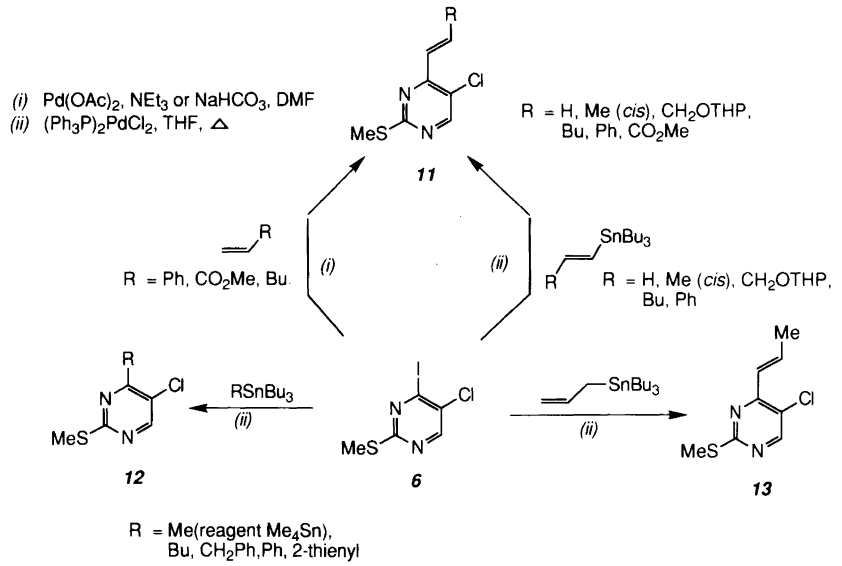
Palladium-(0) or -(II) complexes provide very active catalysts with high chemoselectivity. In the reaction between phenylacetylene and 2-halogenopyrimidines using bis(triphenylphosphine)palladium(II) dichloride and copper(I) iodide in the presence of an amine, the order of reactivity for the halogeno substituents was I > Br > Cl.[7] A chloro substituent in a benzene ring will normally not participate in a coupling reaction, but a chlorine in the electrophilic 2-position in pyrimidine, the 3-position in pyrazine *N*-oxides,[8] and the 4-position in quinazoline is substituted in a coupling reaction.[7] In the 5-chloro-4-iodopyrimidine **6** coupling proceeds exclusively at C-4 for both terminal alkyl- and aryl-acetylenes. Acetylene itself was monosilylated because the acetylenic product was chemically unstable. The 2-silyloxypyrimidine **6** (X = Me_3SiO) is coupled under anhydrous conditions. The acetylene must be substituted on the terminal carbon for the pyrimidinone to be stable enough for isolation after hydrolytic removal of the 2-silyl group.[9] In N-9 alkylated purines,[10] and in N-3 alkylated purines a halogen in the activated 6-position (e.g. **9**) has been exchanged by an alkynyl substituent in Pd-catalyzed coupling reactions.[11]

Alkenes are less reactive than acetylenes in the Heck-type reaction. The reactivity is enhanced by an electron-withdrawing or polarizable substituent.[12,13] Accordingly the coupling in the 4-position in the 5-chloro-4-iodopyrimidine **6** proceeds well for styrene and methyl acrylate but unsatisfactorily for 1-hexene.[12]

An important group of Pd-catalyzed reactions involves another organometallic species which is coupled to an organo halide or ester, preferably a triflate. The organometallic reagents include R–MgX, R–Li, R–ZnX, R–Al=, R–Zr≡, R–B=, R–Sn≡, R–HgX and R–Cu.[14,15] These reagents differ in availability and tolerance to functional groups. An argument in favor of the toxic mercury derivatives is their ease of preparation by simple electrophilic substitution.[16,17] Boronic acid derivatives are useful in Pd-catalyzed coupling reactions, e.g., in thiophenes,[18] in cycloformation of heterocycles,[19] in pyridines,[20] and in uracils.[21] Organozinc derivatives are attractive reagents which have been used to effect Pd(0)-catalyzed coupling between pyridinylzinc chlorides and 6-halogenoquinolines,[22] between 2-iodopyridine and trifluoroethenylzinc halide, and between 2-bromopyridines and 1-methyl-2-pyrrolylzinc chloride.[23]

Most of our work has been associated with organotin derivatives because of their ease of preparation, handling and high reactivity in the presence of Pd-catalysts.[24] Coupling reactions between the 5-chloro-4-iodopyrimidine **6** and substituted alkenyltributylstannanes were stereospecific in the alkene reagent (**11**); stereochemical retention has also been reported for vinylstannanes in coupling reactions with aryl halides.[25]

The reaction between aryl bromides and vinylstan-

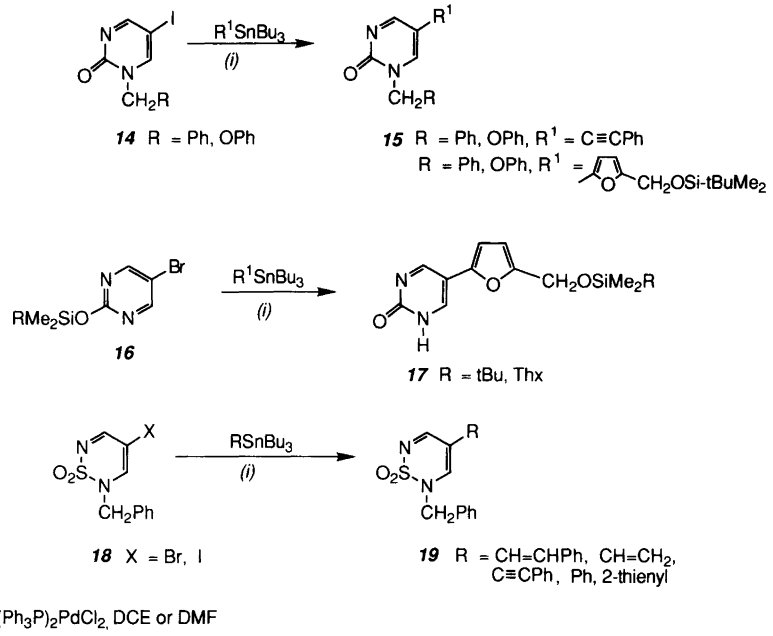


Scheme 2.

nanes has been found to be promoted by electron-withdrawing substituents in the aryl ring.[26] We have shown that in a Pd-catalyzed reaction of an equimolar mixture of the 4-iodopyrimidine **6**, iodobenzene and styryltributylstannane only the coupling product between the 4-iodopyrimidine **6** and the stannane was formed.

sp^3-Hybridized carbon directly attached to the metal is less reactive than lower hybridized carbons in the Pd-catalyzed reactions. The reactivity is enhanced when the sp^3-hybridized carbon is substituted by an electronegative group. Thus the benzyl group in benzyltributylstannane is transferred to the pyrimidine in DMF at elevated temperature. With allyltributylstannane the product was the 4-*trans*-propenylpyrimidine.[12] Presumably the corresponding 4-allylpyrimidine is the primary product, but the activation from the π-electron deficient pyrimidine on the allylic methylene group eventually causes the double bond to move into conjugation with the pyrimidine ring.

Alkynyl groups can be substituted into the pyrimidine ring (**15**) by way of alkynylstannanes and Pd-catalysis.[27] Similarly, biheteroarenes can be formed from stannylated heteroarenes. 5-Bromo- or 5-iodo-uracils have been



Scheme 3.

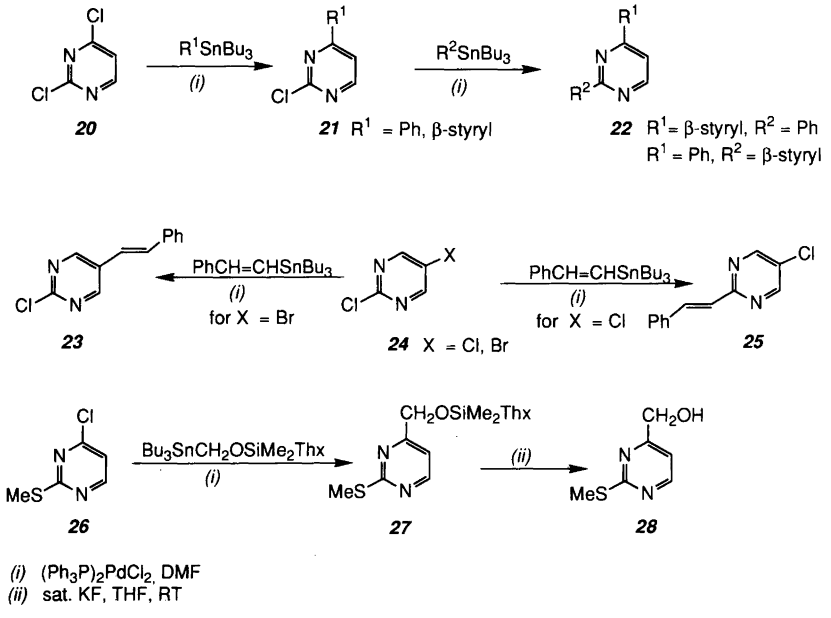
coupled with heteroarylstannanes.[21] The reaction with a silyl-protected 2-stannyl-5-hydroxymethylfuran gives the corresponding protected 5-(2-hydroxymethylfuryl)-pyrimidine **15**.[28] A bulky silyl group is used for protection since it has been found to resist cleavage by the stannyl bromide which is generated in the coupling reaction. The trimethylstannyl reagent was more reactive and effective than the tributyl homolog, which substantiates previous observations.[24] The hydroxy group in the product (**15**) is liberated by fluoride-ion cleavage of the O–Si bond under anhydrous conditions. If no alkylation of the pyrimidinone is desired, the 2-pyrimidinone may initially be converted into a bulky silyl ether **16** and subjected to the coupling reaction. After coupling with tributylstannanes, aqueous potassium fluoride is added in order to precipitate the stannyl bromide coproduct from the coupling reaction as an insoluble stannyl fluoride; the trimethylstannyl bromide is water soluble. In aqueous media there is a selective cleavage of the silyl group on the phenolic pyrimidine oxygen whereby the lactam **17** is formed. The silyl group on the alcoholic hydroxy group is retained.[28]

In the 1,2,3-thiadiazine system carbon substituents can be introduced into the 5-position via adduct formation (*vide infra*). In the benzenoid 4-position coupling reactions proceed readily with the 4-bromo or 4-iodo derivative under catalysis using Pd(II)-complexes.[29]

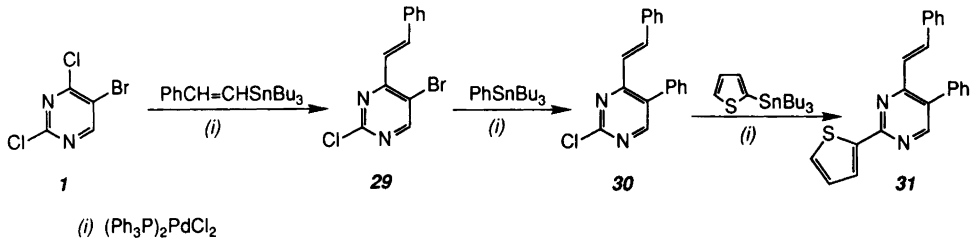
The coupling reaction between aryl halides and organostannanes generally requires the arenes to be bromo or iodo derivatives; replacement of a chlorine substituent requires the presence of a strongly electron-withdrawing group.[24, 26, 30] In π-electron deficient heteroarenes, a chlorine substituent is readily introduced into electrophilically activated positions from hydroxy groups by well established procedures, and to some extent from amino groups. The less readily available bromo and iodo derivatives are often prepared from the chlorides by halogen exchange reactions. This led us to investigate the reactivities of chloropyrimidines towards Pd-catalyzed coupling reactions. This work has shown that chlorines in electrophilic pyrimidine positions can be replaced by carbon substituents using organotin reagents as well as organozinc reagents and Pd-catalysis. The methodology permits the introduction of carbon substituents into all π-electron deficient heteroarenes where the corresponding chloro derivatives are readily available, e.g. in purines and pteridines. In many cases this methodology will obviate cumbersome and often low yielding cyclization reactions for the preparation of heterocycles carrying carbon substituents.

Triflates are another important class of substrate for coupling reactions when the reactive triflates can be obtained from hydroxy-heteroarenes (*vide infra*). An analogy is drawn to triflates of phenols which are becoming important intermediates for cross-coupling reactions.[31] The triflate in the benzenoid 5-uracil position is a phenolic triflate which has been replaced with alkenyl substituents in Pd-mediated coupling reactions.[32]

In the Pd-catalyzed coupling reaction between 2,4-dichloropyrimidine **20** and β-styryl- or phenyl-tributylstannane the carbon substituent is selectively introduced into the 4-position (**21**).[33] The same regioselectivity was found for the Ni-catalyzed coupling with Grignard reagents (*vide supra*), and the regioselectivity corresponds to the relative reactivity of the pyrimidine towards nucleophiles. A second carbon substituent, which may be different from the first one, can be substituted into the 2-position (**22**).[33] In metallation reactions leading to



Scheme 4.



Scheme 5.

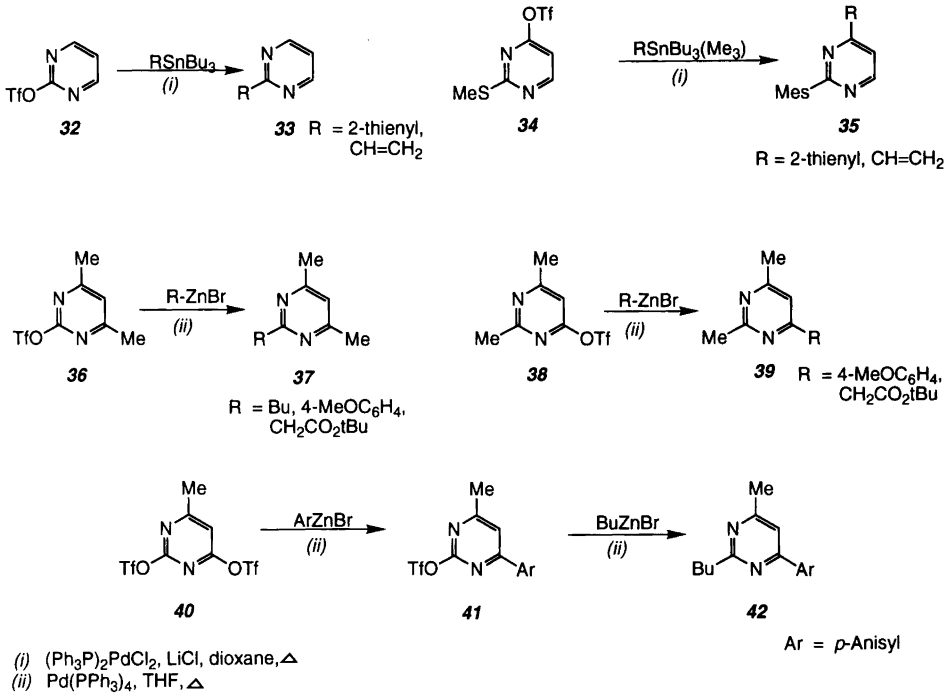
stannylation of the pyrimidine (*vide infra*), however, it is the chlorine in the 2-position which is replaced, which allows for the opposite order of coupling.

A bromine or iodine is required for coupling in the benzenoid 5-position. Coupling in 2,5-dichloropyrimidine is therefore in the activated 2-position (**25**) whereas 5-bromo-2-chloropyrimidine is coupled in the 5-position (**23**).[33] In 2,4,5-trichloropyrimidine the stepwise reactivity order was first the 4-position and then the 2-position with the 5-chlorine resistant to replacement. The difference in reactivity between a 5-bromo and 4-chloro substituent is small. Hydroxymethyl groups, protected by bulky silyl groups are substituted into the 4-position by chlorine replacement (**27**).[34] The reaction is relatively slow because the group to be transferred is bonded to tin through an sp^3-hybridized carbon. The bulky silyl groups were not cleaved by aqueous potassium fluoride during work-up, but the hydroxy compound **28** is liberated by fluoride ion under anhydrous conditions.

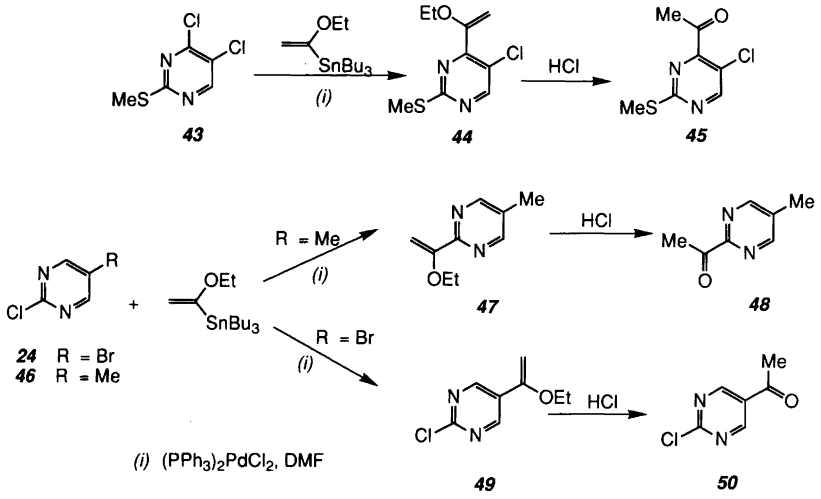
To demonstrate the power of regioselectivity in these reactions, three different substituents were introduced into 5-bromo-2,4-dichloropyrimidine in a sequential and regioselective manner: initial styrylation in the 4-position (**29**), phenylation in the 5-position (**30**) and finally thienylation in the 2-position (**31**). This reaction sequence corresponds to the reactivity order 4-Cl > 5-Br > 2-Cl.[33]

The triflate group in electrophilic pyrimidine positions can be readily displaced in coupling reactions. The triflates are available from reactions between a hydroxypyrimidine and triflic anhydride in the presence of a base at room temperature or below. Coupling between the 2- or 4-pyrimidinyl triflate (**32**, **34**) and organostannanes proceeds well using a Pd(0)-catalyst.[28]

A major advantage of organozinc compounds over organotin compounds is the possibility of introduction of alkyl groups. The 2-pyrimidinyl triflate enters into coupling reactions with both butyl and acetic acid ester zinc reagents giving 2-alkylated pyrimidines **37**. The



Scheme 6.



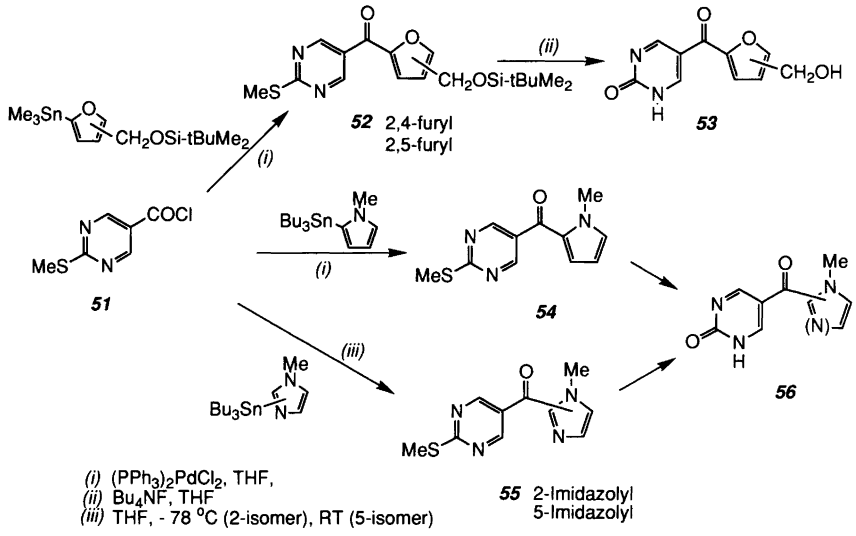
Scheme 7.

4-pyrimidinyl triflate **38** reacts in the same manner. A comparative reaction between triflates and chlorides in the pyrimidine 2- and 4-positions and organozinc reagents showed that the triflates were at least as reactive as the chlorides.[11]

In 2,4-dichloropyrimidine the 4-chloro substituent was the more reactive in the coupling with organostannanes. The same reactivity order holds in the reaction between organozinc compounds and pyrimidine which has triflate groups in the 2- and 4-positions; sequential stepwise substitution has been effected (**40**, **41**, **42**).[11]

Coupling with α-stannylated enol ethers provides a general and convenient method for the introduction of acyl groups.[33] The stannanes are available from enol ethers by α-lithiation and treatment with 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-pyrimidinylvinyl ethers yields the acyl-substituted pyrimidines.

We have a special interest in acylation reactions in the pyrimidine 5-position,[35] and find that pyrimidine-5-carbonyl chlorides and an organostannane under the influence of Pd-catalysis give ketones. Pyrimidinyl hydroxymethylfuryl ketones (**53**) have been prepared.[36] The 5-(pyrrol-2-ylcarbonyl)pyrimidine **54** is prepared from the pyrimidine-5-carbonyl chloride **51** with triphenylarsine as the ligand for the Pd-catalyst because the reaction was not satisfactory using the normal, corresponding phosphine ligand.[37] When the polarization of the reactants is reversed, however, triphenylphosphine is a good ligand for the Pd-catalyst (*vide infra*). 1-Methyl-2- or -5-tributylstannylimidazole is used for the preparation of imidazolyl ketones.[37] The 2-stannylated imidazole



Scheme 8.

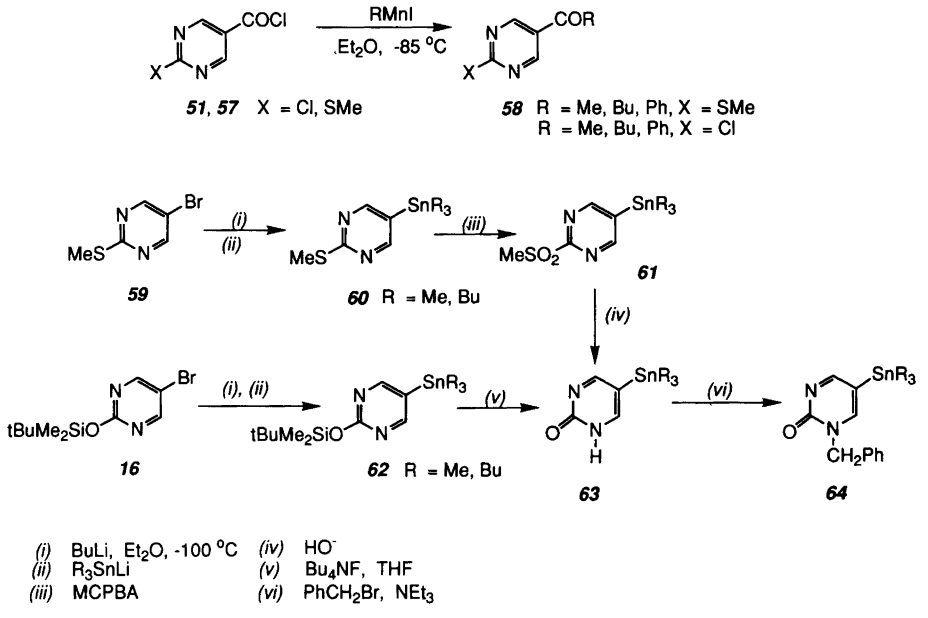
was available by transmetallation of the 2-lithiated species, and the 5-stannyl derivative by 2,5-dilithiation of 1-methylimidazole and subsequent Li–Sn exchange. The resultant 2,5-distannylimidazole is converted into the 5-stannylimidazole by selective hydrolysis of the 2-stannyl group. The coupling reactions, as well as a model reaction with benzoyl chloride, were run without a Pd-catalyst as the method which gave the higher yields at $-78°C$. These reactions presumably go via initial acylation of an imidazole nitrogen by the acid chlorides, and subsequent substitution of the stannyl group by the acyl function in an intra- or inter-molecular process. The coupling products are oxidized to sulfones and hydrolyzed to their respective lactams **56**.

5-Pyrimidinyl ketones (**58**) have also been prepared from pyrimidine-5-carbonyl chloride and organomanganese(II) iodides.[38] The organomanganese reagents are prepared from organolithium compounds and manganese(II) iodide. It has been claimed that organomanganese reagents with acid chlorides give exclusively ketones.[39] In the pyrimidine series the tertiary alcohol was a minor coproduct from manganese reagents with small alkyl groups. Formation of the alcohol is ascribed to the electron-withdrawing effect of the pyrimidinyl ring which activates the carbonyl group for further addition. This interpretation is in accord with the report that the oxo group in α-keto esters is activated for reaction with organomanganese reagents.[40]

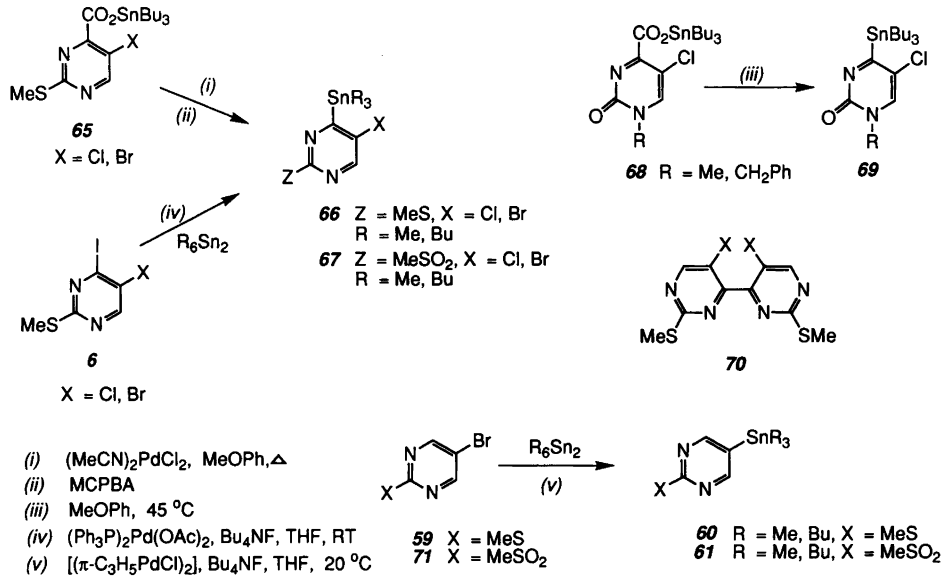
A.1.b. Metallation and cross-coupling reactions. Reversal of the polarization of the reactants to be used in the coupling requires prior metallation of the π-electron deficient heterocycle. Our main emphasis has been on finding conditions for stannylation of pyrimidines. The stannylated pyrimidines are relatively stable compounds which are isolated and purified by conventional methods. Generally, stannylation is effected by a transmetallation reaction between an organostannyl chloride and a lithiated species. This method works well in the benzenoid 5-position in pyrimidines (**60**, **62**). The lithiation is run at low temperature in order to avoid adduct formation between the lithium reagent and the pyrimidine in a free activated position, and the metal–metal exchange is effected by quenching the lithiated species with a trialkylstannyl chloride.[41, 42]

Stannylated pyrimidines can be oxidized without effect on the stannyl function.[42] Preparation of 2-methanesulfonyl-5-stannylpyrimidine **61** involves chemoselective oxidation of the corresponding sulfide **60**. Controlled alkaline hydrolysis yielded the 5-stannylated 2(1*H*)-pyrimidinones **63**. The latter have also been prepared by lithiation and stannylation of the pyrimidinone which was protected as the *tert*-butyldimethylsilyl ether **16**. The bulky silyl group was resistant to cleavage under both the lithiation and stannylation conditions.[42, 43] The silyl group is removed by fluoride ion and the pyrimidinone **63** or its *N*-alkylated derivative **64** is used in the Pd-catalyzed coupling reactions (*vide infra*).

Stannylation in the electrophilic pyrimidine 4-position results from decarboxylation of the corresponding stannyl carboxylate **65** which is prepared from the carboxylic acid and bis(tributylstannyl) oxide.[34] Thermal decarboxylation of **65** in anisole was used to generate the stannyl pyrimidine **66**. The reaction was promoted by palladium complexes but not by free-radical initiators. The stannate of *N*-alkylated 2-oxopyrimidine-4-carboxylic acid **68** was very readily decarboxylated; the 4-stannylated derivative



Scheme 9.

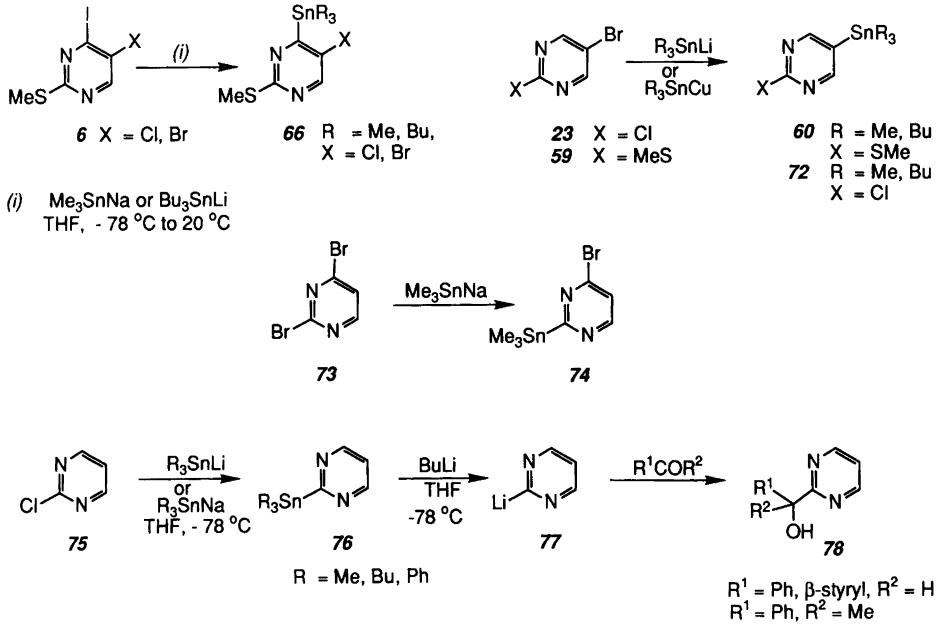


Scheme 10.

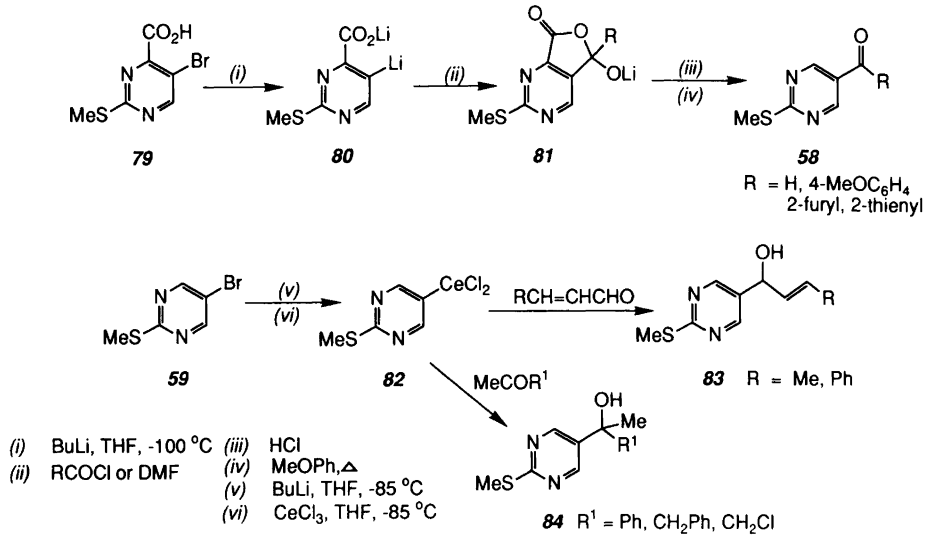
69 was formed from **68** on being heated at 45°C in anisole.[34]

Pd-catalyzed coupling of hexaalkyldistannanes with aryl halides has been reported to yield arylstannanes, especially when the aryl substrates contain electron-withdrawing substituents.[44] We find that stannylation can be effected on the 4-iodopyrimidine **6** using hexaalkyl-distannanes in the presence of 1–2 mole equivalents of fluoride ion and $(PPh_3)_2Pd(II)$ diacetate. Within a Pd(0)-complex in the absence of fluoride ion, the product was the reductively coupled bipyrimidine **70**.[34] Bis(π-allyl)palladium chloride was our best catalyst in the coupling of 5-bromopyrimidines (**59**, **71**) with hexaalkyl-distannanes. The presence of halide ions promotes the reaction, especially fluoride ions.[45] The promoting effect may be due to great affinity of the fluoride ion 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.[46]

A halogeno substituent in an electrophilic position can be substituted using a stannate. Reactions of the 4-iodo derivative **6** with stannyl-lithium, -sodium or -copper reagents were run at −78°C. In 2,4-dibromo- or 2,4-dichloro-pyrimidine, it is the halogen in the 2-position



Scheme 11.



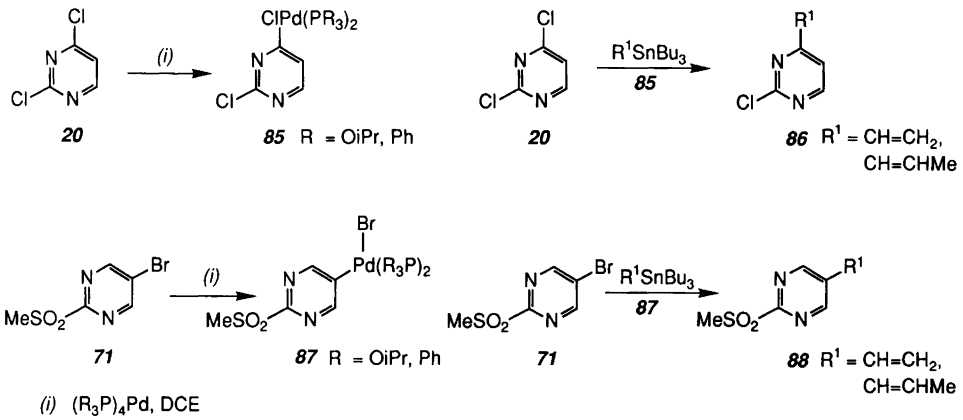
Scheme 12.

which is the more reactive in the stannylation reaction (**74**), which is not in accord with the relative reactivity of pyrimidines towards nucleophiles. In 5-bromo-2-chloropyrimidine chemoselective metallation in the 5-position (**72**) was observed,[11] and stannylation occurs readily in the benzenoid 5-position (**60**) in the 5-bromo-2-methylthiopyrimidine isomer at −78°C.[34, 35] Stannylation is therefore not a simple nucleophile substitution.[47] Pyrimidines stannylated in an electrophilic position can be used for the preparation of lithiated species. 2-Stannylpyrimidine (**76**) was converted into its 2-lithio derivative **77** which reacts with oxo compounds to form 2-α-hydroxyalkyl derivatives (**78**).[28]

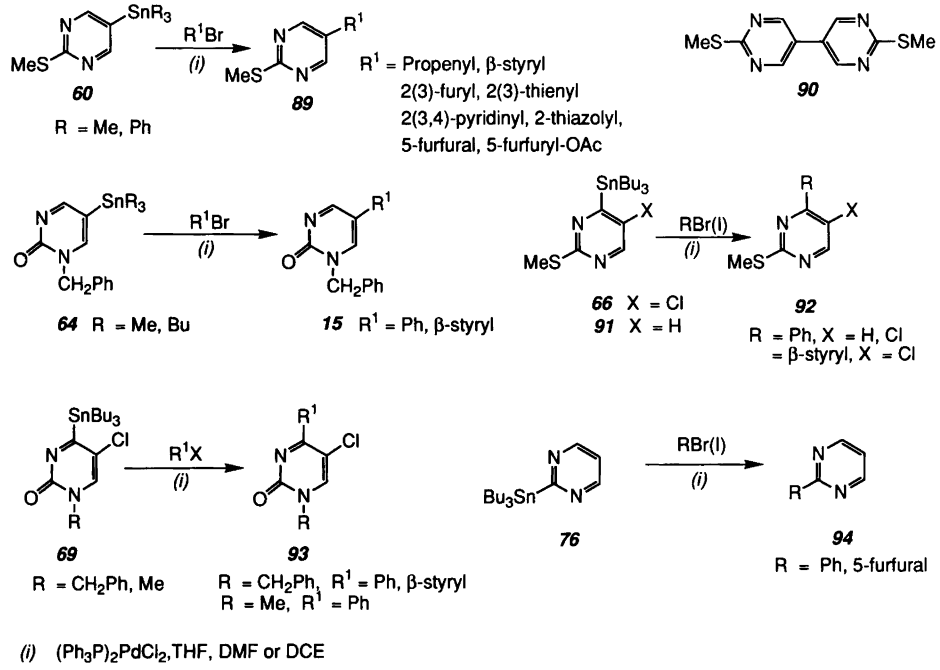
Another useful lithiopyrimidine is prepared from 2-substituted 5-bromopyrimidine-4-carboxylic acid (**79**) which itself is readily available by a cyclization reaction.[48] For the formation of a ketone in the 5-position in the basic, dilithiated species the acyl reagent should be without any α-hydrogen. Complexation with the vicinal lithium carboxylate (**81**) stops the reaction after the first carbonyl group has been introduced. Acidification and heating leads to the formation of the 5-ketone **58**.[48]

The search for metallopyrimidines of low basicity has led us to investigate cerium derivatives. We find that 5-pyrimidinylcerium dichlorides **82** are available by low-temperature metal–metal exchange using cerium trichloride and 5-lithiated pyrimidine.[49] The 5-pyrimidinylcerium dichloride **82** was superior to its 5-lithio analog in its reactions with aldehydes and ketones, especially in reactions with enolizable aldehydes and ketones (**84**), and in the 1,2-addition to α,β-unsaturated carbonyl derivatives (**83**). The results substantiate reports in the literature on the reactivities of organocerium dichlorides.[50]

Our studies of metallation in pyrimidines have led to the preparation and isolation of postulated palladium intermediates in the coupling reaction.[51] Several organopalladium compounds containing α-carbon aryl ligands have been described.[52] Heteroarene complexes have been much less investigated.[53] From reactions



Scheme 13.

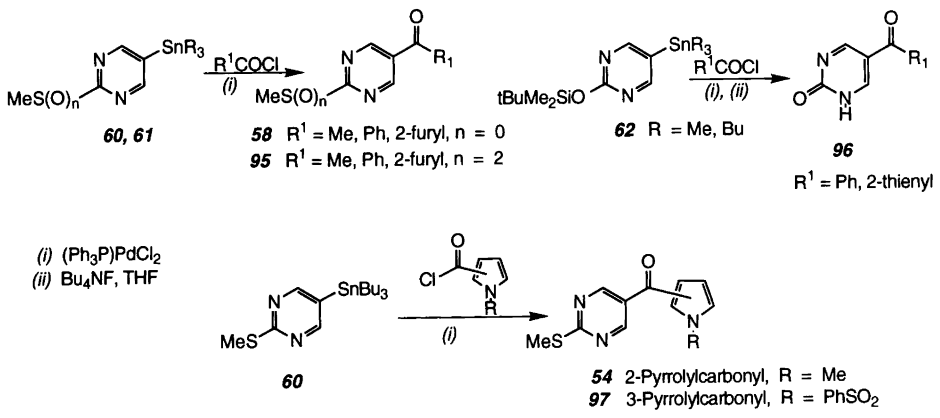


Scheme 14.

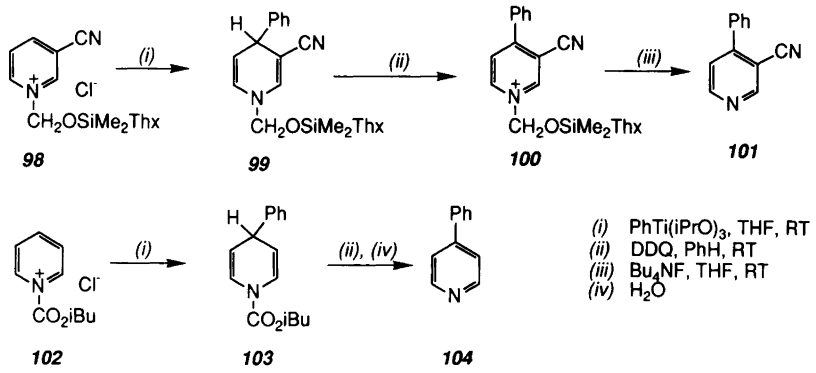
between 2,4-dichloropyrimidine or 5-bromo-2-methylsulfonylpyrimidine and tetrakis(triphenylphosphine)- or tetrakis(triisopropylphosphite)-palladium the 1:1-insertion complex **85** and **87**, respectively, is isolated.[51] The regioselectivity of the insertion reaction in 2,4-dichloropyrimidine is in accord with the 4-regiochemistry in the coupling reactions (*vide supra*). The insertion complexes can be purified by conventional methods. The palladized pyrimidines react readily with organostannanes, and may serve as catalysts in coupling reactions between the respective pyrimidine precursor and stannanes.[51]

The stannopyrimidines are generally good substrates for Pd-catalyzed reactions with organohalides and triflates. The products are the same as those obtained in the oppositely polarized reaction (*vide supra*). Solvents may affect the course of the reaction. In 1,2-dichloroethane (DCE) the reaction between 2-methylthio-5-trimethylstannylpyrimidine and β-bromostyrene or propenyl bromide, in the presence of $(PPh_3)_2Pd(II)$ dichloride, gave the 5-alkenylpyrimidines **89** in good yield. In THF a mixture of the cross-coupled product and the bipyrimidine **90** was obtained, and with vinyl bromide the product isolated was the homocoupled bipyrimidine. The heterocoupled product, however, results from the reaction between the 5-bromopyrimidine and tributylvinylstannane (*vide supra*).[41]

5-Pyrimidinyl biheteroarenes have been prepared from bromofurans, bromothiophenes or bromopyridines and the stannylated pyrimidine.[42,45] 5-Stannylated 2-pyrimidinones (**64**) are also good substrates for coupling



Scheme 15.



Scheme 16.

reactions.[42] Pyrimidines stannylated in the 4-position (**66**, **69**, **91**) are active in coupling reactions. The 2-stannopyrimidine **76** reacts in the same manner.[11, 34]

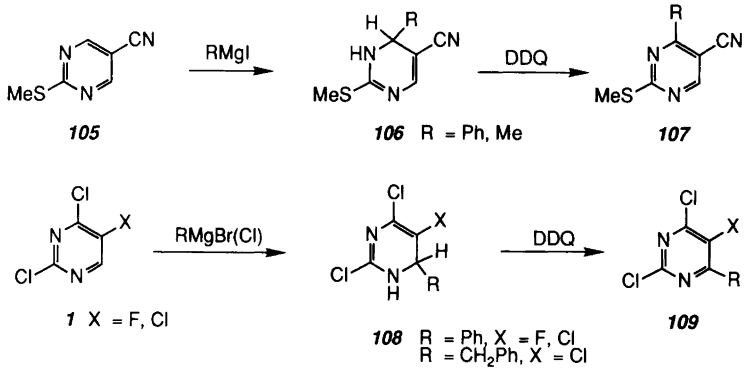
Alkyl, aryl and heteroaryl ketones can be prepared from 5-stannopyrimidines and carbonyl chlorides (**58**, **95**, **96**). The reaction with pyrrole was run on *N*-alkylated or -acylated pyrrolecarbonyl chloride to furnish the ketones **54** and **97**. 2-Pyrimidinones are protected and solubilized as a *tert*-butyldimethylsilyl ether (**62**) for the coupling. During the reaction the silyl group was cleaved off. Presumably the silyl ether function, after acylation in its *para* position, is activated for cleavage owing to the electron-withdrawal properties of the acyl function.[37]

The 2-methylsulfonyl-5-trialkylstannylpyrimidines (**60**, **61**) undergo the coupling reaction under reflux in THF. The relative mild conditions suggest that the sulfonyl group exerts an activating effect on the reactivity of the stannyl function.[42]

A.2. Covalent 1:1-adduct formation with organometallic reagents. Pyridine is the simplest π-electron deficient azine. The 2- and 4-(6-)positions are electrophilic, the 3-(5-)position is benzenoid in its properties. Pyridine itself adds organo-lithium and -magnesium reagents preferentially in the 2-position,[54] but we find that pyridine is not reactive towards phenyltriisopropoxytitanium.[55] This finding parallels the report that the rate of addition of organotitanate in carbonyl reactions is considerably lower than that of the corresponding organo-lithium and -magnesium reagents. Organotitanates were chosen as reagents for regioselective carbon–carbon bond formation in π-electron deficient heterocycles because it was known that organotitanium compounds show high chemoselectivity and regioselectivity in addition reactions with carbonyl derivatives; the selectivity is consistent with high sensitivity to steric and electronic effects.[56]

From studies of *N*-(dimethylthexylsilyloxy)methylpyridinium salts substituted in the 3-position (Cl, CO_2Me and CN), the 3-cyano derivative **98** was found to form selectively the 1,4-adduct with titanate, whereas phenylmagnesium bromide gave a mixture of the 1,4- and 1,6-adducts.[55] Since the titanium reagent is sensitive to steric influences, the observed regiochemistry may be rationalized as being due to steric interaction between the *N*-substituent and the bulky titanium reagent.

Acyl activation, as in the isobutoxycarbonylpyridinium salt **102**, led to the isolation of the 1,4-adduct from the reaction with the titanate.[55] Generally mixtures of the 1,2- and 1,4-dihydro derivatives are formed from organometallics and acylpyridinium derivatives,[57] but conditions have been found for 1,2-addition between Grignard reagents and acyl- or acyloxy-pyridinium salts.[58] Grignard reagents admixed with cuprous iodide, or organocopper reagents, may yield preferentially 1,4-addition.[59] The same regiochemistry has been reported for reactions with titanium ate complexes.[60]



Scheme 17.

3-Cyano-4-phenylpyridine (**101**) is obtained from the adduct **99** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) dehydrogenation and fluoride-ion cleavage of the silyl group in the intermediate pyridinium salt. The carbamoyl derivative **103** can also be aromatized by DDQ and hydrolyzed to form 4-phenylpyridine.[55]

Diazines are more π-electron deficient than pyridine. Pyrimidine is reported to form adducts in the 4-position with aryl- and heteroaryl-lithium reagents at low temperature.[54, 61] Pyridazine and pyrazine form adducts with organolithium reagents in the same manner.[62] In 5-cyano-2-methylthiopyrimidine methyl- and phenyl-magnesium iodide add exclusively to the pyrimidine ring with the carbon substituent in the 4-position (**106**).[63]

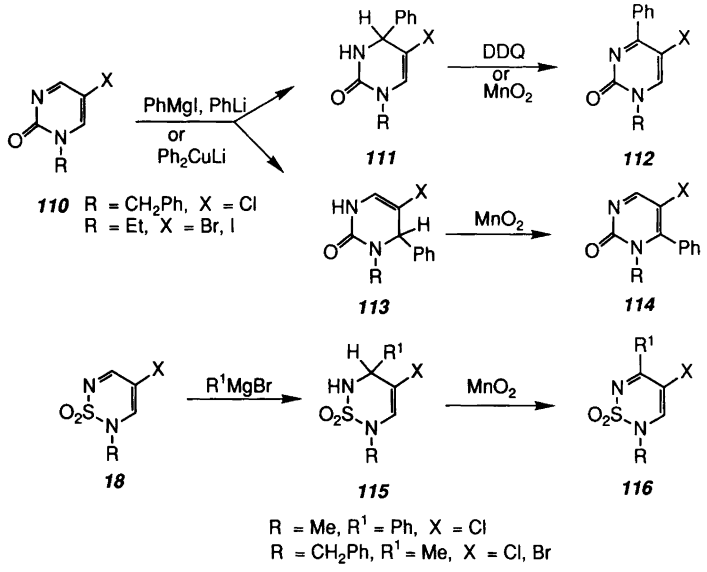
Halogeno substituents in pyrimidine can be replaced by carbon substituents in Ni(II)-catalyzed coupling reactions (*vide supra*). Competition between cross-coupling and addition, however, may arise when there is a free electrophilic position in the heterocycle. In the reaction between phenylmagnesium bromide or benzylmagnesium chloride and 2,4,5-trichloro- or 2,4-dichloro-5-fluoropyrimidines using bis(1,3-diphenylphosphinopropane)-nickel(II) dichloride, (dppp)$NiCl_2$, as the catalyst, the products had the new carbon substituent in the 6-position (**108**).[5, 6] With alkyl Grignard reagents under the same conditions, however, cross-coupling in the 2- and 4-positions gave the main products.[5, 6] The same substrates undergo exclusive cross-coupling with organostannanes under the influence of Pd-catalysis (*vide supra*).

Pyrimidin-2(1*H*)-ones are highly polarized and form adducts with organometallics. The new carbon–carbon bond may be formed in either the 4- or the 6-position. Regioselectivity has been reported with organo-lithium and -magnesium reagents in related reactions.[64, 65] We find, however, that the reaction between 1-benzyl-5-halogenopyrimidin-2(1*H*)-ones and organo-copper, -lithium or -magnesium reagents leads to a mixture of the 3,4- and 3,6-dihydro isomers.[66] In most cases the major product from the Grignard reactions was the 3,6-adduct **113**, whereas organo-lithium and -copper reagents gave larger amounts of the 3,4-dihydro isomer (**111**).

The effect of the halogen in the 5-position is twofold. The electronegativity will serve to activate electronically the pyrimidine, but the bulkiness of the halogen gives rise to steric interference. The steric effect is expected to be most severe in the 6-position with bulky reagents because of the additional interaction with the 1-substituent. The highest activation was seen in the 5-fluoro and 5-chloro derivatives. The 5-iodo derivative was, in most cases, recovered.

Full regioselective formation of 3,4-adducts (**111**) has been achieved with organotitanium reagents.[67] The nature of the 1- and 5-substituents did not affect the regiochemistry in reactions with phenyltriisopropoxytitanium. The regioselectivity observed may in part be rationalized as being due to steric repulsion between the 1-substituent and the bulky aryltriisopropoxytitanium reagent, which would therefore be expected to favor bond formation at C-4 in preference to C-6.

The formation of the 3,4-adduct can be regarded as a 1,2-conjugate addition in accordance with the behavior of titanates in their reactions with α,β-unsaturated carbonyl compounds.[56] In this comparison the N(3)–C(6) part of the pyrimidinone is regarded as possessing electronic properties similar to an α,β-unsaturated carbonyl function, or the closer α,β-unsaturated imine system. Both organo-lithium and -magnesium compounds add to α,β-unsaturated imines, but the organolithium compounds show the greater tendency for 1,2-addition. Carbon–carbon bond formation at C-6 corresponds to 1,4-conjugate addition. The organolithium reagents show a preference for carbon–carbon bond formation at C-4,



Scheme 18.

which corresponds to 1,2-conjugate addition. The reactions with the organo-lithium and -magnesium reagents were run for 10–15 min at ambient temperature or below,[66] whereas the reaction time for the titanium reagents was of the order 20 h,[67] which may, in part, explain the difference in regioselectivity.

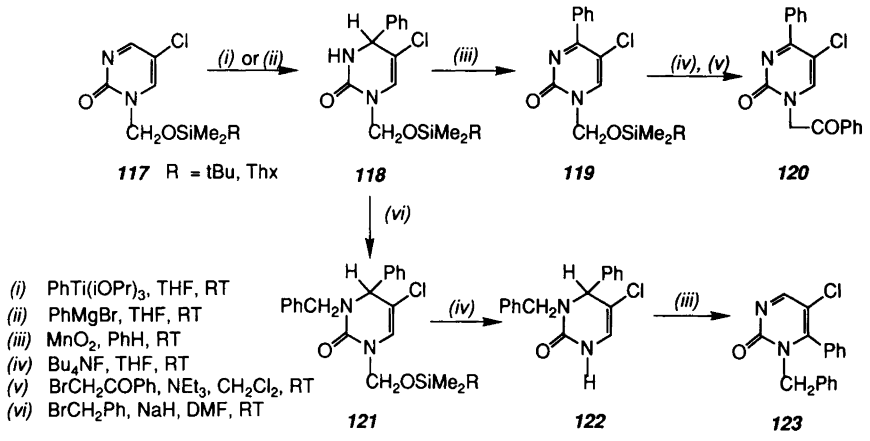
The aromatic substitution sequence at C-4 (**112**, **114**) is completed by oxidation of the dihydro compounds with DDQ or activated manganese dioxide. The latter is the more potent reagent and is used when the yields from the DDQ oxidations are unsatisfactory or in the more difficult oxidation of the 3,6-adducts.[66]

In the π-electron deficient 1,2,6-thiadiazine 1,1-dioxides Grignard reagents form regioselective adducts with the new carbon substituent in the 5-position (**115**), which corresponds to the 4-position in the pyrimidinones.[29] The regioselectivity is attributed to the bulkiness of the SO_2 group which has one oxygen above and one oxygen below the ring plane. Interaction between the 1-substituent and the oxygens may therefore result in a stronger shielding of the 3-position in the thiadiazine than the shielding of the corresponding 6-position by the 1-substituent in the pyrimidinones. A halogen in the benzenoid 4-position activates the thiadiazine for adduct formation. Manganese dioxide was used for the dehydrogenation to the heteroarene.

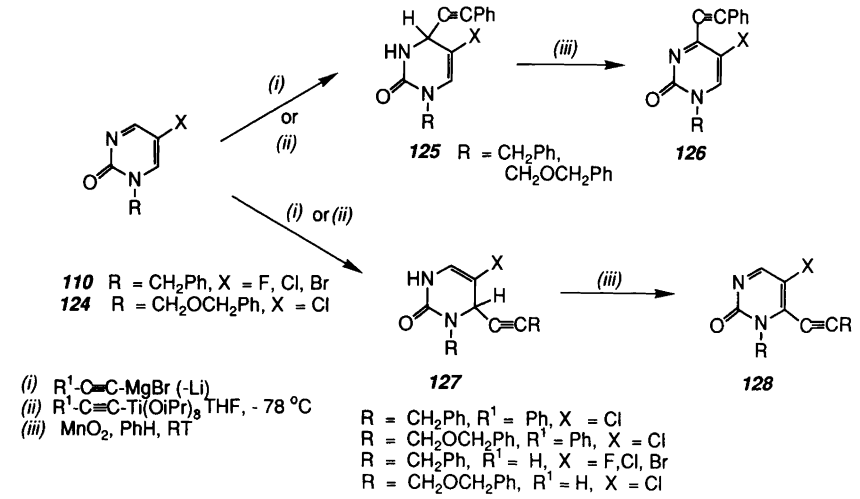
An unsubstituted lactam nitrogen must be protected before the organometallic reaction. The organometallic reaction must also precede introduction of the N-1 substituent when the N-1 substituent is incompatible with the organometallic reagent. We use silyloxymethyl protecting groups which can be removed under mild conditions without hydrogenolysis, which is an advantage since the pyrimidinone is sensitive to reducing conditions. The (*tert*-butyldimethylsilyloxy)methyl and the (dimethylthexylsilyloxy)methyl groups used are resistant to the organometallic reagents employed. The protected pyrimidinones **117** are prepared by alkylation with the chloromethyl silyl ether, and with triethylamine as the base. With the phenyltitanium reagent, clean 3,4-adduct formation (**118**) was seen.[55] With phenylmagnesium bromide a 1:1 mixture of the 3,4-dihydro derivative and its 3,6-dihydro isomer resulted.[68] The 3,4-adduct can be a substrate for the preparation of either a 1,4-disubstituted pyrimidinone (e.g. **120**) or a 1,6-disubstituted pyrimidinone (e.g. **123**). The latter is prepared by *N*-alkylation of the adduct, removal of the protecting group by fluoride ion and aromatization with manganese dioxide. 1,4-Disubstituted isomers are prepared by manganese dioxide dehydrogenation of the adduct, cleavage of the protecting group by fluoride ion and N-1 alkylation.

Phenylethynylmagnesium iodide in reactions with the pyrimidinones gives a mixture of the isomeric 3,4- (**125**) and 3,6- (**127**) dihydro isomers in almost equimolar amounts. The isomers can be separated by chromatography on alumina.[69] These results contrast the recent report that 1-methylpyrimidin-2(1*H*)-one reacts with phenylmagnesium bromide to form the new carbon bond at C-6.[65] Complete regiocontrol and formation of the 4-isomer can be achieved by the use of phenylethynyltriisopropoxytitanium.[69] The latter is prepared *in situ* by quenching the corresponding lithium derivative with triisopropoxytitanium chloride. The adduct formation is slow, and an excess of the titanium reagent has to be used to compensate its partial decomposition. Manganese dioxide is used for dehydrogenation of the adducts to form the 4-alkynylpyrimidinones.

Acetylene itself is substituted into the pyrimidine nucleus with regiochemical control using the corresponding titanium reagent.[70] The latter is generated from lithium acetylide by titanation with triisopropoxytitanium chloride at −80°C. The 3,6-dihydro isomer **127** is formed. The reason for the reversal of the regiochemistry remains unclear; the reactions with both ethynyltitanium reagents were run at low temperature. When the reaction was repeated with lithium acetylide, a mixture of the 3,6-dihydro isomer and its 3,4-dihydro isomer was formed in the ratio 4:1.[69] With ethynylmagnesium bromide an almost equimolar amount of the isomers was formed;[70] the isomers can be separated by chromatography. The ethynyl derivatives are unstable on



Scheme 19.



Scheme 20.

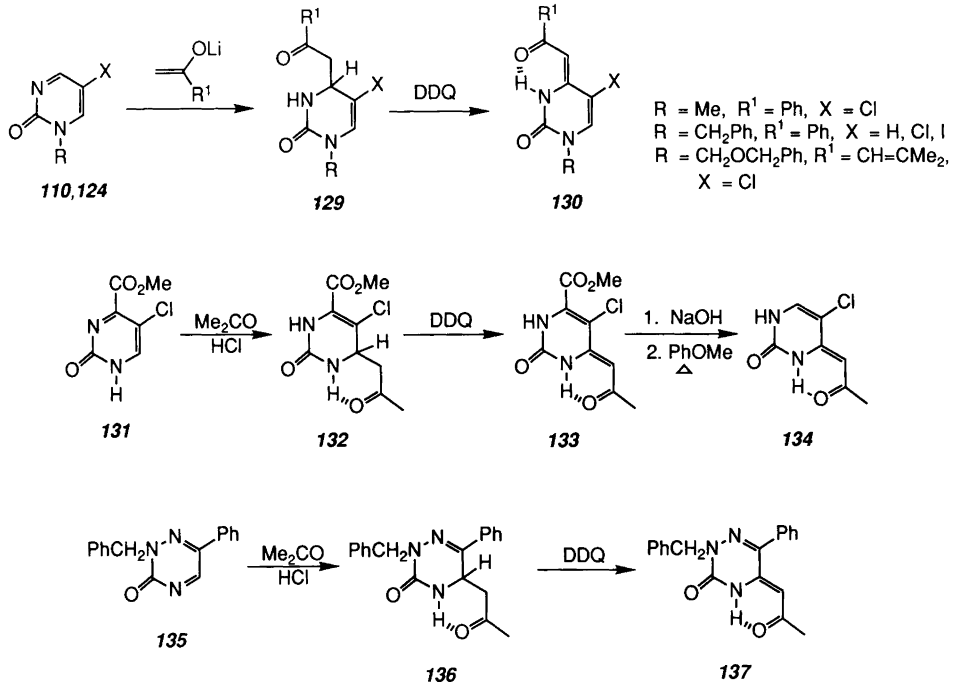
storage when there is no substitution on the terminal acetylenic carbon. Aromatization of the dihydro derivatives is difficult to achieve because the dehydrogenated products are also unstable.[9]

The nature of the 5-halogen substituent in the pyrimidinone may affect the reactivity, because of steric and inductive effects. Thus the chloro and the fluoro derivatives readily form adducts, whereas the 1-benzyl-3-bromo-2(1*H*)-pyrimidinone homolog failed to react under the standard reaction conditions used.

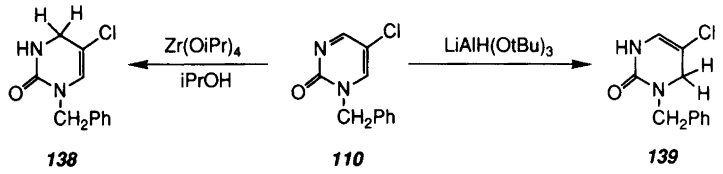
The aldol reaction in carbonyl compounds has its equivalents in π-electron deficient heterocycles. In the carbanion approach, lithiated acetophenone added rapidly and regioselectively to 1-substituted 2-pyrimidinones to form the 3,4-dihydro isomer (**129**).[71] The adducts are readily oxidized to their aromatic equivalents by DDQ. With the lithium enolate of mesityl oxide, however, equal amounts of the two dihydro isomers were formed.[70]

In highly π-deficient heterocyclic systems aldol reactions also take place under the influence of acid catalysis such as in the addition of acetone to substituted pyrimidinones (**131**) and 1,2,4-triazines (**135**).[72, 73]

Metal hydride reduction of pyrimidinones proceeds in the same manner. With lithium tris(*tert*-butoxy)-aluminum hydride a mixture of the 3,4- and 3,6-dihydro isomers **138** and **139** was formed in the ratio 1:9, respec-



Scheme 21.



Scheme 22.

tively; **139** is readily isolated from the crude product.[71] Regioselective formation of the 3,4-isomer (**138**) can be achieved by a zirconate-catalyzed Meerwein–Pondorf–Verley reduction.[74] The application of tetraisopropoxyzirconium to effect regioselective reductions in heterocycles was based on the report that this reagent shows high functional group selectivity due to both steric and electronic effects.[75] The reaction is relatively slow, but is promoted by an electron-withdrawing substituent in the 5-position. Triisopropoxyaluminum reacts less readily. Both the zirconium and the aluminum reagents add 1,2 to α,β-unsaturated carbonyl derivatives.[76] 1,2-Conjugate addition in an α,β-unsaturated imine model would correspond to the observed preference for the formation of the 3,4-dihydropyrimidine.

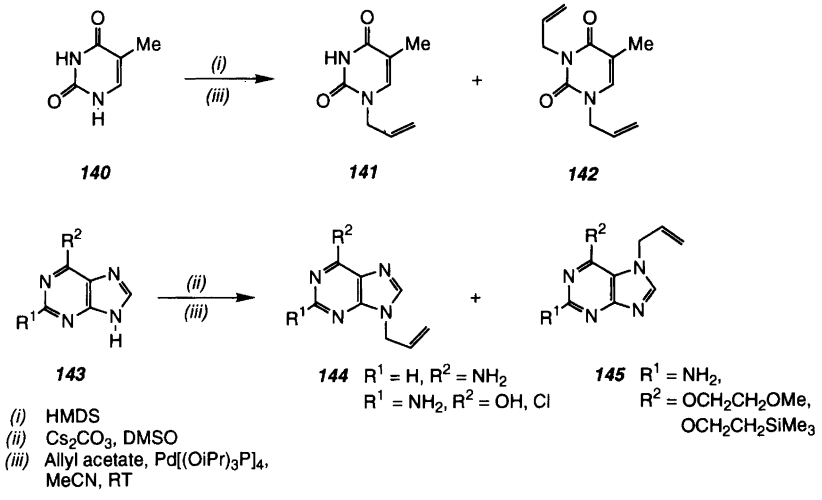
B. Carbon–Nitrogen Bond Formation by Pd-Catalysis.

Carbon–nitrogen bond formation has been effected in 2-pyrimidinones by π-allylpalladium complexes either on a 2-stannyloxypyrimidine,[77] or on pyrimidinone anions.[78]

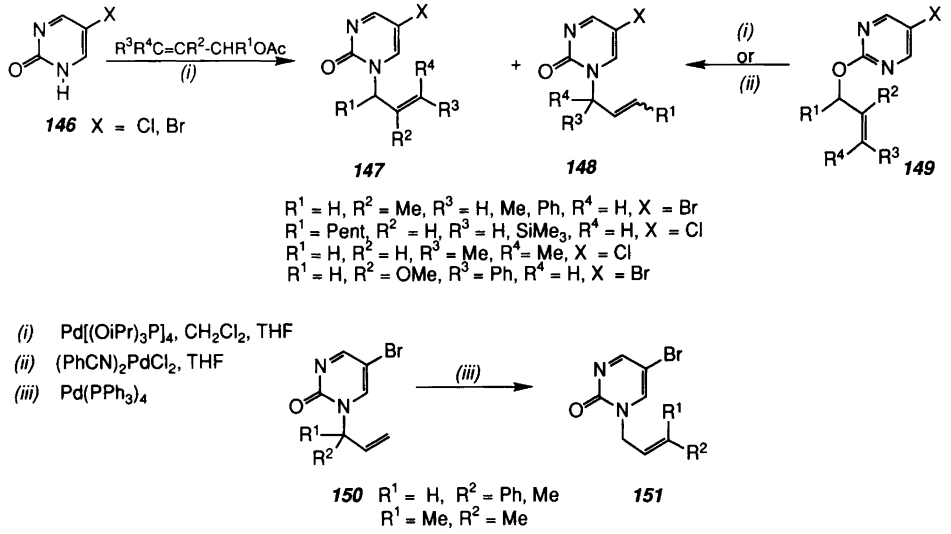
Thymine, activated as its bis(trimethylsilyl) ether, gave a mixture of the mono- (**141**) and diallylated (**142**) thymine.[79] The cesium salt of adenine can be allylated regioselectively on N-9.[79] In guanine difficulties in controlling regioselective alkylation at N-9 have led to the use of various 6-substituted 2-aminopurines as precursors for guanine.[80] Allylation reactions with the 6-chloride, the 6-methoxyethoxy or the 6-(2-trimethylsilylethoxy) derivative yield mixtures of N-7 and N-9 allylated purines (**144, 145**) in variable ratios.[79]

In allylic palladium complexes the nucleophile will preferentially attack the more substituted allylic carbon. With the azines the allylation reaction is reversible, which means that the *N*-allylated product dissociates, and gradually the less substituted carbon becomes attached to the annular nitrogen.[78, 81]

Allylic rearrangements have been studied in some detail for allylated pyrimidinones under the influence of either Pd(0)- or Pd(II)-catalysis. The Pd(0)-catalyst used in the work was generated from palladium(II) diacetate and triethyl phosphite, and the reactions were run in dichloromethane at ambient temperature. No rearrangement was observed in the absence of a catalyst. The product compositions from substituted allylic derivatives depend on the catalyst used. Claisen [3,3] regioselectivity is observed with a Pd(II)-catalyst, whereas Pd(0)-catalysis generally gives both [1,3] and [3,3] rearrangement products. The substitution pattern in the allylic system is important for the nature of the rearrangement product from the Pd(0)-catalyzed reaction, which is assumed to proceed via a π-allylpalladium complex. 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 rearrangement products. The major isomer, which may become the only detectable isomer in some cases, has the less substituted allylic carbon attached to the annular nitrogen.[78]



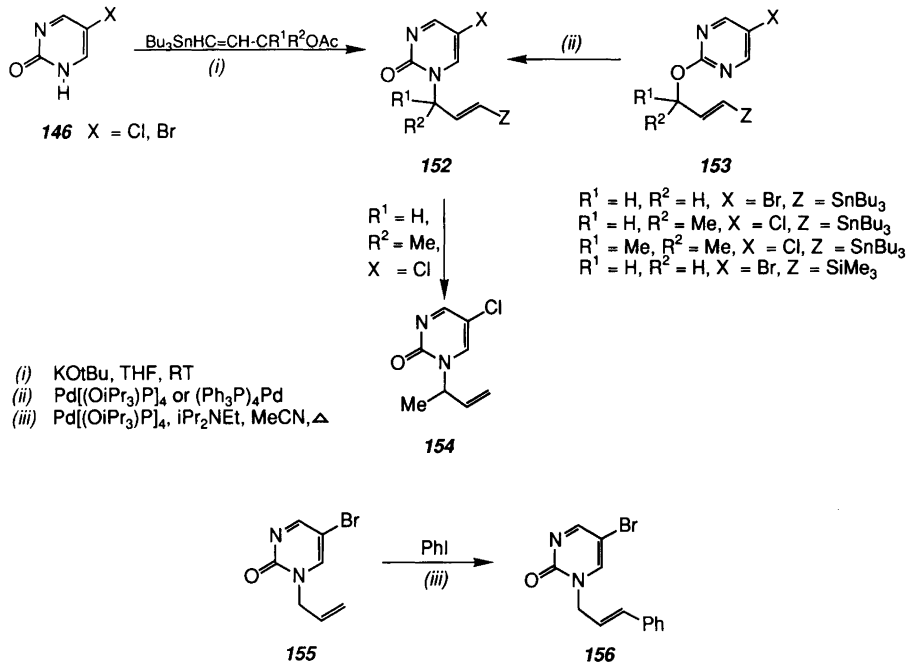
Scheme 23.



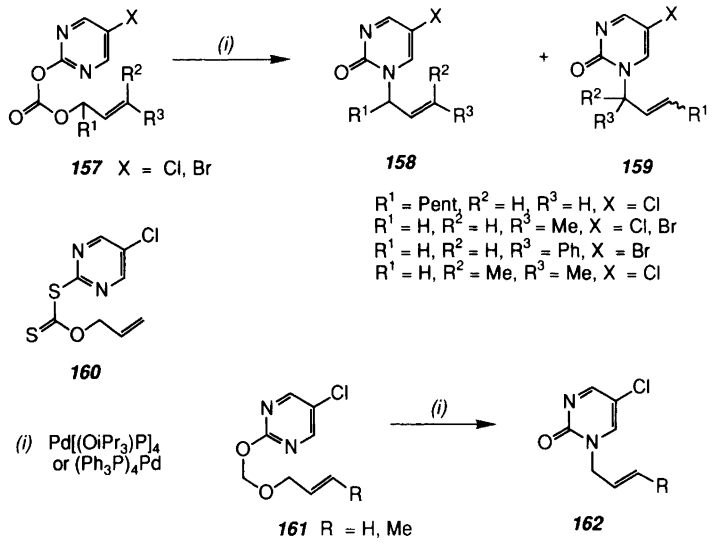
Scheme 24.

A γ-stannyl or -silyl substituent is not affected in the Pd(0)-catalyzed allylic 1,3-rearrangement, nor is the stannyl group affected in the P(0)-catalyzed alkylation when the ring becomes attached to the original allylic carbon.[81] Protonolysis with cleavage of the carbon–tin bond is achieved with iodine under aqueous conditions. The vinylstannyl group is a handle for further reactions. Phenylation by the Heck-coupling between iodobenzene and *N*-allylated 2-pyrimidinone (**155**) is feasible.[81]

The rate of the Pd(0)-catalyzed rearrangement is dependent on the substitution pattern and is sometimes slow, which may be ascribed to slow formation of the intermediate π-allylpalladium complex. Allyl carbonates have high reactivity in allylation reactions with carbon nucleophiles. For rearrangement studies of pyrimidinyl derivatives allyl 2-pyrimidinyl carbonates **157** were prepared by *O*-acylation with allyl chloroformates.[82] In most cases the *N*-allylpyrimidinones are obtained in high yields from reactions of the carbonates **157** run at ambient temperature; for allyloxypyrimidines reflux in THF was used (*vide supra*). Without the catalyst no reaction occurred, and Pd(II)-complexes did not cause any rearrangement. The product distribution was similar to that from the corresponding allyloxypyrimidines which was to be expected since the reaction goes via the same π-allylpalladium complex.



Scheme 25.

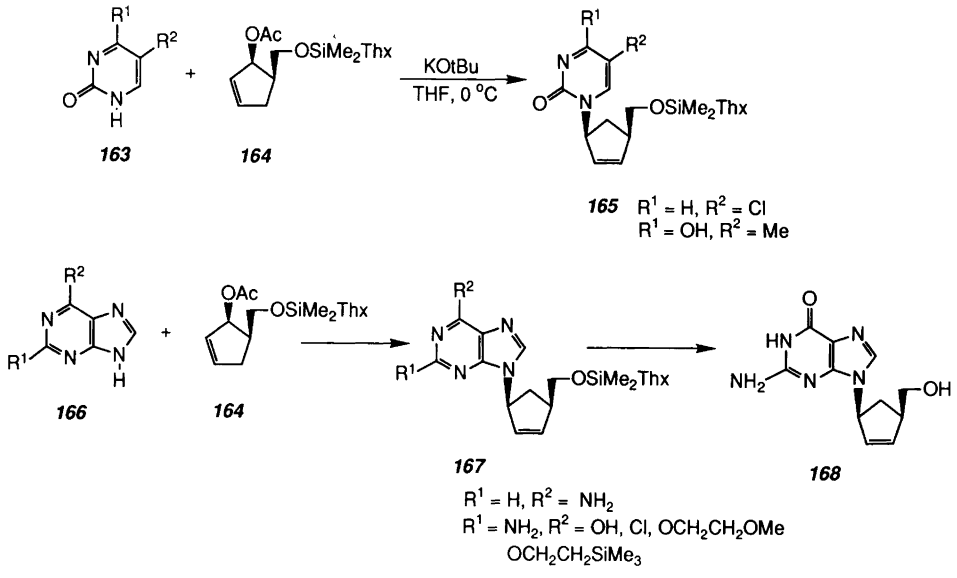


Scheme 26.

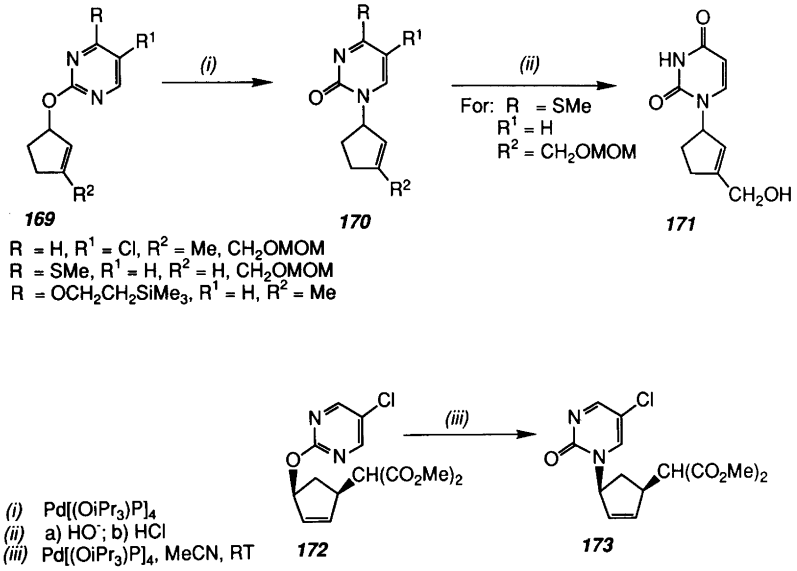
The 2-pyrimidinylthio analog of the allylic carbonate **160** did not rearrange in the presence of Pd-catalysts. From the acetal pyrimidine **161** a moderate yield of the rearranged product **162** was obtained. The reaction was slow and heating in DMF was used.[82]

The allylic alkylations can be used for nucleoside syntheses with stereochemical control of the configuration at the anomeric carbon. In reactions of appropriately substituted olefinic carbohydrates the stereochemical course can be controlled by Pd(0)-catalyzed reaction with an allylic acetate or carbonate. The stereochemical course is controlled by the stereochemistry of the Pd-template. The Pd(0)-catalyst adds on the opposite side of the departing ester group. Subsequently a soft nucleophile will add to the same side of the template as the group which was displaced.[83] The carbonucleoside which is formed, has a carbon–carbon double bond which can be further manipulated. On formation of the Pd-template the original allylic position entity is lost once the leaving group has departed, and the regiochemistry in the bond-forming reaction will be controlled by the substituents on the allyl termini of the template.[83] With the *cis*-cyclopentenyl acetate a *cis*-carbonucleoside is formed. The change in the allylic regiochemistry in the carbocycle is due to non-bonded interactions between the approaching nucleophile and the ether substituent on the cyclopentene ring.

Thymine in the form of its bis(trimethylsilyl) ether was regioselectively alkylated on N-1 (**165**). The reaction with the cesium salt of adenine in DMSO gave alkylation



Scheme 27.



Scheme 28.

on N-9 and hence the desired carbonucleoside **167**. From 2-amino-6-chloropurine a mixture of N-7 and N-9 alkylated products are formed. Complete regioselectivity for N-9 was obtained in the case of the 6-ethoxy derivatives **167** ($R^1 = OCH_2CH_2OMe$, $OCH_2CH_2SiMe_3$). The trimethylsilylethyl group is designed for removal by fluoride ion. Both the silylethyl group and the silyl protecting group on the carbocycle (**167**) are removed on treatment of the carbonucleoside in acetonitrile with tetrabutylammonium fluoride.[79] The product formed (**168**) is the antiviral compound Carbovir.[84, 85]

Pd-catalyzed rearrangements of 2-allyloxypyrimidines can be used in the construction of carbonucleosides.[81] In this approach allylic cyclopentenol is first converted into the corresponding 2-pyrimidinyl ethers **169** by the reaction between the cyclopentenolate and a 2-chloro- or 2-methylsulfonyl-pyrimidine. The rearrangement requires a Pd-complex for catalysis, and Pd(0)-complexes were used. The rearrangements proceed readily in THF in the presence of tetrakis(triisopropyl phosphite)palladium. It is the original allylic carbon which becomes attached to the heterocycle in the γ-substituted derivatives (**170**). The allylic derivatives are acid sensitive, and the presence in the reaction medium of a base such as cesium carbonate or triethylamine is frequently required.

The stereochemical course is elucidated by reactions with the *cis*-4-malonylcyclopentenyl 2-pyrimidinyl ether **172**. The carbonucleoside obtained has *cis* stereochemistry and the desired regiochemistry. The stereochemistry is in agreement with the normal reaction course involved in π-allylpalladium complexes (*vide supra*). Removal of protecting groups in **170**, the MOM-group by HCl in methanol and the $Me_3SiCH_2CH_2$-group by tetrabutylammonium fluoride, furnished carbonucleoside analogs (e.g. **171**).

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